Pharmacology of Antimicrobial Agents

Lecture Outline

• General introduction - scope of the topic, basic concepts

• General principles of antimicrobial therapy

• Mechanisms of action of antimicrobials

• Pharmacology of individual agents

• General clinical considerations
The introduction of antimicrobials has revolutionized the practice of Medicine

“No other group of drugs has contributed more to the reduction of human suffering in the history of man”

“The introduction of antimicrobials into medical practice in the mid 1930’s heralded an era in which millions of people slated for early death or invalidism were spared”
Antimicrobials are among the most widely overused/misused of all therapeutic agents!

**Consequences**: high/unnecessary cost to the health care system and the development of microbial resistance

Examples of inappropriate use: antibacterial agents for **viral** illnesses, prescription without culture or sensitivity data, “routine” antimicrobial **prophylaxis** prior to surgery, use of **overly-broad spectrum** antibacterial agents as substitute for careful diagnosis, use of antibiotics in **animal feeds**
General introduction - scope of the topic – Antimicrobial (mis?)use in Dentistry

• “The routine use of antibiotics in dentistry, for example prophylactically for cleanings and for pre and post-surgical procedures, was the ADA standard of care for many decades and is still widespread today. Many natural health experts believe that dentistry is the medical discipline guilty of some of the most antibiotics abuse”. Mercola, 2016

• “Antibiotics are prescribed by dentists for treatment as well as prevention of infection. Indications for the use of systemic antibiotics in dentistry are limited, since most dental and periodontal diseases are best managed by operative intervention and oral hygiene measures. However, the literature provides evidence of inadequate prescribing practices by dentists, due to a number of factors ranging from inadequate knowledge to social factors”. Dar-Odeh, 2010

• “Our survey findings suggest that antibiotics are prescribed indiscriminately, inappropriately and injudiciously to manage the oral diseases. Dental diseases are predominantly because of local factors; mere removal of the local causative factors reduces the need for prescribing antibiotics considerably. Despite the awareness on antibiotic resistance, dentists show lack of concern in curbing this grave public health problem”. Karibasappa and Sujatha, 2014
General introduction - basic concepts

**Microbial resistance** - two different forms: **intrinsic** (“innate”) and **acquired** (“emergent”)

**Acquired (“emergent”) resistance:**

- spontaneous **random mutations** (microbes have **high turnover rates**) can lead to **partial** or **complete resistance** to antimicrobial agents
- **original** strain killed, **mutant** strain proliferates (“**natural selection**”)
General introduction - basic concepts

Possible mechanisms of antimicrobial resistance
General introduction - basic concepts

Some factors favoring development of “emergent” resistance to antimicrobials:

- indiscriminate overuse of antimicrobials
- inadequate dose/duration of therapy
- unnecessary antimicrobial prophylaxis
- unnecessary use of overly broad-spectrum agents (kill harmless bacteria and lead to overgrowth of resistant pathogenic organisms)
Pharmacology of Antimicrobial Agents

Lecture Outline

• General introduction - scope of the topic, basic concepts

• General principles of antimicrobial therapy

• Mechanisms of action of antimicrobials

• Pharmacology of individual agents

• General clinical considerations
General principles of antimicrobial therapy

• optimal response to antimicrobial agents requires a fully functional host defence system
• “natural” antibiotic is poly-morphonuclear leukocyte (or neutrophil) – “respiratory burst” destroys invading organisms
• when immune function impaired (disease- or drug-related), bacteriocidal agents (kill microorganism) more effective than bacteriostatic agents (only slow growth of microorganism)
General principles of antimicrobial therapy

Optimal antimicrobial therapy typically involves:

• organism identification (e.g., gram stain, morphology) and antimicrobial sensitivity testing

• use of antibacterial with narrowest spectrum of activity, at adequate dose and for appropriate duration

• use of oldest analogue in antibacterial class that retains activity against causative organism

• use of agents in combination (if needed) that differ in their mechanism of action for a synergistic effect
General principles of antimicrobial therapy

Selectivity of antimicrobial action:

- antimicrobials are among the most selective of all pharmacological agents – because of marked differences between “target” and “host” cells.

