

IDSA Guidelines for Preclinical Microbiology and Infectious Diseases

Frederick Southwick, M.D., Peter Katona, M.D., Carol Kauffman, M.D., Sara Monroe, M.D., Liise-anne Pirofski, M.D., Carlos del Rio, M.D., Harry Gallis, M.D., and William Dismukes, M.D.

Key Facts and Concepts in Microbiology and Infectious Diseases

Viral Infections

Editorial comment: A major problem for most of the viruses is that many have similar clinical presentations, making case-based teaching somewhat more difficult. But examples of viruses primarily attacking different organ systems may prove helpful. Also distinct skin rashes should be shown to allow the students to become familiar with characteristic skin lesions of measles, small pox, chicken pox (varicella), rubella, and herpes simplex and other human herpes viruses.

1. Structure and Classification

A. Nucleic acid – multiple forms

- RNA viruses
 - Single stranded + RNA (polio, West Nile)
 - Single stranded – RNA requires viral RNA polymerase to synthesize + mRNA (influenza, measles)
 - Double stranded RNA requires viral RNA polymerase (rotavirus)
 - Single stranded +RNA to DNA incorporated into host cell genome, requires a viral reverse transcriptase (retroviruses, HIV)
- DNA viruses, with the exception of pox viruses all require host RNA polymerase
 - Single-stranded DNA (parvoviruses)
 - Double stranded linear DNA viruses (herpesviruses, adenovirus)
 - Double stranded circular DNA (hepadnaviruses, papillomaviruses)

B. Capsid formation

2. Life cycles and Pathogenesis – review of different strategies used by viruses

- Enveloped
 - Matrix (M) protein
 - Spike formation
 - Budding
- Nonenveloped
 - Apoptosis
 - Cell lysis

3. Epidemiology

- Secretions: aerosolization, hand to mucous membranes
- Transcutaneous
- Fecal-oral
- Sexual
- Hematogenous (blood transfusions, needle sticks)

- Arthropodborne
4. **Sites of infection and types of disease caused**
 - Respiratory tract
 - Gastrointestinal tract and liver
 - Skin
 - Nervous system
 5. **Host Responses to viral infections and strategies for evasion**
 - Toll-like receptor response to viral RNA, DNA or glycoproteins
 - Cell mediated immune response MHC, NK cells
 - Antibody
 - Interferons
 - Complement
 6. **Specific Viruses**
 - **RNA viruses**
 - Orthomyxovirus (influenza)
 - Paramyxovirus (mumps, measles, RSV)
 - Reovirus (rotavirus)
 - Picornavirus (polio, hepatitis A, coxsackie, ECHO, enterovirus 72, rhinovirus)
 - Caliciviridae (norwalk)
 - Togavirus (rubella)
 - Arenavirus (lymphocytic choriomeningitis, Lassa fever)
 - Flavivirus (dengue, hepatitis C, yellow fever)
 - Retroviruses (HIV-1, HIV-2, HTLV)
 - Needs to be covered in greater detail than other viruses
 - Tropism for lymphocytes, macrophages, and effects on the immune system
 - Inaccuracy of reverse transcriptase and implications for therapy
 - Diagnosis: use of ELISA, monitoring using viral load, CD4 count, mutation analysis
 - Associated opportunistic infections
 - Anti-retroviral therapy
 - Nucleotide reverse transcriptase inhibitors (NRTI)
 - Nonnucleoside reverse-transcriptase inhibitors (NNRTI)
 - Protease inhibitors
 - Inhibitors of viral fusion
 - Bunyavirus (California encephalitis, Hantavirus)
 - Rhabdovirus (rabies)
 - Filovirus (Ebola, Marburg) (see arenavirus above)
 - Coronavirus (SARS)
 - **DNA viruses**
 - Adenovirus
 - Papovavirus (papillomavirus)
 - Parvovirus (B19)
 - Herpesvirus (HSV, VZ virus, CMV, EBV, human herpes 6,7)
 - Poxvirus (smallpox virus, Vaccinia virus)

- Hepadnavirus (hepatitis B)
- Polyomavirus

For each virus review:

- Structure
- Replication
- Pathogenesis and virulence factors (Give one or two examples, and ask students to pick an additional virulence factor for one of the viruses and provide experimental evidence for its potential role in virulence)
- Epidemiology and modes of spread
- Clinical disease syndromes
- Virus-host interactions
- Diagnosis
 - clinical
 - specific laboratory
 - tissue culture
- Treatment with antiviral agents
(covered in more detail in anti-infective section except antiretrovirals which should be covered with discussion of HIV)
- Vaccines

Gram positive bacteria

Editorial Comment: These bacteria can be also be covered under organ system infections. For example for the Gram positive organisms: ENT infections can be used to introduce *S. pyogenes* and other Streptococci, *Corynebacterium diptheriae*, and Actinomycosis; Pulmonary infections - *S. pneumoniae*, Legionella, Bordetella; Endocarditis and intravascular device infections - viridans streptococci, Enterococcus, Coagulase neg. Staph; CNS infections – Listeria, Nocardia, *S. pneumoniae*, Soft tissue infections - *S. aureus*, *S. pyogenes*, Clostridia; Bone and joint – *S. aureus*

1. General Structure and Growth

- Teichoic acid
- Peptidoglycan synthesis
- Polysaccharides
- Flagellum and bacterial chemotaxis, quorum sensing
- Pili and bacterial adhesion
- Bacterial growth and division
- Sporulation and germination

2. Virulence factors and pathogenesis

- Toxins and their mechanisms of action
 - Anthrax: Lethal factor, Edema Factor, Protective Antigen
 - Bordetella pertussis – adenylate cyclase toxin AB, pertussis toxin, tracheal cytotoxin

