EPIDEMIOLOGY OF INFECTIOUS DISEASE

**Epidemiology**: Study of how disease produced in a population - includes infectious and non-infectious diseases
- Mode of transmission, susceptibilities
- Ultimate outcome
- Interaction of host with causative agent - causation

**Epidemic**: Incidents of particular infection is significantly increased over norm

**Endemic**: infectious disease which is routinely found among certain populations

**Pandemic**: worldwide epidemic - e.g. AIDS or flu outbreak

PATHOPHYSIOLOGY OF INFECTIOUS DISEASE

**Pathogen**: organism which is capable of producing a disease state in host
**Virulence**: readiness or ability or organism to produce disease state
**Host**: organism which is affected by pathogen (pathogen produces disease state)

**Parasitism**: relationship between host and pathogenic organism where host is harmed
- Parasitism signifies a disease state for the host
- Non-disease states are known to occur involving two organisms
  - **Commensalism**: neither organism is harmed by the relationship
  - **Symbiosis**: both organisms benefit

**Tissue tropism**: propensity of an organism to produce disease in a given tissue

**Infectious organisms**: communicable (transmissible) from one member of a species to another

FACTORS THAT PROMOTE INFECTIOUS DISEASE

1. The virulence of the parasite

   **Virulent Pathogens**: organisms which causes disease in most individuals
   - Mechanism is function of specific organism and resistance of host
   - Number of organisms must be sufficient to overwhelm host defenses

   **Less virulent pathogen**: may cause disease in host with some impairment to defense

   **Opportunistic pathogen** - only cause disease in immunocompromised hosts
   - **HIV disease**: unusual infections caused by normally harmless organisms
     - Type of opportunistic infection changes with disease progression
     - CD4 counts decline progressively
   - **Cancer**: and treatment induces immunosuppression
2. Defense mechanisms of the body

**Skin**: main external defense barrier - intact epidermis virtually impervious to infection

**Mucus membranes**: Line various organs; protective via secreting mucus (prevent adhesion and wash organisms)

**Chemical**
- **Gastric HCl** in stomach - highly acidic - promotes sterile environment
- **Acid pH urine**: promotes sterile urine
- **Lysozyme** enzyme in secretion
- **Normal flora**: mouth, skin, intestine, vagina

**Immune System**: Cellular and non-specific immunity (see separate lecture)

**Host factors**
- Age, genetic factors, psychological factors, nutrition, environment, stress, presence of other disease affect immunity

3. Normal human flora

**Resident bacteria** - crowd out pathogens

Normal intestinal flora crowd pathogens and produce vitamin K in colon
- *C difficile* can result from antibiotic therapy - **pseudomembranous colitis**

Vaginal flora crowd out pathogens
- **Lactobacilli** crowd out pathogenic aerobes

**Carrier state**: Resident organisms (potentially pathogenic) induce no harm to the host but produce disease in others exposed to organism

**Nosocomial infections**: infections caused by exposure to hospital/medical setting
- Infection would not occur if individual were not exposed to medical setting or subjected to particular procedure

**Iatrogenic infection** - infection caused by medical personnel

**CLINICAL MANIFESTATIONS OF INFECTIOUS DISEASE**

**Early symptoms** often non-specific
- Malaise, weakness, myalgias, arthralgias, headache, somnolence, anorexia

**Progressive signs**:
- Flushed skin, chills, dehydration, lymphadenopathy, leukocytosis
  - Confusion, delirium with some infections

**Fever** hallmark symptom of infection
- Pyrogenic agents act on hypothalamus to produce fever
- Interleukin-1 (IL-1), interleukin-6 (IL-6) interferon, tumor necrosis factor (TNF), cytokines

Weight loss not uncommon
- Release of TNF alpha (cachectin)
- Fever-induced decreased intake and increased metabolism
Subclinical infection: symptoms so mild that they are not readily apparent
Carrier state: sub-clinical infection where carrier is reservoir of infection - infects others

Latent infection: disease episodes interrupted by periods of quiescence
Herpes (viral) commonly latent with recurrence triggered by stress, infections, etc

HEMATOLOGIC EFFECTS

Leukocytosis - manifestation with most infections - cell type will vary with type of infection

- Neutrophilia - acute bacterial infections
  - Relative (not absolute) eosinopenia, lymphopenia occurs on CBC
  - Monocytosis and lymphocytosis may occur on resolution of infection

- Shift-to-the-left - immature neutrophils secondary to bacterial infection

- Lymphocytosis: characteristic of viral disease

- Monocytosis: commonly accompany chronic infections e.g. TB (also lymphocytosis)

- Eosinophilia: helminthic infections

Anemia of chronic infection

- Decreased RBC survival, compromised delivery of iron to RBC
- Lack of compensatory increase in erythropoietin production

ESR (erythrocyte sedimentation rate) - non-specific test of inflammation

Coagulation dysfunction - increased platelet and fibrinogen

- DIC (disseminated intravascular coagulation) serious complication of acute infection

CARDIOVASCULAR EFFECTS

- Vascular changes (severe infection) mediated by interleukin-I and TNF
  - Powerful vasodilation secondary to the mediators
  - Hypotension with increased heart rate and cardiac output; septic shock

Septic shock:
- Most cases secondary to gram-negative bacteremia
- Other causes: rickettsial, chlamydial and viral infections

Complement cascade (C3a and C5a) activation enhances vasodilation and hypotension

RENAL EFFECTS

- Proteinuria secondary to fever or direct infection of renal structure
- Glycosuria secondary to stress-mediated decrease in tubular reabsorption of glucose
- Azotemia: increased nitrogen load mediated by tubular cell destruction (infectious agent)
- Oliguria: secondary to decreased renal perfusion -> can lead to hypotension or septic shock
HEPATOBILIARY EFFECTS

