Chapter 7 Outline

- Antiinfective Agents
  - Dental infection "evolution"
  - History
  - Definitions
  - Culture and sensitivity
  - Resistance
  - Indications for antimicrobial agents
  - General adverse reactions and disadvantages associated with antiinfective agents

Antiinfective Agents

- Haveles (pp. 76-77) (Table 7-1)
  - Infection, after pain management, is the dental problem for which drugs are most often prescribed
  - Dental infections can be divided into several types
    - Caries
    - Periodontal disease
    - Localized dental infections
    - Systemic infections

Dental Infection "Evolution"

- Haveles (p. 77)
  - Dental infections often follow similar pathways from beginning to end
    - The organisms initially responsible for a dental infection are primarily gram-positive cocci
    - After a short time, the gram-positive infection begins to include a variety of both gram-positive and gram-negative anaerobic organisms; this is termed a mixed infection
    - Over time, the proportion of organisms that are anaerobic increases until it consists of predominately anaerobic flora

- Pen VK is the drug of choice unless the patient is allergic
  - In an allergic patient, alternatives might include erythromycin or clindamycin

- For gram-positive organisms, the drug of choice is penicillin/amoxicillin or, with penicillin allergy, a macrolide antibiotic
  - For anaerobic organisms, metronidazole is effective
  - Clindamycin affects both gram-positive cocci and gram-negative anaerobes
  - Oral surgeons have been comfortable using it, but other dentists have avoided it because of an association with pseudomembranous colitis
History

- Haveles (pp. 77-78)
  - In 1928, Fleming observed that a mold, *Penicillium notatum*, produced a substance that inhibited the growth of certain bacteria.
  - Chain and coworkers reported the low toxicity and systemic antibacterial effectiveness of penicillin.
- Concern has surfaced about indiscriminate use of antibiotics.
  - Totally resistant strains of bacteria have made this concern more important.

Definitions

- Haveles (pp. 78-79)
  - Antiinfective agents
    - Substances that act against or destroy infections.
  - Antibacterial agents
    - Substances that destroy or suppress the growth or multiplication of bacteria.
  - Antibiotic agents
    - Chemical substances produced by microorganisms that have the capacity, in dilute solutions, to destroy or suppress the growth or multiplication of organisms or prevent their action.

Definitions (cont’d…)

- Haveles (p. 78) (Box 7-2)
  - Bactericidal
    - Ability to kill bacteria.
    - Irreversible; if the bacteria are removed from the drug, they do not live.
  - Bacteriostatic
    - Ability to inhibit or retard the multiplication or growth of bacteria.
    - Reversible; if the bacteria are removed from the agent, they are able to grow and multiply.

Definitions (cont’d…)

- Haveles (p. 78) (Box 7-2)
  - Blood (serum) level
    - Concentration of antiinfective agent in blood or serum.
    - Certain levels of an antibiotic are required to produce an effect on various types of organisms.
  - Infection
    - Invasion by pathogenic microorganisms and reaction of tissue.
    - Presence of a pathogen does not constitute "invasion".

Definitions (cont’d…)

- Haveles (p. 78)
  - Minimal inhibitory concentration (MIC)
    - Lowest concentration needed to inhibit visible growth of an organism on media after 18 to 24 hours of incubation.
  - Resistance
    - The natural or acquired ability of an organism to be immune to or resist the effects of an antiinfective agent.

Definitions (cont’d…)

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Definitions

- Haveles (p. 78)
  - Spectrum
    - Range of activity of a drug
    - May be narrow, intermediate, or broad
  - Superinfection, suprainfection
    - Infection caused by proliferation of microorganisms different from those causing the original infection
    - The practitioner can cause and eliminate infections

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Infection

- Haveles (p. 79)
  - The factors that determine the likelihood of a microorganism causing an infection
    - Disease-producing power of the microorganism (virulence)
    - Number of organisms present (inoculum)
    - Resistance of the host (immunologic response)

Culture and Sensitivity

- Haveles (p. 79) (Box 7-2)
  - Synergism
    - Combination produces more than an additive effect ($1 + 1 > 2$)
    - Bactericidal combinations are generally synergistic; bacteriostatic combinations are merely additive
  - Antagonism
    - Occurs when a combination produces less effect than either agent alone
    - A combination of a bactericidal and bacteriostatic agent is often poorer than either alone ($1 + 1 < 2$)

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Culture and Sensitivity

- Culture and sensitivity
  - The only way to be sure a drug will kill or inhibit the growth of the infecting microorganisms
    - In dentistry, the need for anaerobic culturing makes obtaining a sample and culturing it more difficult
    - Dental infections are often of a mixed nature

Culture

- Haveles (p. 79)
  - Proper collection materials and methods must be used to obtain reliable results
    - The laboratory should perform a Gram stain and report all bacteria present in high numbers
    - Both obligate and facultative anaerobes should be preserved

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Culture
- Depending on the site, the collection method varies
  - Examples include aspiration with a needle for an abscess, a swab from an anaerobic pack for a draining lesion, and properly handled absorbent points for endodontic treatment
  - Care must be taken to avoid contaminating the sample with supragingival plaque

Sensitivity
- Haveles (p. 79) (Fig. 7-1)
  - After the organism is identified, it is grown on culture media
  - Observing whether the organisms are sensitive or resistant to test antibiotics helps determine which antibiotic to use in difficult infections

Resistance
- Haveles (pp. 79-80)
  - Natural resistance
    - When an organism has always been resistant to an antimicrobial agent because of the bacteria’s normal properties
  - Acquired resistance
    - When an organism that was previously sensitive to an antimicrobial agent develops resistance

Indications for Antimicrobial Agents
- Haveles (p. 80)
  - Therapeutic indications
    - Patient
    - Infection
  - Prophylactic indications

Therapeutic Indications
- Considerable controversy exists regarding the need for antimicrobial agents in various situations
  - The two categories of indications are prophylactic and therapeutic
  - No simple rule has been developed to determine whether antimicrobial therapy is needed in dentistry; many infections do not require it
  - Most patients, without immune function deficiencies, in whom drainage can be obtained, do not need antibiotics to manage their dental infections
Antimicrobial Use in Dentistry (Drug[s] of Choice)

Haveles (p. 80) (Table 7-2)