- selectivity of antimicrobial action can involve selective uptake of drug by sensitive organism (e.g., agents preferentially affecting protein synthesis in bacteria).

- selectivity may relate to biochemical differences between enzymes or cellular processes in the “target” versus the “host”.

- selectivity of action may relate to structural differences between sensitive versus resistant cells (e.g., Gram negative and Gram positive bacteria differ in outer surface characteristics).
General principles of antimicrobial therapy

Selectivity of antimicrobial action (cont’d):

Gram positive bacterium

Gram negative bacterium
Pharmacology of Antimicrobial Agents

Lecture Outline

- General introduction - scope of the topic, basic concepts
- General principles of antimicrobial therapy
- Mechanisms of action of antimicrobials
- Pharmacology of individual agents
- General clinical considerations
Mechanisms of action of antimicrobials

Disinfectants/Antiseptics versus Antimicrobials?

**Disinfectants/Antiseptics** (e.g., alcohol, iodine, chlorine, ozone) used for the sterilization of **surfaces** (e.g., skin, diagnostic instruments, surgical spaces) and destroy microorganisms **non-selectively**

**Antimicrobial agents** (for **internal** use) act **selectively** by interfering with vital cellular processes involved in maintaining the growth and/or the viability of microorganisms
Disinfectants/Antiseptics

**Chlorhexidine**: a disinfectant/antiseptic (e.g. 0.12% chlorhexidine-gluconate solution used as mouthwash)

- **mode of action**: non-specific disruption of microbial cell membranes
- **antimicrobial spectrum**: many Gm \(^{+}\)ve and Gm \(^{-}\)ve bacteria, as well as fungi
- **main use**: treatment/prevention of gum diseases (e.g. gingivitis, periodontitis) – effects on dental caries controversial
- **adverse**: long-term use can cause staining of teeth/dentures, as well as altered taste – usually reversible upon discontinuation
Antimicrobials: Mechanisms of action

Antimicrobial agents can act by:

• interference with bacterial cell wall formation
• alteration of cell membrane integrity
• interference with nucleic acid metabolism/function
• interference with protein synthesis
• acting as “anti-metabolites”
Pharmacology of Antimicrobial Agents

Lecture Outline

• **General introduction - scope of the topic, basic concepts**

• **General principles of antimicrobial therapy**

• **Mechanisms of action of antimicrobials**

• **Pharmacology of individual agents**

• **General clinical considerations**
Pharmacology of individual agents

Agents acting on bacterial cell wall:

Penicillins (bactericidal)

- bacterial cells contain high amounts of solutes and are prevented from osmotic rupture by the rigid, highly cross-linked structure of the cell wall (external to the membrane)
- the β-lactam structure common to all penicillins essential for antibacterial activity
- penicillins inhibit transpeptidsase (TP) enzyme involved in cross-linking of polymeric strands comprising cell wall → cells swell and undergo autolysis
Agents acting on bacterial cell wall (cont’d)

- bacterial cell wall polymers of N-acetyl muramic acid (NAM) contain a pentapeptide terminating in two D-alanine residues

- this is the site of cross-linking by TP which is inhibited by penicillin
Agents acting on bacterial cell wall (cont’d)

- Molecular mechanism of penicillin inhibition of TP?

