Adjunctive and Prophylactic Use of Antibacterial Agents in Dentistry

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Conflict of Interest Disclosure Statement

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Short Description

Adjunctive and Prophylactic Use of Antibacterial Agents in Dentistry is a free dental continuing education course that covers a wide range of topics relevant to the oral healthcare professional community.

Course Contents

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 and for prophylactic therapy.

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.
- Discuss indications for the adjunctive administration of antibacterial agent.
- Select the most appropriate agent.
- Discuss indications for antibacterial prophylaxis.
- Select the most appropriate regiment.
- Discuss potential ADEs associated with the administration of antibacterial agents.

Introduction

The human fetus is free of microorganisms.[1] 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.[2,3]

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.[4,5] 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.[6]

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.[7]

Gram-positive bacteria possess a thick peptidoglycan cell wall interspersed with lipoteichoic acid underlain by the cytoplasmic membrane (Figure 1).[8] Gram-negative

Box 1. Gram's Method of Staining.[7]

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

bacteria have an outer membrane with lipopolysaccharides and a lipoprotein layer underlain by a thin peptidoglycan layer and the cytoplasmic membrane (Figure 2).[8] The ability of antibacterial agents to diffusion into bacteria is also affected by these structural differences.

During staining, crystal violet interacts with iodine forming a complex. Acetone extracts lipids from the outer membrane, cell wall, and cytoplasmic membrane of bacteria.[7] 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).[7] Gram-positive bacteria retain their crystal violet-iodine complexes and appear deep purple (Figure 4).[7]

An average adult harbors at least 300 oral bacterial species and more than 700 strains of bacteria have been isolated from test cases.[9-11] Most odontogenic infections are polymicrobial. The number of strains per infection ranges from 1 to 10 with an average number of 4 isolates.[9,12-24] The predominant flora creates an ecosystem of synergism by elaborating a more favorable acidic environment and decreased oxygenation to support the growth and proliferation of its members. Ultimately, facultative and anaerobic gram-positive and gram-negative cocci and bacilli predominate in all types of odontogenic infections (Table 1).[9-31]

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).[32] Drugs targeting unique differences are the least toxic to host cells.

Antibacterial agents are either bactericidal or bacteriostatic. Bactericidal drugs attack targets

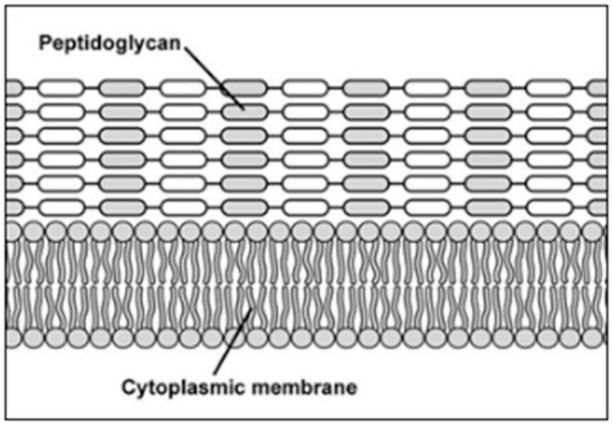

Figure 1. Gram-positive Bacteria.

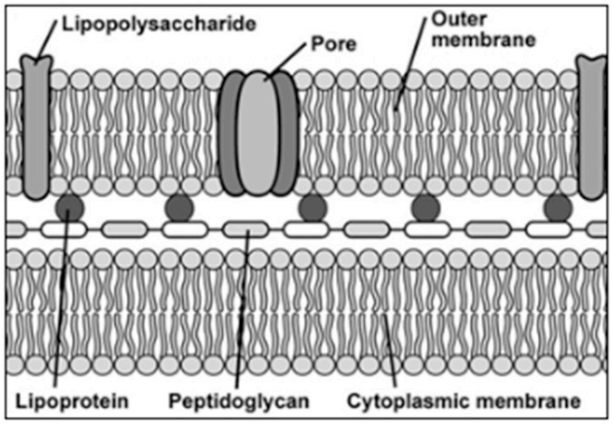

Figure 2. Gram-negative Bacteria.

Figures 1&2, modified from Kasmar AG, Hooper D. Pharmacology of bacterial infections: cell wall synthesis. In Golan DE, Tashjian, Jr. AH, Armstrong EJ, Armstrong AW. Ed. Principles of pharmacology. The pathophysiologic basis of drug therapy. 2nd ed. 2008. Wolters Kluwer/ Lippincott Williams & Wilkins. Baltimore, MD.[8]

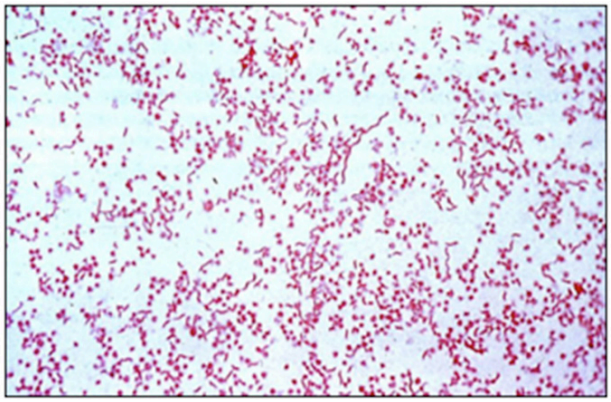

Figure 3. Gram-negative Organisms.

