Pharmacology of Systemic Antibacterial Agents: Clinical Implications

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Continuing Education Units: 3 hours


Disclaimer: Participants must always be aware of the hazards of using limited knowledge in integrating new techniques or procedures into their practice. Only sound evidence-based dentistry should be used in patient therapy.

Participants in this course will be introduced to evidence-based information related to the microbiology of odontogenic infections, the pharmacology of systemic antibacterial agents, and the rationale for the selection of an antibacterial agent for the treatment of odontogenic infections.

Conflict of Interest Disclosure Statement
• Dr. Palomo reports no conflicts of interest associated with this work.
• Dr. Terézhalmy has done consulting work for Procter & Gamble and is a member of the dentalcare.com Advisory Board.

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Overview
Participants in this course will be introduced to evidence-based information related to the microbiology of odontogenic infections, the pharmacology of systemic antibacterial agents, and the rationale for the selection of an antibacterial agent for the treatment of odontogenic infections.

Learning Objectives
Upon completion of this course, the dental professional should be able to:
• Discuss the microbiology of odontogenic infections.
• Discuss the pharmacology of systemic antibacterial agents.
• Select the most appropriate antibacterial agent to treat an odontogenic infection.
• Discuss potential ADEs associated with the administration of antibacterial agents.

Course Contents
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• Microbiology of Odontogenic Infections
• Pharmacology of Systemic Antibacterial Agents
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  ◦ Inhibitors of DNA Synthesis or Integrity
  ◦ Inhibitors of Transcription or Translation
• Strategies for the Treatment of Odontogenic Infections
  ◦ Primary Dental Care
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Introduction
The human fetus is free of microorganisms. After initial exposure at birth, most organisms are soon eliminated, but others become permanently established and the dynamic process of colonization begins. The adult body harbors a dense, diverse, indigenous flora that includes bacteria, viruses, fungi and protozoa. Interaction between these various microbial ecosystems determines the normal flora. Microorganisms of the normal flora establish symbiotic relationships (mutualism, commensalisms, or parasitism) with their human host and each other.

Factors that modify or shift the balanced environment of the normal flora (age, altered anatomy, diet, local and systemic conditions, or pharmacotherapy) may predispose an individual to infection. Infection, the invasion and multiplication of microorganisms in body tissues, results in cellular injury due to competitive metabolism, toxin production, or immune-mediated reactions. An infection may be autogenous, caused by the body’s normal flora; or it may be a cross-infection, related to the proliferation of transient organisms.

Microbiology of Odontogenic Infections
Predicated on their metabolic characteristics, i.e., their metabolic demand for oxygen, bacteria are classified as aerobic, facultative, or anaerobic. Morphologically, they are characterized as cocci or bacilli (rods). Based on Gram’s Method of staining (Box 1), bacteria are further classified as gram-positive or gram-negative. The distinct staining properties of bacteria are related to their architectural and biochemical differences.

Gram-positive bacteria possess a thick peptidoglycan cell wall interspersed with lipoteichoic acid underlain by the cytoplasmic membrane (Figure 1). Gram-negative bacteria have an outer membrane with lipopolysaccharides and a lipoprotein layer underlain by a thin peptidoglycan layer and the cytoplasmic membrane (Figure 2). The ability of antibacterial agents to diffusion into bacteria is also affected by these structural differences.
Box 1. Gram’s Method of staining.\textsuperscript{7}

<table>
<thead>
<tr>
<th>Step</th>
<th>Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Apply a thin film of the specimen to a glass slide and allow it to dry.</td>
</tr>
<tr>
<td>2</td>
<td>Fix the slide in methanol for 1 minute or fix by quickly passing the slide through a flame several times.</td>
</tr>
<tr>
<td>3</td>
<td>Flood the slide with crystal violet stain for 30 seconds.</td>
</tr>
<tr>
<td>4</td>
<td>Rinse gently with running water.</td>
</tr>
<tr>
<td>5</td>
<td>Flood the slide with Gram’s iodine wash for 30 seconds.</td>
</tr>
<tr>
<td>6</td>
<td>Rinse gently with running water.</td>
</tr>
<tr>
<td>7</td>
<td>Apply acetone decolorizer so it runs over stained areas until no more color washes out.</td>
</tr>
<tr>
<td>8</td>
<td>Rinse gently with running water.</td>
</tr>
<tr>
<td>9</td>
<td>Flood the slide with safranin counterstain for 30 seconds.</td>
</tr>
<tr>
<td>10</td>
<td>Rinse gently under running water and allow the slide to air dry.</td>
</tr>
</tbody>
</table>

**Figure 1.** Gram-positive bacteria.

**Figure 2.** Gram-negative bacteria.

During staining, crystal violet interacts with iodine forming a complex. Acetone extracts lipids from the outer membrane, cell wall, and cytoplasmic membrane of bacteria. The damage to gram-negative organisms is more extensive and they lose their crystal violet-iodine complexes, i.e., they are decolorized; and when counterstained with safranin, they appear red (Figure 3). Gram-positive bacteria retain their crystal violet-iodine complexes and appear deep purple (Figure 4).

An average adult harbors at least 300 oral bacterial species and more than 700 strains of bacteria have been isolated from test cases. Most odontogenic infections are polymicrobial. The number of strains per infection ranges from 1 to 10 with an average number of 4 isolates.

Pharmacology of Systemic Antibacterial Agents
Pharmacological strategies are predicated on targeting differences between prokaryotic bacterial and eukaryotic host cells. Selective toxicity can be achieved by (1) attacking targets unique to bacteria, (2) attacking targets in bacteria similar but not identical to those in host cells, and (3) attacking targets that are shared, but vary in importance between bacteria and host cells (Figure 5). Drugs targeting unique differences are the least toxic to host cells.
Antibacterial agents are either bactericidal or bacteriostatic. Bactericidal drugs attack targets essential for bacterial survival, e.g., inhibitors of cell wall synthesis and most inhibitors of DNA synthesis and integrity. Bacteriostatic drugs attack targets that are necessary for bacterial growth but not for survival, e.g., most inhibitors of transcription and translation. Since bacteriostatic drugs block bacterial replication, they antagonize the effects of bactericidal drugs.

**Inhibitors of Bacterial Cell Wall Synthesis**

Most pathogenic bacteria have a cell wall that provides tensile strength and maintains intracellular osmotic pressure. Its synthesis progresses in three steps: (1) monomers are synthesized in the cytoplasm from amino acid and sugar building blocks; (2) Bactoperol transfers the monomers across the cytoplasmic membrane where they are polymerized into linear peptidoglycan chains; finally, (3) transpeptidase cross-links peptidoglycan chains into a three-dimensional mat (Figure 6).
A number of drugs inhibit cell wall synthesis. Most important are Vancomycin, which targets monomer polymerization; and the β-lactams, e.g., penicillins and cephalosporins, which block polymer cross-linking. β-lactam antibacterial agents also activate autolysins. Autolysins punch holes in bacterial cell wall and disrupt its integrity. Transpeptidase antagonism and autolysis prevent bacterial self-maintenance, i.e., remodeling and repair; and replication.

Vancomycin
Vancomycin is bactericidal in susceptible organisms. It is primarily effective against aerobic gram-positive cocci and bacilli. It does have activity against some anaerobic gram-positive, but not against gram-negative bacilli. Since facultative and anaerobic gram-positive and gram-negative cocci and bacilli predominate in all types of odontogenic infections, Vancomycin does not have the requisite spectrum to be considered an empirical option in treating odontogenic infections.