The β-lactam ring of penicillin is isosteric with the D-alanine-D-alanine moiety and competes for binding to TP → inhibition of cross-linking.
Agents acting on bacterial cell wall (cont’d)

- **penicillins** also bind to (and **activate**) proteins mediating cell **autolysis** → completion of **cell destruction**

- **penicillinase** cleaves β-lactam ring and destroys antibacterial activity
Agents acting on bacterial cell wall (cont’d)

• variations in the \( R \) substituent determine the various subclasses of penicillin

• nature of \( R \) group determines:
  - antibacterial spectrum
  - susceptibility to degradation by acid in stomach (and :: effectiveness when given by oral route)
  - susceptibility to inactivation by penicillinase
Agents acting on bacterial cell wall (cont’d)

Class 1: “narrow spectrum” - penicillin G (pen V - chemically modified analogue - acid resistant ∴ more orally effective)

• active mainly against non-penicillinase-producing Gm +ve organisms (e.g., streptococci, pneumococci, clostridia) and some Gm-ve bacteria (e.g., gonococci, meningococci)

• staphylococci are usually insensitive, since most produce penicillinase (especially hospital strains)

• pen V is the agent of choice of treatment of most odontogenic infections
Agents acting on bacterial cell wall (cont’d)

Class 2: “penicillinase resistant” (methicillin first one developed – now replaced by orally effective cloxacillin, dicloxacillin, flucloxacillin)

- acid-stable (∴ effective on oral administration)

- use restricted to treatment of infections by penicillinase-producing strains of staphylococci (N.B. not as effective as pen G or V for other infections)

- emergence of methicillin-resistant strains of staph aureus (MRSA) particularly ominous!
Agents acting on bacterial cell wall (cont’d)

Class 3: “broad spectrum” ampicillin (parenteral), amoxicillin – an acid resistant analogue that is well absorbed following oral administration)

- **NOT** penicillinase-resistant
- combination with clavulanic acid (a β-lactam ring-containing inhibitor of penicillinase) increases effectiveness in penicillinase-producing organisms
- **Augmentin®** – contains amoxicillin and clavulanic acid – widely used preparation
Agents acting on bacterial cell wall (cont’d)

Class 3: “broad spectrum” penicillins (cont’d)

- active against several Gm $^{+ve}$ organisms but major use: infections by Gm $^{-ve}$ bacteria (H. influenzae, Neisseria gonorrhoeae, Neisseria meningitidis, Proteus mirabilis, Salmonella, Shigella and E. coli)

- cross blood-brain barrier: useful in treatment of meningitis – but many strains resistant due to overuse of amoxicillin

- amoxicillin is an agent of choice in acute necrotising ulcerative gingivitis
Toxicity of penicillins:

- **penicillins**: highly selective in their action (our cells do not have cell walls!)
- toxicity relates to “**chemical**” features of molecule
- **penicillins** are the **most allergenic** class of antimicrobial
- opening of “**strained**” β-lactam ring → covalent attachment to proteins → **allergic response** to modified protein now recognized as “**foreign**”
Agents acting on bacterial cell wall (cont’d)

Toxicity of penicillins (cont’d)

- opening of “strained” β-lactam ring → covalent attachment to proteins – allergic response to modified protein now recognized as “foreign”
- it is best to assume that allergy to one penicillin = allergy to all analogues
Agents acting on bacterial cell wall (cont’d)

Cephalosporins (bactericidal)

- broad spectrum antimicrobials containing the \(\beta\)-lactam ring of the penicillins
- \(\beta\)-lactam ring can be cleaved by \(\beta\)-lactamases produced by resistant strains of bacteria
- some (\(\approx 10\%\)) cross-reactivity between penicillin allergy and cephalosporin allergy
Agents acting on bacterial cell wall (cont’d)

- the Cephalosporins are classified as first generation (oldest), second, third, fourth, etc.