- Clostridium – botulinum toxin AB (*C. botulinum*), cytotoxin AB (*C. difficile*), alpha-toxin, beta toxin & enterotoxin (*C. spp*), tetanus toxin (*C. tetani*)
 - Corynebacterium diphtheriae – diphtheria toxin AB
 - Legionella – cytotoxin
 - Listeria – listeriolysin
 - Staph aureus – alpha toxin, beta toxin, Panton-Valentine leukocidin, epidermolytic toxins, superantigen Toxic-shock syndrome toxin (TSST-1), enterotoxin superantigens
 - Strep. pneumoniae – pneumolysin
 - Strep. pyogenes – pyrogenic exotoxins A, B, C, streptolysin O
- B. Enzymes important for virulence
- Staph aureus – catalase, coagulase and clumping factor, proteinases, hyaluronidase, lipases, staphylokinase)
 - S. pneumoniae – IgA proteases
 - Strep pyogenes – streptokinase, streptodornase, hyaluronidase
 - Clostridia - hyaluronidases
- C. Cell wall components causing disease – Thick polysaccharide capsule anti-phagocytic in *S. pneumoniae*, *S. pyogenes*, Gp B Strep, *Staph. aureus*,
- Staph aureus* – Protein A
 - Strep pneumoniae – capsular polysaccharide & Quellung reaction
 - Strep pyogenes – M protein and rheumatic fever
 - Viridans Strep – dextran and extracellular polysaccharides role in adherence to dental enamel and damaged cardiac valves
- D. Biofilms – *Staph aureus* and Coag-neg *Staph* exopolysaccharide matrix

3. Classification

- A. Gram positive cocci: enterococcus, Streptococcus (Lancefield groups) and viridans group, *S pneumoniae* (lancet-shaped diplococci, Optochin sensitivity), Staphylococcus
- B. Endospore-forming gram-positive rods: Bacillus, Clostridia
- C. Nonsporulating gram positive rods – Listeria
- D. Irregular, nonsporulating, gram positive rods – Actinomyces, corynebacterium

4. Role of Virulence factors in Major Diseases caused by Gram positive bacteria

Editorial Comment: The students should not be asked to memorize lists of virulence factors. One to two virulence factors per organ system should be sufficient. The emphasis should be on understanding the concept of virulence factors and their potential to explain many of clinical manifestations of bacterial infections. To improve understanding, each student should be asked to pick one virulence factor and provide supporting experimental evidence to support its role as a true virulence factor. An

alternative is to cover these toxins and organisms in association with specific organ infections as noted above.

A. Bacterial pharyngitis

Strep. pyogenes – pathogenesis of rheumatic fever and glomerulonephritis
(recommended virulence factor: M protein (S pyogenes))

Corynebacterium diphtheriae –
(recommended virulence factor: diphtheria toxins)

B. Dental infections – Viridans Strep, anaerobic strep, actinomycosis
(Recommended virulence factor: dextran (S. viridans))

C. Pneumonia –

S. pneumoniae - colonization nasopharynx, lack of toxins and proteases,
confined to anatomic lobes by fissures, role of IgG and spleen
(Recommended virulence factor: polysaccharide capsule)

B. pertussis – whooping cough
(Recommended virulence factor: pertussis toxin or adenylate cyclase toxin AB)

D. Sinus Infections – S. pneumonia, anaerobic and microaerophilic strep
(No virulence factors predisposing to sinus infection known)

E. Endocarditis and vascular devices –

- Native valve: S. viridans, S. aureus, , enterococcus

- Prosthetic valve: add coagulase negative staph

- Vascular devices: S. aureus, coag. neg. Staphylococcus, enterococcus

(Recommended virulence factors: dextran, extracellular polysaccharides,
and/or biofilm genes)

F. Meningitis – importance of bacteremia for community-acquired. Review how bacteria get into the blood stream

– Community - S. pneumoniae, S. aureus, Listeria (immunocompromised) –
Nosocomial, post-neurosurgery – enterococcus and S. aureus

(Recommended virulence factor: Pneumococcal surface protein C)

- Ventricular-peritoneal shunts – coagulase neg. Staph (similar to vascular device)

G. Soft tissue infections

- cellulitis: S. aureus, S. pyogenes

- necrotizing fasciitis – S. pyogenes, anaerobic strep

[Recommended virulence factors: Pantan-Valentine leukocidin, (methicillin resistant S. aureus), streptokinase, streptodornase, hyaluronidase (S. pyogenes)]

- myonecrosis – Clostridia perfringens and C. septicum

[Recommended virulence factor: alpha toxin (C. septicum & perfringens)]

G. Bone, joint infections

Primarily - *S. aureus*

Prosthetic joints – Coagulase negative Staph and *S. aureus* (virulence factors same as vascular devices)

H. Toxic shock syndrome – *S. aureus* and *Strep pyogenes*

[Recommended virulence factor: Toxic-shock syndrome toxin (TSST-1, *S. aureus*)]

Gram Negative bacilli

Editorial Comment: The basic facts about Gram-negatives can be introduced in the organ systems. Sepsis: introduce LPS and other structural components; Respiratory – *H. influenzae*, *Klebsiella*, *Pseudomonas*, *Serratia*, *Acinetobacter*; Urinary tract infections – *Enterobacteriaceae*, *Klebsiella*, *Proteus*, *Pseudomonas*; Sexually transmitted diseases – *Neisseria gonorrhoea*, anaerobes; Gastroenteritis – *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *E. coli* strains, *Vibrios*; Peptic ulcer disease – *Helicobacter*; CNS – *Neisseria meningitidis*; Zoonotic infections - *Pasteurella*, *Brucella* and *Francisella*;

1. General Structure

A. Outer membrane (exclude hydrophilic compounds)

- O-antigens, K-antigens,

- Porins

B. Lipopolysaccharide (LPS) (linkage by divalent cations)

- Lipid A & ketodeoxyoctanoic acid (KDO)

- Lipooligosaccharides (*Neisseria*)

C. Lipoprotein

D. Periplasmic space

E. Flagella and chemotaxis, H-antigens

F. Pili (fimbriae) and adherence

G. Bacterial growth and division

2. Virulence factors

A. Exotoxins

- *E. coli* – heat-labile and heat stable enterotoxin, cytotoxin (Verotoxin, a shiga-like toxin)

- *Pseudomonas* – exotoxin A, Type III cytotoxins

- *Shigella* – Shiga toxin

- *Vibrio cholerae* – Cholera toxin ABS

- *Yersinia* – heat stable enterotoxin, Type III cytotoxins

- *Helicobacter* - VacA

B. Enzymes and other virulence proteins

- Hemolysins

- Pseudomonas - Elastases, proteases, heat-labile phospholipase C, heat-stable glycolipid
- Shigella – Ipa proteins, IcsA (VirG)
- Helicobacter - cagA

C. Cell wall components

1. Endotoxins (Lipid A)

- Toll-like receptors
- Cytokines IL-1, TNF-alpha
- Complement activation
- Macrophage activation
- Lymphocyte activation
- Shock (see sepsis)