Penicillins
Penicillins are bactericidal in susceptible organisms. Narrow-spectrum penicillin V potassium and broad-spectrum amoxicillin and amoxicillin with clavulanic acid have the requisite spectra to be considered as empirical options in treating odontogenic infections. However, neither narrow-spectrum nor broad-spectrum penicillins are active against β-lactamase producing bacteria; and certain β-lactamases produced by bacteria now confer resistance to clavulanic acid as well.

Penicillin V potassium and amoxicillin formulations are not inactivated by gastric acid and also have the advantage that they may be given with meals. They are widely distributed to most tissues and body fluids, cross the placenta and they are excreted into breast milk. The penicillins undergo hepatic biotransformation. The metabolites and the unchanged fraction of the drugs are excreted rapidly in individuals with normal renal function.

Cephalosporins
The cephalosporins are bactericidal in susceptible organisms. Most are primarily active against aerobic gram-positive cocci and bacilli. Second generation cephalosporins (e.g., cefaclor) have an overlapping spectra with those of penicillin V potassium and amoxicillin formulations.
and are more β-lactamase resistant than the first generation cephalosporins. However, cephalosporins, in general, offer no therapeutic advantage over penicillins as empirical options in treating odontogenic infections.

**Inhibitors of DNA Synthesis or Integrity**

Cell wall inhibitors cannot kill all bacteria because some bacteria lack a cell wall. Other bacteria have unique structures that inherently resist the accumulation or action of cell wall inhibitors. However, bacteria, in preparation for cell division, must replicate their double stranded DNA. To facilitate replication, topoisomerase type II, a bacterial DNA gyrase, must first unwind and separate, and then reassemble the original DNA during the process.

In the replication process, bacteria must synthesize folate. Its synthesis begins with the formation of dihydropteroic acid from pteridine and para-aminobenzoic acid (PAPA), a reaction catalyzed by dihydropteroate synthase (Figure 7). Dihydropteroic acid and glutamate condense to form dihydrofolate (DHF). Dihydrofolate reductase (DHFR) reduces DHF to tetrahydrofolate (THF). THF is an essential cofactor in the synthesis of DNA, RNA, and proteins (Figure 7).

**Fluoroquinolones**

Fluoroquinolones block topoisomerase type II activity and disrupt the integrity of bacterial DNA. They are bactericidal in susceptible organisms and are primarily active against aerobic gram-positive and gram-negative cocci and bacilli. The newer agents (e.g., moxifloxacin) have some anaerobic activity. Fluoroquinolones are indicated for the treatment of infections with designated, susceptible bacteria and are not empirical options in treating odontogenic infections.

**Metronidazole**

A metabolite of metronidazole directly binds DNA, causes loss of its helical structure, and effects strand breakage. It is bactericidal in susceptible organisms. Metronidazole is active against most obligate anaerobes, but lacks clinically relevant activity against obligate aerobes and facultative anaerobes. Metronidazole, in combination with an agent active against aerobic/facultative organisms (e.g., penicillin), is an empirical option in treating odontogenic infections.

Metronidazole is well absorbed after oral administration and reaches peak plasma concentrations in 1 to 2 hours. It is distributed to most body fluids and tissues, including bone; crosses the placenta, and reaches concentrations in saliva and human milk similar to those found in plasma. Metronidazole is metabolized by hepatic oxidation and glucuronic conjugation. The major route of elimination of metronidazole and its metabolites is via the kidneys.

**Antimetabolites**

Sulfamethoxazole (SMX) and trimethoprim (TMP), block succeeding steps in folate synthesis.

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The P-site initially is occupied by the fMet-tRNA complex. As the next charged tRNA binds to the 70S ribosomal unit, but before it is allowed to enter the unoccupied A-site, the rRNA must confirm that the charged tRNA carries the specific amino acid called for by the mRNA codon. If access is allowed, the rRNA catalyzes the formation of a peptide bond between the carboxy-terminal of the fMet residing in the P-site and the new amino acid occupying the A-site (Figure 9).

Once the peptide bond is formed, the tRNA originally linked to fMet is ejected from the P-site and the second tRNA located at the A-site, which is now linked to two amino acids, translocates to the unoccupied P-site (Figure 9). As the process repeats itself, a growing peptide chain emerges from the exit tunnel. Translation continues until a stop codon is encountered in the mRNA and the newly synthesized protein is released from the ribosome.

**Tetracyclines**

Tetracycline and its semi-synthetic derivatives (e.g., minocycline and doxycycline) bind to 30S ribosomal subunits and reversibly block the attachment of the charged tRNA to the aminoacyl or A-site. They have bacteriostatic activity against aerobic gram-positive and gram-negative organisms, but in vivo many strains have been shown to be resistant. Tetracyclines are not empirical options in the treatment of odontogenic infections.

It is also of note that tetracyclines are teratogenic. They produce higher rates of neuronal-tube defect, cleft palate, and multiple congenital abnormalities, e.g., neuronal-tube defect with cardiovascular malformation.
Macrolides
Macrolides bind 50S ribosomal subunits and block translocation and peptide movement through the exit tunnel. They are bacteriostatic in susceptible organisms and are active against aerobic gram-positive cocci and gram-negative bacilli, but anaerobic gram-negative organisms are resistant. Azithromycin has an extended spectrum that includes some anaerobic gram-positive cocci and gram-negative bacilli and may be considered an empirical option in treating odontogenic infections.

Azithromycin is rapidly absorbed after oral administration. When administered with food, however, its rate and extent of absorption is reduced by about 50%. The drug is widely distributed throughout the body, accumulating in high concentration within cells resulting in higher tissue than plasma concentrations. Azithromycin is metabolized minimally and is principally eliminated as unchanged drug via the liver.

Strategies for the Treatment of Odontogenic Infections
Uncomplicated odontogenic infections manifest primarily as caries; and pulpal, periodontal, and pericoronal problems. Signs and symptoms include pain, erythema, edema, and difficulty chewing. Complicated odontogenic infections reflect the extension of an uncomplicated odontogenic infection into surrounding tissues and manifest as cellulitis, osteomyelitis, and space infections. Signs and symptoms include lymphadenitis, trismus, difficulty swallowing or breathing; and less frequently, fever and hypotension.
Primary Dental Care

Reversible Pulpitis
Patients with reversible pulpitis usually report sensitivity or pain in response to hot, cold, sweets, and mechanical stimuli. Caries in proximity of the pulp, defective restorations, exposed dentinal tubules, and traumatic occlusion appear to be common etiologies. Provoked pain, described as sharp or intense, primarily reflects hyperemia or mild inflammation of the pulp and stimulus-induced fluid movement in dentinal tubules.

Reversible pulpitis is a reactive process. Caries should be excavated and a temporary sedative restoration placed. Faulty restorations should be removed and replaced. Exposed dentinal tubules should be etched and sealed. To reduce inflammation and shorten recovery time a disease-modifying analgesic, i.e., a nonsteroidal anti-inflammatory drug (NSAIDs) should be prescribed. It is intuitive that antibacterial agents would have no effect on clinical outcome.

Irreversible Pulpitis
Bacteria may gain access to the pulpal system through caries, defective restorations, and exposed dentinal tubules. Other portals may include apical, lateral, or furcation canals associated with advancing periodontal disease. Pain may be spontaneous, but usually it is in response to hot, cold, sweets, and mechanical stimuli reflects hyperemia or inflammation secondary to infection, fluid movement in dentinal tubules, and increased intrapulpal pressure.

Acute dental pain associated with a tooth with deep carious lesion may reflect a reactive process to caries, but most likely to bacteria that have infected pulpal tissues. In case of irreversible pulpitis endodontic debridement and obturation of the root canal system is the most predictable method of treatment. To reduce inflammation and shorten recovery time a disease-modifying analgesic, i.e., a NSAID should be prescribed.

