INFECTIOUS DISEASES

Dr. S. Walmsley, Dr. A. McGeer, Dr. J. Keystone, and Dr. A. Phillips
Veera Bharatwal and Ryan Foster, editors
Christine Brezden, associate editor

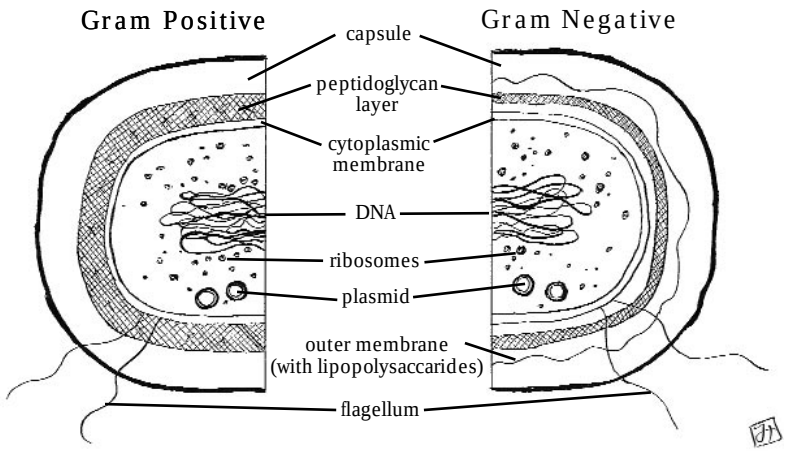


Figure 1. General Schematic of Bacterial Structure

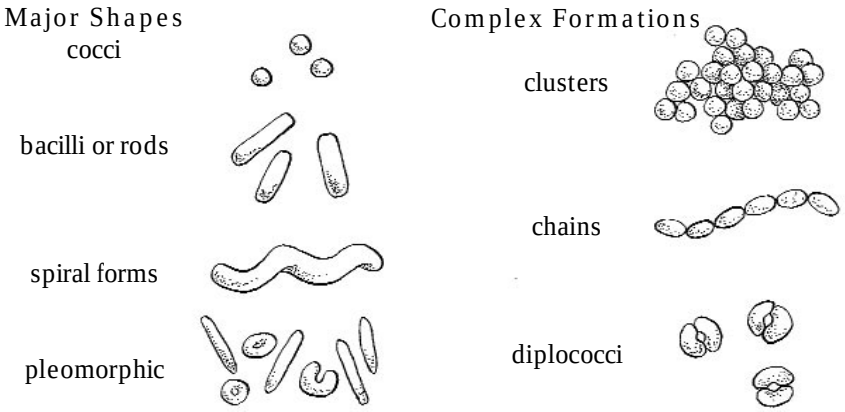


Figure 2. Bacterial Morphology

Drawings by Muyuki Fukuma

GLOSSARY OF BACTERIAL TERMS

Virulence Factors

- ❑ Flagella
  - protein filament tails that propel the bacteria
- ❑ Pili
  - shorter than flagella, serve as adherence factors
  - some bacteria use sex pili for reproduction
- ❑ Capsules
  - protective layer surrounding cell membranes, usually made of secreted carbohydrate residues

Endospores

- ❑ metabolically dormant forms of bacteria, may lie dormant for years
  - only *Bacillus* and *Clostridium*

Toxins

- ❑ Exotoxins
  - proteins released by bacteria that cause disease independent of the bacteria
    - neurotoxins act on nerves or motor endplates
    - enterotoxins act on the GI, etc...
- ❑ Endotoxins
  - normal part of the bacterium that may be shed while living, or released during cell lysis causing disease processes (i.e. septic shock)

GRAM POSITIVE COCCI

Staphylococcus aureus (S. aureus)

- ❑ microbiology
  - Gram positive, catalase-positive cocci in grape-like clusters/tetrads
  - its production of catalase differentiates it from *Streptococcus*
  - coagulase-positive more virulent than coagulase-negative strains
- ❑ mode of transmission
  - normal flora of human skin, respiratory and gastrointestinal tracts
  - colonizes axilla, perineum and nasal mucosa; 40-50% of healthy adults are colonized in anterior nares
  - person-to-person transmission and via contaminated fomites
  - risk factors for infection include: broken skin, young, old, foreign bodies
  - important cause of hospital-acquired infections
- ❑ clinical features

EXOTOXIN DEPENDENT

- staphylococcal gastroenteritis (enterotoxin)
  - sudden onset of vomiting and diarrhea
  - associated with cream, ham, poultry
- toxic shock syndrome (TSS toxin-1)
  - from focal infections and/or colonization
  - sudden onset of high fever, nausea and vomiting, watery diarrhea
  - desquamation of skin on palms and soles
  - hypotension, renal/liver dysfunction
  - associated with tampon use/nasal packing
- scalded skin syndrome (exfoliative toxin)
  - generalized desquamation and bullae formation
  - resembles massive scalding
  - usually neonates with infection of severed umbilicus or children with skin infections

DIRECT INVASION

- abscess formation
  - acute inflammation and abscess formation involving many extracellular toxins (e.g. coagulase, hemolysin, leucocidin, staphylokinase, etc...)
- skin, soft tissue infections are very frequent
  - folliculitis, cellulitis, mastitis, wound infections (most common cause)
  - furuncles (boils), carbuncles (cluster of boils)
  - impetigo (contagious pyoderma)
- bacteremia
  - metastatic focal infection in 15% if undertreated
  - endocarditis is a complication
- endocarditis
  - can affect normal valves
  - a common cause of endocarditis in drug-addicts
  - tricuspid valve involvement unique to IV drug users
- osteomyelitis
  - often history of preceding skin infection (50%), or trauma
- septic arthritis
- pneumonia
  - uncommon but severe
  - often occurs after influenza infection or in those with COPD or chronic bronchitis
- acute bacterial meningitis (uncommon)

- ❑ diagnosis (applicable to all *Staphylococcus* strains)
  - specimens: surface swab, blood, pus, tracheal aspirate or CSF for culture
  - smears of pus or sputum
  - catalase and coagulase tests
- ❑ treatment
  - 95% are penicillin-resistant (beta-lactamase production)
  - beta-lactamase-resistant penicillins (e.g. cloxacillin), cephalosporins, or clindamycin are drugs of choice
  - minor skin infections may be treated without oral/IV antibiotics (i.e. drainage, warm saline soaks +/– topical bacitracin or fusidic acid)

Methicillin-Resistant *Staphyloccus aureus* (MRSA)

- ❑ resistance to methicillin and nafcillin via change in penicillin-binding proteins
  - often in hospitals, transmitted by health-care workers

- ❑ infections require IV vancomycin
  - eradication with topical mupirocin to nares and washing with chlorhexidine soap
  - contact isolation should be enforced

Staphylococcus epidermidis (S. epidermidis)
- ❑ microbiology
  - Gram positive cocci, catalase-positive, coagulase negative, sensitive to novobiocin
- ❑ mode of transmission
  - colonizes skin ubiquitously and intestinal tract
  - person-to-person transmission
- ❑ pathogenic mechanisms
  - adheres to prosthetic surfaces using slime layer
  - highly resistant to antibiotics
- ❑ clinical features
  - foreign body infections: prosthetic joints, prosthetic heart valves, shunts, catheters, intravenous lines, intravascular grafts
  - frequent contaminant in blood cultures
- ❑ treatment
  - vancomycin is drug of choice (for serious infections) since resistant to multiple antibiotics
  - positive cultures may represent contamination (i.e. one positive blood culture bottle of one set)

Staphylococcus saprophyticus (S. saprophyticus)
- ❑ microbiology
  - coagulase-negative, urease-positive, novobiocin-resistant
- ❑ clinical features
  - second most common cause of simple cystitis in sexually active women (after E. *coli*)
- ❑ treatment
  - penicillin

Streptococci
- ❑ microbiology
  - cocci in chains or pairs
  - catalase-negative (vs. *Staph.* catalase-positive)
  - hemolytic patterns on sheep blood agar: alpha (green partially-hemolyzed), beta (clear-hemolyzed), or gamma (non-hemolytic)
  - also grouped based on cell-wall carbohydrates (Lancefield groups A, B, D, etc...)

Group A *Streptococci* (GAS or *S. pyogenes*)
- ❑ microbiology
  - beta-hemolytic
  - sensitive to bacitracin
- ❑ mode of transmission
  - colonizes pharynx (15% of children are carriers)
  - person-to-person transmission
- ❑ pathogenic mechanisms
  - pili for attachment to epithelial cells
  - M protein on cell wall resists phagocytosis
  - production of toxic enzymes such as DNAse, hyaluronidase, streptokinases, streptolysins
- ❑ clinical features

  MILD INFECTIONS
  - tonsillo-pharyngitis
    - purulent exudate on tonsils, fever > 38ºC, tender swollen anterior cervical lymph nodes, and absence of cough
    - 40-60% of patients with all 4 criteria have GAS pharyngitis
    - diagnose with throat culture or rapid antigen test
    - follow-up: negative rapid test with culture
  - skin, soft tissue, and wound infections
    - erysipelas, impetigo, cellulitis, lymphangitis

  SEVERE INFECTIONS
  - scarlet fever (erythrogenic/pyrogenic toxin)
    - pharyngitis, fever, erythema, desquamation of palms and soles, “strawberry” tongue

- necrotizing fasciitis
  - severe pain out of proportion to lesion in early stages
  - fever, well-demarcated expanding area of erythema, hemorrhages, blisters, bullous and gangrenous skin lesions
  - rapid progression
  - renal failure
- streptococcal toxic shock syndrome (TSS toxin)
  - fever, shock, rash or bullous skin lesion
  - early renal failure, thrombocytopenia
  - risk factors: minor trauma, surgery, preceding viral illness (chicken pox)
- bacteremia (rare)

❑ complications

SUPPURATIVE
- local extension and invasion

NON-SUPPURATIVE (ANTIBODY-MEDIATED) - specific to GAS
- rheumatic fever
  - rare but recent resurgence
  - Jones major criteria: myocarditis, polyarthritis, chorea, erythema marginatum, subcutaneous nodules
  - 10-20 years after infection, may develop permanent heart valve damage
- acute post-streptococcal glomerulonephritis (PSGN)
  - tea-colored urine following streptococcal skin or pharyngeal infection

❑ diagnosis (applicable to all streptococcal strains)
- specimens: throat swab, pus, blood for culture
- smears from pus; smears from throat swabs are never helpful because *Strep. viridans* which are always present have the same appearance as GAS
- antibody detection tests
- serological tests; e.g. antibodies to GAS antigens - antistreptolysin O (ASO)

❑ treatment
- penicillin V or G
- erythromycin if allergic to penicillin
- treatment of pharyngitis reduces the chance of rheumatic fever but not PSGN

Group B *Streptococci (S. agalactiae)*

❑ microbiology
- beta-hemolytic

❑ mode of transmission
- colonizes large intestine, vagina (25% of women)
- person-to-person and vertical transmission

❑ clinical features
- perinatal infections (majority: think Group B for BABY)
  - puerperal sepsis
  - septic abortion, chorioamnionitis
  - neonatal sepsis (< 10 days old), neonatal meningitis (> 10 days old), neonatal pneumonia
- bacteremia and soft tissue infections in the elderly and patients with chronic disease

❑ diagnosis
- routine vaginal/rectal cultures in late third trimester (36-37 weeks)
- if positive culture, give prophylactic antibiotics to high-risk mothers

❑ treatment
- penicillin or ampicillin

Group D *Streptococci/Enterococci*

❑ microbiology
- beta-, alpha-, or gamma-hemolytic
- all *Enterococci* are Group D *Streptococci*
- not all Group D *Streptococci* are *Enterococci*
- major species: *Enterococcus faecalis* and *Enterococcus faecium*

❑ reservoir/mode of transmission
- colonize intestinal tract and genitourinary tract
- person-to-person transmission

❑ clinical features
- subacute bacterial endocarditis
- urinary tract, hepatobiliary tract, intra-abdominal infections
- wound and decubitus ulcer infection

❑ treatment
- *Enterococci* only inhibited, not killed by penicillin
- inherently resistant to cephalosporins
- for most urinary tract and minor soft tissue infections, use ampicillin or TMP/SMX
- for more severe infections, use combination of ampicillin and aminoglycoside (for synergy) or vancomycin + aminoglycoside

Vancomycin-Resistant *Enterococci* (VRE)
- resistance via change in peptidoglycan component from D-alanine to D-lactate
  - drugs of choice still ampicillin and gentamycin
  - sensitivity to teicoplanin depends on phenotype
  - new streptogramin therapy under investigation

Streptococci species

Viridans Streptococci (S. mutans, S. mitis)
❑ microbiology
- non-Lancefield Group *Streptococci*
- alpha-hemolytic (green on agar)

❑ mode of transmission
- normal oropharyngeal flora

❑ pathogenic mechanisms
- frequently seed the bloodstream during dental manipulation (tooth brushing)
- produces sticky dextrans that help it adhere to surfaces and other adherent mechanisms - can cause dental plaques

❑ clinical features
- most common cause of subacute bacterial endocarditis
- affects abnormal heart valves
- S. *mutans* causes dental caries

❑ treatment
- penicillin +/– aminoglycoside

S. pneumoniae (pneumococcus)
❑ microbiology
- non-Lancefield Group *Streptococci*
- alpha-hemolytic
- Gram positive cocci in pairs
- growth inhibited by optochin on agar (to differentiate from S. *viridans*)
- 84 serotypes based on capsular antigen, all are pathogenic
- immunity to one type not cross-protective

❑ mode of transmission
- colonizes nasopharynx, person-to-person, airborne

❑ pathogenic mechanisms
- polysaccharide capsule resists phagocytosis

❑ risk factors
- alcoholics, splenectomy, sickle-cell anemia, HIV, hypogammaglobulinemia, multiple myeloma, Hodgkin's Disease

❑ clinical features
- pneumonia
  - often preceded by upper respiratory tract infection (e.g. influenza virus)
  - sudden onset of shaking chills, pleuritic pain, rusty sputum, lobar involvement (dense consolidation on CXR)
  - sterile pleural effusion (50%)
- meningitis
  - second most common cause of bacterial meningitis in adults
  - can occur after pneumonia, sinusitis, or skull fracture
- bacteremia (25%)
- otitis media (in children)

❑ treatment
- polysaccharide vaccine (“pneumovax”)
  - protective against the 23 most common capsular antigens

❑ recommended for elderly, immunocompromised, splenectomized and those with cardiopulmonary, liver or kidney disease, or sickle-cell anemia
- antibiotic treatment
  - penicillin or erythromycin
  - second generation cephalosporin (e.g. cefuroxime)

Penicillin-Resistant *S. pneumoniae*
- in Toronto 7% resistance in adults, 20% resistance in children
- resistance via change in penicillin-binding proteins
- for CNS infection: combine vancomycin and cefotaxime until sensitivities available

GRAM POSITIVE BACILLI

Corynebacterium diphtheriae
- ❑ microbiology
  - club-shaped rods with beaded or barred appearance
  - non-spore-forming
- ❑ mode of transmission
  - colonizes pharynx
  - person-to-person transmission via airborne respiratory droplets
- ❑ pathogenic mechanisms
  - pseudomembrane forms in the upper respiratory tract which serves as a base from which organism secretes exotoxin
  - disease caused by airway obstruction or effect of exotoxin on heart and nervous system (not invasion)
- ❑ clinical features
  - mild sore throat, fever, nasal discharge, hoarseness
  - tenacious gray membrane over the tonsils and pharynx
  - myocarditis (10%)
  - neural involvement (peripheral nerve palsies, Guillain-Barré-like syndrome)
- ❑ diagnosis
  - immunity detected by Schick skin test
- ❑ treatment (see Pediatrics Notes)
  - antitoxin + penicillin or erythromycin
  - prevent by immunization with diphtheria toxoid

Listeria monocytogenes
- ❑ microbiology
  - non-spore-forming, tumbling motility
  - beta-hemolytic on blood agar
- ❑ mode of transmission
  - ingestion of soft cheese (foodborne outbreaks)
  - from soil, decaying matter, feces
  - vertical transmission (vaginal delivery)
- ❑ pathogenic mechanisms
  - facultative intracellular parasite
- ❑ clinical features
  - usually < 1 or > 55 years of age

  ANTENATALLY
  - neonatal meningitis and bacteremia
  - infection is associated with abortions and premature deliveries

  IN THE ADULT POPULATION
  - meningitis in immunosuppressed patients (e.g. alcoholics, pregnancy, diabetics, steroid or immunosuppressive medication users)
  - 3rd most common cause of adult meningitis
  - bacteremia, gastroenteritis
- ❑ treatment
  - ampicillin or TMP/SMX

Bacillus cereus
- ❑ microbiology
  - spore-forming, motile
- ❑ mode of transmission
  - ubiquitous organism
  - transmission via endospores, usually from food such as fried rice
- ❑ pathogenic mechanisms
  - enterotoxins and pyrogenic toxin
- ❑ clinical features
  - food poisoning: nausea, vomiting, and diarrhea
  - opportunistic infections (rare)
- ❑ diagnosis
  - culture specimen from suspected food source