2. Pili and adherence to specific cells and mucous (pseudomonas)

- P- pilus in E. coli
- Bundle forming pilus in Enteropathogenic E. coli

3. Classification

A. Enterobacteriaceae

- Growth characteristics
- Lactose fermenters vs nonfermenters
- Nucleic acid sequencing

B. Pseudomonads

- Growth characteristics
- oxidase positive
- mucoid colony formation and pigment formation
- rRNA homology groups
- antibiotic resistance more common

C. Anaerobes: Bacteroides species

- Growth characteristics
- Usually part of polymicrobial infections

D. Vibrios, Campylobacters, Helicobacter (cover under systems)

E. Haemophilus, Bordetella, Brucella, Francisella (cover under systems)

F. Yersinia and Pasteurella (cover under systems)

G. Neisseria species (cover under systems)

1. Role of Virulence Factors in Major Disease caused by Gram-negative bacilli

Editorial Comment: Provide one example of a contributing virulence factor for each anatomic site. As an exercise have students pick another candidate virulence factor, and provide supporting evidence (See Gram positive bacteria virulence factors).

A. Community-acquired Pneumonia and Tracheobronchitis

- H. influenzae (COPD)
- Klebsiella (alcoholics)
- Pseudomonas (cystic fibrosis patients & COPD)

[Recommended virulence factor pili for adherence to mucous (Pseudomonas) or elastase (Pseudomonas)]

B. Nosocomial pneumonia

- Pseudomonas, Burkholderia cepacia, Stenotrophomonas
- Klebsiella
- Serratia, Acinetobacter,

C. Gastroenteritis

[Recommended virulence factor: Cholera toxin (Vibrio), bundle forming toxin (EPEC), verotoxin (EHEC), Shiga toxin (Shigella) or IcsA (Shigella); possibly choose two or three]

D. Peptic ulcer disease – Helicobacter pylori
(Recommended virulence factors: VacA and/or CagA)

D. Urinary Tract Infection

[Recommended virulence factor: hemolysin (UTI) or P-pilus (E. coli & pyelonephritis)]

E. Soft tissue infection

- Ecthyma gangrenosa
- Burns

(Recommended virulence factor: Pseudomonas flagellin in burns)

Intracellular and other unusual bacteria

Editorial Comment: These organisms lend themselves best to being covered as part of organ system infections: Acute Respiratory – Chlamydia, Mycoplasma; Chronic Respiratory - Tuberculosis and atypical mycobacteria cover M. leprae here as well; CNS – Listeria; STDs: Treponeme pallidum, Mycoplasma, Chlamydia; Zoonotic infections –Rickettsia, Ehrlichia, Anaplasma, Borrelia, Leptospirosis;

1. Mycobacterium Tuberculosis

A. Pathogenesis

- a. Slow growing, aerobic, acid fast bacterium
- b. Mycolic Acids
- c. Cord factor
- d. Other virulence factors

- e. Live intracellularly in monocytes, reticuloendothelial cells, giant cells

B. Immune response and pathology

- a. Acquired cellular immunity
- b. Antibody response
- c. Tuberculin skin test (PPD, used for detection of individuals who have been infected with TB)
- d. Pathology of granulomas, caseating necrosis

C. Epidemiology

- a. Humans only reservoir
- b. Spread by microdroplets (respiratory precautions critical)
- c. Cavitory disease and laryngeal most infectious
- d. High risk groups Immigrants, alcoholics, urban poor, single males, men who have sex with men, prisoners, HIV patients

D. Clinical Manifestations

- a. Primary tuberculosis - pulmonary
- b. Miliary tuberculosis (disseminated); extrapulmonary
- c. Reactivation tuberculosis

E. Diagnosis

- a. CXR: cavities, bronchopneumonia in primary disease & HIV
- b. Sputum smear, correlation with infectiousness
- c. Culture of body fluid or tissue: Lowenstein Jensen, PCR

F. Treatment

- a. Concept of probability of resistance $1/10^6$ (Cavitory Disease 10^9-10^{10})
- b. Requirement of more than one drug, 4 drug regimen because of resistance
- c. Multi-drug resistant TB (MDR TB); extensively drug-resistant TB (XDR TB)
- d. Basic antituberculosis drugs: INH, Rifampin, Pyrazinamide, Ethambutol
- e. Importance of Directly Observed Therapy (DOT)

G. Prevention

- a. PPD placement and interpretation
- b. Prophylaxis recommendations

2. Mycobacterium Leprae

(A rare disease, but illustrates how the immune system can alter the clinical manifestations of a disease)

A. Pathogenesis and immune response

- a. Lepromatous reaction
- b. Tuberculous reaction

B. Epidemiology – person-to-person spread by respiratory or nasal discharge

C. Clinical manifestations

- a. Facial changes
- b. Neuropathy

3. Atypical mycobacteria

A. Organisms of Clinical Importance

- a. Rapid growers: *M. abscessus*, *M. fortuitum*, *M. chelonae*
- b. Intermediate growers: *M. marinum*, *M. goodii*
- c. Slow growers: *M. avium* complex, *M. kansasii*,

B. Epidemiology:

- a. Spread from the environment
- b. Person-to-person transmission not known to occur

C. Clinical Manifestations

- a. Pulmonary disease
- b. Skin and soft tissue infections
- c. Bone and joint infections

Other intracellular pathogens

1. *Listeria monocytogenes* (only *Listeria* spp that is a human pathogen)

A. Pathogenesis

- a. Life cycle; Strategy of entry, escape to the cytoplasm, use of actin to move in the cell, formation of filopodia, cell to cell spread
- b. Virulence factors: ActA induces actin-based motility, Internalins induce phagocytosis, allow *Listeria* to spread without contact with extracellular fluids (can antibody and complement)
- c. Strictly controlled by cell-mediated immunity; increased risk transplant patients

B. Epidemiology:

- a. Grows at room temperature and 4°C, grows on refrigerated food,
- b. Foodborne transmission
- c. Infects the immuno-compromised host

C. Clinical Manifestations

- a. Bacteremia
- b. Meningoencephalitis (see meningitis)

2. *Rickettsia* (*R. rickettsii*, *R. africae*, *R. akari*, *Coxiella burnetii*)

A. Pathogenesis

- a. Gram-negative like cell wall with peptidoglycan-containing muramic acid and lipopolysaccharide
- b. Grow in different parts of the cell: typhus cytoplasm, spotted fever group nucleus, Coxiella cytoplasmic vacuoles

B. Epidemiology

- a. Except for *C. burnetii* transmitted by arthropods
- b. Coxiella endospore structures survive prolonged periods outside of cells, can become airborne