Jaundice heralds liver damage
Infectious agent-induced liver damage
- Direct destruction of hepatocytes
- Formation of infectious lesions in liver
- Hemolytic effects of infection overload liver with heme pigments

BACTERIA

Single cell organisms which do not require living cells for growth
Free-living organisms
Attach to various epithelial tissue and exhibit tissue tropism

TYPICAL VS ATYPICAL BACTERIA - antibiotic susceptibility is significantly different

Typical bacteria: susceptibility variable with organism but most major classes used
Penicillin, cephalosporins, macrolides tetracycline, fluoroquinolones,
sulfonamides, clindamycin, aminoglycoside, others

Atypical bacteria: antibiotic spectrum is much more limited (many antibiotics ineffective)
Macrolides, tetracycline, certain fluoroquinolones are effective

TYPICAL BACTERIA: Rods and spherical cocci - various classification systems used

Gram stain: gram positive (blue) or gram negative (red)

Function of chemical composition of cell wall. Gram positive resist decoloration by acetone alcohol thus retain purple stain vs gram negative which decolorize then secondarily stained with red dye. Difference is related to greater amount of cell wall peptidoglycan and the fact that gram negative bacteria have 2nd membrane - chemically different - external to plasma membrane

Antibiotics and Bacterial Cell Wall - Many antibiotics exert effect via interfering with cell wall formation. Eukaryotic cell has no analog to prokaryotic cell wall thus such antibiotics have little or no effect on plant or animal cells. Cell wall provides rigid structure to keep cell from bursting

Pyogenic (pus-producing) or non-pyogenic

Aerobic (requiring oxygen) or anaerobic (cannot tolerate oxygen)
Facultative anaerobes: prefer oxygen environment but can grow without it
Oxidative capacities
Disease-inducing mechanisms - also used as classifying system
**BACTERIAL MORPHOLOGY**

**Cocci** - spherical shaped - various arrangements
- **Single cocci**: coccus
- **Diplococci**: Streptococcus pneumonia
- **Long chains**: Streptococcus sp.
  - Packets
    - 4 cells - **tetrads**: Pediococcus sp.
    - 8 cells - Sarcina sp.
- **Irregular clusters**: Staphylococcus sp.

**Bacilli**
- Rod shaped
- Coccobacilli - almost as wide as long
- Single, or variable length chains
- Vibrios are curved - comma shaped

**Spirals**
- Spirilla - corkscrew shaped
- Spirochetes - flexible cell walls; wiggle

**Cellular Structure and Components**

**Flagella** - used for locomotion
- Most spiral & about half bacillus are motile
- Single or multiple
  - Monotrichous - 1 on end of cell
  - Amphitrichous - 2, one on each end
  - Peritrichous - many all over cell
- Structure
  - Originates in plasma membrane
  - Basal body - series of plates that anchor flagellum to the layers of cell
  - Hook
- Function
  - Chemotaxis demonstrates movement is not random
  - Flagellum spins like a boat propeller

**Axial filaments** - Used for wiggling motion
- Found only in spirochetes
- Protein fibrils wound around organism

**Fimbriae**
- Composed of proteins that can recognize specific binding sites
- Functions to stick on surfaces
**Pili**
- Similar structure as fimbriae
- Functions during conjugation

**Capsules - Glycocalyx**
- Composed of carbohydrates
- Slime layer if loosely attached
- Common in virulent bacteria - masks from phagocytes
- Prevents dessication

**Plasmids**
- Small circular piece of DNA
- DNA replicates independently of the chromosome
- Codes mainly for antibiotic resistance
- Transferred between cells via **conjugation**

**Ribosomes** - RNA - site of protein synthesis

**Endospores** - survive unfavorable conditions
- Resist: heat, dessication, chemicals, UV light
- Structure: chromosome; little else
- Triple layered wall: outer coat, cortex, core
- Example: Clostridium botulinum- improper food canning

ANTIBIOTIC COVERAGE

GRAM POSITIVE COCCI:

**Staphylococci**: beta-lactamase stable penicillins, first generation cephalosporins, most 2nd generation cephalosporins, macrolides (erythromycin, clarithromycin, azithromycin), fluoroquinolones, vancomycin, clindamycin (Cleocin), aminoglycosides (amikacin, tobramycin, gentamycin), TMP-SMX (Bactrim). Not effective: 3rd generation cephalosporins.

**Streptococci** - penicillin class is first choice; all 1ST and 2ND generation cephalosporins, most 3rd generation cephalosporins, macrolides, 2ND and 3RD fluoroquinolones, vancomycin, clindamycin (Cleocin). TMP-SMX (Bactrim) and tetracycline are not reliable. Aminoglycosides are not effective.

**Anaerobic cocci** - PO: tetracyclines and metronidazole have good coverage. Some penicillins have reasonable coverage. IV: clindamycin has good coverage; vancomycin covers some anaerobes. Newest agents: linezolid (Zyvox) and quinupristin/dalfopristin (Synercid) cover some organisms. Aminoglycosides, TMP-SMX and cephalosporins have no coverage.

GRAM NEGATIVE RODS:

**Enterobacteriaceae**: TMP-SMX, quinolones and 3rd generation cephalosporins have excellent coverage. Antipseudomonal penicillins and some aminopenicillins have reasonable coverage. Urinary agents have limited coverage but do cover the most common urinary pathogens. Metronidazole has no coverage; macrolides have virtually no coverage; tetracyclines have very poor coverage. IV agents: aminoglycosides have good coverage. Clindamycin has no coverage.