- Infection situation
  - Periodontal disease
    - Acute necrotizing ulcerative gingivitis (ANUG): penicillin VK, amoxicillin
    - Abscess (periodontal): penicillin VK
    - Localized juvenile periodontitis (LJP): doxycycline, tetracycline
    - Adult periodontitis: not usually treated with drugs
    - Rapidly advancing periodontitis (RAP): doxycycline, tetracycline, metronidazole
  - Oral infections
    - Soft-tissue infections: penicillin VK, amoxicillin
    - Osteomyelitis: penicillin VK, amoxicillin

- Mixed infections insensitive to penicillin
  - Aerobes: amoxicillin
  - Anaerobes and chronic infections: metronidazole, clindamycin

- Prophylaxis for infective endocarditis
  - Prosthetic heart valve, no penicillin allergy: amoxicillin
  - Patient with LJP: doxycycline for 3 weeks followed by the usual regimen

Patient

Haveles (p. 80)

- The best defense against a pathogen is host response
  - When this defense is lacking, the need for antimicrobial agents is more pressing

Infection

Haveles (p. 80) (Table 7-2)

- Virulence and invasiveness of the microorganism are important in deciding the acuteness, severity, and spreading tendency of an infection
  - An acute, severe, rapidly spreading infection should generally be treated with antimicrobial agents
  - A mild, localized infection in which drainage can be established need not be drained

Infection

- If the periodontal pocket remains active despite repeated root planing, the use of antibiotics that alter the flora should be considered

Prophylactic Indications

Haveles (p. 80)

- Few situations arise for which a definite indication for prophylactic antibiotic coverage exists
  - One clear-cut use of antibiotics for prophylaxis before a dental procedure, such as
    - A history of infective endocarditis
    - Presence of a heart valve prosthesis
    - Congenital heart disease (CHD)
General Adverse Reactions and Disadvantages Associated with Antiinfective Agents

- Haveles (p. 81)
- Superinfection (suprainfection)
- Allergic reactions
- Drug interactions
  - Oral contraceptives
  - Oral anticoagulants
  - Other antiinfectives
- Gastrointestinal (GI) complaints
- Pregnancy
- Dose forms
- Cost

Superinfection (Suprainfection)

- All antiinfective agents can produce an overgrowth of an organism that is different from the original infecting organism and is resistant to the agent being used
  - The wider the spectrum of the antiinfective agent and the longer the agent is administered, the greater the chance of overgrowth
  - This side effect can be minimized by use of the most specific antiinfective agent, the shortest effective course of therapy, and adequate doses

Allergic Reactions

- All antiinfective agents have the potential to produce a variety of allergic reactions from mild rash to anaphylaxis
  - Some agents, such as penicillins and cephalosporins are more allergenic than others
  - Many agents, such as erythromycin and clindamycin have low allergic potential

Drug Interactions

- Oral Contraceptives
  - Most antiinfective agents have been implicated in a drug interaction with oral contraceptives
    - When antibiotics are given, the number of bacteria in the intestine falls
    - Hydrolysis of the estrogen conjugate does not occur
    - Because the estrogen remains conjugated, it will not be reabsorbed
    - The absorption of estrogen decreases and its blood level falls
  - In certain patients, additional birth control measures should be used during antibiotic administration

- Oral Anticoagulants
  - Antiinfective agents potentiate the effect of oral anticoagulants
    - Oral anticoagulants are vitamin K inhibitors; thus interfering with production of vitamin K could increase the anticoagulant effect
  - Bacterial flora in the intestine produce most of the vitamin K in human bodies
    - Antiinfective agents reduce the bacterial flora that produce vitamin K
    - With vitamin K reduced, the oral anticoagulant’s effect is increased

- Other Antiinfectives
  - Antibiotics that act at the same receptor may compete for that receptor and should not be given together
  - An antibiotic with bacteriostatic properties stops bacteria from growing, thereby inhibiting the action of a bactericidal agent
Gastrointestinal Complaints

- All antiinfective drugs can produce a variety of GI complaints
  - Complaints include stomach pain, increased motility, and diarrhea
  - The incidence varies, depending on the agent used, the dose, and whether the patient takes the drug with food
- Erythromycin has the highest incidence of GI complaints of any of the antibiotics

Pregnancy Considerations

- Antimicrobial agents that can be used pregnancy to treat infections are limited
  - Penicillin and erythromycin have not been associated with teratogenicity and are often used
- Before any antibiotics are used in the pregnant dental patient, the patient’s obstetrician should be contacted
  - Metronidazole is not usually used during pregnancy; exceptions exist
  - Tetracyclines are contraindicated during pregnancy

Dose Forms

- Adult dose forms of antibiotics are commonly tablets and capsules
- Children’s dose forms, including liquid and chewable antibiotic dose forms, contain sugar as their sweetening agent

Cost

- Havelos (pp. 81-82) (Fig. 7-2)
  - An important factor in choosing an antibiotic for a patient
    - The best inexpensive antibiotic that can be taken will be more effective than an expensive one that cannot be purchased
    - Common; involves nausea, anorexia, diarrhea, and vomiting
  - Central nervous system (CNS) effects: headache, dizziness, vertigo, ataxia (inability to coordinate muscle activity)
    - Confusion, depression, weakness, insomnia, and serious convulsive seizures are rarely associated

Chapter 7 Outline

- Penicillins
- Macrolides
- Tetracyclines
- Clindamycin
- Metronidazole
- Cephalosporins
- Rational use of antiinfective agents in dentistry
- Antimicrobial agents for nondental use
- Antituberculosis agents
- Antibiotics
- Antibiotic prophylaxis used in dentistry

Penicillins

- Havelos (pp. 81-85)
  - Source and chemistry
  - Pharmacokinetics
  - Mechanism of action
  - Spectrum
  - Resistance
  - Adverse reactions
  - Uses
  - Specific penicillins

cont’d…
Penicillins

- Haveles (pp. 81, 83) (Table 7-3)
- Divided into four major groups
  - Penicillin G and V
  - Penicillinase-resistant penicillins
  - Amoxicillin
  - Extended-spectrum penicillins