- ❑ treatment
  - resistant to beta-lactam antibiotics
  - clindamycin or vancomycin
  - no antibiotic treatment for food poisoning since caused by the pre-formed enterotoxin

Nocardia asteroides, Nocardia farcinica
- ❑ microbiology
  - elongated rods that branch at acute angles and often show irregular staining
  - weakly acid-fast
- ❑ mode of transmission
  - commonly found in the environment (soil)
  - transmitted by inhalation
  - not person-to-person transmission
- ❑ clinical features
  - pulmonary nocardiosis
    - ~50% have underlying disease or compromised immunity due to treatment (e.g. leukemia, lymphoma, COPD, chronic steroid use)
    - can disseminate to distant organs (e.g. brain) where multifocal abscesses are often produced
- ❑ diagnosis
  - Gram stain, acid-fast stain, cultures
- ❑ treatment
  - TMP/SMX and surgical drainage

GRAM NEGATIVE COCCI

Neisseria meningitidis (Meningococcus)
- ❑ microbiology
  - diplococci resembling two kidney beans
  - 9 serogroups based on capsular polysaccharides (A, B, C, W, Y)
  - obligate human pathogen
- ❑ mode of transmission
  - colonizes pharynx (15%)
  - droplet transmission
  - endemic in areas; periodic epidemics
  - risk factors: splenectomy, complement deficiency (C8, C9), hypogammaglobulinemia
  - high risk people: closed populations, e.g. army recruits (carrier rates > 40%)
- ❑ pathogenic mechanisms
  - capsule is antiphagocytic
  - pili for attachment to epithelial cells
  - toxic effects of LPS
- ❑ clinical features
  - asymptomatic colonization in the nasopharynx
  - meningitis
    - fever, vomiting, nuchal rigidity, lethargy
    - petechial rash, hemorrhages, thrombocytopenia
  - meningococcemia
    - fever, petechial rash, hemorrhages, thrombocytopenia
    - hypotension
  - fulminant meningococcemia (Waterhouse-Friedrichsen Syndrome)
    - bilateral adrenal hemorrhage
    - petechial rash, hemorrhages, thrombocytopenia, purpura, gangrene
    - hypotension
- ❑ diagnosis
  - Gram stain and culture of CSF
  - antigen detection (latex agglutination in CSF)
- ❑ treatment
  - polysaccharide vaccine (used in epidemics); A, C, Y, W, B135 covered
  - antibiotics
    - penicillin, third generation cephalosporins
    - rifampin, minocycline, ciprofloxacin used prophylactically for close contacts

Neisseria gonorrhea (Gonococcus/GC)
- ❑ microbiology
  - diplococci

- ❑ mode of transmission
  - obligate human pathogen
  - transmitted sexually via contact with secretions, often by asymptomatic carriers, vertical transmission
- ❑ pathogenic mechanisms
  - pili, antigenic variation
  - endotoxin, IgA protease
- ❑ clinical features
  - asymptomatic (but still infectious)
  - local infection in men
    - urethritis, epididymitis, proctitis and pharyngeal infections
  - local infection in women
    - cervicitis most frequent (vaginal bleeding)
    - urethra, anus, and pharynx can be infected
    - can progress to pelvic inflammatory disease with complications including sterility, ectopic pregnancy, abscess, peritonitis, perihepatitis (Fitz-Hugh Curtis syndrome)
  - disseminated infection in both men and women
    - gonococcal bacteremia
    - pustular skin rash (dermatitis/arthritis syndrome)
    - tenosynovitis
    - septic arthritis: GC arthritis is the most common cause of septic arthritis in sexually active individuals
  - neonatal infection
    - ophthalmia neonatorum (usually within the first 5 days)
  - risk factors for disseminated disease
    - menstruation
    - complement deficiency (C8, C9)
- ❑ diagnosis
  - Gram stain, culture
  - in smears of exudate, GC is typically found in PMN cells
- ❑ treatment
  - neonatal GC and *Chlamydia* conjunctivitis prophylaxis with erythromycin eye drops immediately following birth
  - antibiotic of choice: third generation cephalosporin (e.g. ceftriaxone IM or cefixime PO x 1 dose)
  - second line: spectinomycin, quinolone
  - single dose therapy unless disseminated
  - treat with doxycycline to cover coinfecting *Chlamydia trachomatis*
  - report to public health
  - follow-up cultures to test for cure

Moraxella catarrhalis

- ❑ Gram negative diplococci
- ❑ recently recognized as an important human pathogen
- ❑ upper respiratory tract acts as reservoir and portal of entry for infection
- ❑ causes acute otitis media, sinusitis, bronchopneumonia
- ❑ 75% of strains produce beta-lactamase
- ❑ drugs of choice: amoxicillin-clavulanate, cephalosporins

GRAM NEGATIVE BACILLI

Enterobacteriaceae

- ❑ reservoir in GI tract; fecal-oral transmission
  - ascending migration up the urethra
  - colonization of catheters in hospitalized patients
- ❑ cause urinary tract infections, pneumonia, sepsis, nosocomial infections
- ❑ diagnosis by culture
- ❑ treatment
  - many become antibiotic-resistant
  - aminoglycosides, third generation cephalosporins, piperacillin, quinolones, TMP/SMX

Escherichia coli

- ❑ microbiology
  - normal gut flora, lactose-fermenter
- ❑ pathogenic mechanisms
  - capsule, flagella, pili, adhesins, enterotoxin

❑ clinical features
- gastroenteritis
  1. enterotoxigenic
     - non-invasive, watery traveller's diarrhea
     - produces heat-labile and heat-stable enterotoxins
  2. enterohemorrhagic
     - bloody diarrhea, no pus in stool, no fever
     - strain 0157:H7 causes hemorrhagic colitis, hemolytic uremic syndrome due to verocytotoxins
  3. enteroinvasive - bloody diarrhea, pus in stool, fever
     - urinary tract infections (most common cause)
     - newborn meningitis
     - sepsis

❑ treatment
- invasive disease: cephalosporins, aminoglycosides, TMP/SMX, quinolones

Klebsiella pneumoniae

❑ microbiology
- lactose-fermenter, mucoid colonies on culture

❑ mode of transmission
- inhabits gut of man/animals and in soil/water
- infection either endogenous or acquired by contact spread

❑ pathogenic mechanisms
- encapsulated and resistant to phagocytosis

❑ clinical features
- pneumonia
  - significant lung necrosis, bloody sputum
  - risk factors: alcoholic, diabetes, elderly, underlying lung disease
- hospital-acquired urinary tract infections
- nosocomial sepsis and wound infections

❑ treatment
- third generation cephalosporin, ciprofloxacin, TMP/SMX

Enterobacter spp.

❑ lactose-fermenting, encapsulated, small Gram negative bacillus

❑ part of normal human gut flora

❑ also found free-living on plants

❑ causes ICU infections

❑ causes nosocomial UTI, sepsis

❑ treatment
- quinolones or imipenem, may be resistant to third-generation cephalosporins

Proteus mirabilis

❑ microbiology
- indole-negative, non lactose-fermenting, urease-positive, swarming motility seen as concentric rings on culture plates

❑ mode of transmission
- endogenous infection, fecal contamination

❑ clinical features
- urinary tract infection
  - turns urine alkaline due to urease (splits urea into NH_2 and CO_2)
  - associated with urinary calculi
  - sepsis

❑ treatment
- ampicillin, quinolones, TMP/SMX

Shigella

❑ microbiology
- several species differing in pathogenicity
- nonmotile, non lactose-fermenter

❑ mode of transmission
- obligate human pathogen, not part of normal human flora
- small inoculum suffices (highly communicable)
- fecal-oral contamination

❑ pathogenic mechanisms
- invasion of small intestine mucosa helped by Shiga toxin and adhesins

❑ clinical features
- bloody diarrhea with mucus, pus, tenesmus (similar to EIEC)

- self-limited (3-4 days)
- neurotoxic effects of Shiga toxin including meningismus, coma
- severe illness at extremes of age
- Reiter's syndrome may develop in HLA B27 hosts

❑ treatment
- TMP/SMX, ampicillin, quinolones

Salmonella typhi

❑ mode of transmission
- obligate human pathogen
- motile, non lactose-fermenter
- Canadian cases are imported
- fecal-oral contamination, genital/anal-oral transmission

❑ pathogenic mechanisms
- encapsulated/slime wall resists phagocytosis
- able to multiply in macrophages
- diarrhea probably due to toxins
- antigenic variation of flagellae

❑ clinical features
- typhoid fever
  - insidious onset with headache, malaise, anorexia
  - high fever (stepwise increase in temperature), abdominal pain, enlarged liver and spleen
  - rose spots rash on abdomen
  - no diarrhea (constipation common)
- complications
  - GI hemorrhage and perforation (1%)
  - relapses due to chronic carrier state with biliary tract colonization (5-10%)

❑ diagnosis
- blood or stool for C&S

❑ treatment
- preventable with vaccine
- TMP/SMX, ampicillin, ciprofloxacin

Non-typhoidal Salmonella spp. (S. enteritidis, S. typhimurium)

❑ mode of transmission
- zoonotic (pet turtles, indoor aquaria, chickens, uncooked eggs)
- one of the most prevalent communicable bacterial infections

❑ pathogenic mechanisms
- encapsulated; able to multiply in macrophages
- diarrhea probably due to toxins

❑ clinical features
- gastroenteritis - self-limited (2-5 days); no treatment
- paratyphoid fever - similar to typhoid fever
- osteomyelitis - especially in sickle-cell patients
- bacteremia
- risk factors
  - abnormal cell-mediated immunity
  - in AIDS patients, bacteremia can be recurrent

❑ diagnosis
- stool for C&S

❑ treatment
- prevent with adequate cooking, hygiene, food practices

Pseudomonas aeruginosa

❑ microbiology
- non lactose-fermenter, oxidase-positive, motile

❑ mode of transmission
- commonly found free living in moist environments
- can be cultured from sinks, showers, hot tubs
- pathogen of plants, animals, and humans
- transmission via water, soils, foods, inhalation, ingestion, penetration through breaks in epithelium

❑ clinical features
- opportunistic infections
- pneumonia in cystic fibrosis along with *Burkholderia cepacia* and in immunocompromised patients
- nosocomial infections
- burn wound infections, urinary tract infections

- endocarditis (IV drug users), sepsis
- malignant otitis externa (diabetics)
- corneal infections in contact lens wearers, post trauma or surgery

❑ treatment
- piperacillin + tobramycin, ceftazidime, ciprofloxacin, imipenem

Campylobacter jejuni

❑ microbiology
- comma-shaped rods, motile, oxidase-positive

❑ mode of transmission
- found in GI tract of many animals and fowl (zoonosis)
- transmitted via consumption of contaminated food and water, unpasteurized milk

❑ pathogenic mechanisms
- motile, enterotoxins, adhesins

❑ clinical features
- gastroenteritis
  - usually self-limiting
  - fever, abdominal pain
  - secretory or bloody diarrhea
  - most common cause of bloody diarrhea in children

❑ treatment
- because the disease is usually self-limiting, the effect of antimicrobials on its course remains unclear
- erythromycin, quinolones

Helicobacter pylori

❑ microbiology
- small curved rods, urease-positive

❑ mode of transmission
- person-to-person transmission (oral-oral and fecal-oral)
- prevalence of infection increases with age (about 1% per year) in developed countries
- higher prevalence in developing countries
- exclusive to humans

❑ pathogenic mechanisms
- flagella
- urease aids survival in extreme acid environment of stomach
- urease and cytotoxin cause injury to stomach

❑ clinical features
- causally associated with gastric ulcer (80%), duodenal ulcer (90%), gastric adenocarcinoma and MALT lymphoma
- infection is commonly asymptomatic
- causal association with non-ulcer dyspepsia has not been established

❑ diagnosis
- gastric biopsy, culture, serology and saliva antibody tests
- urease tests: ^{14}C-urea breath test

❑ treatment (see Gastroenterology Notes)
- indicated only if ulcer is present
- triple therapy: clarithromycin, metronidazole, and omeprazole (90% eradication) (refer to Antimicrobial table for doses)
- many other regimens of antibiotics and H_2 blocker/ proton pump inhibitor of comparable efficacy

Vibrio cholerae

❑ microbiology
- short comma-shaped rods, oxidase-positive, thrives in alkaline medium

❑ mode of transmission
- fecal-oral, contaminated food, only in man
- 1991 Latin America epidemic, 1993 epidemic in Bangladesh and India

❑ pathogenic mechanisms
- flagella, fimbriae help with attachment to cells
- enterotoxin (A and B subunits) causes secretion of fluid into the intestinal tract

❑ clinical features
- cholera
  - nausea, vomiting, abdominal cramping
  - massive watery diarrhea (rice water stools)
  - no pus in stools, no tissue invasion

- ❑ diagnosis
  - culture
- ❑ treatment
  - fluid, electrolyte replacement
  - doxycycline, quinolones, TMP/SMX
  - vaccine of limited benefit

Haemophilus influenzae
- ❑ microbiology
  - pleomorphic coccobacillus
  - type B (based on capsule) is most virulent
- ❑ mode of transmission
  - a human commensal
  - type B colonizes pharynx (5%), especially young children
  - transmitted via respiratory route
  - secondary household cases occur in contacts
- ❑ pathogenic mechanisms
  - capsule, IgA protease, slows beating of cilia
- ❑ clinical features
  - meningitis
    - was most common cause of meningitis in children (1-3 years)
    - Hib vaccine in Canada has led to decreasing incidence of invasive Hib disease (see Pediatrics Notes)
  - pneumonia
    - especially in children, alcoholics, COPD
  - acute epiglottitis
  - conjunctivitis
  - septic arthritis in infants
  - cellulitis in children
  - sepsis (especially if asplenic)
  - osteomyelitis in sickle-cell patients
  - nonencapsulated (nontypable) H. *influenzae* causes otitis media, sinusitis
- ❑ diagnosis
  - Gram stain, culture
- ❑ treatment
  - prophylaxis with rifampin for household contacts of meningitis
  - second or third generation cephalosporins since H. *influenzae* can acquire ampicillin resistance by plasmids
  - steroids in children with H. *influenzae* meningitis
  - prevention of invasive disease: Hib polysaccharide vaccine

Haemophilus ducreyi
- ❑ sexually transmitted
- ❑ chancroid: painful genital ulcer often associated with unilateral swollen lymph nodes
- ❑ treatment
  - azithromycin, erythromycin, ceftriaxone IM, ciprofloxacin

Bordetella pertussis
- ❑ microbiology
  - Gram negative coccobacillus
- ❑ mode of transmission
  - colonizes pharynx; transmitted via respiratory route
  - highly contagious
  - high risk groups
    - infants < 1 year
    - adults (since immunity acquired from vaccine wears off)
- ❑ pathogenic mechanisms
  - capsule, adherent fimbriae, phase variation
  - pertussis toxin, tracheal cytotoxin
  - attachment to and immobilization of cilia; never invasive
- ❑ clinical features
  - whooping cough
    1. catarrhal phase (1-2 weeks - patient is highly contagious)
       - low grade fever, runny nose, mild cough
       - antibiotic susceptible
    2. paroxysmal phase (2-10 weeks)
       - whoop on inhalation (nonproductive cough)
       - vomiting, cyanosis
       - antibiotics ineffective during this stage
    3. convalescent stage

- ❑ diagnosis
  - culture, ELISA, identification by immunofluorescence
- ❑ treatment
  - prevent with new acellular pertussis vaccine (see Pediatrics Notes)
  - erythromycin (only if given before paroxysmal phase begins)

Legionella pneumophila

- ❑ microbiology
  - small, nutritionally fastidious pleomorphic rods/coccobacilli
  - weakly acid-fast
  - facultative intracellular parasite
- ❑ mode of transmission
  - thrives in non-maintained water environments (air conditioning systems, cooling towers)
  - transmitted via inhalation of airborne organisms, not person-to-person
  - risk factors: cell-mediated immunodeficiency, chronic steroid usage, nursing homes, elderly, smoking
- ❑ pathogenic mechanisms
  - capsule, motile, cytotoxin, multiplies in macrophages
- ❑ clinical features
  - Legionnaire's disease
    - pneumonia, fever, non-productive cough
    - multilobar pneumonia and diarrhea
  - Pontiac fever
    - headache, fever, muscle aches and fatigue
    - self-limited acute febrile illness
- ❑ diagnosis
  - culture, serology, direct fluorescent antibody, DNA probes
- ❑ treatment
  - erythromycin +/– rifampin, or ciprofloxacin

Yersinia enterocolitica

- ❑ mode of transmission
  - reservoir in wild and domestic animals
  - ingestion of contaminated food, water or unpasteurized milk
- ❑ pathogenic mechanisms
  - motile, enterotoxin
- ❑ clinical features
  - acute enterocolitis (usually in infants and young children)
  - fever, diarrhea, abdominal pain
  - bacteremia
- ❑ diagnosis
  - C&S
- ❑ treatment
  - antibiotics do not alter the course of the diarrhea
  - if bacteremic, treat with quinolone