*“first generation”* (e.g. cephalaxin) - active against Gm\(^{+ve}\) bacteria but limited activity against Gm \(^{-ve}\) species

*“second generation”* (e.g. cefuroxime) – some resistance to inactivation by β-lactamases

*“third generation”* (e.g. ceftibuten) increased resistance to inactivation by β-lactamases
Agents acting on bacterial cell wall (cont’d)

Cephalosporins (cont’d)

“fourth generation” (e.g. cefclidine) increased activity against Gm⁻ve bacteria

“fifth generation” (e.g. ceftaroline) only β-lactam effective against methicillin-resistant Staphylococci aureus (MRSA)

dental applications? lack of advantage over other agents and cost preclude routine use of cephalosprins for most dental infections
Agents acting on bacterial cell wall (cont’d)

Newer agents related to β-lactam antimicrobials (all bactericidal)

**Carbapenems** - e.g. Imipenem – very broad spectrum – used i.v. for serious infections by resistant organisms - low cross-allergenicity with penicillin

**Monobactams** – e.g. Aztreonam – very active against Gm –ve organisms, no cross-allergenicity with penicillins
Mechanisms of action of antimicrobials

Antimicrobial agents can act by:

- interference with bacterial cell wall formation
- alteration of cell membrane integrity
- interference with nucleic acid metabolism/function
- interference with protein synthesis
- acting as “anti-metabolites”
Pharmacology of individual agents

Agents affecting cell membrane integrity

**Antifungal polyenes** e.g., nystatin

- forms a complex with **ergosterol** (stabilizer of fungal cell membrane) - membrane disruption and cell death

- **use in Dentistry**: treatment of *Candida albicans* (yeast) infections in the mouth – including thrush and denture stomatitis

- **preparations**: “swish and spit” mouth rinse, lozenges or ointment (used for denture stomatitis)
Pharmacology of individual agents

Agents affecting cell membrane integrity

Antifungal imidazoles  e.g., miconazole
(other agents include ketoconazole, fluconazole)
• act by inhibiting synthesis of ergosterol
  → membrane disruption and cell death
• use: treatment of yeast infections in mouth, stomach and intestine – also fungal infections of the skin, including tinea pedis (“athlete’s foot”), and tinea corporis (“ringworm“)
• preparations: miconazole (Monostat®, Daktarin® oral gel),
  ketoconazole (Nizoral®), fluconazole (Diflucan®)
Mechanisms of action of antimicrobials

Antimicrobial agents can act by:

- interference with bacterial cell wall formation
- alteration of cell membrane integrity
- interference with nucleic acid metabolism/function
- interference with protein synthesis
- acting as “anti-metabolites”
Agents interfering with nucleic acid metabolism and/or function

**DNA gyrase inhibitors:** Ciprofloxacin (bactericidal)

- **Ciprofloxacin** inhibits gyrase enzyme controlling DNA uncoiling/recoiling during DNA and mRNA synthesis
- “Cipro” used to treat urinary and intestinal infections, as well as infections of the lungs, skin, bones and joints
- **Dental uses:** used to treat certain mouth or periodontal diseases – may be used to effectively treat rare dental infections caused by the *Enterobacteriaceae*
Pharmacology of individual agents

Agents interfering with nucleic acid metabolism and/or function

Inhibition of RNA polymerase:
Rifampin (bactericidal)

• Inhibits RNA polymerase and prevents transcription of RNA from DNA template → protein synthesis inhibited

• Rifampin – use largely restricted to treatment of tuberculosis
Pharmacology of individual agents

Agents interfering with nucleic acid metabolism and/or function

**Inhibition of mitosis: Griseofulvin**

- binds to **tubulin** in microtubules of fungal cells → inhibition of **spindle** formation → inhibition of **mitosis**
- used to treat fungal infections of skin and nails
- preferential binding of griseofulvin to microtubules of **cancer cells** (relative to “healthy” cells) may have **therapeutic potential** (in combination with other antineoplastic agents)
Agents interfering with nucleic acid metabolism and/or function

Degradation of DNA: Metronidazole (bactericidal)

- preferentially taken up by anaerobic bacteria → converted to reactive metabolite → DNA strand breakage and destabilization of the DNA helix

- no effect on aerobic bacteria or human cells

- dental applications: metronidazole (Flagyl®) efficacious in treating: acute ulcerative gingivitis, pericoronitis, certain periapical infections, some cases of osteomyelitis and infected socket - may be of use in chronic progressive periodontitis where anaerobes are implicated as pathogens
Mechanisms of action of antimicrobials