**H influenzae and M catarrhalis**: 2nd generation macrolides and 2nd and 3rd generation cephalosporins and beta-lactamase stable penicillins, fluoroquinolones, tetracyclines have excellent coverage; erythromycin is unreliable for *H influenzae* as is most 1ST generation cephalosporins. TMP-SMX has good coverage against *M catarrhalis* but unreliable against *H. influenzae*. Beta-lactamase susceptible penicillins have no coverage. IV carbapenems, aminoglycosides have coverage. Clindamycin has no coverage.

GRAM NEGATIVE COCCI

**N. Gonorrhoeae** and **N. meningitidis** aminopenicillins and antipseudomonal penicillins, however, amoxicillin and ampicillin do not cover N gonorrhoeae. Carbapenems and fluoroquinolones and rifampin have good coverage. Cephalosporins are as a group unreliable (+/-) and first generation have no coverage. An exception is ceftriaxone (Rocephin) and cefepime (Maxipime) which have reliable coverage against both organisms. Currently, fluoroquinolones and ceftriaxone are the drugs of choice for gonorrhea. Macrolides and tetracycline are unreliable (+/-) against N gonorrhoeae. Erythromycin and azithromycin and tetracycline cover N. meningitidis. The following have no coverage: penicillins other than aminopenicillins or antipseudomonal penicillins, aminoglycosides, clindamycin, metronidazole.
ATYPICAL BACTERIA

- Involve special characteristics concerning shape, size, staining properties
- Commonly atypical pathogens
  
  **Mycobacterium:**
  - *Mycobacterium tuberculosis* - tuberculosis
  - *Mycobacterium leprae* - leprosy
  - *Mycobacterium avium-intracellular* - HIV opportunistic pathogen

  **Spirochetes:** *Treponema pallidum* - syphilis, *Borrelia burgdorferi* - Lyme disease

  **Rickettsia:** *Rickettsia rickettsii* Rocky Mountain spotted fever

  **Mycoplasma:** *Mycoplasma pneumonia* - “walking pneumonia”

**Antibiotic susceptibility** somewhat more narrow vs typical bacteria
- *Macrolides:* erythromycin, clarithromycin (Biaxin), azithromycin (Zithromax)
- Tetracyclines
- Newer fluoroquinolones: Levofloxacin (Levaquin), moxifloxacin (Avelox), gaitfloxacin (Tequin)

MODES OF INFECTION: BACTERIA OVERCOME HOST DEFENSE MECHANISMS

**Adherins:** extracellular bacteria - attach to structures; penetrate underlying tissues
- *Streptococcus salivarius*

**Carbohydrate capsules** which resist phagocytosis (pneumococcus, streptococcus)

**Leukocidins:** antiphagocytic substances - destroy phagocytes (*S pyogenes*)

**Rapid growth:** short incubation period -> illness before primary immune response
- Cholera, group A hemolytic streptococcus

**Toxins:** substances produced by bacteria causing damage to host

**Exotoxins:** secreted from living cells into surrounding medium
- Highly antigenic with variable specificity
- Small quantities can be fatal
- Specific site of action in body; produce specific effects
- Example: staphylococcus food poisoning from mayonnaise at picnic

**Endotoxins:** lipopolysaccharides - component of cell wall of gram negatives
- Release during cell division or destruction
- **Pyrogenic:** fever and inflammation in host
- Invoke production of cytokines
- Activate complement and coagulation cascade
- Release vasoactive peptides -> vasodilation, hypotension
- **Endotoxic shock** or **septic shock**
- Example: E coli O:157 H:7 verotoxins - hemorrhagic colitis
- Example: toxic shock syndrome
COMMON BACTERIAL INFECTIONS IN PRIMARY CARE

TYPICAL BACTERIA - COMMON GRAM NEGATIVE ORGANISMS

ENTEROBACTERIACEAE - gm negative rods

Large group organisms; commonly inhabit colon/GI tract - includes pathogenic and non-pathogenic species (normal flora)

Pseudomonas aeruginosa - gm negative aerobic rod
Skin, mucus membranes esp burns or immunosuppressed or elderly
Common UTI pathogen, **otitis externa**, characteristic **grape-like odor**
Characteristic **greenish** color to wounds esp burns

Proteus - gm negative aerobic negative rod
UTI, ears, skin, localized purulent infections, septicemia

Enterobacter, Klebsiella: gram negative aerobic rods
Common UTI pathogen; **klebsiella pneumonia** common in alcoholics

Shigella - negative rod - **food contaminant** (fecal-oral route, common 3rd world

E coli - gm neg aerobic rod; normal inhabitant of colon; most common UTI pathogen
**Abscess** common, bacteremia common, endotoxic shock
**Traveler's diarrhea** from different strains then what is accustomed

Salmonella - gm neg aerobic rod - **food contaminant** (fecal oral route)
**Bloody diarrhea** and perforation - rare in US; severe enteritis
*S typhi* - **typhoid fever**

NEISSERIA - gram negative cocci

*N. Meningitides* - gm negative single cocci, aerobic
**Meningococcal meningitis** - resides in nasopharynx of carriers; respiratory transmission via bloodstream (septicemia) to meninges

*N. Gonorrhoeae* - gm negative diplococci - intracellular
**Gonorrhea** - sexually transmitted disease (STD) - dysuria, urethral/vaginal discharge, PID, Bartholin glands abscess

OTHER COMMON GRAM NEGATIVE PATHOGENS

Haemophilus - small gm negative pleomorphic - very common respiratory pathogen
Nasopharyngitis, **otitis, sinusitis, pneumonia, meningitis** (rare)
*H influenzae*: aerobic - extremely **common respiratory pathogen** in primary care
*H ducreyi* (**chancroid**) - STD - anaerobic gm neg rod