Source and Chemistry

- Haveles (p. 82) (Fig. 7-3)
- The mold *Penicillium notatum* and related species produce the naturally occurring penicillins
- Semisynthetic penicillins are produced by chemically altering the natural penicillins
- The penicillins structure has a β-lactam ring fused to a five-member, S-containing thiazolidine ring
- When the β-lactam ring is broken, such as in the presence of penicillinase, the antimicrobial activity of the compound is lost

Pharmacokinetics

- Haveles (pp. 82-83) (Table 7-3)
- Penicillin is administered orally or parenterally; too allergenic for topical application
  - After oral administration, the amount absorbed can vary from 0% to more than 90%
  - Penicillin V is absorbed orally better than penicillin G, thus penicillin V is used for oral administration
- Distributed throughout the body, except cerebrospinal fluid (CSF), bone, and abscesses
- Metabolized by hydrolysis in the liver and undergoes tubular secretion in the kidney

Mechanism of Action

- Haveles (pp. 82-83) (Table 7-3)
- Bactericidal agent that attaches to penicillin-binding proteins (PBPs) on the bacterial cell membrane
  - PBPs are enzymes involved in synthesis of the cell wall and maintenance of the cell’s structural integrity
- Penicillin destroys cell wall integrity and leads to lysis

Spectrum

- Haveles (pp. 82-83)
- Penicillin G and V have a narrow spectrum of activity
  - Includes gram-positive cocci, and certain gram-negative cocci
  - Effective against spirochetes and anaerobes
- The spectrum matches the microbes responsible for many periodontal conditions

Resistance

- Haveles (p. 83)
- Can occur by several different mechanisms
  - Penicillinase-producing staphylococci produce enzymes that inactivate penicillin by cleaving the β-lactam ring
  - In hospitals, more than 95% of staphylococci are penicillinase-producing organisms
- Clavulanic acid serves as a substrate, which allows the use of amoxicillin to treat penicillinase-producing organisms
Adverse Reactions

- Haveles (pp. 83-84)
- Reactions to penicillins can be divided into toxic reactions and allergic or hypersensitivity reactions
  - Penicillins are the most common cause of drug allergies

Toxicity

- Haveles (p. 83)
- Penicillin’s toxicity is almost nonexistent
  - Penicillinase-resistant penicillins are significantly more toxic than penicillin G
- GI irritation can manifest as nausea with or without vomiting
- Irritation caused by injection of penicillin can produce sterile abscesses if given intramuscularly or thrombophlebitis if given intravenously

Allergy and Hypersensitivity

- Haveles (pp. 83-84)
- Some studies indicate that 5% to 10% of patients receiving penicillin will have a reaction
- Associated allergic reactions include
  - Anaphylactic reactions: anaphylactic shock occurs within minutes
  - Rash: in 80% to 90% of allergic reactions
  - Delayed serum sickness: fever, skin rash, eosinophilia, up to 2 weeks after treatment
  - Oral lesions: delayed reactions, severe stomatitis, turned tongue, black tongue, acute glossitis, and cheilosis
  - Other reactions: interstitial nephritis, hemolytic anemia, eosinophilia

- An anaphylactic reaction occurs in 0.05% of penicillin-treated patients, with a mortality of 5% to 10%
  - 100 to 300 deaths annually in the United States
- Allergic reactions to penicillin of any type may be followed by more serious allergic reactions on subsequent exposure

Uses

- Haveles (pp. 80, 84) (Table 7-2)
- Use of penicillin in dentistry results from its bactericidal potency, lack of toxicity, and spectrum of action
  - Often used for treatment of dental infections
- Penicillin’s effectiveness in the treatment of dental infections is explained by its effectiveness against many aerobic and anaerobic bacteria

Specific Penicillins

- Haveles (pp. 84-85)
- Penicillin G
- Penicillin V
- Penicillinase-resistant penicillins
- Ampicillins
- Extended-spectrum penicillins
Penicillin G

> Haveles (pp. 84-85) (Fig. 7-4)

- The prototype penicillin, available as sodium, potassium, procaine, or benzathine salts
- The salts differ in their onset and duration of action and the blood plasma levels attained
- The duration of action is inversely proportional to the solubility of the penicillin form; the least soluble is the longest acting

Examples of Penicillin G

> Haveles (p. 83) (Table 7-3)

- penicillin G (Pentids)
- penicillin G procaine (Crysticillin)
- penicillin G benzathine (Bicillin L-A)

Penicillin V

> Haveles (pp. 80, 84) (Table 7-2)

- Has a spectrum of action very similar to that of penicillin G
- The potassium salt of penicillin V is more soluble than the free acid and better absorbed when taken orally

Examples of Penicillin V

> Haveles (p. 83) (Table 7-3)

- penicillin V (Pen-Vee K, V-Cillin K)

Penicillinase-Resistant Penicillins

> Haveles (p. 84)

- Should be reserved for use against only penicillinase-producing staphylococci
- Less effective than penicillin G against penicillin G–sensitive organisms
- Produce more side effects such as GI discomfort, bone marrow depression, and abnormal renal and hepatic function
- Cloxacillin and dicloxacillin are the drugs of choice

Examples of Penicillinase-Resistant Penicillins

> Haveles (p. 83) (Table 7-3)

- methicillin (Staphcillin)
- nafcillin (Unipen, Nafcil)
- oxacillin (Prostaphilin, Bactocill)
Ampicillins

- Haveles (pp. 80, 84-85) (Table 7-2)
  - Ampicillin and amoxicillin are penicillinase-susceptible agents
  - Amoxicillin is most often used to treat infections because it produces higher blood levels, is better absorbed, required less frequent dosing, and its absorption is not impaired by food
  - Amoxicillin is available with clavulanic acid, a $\beta$-lactamase inhibitor (Augmentin)

- Both ampicillin and amoxicillin can produce a wide variety of allergic reactions
  - Ampicillin is much more likely to produce rashes than other penicillins
  - Most agree that the ampicillin rash is not of an allergic or immunologic nature

Examples of Ampicillins

- Haveles (p. 83) (Table 7-3)
  - ampicillin (Polycillin, Omnipen)
  - amoxicillin (Amoxil, Larotid)
  - amoxicillin + clavulanate (Augmentin)

Examples of Extended-Spectrum Penicillins

- Haveles (p. 85)
  - Carbenicillin has a wider spectrum of action than penicillin G
  - It is not penicillinase resistant and is available parenterally to treat systemic infections