Antimicrobial agents can act by:

• interference with bacterial cell wall formation
• alteration of cell membrane integrity
• interference with nucleic acid metabolism/function
• interference with protein synthesis
• acting as “anti-metabolites”
Pharmacology of individual agents

Antimicrobials inhibiting protein synthesis

Summary of steps in protein synthesis

- binding of t-RNA containing triplet nucleic acid base codon to amino acid
- binding of t-RNA containing amino acid to corresponding codon on ribosome-associated m-RNA (for DNA-determined sequence of amino acids in chain)
- peptide bond formation to link amino acids (catalyzed by peptidyl transferase)
- movement of growing peptide chain along ribosome unit
Antimicrobials inhibiting protein synthesis

**Aminoglycosides** (bactericidal)

- **Streptomycin** - first analogue of this class – introduced in 1940’s - newer agents followed (e.g., gentamicin, tobramycin, spectinomycin)

- resistance due to gradual induction of inactivating enzymes ∴ newest analogues most active

- bind to 30s ribosomal subunit and interfere with binding of t-RNA, causes “misreading” of the code

- **bactericidal** action (most protein synthesis inhibitors are only bacteriostatic) may involve additional action to disrupt cell membrane

- aminoglycosides actively accumulated by aerobic organisms ∴ anaerobes resistant
Antimicrobials inhibiting protein synthesis

**Aminoglycosides (cont’d)**

- **Aminoglycosides** (AG) primarily used for infections involving *aerobic, gram-negative* bacteria (e.g., Pseudomonas, Acinetobacter, Enterobacter, and some Mycobacteria - including the bacteria that cause tuberculosis (AG were first drugs to effectively treat TB)

- **AG** sometimes used in combination with a *penicillin* for *synergistic* effect in serious (e.g., blood stream) infections

- major limiting toxicites of AG: *renal damage* and *ototoxicity* (damage to nerves to inner ear → vestibular and hearing impairment)
Antimicrobials inhibiting protein synthesis

**Tetracyclines (bacteriostatic)**

- introduced as “miracle drugs” in 1948 – **broad antibacterial spectrum** – but widespread development of resistance
- **mode of action**: bind to 30s ribosome subunit and prevent binding of t-RNA to m-RNA
- effective against: Chlamydia, Rickettsia (e.g. typus fever), brucellosis and spirochetal infections (e.g., Lyme disease)
Antimicrobials inhibiting protein synthesis

**Tetracyclines** (cont’d)

- **main medical uses**: infections of respiratory tract, sinuses, middle ear, urinary tract

- **dental applications**: tetracyclines concentrate in the gingival fluid - used to treat gingivitis and gum disease - also used to treat acute necrotizing ulcerative gingivitis – but *metronidazole, clindamycin* or *amoxicillin-clavulanate* (Augmentin) preferred

  tetracyclines also **reduce inflammation** and **block collagenase** (destroys connective tissue and bone) - it may be these two actions which contribute most to periodontal protection

- tetracyclines chelate *calcium* and deposit in *teeth and bones* – use in pregnancy or in infants can → **permanent staining of teeth**
Antimicrobials inhibiting protein synthesis

**Chloramphenicol (bacteriostatic)**

- **mode of action:** binds to 50s ribosomal subunit and prevents linking of amino acids via peptide bond formation by inhibiting peptidyl transferase
- “broad” spectrum of activity – acts on Gm\(^+\)ve and Gm\(^-\)ve bacteria, including anaerobic organisms
- readily crosses the blood-brain barrier
- **main medical uses:** treatment of brain abscesses caused by *Staphylococci* (or when causative organism unknown), treatment of *meningitis* (involving Neisseria meningitidis, Streptococcus Pneumoniae or Haemophilus influenzae) in individuals with penicillin allergy
  - also useful to treat infections caused by vancomycin-resistant enterococcus ("VRE")
Antimicrobials inhibiting protein synthesis