C. Clinical manifestations

- a. Fever
- b. Generalized systemic complaints (Headache, muscle aches)
- c. Hemorrhagic vasculitic skin lesions

3. Ehrlichia (*E. chaffeensis*, *Anaplasma phagocytophilum*)

A. Pathogenesis

- a. Small gram-negative bacteria, not seen on Gram stain, seen on Giemsa stain
- b. Intracellular vacuoles in monocytes (*E. chaffeensis*) and neutrophils (*A. phagocytophilum*) form morulae

B. Epidemiology: Humans acquire from ticks

C. Clinical manifestations

- a. Fever
- b. Generalized systemic complaints
- c. Low platelet count, neutropenia (*Anaplasma*)

4. Chlamydia (*C. trachomatis*, *C. pneumoniae*, *C. psittaci*)

A. Pathogenesis

- a. Cell wall gram-negative like, but no typical peptidoglycan, Giemsa stain positive
- b. Obligate intracellular pathogens cannot synthesize ATP
- c. Elementary body (extracellular infectious form), reticulate body (intracellular replicative form), major outer membrane protein, can cause persistent infection

B. Epidemiology

- a. Spread person to person, airborne for *C. pneumoniae*
- b. Mother to infant for *C. trachomatis*
- c. Sexually transmitted for *C. trachomatis*
- d. Airborne bird excreta for *C. psittaci*

C. Clinical manifestations

- a. Atypical pneumonia (*C. pneumoniae* or *C. psittaci*)
- b. Conjunctivitis (*C. trachomatis*)
- c. Pelvic inflammatory disease (*C. trachomatis*)

Unusual Bacteria

1. Mycoplasma (*M. pneumoniae*, *Ureaplasma urealyticum*)

A. Pathogenesis and virulence

- a. An extracellular bacteria, the smallest free-living organism that can self-replicate on cell-free laboratory media
- b. Pleomorphic, sterol containing unit membrane,
- c. Possesses proline-rich adherence molecules and binds with high affinity for mammalian cell membranes
- d. Generates hydrogen peroxide and superoxide causing cytotoxicity
- e. Attracts mononuclear cells and induces antigen antibody responses

B. Epidemiology

- a. Person to person spread

C. Clinical manifestations

- a. Respiratory infections (*M. pneumoniae*)
- b. Urogenital infections (*Ureaplasma urealyticum*)

2. Spirochetes focus on *Treponema Pallidum*

(See Zoonotic infections for Leptospirosis and Lyme disease)

A. Pathogenesis

- a. Structure – slender corkscrew (0.1-0.2 μm x 20 μm), outer sheath glycosaminoblycan, outer membrane peptidoglycan. Endoflagella
- b. Cannot be cultured in vitro
- c. Invasion through skin to bloodstream, little known about virulence factors
- d. Host develops antibodies directed against the surface proteins

B. Epidemiology

- a. Sexually transmitted
- b. Cross the placenta congenital infection
- c. 28,000 cases/yr US

C. Clinical Manifestations

- a. Primary syphilis – genital chancre
- b. Secondary syphilis – rash, adenopathy, mucosal lesions
- c. Tertiary (late) syphilis: neurosyphilis, cardiovascular, gummas

d. Congenital syphilis

D. Diagnosis

- a. Nontreponemal tests RPR, VDRL
- b. Specific treponemal test FTA-abs
- c. CSF analysis

Fungal Diseases

Editorial Comment: These pathogens often have a pulmonary component, but also disseminate and cause multi-system disease. Best covered as group rather than by organ systems. The concept of endemics vs opportunists should be emphasized. Certain specific pathogens can be reemphasized in the organ system section.

1. The differences between fungi and bacteria:

- A. Cell volume
- B. Nucleus
- C. Cytoplasmic membrane (ergosterol in fungi)
- D. Metabolism
- E. Dimorphism
- F. Reproduction

2. Fungal growth and morphology

- A. Yeast forms multiply by budding off blastoconidia. Mold forms grow by developing septate or nonseptate hyphae.
- B. Mycelium is an intertwined mass of hyphae.
- C. Vegetative mycelium acts as a root.
- D. Aerial mycelium bears reproductive structures.
- E. Pseudohyphae differ from true hyphae in having recurring bud-like constrictions and less rigid cell walls.

3. Reproduction

- A. Asexual conidia arise directly from hyphae or on a stalk-like structure, the conidiophore.
 - Microconidia and macroconidia indicate size and complexity.
 - Chlamydoconidia or arthroconidia develop within the hyphae.
- B. Most common sexual spore is an ascospore.
- C. Dimorphic fungi, including several human pathogens
 - yeast form in infected tissue
 - mold form in their environmental reservoir (e.g., soil) and in laboratory cultures at ambient temperatures.

4. **Virulence factors (examples) and Pathogenesis**

- A. Surface adhesins on *Candida* species; these require a receptor on mucosal or epithelial cells. (intravascular device infections)
- B. Proteases and elastases facilitate invasion.
- C. Large hyphae also facilitate invasion; these resist ingestion and killing by neutrophils and macrophages.
- D. Antiphagocytic properties, e.g., the spherule of *C. immitis* and the polysaccharide capsule of *C. neoformans*.

5. **Classification** – Clinically important fungi usually grouped based on types of tissue they infect and the diseases they produce, rather than on principles of basic mycologic taxonomy.

A. **Superficial fungi** called dermatophytes, cause indolent lesions of skin and appendages.

- Three genera of dermatophytes:
 - Epidermophyton
 - Microsporum
 - Trichophyton
- Special propensity to invade and destroy keratin.
- Transmission by person-to-person route or by contaminated inanimate objects.

B. **Chronic subcutaneous fungal diseases** - usually enter the skin or subcutaneous tissue by traumatic inoculation with contaminated material. Disease occasionally extends into lymphatic system.

- Sporothrichosis caused by *Sporothrix schenckii*

C. **Systemic fungal diseases** (systemic mycoses).

- **Endemic mycoses** - restricted to specific geographic areas.
 - **Blastomycosis** caused by *Blastomyces dermatitidis*. Principal geographic areas – midcentral USA and Canada.
 - **Histoplasmosis** caused by *Histoplasma capsulatum*. Principal geographic areas – south central and midwestern USA, especially along river basins (Mississippi R., Tennessee R., Ohio R., St Lawrence R.)
 - **Coccidioidomycosis** caused by *Coccidioides immitis* (found only in California) and *C. posadasii* (found elsewhere). Principal geographic areas – semiarid regions of southwestern USA, Central America and South America.