Bordetella - gm negative aerobic rod - epidemics - very contagious
*B pertussis* - “**Whooping cough**” - no life-long immunity
Catarrhal stage then paroxysmal cough and laryngeal stridor
**Vibrio cholera** - gm negative short rod - causes cholera (hypovolemic shock, acidosis)
- Causes profuse non-invasive diarrhea resulting in hypovolemic shock
- Metabolic acidosis; convalescent carrier sheds organism for 1 year

**Vibrio parahaemolyticus** - contaminant of undercooked/raw seafood
- Explosive watery diarrhea; fever, h/a, vomiting - 10 days

**Helicobacter pylori** - gastric/duodenal ulcers
- Successful treatment of ulcers requires eradicating bacteria
- May be asymptomatic and not warranting treatment (no ulcer)

**TYPICAL BACTERIA** - **COMMON GRAM POSITIVE ORGANISMS**

**STAPHYLOCOCCUS** - gm positive aerobic - spherical grape-like clusters -
- Common skin inhabitant - both pathogenic and normal flora

**S. aureus** - coagulase positive - common skin pathogen
- Skin infections: furuncles, boils, carbuncles, cellulitis
- Impetigo: exfoliative toxin from specific form S aureus
- Pneumonia - usually iatrogenic, Empyema
- Bacteremia - 50% mortality
- Acute osteomyelitis - open or closed trauma - osseous destruction
- UTI - most commonly from indwelling catheters, pyelonephritis
- Toxic shock syndrome: tampon-use, other causes

**S. epididymis** - normal skin flora - usually coagulase negative
- Occasionally causes disease - very drug resistant when it does

**STREPTOCOCCUS** - gm positive anaerobes - non-motile

**S. pyogenes** - group A (60 sub-types) B hemolytic
- Streptococcal pharyngitis - “strep throat”
- Scarlet fever from specific strain of toxin producing Streptococcus A
- Severe pharyngitis with sandpapery erythematous skin rash,
  “strawberry” tongue followed by red beefy tongue - desquamation of
  skin may occur up to 3-4 weeks after disease
- Rheumatic fever following acute streptococcal infection
- Acute glomerular nephritis may follow acute streptococcal infection
- Erysipelas - acute infection of skin and sub-Q tissues
- Skin lesions and cellulitis - localized
- Pneumonia

**S Agalactiae** - Group B - colonize female genital tract, throat, rectum
- Septicemia in puerperium; pulmonary disease, newborn meningitis

**S. pneumoniae** (pneumococcus) diplococcus, lancet-shaped
- Pneumococcal pneumonia (rust colored sputa)
- Commonly causes otitis and sinusitis
GRAM POSITIVE ANAEROBIC COCCI - spore bearing (very resistant to destruction)

*Clostridia tetani* - tetanus
- Soil, intestinal tract of humans/animals - puncture wound usual entry modality
- Spasms, rigidity, *“lockjaw,”* laryngospasm, mortality 40-60%
- Vaccination: dT, DPT

*Clostridium difficile* - pseudomembranous colitis (clostridia difficile toxin)
- Toxin producing anaerobe associated with antibiotic use
- Profuse diarrhea, leukocytosis, fever, abdominal pain
- Antibiotics wipe out normal flora allowing overgrowth of organism

*Clostridium botulinum* - botulism
- Severe, usually fatal food poisoning from improper canning
- Spores survive canning process and grow anaerobically
- One of most potent organic toxins known - minute quantities are fatal
- Neurotoxin

OTHER GRAM POSITIVE PATHOGENS

*Listeria monocytogenes* - facultative intracellular organism - micro-aerophilic
- Food transmission - soil, animal feces
- Transplacental transmission during birth
- Neonatal infection - mother typically asymptomatic
- Meningitis esp in cancer and transplant patients

COMMON ATYPICAL ORGANISMS CAUSING INFECTION

*Mycobacterium* - Acid fast organisms
- Organism surrounded by waxy coat - require special staining
- Waxy coat makes organism very resistant to destruction or antibiotics

*M. tuberculosis* - tuberculosis
- Facultative intracellular parasite - grows within macrophage
- Can also proliferate in intracellular spaces
- Induces hypersensitivity immune reaction -> chronic inflammation
- Granulomatous lesions

*M. leprae* (Hansen’s bacillus) - Leprosy
- Chronic skin infection, mucus membranes and peripheral nerves
- Requires direct and prolonged contact with infected individual
- Considered least contagious of the infectious diseases
- Incidence in US increasing due to 3rd world immigration

*Spirochetes* - helical shaped; resembling a spring - very fastidious

*Treponema pallidum* - syphilis - STD
*Borrelia burgdorferi* - Lyme disease - tick born infection
Borrelia recurrentis - relapsing fever
Leptospirosis - leptospira
Chlamydia - obligate intracellular parasites

Tropism for columnar epithelium of mucus membranes
Cannot be cultured; biphasic life cycle - elementary body is infectious form

*C. trachomatis* - sexually transmitted infections; also during birth process
Results in PID, non-specific urethritis, urogenital infections
Common cause of sterility in females - ectopic pregnancies
*Lympographanuloma venereum* - different strain from other STDs
Common comorbid infection of gonorrhea
Neonatal conjunctivitis and pneumonia

*C. pneumoniae* - respiratory infections - common pathogen in primary care
Variable: mild URI, pharyngitis, bronchitis, pneumonia
Sometimes call Chlamydia TWAR

*C. psittaci* - psittacosis - infected bird droppings

Rickettsia - small obligate parasites - multiply only intracellularly

Three groups: spitted fever group, typhus group, others (incl Q fever)
Arthropods esp ticks are normal reservoir for infection
Mites, lice, fleas, ticks - transmitted through bite or infected feces
Transmission exception Q fever: person to person transmission