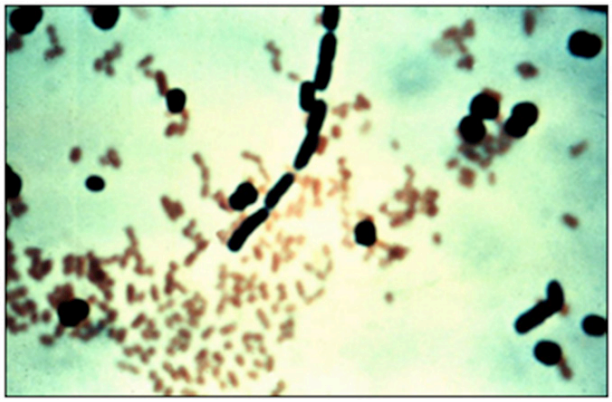

Figure 4. Mixed Gram-positive and Gram-negative Organisms.

essential for bacterial survival, e.g., inhibitors of cell wall synthesis and most inhibitors of DNA synthesis and integrity.[32] Bacteriostatic drugs attack targets that are necessary for bacterial growth but not for survival, e.g., most inhibitors of transcription and translation.[32] Since bacteriostatic drugs block bacterial replication, they antagonize the effects of bactericidal drugs.

Bacterial Cell Wall Synthesis Inhibitors

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).[8]

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.[8,33-41] β-lactam antibacterial agents also activate autolysins. Autolysins punch holes in bacterial cell wall and disrupt its integrity.[8] 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.[8,38-40] 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

Table 1. Bacteria Detected in Odontogenic Infections.[26,27]

Gram-staining and morphologic characteristics	Facultative anaerobes	Obligate anaerobes
Gram-positive cocci	*Streptococcus* *Enterococcus*	*Streptococcus* *Peptostreptococcus*
Gram-positive bacilli	*Actinomyces* *Lactobacillus*	*Actinomyces* *Lactobacillus* *Proprionibacterium* *Bificobacterium* *Eubacteria*
Gram-negative cocci	*Neisseria*	*Veillonella*
Gram-negative bacilli	*Capnocytophaga* *Eikenella*	*Porphyromonas* *Prevotella* *Fusobacterium* *Campylobacter* *Bacteroides*
Spirochetes		*Treponema*
Crescent-shaped		*Selenomonas*

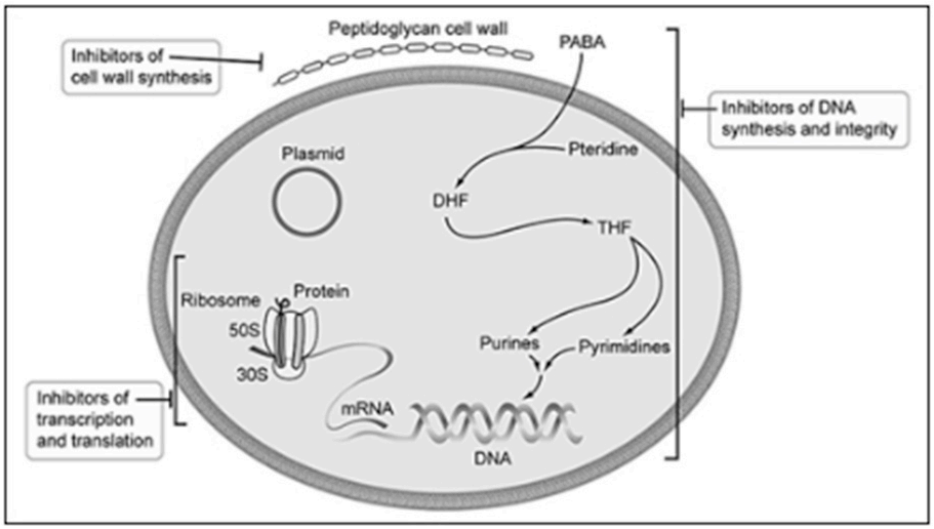

Figure 5. Mechanisms of Action of Antibacterial Agents.
Based on Harbison H, Rose HS, Coen DM, Golan DE. Principles of antibacterial and antineoplastic pharmacology. In Golan DE, Tashjian, Jr. AH, Armstrong EJ, Armstrong AW. Ed. Principles of pharmacology. The pathophysiologic basis of drug therapy. 2nd ed. 2008. Wolters Kluwer/Lippincott Williams & Wilkins. Baltimore, MD.[32]