Yersinia pesits

- ❑ mode of transmission
  - reservoir mainly in squirrels, prairie dogs, rats in southwest U.S.
  - fleas serve as vectors between rodents and humans
- ❑ pathogenic mechanisms
  - virulence factors allow organism to resist phagocytosis
  - reproduce intracellularly
- ❑ clinical features
  - swollen, hot, painful lymph node (usually inguinal)
  - fever, headache, general malaise
  - hemorrhages under skin turn blackish: “Black Death”
  - death in a few days if untreated
- ❑ diagnosis
  - C&S
- ❑ treatment
  - TMP/SMX or quinolone

Pasteurella multocida

- ❑ mode of transmission
  - part of normal flora of domestic and wild animals
  - transmitted by bite from dog or cat along with other organisms
- ❑ pathogenic mechanisms
  - capsule
- ❑ clinical features
  - wound infections may progress to nearby bones and joints
- ❑ diagnosis
  - culture
- ❑ treatment
  - penicillin, doxycycline, third generation cephalosporins

GRAM POSITIVE COCCI

Anaerobic *Streptococci/ Peptostreptococci/ Peptococci*

- ❑ microbiology
  - Gram positive cocci in chains
- ❑ mode of transmission
  - normal colonization of oral cavity, GI tract, vagina
- ❑ clinical features
  - sinusitis
  - dental, abdominal, lung, brain abscesses
  - postpartum endometritis
- ❑ diagnosis
  - culture
- ❑ treatment
  - penicillin, clindamycin

GRAM POSITIVE BACILLI

Clostridium tetani

- ❑ microbiology
  - large Gram positive rods, spore-former
- ❑ mode of transmission
  - soil reservoir, splinters, rusty nails
  - endospores introduced through wound, germinate under anaerobic conditions
  - 50% of wounds can have history of minor or no environmental contamination
- ❑ pathogenic mechanisms
  - tetanospasmin inhibits release of GABA from nerve cells leading to sustained muscle contraction
- ❑ clinical features
  - tetanus
    - symptoms after approximately 14 days
    - muscle spasms, lockjaw (trismus), risus sardonicus (facial spasm)
    - respiratory muscle paralysis
    - mentally alert
    - mortality 50%
- ❑ diagnosis
  - clinical
  - Gram stain, culture
- ❑ treatment (see Pediatrics Notes)
  - prevent with tetanus toxoid vaccination
  - treat as follows
    - clean wound
    - antitoxin (TIG)
    - metronidazole
    - penicillin (may potentiate GABA inhibition)
    - supportive therapy (e.g. intubation and ventilation)

Clostridium botulinum

- ❑ mode of transmission
  - reservoir: soil, stored vegetables (home-canned/zip-lock storage), fresh honey
  - ingestion of heat-resistant endospores
- ❑ pathogenic mechanism
  - neurotoxin inhibits release of acetylcholine from peripheral nerves
- ❑ clinical features
  - food-borne botulism
    - severe dryness of mouth and pharynx
    - progressive descending paralysis
    - cranial nerve palsies, muscle weakness, respiratory paralysis
  - infant botulism (< 6 months)
    - associated with ingestion of fresh honey
    - constipation, flaccid paralysis
- ❑ diagnosis
  - Gram stain, culture, toxin in serum
- ❑ treatment
  - antitoxin
  - penicillin
  - supportive therapy

Clostridium perfringens

- ❑ mode of transmission
  - reservoir: ubiquitous in dust, soil, air and GI tract of humans and mammals
  - wound contamination or ingestion of endospores
- ❑ pathogenic mechanism
  - alpha toxin acts as a lecithinase
  - collagenase facilitates spread
  - beta toxin destroys neutrophils
- ❑ clinical features
  - food poisoning
    - mediated by enterotoxin
    - symptoms within 24 hours
    - self-limited diarrhea (lasting 24 hours)
  - soft tissue infections
    - simple wound contamination without disease
    - superficial skin ulcers/bed sores, not systemically ill
    - necrotizing fasciitis
      - cellulitis with fasciitis and gas in fat layer
    - gas gangrene
      - clostridial myonecrosis: sudden pain around wound, frothy discharge, edema, fatal if untreated
    - uterine infections
      - following instrumentation
- ❑ diagnosis
  - Gram stain, culture, x-rays
- ❑ treatment
  - radical surgery (may require amputation)
  - penicillin, clindamycin +/– hyperbaric oxygen

Clostridium difficile

- ❑ mode of transmission
  - reservoir: intestinal tract, endospores contaminate environment (hospitals, nursing homes)
  - ingestion of endospores
- ❑ pathogenic mechanism
  - toxin A: induces watery fluid secretion
  - toxin B: cytotoxic to colonic epithelial cells
- ❑ clinical features
  - variable severity
  - pseudomembranous colitis (antibiotic-associated diarrhea)
    - usual suspect antibiotics: clindamycin, ampicillin, cephalosporins
- ❑ diagnosis
  - immunoassay test for C. *difficile* toxin B
  - colonoscopy to look for pseudomembranous colitis
- ❑ treatment
  - terminate use of the causative antibiotic (when possible)
  - metronidazole PO, or metronidazole IV; or vancomycin PO
  - metronidazole-resistant C. *difficile* strains isolated and yet despite this, it is preferred because equally effective and costs less

GRAM NEGATIVE BACILLI

Bacteroides fragilis

- ❑ microbiology
  - non-spore-forming, slender rods
- ❑ mode of transmission
  - normal flora of GI tract and vagina
- ❑ clinical features
  - abscesses in abdomen, pelvis, and lungs, often as part of mixed infection
- ❑ diagnosis
  - Gram stain, culture
- ❑ treatment
  - penicillin resistant
  - metronidazole, clindamycin, cefoxitin or piperacillin
  - surgically drain abscesses

ACID-FAST

Mycobacterium tuberculosis (TB)

- ❑ microbiology
  - slow growth rate, culture requires 4-6 weeks
  - resistant to drying
  - intracellular survival and replication in macrophages
- ❑ mode of transmission
  - infection transmitted by inhalation of droplets
  - most disease is reactivation of latent infection years after primary infection
- ❑ risk factors
  - immunosuppression (e.g. AIDS, steroid use)
  - First Nations people, health-care workers, contact with active case
  - elderly
  - silicosis
- ❑ clinical features
  - primary TB
    - asymptomatic (self-limited pneumonitis)
    - overt disease, involving the lungs or other organs
  - reactivation or secondary TB
    - pneumonia
      - systemic signs (fatigue, weight loss, night sweats) common
      - apical, posterior upper and superior lower lobes
      - caseating necrosis/cavitation
      - chronic cough, sputum +/– hemoptysis
      - extrapulmonary TB
      - pleurisy with effusion, lymphadenitis, skeletal, GU, meningitis
    - miliary TB
      - wide-spread dissemination
      - multiple nodules in lung (small, millet seeds)
- ❑ diagnosis
  - positive skin test (PPD) indicates infection but not necessarily disease (PPD may be negative secondary to anergy), see Community Health Notes
  - acid-fast stain, ZN stain
  - culture, CXR
- ❑ prevention
  - BCG (Bacille Calmette-Guerin) vaccine - questionable efficacy
  - INH prevention for positive skin test (if converted within 2 years)
- ❑ treatment
  - INH, rifampin, pyrazinamide x 2 months
  - then INH and rifampin for further 4 months
  - suspected drug resistance
    - multi-drug resistant strains emerging in inner city USA
    - INH, rifampin, pyrazinamide plus either ethambutol or IM streptomycin for 12 months

Mycobacterium avium-intracellulare

- ❑ microbiology
  - acid-fast, grows slightly faster than M. *tuberculosis*
- ❑ mode of transmission
  - ubiquitous in soil, water
- ❑ pathogenic mechanism
  - relatively nonpathogenic
- ❑ clinical features
  - disseminated infections in AIDS (with CD4 cell count <100/mL), including bacteremia
  - persistent fever, weight loss
- ❑ treatment
  - prophylaxis with rifabutin may be considered in AIDS patients with CD4 < 100/mL
  - combination therapy: clarithromycin, ethambutol, rifabutin, +/– ciprofloxacin

Mycobacterium leprae

- ❑ microbiology
  - culture requires inoculation into live mice/armadillos

- ❑ mode of transmission
  - low infectivity
  - transmission via contamination of nasal mucosa or minor skin lesions with infected nasal secretions
  - infection requires prolonged close contact
- ❑ clinical features
  - causes lepromatous and tuberculoid leprosy (Hansen's Disease)
  - chronic granulomatous disease
  - involves peripheral nerves and nasal septum
  - total cutaneous anesthesia, facial deformities
- ❑ diagnosis
  - cultured in certain animals (armadillo)
- ❑ treatment
  - rifampin, dapsone, clofazimine

Nocardia (see Aerobic Gram Positive Bacilli Section)

- ❑ Gram positive but weakly acid-fast

SPIROCHETES

Treponema pallidum

- ❑ microbiology
  - detectable by dark-field microscopy
  - thick, rigid, spiral-shaped, and motile
  - extremely sensitive to heat and drying
- ❑ mode of transmission
  - humans only
  - transmitted sexually, vertically, or by blood
- ❑ clinical features
  - primary syphilis (see Colour Atlas F11)
    - painless genital chancre at ~ 21 days following infection
    - regional lymphadenopathy
  - secondary syphilis (see Colour Atlas F13)
    - occurs at 4-8 weeks after infection
    - rash on palms and soles, scaly, non-pruritic
    - generalized lymphadenopathy
    - condyloma latum: painless, wart-like lesion in warm, moist places (vulva or scrotum)
    - CNS, eyes, bones, kidneys, and/or joints can be involved
  - latent syphilis
    - asymptomatic disease > 1 year
  - tertiary syphilis
    - occurs 15-20 years after initial infection
    - gummas (nodular granulomas) of skin and bone
    - cardiovascular syphilis (aortitis, aneurysms)
    - neurosyphilis (strokes, dementia, personality changes, Argyll-Robertson pupils, tabes dorsalis)
  - congenital syphilis
    - causes spontaneous abortion, stillbirths, congenital malformations, mental retardation
    - infant presents with rhinitis, bone and cartilage degeneration, hepatosplenomegaly, rash
    - Jarisch-Herxheimer reaction: acute worsening of symptoms after antibiotics are started (release of endotoxin)
- ❑ diagnosis
  - screening tests (VDRL or RPR)
  - confirmatory tests (TPI, FTA-ABS, MHA-TP)
  - cutaneous lesions examined by dark-field microscopy, silver stain
- ❑ treatment
  - IM penicillin (drug of choice)/erythromycin/doxycycline
  - neurosyphilis: penicillin

Borrelia burgdorferi
- ❑ microbiology
  - motile, spiral organism
- ❑ mode of transmission
  - reservoir: white-footed mouse, white-tailed deer
  - carried and transmitted by tick bite (*Ixodes dammini*) in wooded areas in summer and fall
- ❑ clinical features
  - Lyme disease
    - stage 1 (early localized stage)
      - erythema chronicum migrans (ECM)
      - large expanding bull's eye lesion at site of tick bite
    - stage 2 (early disseminated stage)
      - multiple smaller ECM
      - aseptic meningitis, CN palsies, peripheral neuropathy
      - transient heart block or myocarditis
      - brief attacks of arthritis of large joints
    - stage 3 (late stage)
      - chronic arthritis
      - encephalopathy, meningitis, neuropathy
- ❑ diagnosis
  - ELISA, western immunoblotting, PCR
- ❑ treatment
  - doxycycline or ceftriaxone or amoxicillin
- ❑ prevention
  - insect repellent, inspecting for ticks after exposure

INTRACELLULAR PARASITIC BACTERIA

Chlamydia trachomatis
- ❑ microbiology
  - not detectable by Gram stain
  - grown in cell culture
  - multiply in macrophages
- ❑ mode of transmission
  - human reservoir only
  - sexually transmitted (commonly occurs with GC)
  - vertical transmission
- ❑ clinical features
  - sexually transmitted disease
    - women: urethritis, cervicitis, PID
    - men: nongonococcal urethritis, epididymitis, prostatitis
  - trachoma (Chronic Follicular Keratoconjunctivitis)
    - organism grows in conjunctival cells, causes scarring of the inside of the eyelid
    - redirection of the eyelashes onto the cornea resulting in scarring and blindness
    - worldwide most common cause of blindness
  - lymphogranuloma venereum
    - STD characterized by painless papules on external genitalia and inguinal lymphadenopathy
    - leads to genital enlargement and swelling
  - neonatal pneumonia and conjunctivitis
- ❑ diagnosis
  - serology (ELISA), poor sensitivity assay
  - detection of antibody by swab
- ❑ treatment
  - doxycycline or erythromycin (see Gynecology Notes)

Chlamydia pneumoniae (strain TWAR)
- ❑ human reservoir with respiratory person-to-person transmission
- ❑ causes atypical pneumonia in young adults
  - viral-like, similar to mycoplasmal pneumonia

- ❑ diagnosis by serology
- ❑ treat with erythromycin or doxycycline

Bartonella henselae

- ❑ Gram negative pleomorphic rods
- ❑ seen on Warthin-Starry stain
- ❑ transmitted via cat scratch or dog contact
- ❑ causes Cat-Scratch disease
- ❑ primary papule, regional lymphadenopathy, hepatosplenic involvement, fever
- ❑ diagnosis by suggestive history and physical, skin test, lymph node histopathology, serology
- ❑ usually self-limited

MISCELLANEOUS

Mycoplasma pneumoniae

- ❑ microbiology
  - smallest known bacteria capable of growth and reproduction outside a living cell
  - not detectable by Gram stain; no cell wall
  - highly pleomorphic
  - small colonies resembling 'fried eggs' on culture
- ❑ mode of transmission
  - reservoirs: human carriers, animals, environment
  - person-to-person via inhaled droplets
- ❑ clinical features
  - classic atypical pneumonia (walking pneumonia)
    - fever with a dry, non-productive hacking cough
    - headache prominent, sore throat, myalgias
    - occasionally, hemolytic anemia occurs
    - most common in 15-40 year old age group
    - clinical findings and CXR are much worse than symptoms
- ❑ diagnosis
  - 60-80% by presentation and CXR (typically bronchopneumonia)
  - cold agglutins, complement fixation test, culture (requires 2-3 weeks), DNA probes
- ❑ treatment
  - self-resolving
  - can use erythromycin or doxycycline

ANTIMICROBIALS

GENERAL PRINCIPLES

- ❑ bactericidal vs. bacteriostatic therapy
- ❑ bacteriostatic = nonlethal inhibition of growth
- ❑ bactericidal therapy is indicated for patients with immunologic compromise or life-threatening infection
- ❑ bactericidal drugs for infections characterized by impaired regional host defences, such as endocarditis, meningitis, and osteomyelitis
- ❑ most other infections can be treated effectively with either bactericidal or bacteriostatic drugs

Table 1. Treatment Guidelines for Common Bacterial Infections

Infection	Organisms	Drug of Choice	Alternative
Pharyngitis	Group A *Strep.*	Penicillin V 300 mg TID	Erythromycin 250 mg QID
Otitis media	*S. pneumoniae* H. *influenzae* M. *catarrhalis*	Amoxicillin 250 mg TID Amox/Clavulanate 250 mg TID	TMP/SMX DS 1 tab BID Cefaclor 250 mg TID
Otitis externa	*S. aureus*	Garamycin eardrops Coliform bacilli	Cortisporin eardrops
Sinusitis	*S. pneumoniae* H. *influenzae* M. *catarrhalis*	Amoxicillin 500 mg TID TMP/SMX DS 1 tab BID Azithromycin 250-500 mg OD	Amox/Clavulanate 500 mg TID Cefuroxime 250 mg BID
Community-acquired pneumonia (mild)	*S. pneumoniae* M. *pneumoniae* C. *pneumoniae*	Erythromycin 250 mg QID	Clarithromycin 250 mg BID
Community-acquired pneumonia (severe)	*S. pneumoniae* L. *pneumophila* C. *pneumoniae*	Cefotaxime IV 1g q6h + Erythromycin IV 1g q6h	TMP/SMX IV 200 mg q12h + Erythromycin IV 1g q6h
Bronchitis	M. *pneumoniae* C. *pneumoniae* S. *pneumoniae*	Tetracycline 250 mg QID Erythromycin 250 mg QID	Clarithromycin 250 mg BID Azithromycin 250-500 mg OD
Cellulitis	*S. aureus* Group A *Strep.*	Cloxacillin 250 mg QID Cephalexin 250 mg QID	Erythromycin 250 mg QID Clindamycin 300 mg QID
Simple UTI	E. *coli* *Enteric bacilli* S. *saprophyticus*	TMP/SMX DS 1 tab BID Nitrofurantoin 50 mg QID	Ciprofloxacin 500 mg BID Amoxicillin 250 mg TID
Pyelonephritis	*Enteric bacilli* *Enterococci*	TMP/SMX DS 1 tab BID	Amox/Clavulanate 500 mg TID Ciprofloxacin 500 mg BID
Pelvic inflammatory disease	*N. gonorrheae* C. *trachomatis* Anaerobes *Enteric bacilli*	Ceftriaxone IM 250 mg x 1 + Doxycycline 100 mg BID	Ofloxacin PO 400 mg x 1 + Doxycycline 100 mg BID
Urethritis	N. *gonorrheae* C. *trachomatis*	Ceftriaxone IM 250 mg x 1 + Doxycycline 100 mg BID	Spectinomycin IM 2g x 1 + Doxycycline 100 mg BID
Meningitis-adults and children	S. *pneumoniae* N. *meningitidis* H. *influenzae*	Cefotaxime IV 2g q6h + Vancomycin IV 1g q12h	Ceftazidime IV 2g q6h Chloramphenicol IV 100 mg q6h
Meningitis-infants	E. *coli* Group B *Strep.* L. *monocytogenes*	Ceftriaxone IV 200 mg/kg/day	Cefotaxime IV 200 mg/kg/day + Ampicillin IV 200 mg/kg/day
Peptic ulcer disease	H. *pylori*	Triple Therapy: Clarithromycin 500 mg BID Metronidazole 500 mg BID Omeprazole 20 mg BID	Triple Therapy: Amoxicillin 1g BID Metronidazole 500 mg BID Omeprazole 20 mg BID