Examples of Extended-Spectrum Penicillins

- Haveles (p. 83) (Table 7-3)
  - carbenicillin indanyl (Geocillin)
  - carbenicillin (Geopen, Pyopen)
  - ticarcillin (Ticar)
  - piperacillin (Piperacil)

Macrolides

- Haveles (pp. 85-86) (Table 7-4)
  - Consist of erythromycin, azithromycin and clarithromycin
Erythromycin

- Haveles (pp. 85-86)
- **Mechanism and spectrum**
  - Usually bacteriostatic
    - Interferes with protein synthesis by inhibiting the enzyme peptidyl transferase at the P site of the 50S ribosomal subunit
  - Spectrum of action closely resembles penicillin against gram-positive bacteria
    - Not effective against many infections caused by obligate anaerobes involved in some dental infections

Pharmacokinetics

- Haveles (pp. 85-86) (Table 7-4)
- Usually administered orally as tablets, capsules, oral suspensions in intravenous or intramuscular forms, and in topical preparations
  - Formulated as an enteric-coated tablet, capsule, or insoluble ester to reduce degradation by stomach acid
  - Food reduces absorption, but administering with food may be necessary to minimize adverse GI effects

Adverse Reactions

- Haveles (p. 86)
- With usually therapeutic doses, side effects other than GI are usually minimal
  - GI effects: include stomatitis, abdominal cramps, nausea, vomiting, and diarrhea
  - Cholestatic jaundice: has been reported primarily with the estolate form; has also been reported with the ethylsuccinate form
    - Erythromycin base has not been associated with this reaction

Drug Interactions

- Haveles (p. 86) (Table 7-5)
- Erythromycin can increase serum concentrations of theophylline, warfarin, triazolam, carbamazepine, and cyclosporine
  - This effect can produce toxicity
- The mechanism of the drug interactions may involve inhibition of hepatic metabolism of these drugs

Uses

- Haveles (p. 86)
- Active against the same aerobic microorganisms as penicillin, it is the drug of first choice against these organisms in penicillin-allergic patients
  - Not effective against the anaerobic Bacteroides species implicated in many dental infections

Examples of Macrolides

- Haveles (p. 85) (Table 7-4)
- Erythromycin base (E-mycin, Ery-Tab, Eryc, PCE, various)
- Erythromycin stearate (Erythromycin)
- Erythromycin estolate (Ilosone)
- Erythromycin ethylsuccinate (EES)
- Azithromycin (Zithromax)
- Clarithromycin (Biaxin)
Azithromycin and Clarithromycin

- Haveles (p. 86)
- Both are newer macrolide antibiotics, such as erythromycin
- Inhibit RNA-dependent protein synthesis by binding to the 50S ribosomal subunit
  - Activity against gram-positive cocci and gram-negative aerobes
  - In contrast to erythromycin, azithromycin and clarithromycin have variable action against some anaerobes
- Bacteriostatic; taken without regard to meals

Azithromycin and Clarithromycin

- GI adverse reactions include dyspepsia, diarrhea, nausea, and abdominal pain
  - Much less frequent than with erythromycin
- Several drug interactions can occur with both agents because of their reduction in the metabolism of certain drugs metabolized in the liver
- Indicated as alternative antibiotics in the treatment of common orofacial infections caused by aerobic gram-positive cocci and susceptible anaerobes

Tetracyclines

- Haveles (pp. 87-89) (Table 7-6)
- Pharmacokinetics
- Spectrum
- Adverse reactions
- Drug interactions
- Uses

Tetracyclines

- Haveles (p. 87) (Table 7-6)
- Broad-spectrum antibiotics affecting a wide range of microorganisms
  - Adverse effects on developing teeth
- First isolated from a strain of Streptomyces in 1948
  - Since then, other tetracyclines have been derived from different species of Streptomyces; the rest have been produced semisynthetically

Pharmacokinetics

- Haveles (p. 87)
- Usually administered orally; absorption after oral administration varies but is fairly rapid
  - Wide tissue distribution; tetracyclines are secreted in the saliva and milk of lactating mothers
  - Concentrated by the liver and excreted into the intestines via the bile
  - Stored in dentin and enamel of unerupted teeth and concentrated in gingival crevicular fluid (GCF)
- All tetracyclines cross the placenta and enter fetal circulation

Spectrum

- Haveles (p. 87)
- All tetracyclines are bacteriostatic and interfere with synthesis of bacterial protein by binding at the 30S subunit of bacterial ribosomes
  - Broad spectrum; effective against a wide variety of gram-positive and gram-negative bacteria
  - Bacterial resistance develops slowly in a stepwise fashion
Adverse Reactions

- Haveles (p. 87)
  - GI effects
    - Anorexia, nausea, vomiting, diarrhea, gastroenteritis glossitis, stomatitis, xerostomia, and superinfection
  - Largely related to local irritation from alteration of flora

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Adverse Reactions

- Haveles (pp. 87-88)
  - Effects on teeth and bones
    - Tetracycline can produce permanent discoloration and enamel hypoplasia
    - Minocycline can cause black pigmentation of mandibular and maxillary alveolar bone and the hard palate

contin'd...

Adverse Reactions

- Haveles (p. 88)
  - Hepatotoxicity: incidence of liver damage increases with intravenous use
  - Nephrotoxicity: reported after use of old (degraded) tetracycline
  - Hematologic effects: uncommon; hemolytic anemia, leukocytosis, and thrombocytopenic purpura have been reported
  - Superinfection: an overgrowth of Candida albicans is especially prevalent in the compromised host

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Adverse Reactions

- Photosensitivity: patients taking tetracyclines who are exposed to sunlight sometimes react with an exaggerated sunburn
- Other effects: minocycline has been associated with CNS side effects
- Allergy: anaphylactic and various dermatologic reactions have occasionally occurred

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Drug Interactions

- Haveles (p. 88)
  - Cations: reduce intestinal absorption of tetracyclines by forming nonabsorbable chelates of tetracycline with calcium, for example
  - Enhanced effect of other drugs: tetracycline enhances the effect of the oral sulfonlureas
  - Reduced doxycycline effect: barbiturates and phenytoin can reduce the action of doxycycline
  - General antibiotic interactions: as with all antibiotics, tetracycline may reduce effectiveness of oral contraceptives or increase effectiveness of oral coagulants