- **Opportunistic mycoses** - mainly develop in immunocompromised hosts, e.g., steroid treated patients, transplant recipients, HIV/AIDS patients, and patients with malignancies.
 - **Candidiasis** - *Candida albicans* commonly infects intravascular devices
 - **Cryptococcosis** – the most common fungal disease involving the central nervous system, e.g., meningitis and meningoencephalitis.
 - **Aspergillosis** caused by a number of *Aspergillus* spp. including *A. fumigatus* (the most common species) and *A. flavus*. Cause invasive aspergillosis, allergic bronchopulmonary aspergillosis, and pulmonary aspergilloma (a fungal ball which develops in an existing lung cavity).
 - **Zygomycosis** caused by several different species of order Mucorales. Cause thrombosis, infarction, and necrosis of infected organs, including the sinuses, central nervous system, and lungs.
 - **Pneumocystosis** is most often observed in severely compromised HIV/AIDS patients, but may develop in any immunosuppressed patients. The organism, formerly called *Pneumocystis carinii* and now called *Pneumocystis jirovecii*, is an extracellular pathogen which exists in two distinct forms: trophozoites and cysts, which are usually present as a tight mass in lung and other infected sites.

6. Relationship of host status to fungal disease

<u>Alteration in Host Defense</u>	<u>Opportunistic Fungal Disease(s)</u>
A. Interruption of mechanical barriers or indwelling foreign bodies. Examples: intravascular catheters, artificial heart valves, pacemakers, prosthetic joints.	Candidiasis (candidemia)
B. Granulocyte dysfunction (quantitative or qualitative). Example: neutropenia associated with chemotherapy or bone marrow transplant.	Aspergillosis Zygomycosis Candidiasis
C. Depressed cell-mediated immunity. Examples: solid organ transplant recipients, steroid therapy, AIDS.	Candidiasis(mucosal disease) Coccidioidomycosis Cryptococcosis Histoplasmosis Pneumocystosis

7. Diagnosis of systemic mycoses

- A. Culture of tissues, blood, and other body fluids is mainstay.
- B. Histopathology of tissues with special stains can provide presumptive diagnosis.
- C. Skin tests – no role.
- D. Serologic tests.
 - Most sensitive and specific tests:
 - Cryptococcosis – latex agglutination for antigen
 - Coccidioidomycosis – CF or immunodiffusion (ID) for Ab
 - Histoplasmosis – EIA for antigen
 - Aspergillosis – EIA for galactomannan antigen
- D. Molecular methods – largely investigational at this time and do not need to cover.

Parasitic infections

Editorial Comment: These nonfungal eukaryotic human pathogens are best taught as groups of pathogens with similar morphology and life cycles. The life cycles need to be taught, because they help to explain the epidemiology, as well as the clinical manifestations of these diseases.

For each parasite the epidemiology, life cycle, clinical manifestations, diagnosis and treatment should be covered; specific issues that should be emphasized are in parenthesis)

1. Blood protozoa
 - A. Plasmodium species (differences in life cycles of *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*, host genetic determinants of susceptibility, chloroquine-resistance)
 - B. Babesia (risk factors for severe disease)
2. Tissue protozoa
 - A. Leishmania (visceral, cutaneous, and mucosal; problem of HIV and visceral disease)
 - B. *Trypanosoma cruzi* (Chagas' diseases)
3. Intestinal helminthes
 - A. Hookworm (iron deficiency)
 - B. Ascaris (malabsorption and malnutrition)
 - C. Strongyloides (persistence of infection and hyperinfection syndrome in the immunocompromised host; filarial forms seen in stool.
 - D. Enterobius (scotch tape test)
4. Tissue and Blood helminths
 - A. Trichinella (problem of raw pork)
 - B. Echinococcus (massive liver and lung cysts)
 - C. Cysticercosis (problem of seizures and CNS disease)
 - D. Schistosomiasis (importance of fresh water snails, granulomatous reactions to eggs)
 - E. Microfilaria (eosinophilia, lymphatic obstruction)
 - F. Onchocerciasis and River blindness
 - G. *Toxoplasma gondii* and toxoplasmosis (problem in HIV patients, pregnant women)
5. Travel medicine – prevention for tourists, in addition to Malaria, includes preventative measures for Hepatitis A, Meningococcal disease, Yellow fever, and traveler's diarrhea

Anti-infective Agents

Editorial Comment: Antimicrobial therapy is often taught as part of Pharmacology. The committee felt that the concepts of resistance, mechanisms of action, and the strategies for utilizing antibiotics would best be taught in Microbiology and Infectious diseases, while pharmacokinetics, toxicity and dosing could be taught in Pharmacology. The specific antibiotics can be covered in an overview and then reinforced for each organ system infection.

1. Bacterial genetics, resistance gene transfer, and biochemical mechanisms of antimicrobial resistance

- A. Bacterial genome
 - Single circular or less commonly linear double-stranded DNA
 - Pathogenicity islands and operons
 - Supercoiling, DNA gyrase & topoisomerase I
 - DNA polymerase function
 - Protein synthesis (ribosomes, RNA polymerase, initiation, elongation)
- B. Mechanism of transferring bacterial resistance
 - Point mutations
 - Conjugation (plasmids)
 - Transduction (bacteriophages)
 - Transformation (transposons)
- C. Biochemistry of microbial resistance
 - Enzymatic degradation and modification
 - o beta-lactamases
 - o esterases
 - o acetyltransferases
 - o phosphorylation and adenylation
 - Reduction in bacterial antibiotic concentration
 - o Interference with antibiotic entry: porin mutations
 - o Efflux pumps: Gram-negative bacilli also Staphylococci and Streptococci (fluoroquinolones, macrolides, tetracyclines)
 - Modification of the antibiotic target
 - o Alterations in cell wall precursors: VanA gene (VRE)
 - o Alterations in target enzymes: Penicillin binding proteins (S. pneumoniae, and MRSA for beta-lactam antibiotics): DNA gyrase (Gram-negative bacilli for fluoroquinolones)
 - o Alterations in Ribosomal binding site (tetracyclines, macrolides, aminoglycosides)