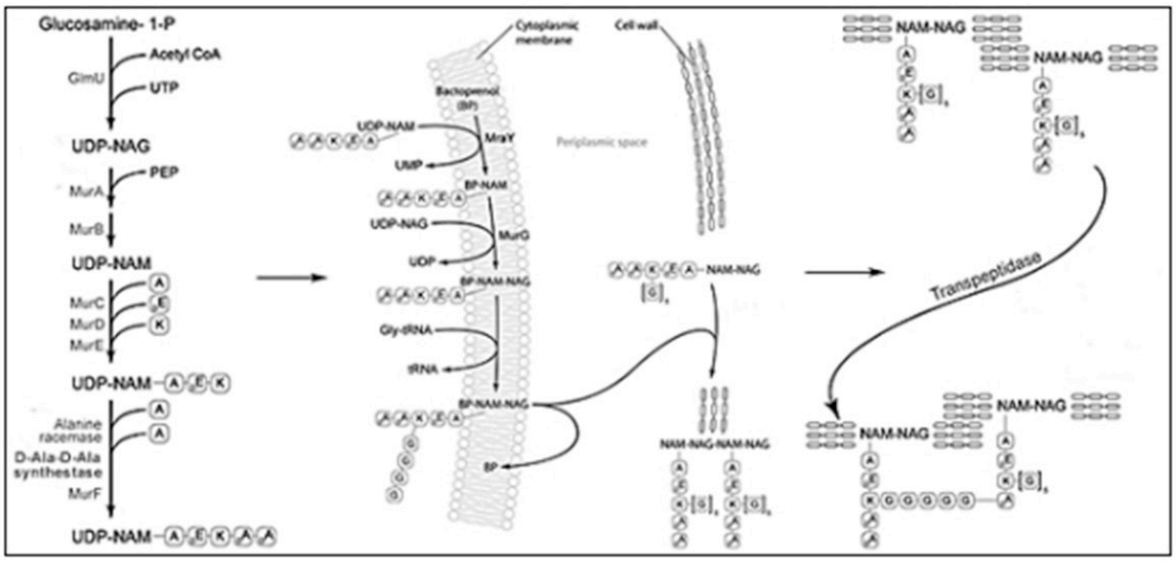

Figure 6. Bacterial Cell Wall Synthesis.
Step 1. Monomer synthesis | Step 2. Monomer polymerization | Step 3. Polymer cross-linking
Modified from Kasmar AG, Hooper D. Pharmacology of bacterial infections: cell wall synthesis. In Golan DE, Tashjian, Jr. AH, Armstrong EJ, Armstrong AW. Ed. Principles of pharmacology. The pathophysiologic basis of drug therapy. 2nd ed. 2008. Wolters Kluwer/Lippincott Williams & Wilkins. Baltimore, MD.[8]

spectrum to be considered an *empirical* option in treating odontogenic infections.

Penicillins
Penicillins are bactericidal in susceptible organisms.[8,34,37] 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.[11,42] 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.[8,43-51]

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.[8,33,35,36,52] 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.[53]

In the replication process, bacteria must synthesize folate. Its synthesis begins with the formation of dihydropteroic acid from

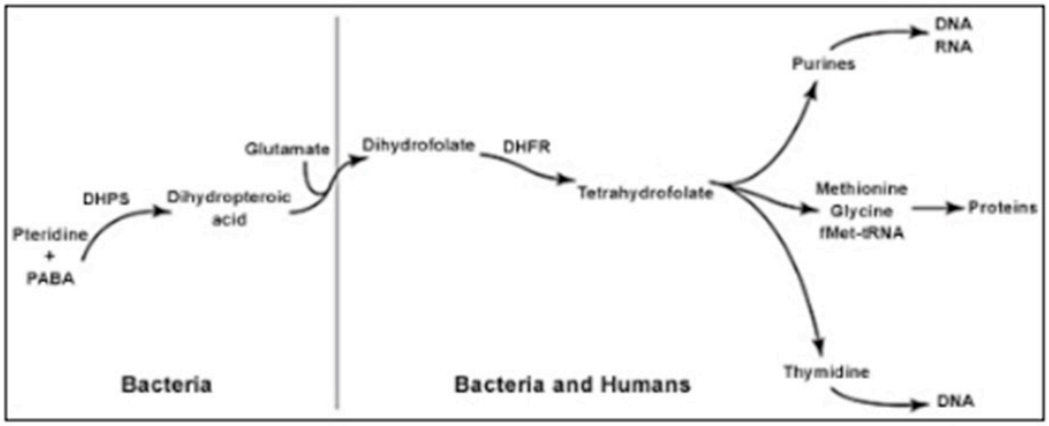

Figure 7. Folate Synthesis.
Modified from Harbison H, Rose HS, Coen DM, Golan DE. Principles of antibacterial and antineoplastic pharmacology. In Golan DE, Tashjian, Jr. AH, Armstrong EJ, Armstrong AW. Ed. Principles of pharmacology. The pathophysiologic basis of drug therapy. 2nd ed. 2008. Wolters Kluwer/Lippincott Williams & Wilkins. Baltimore, MD.[32]

pteridine and para-aminobenzoic acid (PAPA), a reaction catalyzed by dihydropteroate synthase (Figure 7).[32] Dihydropteroic acid and glutamate condense to form dihydrofolate (DHF).[32] Dihydrofolate reductase (DHFR) reduces DHF to tetrahydrofolate (THF). THF is an essential cofactor in the synthesis of DNA, RNA, and proteins (Figure 7).[32]

Fluoroquinolones
Fluoroquinolones block topoisomerase type II activity and disrupt the integrity of bacterial DNA.[53-57] They are bactericidal in susceptible organisms and are primarily active against aerobic gram-positive and gram-negative cocci and bacilli.[53-57] The newer agents (e.g., moxifloxacin) have some anaerobic activity.[11,58,59] Fluoroquinolones are indicated for the treatment of infections with designated, susceptible bacteria and are not empirical options in treating odontogenic infections.[54-56]

Metronidazole
Metronidazole is a pro-drug. One of its metabolite directly binds to bacterial DNA, causes loss of its helical structure, and effects strand breakage.[45,60,61] It is bactericidal in susceptible organisms and is active against most obligate anaerobes. However, it lacks clinically relevant activity against obligate aerobes and facultative anaerobes.[61,62] Metronidazole, in combination with an agent active against aerobic/facultative organisms (e.g., a penicillin), is an empirical option in treating odontogenic infections.[61,62]"

Metronidazole is well absorbed after oral administration and reaches peak plasma concentrations in 1 to 2 hours.[61] 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.[61] The drug is metabolized by hepatic oxidation and glucuronic conjugation.[61] The major route of elimination of metronidazole and its metabolites is via the kidneys.[61]

Antimetabolites
Sulfamethoxazole (SMX) and trimethoprim (TMP), block succeeding steps in folate synthesis (see Figure 7).[32,63] SMX-TMP formulations are bacteriostatic in susceptible organisms. It has activity against a broad spectrum of aerobic gram-positive and gram-negative organisms, but it is not active against anaerobes.[63] SMX-TMP does not have the requisite spectrum to be considered an *empirical* option in treating odontogenic infections.