CELL WALL SYNTHESIS INHIBITORS (BACTERICIDAL)

Beta-Lactams (e.g. Penicillins, Cephalosporins, Carbapenems)

- ❑ mechanism of action
  - competitively inhibit penicillin binding proteins (PBP's) which prevents cross linking of peptidoglycan strands normally needed for cell wall integrity —> osmotic lysis of the bacterium
- ❑ mechanisms of beta-lactam resistance
  - altered PBP
  - production of beta-lactamase (cleaves beta-lactam ring)
  - decreased outer membrane permeability

Penicillins

- ❑ benzyl penicillin (susceptibility)
  - benzyl penicillin (narrow spectrum, resistance by beta-lactamase production)
    - e.g. penicillin G (IV or IM), penicillin V (PO)
    - effective against *Streptococci*, (PSSA), most anaerobes (not B. *fragilis*), *Neisseria*, and T. *pallidum* (syphilis)
  - isoxazoyl penicillin (narrow spectrum, beta-lactamase resistant)
    - e.g. methicillin, cloxacillin, oxacillin, nafcillin
    - effective against *Staphylococci* and some *Streptococci*; drug of choice for penicillin-resistant S. *aureus* (PRSA)
- ❑ aminopenicillins (broad spectrum, resistance by beta-lactamase production)
  - e.g. ampicillin, amoxicillin
  - effective against most Gram positives including *Enterococci*, and some Gram negatives
- ❑ ureidopenicillins (extended spectrum, beta-lactamase sensitive)
  - e.g. piperacillin, carbenicillin, ticarcillin
  - effective against Gram positives
  - effective against *Pseudomonas*, Gram negatives (e.g. *Enterobacter*), and anaerobes (e.g. *Bacteroides fragilis*)
- ❑ combination of beta-lactam with beta-lactamase inhibitors (extended spectrum, beta-lactamase resistant)
  - e.g. amoxicillin-clavulanic acid, piperacillin-tazobactam, ampicillin-sulbactam
- ❑ side-effects
  - hypersensitivity
    - 1-5% of people are allergic
    - immediate onset allergic reactions: anaphylaxis, urticaria, angioneurotic edema
    - late onset allergic reactions: urticaria, maculopapular rashes, drug induced fever, serum sickness
  - dose related toxicities: seizures, electrolyte disturbances, bleeding diathesis
  - interstitital nephritis

Cephalosporins

- ❑ susceptibility
  - note: cephalosporins are ineffective against *Enterococci, Listeria*
  - 1st generation (e.g. cefazolin, cephalexin)
    - Gram positive cocci (except MRSA and *Enterococci*),
    - Gram negative bacilli (mainly E. *coli*, *Klebsiella*, *P. mirabilis*)
  - 2nd generation (e.g. cefuroxime, cefotetan)
    - less Gram positive activity but more Gram negative coverage than 1st generation (*H. influenzae*, *E. coli*, *Klebsiella*, *Proteus*)
    - cefotetan has anaerobic activity and is used in intra-abdominal and pelvic infections
  - 3rd generation (e.g. cefotaxime, ceftazidime, ceftriaxone)
    - broad spectrum activity against Gram negatives, less Gram positive coverage than 1st generation (cephalexin)
    - crosses blood-brain barrier (unlike 1st and 2nd generation)
    - ceftazidime should be used if *Pseudomonas* coverage is required
  - 4th generation (e.g. cefepime, cefpriome)
    - broad spectrum activity against Gram negatives (including P. *aeruginosa*) and good coverage of Gram positive cocci (MRSA and *Strep. pneumoniae*)
    - useful in severe hospital or community-acquired infections (pneumonia, bacteremia)

❑ side-effects
- hypersensitivity reactions as described for penicillin
- 15% cross-reactivity to penicillin
- dose-related nephrotoxicity

Carbapenems (e.g. Imipenem)
❑ mechanism of action
- imipenem inhibits cell wall synthesis
- cilastin protects the kidney from toxicity and inhibits a renal enzyme that metabolizes imipenem, increasing its half-life

❑ susceptibility
- broadest spectrum of activity against anaerobes, Gram positives (except *Enterococcus faecium* and MRSA), and Gram negatives, including P. *aeruginosa*

❑ side-effects
- seizures
- cross-reactivity in patients with anaphylaxis to penicillin

Glycopeptides (e.g. Vancomycin)
❑ mechanism of action
- blocks cell wall peptidoglycan polymerization resulting in loss of cell wall integrity and osmotic rupture of the bacterium

❑ susceptibility
- only active against Gram positive organisms (e.g. S. *aureus*)

❑ side-effects
- red person syndrome: histamine-mediated reaction with erythematous flushing of the trunk, neck, and face during infusion +/– associated hypotension
- nephrotoxicity, ototoxicity, neutropenia, thrombocytopenia, rash, hypersensitivity

❑ clinical indications
- true major penicillin allergic patients (e.g. anaphylaxis, exfoliative dermatitis, vasculitis, or severe urticaria)
- MRSA infection
- coagulase-negative *Staphylococcus* (e.g. S. *epidermidis*) in patients with prosthetic valves with joint or line infections
- infections due to ampicillin-resistant *Enterococci*
- 2nd line treatment for antibiotic-associated pseudomembranous colitis (C. *difficile*)

PROTEIN SYNTHESIS INHIBITORS - VIA THE 50S RIBOSOME (BACTERIOSTATIC)

Chloramphenicol
❑ mechanism of action
- inhibits protein synthesis by binding to the ribosomal 50S subunit, which prevents the aminoacyl end of tRNA from associating with peptidyl transferase

❑ susceptibility
- excellent coverage of most Gram positives and Gram negatives, including anaerobes

❑ side-effects
- reversible or irreversible bone marrow depression, leukopenia, aplastic anemia, gray baby syndrome (toxic levels in newborns unable to conjugate drug; symptoms include abdominal distension, vomiting, cyanosis, hypothermia, death)

Macrolides (e.g. Erythromycin, Clarithromycin, Azithromycin)
❑ mechanism of action
- inhibit protein synthesis by binding to the P site of the ribosomal 50S subunit, which prevents translocation of polypeptide chain

❑ susceptibility
- cover *Mycoplasma, Legionella, Chlamydia, Treponema, Helicobacter pylori, Staphylococci, Streptococci*, Gram positives

❑ side-effects
- GI upset, hepatotoxicity

❑ clinical indications
- staphylococcal and streptococcal infections in patients allergic to penicillin

Lincosamides (e.g. Clindamycin)
❑ mechanism of action
- inhibit protein synthesis by binding to 50S ribosomal subunit

❑ susceptibility
- covers Gram positives and most anaerobes

❑ side-effects
- pseudomembranous colitis, rashes, thrombophlebitis, reversible elevation of liver enzymes, blood dyscrasias (rare)

~ VIA THE 30S RIBOSOME (BACTERICIDAL)

Aminoglycosides (e.g. Gentamicin, Tobramycin, Amikacin, Streptomycin, Neomycin)
❑ mechanism of action
- inhibit protein synthesis initiation by binding to the 30S ribosomal subunit thereby causing misreading of mRNA

❑ susceptibility
- primarily active against Gram negative aerobes and mycobacteria
- tobramycin is most active against *Pseudomonas aeruginosa*
- synergistic with penicillins against *Enterococci* and *Pseudomonas*

❑ side-effects
- nephrotoxicity, ototoxicity, vertigo, neurotoxicity

~ VIA THE 30S RIBOSOME (BACTERIOSTATIC)

Tetracyclines (e.g. Tetracycline, Doxycycline)
❑ mechanism of action
- inhibit protein synthesis by binding to the 30S ribosomal subunit thereby blocking amino acid linked tRNA from binding to the A site of the ribosome

❑ susceptibility
- *Chlamydia, Mycoplasma, Rickettsia*, Gram positive cocci

❑ side-effects
- GI upset, hepatotoxicity
- photosensitivity, dental staining (contraindicated in pregnancy, neonates, children)

❑ clinical indications
- used for acne and chlamydial infections
- doxycycline used for malaria prophylaxis and treatment

FOLIC ACID METABOLISM INHIBITORS (BACTERIOSTATIC)

Co-Trimoxazole (Trimethoprim-Sulfamethoxazole, TMP/SMX)
❑ mechanism of action
- 2 mechanisms of interfering with folic acid synthesis as described for TMP and SMX (synergistic)
  - TMP inhibits dihydrofolate reductase which inhibits nucleic acid synthesis and bacterial growth
  - SMX competes with paraaminobenzoic acid for incorporation into folic acid which also inhibits nucleic acid synthesis and bacterial growth

❑ susceptibility
- broad spectrum Gram positives and Gram negatives
- *Pneumocystis carinii*
- *Isospora* and *Cyclospora spp.*

❑ side-effects
- kernicterus (sulfonamides compete with bilirubin for albumin sites), renal toxicity, photosensitivity, hemolysis, hepatotoxicity, fever, Stevens-Johnson Syndrome

❑ clinical indications
- UTI, traveller's diarrhea
- *Pneumocystis carinii* pneumonia, *Isospora, Nocardia, Toxoplasma* infections

DNA GYRASE INHIBITORS (BACTERICIDAL)

Quinolones (Ciprofloxacin, Norfloxacin, Ofloxacin, Nalidixic Acid)

- ❑ mechanism of action
  - prevents supercoiling of nucleic acids
- ❑ susceptibility
  - enteric Gram negative bacilli
  - limited Gram positive coverage
  - unreliable activity against *S. pneumoniae*
  - no anaerobic coverage
- ❑ side-effects
  - CNS: seizures, headache, dizziness, ophthalmologic changes
  - nausea, rash, pruritus, photosensitivity
  - not recommended for children and pregnant women
- ❑ clinical indications
  - mainly for UTI
  - only ciprofloxacin and ofloxacin can be used for infection outside the urinary tract due to high bioavailability

DNA-DIRECTED RNA POLYMERASE INHIBITORS (BACTERICIDAL)

Rifampin

- ❑ mechanism of action
  - inhibits bacterial protein synthesis by interacting with the DNA-dependent RNA polymerase, thus preventing chain initiation
- ❑ susceptibility
  - covers Gram positive cocci, many Gram negative bacilli, most *Mycobacterium* species
- ❑ side-effects
  - dizziness, abdominal pain, nausea, vomiting, diarrhea, visual changes, pruritus, rash, renal dysfunction
  - transient abnormalities in liver function, jaundice
  - turns tears, saliva, and urine orange-red
  - induces P450 enzymes and alters metabolism of oral contraceptives, oral hypoglycemics, coumadin, corticosteroids, digoxin, methadone

DNA COMPLEX DAMAGING AGENTS (BACTERICIDAL)

Metronidazole

- ❑ mechanism of action
  - intrabacterial activation of the drug leads to release of toxic metabolites that cause damage to the microbial DNA
- ❑ susceptibility
  - covers strictly anaerobic bacteria and several protozoan parasites (*Trichomonas vaginalis, Giardia lamblia, Entamoeba histolytica*)
- ❑ side-effects
  - major: disulfiram type reaction with alcohol, peripheral neuropathy
  - minor: anorexia, nausea, diarrhea, reversible neutropenia, metallic taste, dark or red-brown urine, rash
- ❑ clinical indications
  - anaerobic infections
  - *Trichomonas vaginitis*
  - invasive amoebiasis including liver abscesses
  - giardiasis
  - first line for pseudomembranous colitis (C. *difficile*)

ANTI-TUBERCULOSIS DRUGS

1ST LINE DRUGS
(e.g. Isoniazid, Rifampin)

Isoniazid (INH)
- ❑ bactericidal agent that inhibits mycolic acid synthesis in mycobacterial cell walls
- ❑ side-effects include hepatitis, peripheral neuropathies (prevent by pretreating with pyridoxine Vitamin B6)

Rifampin
(see Antibacterials Section)

2ND LINE DRUGS
(e.g. Ethambutol, Pyrazinamide)

Ethambutol
- ❑ bactericidal agent that inhibits mycolic acid synthesis in mycobacterial cell walls
- ❑ side-effects include retrobulbar neuritis resulting in loss of central vision

Pyrazinamide (PZA)
- ❑ unknown mechanism of action
- ❑ side-effects include hepatotoxicity, gout, gastric irritation

Streptomycin (aminoglycoside)
(see Antibacterials Section)

3RD LINE DRUGS
(e.g. Ethionamide, Cycloserine, Clofazimine)
- ❑ see below

ANTI-M. AVIUM-INTRACELLULARE COMPLEX DRUGS

Clarithromycin, Ciprofloxacin
(see Antibacterials Section)

Ethambutol, Clofazamine, Cycloserine

ANTI-LEPROSY DRUGS

Sulfones (e.g. Dapsone, Sulfoxone)
- ❑ action similar to that of sulfonamides (see Antibacterials Sulfonamides Section)
- ❑ side-effects include skin rash, drug fever, agranulocytosis

Clofazimine
- ❑ functions by binding to *Mycobacterium Ieprae* DNA
- ❑ also has anti-inflammatory actions for treating the leprosy reactions
- ❑ major toxicity: skin discoloration

Rifampin
(see Antibacterials Section)

- ❑ viruses are composed of an internal core containing single or double-stranded DNA or RNA, covered by a protein coat, and may have a surrounding envelope of glycoprotein
- ❑ virion is a single virus particle
- ❑ classification of human viruses based on:
  - nature of nucleic acid (DNA vs. RNA)
  - structure of virion (symmetry, size)
  - presence or absence of a viral envelope

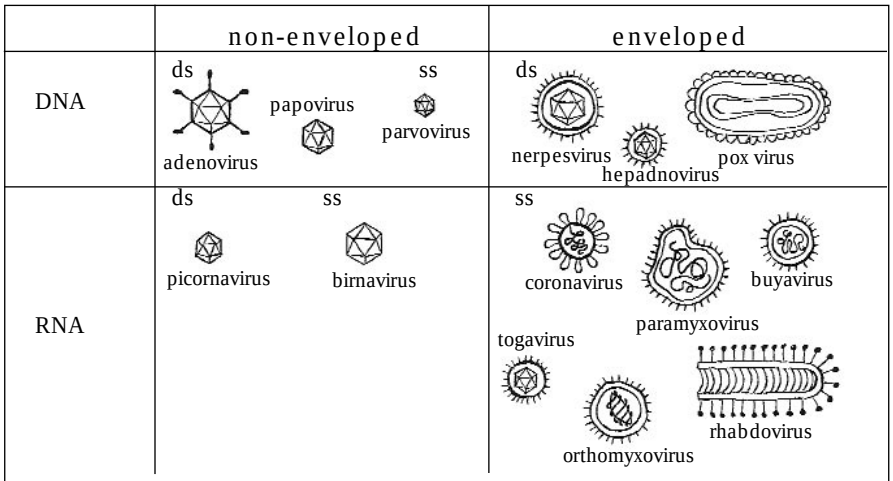


Figure 3. Representative Families of Viruses

Drawing by Muyuki Fukuma

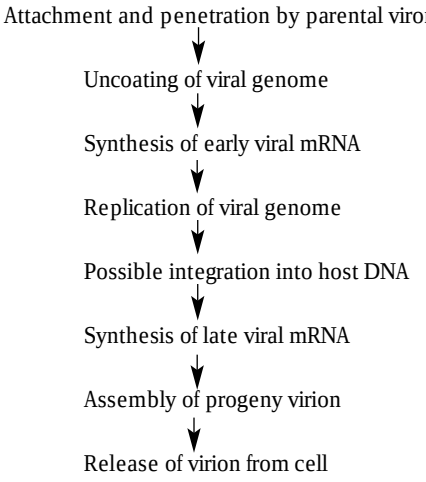


Figure 4. Stages of Viral Growth Cycle

DNA VIRUSES

HERPES VIRUSES

- ❑ large, enveloped viruses that encode own DNA polymerase
- ❑ include HSV1, HSV 2, VZV, EBV, CMV, HHV6, HHV7, HHV8 (the virus causing Kaposi's sarcoma)

Herpes Simplex Virus (HSV) Types 1 and 2

- ❑ modes of transmission
  - HSV 1 or 2 transmitted via saliva, mouth-to-skin contact, autoinoculation of eyes or via sexual intercourse, and birth canal
- ❑ pathogenic mechanisms
  - dormant in nerve root ganglion
  - reactivation under stress, illness, fever, change in temperature, immunocompromise