Clinical presentation: fever, rash (rickettsial multiplication in small vessels)
Cause inflammation, swelling and necrosis to vessels causing vascular
lesions on through skin - aggregations of lymphocytes, granulocytes and
macrophages accumulate in vessels of heart, brain, other organs

*Rickettsia rickettsii* - Rocky Mountain spotted fever
*Rickettsia prowazekii* - epidemic typhus
*Rickettsia typhi* - endemic typhus
Coxiella burnetii - Q fever
Rickettsia quintana - Trench fever
Rickettsia tsutsugamushi - scrub typhus
Rickettsia akari - rickettsial pox

Legionella

*Legionella pneumophila* (Legionella) - Legionnaires disease
Mild to severe pneumonia

Mycoplasma - small pleomorphic microorganisms

- Classified with bacteria but distinctly different
- P1 protein is adherent allowing for attachment to respiratory and GU tract

*M. pneumoniae* - rhinitis, wheezing pneumonia, pharyngitis, URI/LRI
*Mycoplasma pneumoniae* ("walking pneumonia")
Children commonly affected - infect family members
College students, military recruits - persons living in close contact
Affects children and young to middle age adults; less common in elderly
Rales; patchy infiltrates on CXR
Ureaplasma urealyticum - nonspecific urethritis; also opportunistic in GU tract
Non-gonococcal STDs, possible perinatal morality

M hominis - STD and other non-STD urogenital infection
Post-partum fever, post-abortal fever, PID, pyelonephritis, non-specific urethritis; opportunistic in GU tract

VIRUSES

- Small obligate intracellular organisms - parasites on living cells
- Use biochemical products and cellular machinery to replicate (commandeer cell)
- Vary size, appearance and behavior - classed as either RNA or DNA viruses

Capsid - closed protein shell surrounding nucleic acid
Capsomers - protein subunits making up capsid
Nucleocapsid: nucleic acid and capsid
Virions: mature infective virus particles - core of either DNA or RNA

Mode of infection

Protein surface structure is responsible for attachment to particular cell receptors
Infection dependant on viral surface - host cell-receptor compatibility
  Certain persons exposed to HIV virus do no seroconvert because they lack the requisite receptor site on which the virus binds
Lock and key attachment
Species and organ specific
Bacteriophage: virus which attaches to bacteria

Viral multiplication
1. Recognition and attachment (adsorption) of virus onto host cell
2. Penetration or ejection of viral DNA into cell
   - Some enter via endocytosis; some fuse with cellular membrane
3. Replication within cell - new virions are created using cellular machinery
4. New virus so formed are released from cell
   - Survive outside cell for variable length time
   - Seek and enter new cell

Immune system response
Virus stimulate immune system antibody production
Neutralizing antibodies during viremia
Cell-mediated immunity is main defense
Initial response via mononuclear cells: monocytes and lymphocytes
Immunocompetent cells (antigen-specific) accumulate -> inflammatory response
Macrophage attach to virus - enhance T and B cell interaction
Specific immunity via IgM followed (10 d) by IgG antibodies
   - Synthesized by cellular components
   - Coat virus rendering it noninfective
Interferon - antiviral proteins which inhibit cell to cell viral spread

See ID Fig 4, 7, 8
See ID Fig 5
See ID Fig 9
Eclipse stage may follow attachment - viral DNA becomes part of host chromosome. 
Remains latent.
Activation or induction causes latent virus to initiate rapid reproductive cycle.
The more rapid a reproductive cycle - the more virulent the virus.
Few viral cells may escape lysis and remain latent.
Host cells carry latent viral DNA as part of host tissue throughout life of cell.

Factors initiating latent virus: cold temperatures, carcinogens, materials in food, water, air.

Clinical manifestations

Each virus has its own unique clinical presentation.
Sometimes no apparent clinical change as virus adopts symbiotic state with host.
Viral induced pathologies:
  - Cellular death or viral-induced hyperplasia
  - Cytopathic effects: aggregation of host cells into clusters
  - Shrinkage, lysis, fusion of cells
Pathologies are function of viral effect cellular function:
  - Cellular synthesis of macromolecules
  - Alteration of cellular organelles e.g. lysosomes
  - Changes in host cell membrane

Common viral diseases: hepatitis, meningitis, pneumonia, rhinitis, skin diseases.

Oncogenic viruses: cofactors in etiology of cancer in cells.
- Epstein-Barr viruses (EBV) - lymphomas
  Human T-cell lymphotropic virus (HTLV) - lymphomas; Kaposi sarcoma
  Hepatitis B virus - liver cancer
- Human papilloma virus (HPV) - cervical cancer

Endogenous viruses - can remain latent for years then reactivate

Herpes simplex virus - Herpes zoster, genital herpes, oro-labial herpes (cold sore)

  Herpes zoster results from initial infection with chickenpox from HSV infection.
  Chickenpox resolves then HSV resides in dorsal root ganglia where it later
  reactivates (usually with some degree of host immunosuppression or stress)
  and appears as herpes zoster along a dermatome.

  Genital herpes: initial infection results in painful herpetic lesions to genitalia
  which subsequently resolve. Periodically lesions will reappear (albeit usually the
  presentation is more mild) particularly when the host is stressed.

  Oro-labial herpes: “cold sore” reappears periodically particular during illness or
  at times when host is stressed.