2. Factors that Determine Anti-infective Agent Dosing

A. MIC and MBC

B. Pharmacokinetics

- Time above MIC ($T > MIC$) importance for beta-lactam antibiotics
- Area under the curve in relationship to MIC (AUC/MIC)
- Peak concentration in relationship to MIC (C_{max}/MIC)
- Concepts of concentration killing and post antibiotic-effect (aminoglycosides and quinolones)
- Mechanisms of antibiotic clearance, half-life determinations and adjustments for renal and hepatic dysfunction

3. Basic strategies for administering antibiotics

A. Concept of broad and narrow-spectrum antibiotics

B. Steps for choosing an antibiotic

- Decide whether or not the patient has a bacterial infection (importance of not using antimicrobial agents for viral infections)
- Make a statistical guess as to the likely organism depending on the site of infection and whether community or hospital acquired
- Cover with broad-spectrum antibiotics initially until cultures results are available, particularly in very ill patients
- Take into account susceptibility patterns in hospital & community
- Take into account host factors (immunocompromised, elderly, severity of illness)
- Use the fewest drugs possible
- Switch to narrower spectrum antibiotics within 3 days
- Pick the most cost-effective approach

C. Colonization versus infection: How do you differentiate?

4. Specific Antibiotics

Editorial comment: The students should become familiar with the specific generic names of the antibiotics and the concepts of narrow spectrum versus broad spectrum. The choice of specific antibiotics to cover infections at different anatomic sites should also be emphasized.

A. Beta-lactam antibiotics

- Structure of penicillin and cephalosporins, principles of how side chains (R groups) alter absorption, clearance and spectrum
- Mechanism of action, penicillin-binding proteins and effects on transpeptidases, carboxypeptidases etc.
- Toxicity primarily allergic reactions
- Resistance – PBP mutations, *MecA* gene
- Pharmacokinetics: $t_{1/2}$ life and mechanisms of clearance

- Indications – emphasis on narrow-spectrum when possible
- Penicillins
 - PCN-G
 - Ampicillin
 - Oxacillin, methicillin, nafcillin
 - Carboxy and Ureidopenicillins
- Cephalosporins
 - 1st generation: cefazolin
 - 2nd generation: cefoxitin, cefotetan, cefuroxime
 - 3rd generation: ceftriaxone, cefotaxime, ceftazidime
 - 4th generation cefepime
 - Monobactam: aztreonam
- Carbapenems
 - Imipenem
 - Meropenam
 - Ertapenam
- Aminoglycosides
 - Structure of aminoglycosides
 - Mechanism of action, positive charge effects, ribosomal binding interference with translation, concentration-dependent killing
 - Toxicity major concern, nephrotoxicity and ototoxicity
 - Resistance – modifying enzymes, alteration ribosomal binding site, reduced transport into the bacteria
 - Pharmacokinetics: Importance of corrections for renal dysfunction, once per day dosing
 - Specific drugs: gentamicin, tobramycin, amikacin
- Macrolides and Ketolides
 - Structure and mechanism of action, ribosomal binding inhibits protein synthesis. Ketolides have two ribosomal binding sites effective against PCN-resistant *S. pneumoniae*
 - Toxicity: stimulate bowel motility, hypersensitivity, prolonged QT interval, telithromycin- high incidence of serious hepatotoxicity
 - Resistance – cross-resistance for some penicillin resistant *S. pneumoniae*
 - Pharmacokinetics: Hepatic metabolism, cytochrome P450

- Specific drugs: erythromycin, clarithromycin, azithromycin
- Fluoroquinolones
 - Structure and mechanism of action inhibit DNA gyrase, topoisomerase
 - Toxicity: arthropathy due to cartilage damage, not recommended for children,
 - Resistance – alterations in gyrase, activation of efflux pumps
 - Pharmacokinetics: renal clearance, moxifloxacin partial hepatic clearance
 - Specific drugs: ciprofloxacin, levofloxacin, moxifloxacin
 - Indications –
- Glycopeptides
 - Structure and mechanism of action: binding to D-alanine-D-alanine of peptidoglycan precursor
 - Toxicity: red man syndrome, nephrotoxicity
 - Resistance: VanA gene, VRE
 - Specific drugs: vancomycin, teichoplanin
 - Indications: MRSA
- Other Agents
 - Oxazolidinones – Linezolid
 - Daptomycin
 - Doxycycline
 - Clindamycin
 - Trimethoprim-sulfamethoxazole
 - Rifamycin
 - Metronidazole

5. Antifungal agents

A. Fungal wall synthesis versus mammalian membranes, sterols

B. Polyenes - Amphotericin B

- Structure and mechanism of action: binds to ergosterol
- Toxicity: nephrotoxicity, fever
- Resistance – alterations in sterol structure alterations
- Pharmacokinetics: slow degradation
- Different preparations: conventional deoxycholate, lipid complex, and liposomal

- Indications

C. Azoles

- Structure and mechanism of action: decreased production of ergosterol
- Toxicity: minimal except voriconazole: changes in light perception and drug-drug interactions due to alterations cytochrome P450-dependent metabolism pathway
- Resistance – alterations in sterol structure alterations
- Pharmacokinetics: primarily hepatically metabolized
- Specific drugs: fluconazole, itraconazole, voriconazole, posaconazole
- Indications in very general terms:

D. Echinocandins

- Structure and mechanism of action: semisynthetic lipopeptide that blocks synthesis of β (1,3)-d-glucan, critical to cell wall integrity (the PCN of anti-fungal agents).
- Specific drugs: caspofungin, micafungin, anidulafungin
- Effective for *Aspergillus* and *Candida*

6. Antiviral agents other than antiretrovirals

A. Acyclovir, valacyclovir, famciclovir:

- Structure function: synthetic analogue of guanine in which a side chain has been substituted for a sugar moiety. Requires phosphorylation by viral thymidine kinase forming a monophosphate compound
- Toxicity: mental status changes
- Resistance: viral thymidine kinase mutation
- Pharmacokinetics: hepatic metabolism
- Indications – HSV1 and 2, *Zaricella zoster* (high dose)

B. Ganciclovir, valganciclovir

- Similar structure and function to acyclovir, but higher intracellular concentration: effective against CMV
- Toxicity: granulocytopenia, mental status changes
- Resistance: viral thymidine kinase mutation
- Indications – CMV

D. Agents effective against Influenza virus

- Amantadine and Rimantadine – viral resistance a growing problem
- Neuraminidase inhibitors

INFECTIOUS DISEASES BY ORGAN SYSTEM

Sepsis (Could introduce the basics of Gram positive and Gram negative organisms here)

1. Definitions

- SIRS
- Sepsis
- Severe sepsis
- Septic shock

2. Pathogenesis

- Bacterial factors
 - Cell wall products
 - Secreted factors
- Host responses to infection
 - Innate Immune response
 - Toll-like Receptors
 - Cytokine and Pro-Inflammatory Mediator Production
- Mechanisms underlying septic shock
 - Cytokine storm
 - Coagulation activation
 - Complement activation
 - Endothelial damage, DIC, end organ damage

3. Clinical Manifestations

- By organ system

4. Diagnosis

- SIRS criteria
- Common lab abnormalities

5. Therapy

- Supportive care
- Empiric antibiotic selection
- Anti-inflammatory drugs
- Anti-coagulation (activated protein C)

Ear Nose and Throat Infections

1. Oral infections

A. Pathogenesis and microbiology

- Normal flora
- Strep. pyogenes, Gp B and C strep.