In untreated irreversible pulpitis, penicillin does not reduce spontaneous pain, percussion induced pain, or the amount of analgesics taken by patients. In a prospective study, a five-day course of penicillin administered to patients with acute pain related to a tooth with an amalgam restoration without clinical signs of infection, in the absence of definitive dental care, did not prevent the emergence of clinical signs of infection within 5 days.

Acute Apical Periodontitis
Irreversible pulpsitis and pulpal necrosis (an asymptomatic complication of irreversible pulpitis), if left untreated, lead to the spread of irritants and bacteria into periapical tissues and result in acute apical periodontitis. Patients complain of tenderness or mild to moderate pain associated with the apical area of the offending tooth. The pain may be intermittent, secondary to manipulation of the tooth, or unprovoked and continuous.

The removal of bacteria and their byproducts by debridement and obturation of the root canal system effectively eliminates infection, curtails inflammation, and promotes healing. The administration of a disease modifying analgesic, i.e., a NSAID, may shorten recovery time. It has been shown that once the source of infection is eliminated, the administration of penicillin provides no statistically significant added benefit.

Acute Apical Abscess
Infection associated with acute apical periodontitis may extend into alveolar bone and soft tissues initiating apical abscess formation. The pain is usually severe, unprovoked and constant. The tooth is usually mobile and the accumulation of fluid in the periodontal ligament space may cause supraeruption. Manipulation of the tooth causes exquisite sensitivity and mastication is difficult; swelling, malaise and fever may be present.

The removal of bacteria and their byproducts by debridement and obturation of the root canal system effectively eliminates infection, curtails inflammation, and promotes healing. The swelling, when present, may be drained through the tooth, by a soft tissue incision, or there may already be drainage through a naturally occurring sinus tract. A disease modifying analgesic, i.e., a NSAID, may shorten recovery time.

In a prospective study, a five-day course of penicillin administered to patients with acute
pain related to a tooth with large periapical radiolucency, but without clinical signs of infection, in the absence of debridement did not prevent the development of clinical signs of infection within 5 days. Another study confirmed that once the source of infection is eliminated, the administration of penicillin provides no statistically significant added benefit.

**Draining Sinus Tract**

Inflammatory degeneration of the pulp and periradicular tissues may follow a chronic subclinical course. The infection progresses slowly through cancellous bone along the path of least resistance. It perforates the thin cortical plate and forms a subperiosteal abscess. Once through the periosteum, it spreads into surrounding soft tissues and leads to the formation of either an intraoral or extraoral draining sinus tract; swelling and pain are usually absent.

In restorable teeth, chronic draining sinus tracts will respond to nonsurgical endodontic therapy. Successful healing depends on optimal debridement and obturation of the canal system. Non-restorable teeth and/or those with extensive alveolar bone loss require extraction. There is no evidence that the routine administration of an antibacterial agent improves therapeutic outcome. The residual cutaneous defect or scar may require subsequent surgical revision.

**Gingival Abscess**

Gingival abscess is a localized, rapidly evolving, painful infection of the marginal or interdental gingiva usually secondary to the impaction of foreign bodies, e.g., popcorn shells, peanut husks, seeds, fish bones, toothbrush bristles, or toothpick splinters into the gingival crevice. The abscess may drain through the crevice or a draining sinus tract through the gingiva. Affected teeth may be extruded and tender to percussion.

Foreign objects tend to adhere to the soft tissue wall of the gingival crevice. Following the application of a topical anesthetic agent, the gingival tissue should be gently distended; the foreign object removed, the soft tissue wall of the lesion should be gently curetted to induce drainage, and the area should be irrigated with warm saline. The patient should continue to

**Periodontal Abscess**

A periodontal abscess may be secondary to impacted foreign objects into the orifice of a periodontal pocket, closure or narrowing of the pocket orifice, or improper use of irrigating devices. Mild to moderate pain may be acute or chronic. The swelling rarely spreads beyond the mucogingival junction and may be associated with a draining sinus tract located in the gingival crevice or at the mucogingival junction.

Drainage should be established with the careful use of a periodontal probe. Once the opening to the pocket is located, the root surface should be gently debrided. If drainage cannot be established through the orifice of the pocket, a vertical incision should be made and the area should be irrigated with warm saline. The patient should continue to rinse with warm saline every 2 hours for two days. Routine antibacterial therapy is not indicated.

**Necrotizing Ulcerative Gingivitis**

Necrotizing ulcerative gingivitis (NUG) is characterized by localized necrosis and ulceration usually of the interdental papillae, which may extend to the marginal gingiva and rarely the whole mouth. Microorganisms have been implicated, but it is unclear if they are causative or opportunistic. Patients report a putrid odor, a foul metallic taste, and constant radiating pain intensified by spicy or hot foods, and gentle probing.

The initial treatment of necrotizing ulcerative gingivitis includes gentle irrigation of the affected areas with warm saline; followed by careful curettage of necrotic/ulcerative lesions and root surfaces to reduce the bioburden. Patients are instructed to rinse with warm saline every 2 hours and undergo daily repeat debridement until the lesions have resolved. Routine antibacterial therapy is not indicated and response to debridement is noted within 2-3 days. Patients may require gingivoplasty to correct residual crater-like gingival defects.

**Alveolar Osteitis**

Alveolar osteitis is a relatively common complication of tooth extraction, usually of mandibular molars. A foul taste, putrid odor, and
When pulpal, periodontal or pericoronal infections overwhelm host resistance, the infection may extend into the surrounding tissues and cause cellulitis. The affected area becomes edematous and feels indurated when palpated suggesting diffuse inflammation. Patients present with pain, malaise, trismus, regional lymphadenopathy, and fever. The tissues overlying the infected area may appear bluish.

Patients with cellulitis should be referred to a surgical specialist who may collect a sample of the purulent exudate, usually by aspiration, and initiate empirical, usually oral antibacterial chemotherapy. As the infection consolidates and becomes fluctuant, it will be incised at its most dependent area, the purulent material evacuated, and a drain inserted. Once a subacute condition has been attained appropriate primary dental intervention should be initiated.

Osteomyelitis is another potential complication of odontogenic infection. It most often affects cancellous medullary bone of the mandible. As purulence accumulates, it restricts blood flow to the area, which causes osseous necrosis and the formation of sequestrum. Signs and symptoms include paresthesia or deep persistent pain, malaise, fever, lymphadenopathy, loose teeth, and in the later stages, alveolar radiolucencies.

When osteomyelitis is suspected, the patient should promptly be referred to a surgical specialist who will collect a sample of the purulent exudate, usually by aspiration, for culture and susceptibility testing and begin immediate empirical, usually intravenous antibacterial chemotherapy. Drainage is established at the earliest possible time. Close monitoring and modification of antibacterial chemotherapy, if indicated, is imperative.

The inflammatory process associated with cellulitis is usually restricted to the jaws. However, if timely treatment is not initiated, the infection may spread through the fascial planes of the head and neck into the canine, buccal, masticatory, submental, sublingual, submandibular, vestibular, parotid,
patients, into anatomical spaces contiguous with fascial planes and can lead to serious, even life-threatening infections.\textsuperscript{30,101} Adjunctive antibacterial chemotherapy, predicated on sound principles, is imperative in the treatment of complicated odontogenic infections (Table 2).\textsuperscript{71,101,102}

Based on best available evidence, penicillin V potassium or amoxicillin formulations, alone or in combination with metronidazole; and clindamycin are reasonable empirical options to consider for the treatment of complicated odontogenic infections (Figure 10).\textsuperscript{10,42,71} Azithromycin may be an empirical option in some instances. Ultimately, the empirical drug of choice should be an effective agent with the narrowest spectrum and the least potential for adverse drug effects.