Exogenous virus - direct contact with infected host or indirect contact (water, shellfish, etc.)
Laboratory diagnosis

**Complement fixation** (serology and antibody titering techniques

Titer refers to concentration of antibody in blood
High titre suggests recent exposure; low titer may suggest past disease
Titering important where viral seropositivity is long-lasting e.g. syphilis

**Polymerase chain reaction** - amplify single DNA molecule

Yields detectable signal esp for viral disease
Detects hepatitis B in chronic hepatitis and HIV
Typing of genital HPV

**COMMON VIRAL INFECTIONS IN PRIMARY CARE**

**Adenovirus** (DNA) - many strains - incubation 7-14 days
Febrile pharyngitis, URI, headache, regional lymphadenopathy, rhinorrhea/congestion, conjunctivitis, pneumonia

**Papovavirus** (DNA) - Human Papilloma Virus (HPV)

Papillomavirus - incubation 1-20 months - Sin contact with secretions, STD
- Genital warts and warts to other areas (hands, neck, shins, forearms)
- Solid, rounded tumors with horny projections - cauliflower-like
- Various genital morphology - acetowhitenin with acidic acid solution
- Associated with cervical cancer; changes apparent on Pap
- Topical immune response modulator (Imiquimod - Aldara) useful to treat
- Older treatment modalities: podophyllin, TCA, BCA less effective

**Picornavirus** (RNA) - fecal-oral contact; insects may be passive vectors

Coxsackievirus A and BC (many strains) - incubation 2-5 days - "hand-foot-mouth disease" - fecal-oral route
Acute myocarditis, fever, muscle/pleuritic pain, vesicular lesions on soft palate/tonsils, pharyngitis, systemic problems - lesions on hands, feet and mouth typically occur - usually affects children

Polio virus - incubation 2-5 days - poliomyelitis - fecal-oral route
Undifferentiated febrile illness affecting spinal cord and cranial nerves resulting in muscle paralysis, hemiplegia, paraplegia, bladder/respiratory dysfunction.
**Polio vaccines** prevent disease (rare since vaccine; previously common)

Rhinovirus - incubation 1-2 days - respiratory droplet
Common cold, fever, cough, croup; pneumonia esp in children, pharyngitis, rhinorrhea/congestion, afebrile rhinitis common in adults

Coronavirus (RNA) - incubation 1-2 days, respiratory droplet

Coronavirus - various strains
Common cold, rhinitis, pneumonia, bronchitis
**Paramyxovirus (RNA)**

**Morbillivirus** - incubation 3-5 days - respiratory droplet - **Rubeola** (measles)

Measles rash follows exposure - rhinorrhea, disseminated body-wide rash, conjunctivitis, fever, malaise, Koplik spots on buccal mucosa - prevented with vaccine (component of the “**MMR**” vaccine - measles-mumps-rubella)

**Paramyxovirus** - 15-21 d, upper respiratory secretions - **Mumps** (epidemic parotitis)

Painful enlargement of salivary glands (bilateral), fever, malaise; orchitis with risk of sterility in postpubertal males (20%-35%); meningitis (rare), other glands can be affected. Prevented with vaccine (component of “**MMR**” vaccine)

**Orthomyxovirus (RNA) - Influenzae A, B, C - “The Flu”**

Incubation: 18-36h up to 7 days. **Epidemic outbreaks** - new strains evolve rapidly, transmitted by infected respiratory secretions; respiratory symptoms - **dry cough**, myalgia, high fevers esp with sudden onset and **prostration**, chills, rhinorrhea, sneezing. Risk of pneumonia particular with virulent strains. Several antiviral agents are available to abort or ameliorate symptoms: zanamivir (Relenza), amantadine (Symmetrel), rimantadine (Flumadine), oseltamivir (Tamiflu)

**Togaviruses** (alphavirus) (RNA) - **Encephalitis**

Arthropod vectors esp in summer and fall
Incubation period variable with strain

**Filovirus (RNA) - Ebola**

Hemorrhagic fever - transmitted via infected blood or body fluids
Incubation: 15-15 days

**Bunyavirus (RNA) - Hantavirus**

Hemorrhagic fever with renal syndrome, ARDS
Ingestion/contact urine/feces rodent, rodent bites, inhalation from rodent quarters
Incubation: up to 6 weeks

**Arenavirus** (RNA)- Lassa virus - **Lassa Fever**

Hemorrhagic fever - Rat reservoir - blood and body fluid precautions
Incubation: 10 days

**Norwalk-like virus** (RNA) - **viral gastroenteritis**

Nausea, vomiting, abdominal cramps, diarrhea, fever, chills
Causes over ½ cases of gastroenteritis
Ingestion of contaminated food/water and person-to-person spread
Incubation: 48 hours - common in primary care - **Treatment is symptomatic**

**Rhabdovirus (RNA) - rabies**

Animal bite from infected mammals - esp vulnerable: fox, bat, raccoons, skunk, wolves
Introduced via mucus membranes or epidermis
Replicates in striated muscle spreads to peripheral nerve bundles to CNS
Acute encephalitis, brain stem dysfunction, death - rapidly fatal without treatment
Excessive salivation (hydrophobia) is characteristic
Incubation: 2-4 weeks in humans. **Pre and post exposure vaccine available**
**Arbovirus (RNA)** - 4 groups causing **CNS disease**  
Mosquito bite; reservoir is horse, bird, bats, snakes, insects  
Age-related symptoms - young have high fever/convulsions  
Headache, fever, drowsiness, confusion, disorientation  
Some manifest primarily lethargy - “sleeping sickness”, muscle weakness  
Residue effects: none to convulsion; speech difficulties. Incubation: 4-14d

**Hepatitis A (RNA)** - Hepatitis  
Fecal-oral route enhanced by poor hygiene, sanitation, overcrowding  
Contaminated seafood is common cause; other food/water transmission  
Sexual and percutaneous (uncommon) transmission  
Anorexia, malaise with jaundice, dark urine, clay-colored stools  
Acute onset; incubation 15-45 days; recovery usually complete - **Vaccine available**