- Viral infection
 - B. Clinical presentation, diagnosis, and treatment
 - Pharyngitis
 - Clinical differentiation of viral versus bacterial pharyngitis
 - Use of rapid antigen tests for Strep. pyogenes
 - Complications
 - Vincents Angina
 - Peritonsillar abscess and retropharyngeal abscess
 - Danger space
 - Purulent pericarditis
 - Epiglottitis – clinical manifestations, diagnosis, treatment
- 2. Ear Infections**
 - A. Pathogenesis and microbiology
 - Otitis externa
 - Otitis media and mastoiditis
 - B. Clinical manifestations and risk factors
 - C. Treatment
- 3. Air sinus infections**
 - A. Pathogenesis, predisposing factors and microbiology
 - B. Clinical manifestations
 - Maxillary sinuses
 - Frontal sinuses
 - Ethmoid sinuses
 - Sphenoid sinuses
 - C. Diagnosis
 - D. Treatment
- 4. Complications associated with ENT infections**
 - A. Brain Abscess (dental infections and frontal sinusitis)
 - B. Septic thrombophlebitis
 - Jugular veins (facial space infections, otitis media, and mastoiditis)
 - Cavernous sinus (ethmoid and sphenoid sinusitis)

Pulmonary Infections

- 1. Pathogenesis of bacterial and viral pneumonia**
 - A. Mechanisms by which the tracheo-bronchial tree normally maintain sterility

- B. Factors that overcome these host-defense mechanisms and predispose to pneumonia
2. **Symptoms and signs of Pneumonia**
 - A. Concept of acute, subacute, and chronic pulmonary infections
 - B. Concept of nosocomial and community-acquired infection
 - C. Concepts of typical and atypical pneumonia
 - D. Bacteremia and rigors
 - E. Cough, chest pain, shortness of breath, rigors
 3. **Diagnosis**
 - A. CXR
 - B. Analysis of sputum
 - a. normal mouth flora
 - b. adequacy of sputum sample and interpretation of Gram stain
 - c. importance of sputum culture being accompanied by Gram stain
 - C. Other tests to assess the etiology of pneumonia
 - D. Evaluation of severity, ABG, WBC, Vital signs, Electrolytes
 4. **Colonization vs true infection.**
 5. **Acute bacterial pneumonia - specific etiologies and unique characteristics**
 - A. S. pneumoniae
 - B. H. influenzae
 - C. S. aureus
 - D. Legionella
 - E. Aspiration pneumonia (mouth flora)
 6. **Subacute or atypical pneumonia – specific etiologies and unique characteristics**
 - A. Chlamydia
 - B. Mycoplasma
 - C. Viral
 - D. Pneumocystis
 7. **Complications of Pneumonia**
 - A. Chronic pneumonia
 - B. Empyema

- C. Lung abscess
- 8. **Treatment of Community-acquired pneumonia (Basic antibiotic regimens)**
- 9. **Chronic pulmonary infections** – specific etiologies and unique characteristics
 - A. **Tuberculosis** – epidemiology, pathogenesis, primary and secondary forms, diagnosis, treatment, prevention
 - B. **Histoplasmosis**
 - C. **Coccidioidomycosis**

Central Nervous System Infections

1. **Anatomy of the meninges and other CNS spaces**
2. **Primary etiologies of community-acquired bacterial meningitis**
 - A. *S. pneumoniae*
 - B. *N. meningitidis*
 - C. *Listeria monocytogenes*
 - D. *H. influenzae*
3. **Portals of entry leading to meningitis and risk factors which predispose to specific forms of meningitis**
4. **Characteristic symptoms and neurological manifestations of meningitis**
5. **Diagnosis of meningitis**
 - A. Lumbar puncture and usefulness of Gram stain
 - B. CSF formula interpretation
 - a. pyogenic
 - b. fungal and tuberculous
 - c. viral or aseptic
 - d. parameningeal
 - C. CT scan timing
 - D. Blood cultures
6. **Principles of treatment**
 - A. Importance of early administration of antibiotics
 - B. Concept of blood brain barrier and the antibiotics that do not penetrate the blood brain barrier and use of high doses of antibiotics
 - C. Use of systemic corticosteroids
7. **Etiologies and treatment of hospital acquired meningitis**
8. **Complications of bacterial meningitis**

9. **Other forms of meningitis**
 - A. **Viral meningitis** – epidemiology, clinical presentations, CSF formula
 - B. **Tuberculous meningitis** - epidemiology, clinical presentation, CSF formula and treatment
 - C. **Cryptococcal meningitis** - risk factors and clinical presentation, CSF formula, cryptococcal antigen, treatment
10. **Viral encephalitis**
 - A. Epidemiology including specific vectors
 - B. Etiologic agents
 - C. Clinical differences from meningitis
 - D. Diagnosis
 - E. Treatment

11. **Brain Abscess**

Cardiovascular Infections

1. **Ways bacteria can get into the blood stream**
2. **Host factors predisposing to infective endocarditis**
 - A. Nonbacterial thrombotic endocarditis (NBTE) or fibrin-platelet aggregates
 - a. Rheumatic heart disease
 - b. Congenital heart diseases (bicuspid valve, VSD)
 - c. Mitral valve prolapse
 - d. Degenerative valve disease
 - e. Prosthetic valves
 - B. High pressure to low pressure hemodynamic set up called the Venturi effect.
3. **Bacterial characteristics that favor endocarditis and etiologies of IE**
 - A. Viridans Strep, S. bovis, enterococci
 - B. Staphylococcus aureus and Coag-neg Staph
 - C. HACEK
 - D. Other less common causes, Gram-negative bacilli, Corynebacteria, Fungi
4. **Causes of transient bacteremia and concepts of antibiotic prophylaxis & timing**
5. **Symptoms and signs of infective endocarditis**
6. **Diagnosis of infective endocarditis**
 - A. Duke Modified major and minor criteria