Chloramphenicol (cont’d)

Toxicities:

• 1 in 24,000–40,000 risk of potentially fatal aplastic anemia (unpredictable!) – risk **highest** with oral admin, **lowest** with eye drops

• **Gray Baby Syndrome**: immaturity of glucuronyl transferase in newborn → impaired inactivation of chloramphenicol (risk greatest with iv administration)

Symptoms include hypotension, cyanosis and cardiovascular collapse – usually preventable by adjusting drug dose
Antimicrobials inhibiting protein synthesis

**Clindamycin (bacteriostatic)**

- **mode of action**: binds to 50s ribosomal subunit and blocks translocation of growing peptide chain

- **antibacterial spectrum**: – aerobic Gm\(^{+ve}\) cocci (e.g., staphylococci, streptococci but NOT enterococci), and anaerobic Gm \(^{-ve}\) rods (e.g., Bacteroides, Fusobacterium)

- **main medical uses**: infections by above bacteria – especially in patients with penicillin allergy; used topically to treat acne
Antimicrobials inhibiting protein synthesis

**Clindamycin** (cont’d)

- **dental applications**: Clindamycin is very effective in treating dental infections – it is well absorbed (90%), and achieves high concentrations in gingival fluid - clindamycin penetrates deeply into the soft tissues of the body, as well as bone, where dental infections reside

- **major toxicity**: pseudomembranous colitis - due to overgrowth of *Cl. difficile* (resistant to clindamycin) – condition can be fatal – oral vancomycin can provide effective treatment of colitis (may need to be repeated)
Antimicrobials inhibiting protein synthesis

**Macrolides** *(bacteriostatic)*

*(erythromycin - clarithromycin is a more acid-stable analogue)*

- **mode of action**: binds to 50s ribosomal subunit of 70s complex, prevents binding of amino acid-linked to t-RNA to template, blocks peptide elongation

- **antibacterial spectrum**: similar to penicillin (mainly Gm\(^+\)ve organisms) but Staph usually resistant

- **main medical use**: alternative to penicillin in patients with proven penicillin allergy, respiratory infections (e.g., Mycoplasma pneumonia)
Antimicrobials inhibiting protein synthesis

Macrolides (cont’d)

- **dental applications**: Erythromycin has been used to treat mild, acute odontogenic infections in penicillin-allergic patients

- **major toxicity**: gi disturbance – due to activation of motilin receptors in gut
Mechanisms of action of antimicrobials

Antimicrobial agents can act by:

- interference with bacterial cell wall formation
- alteration of cell membrane integrity
- interference with nucleic acid metabolism/function
- interference with protein synthesis
- acting as “anti-metabolites”
Antimicrobials acting as antimetabolites

**Acyclovir** (antiviral)

- structural analogue ("antimetabolite") of purine nucleoside guanosine
- inactive parent drug (a “pro-drug”) is converted to monophosphate by viral thymidine kinase → further phosphorylation by host cell kinases to acyclovir triphosphate → inhibition of viral “reverse transcription”
- “reverse transcription” involves synthesis of double-stranded DNA from viral DNA (e.g. herpes) or RNA (e.g. retroviruses) templates
**Antimicrobials acting as antimetabolites**

**Acyclovir** (antiviral)

- structural analogue ("antimetabolite") of purine nucleoside guanosine

- active against sensitive strains of **herpes simplex virus** (e.g., cold sores) – but has low activity against **cytomegalovirus**

- inactive parent drug (a “pro-drug”) is converted to **monophosphate** by viral **thymidine kinase** → further phosphorylation by host cell kinases to **acyclovir triphosphate** → incorporation into viral DNA → viral DNA synthesis halted

- “reverse transcription” involves synthesis of double-stranded DNA from viral DNA (e.g.
Antimicrobials acting as antimetabolites