**Hepatitis C (RNA)** - Hepatitis  
Parenteral, possible fecal-oral route  
Debilitation, liver dysfunction; chronic hepatitis is common sequelae  
Incubation: 60-160 days - Treatment with interferon

**Hepatitis B (DNA) Hepatitis**  
Percutaneous, sexual, maternal-infant; fecal-oral route is uncommon  
Jaundice, fever, malaise, dark urine, clay colored stool, anorexia  
May progress to liver failure and death - **fulminant hepatitis**  
Incubation 45-160 days - recovery slow - **Vaccine available**

**Delta Virus - Hepatitis D (RNA)** - Hepatitis  
Blood, homosexual contact; requires co-infection with Hepatitis B  
Similar picture to hepatitis B - may progress to chronic hepatitis  
Incubation: 14-56 days

**Hepatitis E (RNA)** - Hepatitis  
Fecal-oral route, contaminated water - incubation 14-15 days  
Chronic active hepatitis, cirrhosis, chronic carrier similar to hepatitis B

**Retrovirus (RNA) - Human Immunodeficiency Virus (HIV)**  
Transmission: sexual contact esp homosexual; parenteral, perinatal  
Immunodeficiency with progressive opportunistic infections (AIDS) -> death  
Incubation: variable - 5-10 yrs adults; more rapid onset in children  
Treatment: extensive agents available to treat opportunistic infections plus numerous **antiretroviral drugs available**
PRIONS

Small infectious particles that contain protein which is encoded by host gene
Unknown whether or not they contain nucleic acids
Resistant to procedures which normally inactivate nucleic acids
    Nucleases, UV light, chemical modification by nucleophiles
Two forms of prior protein
    Prior protein cellular - PrPc
    Prion protein scrapie - PrPsc - abnormal form which causes disease
Normal function of prior protein is unknown
Abnormal form believed to transmit transmissible neurodegenerative diseases (TND)
    Kuru, Creutzfeldt-Jacob disease (CJD), Gerstmann-Straussler syndrome (GSS) fatal
    familial insomnia (FFI)
CJD, GSS, FFI have mutations in their prion protein gene - can pass disease to offspring

Human transmissible neurodegenerative diseases (TND) - 4 common characteristics
    - Pathological manifestations primarily occur in CNS
    - Long incubation times - 6 months for CJD; 30 yrs for kuru
    - Disorders are progressively fatal
    - Neuropathological identifying features
        - Reactive astrocytosis with little inflammation
        - Spongiform changes: small vacuoles in neutrophils of brain

Fungi

50,000 different species of fungi
Less than one dozen cause 90% of all fungal infections
Fungi are eukaryotic organisms - rigid cell wall (unlike peptidoglycan of bacteria)
Cell membranes similar to higher eukaryotes
    Fungi contain ergosterol and zymosterol
    Mammalian cells contain cholesterol
Ergosterol/zymosterol vs cholesterol in membrane accounts for selectivity of antifungals
    Amphotericin B
    Azoles - e.g. ketoconazole (Nizoral)

Classification

2 Forms - Yeasts and molds
    Yeasts reproduce via budding
    Molds grow via intertwined hyphae called mycelium

Dimorphic: fungi
    Can grow as either yeast or mold pending conditions
    Includes several categories of pathogenic yeast
    Pathogens: blastomycosis, histoplasmosis, coccidioidomycosis

See ID Fig 10,11, 12, 13, 14
Modes of Infection

3 Mechanisms for producing disease
1. Individual sensitized to specific fungous antigens -> **allergic reaction**
2. Fungal generated toxic substances - **mycotoxins**
   - Amatoxin - produced by poisonous mushrooms
   - Aflatoxin - mutagenic and potent hepatic carcinogen
3. **Mycosis**: fungus with ability to grow in human host

Mycoses - 3 groups according to body system infected

**Systemic or deep mycoses** - affect internal organs or viscera (potentially **lethal**)
**Subcutaneous mycoses** - skin, subcutaneous tissue, fascia, bone
- Normally occurs via direct contamination with fungal spores or mycelia
- Mycelia (filamentous parts of fungi) enter via wound or broken skin
**Superficial mycoses** or **dermatophytes** - involve only epidermis, hair, nails
- Mammalian skin is principle habitat

Factors affecting mycosis

- Host defense capabilities
  - Immunosuppressed are esp vulnerable
  - Fungi are often opportunistic pathogens
  - **Pneumocystis carinii** - pneumonia in HIV patients
    - Fatal if not treated - cough, fever, interstitial lung infiltration
    - Previously classed as protozoan
  - **Thrush** - **oral candida albicans** - common in CA and HIV disease

- Route of exposure
- Amount of exposure
- Virulence of fungus
COMMON FUNGAL INFECTIONS IN PRIMARY CARE

Superficial dermatophytoses - Tinea

- **Tinea pedis** - “Athlete’s foot”; **tinea corporis** - body ringworm
- **Tinea capitis** - scalp ringworm; **Tinea cruris** - “Jock Itch”
- Found on keratinized skin, nail, hair; branching hyphae
- Contact with fungus, maceration/poor hygiene favor
- Fissuring, itching, irritation, alopecia, scaling
- Circumcised lesion, round borders of inflammation
- Drugs available as solution, spray, lotion, cream, ointment, powder

**Clotrimazole (Lotrimin), miconazole (Lotrimin AF) *, tolnaftate (Tinactin)*, naftifine (Naftin), terbinafine (Lamisil) Econazole (Spectazole), ketoconazole (Nizoral), oxiconazole (Oxistat), Sulconazole (Exelderm), butenafine (Mentax), ciclopirox (Loprox), haloprogin (Halotex), Undecylenate (Cruex) * * available OTC