**Primary Line of Antibacterial Chemotherapy**

Unless the patient has an allergy to the penicillins, the empirical drug of first choice for the treatment of odontogenic infections is narrow spectrum penicillin V potassium (Table 3).\textsuperscript{5,16,42} Most infections require 5 days of antibacterial chemotherapy. An initial loading dose is followed by maintenance doses for the remainder of the time. It is prudent to schedule the patient for a follow-up in 2 to 3 days. This will provide an opportunity to assess response to treatment. Hypersensitivity reactions are potentially the most serious adverse drug effects (see the *Prescription-precautions Associated with the Administration of Antibacterial Agents* section).\textsuperscript{103}

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**Figure 10.** Percent antibacterial susceptibility of 98 strains of oral bacteria.

Table 2. Principles of adjunctive antibacterial chemotherapy.

- Establish a clear indication for adjunctive antibacterial chemotherapy
  - The patient presents with malaise, fever, chills, trismus, rapid respiration, swelling, lymphadenopathy, or hypotension
    - The signs and symptoms of infection escalated rapidly (within 24 to 48 hours)
    - The oral soft tissue swelling appears to be spreading into adjacent anatomical spaces and affects breathing and swallowing
    - Patients presenting with signs of impending airway obstruction, marked trismus (< 25mm), dehydration, malaise, disorientation, tachycardia, and hypotension should be admitted to the hospital for urgent or emergent care.

- Determine the patient’s health status
  - Systemic considerations
  - History of adverse drug reactions
  - Potential drug-drug interactions

- Select an appropriate antibacterial agent with a narrow spectrum and low toxicity
  - Immune status of the patient
    - Bactericidal versus bacteriostatic antibacterial agent
  - *empirical* therapy (correlate to most likely organisms associated with odontogenic infections)
  - Focused therapy (correlate to culture and susceptibility tests)

- Establish a dosage regimen, duration of therapy, and route of administration
  - Consider the seriousness of the illness
  - Consider potential compliance issues

- Follow-up in 48 to 72 hours
  - Determine efficacy
    - Inadequate debridement
    - Inadequate bacteriological information
    - Sub-optimal doses of antibacterial agents
    - Noncompliance (including the issue of cost)
  - Monitor patient for adverse drug effects
If significant improvement is not noted in 48 to 72 hours, the *empirical* addition (for 5 days) of metronidazole to penicillin V potassium is reasonable. Metronidazole is β-lactamase resistant and it provides excellent coverage for obligate anaerobes (Table 3).\textsuperscript{61,104,105} The safety and effectiveness of metronidazole in pediatric patients have not been established. In patients receiving metronidazole, the concurrent use of alcohol may produce severe gastrointestinal symptoms; serious convulsive seizures and peripheral neuropathy have also been reported (see the *Prescription-precautions Associated with the Administration of Antibacterial Agents* section).

Secondary Line of Antibacterial Chemotherapy
A macrolide is an *empirical* option for the treatment of odontogenic infections in patients allergic to β-lactam antibiotics. While there is a paucity of data demonstrating the efficacy of azithromycin in the treatment of odontogenic infections, among macrolides it may be the best alternative because of its extended spectrum against facultative and some obligate anaerobes (Table 3).\textsuperscript{75,76} However, a recent FDA drug safety communication warns about the risk of QT prolongation and cardiac arrhythmias (see the *Prescription-precautions Associated with the Administration of Antibacterial Agents* section).\textsuperscript{106}

It is also of note, that the single most important driver of the emergence of macrolide resistance *in vivo* is macrolide use.\textsuperscript{107} Macrolide-resistant organisms can block ribosomal macrolide-receptor sites, and because of receptor-site overlap, these organisms will also be resistant to clindamycin; and efflux pump-related macrolide-resistance also affects the intracellular concentration of β-lactam antibiotics and β-lactamase inhibitor, i.e., macrolide-resistance.

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**Table 3. *Empirical* antibacterial agents for the treatment of complicated odontogenic infections.**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Adult dosages (Pediatric dosages*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary line of treatment:</strong></td>
<td>Rx</td>
</tr>
<tr>
<td>• Patient has no history of allergy to β-lactam antibacterial agents.</td>
<td>Penicillin V potassium, 500 mg tablets&lt;br&gt;Disp. 21 tablets&lt;br&gt;Sig. Take two tablets stat, then one tablet four times a day for 5 days.</td>
</tr>
<tr>
<td>• Patient did not respond optimally to penicillin VK in 48 to 72 hours.</td>
<td>Metronidazole, 500 mg tablets&lt;br&gt;Disp. 21 tablets&lt;br&gt;Sig. Take one tablet stat, then one tablet four times a day 5 days.</td>
</tr>
<tr>
<td><strong>Secondary line of treatment:</strong></td>
<td>Rx</td>
</tr>
<tr>
<td>• Patient has a history of allergy to β-lactam antibacterial agents.</td>
<td>Azithromycin, 250 mg tablets&lt;br&gt;Disp. 6 Tablets&lt;br&gt;Sig. Take two tablets stat, then one tablet a day for 5 days.</td>
</tr>
<tr>
<td><strong>Tertiary line of treatment:</strong></td>
<td>Rx</td>
</tr>
<tr>
<td>• Patient has a history of allergy to β-lactam antibacterial agents.</td>
<td>Clindamycin, 300 mg capsules&lt;br&gt;Disp. 21 tabs&lt;br&gt;Sig. Take two capsules stat, then one capsule four times a day for 5 days.</td>
</tr>
<tr>
<td>• Unresolved infection following treatment with a β-lactam drug.</td>
<td></td>
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<tr>
<td>• Initial empirical drug for the treatment of serious infections.</td>
<td></td>
</tr>
</tbody>
</table>

*Pediatric dosages: penicillin V potassium, 25-50 mg/kg/day, divided q6-8h; metronidazole, 30 mg/kg/day, divided q6h; azithromycin, 5-10 mg, once daily; clindamycin, 10 mg/kg, q8h. Pediatric dosages should not exceed maximum adult doses.

** Metronidazole is added in addition to, not in lieu of, penicillin V regimen.
Consequently, antibacterial agents given to healthy people in association with third molar extractions to prevent infection may cause more harm than benefit, both to patients and the community at large.\textsuperscript{118}

**Prevention of Surgical-site Infection in Patients Undergoing Placement of Dental Implants**

Bacteria introduced during the placement of dental implants can lead to infection and implant failure. A critical review of the literature identified four randomized controlled clinical trials, with a follow up of at least 3 months, comparing the efficacy of various prophylactic antibacterial regimens versus no antibiotics in patients undergoing dental implant placement.\textsuperscript{119} The implant failure rate among patients not receiving antibiotics was 5%.\textsuperscript{119} There is some evidence to suggest that amoxicillin 2g administered 1 hour preoperatively significantly reduces the failure rate of dental implants placed under ordinary conditions.\textsuperscript{119} The number needed to treat (NNT) to prevent one individual from having an implant failure is 33. No significant adverse drug effects were reported, although the issue of antibacterial drug resistance was not addressed. There is no evidence that postoperative antibacterial agents are beneficial.\textsuperscript{119}

**Prevention of Infective Endocarditis in Patients Undergoing Dental Procedures**

The American Heart Association (AHA) publishes a clinical practice guideline, with periodic updates, for the prevention of infective endocarditis in patients undergoing dental procedures.\textsuperscript{120} The 2007 guideline stratifies cardiac conditions to the risk of developing endocarditis and the severity of associated morbidity. Only patients with the highest-risk of adverse outcome from endocarditis (Table 4) should be considered for antibacterial prophylaxis prior to invasive dental procedures (Table 5).\textsuperscript{120}

In situations where no chemoprophylaxis was given, but in which unexpected bleeding occurred, the institution of antibacterial therapy within 2 hours is recommended. Patients at risk already taking an antibacterial agent should be prescribed one of the drugs from a different class recommended for chemoprophylaxis.
The 2012 AAOS-ADA Clinical Practice Guideline, which was developed using a systematic evidence-based process, replaces all previous advisory or information statements. It provides no specific direction in managing individual patients (Table 6). Until scientific prospective data becomes available, the development of

**Table 4. Conditions associated with the highest risk of adverse outcome from endocarditis for which antibacterial prophylaxis is reasonable.**

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair.
- Previous infective endocarditis.
- Congenital heart disease (CHD).
  - Unrepaired cyanotic CHD, 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 6 months after the surgery.
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device, which inhibit endotherialization.
- Cardiac transplantation recipients who develop cardiac myopathy.