**Acyclovir (cont’d)**

**Viral infection and replication**

**Mode of action of acyclovir**

**Retrovirus replication**
Antimicrobials acting as antimetabolites

**Acyclovir** (cont’d)

- affinity of acyclovir triphosphate for viral reverse transcriptase orders of magnitude greater than that for corresponding host enzyme (DNA polymerase)
  
  ⊳ acyclovir has **high selectivity** and **low toxicity**

- resistance to acyclovir is **rare** – but can occur as a result of mutations in viral transcriptase leading to markedly reduced affinity for acyclovir triphosphate

- **commonly used oral preparations:** acyclovir (Zovirax®), famciclovir (Famvir®) and valacyclovir (Valtrex®).
Antimicrobials acting as antimetabolites

**Sulfonanamides (bacteriostatic)**

- sulfonamides were the first chemicals ever used to treat bacterial infections
- **Mechanism of action:** “sulfa” drugs are structural analogues of p-amino-benzoic acid (PABA) – a component of folic acid (an essential B vitamin) – they block folate synthesis by acting as PABA antagonists

- folic acid is a **essential co-factor** for certain enzymes involved in production of the nucleic acid base **thymidine** and in the synthesis of the amino acid **methionine**
Antimicrobials acting as antimetabolites

**Sulfonanamides** (cont’d)

- **two steps** in the formation of **tetrahydrofolate** (the active form of folic acid) are targets of **antimicrobial action**:  
  - the incorporation of PABA is blocked by **sulfonamides**, and **trimethoprim** inhibits the enzyme converting dihydrofolate to active **tetrahydrofolate** (the **active** form)

- the **synergistic** action of a “sulfa” and **trimethoprim** is exploited in two widely used commercial preparations containing both **sulphamethoxazole** and **trimethoprim**:  
  **Bactrim®** and **Septra®**
Antimicrobials acting as antimetabolites

Sulfonanamides (cont’d)

- **basis of sulfonamide selectivity**: sensitive bacteria must synthesize their own folic acid - resistant bacteria and host cells can use pre-formed folate.

- **antibacterial spectrum**: originally active against many Gm +ve and Gm −ve organisms (NOT Group A streptococci), but resistance now widespread.

- bacteria resistant to a sulfonamide alone may respond to the combination of a “sulfa” and trimethoprim.

- **major clinical use**: infections of urinary tract (“sulfas” concentrated in urine), upper respiratory tract and ear – **dental use** of sulfonamides is minimal.
Antimicrobials acting as antimetabolites

Sulfonanamides (cont’d)

Adverse effects

- hypersensitivity (allergic) reactions common – may be delayed – usually starts 2-8 weeks after initiating therapy
- contraindicated in late pregnancy, in neonates and in breast feeding mothers: - risk of kernicterus

Mechanism of kernicterus development: in neonate, levels of bilirubin high (breakdown of fetal hemoglobin and immaturity of glucuronyl transferase), binding of bilirubin to plasma albumin reduced by competition with sulfonamide → increased levels of unbound bilirubin – crosses blood-brain barrier incompletely developed in neonate) → → → brain damage
Antimicrobials

Overview of antibacterial spectra of activity
Pharmacology of Antimicrobial Agents

Lecture Outline

- **General introduction - scope of the topic, basic concepts**
- **General principles of antimicrobial therapy**
- **Mechanisms of action of antimicrobials**
- **Pharmacology of individual agents**
- **General clinical considerations**
Some clinical issues re: use of antimicrobials in Dentistry

Antimicrobial prophylaxis and dental surgery

• unnecessary antimicrobial prophylaxis has been a significant factor in development of bacterial resistance

• prophylaxis most effective when directed at specific organisms, at a time when risk of infection known to be high

• use of antimicrobial prophylaxis prior to certain dental procedures in patients at risk more dictated by “legal” concerns rather than proof of benefit (which is lacking!)
  - indeed, it has been suggested that risks (adverse effects of antimicrobial) far outweigh potential benefits!
Antimicrobial prophylaxis (cont’d)