- ❑ clinical features
  - vesicular lesions in clusters on an erythematous base
  - HSV 1 or 2: gingivostomatitis (cold sores), herpetic keratitis, encephalitis, genital/anal herpes, neonatal herpes, aseptic meningitis
- ❑ diagnosis
  - immunofluorescence
  - PCR
  - viral culture: "gold standard"
  - Tzanck smear
  - specimen scraped from base of lesion reveals multinucleated giant cells (syncytia) and intranuclear inclusion bodies
  - serology (retrospective diagnosis)
- ❑ treatment and prevention
  - acyclovir, valacyclovir or famciclovir for primary episode of genital infection, neonatal infection, encephalitis
  - chronic suppressive treatment in severe or frequent recurrent genital disease, or in compromised host
  - virus can be shed even in the absence of visible lesions
  - avoid contact with vesicular lesions or ulcers
  - Cesarean section for pregnant women who have genital lesions and ruptured membranes for less than 4 hours, especially if a primary infection

Varicella-Zoster Virus (VZV)

- ❑ mode of transmission
  - highly contagious
  - transmitted via aerosolized droplets (i.e. air-borne for chicken pox); contact with ruptured vesicles (shingles or chicken pox)
- ❑ pathogenic mechanisms
  - zoster (or shingles) is reactivation of dormant virus in dorsal root ganglion
- ❑ clinical features
  - varicella (chicken pox) – (see Pediatrics Notes)
    - primary infection usually in childhood
    - incubation period 10-21 days, average 14 days
    - fever and headache (2 days prior to skin rash)
    - pruritic rash (maculopapules, vesicles, crusts) starting on trunk and face and then spreading
    - hallmark is the simultaneous presence of different stages of eruption
    - infectious 1 day before lesions appear and several days after
    - complications include secondary bacterial skin infection (including GAS), thrombocytopenia, interstitial pneumonia (adults), cerebellar ataxia, and death in neonates and immunocompromised patients
  - zoster (shingles)
    - pain may precede eruption
    - painful eruption of vesicles isolated to a single dermatome (may involve adjacent dermatomes, may be multidermatomal, e.g. HIV disease or immunosuppressed)
    - if involves CN V_1 dermatome, high risk of corneal involvement (see Ophthalmology Notes)
    - vesicles dry up and form crusts, which disappear in 3 weeks
    - complication: post-herpetic neuralgia in a dermatomal distribution
- ❑ diagnosis
  - clinical presentation (most important)
  - culture and immunofluorescent stains
  - Tzanck smear reveals multinucleated giant cells and intranuclear inclusion bodies
- ❑ treatment
  - symptomatic: antihistamine, oatmeal colloid bath, calamine lotion
  - acetaminophen for fever (avoid ASA in children because of association with Reye's syndrome)
  - antiviral medications if immunocompromised host or if immunocompetent host within 72 hour of onset of illness to shorten illness duration and to decrease post-herpetic neuralgia
  - famciclovir and valacyclovir have higher bioavailability and less frequent dosing prevention
  - acyclovir to prevent disseminated zoster or visceral disease in immunocompromised patient
  - VZIG post-exposure for high risk patients
  - vaccine effective and available in Canada (recommended by Canadian Pediatrics Association)

Epstein-Barr Virus (EBV)

- ❑ mode of transmission
  - transmitted through saliva, bodily secretions, organ/blood donation
  - intimate contact, e.g. kissing
- ❑ clinical features
  - lifelong infection
  - asymptomatic (most infections)
  - infectious mononucleosis (see Pediatrics Notes)
    - fever, exudative pharyngitis, severe lethargy, lymphadenopathy, splenomegaly, atypical lymphocytosis
    - rash if given ampicillin
  - lymphoproliferative disease (Burkitt's lymphoma, nasopharyngeal carcinoma, transplant-associated lymphomas)
  - hairy oral leukoplakia (HIV-associated infection)
- ❑ diagnosis
  - atypical lymphocytes, lymphocytosis
  - monospot test to detect presence of heterophile antibodies (false negative common in children)
  - serology
- ❑ treatment and prevention
  - supportive
  - avoid contact sports for one month (risk of splenic rupture)
  - steroids for pharyngeal swelling causing airway obstruction, severe thrombocytopenia, hemolytic anemia
  - antibiotics for secondary bacterial infection
  - no EBV vaccine available

Cytomegalovirus (CMV)

- ❑ mode of transmission
  - common pathogen present in breast milk, saliva, urine, tears, genital secretions
  - sexual transmission/prolonged intimate exposure
  - vertical transmission (TORCH infection)
  - through blood products, transplants
- ❑ clinical features
  - congenital disease (severity ranging from rash and hearing loss to microcephaly and mental retardation)
  - asymptomatic infection (most common)
  - CMV “mononucleosis” syndrome
  - reactivation in immunocompromised patients (e.g. HIV, transplants)
  - retinitis (HIV), pneumonitis, colitis, esophagitis
- ❑ diagnosis
  - culture
  - cytology (owl's eye inclusion bodies)
  - serology
  - antigen detection, PCR
- ❑ treatment and prevention
  - foscarnet, ganciclovir, or cidofovir
  - ganciclovir, acyclovir used in transplant patients
  - safer sex practices
  - no effective vaccine available
  - CMV antibody-negative blood products, match donor and recipient status with organ transplant

Human Herpes Virus 6 (HHV6)

- ❑ mode of transmission
  - transmitted by saliva
- ❑ clinical features
  - roseola (exanthem subitum)
    - most common in children under two years of age
    - high fever (non-toxic, child looks well) lasting 3-5 days, post-auricular lymphadenopathy
    - followed by (rose-pink) rash as fever subsides, mostly on the trunk, lasting 1-2 days
- ❑ diagnosis
  - clinical presentation
- ❑ treatment
  - supportive

PAPOVAVIRUS

- ❑ small viruses with double-stranded, circular DNA

Human Papilloma Virus (HPV)

- ❑ microbiology
  - over 50 antigenic types, some more oncogenic (types 16, 18)
- ❑ mode of transmission
  - sexually transmitted (genital, oral warts)
  - contact (plantar, hand warts)
- ❑ clinical features
  - common warts, genital warts, laryngeal warts (recurrence common)
  - cervical dysplasia and cancer (types 16, 18), anal dysplasia
- ❑ diagnosis
  - PAP smear (see Gynecology Notes)
  - ELISA, PCR
- ❑ treatment and prevention
  - difficult
  - wart removal by: liquid nitrogen, excision, electrocautery, podophyllin, alpha-interferon, trichloroacetic acid
  - many warts resolve spontaneously in 1-2 years
  - relapses are common after treatment because HPV DNA is found in normal appearing tissue around the wart
  - use condoms and avoid contact with infected tissue

ADENOVIRUSES

- ❑ microbiology
  - non-enveloped viruses with double-stranded DNA
  - almost 100 different serotypes, 47 affecting humans and subdivided into 6 subgroups
- ❑ mode of transmission
  - aerosol, close contact, fecal-oral route, and fomites
- ❑ clinical features
  - potential for prolonged infection without disease
  - upper respiratory infections, conjunctivitis (pharyngoconjunctival fever)
  - epidemic keratoconjunctivitis
  - acute hemorrhagic cystitis in children
  - gastroenteritis
- ❑ diagnosis
  - virus isolates from lung biopsy, conjunctival swabs, urine
- ❑ treatment and prevention
  - no specific therapy
  - live, non-attenuated vaccine used in military but no vaccine for civilian use

RNA VIRUSES

HIV (see Infections in the Compromised Host Section)

Human T-Cell Lymphotropic Virus (HTLV) Types I and II

- ❑ HTLV Type I: causative agent of certain cutaneous adult T-cell leukemia/lymphoma; implicated in HTLV-I myelopathy (tropical spastic paraparesis)
- ❑ transmission by blood, breast milk, and sexual intercourse
- ❑ increased incidence in those of Japanese or Caribbean descent

PICORNA VIRUSES

- ❑ 5 genera (enterovirus, rhinovirus, aphthovirus, cardiovirus, hepatovirus)
- ❑ small, naked icosahedral capsid virus with single-stranded RNA

Enteroviruses

- ❑ microbiology
  - includes poliovirus, coxsackie A and B, echoviruses
- ❑ mode of transmission
  - fecal-oral route
  - humans are only natural host
- ❑ clinical features
  - poliovirus: poliomyelitis
  - coxsackie A: hemorrhagic conjunctivitis, aseptic meningitis, herpangina, hand, foot and mouth disease

- coxsackie B: myocarditis, pleurodynia
- echovirus: aseptic meningitis, maculopapular rash, febrile illness
- target organs include meninges, myocardium, and skin

❑ diagnosis
- CSF: high lymphocytosis, normal to slightly decreased glucose, normal to slightly increased protein
- culture (pharynx, feces)
- serology

❑ treatment and prevention
- supportive
- poliomyelitis can be prevented by killed (Salk) and live-attenuated vaccine (Sabin)
- no vaccine available for echovirus, coxsackie
- good personal hygiene

Rhinoviruses

❑ microbiology
- more than 100 serological types
- also known as common cold viruses

❑ mode of transmission
- transmitted via respiratory route, or by hands to mucosa
- replication in nose

❑ clinical features
- major causes of mild URI syndromes in all age groups, especially older children and adults
- incubation period 2-4 days followed by rhinorrhea, sneezing, cough, sore throat and headache

❑ diagnosis
- clinical presentation
- serological tests are not done

❑ treatment and prevention
- no specific therapy but zinc lozenges may shorten symptomatic period
- no vaccine available
- hand washing and disinfecting contaminated objects

ORTHOMYXO VIRUSES

❑ includes influenza A, B
❑ enveloped viruses with segmented, negative-sense RNA genome

Influenza Virus

❑ microbiology
- type A has greatest virulence and potential epidemic and pandemic spread
- antigenic drift every few years with type A

❑ mode of transmission
- human and animal reservoirs (birds)
- aerosol spread

❑ clinical features
- "the flu": fever, coryza, cough, myalgias, arthralgias
- incubation period 1-4 days
- complications: secondary bacterial pneumonia in the elderly

❑ diagnosis
- clinical presentation, culture, IFA of nasopharyngeal swabs, serology

❑ treatment and prevention
- amantadine prophylaxis (in outbreaks)
- zamnamivir for treatment or prevention
- acetaminophen for fever (avoid ASA)
- vaccine recommended annually for high risk groups consists of killed influenza A and B viruses and is reformulated each year to contain current antigenic strains

PARAMYXO VIRUSES

❑ viruses with negative sense, single-stranded RNA
❑ transmitted in respiratory droplets and initiate infection in respiratory tract

Parainfluenza Virus

❑ microbiology
- four subtypes (1-4)

❑ mode of transmission
- respiratory droplets

❑ clinical features
- type 1: acute croup (laryngotracheobronchitis)

- type 2: less significant than types 1 or 3; associated with croup and mild URI and occasionally with acute lower respiratory disease; outbreaks usually in fall months
- type 3: major cause of severe lower respiratory disease in infants and young children; often causes bronchiolitis, pneumonia, croup in those < 1 year; infections are common and can occur in any season
- type 4: least common; generally associated with mild URI

❑ diagnosis
- serology
- virus isolation
- direct immunofluorescence for antigen detection

❑ treatment and prevention
- supportive; currently no method of control or specific therapy
- live-attenuated vaccine given to children at 15 months of age
- for treatment of croup, (see Pediatrics Notes)

Respiratory Syncytial Virus (RSV)

❑ mode of transmission
- spread to the upper respiratory tract by contact with infective secretions on hands, fomites, or via respiratory route

❑ clinical features
- most children infected by age 4
- incubation period of 4-5 days
- causes infant bronchiolitis and pneumonitis lasting up to 2 weeks
- children and adults have milder illness

❑ diagnosis
- virus isolation, direct immunofluorescence of nasopharyngeal swab

❑ treatment
- supportive
- ribavirin aerosol treatment might be effective in some circumstances (e.g. patient with underlying chronic heart/lung disease or immunodeficiency), but difficult to administer
- no vaccine available

Measles (Rubeola)

❑ microbiology
- also known as morbillivirus

❑ mode of transmission
- epidemics in nonimmunized groups
- transmitted via the respiratory route
- highly communicable

❑ clinical features
- incubation period 10 days (range 5-21)
- typical illness lasts 7-11 days
- symptoms include high fever, cough, coryza and conjunctivitis (the 3C's)
- 1-3 days after onset, pinpoint gray-white spots surrounded by erythema appear on mucous membranes (Koplik's spots)
- 12-24 hours later, the maculopapular and semiconfluent measles rash begins, starting on the head, then on the trunk and extremities (descending pattern of rash)
- complications
  - bacterial superinfections e.g. pneumonia
  - thrombocytopenia, purpura and bleeding in acute phase
  - meningoencephalitis (1/1000)
  - subacute sclerosing panencephalitis (1/500 000)

❑ diagnosis
- usually clinical diagnosis
- virus isolation from the oropharynx or urine only required in atypical cases
- rapid diagnosis by immunofluorescence

❑ treatment and prevention
- no specific therapy is available
- close observation and supportive measures for the development of complications
- live-attenuated vaccine given to children after 12 months of age and at 4-6 years of age (see Pediatrics Notes)
- vaccine not given to pregnant women, immunocompromised patients

Mumps

❑ microbiology
- 1 serotype

- ❑ mode of transmission
  - respiratory route
  - person-to-person contact
  - life-long immunity follows infection
- ❑ clinical features
  - after an incubation period of 12 to 29 days, the typical case is characterized by fever with tender swelling of the salivary glands, especially the parotid glands
  - swelling may be unilateral or bilateral persisting for 7-10 days
  - complications
    - usually within 1-3 weeks of onset of illness
    - meningitis, encephalitis, transverse myelitis, pancreatitis, orchitis, oophoritis, nephritis, arthritis
- ❑ diagnosis
  - increased serum amylase
  - cell culture from saliva, throat, CSF, urine
  - viral antigen detected by immunofluorescence
  - EIA detects IgM and IgG responses
- ❑ treatment and prevention
  - no specific treatment
  - live-attenuated vaccine given to children after 12 months of age and at 4-6 years (see Pediatric Notes)
  - vaccine not given to pregnant women, immunocompromised patients

TOGA VIRUSES

❑ enveloped viruses with single-stranded RNA

Rubella

- ❑ microbiology
  - also known as rubivirus
- ❑ mode of transmission
  - respiratory route
- ❑ clinical features
  - mild URTI with lymphadenopathy
  - macular rash prominent over the head, neck, and trunk; may be quite faint and last 1-3 days
  - arthralgia, arthritis most common in women
  - congenital rubella syndrome
    - fetal damage with infection in first trimester
    - cataract formation, hearing impairment, small for gestational age, mental retardation, developmental delay result
    - increases *in utero* mortality
    - complications (rare) include thrombocytopenia, post-infectious encephalitis
- ❑ diagnosis
  - hemagglutination inhibition test used for serodiagnosis
  - IgM and IgG tests can help detect acute and congenital infection
- ❑ treatment and prevention
  - no specific treatment
  - live-attenuated vaccine given after 15 months and at 4-6 years (see Pediatrics Notes)
  - preconception counselling and screening for immunity

RHABDO VIRUSES

❑ bullet-shaped, enveloped viruses containing single-stranded RNA

Rabies Virus

- ❑ mode of transmission
  - zoonotic infection, i.e. transmission via animal bites
  - reservoirs: all warm-blooded animals (dogs, cats, skunks, coyotes, foxes, raccoon, bats) but not rodents
- ❑ clinical features
  - incubation can be from 2 weeks to years
  - prodrome: fever, headache, sore throat, increased sensitivity around the healed wound site (duration of 2-10 days)
  - acute encephalititis
    - hyperactivity, agitation, confusion, seizures, (duration of 2-10 days)
  - classic brainstem encephalitis
    - cranial nerve dysfunction, painful contraction of pharyngeal muscles when swallowing liquids, resulting in hydrophobia and foaming of the mouth
    - duration of 2-10 days

- coma
- death due to respiratory centre dysfunction
- fatal unless treated with post-exposure vaccine and immunoglobulin

❑ diagnosis
- microscopic examination of the CNS reveals Negri bodies (inclusion bodies in neurons)

❑ treatment and prevention (see Emergency Medicine Notes)
- post-exposure vaccine is effective
- treatment depends on regional prevalence (contact Public Health)
- if bitten by a possibly rabid animal (i.e. unusual behavior or wild animals)
  - capture animal and observe for 10 days
  - sacrifice animal and examine brain for Negri bodies
  - treat immediately if the animal cannot be captured, or if the animal is found to have rabies
- clean wound
- passive immunization with Human Rabies Ig
- active immunization with killed rabies virus vaccine (human diploid cell vaccine x 5 doses over 1 month)
  - available for persons at high risk of exposure
  - vaccinate animals

ANTIVIRALS

NON-NUCLEOSIDE POLYMERASE INHIBITORS

Interferon-alpha 2B

❑ mechanism of action
- induces production of immune proteins that inhibit RNA synthesis
- inhibits viral mRNA
- available for subcutaneous injection

❑ susceptibility
- used for chronic Hepatitis B and C, condyloma acuminatum (caused by HPV), Kaposi's sarcoma