**Table 5. Antibacterial prophylaxis before procedures that involve manipulation of gingival tissue, periapical region of teeth, or perforation of the oral mucosa.**

<table>
<thead>
<tr>
<th>Situation</th>
<th>Agent</th>
<th>Regimen: single dose, 30-60 minutes before procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>Patient not allergic to β-lactams AND able to take oral medications</td>
<td>Amoxicillin</td>
<td>2.0g, PO</td>
</tr>
<tr>
<td>Patient not allergic to β-lactams BUT unable to take oral medications</td>
<td>Ampicillin</td>
<td>2.0g, IM or IV</td>
</tr>
<tr>
<td>Cefazolin or ceftriaxone</td>
<td>1g, IM or IV</td>
<td>50 mg/kg, IM or IV</td>
</tr>
<tr>
<td>Patient allergic to β-lactams AND able to take oral medications</td>
<td>Clindamycin</td>
<td>600mg, PO</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>500mg, PO</td>
<td>15mg/kg, PO</td>
</tr>
<tr>
<td>Patient allergic to β-lactams AND unable to take oral medications</td>
<td>Clindamycin</td>
<td>600mg, IM or IV</td>
</tr>
</tbody>
</table>

Clinicians should allow at least 9-14 days between appointments to reduce the risk for the development of resistant organisms.

**Prevention of Orthopaedic Implant Infection in Patients Undergoing Dental Procedures**

The American Academy of Orthopedic Surgeons (AAOS) in cooperation with the American Dental Association (ADA) publishes a clinical practice guideline, with periodic updates, for the prevention of orthopaedic implant infection in patients undergoing dental procedures. The 2003 guideline was prescriptive, patients with one or more high-risk conditions were considered candidates for antimicrobial prophylaxis in association with invasive dental procedures.
therapeutic and preventive strategies for each patient should be based on dialogue between oral healthcare provider, physician, and patient.\textsuperscript{121}

**Prevention of Infection in Patients with Various Medical Conditions Undergoing Dental Procedures**

A number of systemic conditions, e.g., neutropenia, asplenia, diabetes mellitus, end-stage renal disease, immunosuppression, systemic lupus erythematosus, and others are commonly cited as conditions that predispose a patient to bacteremia-induced infections. Evidence that a particular bacteremia-producing dental procedure caused a specific case of infection is circumstantial at best and no definitive, scientific evidence supports the use of prophylactic antibiotics.\textsuperscript{123-125}

Most importantly, clinicians should amplify their efforts to ensure that all patients understand the critical importance of maintaining optimal oral health, which could serve to reduce the severity of both self-induced and treatment-induced bacteremia. In the absence of evidence or consensus on the issue, oral healthcare providers should weigh the benefits of antibacterial prophylaxis against the risks of ADEs, including the development of drug resistance.

**Prevention of Surgical-site Infection in Patients Undergoing Open Reduction and Fixation of Mandibular Fractures**

The benefit of pre- and intra-operative antibacterial chemotherapy when treating open mandibular fractures has long been established.\textsuperscript{126-128} More recently, a prospective randomized trial evaluated the efficacy of post-operative prophylactic antibacterial chemotherapy in association with open reduction and internal fixation of mandibular fractures and found no statistically significant benefit.\textsuperscript{129} However, investigators concluded that tobacco and alcohol appear to be significant risk factors for post-operative infections.

**Prevention of Surgical-site Infection in Patients Undergoing Head and Neck Oncology Surgery**

The incidence of wound infection in patients undergoing head and neck oncology surgery has been reported to be as high as 87\%, often with devastating consequences.\textsuperscript{130} Based on the best current evidence, it is recommended that prophylactic antibacterial agents, covering aerobic gram-positive cocci and gram-negative bacilli, and anaerobic bacteria be administered in association with clean and clean-contaminated head and neck oncology surgery.\textsuperscript{130} There is no evidence that prophylactic antibacterial agents offer any benefit in clean surgery for benign disease.

**Prescription-precautions Associated with Antibacterial Agents**

There are no “absolutely” safe biologically active therapeutic agents, i.e., drugs seldom exert their beneficial effects without also causing adverse drug events (ADEs). The penicillins, metronidazole, azithromycin, and clindamycin, like other drugs, even after the administration of a single dose, can produce ADEs.

**Antibacterial Drug-resistance**

The widespread and ever increasing use of antibacterial agents contributes to the development

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Table 6. Recommendations of the 2012 AAOS-ADA clinical practice guideline.\textsuperscript{121}

<table>
<thead>
<tr>
<th>Recommendation 1</th>
<th>Recommendation 2</th>
<th>Recommendation 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>The practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures.</td>
<td>We are unable to recommend for or against the use of topical oral antimicrobials in patients with prosthetic joint implants or other orthopaedic implants undergoing dental procedures.</td>
<td>In the absence of reliable evidence linking poor oral health to prosthetic joint infection, it is the opinion of the work group that patients with prosthetic joint implants or other orthopaedic implants maintain appropriate oral hygiene.</td>
</tr>
<tr>
<td>Grade of recommendation: Limited</td>
<td>Grade of recommendation: Inconclusive</td>
<td>Grade of recommendation: Consensus</td>
</tr>
<tr>
<td>Clinicians should be cautious in deciding whether to follow this recommendation.</td>
<td>Clinicians should feel little constraint in deciding whether to follow this recommendation.</td>
<td>Clinicians should be flexible in deciding whether to follow this recommendation.</td>
</tr>
</tbody>
</table>

Clinicians should exercise judgment and be alert to emerging publications that report evidence. Patient preference should have a substantial influencing role.
Gastrointestinal Distress
Common ADEs associated with antibacterial agents, but especially with macrolides, are nausea, vomiting, epigastric distress, and diarrhea. These symptoms may be amplified in patients on metronidazole with concurrent use of alcohol. When a patient has been taking an antibacterial agent for 1 to 2 days, diarrhea is probably due to the mild irritating action of the drug; however, bloody diarrhea with abdominal cramping is highly suggestive of pseudomembranous colitis, a superinfection with *Clostridium difficile*. Colitis has been reported with the use of nearly all antibacterial agents, but especially with clindamycin.

Hypersensitivity Reactions
Hypersensitivity reactions, characterized by maculopapular to exfoliative dermatitis, urticaria, angioedema, and rarely, anaphylaxis may occur with all antibacterial agents, but especially with the β-lactams. Allergic reaction to the penicillins is more likely to occur in individuals with sensitivity to multiple allergens and in those with asthma; and patients with a history of allergy to the penicillins have experienced allergic reactions when treated with cephalosporins. Rare instances of erythema multiforme and Stevens-Johnson syndrome have been reported with clindamycin and azithromycin.