Uses of Tetracyclines

- Haveles (pp. 88-89)
  - Extensive medical and dental use
  - Medical: rarely the drug of choice for a specific infection
    - Used to treat acne, pulmonary infections in patients with chronic obstructive pulmonary disease and traveler's diarrhea
  - Dental: often used for certain periodontal conditions
    - Concentrated in GCF
Examples of Tetracyclines

- Haveles (p. 87) (Table 7-6)
  - tetracycline (Sumycin)
  - tetracycline fibers (Actisite)
  - doxycycline caps (Vibramycin)
  - caps (Periostat)
  - gels (Atridox)
  - minocycline (Minocin)

clindamycin (Cleocin)

- Haveles (p. 89)
  - Bacteriostatic
    - Effective primarily against gram-positive organisms and anaerobic Bacteroides species
    - Derived from lincomycin; elaborated by Streptomyces lincolnensis, found in a soil sample near Lincoln, Nebraska

Pharmacokinetics

- Haveles (p. 89)
  - Absorption: oral is well absorbed; food does not interfere with absorption
  - Distribution: throughout most body tissues, including bone, but not the CSF
  - Excretion: in urine and feces (via bile)

Spectrum

- Haveles (p. 89)
  - Antibacterial spectrum includes many gram-positive and some gram-negative organisms
  - Antibacterial action results from interference with bacterial protein synthesis
  - Bacteriostatic, occasionally can be bactericidal at higher blood levels
  - Resistance develops in a slow, stepwise fashion
  - Cross-resistance between clindamycin and erythromycin is often noted

Adverse Reactions

- Haveles (p. 89)
  - GI effects
    - The most common side effects are GI, including diarrhea, nausea, vomiting, enterocolitis, and abdominal cramps
    - Can lead to pseudomembranous colitis (PMC), also known as antibiotic associated colitis (AAC)
      - Characterized by severe, persistent diarrhea and the passage of blood and mucus
  - Superinfection: C. albicans is sometimes associated with use of clindamycin
  - Other effects: adverse reactions involving formed elements of blood
  - Allergy: morbilliform (resembling measles) skin rashes
    - More severe reactions include urticaria, angioneurotic edema, erythema multiforme, serum sickness, and anaphylaxis

Adverse Reactions

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Uses

- Haveles (p. 89)
  - Indications are limited to infections caused by anaerobic organisms, especially *Bacteroides* species, and some staphylococcal infections when the patient is allergic to penicillin
  - The patients should be warned of the potential for pseudomembranous colitis and informed of its symptoms

metronidazole (Flagyl)

- Haveles (pp. 90-91)
  - An antiinfective with trichomonacidal, amebicidal, and bactericidal action
  - Exceptional against most obligate anaerobes such as *Bacteroides*
  - Inhibits nucleic acid synthesis leading to death of the organism
  - Also has antiinflammatory effects
    - Affects neutrophil motility, lymphocyte action, and cell-mediated immunity

Pharmacokinetics

- Haveles (p. 90)
  - Absorption: taken orally, it is well absorbed
  - Distribution: will travel into the CSF, saliva, and breast milk
    - Somewhat concentrated in GCF

Spectrum

- Haveles (p. 90)
  - Bactericidal
  - Effective against the protozoa *Trichomonas vaginalis* and *Entamoeba histolytica* and obligate anaerobic bacteria

Adverse Reactions

- Haveles (p. 90)
  - GI effects
    - Most common; involves nausea, anorexia, diarrhea, and vomiting
  - Central nervous system effects
    - Headache, dizziness, vertigo, ataxia (inability to coordinate muscle activity)
      - Confusion, depression, weakness, insomnia, and serious convulsive seizures are rarely associated

  - Renal toxicity
    - Cystitis, polyuria (excessive excretion of urine), dysuria (difficulty or pain in urination), and incontinence can occur
  - Oral effects
    - Dry mouth; often, an unpleasant or metallic taste has been noted
  - Other effects
    - Transient neutropenia in humans
      - Carcinogenicity, mutagenicity, and tumorigenicity in lower life forms have been reported
      - Administration for dental infections during pregnancy is contraindicated
Drug Interactions

- When alcohol is ingested with metronidazole, it can produce a mild form of the reaction that occurs when a recovering alcoholic drinks alcohol while taking disulfiram (Antabuse)
  - Symptoms include nausea, abdominal cramps, flushing, vomiting, and headache
- Metronidazole can potentiate the effect of warfarin

Uses

- Special usefulness because of its anaerobic spectrum
  - Medical
    - Treatment of trichomoniasis, giardiasis, amebiasis, and susceptible anaerobic bacterial infections
  - Dental
    - Useful in the treatment of periodontal infections
    - May be combined with amoxicillin

Cephalosporins

- Structurally related to penicillins
- Active against a wide variety of gram-positive and gram-negative organisms
- Isolated in 1948 from a fungus of genus Cephalosporium acremonium in a sewer outlet near Sardinia, Italy
- Those available for oral use are destroyed by cephalosporinase, an enzyme elaborated by some microorganisms

Pharmacokinetics

- Absorption: oral cephalosporins are well absorbed
- Distribution: widely distributed throughout tissues
- Excretion: by glomerular filtration and tubular excretion into the urine

Spectrum

- Bactericidal, effective against most gram-positive cocci, penicillinase-producing staphylococci, and some gram-negative bacteria
- The generation designates the width of antimicrobial action
  - Third-generation cephalosporins have the broadest spectrum of action

Mechanism of Action

- Similar to that of penicillins
  - Inhibit cell wall synthesis producing a deficiency in cell walls leading to lysis
Adverse Reactions

- GI effects
  - The most common adverse reaction, including diarrhea, nausea, vomiting, abdominal pain, anorexia (aversion to food), dyspepsia (gastric indigestion), and stomatitis
- Nephrotoxicity
  - May produce nephrotoxic effects under certain conditions; may be an allergic reaction
- Superinfection
  - As with all antibiotics, especially those with a broader spectrum of action

Cont'd...