❑ side-effects
- flu-like syndrome: fever, headache, nausea, myalgias
- neutropenia, thrombocytopenia
- neurotoxicity, confusion

Amantadine/Rimantadine

❑ mechanism of action
- inhibits the viral uncoating after entering the cell thereby blocking the release of viral genome into the cell

❑ susceptibility
- orthomyxo viruses (influenza A)
- paramyxo viruses
- toga virus (rubella)

❑ side-effects
- anticholinergic effects: dry mouth, urinary retention
- CNS (rare): confusion, anxiety, insomnia
- teratogenicity: pregnant women should not use

Phosphonoformate

❑ mechanism of action
- pyrophosphate analog inhibits viral DNA polymerase and reverse transcriptase by competing for pyrophosphate sites

❑ susceptibility
- all Herpes viruses

❑ side-effects
- reversible nephrotoxicity
- nausea, headache, fatigue, tremor
- anemia, hypocalcemia, hypomagnesemia, hypophosphatemia

NUCLEOSIDE ANALOGS

- ❑ chemically modified nucleoside that are incorporated into growing viral DNA chains, thereby preventing elongation of the chains and inhibiting DNA polymerase
- ❑ new formulations of pro-drugs lead to increased serum concentrations

Anti-Retrovirals (see HIV/AIDS Section)

Acyclovir

- ❑ mechanism of action
  - guanosine analogue uses viral thymidine kinase for phosphorylation into its active form
- ❑ susceptibility
  - highly potent, highly specific anti-herpetic agent
  - very potent against HSV 1, HSV 2, and VZV infections
  - only minor activity against EBV and CMV
- ❑ side-effects
  - inflammation at injection site
  - crystalline nephropathy if drug is infused rapidly without adequate hydration
  - neurotoxic at high doses: confusion, lethargy, seizures

Ganciclovir

- ❑ mechanism of action
  - guanosine analog, activated by host cell thymidine kinase
  - induced by CMV infection
- ❑ susceptibility
  - CMV: retinitis, pneumonitis, esophagitis, prophylaxis in organ transplant patients
  - also effective against HSV, VZV, EBV but not used due to its high toxicity
- ❑ side-effects
  - hematologic: neutropenia, thrombocytopenia, anemia
  - rash, CNS toxicity, confusion, GI upset

Ribavirin

- ❑ mechanism of action
  - guanosine analog
- ❑ susceptibility
  - RSV bronchiolitis or pneumonia
  - influenza A or B infections
  - Lassa fever, Hanta virus pulmonary syndrome
- ❑ side-effects
  - little toxicity when given via aerosol (conjunctivitis)
  - extremely expensive
  - teratogenic

Table 2. Specific Viruses Targeted by Available Antiviral Drugs

Virus	Antiviral Drug (Generic/Trade Name)	Class of Drug
HSV, VZV	acyclovir/Zovirax valacyclovir/Valtrex famciclovir/Famvir	nucleoside analog
CMV	phosphonoformate/Foscarnet	non-nucleoside polymerase inhibitor
	ganciclovir/Cytovene	nucleoside analog
Influenza A	ribavirin/Virazole	nucleoside analog
	amantadine/Symmetrel	non-nucleoside polymerase inhibitor
RSV	ribavirin/Virazole	nucleoside analog
HPV, Hep C/B	interferon alpha	immune system modulation

- ❑ mechanisms by which fungi cause disease:
  - mycotoxicoses e.g. aflatoxin, hallucinogenic mushrooms
  - hypersensitivity disease
  - colonization of host and resulting disease

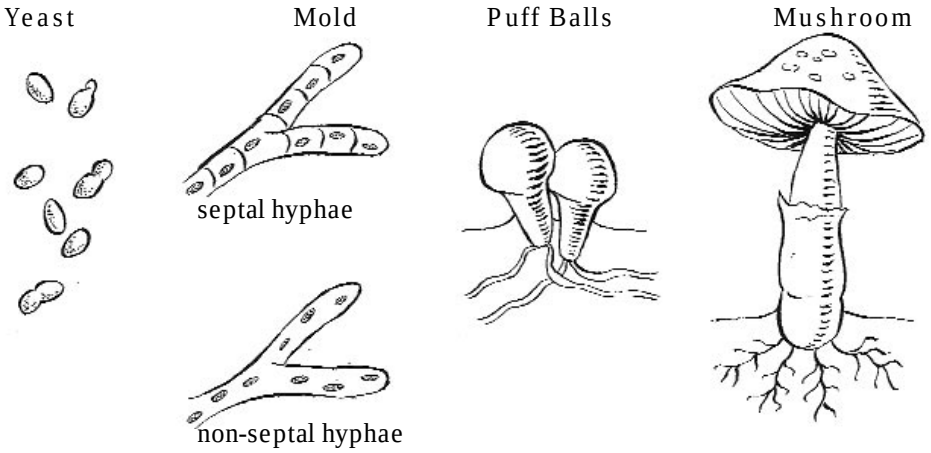


Figure 5. Common Fungus Morphology

Drawing by Muyuki Fukuma

PRIMARY PATHOGENIC FUNGI

Histoplasma capsulatum

- ❑ microbiology
  - dimorphic: has both yeast and mycelial forms
  - mycelium in the environment
  - in tissue, a budding yeast usually found within phagocytes
- ❑ mode of transmission
  - endemic in central USA, St. Lawrence Valley
  - exposure to bird/bat excrement
  - inhalation of airborne spores in environment
  - present in soil of endemic regions
- ❑ clinical features
  - asymptomatic
  - pneumonia: calcified lesions can be seen on CXR (may look similar to TB)
  - disseminated infection in immunocompromised - especially in lung, spleen, liver, lymph node
- ❑ diagnosis
  - biopsy, serology, culture, exoantigen test
- ❑ treatment
  - itraconazole
  - amphotericin B (if immunocompromised patient, treatment failure, or rapidly progressive disease)

Blastomyces dermatitidis

- ❑ microbiology
  - dimorphic (mycelial and yeast forms)
  - large, budding yeast in tissue
- ❑ mode of transmission
  - outbreaks primarily in midwest USA
  - Red River Valley, St. Lawrence Valley, Northern Ontario (Timmins)
  - inhalation of airborne spores in environment
  - infects and causes disease in humans, horses and dogs
- ❑ clinical features
  - also known as Chicago disease or Gilchrist's disease
  - symptoms may resemble TB
  - chronic granulomatous infection
  - characteristically forms abscesses
  - pneumonia, bone lesions, skin lesions
- ❑ diagnosis
  - CXR: non-specific pulmonary infiltrates without calcification
  - bronchoalveolar lavage, skin biopsy
  - serology, culture
- ❑ treatment
  - itraconazole, amphotericin B

Coccidioides immitis

- ❑ microbiology
  - dimorphic (sporangia and mycelial forms)
- ❑ mode of transmission
  - desert areas of the southwest USA (San Joaquin Valley) and northern Mexico
  - epidemics associated with dust storms
  - inhalation of airborne arthrospores from environment (e.g. soil)
- ❑ clinical features
  - also known as desert rheumatism, and San Joaquin Valley fever
  - acute, self-limiting, benign respiratory infection in most persons
  - influenza-like syndrome: fever, chills, cough, chest pain, sore throat
  - disseminated - can affect the lungs, skin, bones and meninges
  - common opportunistic infection in AIDS patients from the southwest USA
- ❑ diagnosis
  - KOH preparation and microscopy of specimen looking for doubly refractile spherules
  - culture, serology
- ❑ treatment
  - amphotericin B, ketoconazole, fluconazole

OPPORTUNISTIC FUNGI

- ❑ fungi which become pathogens due to an immunocompromised state (e.g. HIV infection, transplantation, use of corticosteroids or cytotoxic drugs, hematologic malignancies)

Pneumocystis carinii

- ❑ microbiology
  - previously classified as a protozoan
  - unicellular fungi
- ❑ mechanism of transmission
  - acquired at an early age by the respiratory route
  - remains latent in immunocompetent hosts
  - common opportunistic infection in AIDS patients
    - occurs when CD4 count < 200 x 10^6/L
    - 80% lifetime risk without prophylaxis
- ❑ clinical features
  - interstitial pneumonia (PCP)
    - bilateral interstitial disease
    - may also present with pneumothorax
    - fever, dry, nonproductive cough, progressive dyspnea
  - elevated LDH in about 90% of patients
- ❑ diagnosis
  - monoclonal staining of induced sputum or bronchoalveolar lavage
- ❑ treatment and prevention
  - oxygen to keep SaO_2 > 90%
  - TMP/SMX (PO or IV), TMP-dapsone (PO), pentamidine (IV), trimetrexate (IV), clindamycin + primaquine (PO), atovaquone (PO)
  - corticosteroids used as adjuvant therapy in those with severe hypoxia (pO_2 < 60 mmHg or A-a O_2 gradient > 35 mmHg)
  - prophylactic TMP/SMX or dapsone, aerosolized pentamidine, atovaquone for those at risk

Cryptococcus neoformans

- ❑ microbiology
  - encapsulated yeast
  - serotypes A, B, C, D
- ❑ mode of transmission
  - long survival in pigeon droppings
  - inhalation of airborne yeast from environment
  - risk factor: immunocompromised state
- ❑ clinical features
  - primary pulmonary infection (usually asymptomatic)
  - subacute or chronic meningitis
  - pneumonia usually asymptomatic and self-limited
  - skin lesions - resembles *Molluscum contagiosum*
  - osteolytic bone lesions
- ❑ diagnosis
  - CSF: India-ink stain for oval budding cells surrounded by thick gelatinous capsule; cryptococcal antigen test
  - fungal culture (blood, urine, sputum, CSF)
- ❑ treatment
  - amphotericin B, flucytosine, fluconazole

Candida albicans

- ❑ microbiology
  - pseudohyphae and yeast forms
  - grows readily on ordinary culture media
- ❑ mode of transmission
  - normal flora of skin, mouth, vagina and GI tract
  - risk factors: immunocompromised state, broad-spectrum antibiotics, diabetes, corticosteroids
- ❑ clinical features
  - immunocompetent host: oral thrush, vulvovaginal candidiasis (see Gynecology Notes), cutaneous (diaper rash, skin folds)
  - immunocompromised host:
    - thrush, vaginitis and/or cutaneous
    - esophageal (retrosternal chest pain, odynophagia, fever)
    - endophthalmitis, endocarditis, UTI
    - chronic mucocutaneous candidiasis
- ❑ diagnosis
  - mount scrapings in 10% KOH
  - Gram stain and culture
- ❑ treatment
  - thrush: swish and swallow nystatin or imidazole
  - vulvovaginal candidiasis: topical imidazole or nystatin; or oral fluconazole
  - cutaneous infection: topical imidazole
  - AIDS opportunistic infections (thrush, esophageal, vaginal): fluconazole, itraconazole, ketoconazole
  - systemic candidiasis: amphotericin B, fluconazole
  - chronic mucocutaneous candidiasis: ketoconazole, fluconazole, itraconazole, or amphotericin B

Aspergillus spp.

- ❑ microbiology
  - branching septate hyphae
  - common species causing disease include A. *fumigatus, A. flavus*
- ❑ mode of transmission
  - ubiquitous in environment
- ❑ clinical features
  - risk of respiratory distress increases with age
  - allergic bronchopulmonary aspergillosis
  - IgE-mediated asthma-type reaction with dyspnea, high fever, and transient pulmonary infiltrates
  - secondary colonization - aspergilloma formation
  - fungus ball formation in pre-existing cavity (i.e. from old TB)
  - invasive aspergillosis
    - necrotizing pneumonia
    - may disseminate to other organs in immunocompromised patients (e.g. brain)
    - fatal if not treated early and aggressively
  - mycotoxicosis
    - aflatoxin produced by *A. flavus*
    - toxin contaminates nuts, grains, rice
    - results in liver hemorrhage, necrosis, and hepatoma formation
- ❑ diagnosis
  - tissue biopsy with silver staining, culture (often negative)
  - CXR, CT
- ❑ treatment
  - itraconazole, amphotericin B
  - oral prednisone for allergic bronchopulmonary aspergillosis (no antifungal)
  - surgical resection of aspergilloma and hemorrhage

POLYENES

❑ bind to fungal cytoplasmic membrane sterols, particularly ergosterol, and change membrane permeability, resulting in cell death

Amphotericin B

❑ side-effects
- acute: hypotension, fever, chills, nausea, vomiting, thrombophlebitis
- reversible nephrotoxicity resulting in hypokalemia, hypomagnesemia
- anemia, headache, thrombocytopenia, anaphylaxis, burning sensation in hands and feet

❑ clinical indications
- systemic fungal infections: candidiasis, cryptococcosis, blastomycosis, histoplasmosis, coccidioidomycosis, aspergillosis, sporotrichosis, mucormycosis

Nystatin

❑ used for mucocutaneous candidiasis

❑ side-effects
- few adverse effects when administered orally
- large doses cause occasional GI distress and diarrhea

IMIDAZOLES

❑ mechanism of action
- inhibit fungal cytochrome P450-dependent 14-alpha-demethylase —> abnormal ergosterol synthesis —> altered membrane permeability —> cell death

Clotrimazole

❑ side-effects
- insignificant toxicity when used topically

❑ clinical indications
- topical fungal infections: *Tinea versicolor*, cutaneous candidiasis, dermatophytosis, vaginal candidiasis

Miconazole

❑ used topically for vaginal candidiasis

❑ side-effects include phlebitis, pruritus, nausea, fever, rash, vomiting

Ketoconazole

❑ pharmacokinetics
- available in topical and oral forms (requires stomach acid for systemic absorption)
- poor CSF penetration

❑ side-effects
- GI: anorexia, nausea, vomiting, diarrhea, fatal hepatic necrosis (rare)
- endocrine: dose-dependent increased serum testosterone and cortisol which can be manifested as gynecomastia, breast pain
- skin: rash, pruritus
- other: headache, dizziness

❑ clinical indications
- chronic mucocutaneous candidiasis
- ringworm, *Tinea versicolor*
- nonmeningeal histoplasmosis and blastomycosis infections in immunocompetent hosts

TRIAZOLES

❑ mechanism of action as described for imidazoles

Fluconazole

❑ available in oral and IV forms
- excellent CSF penetration (80% of serum levels)

❑ side-effects
- less toxic than ketoconazole with no effect on testosterone or cortisol levels in serum
- nausea, headache, rash, vomiting, diarrhea

❑ clinical indications
- mucocutaneous candidiasis (including esophageal)
- alternative to amphotericin B for treatment of systemic candidiasis, cryptococcal meningitis, coccidioidomycosis

Itraconazole
❑ available in oral form (requires stomach acid for absorption)
❑ side-effects
- less toxic than ketoconazole with no effect on testosterone or cortisol levels
- nausea, hepatitis, edema (rare)

❑ clinical indications
- mucocutaneous candidiasis (including esophageal)
- local *Tinea versicolor* and *Tinea corporis*
- shows promise in treating severe systemic fungal infections (a safer altemative to amphotericin B)
- active against *Aspergillus spp.*

PARASITES

Table 3. Comparison of Protozoa and Helminths

Protozoa	Helminths
• unicellular • trophozoite—> cyst • multiplication • no eosinophilia • indefinite life span i.e. will continue to multiply in host	• multicellular • adult —> egg —> larva • no multiplication* • eosinophilia** • limited life span i.e. will die in host

* exceptions *Strongyloides stercoralis, Hymenolepsis nana*
** highest eosinophilias are associated with tissue invading parasitic infections such as trichinosis, toxocariasis and filariasis
** helminths which do not invade (adult *Ascaris*, tapeworms) do not produce eosinophilia

PARASITES (PROTOZOA)

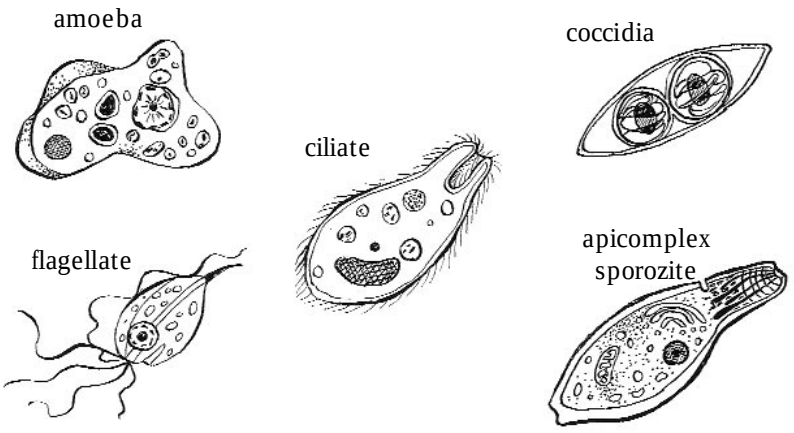


Figure 6. Representative Protozoa

Drawing by Muyuki Fukuma

INTESTINAL AND VAGINAL

Flagellates

- ❑ protozoa with flagella for motility
- ❑ commonly cause disease via mechanical irritation and inflammation

Giardia lamblia

- ❑ mechanism of transmission
  - reservoir is infected humans and other mammals
  - waterborne transmission (especially in the Rockies) and fecal-oral transmission of infectious cysts
  - risk factors: institutions, daycare centres, homosexual men
- ❑ clinical features (Beaver Fever, giardiasis)
  - asymptomatic intestinal infection
  - watery diarrhea; may rarely cause steatorrhea and malabsorption
  - nausea, abdominal cramps, bloating, flatulence, fatigue, weight loss
- ❑ diagnosis
  - multiple stool samples (1 per day x 3 days)
  - occasionally, small bowel aspirate or biopsy for diagnosis
  - antigen detection in stool
- ❑ treatment and prevention
  - metronidazole, furazolidone, paromomycin, albendazole
  - good personal hygiene and sanitation
  - municipal water should be filtered
  - avoid contaminated food

Trichomonas vaginalis

- ❑ mechanism of transmission
  - sexually transmitted
  - via birth canal
- ❑ clinical features (see Gynecology Notes)
  - painful vaginal itching
  - burning on urination; males often asymptomatic
  - yellow-green, malodorous, frothy vaginal discharge (pH > 4.5)
- ❑ diagnosis
  - highly motile flagellated protozoa on examination of vaginal discharge or urine
- ❑ treatment
  - metronidazole to patient and partner

Coccidia

- ❑ part of *Apicomplexa* phylum
- ❑ intracellular parasite
- ❑ capable of asexual and sexual reproduction

Cryptosporidium spp.