Cardiovascular Effects
Azithromycin and other macrolides can cause abnormal electrical activity in the heart that may lead to a potentially fatal irregular heart rhythm. Patients at particular risk for developing this condition include those with known risk factors such as existing QT interval prolongation, bradycardia, and those taking medications for the treatment of abnormal heart rhythm or arrhythmias. Increased risk of death from cardiovascular causes has been reported in persons treated with a 5-day course of azithromycin.

Central Nervous System Effects
Metronidazole should be administered with caution to patients with central nervous system disorders. Severe convulsive seizures and peripheral neuropathy, characterized by numbness or paresthesia of the extremities, have been reported. Infrequently, neuropathy has been noted with penicillin formulations, but when present, it is usually associated with high doses of parenteral penicillin.

Oral Candidiasis
Superinfections with *Candida sp.* can occur in association with all, but especially broad-spectrum antibacterial agents. Acute pseudomembranous oral candidiasis appears as white, raised, or cottage cheese-like that can be scraped off, leaving a red, sometimes hemorrhagic base. Patients may also present with hairy tongue and complain of burning, itching, or a metallic taste. Candidiasis occurring in a patient with a dry mouth may present as areas of patchy erythema with little or no evidence of cottage cheese-like curds. *Candida sp.* may spread to the esophagus or lungs via swallowing or droplet aspiration; or systemically via the blood stream, especially in immunosuppressed patients.

Antibacterial Drugs and Pregnancy
There is no firm evidence that the penicillins, metronidazole, azithromycin, and clindamycin are teratogenic in humans; however, drugs in general should be prescribed with caution during pregnancy. To assist practitioners in prescribing drugs for the pregnant patient, the Food and Drug Administration (FDA) has established a code for categorizing drugs according to their potential to cause fetal injury.

The penicillins, metronidazole, azithromycin, and clindamycin all have an FDA Pregnancy Category B rating, i.e., animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women. Since animal studies...
are not always predictive of a drug’s teratogenic effect in humans, antibacterial agents should only be prescribed during pregnancy if clearly indicated.\textsuperscript{38,39,61,70,73,145}

**Antibacterial Drugs and Nursing**

Mechanisms of drug excretion in human milk include both passive diffusion and carrier-mediated transport. The amount of drug excreted in milk depends on the drug's molecular weight, lipid solubility, pH, and plasma protein binding.\textsuperscript{146,147} Once in milk, the pH of the drug is an important determinant of the drug’s concentration in milk. Consequently, at equilibrium some drugs may accumulate in milk in higher concentration relative to plasma.

The penicillins are excreted in milk and may lead to sensitization of infants.\textsuperscript{38,39} Metronidazole, which has been shown to be carcinogenic in rats and mice, is excreted in milk in concentrations similar to those found in plasma.\textsuperscript{61} Clindamycin is also excreted in milk.\textsuperscript{70} The fate of azithromycin is unknown.\textsuperscript{73} Considering the potential risks to the nursing infant and benefits to the mother, a decision should be made whether to discontinue nursing or not to prescribe an antibacterial agent.\textsuperscript{38,39,61,70,73}

**Drug-drug Interactions**

Two or more drugs administered in therapeutic dosages at the same time or in close sequence, may act (1) independently, (2) interact to increase or diminish the effect of one or more drugs, or (3) interact to cause an unintended reaction. Potentially serious interactions can occur between antibacterial agents and other medications. An awareness of the patient’s medical history, including medications taken, is helpful in minimizing or avoiding potential drug-drug interactions. Two excellent reviews of the subject are presented elsewhere.\textsuperscript{148,149}

However, the theoretical possibility that antibacterial agents may reduce the efficacy of oral contraceptives must be addressed directly. An exhaustive review of the literature found no credible pharmacokinetic data, with the possible exception of rifampin, to substantiate such interactions. The U.S. District Court for the Northern District of California also concluded that “scientific evidence regarding the alleged interaction between antibacterial agents and oral contraceptives” does not satisfy the “Daubert standard of causality.”\textsuperscript{151}

However, the American Medical Association states that such interactions cannot be completely discounted and recommends that women be informed of the possibility of such interactions.\textsuperscript{152} Similarly, the American Dental Association Council on Scientific Affairs recommends (1) that patients be advised of the potential risk, (2) that patients comply with their oral contraceptive regimen, and (3) that patients consider alternative contraception during periods of antibacterial chemotherapy.\textsuperscript{152,154}

**Conclusion**

The *routine use of antibacterial agents* in the treatment of uncomplicated odontogenic infections has not been shown to be effective. Most such infections respond to timely debridement. When treating complicated odontogenic infections, the *adjunctive use of antibacterial agents* is justified. The *empirical* drug of choice should be the most effective and least toxic agent with the narrowest spectrum. *Prophylactic antibacterial chemotherapy* in dentistry should be limited to the prevention of those infections that have been proven or are strongly suspected to be procedure-specific. It is axiomatic that before prescribing an antibacterial agent, the clinician must consider the diagnosis, the need for drug therapy, and the benefits versus risks of treatment.
Course Test Preview
To receive Continuing Education credit for this course, you must complete the online test. Please go to: www.dentalcare.com/en-US/dental-education/continuing-education/ce450/ce450-test.aspx

1. Invasion and multiplication of bacteria in body tissues result in local cellular injury due to _______________.
   a. competitive metabolism
   b. toxin production
   c. immune-mediated reactions
   d. All of the above.

2. Which of the following statements is correct with respect to Gram-positive and Gram-negative bacteria?
   a. Acetone extracts lipids from the outer membrane, cell wall, and cytoplasmic membrane of bacteria.
   b. The damage to gram-negative organisms is more extensive and they lose their crystal violet-iodine complexes, i.e., they are decolorized; and when counterstained with safranin, they appear red.
   c. Gram-positive bacteria retain their crystal violet-iodine complexes and appear deep purple.
   d. All of the above.

3. All of the following statements is correct with respect to odontogenic infections EXCEPT which one?
   a. Most odontogenic infections are polymicrobial.
   b. The predominant flora create an ecosystem of synergism by elaborating a more favorable alkaline environment and increased oxygenation to support the growth and proliferation of its members.
   c. In odontogenic infections, the number of isolated strains ranges from 1 to 10 organisms.
   d. The average number of organisms responsible for an odontogenic infection is 4.

4. Pharmacological strategies are predicated on targeting differences between prokaryotic bacterial and eukaryotic host cells. Selective toxicity can be achieved by _________________.
   a. attacking targets unique to bacteria
   b. attacking targets in bacteria similar but not identical to those in host cells
   c. attacking targets that are shared, but vary in importance between bacteria and host cells
   d. All of the above.

5. Which of the following statements is correct with respect to bacterial cell walls?
   a. Monomers are synthesized in the cytoplasm from amino acid and sugar building blocks.
   b. Bactoperol transfers the monomers across the cytoplasmic membrane where they are polymerized into linear peptidoglycan chains.
   c. Transpeptidase cross-links peptidoglycan chains into a three-dimensional mat.
   d. All of the above.