Transcription or Translation Inhibitors
Bacteria, like mammalian cells, must synthesize proteins for self-maintenance and replication. DNA serves as the "instruction manual;" it provides the information necessary for protein

synthesis. The first step in this process is transcription, the synthesis of a single-stranded ribonucleic acid (RNA) from the DNA template catalyzed by RNA polymerase.[53] The function of the newly synthesized RNA is translation.

In the process of translation, RNA serves three functions: (1) as messenger RNA (mRNA), it tells ribosomes which proteins to synthesize; (2) as transfer RNA (tRNA), it transports specific amino acids called for by mRNA codons from the cytoplasm to ribosomes; and (3) as ribosomal RNA (rRNA), it ensures that the amino acid carried by the charged tRNA is the one called for by the corresponding mRNA codon.[53]

Protein synthesis is initiated when the mRNA joins with the 30S ribosomal subunit and tRNA-linked formyl methionine (fMet).[53] As the first amino acid encoded by every bacterial mRNA, fMet binds the initiation codon on the mRNA.[53] Next, the 30S-fMet-tRNA complex joins with the 50S ribosomal subunit to form the complete initiation complex, i.e., the 70S ribosomal unit, which contains two binding sites, an aminoacyl or A-site and a peptidyl or P-site (Figure 8).[53]

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.[54] 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).[53]

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).[53] As the process repeats itself, a growing peptide chain emerges from the exit tunnel.[53] Translation continues until a stop codon is encountered in the mRNA and the newly synthesized protein is released from the ribosome.[53]

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 aminoacryl or A-site.[53,64-66] 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.[65-67] They produce higher rates of neuronal-tube defect, cleft palate, and multiple congenital abnormalities, e.g., neuronal-tube defect with cardiovascular malformation. Furthermore, tetracyclines induce enamel hypoplasia and discoloration of teeth. Before prescribing tetracycline during pregnancy and/or tooth development the benefits and risks must be considered.[65-67]

Aminoglycosides

Aminoglycosides (e.g., gentamicin) bind to 30S

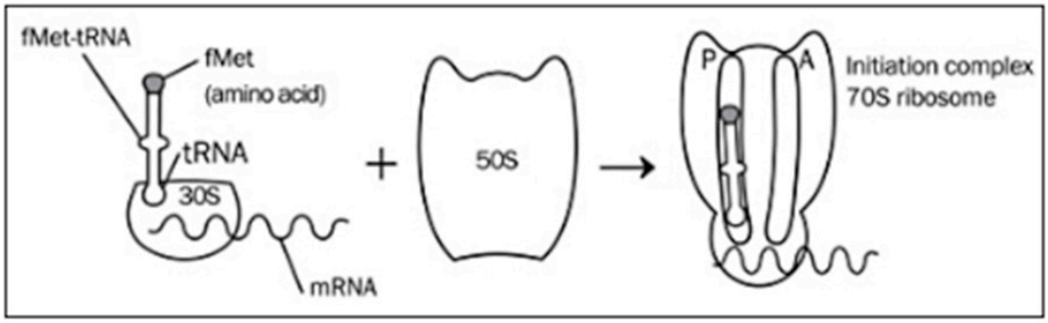

Figure 8. Formation of the 70S Ribosomal Initiation Complex.
Modified from Ryou M, Coen DM. Pharmacology of bacterial infections: DNA replication, transcription, and translation. In Golan DE, Tashjian, Jr. AH, Armstrong EJ, Armstrong AW. Ed. Principles of pharmacology. The pathophysiologic basis of drug therapy. 2nd ed. 2008. Wolters Kluwer/Lippincott Williams & Wilkins. Baltimore, MD.[53]

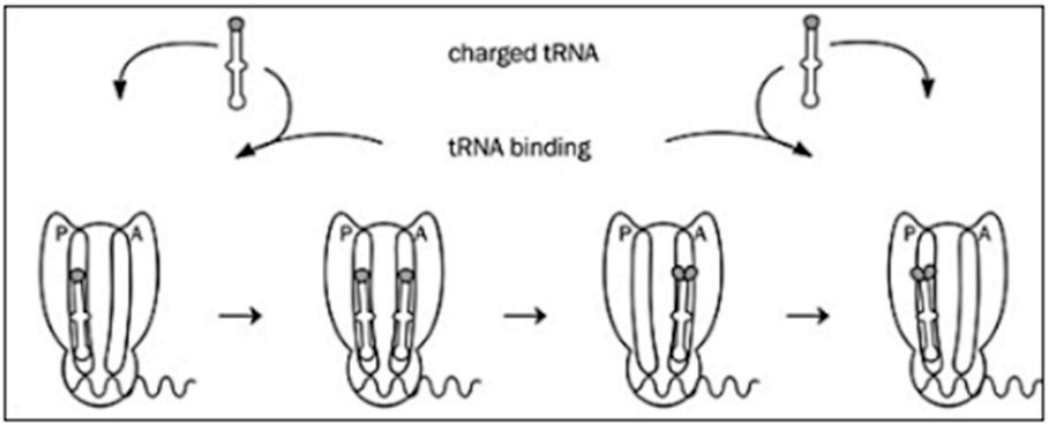

Figure 9. The Process of Protein Synthesis.
Modified from Ryou M, Coen DM. Pharmacology of bacterial infections: DNA replication, transcription, and translation. In Golan DE, Tashjian, Jr. AH, Armstrong EJ, Armstrong AW. Ed. Principles of pharmacology. The pathophysiologic basis of drug therapy. 2nd ed. 2008. Wolters Kluwer/Lippincott Williams & Wilkins. Baltimore, MD.[53]

ribosomal subunits and induce misreading of mRNA codons.[53,68,69] They are bactericidal in susceptible organisms and are active against many aerobic and facultative gram-positive and gram-negative cocci and bacilli, but most species of streptococci and anaerobic gram-negative bacilli are resistant.[53,68,69] Aminoglycosides do not have the requisite spectra to be considered *empirical* options in treating odontogenic infections.