Adverse Reactions

- Local reaction
  - Can produce localized pain, induration, and swelling when given intramuscularly
- Hemostasis and disulfiram-like reaction
  - With parenteral administration
- Allergy
  - Reported in approximately 5% of patients, including fever, eosinophilia, serum sickness, rashes, and anaphylaxis
  - Cross-hypersensitivity with penicillin is about 10%

Uses of Cephalosporins

- Haveles (p. 92)
- Indicated for infections sensitive to these agents but resistant to penicillin
- Especially useful in certain infections caused by gram-negative organisms

Cephalosporins

- Haveles (p. 91) (Box 7-3)
- First generation
  - cephalexin (Keflex)
  - cephradine (Velosel, Anspor)
  - cefadroxil (Duricef, Ultrasef)
- Second generation
  - cefaclor (Ceclor, Raniclor)
  - cefuroxime (Ceftin, Kefurox, Zinacef)
  - cefprozil (Cefzil)
- Third generation
  - cefixime (Suprax)
  - cefpodoxime proxetil (Vantin)
  - cefdinir (Omnicef)

Rational Use of Antiinfective Agents in Dentistry

- Haveles (pp. 92-93) (Fig. 7-5)
- The progression of most dental infections
  - The early phase, stage 1, is primarily gram-positive organisms
  - The mixed stage, stage 2, has both aerobes and anaerobes
  - The last stage, stage 3, is exclusively anaerobes

Stage 1

- Acute abscess and cellulitis are primarily the result of gram-positive organisms
  - The drug of choice is penicillin V for patients who are not allergic to penicillin
    - 500 mg every 6 hours for 5 to 7 days
  - Erythromycin ethylsuccinate or clindamycin for patients who are allergic to penicillin
Stage 2

- Infection is mixed; can be handled by attacking either the gram-positive organisms or the anaerobes
  - Gram-positive organisms can be managed with the same drugs as in stage 1
  - For anaerobes, an antibiotic with good anaerobic coverage is needed
    - The two antibiotics with the most anaerobic coverage are clindamycin and metronidazole
    - Penicillin V also has anaerobic coverage

Stage 3

- The organisms have coalesced into one area and are almost solely anaerobic
  - Most often, incision and drainage is sufficient
  - If chronic infection persists or the patient is immune compromised, use of antibiotic with anaerobic coverage is warranted

Rational Use of Antiinfective Agents in Dentistry

- When a prescribed antibiotic is not effective, the patient must be reevaluated to determine why
  - Patient compliance: they may not be taking the antibiotic
  - Ineffective antibiotic: may not be effective against the organism producing the infection
  - Poor debridement: dead tissue, purulent exudate, or foreign bodies were not removed from site of infection
  - Resistant organism: the organism may be resistant to the antibiotic chosen
  - Concentration did not reach the site of infection
  - Host defenses are inadequate

Antimicrobial Agents for Nondental Use

- Haveles (pp. 93-95)
  - Vancomycin
  - Aminoglycosides
  - Chloramphenicol
  - Sulfonamides
  - Sulfamethoxazole-trimethoprim
  - Nitrofurantoin
  - Quinolones (fluoroquinolones)

vancomycin (Vancocin)

- Haveles (p. 93)
- An antibiotic elaborated by Streptomyces orientalis found in soil samples from India and Indonesia
  - Unrelated to any other antibiotic currently marketed
  - Usually administered only intravenously for systemic effect
    - When used by mouth, it is being used to eradicate organisms within the GI tract

Spectrum of Vancomycin

- Haveles (p. 93)
- Bactericidal, has a narrow spectrum of activity against many gram-positive cocci
  - Inhibits bacterial cell wall synthesis
- Recently, vancomycin-resistant organisms have appeared
  - When bacterial resistance to antibiotics was uncommon, vancomycin was rarely used
  - After resistance to other antibiotics increased, use of vancomycin increased
  - This led to an increase in resistance to vancomycin
Adverse Reactions with Vancomycin

- Significant toxic reactions are infrequent except when vancomycin is given in large doses.
- With oral use, nausea, vomiting, and bitter taste may occur.
- With intravenous use, an erythematous rash on face and upper body has been reported (red man syndrome).
- Hypotension accompanied by flushing, chills, and drug fever are also associated with vancomycin.

Aminoglycosides

- In 1943, a strain of *Streptomyces griseus* was isolated that elaborated streptomycin.
- Further strains of *Streptomyces* have furnished additional antibiotics.
- Bactericidal and appear to inhibit protein synthesis and to act on the 30S subunit of the bacterial ribosome.

Pharmacokinetics of Aminoglycosides

- Poorly absorbed orally; must be administered intramuscularly or intravenously for a systemic effect.
- Used orally for their local effect within the intestines.

Spectrum of Aminoglycosides

- Bactericidal; have a broad antibacterial spectrum.
- Used primarily against aerobic gram-negative infections when other agents are ineffective.

Adverse Reactions of Aminoglycosides

- Adverse reactions limit their use in clinical practice.
  - Ototoxicity
    - Toxic to the eighth cranial nerve, which can lead to auditory and vestibular (in the ear) disturbances.
  - Nephrotoxicity
    - Can cause kidney damage by concentrating in the renal cortex.

Uses of Aminoglycosides

- Indicated for hospitalized patients with serious gram-negative infections.
  - Topical aminoglycosides are used to treat certain eye infections and skin infections.
Examples of Aminoglycosides

- Haveles (p. 93)
  - neomycin (Neo-Fradin, Neo-Rx)
  - gentamycin (Garamycin)
  - tobramycin (AK Tob, TOBI, Tobrex)
  - amikacin (Amikin)

chloramphenicol (Chloromycetin)

- Haveles (pp. 93-94)
  - A broad-spectrum, bacteriostatic antibiotic
  - Inhibits bacterial protein synthesis by acting primarily on the 50S ribosomal unit
  - Active against a large number of gram-positive and gram-negative organisms, ricketsiae, and some chlamydia
  - Fallen into disuse, serious adverse effects include fatal blood dyscrasias and bone marrow suppression

Sulfonamides

- Haveles (p. 94)
  - The first antibiotics that went on to pave the way for the antibiotic revolution

Mechanism of Action

- Haveles (p. 94) (Fig. 7-6)
  - The structural similarity between sulfonamide agents and para-aminobenzoic acid (PABA) is the basis for most of their antibacterial activity
  - Many bacteria are unable to use preformed folic acid, which is essential for their growth
  - They must synthesize folic acid from PABA
  - Sulfonamides competitively inhibit the bacterial enzyme that incorporates PABA into an immediate precursor of folic acid