Candida albicans - Skin infections, oral thrush, vaginal yeast, systemic candidiasis

- Small yeastlike cells, blastopores with budding; round clusters on agar
- May be superficial or systemic esp in immunosuppressed
- Contact with normal flora of mouth, stool, vagina
- **Thrush:** oral lesions - white plaques can be scraped off leaving friable base; fissures
- **Vaginal yeast:** curd-like white discharge with pruritus, erythema and swelling
- **Cutaneous candidiasis:** erythema with satellite lesions, pruritus, erythema, swelling
- Diabetics are particularly are susceptible; balanitis suggests DM
- Can be systemic in the immunosuppressed

**Clotrimazole (Lotrimin), miconazole (Monistat-Derm) *, Econazole (Spectazole), ketoconazole (Nizoral), oxiconazole (Oxistat), ciclopirox (Loprox), haloprogin (Halotex), Amphotericin B (Fungizone), nystatin (Mycostatin) * * available OTC

C. Immitis - coccidioidomycosis

- Yeastlike cells; no budding; divided into multiple small cells
- Soil saprophyte in southern US, Mexico and S. America
- Infection via inhalation of arthrospores; symptoms 10-14 days after exposure
- Primary form: respiratory - flu-like symptoms; pneumonia, pleural effusion
- **Progressive form:** dissemination to regional nodes, skin, meninges
  - Affects particular the immunosuppressed
  - Fever, cough, chest pain, pulmonary coin lesion

**Amphotericin B (Fungizone) and azoles * * available OTC

* Azoles: fluconazole (Diflucan), itraconazole (Sporanox), ketoconazole (Nizoral), miconazole (Monistat IV), voriconazole (V-Fend)

H. capsulatum - histoplasmosis

- Dimorphic fungus; forms cotty white growth on agar
- Grows as mold - prefers moist soil; airborne in chicken coops or soil exposure
- Cough, fever, weight loss, hilar adenopathy; progressive fibrosis of mediastinum
- Diagnosis is difficult; **amphotericin B** may not succeed; **prognosis is poor**
B. dermatitidis - blastomycosis
- Dimorphic fungus, budding, round, yeastlike cells
- Most cases in southeast, central and mid-Atlantic US
- Infection via inhalation of fungus; reservoir is unknown; incubation 4 weeks
- Fever, cough, weight loss, chest pain, pneumonia, large skin lesions
- Responds well to amphotericin B (Fungizone)

C. neoformans - cryptococcosis
- Yeastlike, budding
- Inhalation exposure; often opportunistic with immunosuppressed
- Fungus excreted in pigeon droppings; infection more common in males
- Pulmonary infection: chest pain, cough, infiltrates
- Meningoencephalitis:
  - Headache, dementia, confusion, cranial nerve palsy, cerebral edema, death in 2 weeks to several years
  - Amphotericin B (Fungizone) and flucytosine (Ancobon), fluconazole (Diflucan)

Pneumocystis carinii (PCP) - Pneumocystic pneumonia
- Fungus-like cysts with dark bodies
- Primarily affects immunosuppressed esp AIDS
- Transmitted via respiratory droplets; often fatal without treatment
- Fever, nonproductive cough, SOB, pneumonitis progressive to pneumonia
  - Dapsone, trimethoprim-sulfamethoxazole (Bactrim), Clindamycin (Cleocin) and primaquine, atovaquone (Mepron), pentamidine (Pentam 300), pyrimethamine (Daraprim)

Aspergillus fumigatus - aspergilloses
- Molds in colonies, smoky grey color
- Opportunistic with immunosuppression esp neutropenia
- Allergic bronchopulmonary asthmatic response, focal consolidation, lobar pneumonia
  - Itraconazole (Sporanox), amphotericin B (Fungizone)
PROTOZOA

- Complex, unicellular organisms - spherical, spindle-shaped or cup-shaped
- All are motile; many can absorb fluids through cell membrane
- Common sites of infection: GI tract, genitourinary tract, circulatory system
- Reproduction varies with species: sexual or asexual
  Sexual cycle: occurs with definitive host - protozoa called gametes
  Asexual cycle: intermediate host - protozoa called zygotes
- Cysts: protozoa can surround with resistant membrane resisting destruction

Classification - 4 groups

Flagellates: flagella or undulating membrane
- Motility via flagella: whip-like projections causing rapid movement
- Considered primitive protozoa
- Common genera: 
  GI/GU pathogens: *Giardia lamblia, Trichomonas vaginalis*, *enteromonas*
  Skin/mucus membranes: *Leishmania*
  Systemic: *Trypanosoma*

Ameba - Motility via pseudopods
- Projection pressed forward followed by rest of organism
- Movement is directional toward specific focus
- Common genera: Sarcodina (rhizopod) - *entamoeba, Endolimax, Iodamoeba*

Sporozoa - life cycle involving two different hosts
- Hosts often arthropod and vertebrate
- *Plasmodium sp* - genus of *malarial parasites*

Ciliata - most complex of protozoa - cilia in rows or patches
- Motility via cilia
  Synchronous action of short delicate structures covering entire outer surface
  Rapid movement
- Shape varies with amount of ingested material
  *Balantidium coli* - only human pathogen
  Rare cause of diarrhea similar to amebiasis

HELMINTHS

- Pathologic worms; many are parasitic
- Three genre: *nematodes* (roundworms), *trematodes* (flukes), *cestodes* (tapeworms)
- Complex organisms re: structure and life cycle
- Different stages of life cycle may involve different hosts (fish, hogs, snails, rats, humans)
- Egs/larvae often eliminated in feces or urine - diagnosed on microscopy
- Transmission mainly via fecal-oral route or broken skin
- Commonly produce eosinophilia

See ID Fig 15, 16, 17