Clindamycin
Clindamycin binds to 50S ribosomal subunits and blocks peptide bond formation between amino acids located in the P- and A-sites (Figure 8).[53,62,70] It has excellent activity against gram-positive aerobes and anaerobes, as well as gram-negative anaerobes.[11,42,71] Consequently, clindamycin has the requisite spectrum to be considered an *empirical* option in treating odontogenic infections.

Clindamycin is rapidly and almost completely absorbed after oral administration and reaches peak plasma concentration in about 45 minutes. It is widely distributed in body fluids and tissues (including bone). Clindamycin is extensively metabolized in the liver and its metabolites are excreted primarily by the kidneys.

Macrolides
Macrolides bind 50S ribosomal subunits and block translocation and peptide movement through the exit tunnel.[53] 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.[72-78]

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.

Treatment Strategies for 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.[71,79] *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.[71,79,80]

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.[80]

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.[80-86] In case of irreversible pulpitis endodontic debridement and obturation of the root canal system is the most predictable method of treatment.[87] 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.[88,89] 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.[90]

Acute Apical Periodontitis

Irreversible pulpitis and pulpal necrosis (an asymptomatic complication of irreversible pulpitis), if left untreated, lead to the spread of irritants and bacteria into periradicular 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.[91]

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.[80]

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.[90] Another study confirmed that once the source of infection is eliminated, the administration of penicillin provides no statistically significant added benefit.[92]

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.[93]

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.[93] 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.[94] 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 rinse with warm saline every 2 hours for two days. Routine antibacterial therapy is not indicated.

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.[94] 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.[94] 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 deep, radiating pain of increasing intensity is noted three to four days following extraction. The surrounding soft tissues appear normal but the alveolar socket is empty or contains necrotic debris. Alveolar osteitis is primarily an inflammatory condition, which may become secondarily infected.

A common protocol to manage alveolar osteitis consists of gentle debridement of the socket, irrigation with warm saline, and placement of an iodophor gauze impregnated with eugenol. The patient should be reevaluated every 24 to 48 hours, the dressing removed, the socket irrigated with warm saline and redressed. This cycle may have to be continued for up to 14 days. Routine antibacterial therapy is not indicated.

Pericoronitis
Pericoronitis is an acute infection most often associated with soft tissue overlying a partially erupted mandibular third molar. Signs and symptoms include pain, malaise, fever, lymphadenopathy, trismus, and difficulty swallowing. Abscess formation may be evident buccally or lingually to the offending tooth, which may progress to cellulitis or osteomyelitis; or spread through the fascial planes of the head and neck.

To establish drainage from under the operculum, a periodontal probe should be inserted into the follicular space enlarging the opening. The area under the operculum should be irrigated with warm saline and iodophor gauze impregnated with eugenol placed to maintain drainage. If the opposing maxillary tooth is traumatizing the operculum and deemed nonfunctional, it may be extracted. Otherwise, the cusps may be slightly reduced to minimize further trauma to the soft tissue below.

The patient should rinse with warm saline every 2 hours. Depending on associated signs and symptoms, i.e., clinical evidence of induration as the infection is spreading buccally or lingually and the presence of trismus, *empirical* antibacterial therapy may be initiated. When a subacute condition has been attained, usually within 48 hours, and the tooth is to be maintained, the operculum should be removed at this time; otherwise the tooth may now be extracted.

Cellulitis
When pulpal, periodontal or pericoronal infections overwhelm host resistance, the infection may extend into the surrounding tissues and cause cellulitis.[95,97] 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
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.

Space Infections

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, parapharyngeal, retropharyngeal, and deep spaces of the head and neck and mediastinum creating life-threatening situations.

When space infection is suspected, the patient should *immediately* be referred to a surgical specialist for evaluation and management. The specialist will collect a sample of the purulent exudate, usually by aspiration, for culture and susceptibility testing and begin immediate *empirical* intravenous antibacterial chemotherapy.[95-98] Drainage is established at the earliest possible time and measures to protect the airway are instituted if necessary. Close monitoring and modification of antibacterial chemotherapy, if indicated, is imperative.

Adjunctive Antibacterial Chemotherapy

Routine antibacterial chemotherapy for the treatment of uncomplicated odontogenic infections, in the absence of timely debridement, i.e., primary dental care, has not been shown to be effective.[11,12,15,20,71,80-87,89-93,97-102] Consequently, clinicians should avoid "rational activism" and "reflex prescribing." The rational activist assumes that it is better to over-treat than not to treat at all; the reflex prescriber caters to the patient's expectations regardless of the diagnosis.

Uncomplicated odontogenic infections that have not been debrided in a timely manner or have failed to respond to debridement may spread, especially in immunocompromised patients, into anatomical spaces contiguous with fascial planes and can lead to serious, even life-threatening infections.[15,103] Adjunctive antibacterial chemotherapy, predicated on sound principles, is imperative in the treatment of complicated odontogenic infections (Table 2).[71,103,104]

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).[11,42,71] 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).[9,20,42] 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).[105]

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).[61,106,107] 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

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.