Spectrum of Sulfonamides

- Haveles (p. 94)
  - Bacteriostatic against many gram-positive and some gram-negative bacteria
  - Used for otitis media in children, acute exacerbations of chronic bronchitis in adults, and urinary tract infections
  - Readily absorbed sulfonamides are used for systemic effects, poorly soluble sulfonamides act locally

Adverse Reactions of Sulfonamides

- Haveles (p. 94)
  - The most common side effect is an allergic skin reaction
  - May manifest as rash, urticaria, pruritus, fever, a fatal exfoliative dermatitis, or periarteritis nodosa
Uses of Sulfonamides

- No use in dentistry

sulfamethoxazole-trimethoprim (SMX-TMP)

- Haveles (pp. 94-95) (Fig. 7-6)
- Trimethoprim, an antibacterial and antimalarial agent, and sulfamethoxazole, a sulfonamide, are commonly used in combination
  - Inhibits two separate steps in the essential metabolic pathway of the bacteria, delaying resistance and leading to a synergistic effect
  - Bacteriostatic against a wide variety of gram-positive and some gram-negative bacteria

cont’d…

sulfamethoxazole-trimethoprim (SMX-TMP)

- Haveles (pp. 94-95)
- Most adverse reactions involve skin disorders
- Indicated in the treatment of selected urinary tract infections and selected respiratory and GI infections
- Pediatric patients may be taking it prophylactically for prevention of chronic ear infections

Most common adverse reactions are nausea, vomiting and diarrhea

Associated with many hypersensitivity reactions

Used in the treatment or prophylaxis of certain urinary tract infections

nitrofurantoin (Macrodantin)

- Haveles (p. 95)
- A wide antibacterial spectrum, including gram-positive and gram-negative bacteria
  - Bacteriostatic against many common urinary tract pathogens
  - Most common adverse reactions are nausea, vomiting and diarrhea
  - Associated with many hypersensitivity reactions
  - Used in the treatment or prophylaxis of certain urinary tract infections

quinolones (Fluoroquinolones)

- Haveles (p. 95)
- A group of orally effective antibacterial agents chemically related to nalidixic acid (NegGram)
  - Bactericidal against most gram-negative organisms and many gram-positive organisms
  - The first orally active agents against certain Pseudomonas species

cont’d…

quinolones (Fluoroquinolones)

- Haveles (p. 95) (Box 7-4)
- Mechanism of action involves antagonism of the A subunit of DNA gyrase; the enzyme is involved in DNA synthesis
  - DNA gyrase found only in microorganisms; human cells are unaffected by quinolones’ action

cont’d…
Pharmacokinetics of Quinolones

- Haveles (p. 95)
  - Ciprofloxacin is well absorbed orally
    - Both antacids and probenecid interfere with ciprofloxacin's absorption and serum concentration
    - Patients should be well hydrated to prevent crystalluria

Spectrum of Quinolones

- Haveles (p. 95)
  - Ciprofloxacin is bactericidal against a wide range of gram-negative and gram-positive organisms
    - Special spectrum is against Pseudomonas organisms
    - Unlike other antinfective agents, an additive action may result when ciprofloxacin is combined with other antimicrobial agents

Adverse Reactions of Quinolones

- Haveles (p. 95)
  - GI effects: nausea, diarrhea, vomiting, painful oral mucosa, bad taste, oral candidiasis, and pseudomembranous colitis
  - CNS effects: headache, restlessness, lightheadedness, and insomnia
  - Hypersensitivity: rash, pruritus, urticaria, hyperpigmentation, and edema of the lips
    - Associated with photosensitivity
    - cont'd...

Adverse Reactions of Quinolones

- Other effects: disturbed vision, joint pain, renal problems, and palpitations have rarely been reported
  - Associated with possibility of tendonitis and tendon rupture
  - Pregnancy and nursing: contraindicated in pregnant or nursing women

Uses of Ciprofloxacin

- Haveles (p. 95)
  - Indicated for lower respiratory tract, skin, bone and joint, and urinary tract infections
    - May be used for periodontal disease in the future
    - Their unique mechanism of action makes the development and transfer of resistance more difficult

Examples of Fluoroquinolones

- Haveles (p. 95) (Box 7-4)
  - Ciprofloxacin (Cipro)
  - Enoxacin (Penetrex)
  - Levofloxacin (Levaquin)
  - Lomefloxacin (Maxaquin)
  - Norfloxacin (Noroxin)
  - Ofloxacin (Floxin)
  - Sparfloxacin (Zagam)
  - Trovafloxacin (Trovan)
Antituberculosis Agents

- Haveles (pp. 96-97)
  - isoniazid
  - rifampin
  - pyrazinamide
  - ethambutol

cont’d…

Tuberculosis (TB) is caused by the acid-fast bacterium *Mycobacterium tuberculosis*.

Treatment is difficult for several reasons:

- Patients with TB often have inadequate defense mechanisms.
- Tubercle bacilli develop resistant strains easily and have long periods of inactivity when they are resistant to treatment.
- Most of the drugs available are not bactericidal and because of their toxicity often cannot be used in sufficient doses.
- People using antituberculosis agents often do not take them as prescribed.

Multidrug-resistant TB (MDR TB) has increased because of its spread in patients with human immunodeficiency virus and homeless patients.

cont’d…

Isoniazid (INH), rifampin, and pyrazinamide are combined for the treatment of pulmonary TB.

Bactericidal only against actively growing tubercle bacilli.

The mechanism of action may relate to inhibition of mycolic acid synthesis, resulting in disruption of the bacterial cell wall.

“Resting” bacilli exposed to the drug are able to resume normal growth when the drug is removed.

The incidence of all adverse reactions to INH is approximately 5%.

The most common adverse reaction (20% of patients who have a reaction) involves the nervous system.

- Includes peripheral and optic neuritis, muscle twitching, toxic encephalopathy, insomnia, restlessness, sedation, incoordination, convulsions, and even psychoses.