Procedures that can produce bacteremia and where prophylaxis may be indicated

• procedures where significant oral bleeding and/or exposure to potentially contaminated tissue is anticipated

• these may include dental extractions and other oral surgery, subgingival scaling and the sub-gingival placement of dental dam clamps, restorations or orthodontic bands

• simple adjustment of orthodontic appliances, tooth brushing or spontaneous loss of primary teeth should not require antibiotic prophylaxis
Antimicrobial prophylaxis (cont’d)

Conditions for which antibiotic prophylaxis was previously recommended include:

- previous episode of **bacterial endocarditis**
- **heart valve replacement** or recent surgical repair of cardiovascular defects (within 6 months)
- **rheumatic heart disease** or other acquired heart disease
- **hypertrophic cardiomyopathy**
- **congenital heart disease** (e.g., ventricular septal defects (unrepaired), patent ductus arteriosus, coarctation of the aorta, tricuspid valve disease, aortic stenosis)
- **mitral valve prolapse** with mitral insufficiency, regurgitation, and/or holosystolic murmur, post-mitral valve surgery
- patients with drug/disease-related **immunodeficiency**
Currently recommended indications for prophylaxis – ADA 2015

• Compared with previous recommendations, there are currently relatively few patient subpopulations for whom antibiotic prophylaxis may be indicated prior to certain dental procedures.

• In patients with prosthetic joint implants, a 2014 systematic review states, “In general, for patients with prosthetic joint implants, prophylactic antibiotics are not recommended prior to dental procedures to prevent prosthetic joint infection.”

• For patients with a history of complications associated with their joint replacement surgery who are undergoing dental procedures that include gingival manipulation or mucosal incision, prophylactic antibiotics should only be considered after consultation with the patient and orthopedic surgeon; in cases where antibiotics are deemed necessary, it is most appropriate that the orthopedic surgeon recommend the appropriate antibiotic regimen and, when reasonable, write the prescription.
Currently recommended indications for prophylaxis – ADA 2015 (cont’d)

- Infective endocarditis prophylaxis for dental procedures should be recommended only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from infective endocarditis (see “Patient Selection,” in the main text). For patients with these underlying cardiac conditions, prophylaxis is recommended for all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa.

Currently recommended prophylaxis regimens

**Standard regimen:** Amoxicillin 2 grams orally 1 hour before procedure

**Unable to take oral medications:** Ampicillin 2 grams im or iv 30 minutes before procedure

**Allergic to penicillin:** Clindamycin 600mg orally 1 hour before or Cephalexin 2 grams 1 hour before or Azithromycin or Clarithromycin 500mg 1 hour before

**Unable to take oral meds and allergic to penicillin:** Clindamycin 600mg IV 30 minutes before procedure or Cefazolin 1 gram im or iv 30 minutes before procedure
Antimicrobials and pregnancy

- many antimicrobials used in dentistry (e.g., penicillins, clindamycin, erythromycin, cefotaxime, cefazolin) have been deemed safe by FDA, metronidazole - probably safe
- tetracyclines should be avoided (can damage liver in pregnancy and cause permanent staining of baby’s teeth)
- sulfonamides should be avoided (risk of kernicterus, and evidence for birth defects)

Note: physiologic changes (e.g., increases in blood volume and GFR) that occur in pregnancy may lead to lower serum concentrations following “standard” doses of antimicrobials
Drug interactions involving antimicrobials

- erythromycin, clarithromycin and metronidazole, and certain antifungal agents (e.g., ketoconazole and itraconazole) can result in potentially life-threatening interactions with a number of drugs whose metabolism (by competition or inhibition at level of cytochrome P_450 enzymes in liver) is impaired by the antimicrobial agent

- purported interference of antimicrobials with effectiveness of oral contraceptives (as a result of impaired “salvage” by bacterial enzyme-mediated “enterohepatic recirculation”) unproven – may be a “rare” event not picked up by clinical trials – should discuss with patient