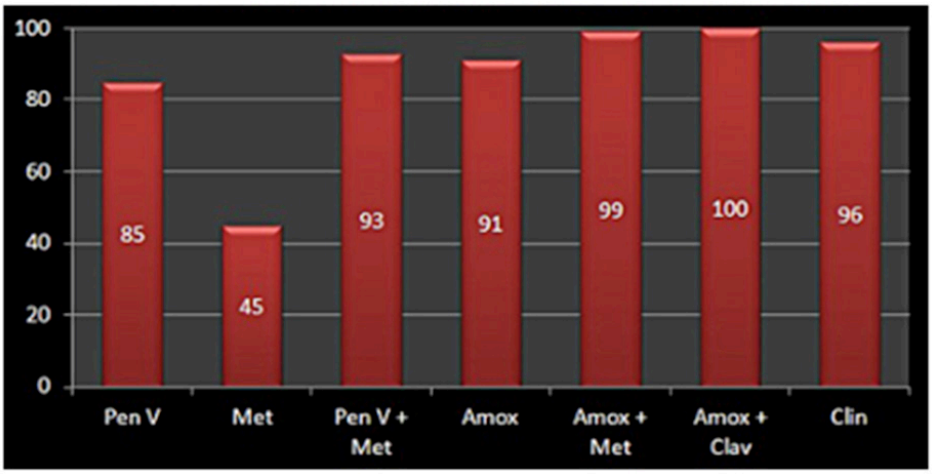

Figure 10. Percent Antibacterial Susceptibility of 98 Strains of Oral Bacteria.
Based on data from Baumgartner JC, Xia T. Antibiotic susceptibility of bacteria associated with endodontic abscesses. J Endod 2002;29(1):44-47.[42]

symptoms; serious convulsive seizures and peripheral neuropathy has 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).[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).[108]

It is also of note, that the single most important driver of the emergence of macrolide resistance in vivo is macrolide use.[109] 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 often confers multidrug-resistance. **Clindamycin** may also be an *empirical* option (see below).[110]

Tertiary Line of Antibacterial Chemotherapy

Clindamycin is the *empirical* drug of choice for unresolved infections following treatment with a β-lactam antibacterial agent.[71,111] It is also the initial *empirical* drug of choice for the treatment of severe complicated odontogenic infections (Table 3).[15,50,51,112,113] It is β-lactamase resistant and has excellent activity against gram-positive cocci and most gram-negative anaerobes.[47,50,112,114-117] However, the risk of *Clostridium difficile*-associated superinfections, which may range in severity from mild diarrhea to fatal colitis, should prompt caution and mandates close follow-up (see the *Prescription-precautions Associated with the Administration of Antibacterial Agents* section).[118,119]

Prophylactic Antibacterial Chemotherapy

A significant percentage of antibacterial agents are putatively prescribed by dental practitioners to prevent infections. In general, when an *effective antibacterial agent* is used to prevent infection by *specific bacteria* or to eradicate them immediately or soon after they have become established, the strategy is frequently successful. However, *prophylactic antibacterial chemotherapy* in dentistry should be limited to the prevention of those infections that are proven or strongly suspected to be procedure-specific.

Table 3. Antibacterial Agents for the Treatment of Complicated Odontogenic Infections.

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

*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.

Prevention of Surgical-site Infection in Patients Undergoing Tooth Extractions
Tooth extraction is the indicated therapy for teeth deemed non-restorable. However, there is no evidence to support the prophylactic use of antibacterial agents in association with the extraction of non-restorable teeth.[120] Another common reason for tooth extraction is poorly aligned or impacted third molars.

Antibacterial drugs administered just before and/or just after third molar extractions do reduce the risk of infection and dry socket, but there is no evidence that antibacterial agents prevent pain, fever, swelling, or trismus. The number needed to treat (NNT) to prevent one individual from having an extraction-related infection was estimated to be 19.[120] However, the practice of administering a prophylactic antibacterial agent contributes to adverse drug effects, including the likelihood of bacterial drug resistance. 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.[120]

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 recent critical review of 3 randomized double-blinded trials assessing 711 patient (1225 implants) revealed no statistically significant evidence to support the use of routine prophylactic antibacterial agents to reduce the risk of implant failure.[121]

In one of the studies assessed, the use of amoxicillin 2 g administered 1 hour preoperatively reduced the failure rate of dental implants placed under ordinary conditions; however the improvement was statistically insignficant.[121] The number needed to treat (NNT) to prevent one individual from having an implant failure was estimated to be 33. Given the potential for adverse drug events and the contribution to antibacterial resistance, the authors questioned the use of prophylactic antibacterial agents to reduce implant failure.[121]

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.[122] The 2021 update stratifies cardiac conditions as to the risk of developing endocarditis and the severity of associated morbidity. Due to its high adverse effect risk, clindamycin is no longer recommended as a prophylactic agent. Only patients with the highest-risk of adverse outcome from endocarditis (Table 4) should be considered for antibacterial prophylaxis prior to dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa (Table 5).[122]

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. For patients undergoing sequential care, Clinicians should allow at least 10 days (ideally 4 weeks) between appointments to reduce the risk for the development of resistant organisms.[122]

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) published a clinical practice guideline, with periodic updates, for the prevention of orthopaedic implant infection in patients undergoing dental procedures.

The 2012 AAOS-ADA Clinical Practice Guideline, which was developed using a systematic evidence-based process, provided no specific direction in managing individual patients and created confusion.[123] **In 2014, the American Dental Association Council of Scientific Affairs convened a panel of experts to develop an evidence based clinical practice guideline intended to clarify the issue.**

The 2014 Panel found (1) no association between dental procedure-related transient

Table 4. Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for Which Antibacterial Prophylaxis is Reasonable. [122]

- ✓ Prosthetic cardiac valve or material.
  - Presence of cardiac prosthetic valves.
  - Transcatheter implantation of prosthetic valves.
  - Cardiac valve repair with devices, including annuloplasty, rings, or clips.
  - Left ventricular assist devices or implantable heart.
- ✓ Previous infective endocarditis.
- ✓ Congenital heart disease (CHD).
  - Unrepaired cyanotic CHD, including palliative shunts and conducts.
  - 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.
  - Surgical or transcatheter pulmonary artery valve or conduit placement such as Melody valve and Contegra conduit.
- ✓ Cardiac transplantation recipients who develop cardiac valvulopathy.