Hepatotoxicity: 1% of patients taking INH exhibit clinical hepatitis, and up to 10% develop abnormal laboratory values.
Uses of Isoniazid

- Haveles (p. 97)
- INH is used alone for prophylaxis or for converters (change in TB test results)

rifampin (Rifadin, Rimactane)

- Haveles (p. 97)
- A semisynthetic derivative of rifamycin, an antibiotic produced by *Streptomyces mediterranei*
  - The mechanism of action involves inhibition of DNA-dependent ribonucleic acid (RNA) polymerase, which suppresses initiation of chain formation

Pharmacokinetics of Rifampin

- Haveles (p. 97)
- Absorbed from the GI tract and eliminated in the bile, where enterohepatic circulation occurs

Adverse Reactions of Rifampin

- Haveles (p. 97)
- The most common adverse reactions are GI, including anorexia, stomach distress, nausea, vomiting, abdominal cramps, and diarrhea
  - Rifampin gives a red-orange color to body fluids

Uses of Rifampin

- Haveles (p. 97)
- Used in combination with other agents for treatment of TB
  - Used to treat meningococcal carriers prophylactically in and children exposed to *Haemophilus influenzae* meningitis

pyrazinamide (PZA)

- Haveles (p. 97)
- A relative of nicotinamide, well absorbed and widely distributed throughout the body
  - Hepatotoxic and can produce rash, hyperuricemia, and GI disturbances
  - Centers for Disease Control and Prevention recommends PZA for use during the first 2 months with INH and rifampin to treat TB
Treatment with Pyrazinamide

- Haveles (pp. 97-98) (Fig. 7-7)
- One treatment regimen includes use of isoniazid and rifampin every day for 9 to 12 months
  - Pyrazinamide is continued for 2 months
- If a patient is compliant and the organisms susceptible, the patient usually becomes noninfective within 2 to 3 weeks to 2 to 3 months

ethambutol (Myambutol)

- Haveles (p. 97)
- A synthetic tuberculostatic agent
  - Resistance develops rapidly when this drug is used alone
- The most important side effect is optic neuritis
  - Others include rash, joint pain, GI upset, malaise, headache, and dizziness

Examples of Antituberculosis Agents

- Haveles (p. 96) (Table 7-7)
  - isoniazid (INH, Laniazid)
  - rifampin (Rifadin, Rimactane)
  - rifapentine (Priftin)
  - pyrazinamide (PZA)
  - Rifater (isoniazid + rifampin + pyrazinamide)
  - ethambutol (Myambutol)
  - streptomycin

Topical Antibiotics

- Haveles (pp. 97-98)
  - In general, the use of topical antibiotics is discouraged
  - If an agent is used topically, it should be one that cannot be used systemically

Neomycin, Polymyxin, and Bacitracin

- Haveles (pp. 97-98)
  - A combination of an aminoglycoside, neomycin, and two polypeptide antibiotics, polymyxin and bacitracin available in ointment form (Neosporin)
  - Neomycin affects gram-negative organisms
  - Polymyxin and bacitracin affect gram-positive organisms

mupirocin (Bactroban)

- Haveles (p. 98)
  - A topical antibacterial produced by *Pseudomonas fluorescens*
  - Inhibits protein synthesis
  - Indicated for the topical treatment of impetigo
  - Can be used to treat the bacterial infection from streptococci or staphylococci that are occasionally present with angular cheilitis
  - Because angular cheilitis most commonly is a fungal infection, antifungal agents should be used first
Antibiotic Prophylaxis Used in Dentistry

- Haveles (pp. 98-100)
  - Prevention of infective endocarditis
    - Dental procedures
    - Cardiac conditions
    - Antibiotic regimens for dental procedures
  - Prosthetic joint prophylaxis
  - Noncardiac medical conditions

Prevention of Infective Endocarditis

- Haveles (p. 98)
  - “Prophylaxis for infective endocarditis is based on the concept that giving certain antibiotics to certain patients before certain procedures can prevent these patients from getting infective endocarditis”

Dental Procedures

- Haveles (pp. 98-99)
  - Organisms are more likely to enter the blood supply when dental treatment is rendered and cause bacteremia
    - Bacteremia is also produced when eating potato chips, brushing teeth, or chewing wax

Antibiotics Prophylaxis Used in Dentistry

- Haveles (p. 98)
  - Infective endocarditis is caused by an infection of the heart valves or endocardium with an organism
    - Often begins with sterile vegetative cardiac lesions consisting of amalgamations of platelets, fibrin, and bacteria
    - When bacteria are introduced into the bloodstream, they may infect the damaged valves

- Prevention of infective endocarditis
  - For every situation, three factors must be considered
    - The specific dental procedure
    - The cardiac and medical condition of the patient
    - The drug and dose that may be needed

- Dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa
  - No prophylaxis necessary
    - Routine anesthetic injections through uninfected tissue
    - Oral radiographs
    - Placement of removable prosthetic or orthodontic appliances
    - Adjustment of orthodontic appliances
    - Placement of orthodontic brackets
    - Shedding of deciduous teeth
    - Bleeding from trauma to the lips or oral mucosa
Cardiac Conditions

- Prophylaxis reasonable
  - Prosthetic cardiac valve
  - Previous infective endocarditis
  - 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 first 6 months after the procedure
    - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or device (which inhibit endothelialization)
  - Cardiac transplantation recipients who develop cardiac valvulopathy

- No prophylaxis necessary
  - Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD
    - Mitral valve prolapase
    - Rheumatic heart disease
    - Bicuspid valve disease
    - Calcified aortic stenosis
    - Congenital heart conditions
    - Ventricular septal defect
    - Atrial septal defect
    - Hypertrophic cardiomyopathy

Prophylactic Antibiotic Drug Regimens for Dental Procedures

- No allergies to penicillin or amoxicillin (oral)
  - Amoxicillin 2 g

- Allergic to penicillins or ampicillin and can take oral medication
  - Cephalexin*† 2 gm OR clindamycin 600 mg OR azithromycin or clarithromycin 500 mg
  - *Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric doses
  - † Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin

Prosthetic Joint Prophylaxis

- Recommended that patients with prosthetic joints receive antibiotic prophylaxis for 2 years after surgery
  - "Whether the use of antibiotics is indicated after the patient is 2 years postreplacement surgery should be determined by those involved most closely with the patient’s condition"

Noncardiac Medical Conditions

- Patients with noncardiac medical conditions may also require prophylactic antibiotic coverage before dental procedures, "but lack of agreement among practitioners for these situations causes confusion"