6. All of the following statements are correct with respect to inhibitors of cell wall synthesis EXCEPT which one?
   a. Vancomycin targets monomer polymerization, it is bactericidal, but does not have the requisite spectrum to be considered an empirical option in treating odontogenic infections.
   b. Penicillin V potassium and amoxicillin formulations, which block polymer cross-linking, are bactericidal, and have the requisite spectra to be considered as empirical options in treating odontogenic infections.
   c. Second generation cephalosporins have an overlapping spectra with those of penicillin V potassium and amoxicillin formulations.
   d. 2nd generation cephalosporins are more β-lactamase resistant and offer a significant therapeutic advantage over the penicillins as empirical options.
7. Which of the following statements relative to inhibitors of DNA synthesis and integrity is correct?
   a. Fluoroquinolones block topoisomerase type II activity, disrupt the integrity of bacterial DNA, and are bactericidal.
   b. Sulfamethoxazole (SMX) and trimethoprim (TMP), block succeeding steps in folate synthesis and the combination is bactericidal.
   c. A metabolite of metronidazole directly binds DNA, causes loss of its helical structure, effect strand breakage, and is bactericidal.
   d. Metronidazole, in combination with penicillin V potassium or amoxicillin, is an empirical option in treating odontogenic infections.

8. Which of the following statements is correct with respect to inhibitors of transcription and translation?
   a. Tetracyclines are teratogenic and produce higher rates of neuronal-tube defect, cleft palate, and multiple congenital abnormalities.
   b. Clindamycin has excellent activity against gram-positive aerobes and anaerobes, as well as gram-negative anaerobes.
   c. Azithromycin has an extended spectrum that includes some anaerobic gram-positive cocci and gram-negative bacilli.
   d. All of the above.

9. Uncomplicated odontogenic infections manifest primarily as caries; and pulpal, periodontal, and pericoronal problems with signs and symptoms that include pain, erythema, edema, and difficulty chewing.
   a. True
   b. False

10. Complicated odontogenic infections reflect the extension of an uncomplicated odontogenic infection into surrounding tissue with signs and symptoms that include lymphadenitis, trismus, difficulty swallowing or breathing; and less frequently, fever and hypotension.
    a. True
    b. False

11. Which of the following statements about the routine use of antibacterial agents in the treatment of uncomplicated infections is correct?
    a. Reversible pulpitis is a reactive process and there is no evidence that antibacterial agents would have any effect on clinical outcome.
    b. In untreated irreversible pulpitis, penicillin does not reduce spontaneous pain, percussion induced pain, or the intake of analgesics.
    c. In the treatment of acute apical periodontitis, once the source of infection is eliminated, the administration of penicillin provides no added benefit.
    d. All of the above.

12. In a prospective study, a five-day course of penicillin administered to patients with acute pain related to a tooth with an amalgam restoration without clinical signs of infection, in the absence of definitive dental care, did not prevent the emergence of clinical signs of infection within 5 days.
    a. True
    b. False
13. In a prospective study, a five-day course of penicillin administered to patients with acute pain related to a tooth with large periapical radiolucency, but without clinical signs of infection, in the absence of debridement did not prevent the development of clinical signs of infection within 5 days.
   a. True
   b. False

14. In the treatment of draining sinus tract, there is convincing evidence that the routine administration of an antibacterial agent improves therapeutic outcome.
   a. True
   b. False

15. There is convincing evidence that the routine administration of an antibacterial agent improves therapeutic outcome in association with which of the following conditions?
   a. Gingival and periodontal abscesses
   b. Necrotizing ulcerative gingivitis
   c. Alveolar osteitis
   d. None of the above.

16. Depending on pericoronitis-associated signs and symptoms, i.e., clinical evidence of induration as the infection is spreading buccally or lingually and the presence of trismus, the adjunctive antibacterial therapy may be appropriate.
   a. True
   b. False

17. Which of the following conditions should be considered a complicated odontogenic infection and an indication for adjunctive antibacterial chemotherapy?
   a. Cellulitis
   b. Osteomyelitis
   c. Space infections
   d. All of the above.

18. Based on best available evidence, penicillin V potassium or amoxicillin formulations, alone or in combination with metronidazole; and clindamycin are reasonable empirical options to consider for the treatment of complicated odontogenic infections.
   a. True
   b. False

19. The empirical antibacterial agent drug of choice should be an effective agent with the narrowest spectrum and the least potential for adverse drug effects.
   a. True
   b. False

20. Which of the following statements is correct with respect to primary line antibacterial chemotherapy?
   a. Unless the patient has an allergy to the penicillins, the empirical drug of first choice for the treatment of odontogenic infections is narrow spectrum penicillin V potassium.
   b. Most infections require 5 days of antibacterial chemotherapy - an initial loading dose followed by maintenance doses for the remainder of the time.
   c. If significant improvement is not noted in 48 to 72 hours, the addition (for 5 days) of metronidazole to penicillin V potassium is reasonable.
   d. All of the above.
21. **Which of the following statements is correct with respect to secondary line antibacterial chemotherapy?**
   a. A macrolide is an empirical option for the treatment of odontogenic infections in patients allergic to β-lactam antibiotics.
   b. While there is a paucity of data demonstrating the efficacy of azithromycin in the treatment of odontogenic infections.
   c. Clindamycin may be a better empirical option in patients allergic to β-lactam antibacterial agents.
   d. All of the above.

22. **Which of the following statements is correct with respect to tertiary line antibacterial chemotherapy?**
   a. Clindamycin is the empirical drug of choice for unresolved infections following treatment with a β-lactam antibacterial agent.
   b. Clindamycin is the initial empirical drug of choice for the treatment of severe complicated odontogenic infections.
   c. Clindamycin is β-lactamase resistant and has excellent activity against gram-positive cocci and most gram-negative anaerobes.
   d. All of the above.

23. **All of the following statements are correct with respect to the prevention of surgical-site infection in patients undergoing tooth extractions EXCEPT which one?**
   a. There is no evidence to support the prophylactic use of antibacterial agents in association with the extraction of non-restorable teeth.
   b. The infection rate after third molar extraction is about 10%.
   c. In debilitated or immunocompromised patients, the infection rate after third molar extraction may be as high as 25%.
   d. Antibacterial drugs administered just before and/or just after third molar extractions do reduce the risk of infection, pain, and dry socket.
   e. There is solid evidence that an antibacterial agent given to healthy people in association with third molar extractions is more beneficial than harmful.

24. **All of the following statements are correct with respect to the prevention of surgical-site infection in patients undergoing placement of dental implants EXCEPT which one?**
   a. Bacteria introduced during the placement of dental implants can lead to infection and implant failure.
   b. The implant failure rate among patients not receiving antibiotics is about 5%.
   c. There is no evidence to suggest that amoxicillin 2g. administered 1 hour preoperatively significantly reduces the failure rate of dental implants placed under ordinary conditions.
   d. There is no evidence that postoperative antibacterial agents are beneficial to reduce infection and implant failure.

25. **All of the following statements are correct with respect to the prevention of infective endocarditis in patients undergoing dental procedures EXCEPT which one?**
   a. The 2007 guideline stratifies cardiac conditions as to the risk of developing endocarditis and the severity of associated morbidity.
   b. Only patients with the highest-risk of adverse outcome from endocarditis require antibacterial prophylaxis prior to dental procedures.
   c. Antibacterial prophylaxis is indicated before procedures that involve manipulation of gingival tissue, periapical region of teeth, or perforation of the oral mucosa.
   d. In situations where no chemoprophylaxis was given, but in which unexpected bleeding occurred, the institution of antibacterial therapy within 24 hours is recommended.
26. Which of the following statements is correct with respect to the prevention of orthopaedic implant infection in patients undergoing dental procedures?
   a. The practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures.
   b. There is no evidence to recommend for or against the use of topical oral antimicrobials in patients with prosthetic joint implants or other orthopaedic implants undergoing dental procedures.
   c. In the absence of reliable evidence linking poor oral health to prosthetic joint infection, it is the consensus that patients with prosthetic joint implants or other orthopaedic implants maintain appropriate oral hygiene.
   d. All of the above.