- ❑ mechanism of transmission
  - reservoir: infected humans and a wide variety of young animals
  - fecal-oral transmission by the ingestion of feces containing infectious cysts; waterborne
  - risk factors: summer and fall, young children, homosexual men, contact with farm animals, HIV infection
- ❑ clinical features
  - asymptomatic carrier
  - immunocompetent patients: self-limited (within 10 days) watery diarrhea
  - immunocompromised patients: severe, large volume diarrhea with cachexia, weight loss and possible death
- ❑ diagnosis
  - modified acid-fast or acridine orange stain of stool specimen
- ❑ treatment and prevention
  - not usually effective
  - no treatment usually required for immunocompetent hosts
  - paromomycin partially effective in AIDS
  - good hygiene, sanitation
  - municipal water filtered

Cyclospora spp.

- ❑ mechanism of transmission
  - fecal-oral route

- seen in travellers, sporadic cases elsewhere
- recent outbreaks associated with contaminated water sources, Central American raspberries, and basil
- parasite requires period of time outside host for maturation

❑ clinical features
- clinically indistinguishable from giardiasis
- often waxes and wanes
- self-limited diarrheal illness, frequent watery stools, anorexia, fatigue, bloating
- asymptomatic biliary tract disease

❑ diagnosis
- stool specimen
- acid-fast stain of stool
- parasite fluoresces under UV light

❑ treatment and prevention
- TMP/SMX
- wash produce, filter municipal water
- good hygiene and sanitation

Amoebae

❑ primitive unicellular parasites which reproduce via binary fission
❑ motility via pseudopod (false foot)

Entamoeba histolytica

❑ mechanism of transmission
- reservoir: infected humans
- fecal-oral transmission by the ingestion of feces containing infectious cysts or by insects carrying cysts (e.g. flies, cockroaches); waterborne
- seen in immigrants, travellers, institutionalized individuals, Native Canadians
- most strains are noninvasive and nonpathogenic, now designated *Entamoeba dispar*, indistinguishable microscopically from E. *histolytica*

❑ clinical features
- asymptomatic carrier state (most often)
- intestinal amoebiasis: abdominal pain, cramping, colitis, dysentery, low grade fever with bloody diarrhea secondary to local tissue destruction of large intestine
- extraintestinal amoebiasis: liver abscesses, leukocytosis, fever

❑ diagnosis
- stool exam
- serology when invasive disease suspected
- E. *dispar* distinguished from E. *histolytica* by stool antigen detection and PCR
- serology usually negative in E. *dispar* infections

❑ treatment and prevention
- invasive: metronidazole plus iodoquinol or paromomycin
- cyst/trophozoite passer: iodoquinol or paromomycin alone
- good personal hygiene
- purification of water supply

BLOOD AND TISSUE

Apicomplexa

❑ phyla consisting of coccidia and sporozoan protozoa
❑ intracellular, unicellular parasites with organelles at apex

Plasmodium spp.

❑ microbiology
- common species include: P. *falciparum, P. vivax, P. ovale, P. malariae*
- require two hosts for reproduction cycle: human host for asexual reproduction and mosquito for sexual reproduction

❑ mechanism of transmission
- reservoir: infected human
- transmission by the night-biting female Anopheles mosquito, congenital, and blood transfusion
- P. *vivax* and P. *falciparum* most frequently imported malarias

- ❑ clinical features
  - malaria
    - headache, myalgia
    - periodic episodes (that occur with red cell lysis) of high fever and shaking chills, followed by diaphoresis
      - Tertian malaria: episodes occur every 48 hours (P. *vivax, P. ovale*)
      - Quartan malaria: episodes occur every 72 hours (P. *malariae*)
      - P. *falciparum* (most deadly): irregular fever spikes
      - anemia, thrombocytopenia, hepatosplenomegaly
  - complications of P. *falciparum* malaria
    - cerebral malaria, jaundice, hemoglobinuria, renal failure, ARDS
    - P. *falciparum* parasitemia > 5% fatal, often within several days
    - only P. *vivax* and P. *ovale* have dormant relapsing forms in liver
- ❑ diagnosis
  - thick films: sensitive
  - thin films: to distinguish species - blood should be examined at 12-24 hour intervals (x 3) to rule out infection
- ❑ treatment
  - P. *vivax*, *P. ovale*: chloroquine plus primaquine to eradicate liver forms
  - P. *malariae*: chloroquine
  - P. *falciparum*
    - most areas of world show drug resistance
    - quinine plus doxycycline, Fansidar or clindamycin
    - alternative is mefloquine alone or atovaquone/proguani (Malaxone) combination
    - if severe illness (> 10% parasitemia), then consider exchange transfusion
- ❑ prophylaxis/prevention
  - chloroquine (in chloroquine-sensitive areas)
  - if chloroquine resistance: mefloquine, doxycycline, primoquine, Malaxone
  - mosquito repellents, bed nets, screens

Toxoplasma gondii

- ❑ mechanism of transmission
  - 1/3 of Ontario population infected
  - acquired from ingestion of cat feces or poorly cooked meat from animals which are intermediate hosts (e.g. sheep, goats, cattle)
  - congenital infections only with a primary maternal infection (TORCH infection); as pregnancy progresses morbidity of fetus decreases but likelihood of infection increases
- ❑ clinical features
  - congenital disease
    - stillbirth, chorioretinitis, blindness, seizures, mental retardation, microcephaly
    - normal appearing infant may develop reactivation of chorioretinitis as adolescent or adult
  - acquired disease
    - usually asymptomatic
    - mononucleosis-like syndrome in immunocompetent patient
    - infection remains latent for life unless reactivation due to immunosuppression
    - immunocompromised patients (most commonly AIDS)
      - encephalitis with multiple ring enhancing masses on CT
      - lymph node, liver, and spleen enlargement and pneumonia
- ❑ diagnosis
  - serology, histopathology, antigen or DNA detection (PCR)
- ❑ treatment and prevention
  - pyrimethamine + sulfadiazine (add folinic acid), clindamycin
  - spiramycin in early pregnancy; pyrimethamine/sulfadiazine in late pregnancy
  - corticosteroids for eye disease
  - cook meat thoroughly
  - pregnant women to avoid undercooked meat and refrain from emptying cat litter boxes

Flagellates

Trypanosoma cruzi

- ❑ South and Central America
- ❑ vector-borne - reduviid bug, congenital and blood transfusion

- ❑ Chagas' Disease (American trypanosomiasis)
  - chronic cardiomyopathy +/– achalasia and constipation 10-25 years after acute, flu-like illness
- ❑ treatment
  - treat acute cases with nitrofurtimox, benznidazole
  - no treatment for chronic manifestations
- ❑ prevention
  - insect control, bed nets when sleeping in adobe huts (mud walls, thatched roof)

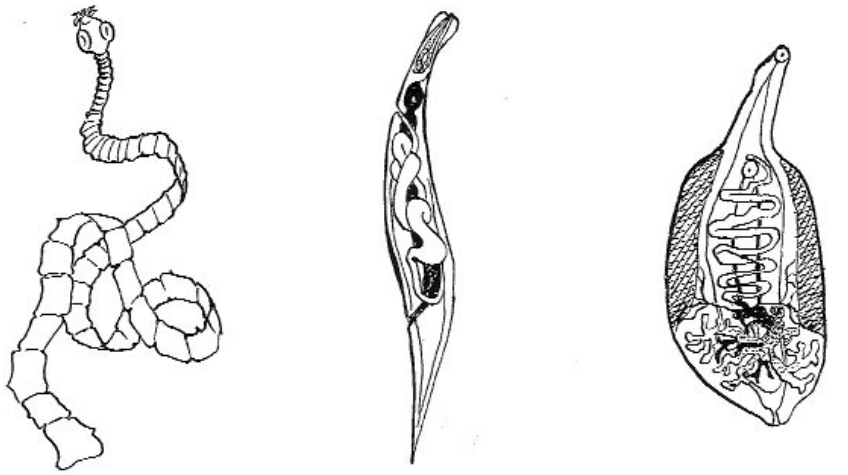
Trypanosoma rhodensiense, T. gambiense

- ❑ East and West Africa
- ❑ vector-borne - tsetse fly bite and contaminated blood transfusion
- ❑ causes sleeping sickness (African trypanosomiasis)
  - systemic illness progresses to CNS involvement and coma
- ❑ treat with suramin, melarsoprol (for CNS involvement) or eflornithine (T. *gambiense*)

Leishmania spp.

- ❑ Africa, Middle East, and Latin America
- ❑ vector-borne - sandfly bite
- ❑ clinical picture depends on species and on patient's cell-mediated immune response
  - cutaneous —> single ulcer
  - diffuse cutaneous —> nodules all over body
  - mucocutaneous —> erodes nasal septum, lips, soft palate
  - visceral (Kala Azar) —> hepatosplenomegaly, fever; often fatal
- ❑ treatment
  - efficacy and choice of treatment depends on infecting species
  - treat cutaneous disease with stibogluconate, pentamidine, itraconazole, local heat or nothing
  - treat visceral disease with stibogluconate, pentamidine, amphotericin B

PARASITES (HELMINTHS)



Nestode (tapeworm) | Nematode (roundworm) | Trematode (fluke)

Figure 7. Morphology of Helminths

Drawing by Muyuki Fukuma

Table 4. General Features of Helminths

Helminth	Shape	Reproduction
Nematode	• roundworm • large, cylindrical, unsegmented • filiariae form (slender, long worm) in blood, lymph and subcutaneous tissue	male and female worms
Cestodes	• flatworms • flat, segmented, ribbonlike • each segment is called a proglottid • head comprised of four suckers and a crown of hooklets	hermaphroditic
Trematodes	• flukes • flat, fleshy, leaf-shaped • two muscular suckers • require intermediate hosts (e.g. snails) for asexual reproduction	hermaphroditic (except *Schistosoma*)

INTESTINAL

Nematodes (Roundworms)

Strongyloides stercoralis (roundworm)

❑ mechanism of transmission
- transmission through unbroken skin, barefoot walking
- adult worms live embedded in mucosa of small intestine
- capable of maintaining life cycle both in human host and in soil
- source of infection: fecal contamination of soil; autoinfection (larvae penetrate skin, enter circulation, migrate through lungs to the trachea, and are swallowed; adults reside in the small intestine)

❑ clinical features
- mostly asymptomatic
- pruritic dermatitis at site of larval penetration
- transient pulmonary symptoms during pulmonary migration of larvae
- epigastric pain, rash, pruritus ani
- vomiting, diarrhea uncommon
- occasional fatal cases caused by massive auto-infection in immunocompromised host: triad of pneumonia, diarrhea and Gram negative bacteremia

❑ diagnosis
- fecal exam for larvae (no eggs), larval culture on agar
- small bowel biopsy
- serology most sensitive (88%)
- eosinophilia common

❑ treatment
- albendazole, ivermectin, thiabendazole

Ascaris lumbricoides (roundworm)

❑ mechanism of transmission
- ingestion
- source of infection: fecal contamination of soil and vegetables, particularly in regions using human feces as fertilizer

❑ clinical features
- asymptomatic in many individuals
- adult worms live in small intestine and may exit nose or mouth of infected person
- occasional obstruction of pancreatic or bile duct, appendix, or small bowel
- dry cough, fever, transient pulmonary infiltrates (Loffler's syndrome), eosinophilia while larvae migrate in the lungs
- children may develop malnutrition due to protein loss

❑ diagnosis
- stool exam for eggs
- dead adult worms in feces or vomitus
- eosinophilia during migration phase, none during adult phase

❑ treatment and prevention
- mebendazole, pyrantel pamoate, albendazole
- good hygiene and sanitation

Necator americanus, Ancylostoma duodenale (hookworms)
- ❑ mechanism of transmission
  - through unbroken skin (barefoot walking)
  - source of infection is fecal contamination, ingestion of larvae
- ❑ clinical features
  - usually asymptomatic in light infections
  - itching at site of skin penetration
  - GI symptoms
  - worms attach to and suck blood from mucosa of small intestine leading to iron-deficiency anemia, peptic ulcer-like symptoms in heavy infections
- ❑ diagnosis
  - stool exam for eggs
  - mild eosinophilia
- ❑ treatment
  - mebendazole, pyrantel pamoate, albendazole

Enterobius vermicularis (pinworm)
- ❑ mechanism of transmission
  - humans only host
  - adult worms live in cecum and migrate at night to perianal skin to deposit eggs
  - self-inoculation by fecal contaminated hand-to-mouth, person to person contact, autoinfection
- ❑ clinical features
  - asymptomatic carrier state
  - severe nocturnal perianal itching
  - occasionally vaginitis
- ❑ diagnosis
  - sticky tape test (5-7 tests required to rule out infection)
    - examination of perianal area at night may reveal adult worms seen with unaided eye
    - no eosinophilia usually
- ❑ treatment and prevention
  - mebendazole, pyrantel pamoate, albendazole, pyrvinium pamoate
  - clean underwear change, pajamas to sleep, bathe in morning, wash hands after BM
  - treat all members of family simultaneously
  - reinfection common

Trichuris trichiura (whipworm)
- ❑ mechanism of transmission
  - ingestion of eggs in soil or on vegetables
  - large bowel parasite
- ❑ clinical features
  - rarely symptomatic
  - heavy infections: diarrhea, abdominal pain, rectal prolapse, stunted growth
- ❑ diagnosis
  - stool exam for eggs
  - mild/no eosinophilia
- ❑ treatment: mebendazole, albendazole

Cestodes (flatworms)

Taenia solium (pork tapeworm)
- ❑ mechanism of transmission
  - ingestion of cestode eggs or undercooked pork containing larvae
- ❑ clinical features
  - ingestion of larval cestode in pork leads to intestinal adult tapeworm infection
  - usually asymptomatic
  - ingestion of eggs (results in cysticercosis)
  - eggs hatch within the small intestine and larvae travel to subcutaneous tissue, muscle, CNS, and/or the eye, where they eventually form cysts to which the host responds with an inflammatory response as they die (after 4-5 years)
    - can develop blindness or neurological manifestations
    - neurocysticercosis is most frequent
    - headache, seizures, focal neurologic deficits, hydrocephalus

- ❑ diagnosis
  - stool exam for eggs or gravid proglottids to diagnose adult tapeworm
  - CT scan, MRI, biopsy of brain or soft tissue X-ray of muscle may reveal multiple cysts
  - serology is the most important diagnostic test for cysticercosis (no need to examine CSF serology)
  - no eosinophilia
- ❑ treatment and prevention
  - cysticercosis: albendazole is treatment of choice, praziquantel alternative
  - corticosteroids to treat “dead worm" reaction (inflammatory response due to larval death), associated with treatment of neurocysticercosis
  - treat tapeworm with albendazole or praziquantel
  - good sanitation and personal hygiene
  - avoid uncooked pork

Taenia saginata (beef tapeworm)
- ❑ mechanism of transmission
  - ingestion of undercooked beef containing larvae
- ❑ clinical features
  - can grow to 25 m in length in the small bowel
  - usually asymptomatic
  - occasionally develop abdominal discomfort, weight loss, and diarrhea; segments (proglottids) can crawl out of anus
- ❑ diagnosis
  - fecal exam for eggs or gravid proglottids
  - no eosinophilia
- ❑ treatment
  - praziquantel, niclosamide

Diphyllobothrium latum (fish tapeworm)
- ❑ mechanism of transmission
  - ingestion of raw freshwater fish containing larvae
- ❑ clinical features
  - can grow to 15 m in length in the small bowel
  - nonspecific abdominal symptoms
  - vitamin B_{12} deficiency, leading to macrocytic anemia and neurological findings
- ❑ diagnosis
  - fecal exam for eggs or gravid proglottids
  - no eosinophilia
- ❑ treatment and prevention
  - praziquantel
  - cook fish well before consumption
  - good sanitation

Trematodes (Flukes)