- B. Blood cultures as a diagnostic technique and the spacing of blood cultures
- C. Use of echocardiography

7. Major complications of endocarditis

8. Therapy of infective endocarditis

- A. Emphasis on cidal agents and prolonged therapy,
- B. Aminoglycoside synergy

9. Prosthetic valve and intravascular device infections

A. Epidemiology and risk factors

B. Etiologies: Coag-neg. Staph, S. aureus, enterococci, corynebacteria, Gram-negative bacilli

C. Diagnosis

- a. Quantitative blood cultures for catheters: peripheral vs central line cultures
- b. Catheter tip cultures

D. Treatment

- a. line or prosthetic valve removal
- b. systemic antibiotics (deciding duration)

Gastrointestinal and Hepatic infections

Acute Infectious Diarrhea

1. Protective mechanisms and predisposing factors

2. Pathogenesis and epidemiology of

A. Salmonella

B. Shigella

C. Campylobacter

D. E. Coli

- a. ETEC (enterotoxigenic)
- b. EPEC (enteropathogenic)
- c. EHEC (enterohemorrhagic, emphasize O157:H7)
- d. EIEC (enteroinvasive)
- e. EaggEC (enteroaggregative)

E. Vibrio cholera and parahaemolyticus

F. C. difficile colitis (cytotoxins A and B)

G. Viral (noravirus, rotavirus, adenovirus, astrovirus)

H. Amebiasis

I. Giardiasis

- 3. Clinical manifestations including enteric fever and hemolytic uremic syndrome**
- 4. Diagnosis**
 - A. Cellular responses in diarrhea, methylene blue stain
 - a. PMN, Monocytes
 - b. Blood
 - B. Bacteriologic work up of stool
- 5. Treatment**
 - A. Avoidance of agents that slow bowel motility
 - B. When to use antibiotics in infectious diarrhea
- 6. Prevention**
 - A. Asymptomatic carrier state in Salmonella
 - B. Strategies for investigating a diarrhea outbreak

Intraabdominal infections

- 1. Peritonitis**
- 2. Appendicitis**
- 3. Spontaneous or primary peritonitis**
- 4. Cholangitis**
- 5. Abdominal and liver abscess**
- 6. Diverticulitis**

Peptic Ulcer Disease

- 1. Etiology: Helicobacter pylori**
- 2. Clinical manifestations**
- 3. Diagnosis**
- 4. Treatment**

Viral Hepatitis

1. Etiologies

- A. Hepatitis A
- B. Hepatitis B
- C. Hepatitis C
- D. Hepatitis B and D
- E. Hepatitis E

2. Clinical characteristics

3. Diagnosis –

4. Treatment

5. Prevention

Genitourinary tract infections and Sexually Transmitted Diseases (STDs)

Urinary Tract Infections

1. Major UTI pathogens

- A. E. coli – most common
- B. Klebsiella
- C. Proteus
- D. Enterococcus
- E. Staph. saprophyticus
- F. Group B Strep
- G. Pseudomonas

2. Pathogenesis

A. Host factors

- a. Male vs female risk factors
- b. Sexual intercourse
- c. Incomplete bladder emptying
- d. Other anatomic defects
- e. Pregnancy
- f. Indwelling bladder catheters

B. Bacterial factors – adherence by fimbria mannose binding and glycolipid binding

3. Clinical manifestations of pyelonephritis versus cystitis

4. Diagnosis

- A. Urinalysis and definition of pyuria

- B. Urine culture
 - a. Concept of contaminant versus true positive
 - b. Use of colony counts
 - c. Unspun Gram-stain
- C. Use of ultrasound and CT scan in work up of UTI

5. **Treatment of cystitis versus pyelonephritis**
6. **Concepts of relapse vs recurrence**
7. **Asymptomatic bacteruria**
8. **Antibiotic prophylaxis and prevention**

Sexually Transmitted Diseases (STDs)

Urethritis

1. Etiologies
2. Differentiation from UTI clinically
3. Diagnosis
4. **Treatment**

Pelvic Inflammatory Diseases

1. **Etiology, epidemiology and pathogenesis**
2. **Clinical manifestations**
3. **Diagnosis**
 - A. Pelvic exam
 - B. Cervical Gram-stain
4. **Treatment and sequelae**

Genital ulcers

1. **Etiologies and differences in appearance**
 - A. Herpes simplex
 - B. Syphilis
 - C. Chancroid
 - D. Lymphogranulosum venereum
 - E. Donovanosis (granuloma inguinale)
 - F. Bechet's syndrome

2. Diagnosis

3. Treatment

Skin and Soft Tissue infections

1. Impetigo
2. Erysipelas
3. Cellulitis
4. Necrotizing fasciitis
5. Myonecrosis

Bone and Joint Infections

1. Osteomyelitis
2. Septic Arthritis

Immunocompromised host

1. Classification

- A. Cell mediated immune deficits seen in solid organ transplant patients, HIV, arthritis patients on rituximab
- B. Neutropenia following chemotherapy
- C. Mixed: Bone marrow transplant patients

2. Types of infections

- A. Viral infections: CMV, HSV, EBV
- B. Bacterial: Legionella, Listeria, Nocardia, M. Tuberculosis
- C. Fungi: Cryptococcus, Coccidioidomycosis, Histoplasmosis, Pneumocystis, Aspergillus (neutropenia), Candida
- D. Parasites: Strongyloides

3. Diagnosis, prophylaxis and treatment

Epidemiology and Bioterrorism

1. Background

- A. Infection Control
- B. Biopreparedness

2. Problem of Antibiotic-resistant pathogens and nosocomial infections

- A. Factors increasing the risk of resistant pathogen
- B. Isolation protocols, emphasis on hand washing

3. Investigation of outbreaks

- A. Defining and comparing rates
- B. Case control and cohort studies
- C. Use of 2 x 2 tables
- D. Common source vs person-to-person outbreaks
- E. Epidemic vs pandemic outbreaks

4. Categories of bioterrorist agents: A, B, C agents and beyond

- A. What makes an agent a good candidate for a weapon?
- B. Approaches to minimizing spread (pharmacologic vs nonpharmacologic)