27. Which of the following statements is correct with respect to the prevention of infection in patients with various medical conditions undergoing dental procedures?
   a. Evidence that a particular bacteremia-producing dental procedure caused a specific case of infection is circumstantial at best.
   b. No definitive, scientific evidence supports the use of prophylactic antibiotics in patients with various medical conditions undergoing dental procedures.
   c. Clinicians should amplify their efforts to ensure that all patients understand the critical importance of maintaining optimal oral health, which could serve to reduce the severity of both self-induced and treatment-induced bacteremia.
   d. All of the above.

28. Which of the following statements is correct with respect to the prevention of surgical-site infection in patients undergoing open reduction and fixation of mandibular fractures?
   a. The benefit of pre- and intra-operative antibacterial chemotherapy when treating open mandibular fractures has long been established.
   b. A prospective randomized trial evaluated the efficacy of post-operative prophylactic antibacterial chemotherapy in association with open reduction and internal fixation of mandibular fractures and found no statistically significant benefit.
   c. A prospective randomized trial evaluated the efficacy of post-operative prophylactic antibacterial chemotherapy in association with open reduction and internal fixation of mandibular fractures concluded that tobacco and alcohol appear to be significant risk factors for post-operative infections.
   d. All of the above.

29. Which of the following statements is correct with respect to the prevention of surgical-site infection in patients undergoing head and neck oncology surgery?
   a. The incidence of wound infection in patients undergoing head and neck oncology surgery has been reported to be as high as 87%, often with devastating effect.
   b. Based on the best current evidence, it is recommended that prophylactic antibacterial agents, covering aerobic gram-positive coci and gram-negative bacilli, and anaerobic bacteria be administered in association with clean and clean-contaminated head and neck oncology surgery.
   c. There is no evidence that prophylactic antibacterial agents offer any benefit in clean surgery for benign disease.
   d. All of the above.

30. Which of the following statements is correct with respect to antibacterial drug-resistance?
   a. The widespread and ever increasing use of antibacterial agents contributes to the development of antibacterial drug-resistance.
   b. Unless healthcare providers change their practices, many currently available antibacterial agents may become ineffective.
   c. When other therapeutic means are available, antibacterial agents should not be routinely prescribed to treat or to prevent infections.
   d. All of the above.
31. All of the following statements are correct with respect to gastrointestinal disturbances in association with antibacterial agents EXCEPT which one?
   a. Common ADEs associated with antibacterial agents, but especially with macrolides, are nausea, vomiting, epigastric distress, and diarrhea.
   b. Gastrointestinal symptoms may be amplified in patients on clindamycin with concurrent use of alcohol.
   c. When a patient has been taking an antibacterial agent for 1 to 2 days, diarrhea is probably due to the mild irritating action of the drug.
   d. Bloody diarrhea with abdominal cramping is highly suggestive of pseudomembranous colitis, a superinfection with Clostridium difficile.

32. Which of the following statements is correct with respect to hypersensitivity or other immune-related reactions to antibacterial agents?
   a. Maculopapular to exfoliative dermatitis, urticaria, angioedema, and rarely, anaphylaxis may occur with all antibacterial agents.
   b. Allergic reaction to the penicillins is more likely to occur in individuals with sensitivity to multiple allergens and in those with asthma.
   c. Rare instances of erythema multiforme and Stevens-Johnson syndrome have been reported with clindamycin and azithromycin.
   d. All of the above.

33. Which of the following statements is correct with respect to potential cardiac complications associated with macrolides antibacterial agents?
   a. Azithromycin and other macrolides can cause abnormal electrical activity in the heart that may lead to a potentially fatal irregular heart rhythm.
   b. Patients at particular risk for developing cardiac complications include those with existing QT interval prolongation and bradycardia; and those taking medications for the treatment of abnormal heart rhythm or arrhythmias.
   c. Increased risk of death from cardiovascular causes has been reported in persons treated with a 5-day course of azithromycin.
   d. All of the above.

34. Penicillins should be administered with caution to patients with central nervous system disorders because severe convulsive seizures and peripheral neuropathy, characterized by numbness or paresthesia of the extremities are common.
   a. True
   b. False

35. Superinfections with Candida sp. can occur in association with all, but especially broad-spectrum antibacterial agents.
   a. True
   b. False

36. Which of the following statements is correct with respect to antibacterial agents and pregnancy?
   a. There is no firm evidence that the penicillins, metronidazole, azithromycin, and clindamycin are teratogenic in humans.
   b. The penicillins, metronidazole, azithromycin, and clindamycin all have an FDA Pregnancy Category B rating, i.e., animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women.
   c. Since animal studies are not always predictive of a drug’s teratogenic effect in humans, antibacterial agents should only be prescribed during pregnancy if clearly indicated.
   d. All of the above.
37. Which of the following statements is correct with respect to antibacterial agents and nursing?
   a. The penicillins are excreted in milk and may lead to sensitization of infants.
   b. Metronidazole, which has been shown to be carcinogenic in rats and mice, is excreted in milk in concentrations similar to those found in plasma.
   c. Considering the potential risks to the nursing infant, a decision should be made whether to discontinue nursing or not to prescribe an antibacterial agent to the mother.
   d. All of the above.

38. Which of the following statements are correct in relation to interactions between antibacterial agents and oral contraceptives EXCEPT which one?
   a. There are no pharmacokinetic data at this time to support the contention that antibacterial agents reduce the efficacy of oral contraceptives, except for rifampin, an antituberculin drug.
   b. The United States District Court for the Northern District of California concluded that “scientific evidence regarding alleged interaction between antibacterial agents and oral contraceptives did not satisfy the "Daubert" standard of causality.
   c. According to the American Medical Association, such interactions cannot be completely discounted.
   d. All of the above.

39. The ADA recommends that patients prescribed an antibacterial agent while also taking an oral contraceptive _______________.
   a. be advised of the potential risk
   b. comply with their oral contraceptive regimen
   c. consider alternative contraception during periods of antibacterial chemotherapy
   d. All of the above.

40. All of the following statements are correct with respect to the administration of antibacterial agents in oral healthcare settings EXCEPT which one?
   a. The routine use of antibacterial agents in the treatment of uncomplicated odontogenic infections has not been shown to be effective.
   b. When treating complicated odontogenic infections, the adjunctive use of antibacterial agents is justified.
   c. Prophylactic antibacterial chemotherapy in dentistry should be limited to the prevention of those infections that have been proven or are strongly suspected to be procedure-specific.
   d. The empirical drug of choice should be the most effective and least toxic agent with the broadest spectrum.
References

About the Authors

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Dr. Palomo is Associate Professor of Periodontics and director DMD periodontics. She is a diplomate of the American Board of Periodontology. She published several articles in medical and dental journals. Additionally, she has been invited for presentations at national and international professional meetings. Her commitment to our dental students has been recognized. She earned her undergraduate as well as DDS and MSD degrees from Case Western Reserve University in 1996 and 2004 respectively.

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Dr. Terézhalmy earned a B.S. degree from John Carroll University; a D.D.S. degree from Case Western Reserve University; an M.A. in Higher Education and Human Development from The George Washington University; and a Certificate in Oral Medicine from the National Naval Dental Center. Dr. Terézhalmy is certified by the American Board of Oral Medicine and the American Board of Oral and Maxillofacial Radiology (Life).

Dr. Terézhalmy has many professional affiliations and over the past 40 years, has held more than 30 positions in professional societies. He has served as editor or contributing editor for several publications, co-authored or contributed chapters for several books and has had over 200 papers and abstracts published. Dr. Terézhalmy has accepted invitations to lecture before many local, state, national, and international professional societies.

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