Table 5. Antibacterial Prophylaxis before Procedures that Involve Manipulation of Gingival Tissue, Periapical Region of Teeth, or Perforation of the Oral Mucosa.[122]

Situation	Agent	Regimen: single dose, 30-60 minutes before procedure	
		Adults	Children
Patient not allergic to β-lactams AND able to take oral medications	Amoxicillin	2.0g, PO	50mg/kg, PO
Patient not allergic to β-lactams BUT unable to take oral medications	Ampicillin	2.0g, IM or IV	50mg/kg, IM or IV
	Cefazolin *or* Ceftriaxone	1.0g, IM or IV	50mg/kg, IM or IV
Patient allergic to β-lactams AND able to take oral medications	Cephalexin*†	2.0g, PO	50mg/kg,PO
	Azithromycin *or* Clarithromycin	500mg, PO	15mg/kg < 45kg, PO 4.4mg/kg >45kg, PO
	Doxycycline	100mg, PO	100mg, PO
Patient allergic to β-lactams AND unable to take oral medications	Cefazolin *or* Ceftriaxone†	1.0g, IM or IV	50mg/kg, IM or IV

* Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosing.
† Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillin or ampicillin.

bacteremia and prosthetic joint infection, and (2) no evidence that antibacterial agents administered prior to dental procedures prevent joint infarctions. The Panel also concluded that because of potential harmful effects of antibacterial agents such as allergic reaction and superinfections, the risks of antibacterial prophylaxis may exceed any benefit for most patients. Therefore, in general, the administration of antibacterial prophylaxis is not recommended for patients with prosthetic joints undergoing dental procedures.[124]

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.[125-127] 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.[128-130] 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.[131] 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.[132] 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.[132] 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 of antibacterial drug-resistance.[104,109,133-145] Unless healthcare providers change their practices, many currently available antibacterial agents may become ineffective. In a retrospective cohort study assessing 168,420 prophylactic prescriptions prescribed in dental practice, the authors determined 80.9% of the prescriptions were unnecessary.[146] When antibacterial agents are used appropriately to treat complicated odontogenic infections or to prevent infections in high-risk patients, clinicians must accept the ecological consequences of antibacterial chemotherapy. However, when other therapeutic means are available, antibacterial agents should not be routinely prescribed to treat or to prevent infections.

Gastrointestinal Distress

Common ADEs associated with antibacterial agents, but especially with macrolides, are nausea, vomiting, epigastric distress, and diarrhea.[34,37,61,70,77] These symptoms may be amplified in patients on metronidazole with concurrent use of alcohol.[70] 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 *Clostridiodes difficile*.[118] Colitis has been reported with the use of nearly all antibacterial agents, but especially with clindamycin.[34,37,61,70,77] Up to 15% of community-acquired *C difficile* infection may be attributable to antibiotics prescribed for a dental procedure and a single dose of clindamycin may cause complications, including death, from *C difficile* infection.[122]

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.[37,61,70,77,105] 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.[70,77]

Cardiovascular Effects

Azithromycin and other macrolides can cause abnormal electrical activity in the heart that may lead to a potentially fatal irregular heart rhythm.[77,108] 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.[147]

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.[61] Infrequently, neuropathy has been noted with penicillin formulations, but when present, it is usually associated with high doses of parenteral penicillin.[34,37]

Oral Candidiasis

Superinfections with *Candida* sp. can occur in association with all, but especially broad-spectrum antibacterial agents.[34,37,61,70,77] 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

The Food and Drug Administration (FDA) instituted a product labeling schema (A, B, C, D, X) in 1979, to categorize drugs according to their teratogenic risk to the fetus.[148] The FDA issued a new rule on December 3, 2014, addressing pregnancy and lactation labeling information for prescription drug and biologic products.[149] The new labeling requirement, to be phased in starting June 2015, replaces the letter categories with three detailed subsections that more accurately explain the real-world risks associated with a given drug exposure for a pregnant woman. (Table 6)

There is no firm evidence that the penicillins, metronidazole, azithromycin, and clindamycin are teratogenic in humans. Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women.[34,37,61,70,77,149] Since animal studies are not always predictive

Table 6. Pregnancy & Lactation Labeling Requirements of Prescription Drugs and Biological Products[149]

Subsection	Requirement
Pregnancy	✓ Information relevant to the use of the drug in pregnant women, such as dosing and potential risks to the developing fetus ✓ Information about whether there is a registry that collects and maintains data on how pregnant women are affected when they use the drug or biological product. ✓ Subheadings addressing: "risk summary", "clinical considerations", and "data".
Lactation	✓ Information about using the drug while breastfeeding, such as the amount of drug in breast milk and potential effects on the breastfed child. ✓ Subheadings addressing: "risk summary", "clinical considerations", and "data".
Females and Males of Reproductive Potential	✓ Information about pregnancy testing, contraception and about infertility as it relates to the drug.

of a drug's teratogenic effect in humans, antibacterial agents should only be prescribed during pregnancy if clearly indicated.[34,37,61,70,77,149]

Antibacterial Drugs and Nursing

Mechanisms of drug excretion in human breast milk include both passive diffusion and carrier-mediated transport. The amount of drug excreted in breast milk depends on the drug's molecular weight, lipid solubility, pKa, and plasma protein binding.[150,151] Once in breast milk, the pKa of the drug is an important determinant of the drug's concentration in breast milk. Consequently, at equilibrium some drugs may accumulate in breast milk in higher concentration relative to plasma.

The penicillins are excreted in breast milk and may lead to sensitization of infants.[34,37] Metronidazole, which has been shown to be carcinogenic in rats and mice, is excreted in breast milk in concentrations similar to those found in plasma.[61] Clindamycin is also excreted in breast milk.[70] The fate of azithromycin is unknown.[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.[34,37,61,70,77]

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.[152,153]

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.[154] 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."[155]

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.[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.[157,158]

Conclusion

According to recent JADA study, dentists show differing prescribing beliefs and behaviors when prescribing while another JADA survey concludes dentists frequently prescribe antibiotics for long periods of time and often use broad-spectrum antibiotics. Taken together, both studies underscore the practical implication that there is significant variation in antibiotic selection and treatment duration among dentists across the specialties; and it implies the need for continuing investigation to improve and standardize practice.[159,160]

Still, continuing education, guidance and accessibility to information is noted to be helpful in informing targeted interventions and improve prescribing protocols.[161]

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/ce-courses/ce475/start-test*

1. Several factors are responsible for bacterial invasion and multiplication in host tissues and result in local cellular injury. Which is NOT one such factor?

A. competitive metabolism
B. toxin production
C. immune-mediated reactions
D. genomic alteration.

2. Which of the following statements is NOT correct regarding Gram-positive and Gram-negative bacteria?

A. Acetone extracts lipids from the outer membrane, cell wall, and cytoplasmic membrane of bacteria.
B. Gram negative bacteria possess a thick peptidoglycan cell wall.
C. 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.
D. Gram-positive bacteria retain their crystal violet-iodine complexes and appear deep purple.

3. Which of the following statements is NOT correct with respect to odontogenic infections?

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. Which of the following is NOT a valid means to achieve this selective toxicity?

A. attacking targets unique to eukaryotic cells.
B. attacking targets unique to bacteria.
C. attacking targets in bacteria similar but not identical to those in host cells.
D. attacking targets that are shared, but vary in importance between bacteria and host cells.

5. Which of the following statements is NOT true of 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. Monomers are synthesized in the nucleus from fatty acid and sugar building blocks.

6. Which of the following statements is NOT true with respect to cell wall synthesis inhibitors?

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. Second 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 is NOT correct relative to DNA synthesis inhibitors?

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 NOT correct with respect to transcription and translation inhibitors?

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. Macrolides are highly effective against anaerobic gram negative organisms.
D. Azithromycin has an extended spectrum that includes some anaerobic gram-positive cocci and gram-negative bacilli.

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 statement about the routine use of antibacterial agents in the treatment of uncomplicated infections is NOT 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. In the treatment of acute apical periodontitis, the administration of penicillin significantly reduced pain.

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. Which of the following conditions lacks convincing evidence to support routine antibacterial administration to improve therapeutic outcome?

A. gingival and periodontal abscesses
B. necrotizing ulcerative gingivitis
C. alveolar osteitis
D. progressing pericoronitis.

16. Regarding pericoronitis, when a subacute condition has been attained, usually within 48 hours, and the tooth is to be maintained, the operculum should be removed at this time; otherwise, the tooth may now be extracted.

A. True
B. False

17. Which conditions should NOT be considered a complicated odontogenic infection with an indication for adjunctive antibacterial chemotherapy?

A. pain
B. cellulitis
C. osteomyelitis
D. space infections

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 NOT 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. Metronidazole provides excellent coverage for obligate aerobes.

21. Which of the following statements is NOT 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. Azithromycin use is not associated with an increased arrhythmia risk.
C. While there is a paucity of data demonstrating the efficacy of azithromycin in the treatment of odontogenic infections, it appears to be the best choice because of its extended spectrum against facultative and some obligate anaerobes.
D. Clindamycin may be a better empirical option in patients allergic to β-lactam antibacterial agents.

22. Which of the following statements is NOT 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. Clindamycin use is associated with a very low risk of developing a Clostridioides difficile-associated superinfection.

23. Which of the following statements is NOT correct with respect to the prevention of surgical-site infection in patients undergoing tooth extractions?

A. There is no evidence that antibacterial agents prevent pain, reduce fever, swelling, or trismus.
B. Antibacterial drugs administered just before and/or just after third molar extractions may reduce the risk of infection and dry socket.
C. The number needed to treat (NNT) to prevent one individual from having an extraction-related infection was estimated to be 19.
D. There is solid evidence that an antibacterial agent given to healthy people in association with third molar extractions is more beneficial than harmful.

24. Which of the following statements is NOT correct with respect to the prevention of surgical-site infection in patients undergoing placement of dental implants?

A. Bacteria introduced during the placement of dental implants can lead to infection and implant failure.
B. The number needed to treat (NNT) to prevent one individual from having an implant failure was estimated to be 19.
C. The evidence to suggest that amoxicillin 2g. administered 1 hour preoperatively reduces the failure rate of dental implants placed under ordinary conditions is statistically insignificant.
D. There is no statistically significant evidence that postoperative antibacterial agents are beneficial to reduce infection and implant failure.

25. Which of the following statements is NOT correct with respect to the prevention of infective endocarditis in patients undergoing dental procedures?

A. The 2021 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 NOT 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. The potential adverse effects associated with antibacterial prophylaxis has no bearing on the decision to use prophylaxis in patients with a medical condition.

27. Which of the following statements is NOT 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 current evidence, it is recommended that prophylactic antibacterial agents covering aerobic gram-positive cocci, gram-negative bacilli, and anaerobic bacteria be used for 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. There is strong evidence that prophylactic antibacterial agents offer clear benefits in clean surgery for benign disease.

28. Which of the following statements is NOT 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. Prescribing habits indicate the profession of dentistry does not tangibly contribute to problem of antibacterial drug resistance.

29. Which of the following statements is NOT correct with respect to gastrointestinal disturbances in association with antibacterial agents?

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 Clostridioides difficile.

30. Which of the following statements is NOT 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. Hypersensitivity reactions appear to rarely occur with the β-lactams.

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