Clonorchis sinensis
- ❑ mechanism of transmission
  - ingestion of raw fish
- ❑ clinical features
  - mostly asymptomatic
  - worms reside in biliary tree
  - complications
    - bile duct stones; recurrent pyogenic cholangitis
    - association with cholangiocarcinoma
- ❑ diagnosis
  - fecal exam for eggs
  - no eosinophilia
- ❑ treatment
  - praziquantel

BLOOD AND TISSUE

Nematodes

Wuchereria bancrofti, Brugia malayi
- ❑ adult worms produce larvae called microfilaria

- ❑ mechanism of transmission
  - transmitted through mosquito bite
  - migrate from bite site to lymphatic system
  - W. *bancrofti*: worldwide in tropics
  - B. *malayi*: Southeast Asia
- ❑ clinical features
  - disease caused by inflammatory response to adult worms living in lymphatics, and in TPE, to microfilariae
  - filarial fever
    - febrile episodes associated with headache and painful, enlarged lymph nodes, and lymphangitis spreading distally in affected limbs
  - elephantiasis
    - following repeated infections, dying worms cause lymphadenitis and damage to lymphatics (dilatation and impeded flow)
    - results in swelling of the legs and genitals; damaged lymphatics lead to recurrent bacterial cellulitis
    - thick, scaly skin covers the edematous lower extremities, giving the appearance of elephant legs
  - tropical pulmonary eosinophilia (TPE)
    - hypersensitivity reaction with bouts of wheezing and coughing, associated with hypereosinophilia due to hyperimmune response to dying microfilariae in lungs
- ❑ diagnosis
  - look for microfilariae in blood drawn at nighttime
  - biopsy not optimal because nodes already damaged
  - serology (nonspecific but very sensitive)
  - negative serology excludes viable infection
  - TPE shows marked increase in filaria antibodies, hypereosinophilia, reticular-nodular pattern on CXR, restrictive pattern on PFTs
- ❑ treatment and prevention
  - diethylcarbamazine, albendazole
  - insect repellants, protective clothing, mosquito control

Onchocerca volvulus

- ❑ mechanism of transmission
  - transmitted through blackfly bite (breeds in fast moving rivers and streams)
  - found in Africa and Central and South America; human reservoir
- ❑ clinical features
  - disease caused by inflammatory response to microfilariae
  - skin nodules contain adult worms
  - allergic reaction to microfilariae migrating through the dermis causes pruritic rash with depigmentation and thin scaly skin called “leopard skin” which may hang in folds
  - river blindness (onchocerciasis)
    - microfilariae migrate across the cornea or retina
    - an inflammatory response occurs with their death, which can lead to blindness due to keratitis or chorioretinitis
- ❑ diagnosis
  - skin snips reveal microfilariae
  - nodulectomy shows adult worms
  - eosinophilia common
- ❑ treatment and prevention
  - ivermectin; kills only microfilariae; need to repeat treatment every 6-12 months until adult dies in 10-20 years
  - excise nodules containing adult worms
  - protective clothing against insect bites, insect repellant

Cestodes

Echinococcus granulosus (canine tapeworm)

- ❑ mechanism of transmission
  - through ingestion of fertilized eggs
  - adults found in canines’ intestines and pass in feces
- ❑ clinical features
  - hydatid disease
  - larval cysts bud internally to produce daughter cysts
  - hydatid cysts form most often in the liver, lung, and peritoneal cavity
  - the cysts slowly enlarge over 5 to 20 years

- symptoms secondary to pressure effects of growing cyst
- leakage of hydatid cyst fluid can cause an anaphylactic reaction (rare) or bile duct obstruction if leakage into biliary tree

❑ diagnosis
- CT scan or U/S reveals cysts in the liver or lung
- serology (very sensitive and specific)
- eosinophilia (in 25% of cases)

❑ treatment and prevention
- surgical evacuation of cysts: extreme caution is required, as leakage of cystic fluid can induce an anaphylactic reaction or give rise to new cysts in pleural or peritoneal cavities
- cyst aspiration with scolicide instillation
- albendazole used adjunctively or for cure (40% cure rate with albendazole alone)
- protect sites of food preparation or animal slaughter against canines, particularly dogs

Trematodes

Schistosoma spp.

❑ species
- S. *mansoni, S. hematobium, S. japonicum, S. mekongi, S. intercalatum*

❑ mechanism of transmission
- found in tropics
- through unbroken skin
- acquired when larvae, released from snail, penetrate unbroken skin during exposure to slow-moving infested fresh water
- adult worms live in terminal venules of bladder/bowel passing eggs into urine/stool
- eggs must reach freshwater to hatch; schistosomes cannot multiply in humans
- no person-to-person transmission because snail intermediate host is required

❑ immunology
- molecular mimicry: incorporation of host antigens onto the surface of the schistosomes to mask themselves from host immune system
- disease results from granulomatous response and fibrosis secondary to egg deposition in tissues

❑ clinical features
- pruritic skin rash at site of penetration (cercarial dermatitis)
- acute schistosomiasis (Katayama fever) at time of egg deposition (4-8 weeks after infection)
  - fever, hives, headache, weight loss, cough, abdominal pain, diarrhea (lasts up to 3 months), eosinophilia
- complications
  - caused by granulomatous response and fibrosis secondary to egg deposition by adults in the veins surrounding the intestine or bladder
  - S. *mansoni, S. japonicum*
    - worms in mesenteric vein; eggs in portal tracts of liver and bowel
    - mostly asymptomatic
- heavy infections: intestinal polyps, portal and pulmonary hypertension
- S. *hematobium*
  - worms in vesical plexus; eggs in distal ureter and bladder
- terminal hematuria and rarely obstructive uropathy
  - associated with bladder cancer

❑ diagnosis
- serology (very sensitive and specific)
- rectal biopsy for S. *mansoni* and S. *japonicum*
- eosinophilia often
- S. *mansoni, S. japonicum*: eggs in stool, liver U/S shows fibrosis
- S. *hematobium*: bladder biopsy (eggs in urine and bladder wall)

❑ treatment
- praziquantel
- control with proper disposal of human fecal waste, mass chemotherapy and reduced exposure to infested water

ANTI-PROTOZOAL DRUGS

Iodoquinol
(see Amoebiasis Section)

Metronidazole
(see Antibacterials Section)

TMP/SMX
(see Antibacterials Section)

Pentamidine
- ❑ unknown mechanism of action
- ❑ side-effects include dangerous hypotension, hypoglycemia, hypocalcemia if administered rapidly by IV
- ❑ used against *Pneumocystis carinii* and leishmaniasis

ANTI-MALARIAL DRUGS

Chloroquine
- ❑ mechanism of action
  - inhibition of heme polymerase causing build-up of toxic heme products
  - kills erythrocyte form but not liver form of *Plasmodium vivax* and P. *ovale*
- ❑ side-effects
  - ophthalmologic: colour vision changes, central visual loss, and retinal damage (do not occur in doses used to prevent malaria)
  - GI disturbances, dizziness, headache, non-allergic pruritus (in black skin)
- ❑ clinical indications
  - treatment and prophylaxis against malaria caused by non-resistant P. *falciparum* and P. *malariae*
  - used in combination with primaquine for nonresistant P. *vivax* and P. *ovale*

Primaquine
- ❑ mechanism of action
  - kills liver hypnozoites of P. *vivax* and P. *ovale*
  - mechanism unclear but likely to involve crosslinking of glutathione
- ❑ side-effects
  - acute hemolytic anemia if G6PD deficient, GI upset
- ❑ clinical indications
  - use in combination with chloroquine for liver stage of P. *vivax* and P. *ovale*; prophylaxis of all malaria species including multidrug-resistant P. *falciparum*

Quinine
- ❑ mechanism of action
  - mechanism as for chloroquine; kills erythrocytic forms
- ❑ side-effects
  - cinchonism = quinine adverse effects = ears (tinnitus, vertigo), eyes (visual disturbances), GI (nausea, vomiting, diarrhea), CNS (headache, fever); occurs in most users
  - acute hemolytic anemia if G6PD deficient (rare)
  - hypotension when given IV too rapidly
  - blackwater fever (rare): massive lysis of RBC causing dark urine with hemoglobinuria, renal failure, DIC, and possibly death
  - hypoglycemia due to insulin release from pancreas
- ❑ clinical indications
  - use in combination with fansidar, clindamycin or doxycycline for chloroquine-resistant P. *falciparum* or parenterally for those who cannot tolerate oral medication

Mefloquine
- ❑ mechanism of action
  - mechanism as for chloroquine; kills erythrocyte forms only
- ❑ side-effects
  - GI upset, headache, nightmares, irritability, depression (moderately severe 1:200)
  - seizures and psychosis (1/250 for treatment, 1/13 000 for prophylaxis)
- ❑ clinical indications
  - used for treatment of chloroquine-resistant P. *falciparum* as second line drug
  - drug of choice for prophylaxis when entering regions of chloroquine resistance

Pyrimethamine/Sulfadoxine (Fansidar)
- ❑ competitive inhibitor of folic acid production thereby inhibiting synthesis of DNA
- ❑ side-effects include severe cutaneous reactions (Stevens-Johnson syndrome 1/25 000)
- ❑ used with quinine in areas of chloroquine-resistant P. *falciparum*

Doxycycline
- ❑ inhibits protein synthesis
- ❑ side-effects include GI upset, UVA photodermatitis, *Candida* vaginitis
- ❑ prophylaxis in areas of resistant P. *falciparum* malaria and treatment in combination with quinine
- ❑ drug of choice to prevent mefloquine-resistant falciparum malaria on the borders of Thailand

ANTI-HELMINTHIC DRUGS

Mebendazole, Thiabendazole, Albendazole
- ❑ mechanism of action
  - paralyzes worms by inhibiting glucose uptake and microtubule synthesis
- ❑ side-effects
  - mild abdominal pain
  - thiabendazole very toxic, causes nausea, vomiting, headache, dizziness
- ❑ clinical indications
  - albendazole: useful against intestinal nematodes: *Ascaris lumbricoides, Necator americanus* (hookworm), *Strongyloides stercoralis, Trichinella spiralis, Enterobius vermicularis* (pinworm), *Trichuris trichiura* (whipworm)
  - adjunctive therapy for hydatid disease and treatment for cysticercosis
  - mebendazole: drug of choice to treat pinworm, roundworm, hookworm and whipworm
  - thiabendazole: strongyloidiasis only

Praziquantel
- ❑ mechanism of action
  - increases calcium permeability across cell membranes resulting in calcium loss and paralysis of worms
- ❑ side-effects
  - abdominal pain, lethargy, headache, dizziness
- ❑ clinical indications
  - all trematodes, e.g. *Schistosomes,* except *Fasciola hepatica* (liver fluke)
  - cestodes (tapeworms)

Pyrantel Pamoate
- ❑ paralysis of worm, allowing expulsion by body
- ❑ causes mild GI upset
- ❑ used for roundworm (*Ascaris*), hookworm or pinworm

HIV AND AIDS

Immunopathogenesis

- ❑ microbiology
  - retrovirus
  - HIV I: causative agent of AIDS
  - HIV II: related to but distinct from HIV I, described as a cause of AIDS, particularly in West Africa
- ❑ pathogenesis
  - target cell preference for HIV infection is determined by interaction between the host cell surface molecule, CD4, along with a co-receptor molecule (CCR5 or CXCR4), and the HIV envelope (env) glycoprotein (gp160) as the virus binds to and enters the host cell
  - target cells of HIV include CD4 T helper cells, macrophages, monocytes, microglial cells
  - once it enters a cell, HIV can replicate and cause cell fusion (syncytium formation) or death
  - follicular dendritic cells and other antigen-presenting cells (macrophages, B cells) are involved in the initiation and propagation of HIV infection in CD4 T cells, and can act as viral reservoirs
  - after primary infection, acute viremia occurs with wide-spread dissemination of HIV
  - inappropriate immune activation and increased secretion of certain proinflammatory cytokines upregulate HIV expression in tissues, paradoxically propagating HIV infection
  - key element in HIV pathogenesis is the high level of productive infection, which is characterized by a high level of virion turnover (10 billion virions produced daily)
  - viral replication is partially contained by an appropriate immune response, resulting in a markedly decreased amount of virus in the blood to a "set point" which has prognostic significance (i.e. higher the load, the faster the clinical progression to AIDS and death)
  - virus is not completely eliminated from the body, and a state of chronic, persistent viral replication ensues
- ❑ mechanism of immunocompromise
  - the damage inflicted by HIV infection is mainly the direct active viral replication and destruction of CD4 T cells
  - this allows immunodeficiency to develop and the patient becomes susceptible to opportunistic infections and malignancies
  - decline in CD4 T cell levels and the rise in viral load vary considerably throughout the stages of HIV infection and from person to person
- ❑ lymphoid tissue and the CNS are the major reservoirs for and possible sites of persistent viral replication
- ❑ mode of transmission
  - sexual intercourse
  - contaminated blood or blood products (IV drug users, transfusion recipients before 1985, occupational exposure through needles)
  - organ or tissue transplantation
  - vertical transmission from mother to child *in utero*, during delivery or through breast milk
  - infection is NOT transmitted by casual contact, kissing, mosquitoes

Epidemiology (Health Canada, 1998)

- ❑ in 1998, 41 000 Canadians were living with HIV
- ❑ number of cases of AIDS (1998): 279, marking a dramatic decline in AIDS incidence in Canada
- ❑ males and females represent approximately 87.4% and 12.6%, respectively, of the total number of positive HIV test reports with known gender
- ❑ percentage of positive HIV test reports by exposure category (1994-1998)
  - men who have sex with men (67.7%)
  - heterosexual contact (10.1%)
  - men who have sex with men and injection drug use (2.3%)
  - blood product/transfusion recipients (3.7 %)
  - injection drug use (13.9%)

Clinical Perspective

❑ clinical features
- 50% to 70% of persons with primary HIV infection have a clinical syndrome of "flu-like" symptoms and signs (fever, sore throat, skin rash, lymphadenopathy, neutropenia, splenomegaly, myalgia, arthritis)
- acute syndrome occurs 3-6 weeks after primary infection and is associated with high level plasma viremia
- immune response curtails viremia 1 week to 3 months after onset of acute syndrome
- many individuals with HIV infection remain asymptomatic for years
- in adults, the average time to development of AIDS after initial HIV infection is approximately 10 years without antiretroviral therapy
- systemic complaints such as fever, night sweats, weight loss, anorexia, and muscle weakness are common

❑ diagnosis of HIV infection
- two or more reactive screening tests (i.e. ELISA) that detect serum HIV antibodies followed by a confirmatory test (i.e. Western blot or recombinant ELISA) that detect specific antibodies against HIV antigens
- other tests that can be used to identify HIV include viral culture, p24 antigen detection, PCR

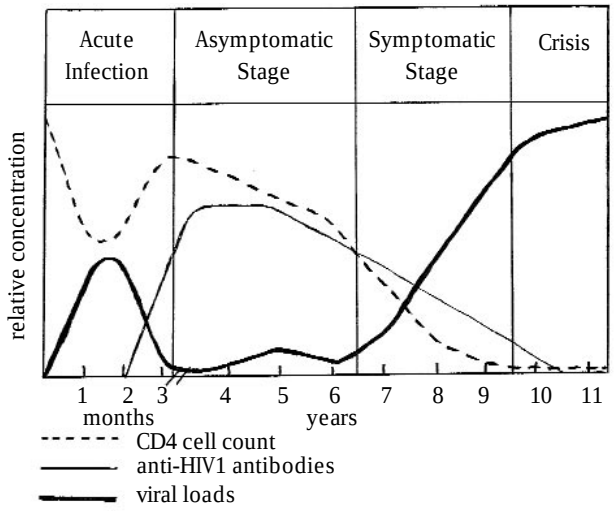


Figure 8. Relationships Between CD4 T cell Count, Viral Load, and Anti-HIV Antibodies

Drawing by Muyuki Fukuma

❑ diagnosis of AIDS
- criteria: the 1993 revised CDC HIV classification system and expanded AIDS surveillance definition
- based on 3 ranges of CD4 counts and 3 clinical categories giving a matrix of 9 exclusive categories, 5 of which are considered diagnostic for AIDS
- CD4 count categories:
  1: CD4 count > 500 x 10^6/L
  2: CD4 count 200-499 x 10^6/L
  3: CD4 count < 200 x 10^6/L
- clinical categories
  - A: asymptomatic HIV infection, persistent generalized lymphadenopathy, acute HIV infection
  - B: symptomatic, not A or C (e.g. persistent vulvovaginal candidiasis, oropharyngeal candidiasis, constitutional symptoms such as fever or diarrhea > 1 month)
  - C: opportunistic infections (e.g. PCP, cryptococcal meningitis, CNS toxoplasmosis) or malignancy (e.g. Kaposi's sarcoma, CNS lymphoma), HIV wasting syndrome, HIV encephalopathy

- 9 exclusive categories are

	A	B	C	* Indicates AIDS surveillance definition
1	–	–	*	
2	–	–	*	
3	*	*	*	

- other infections suggestive (not diagnostic) of early HIV infection include oral candidiasis, oral hairy leukoplakia, ITP and multidermatomal Herpes Zoster

❑ evaluation of newly diagnosed HIV infection
- HIV viral load
- CD4 cell count
- CBC, liver transaminases, creatinine, creatine kinase
- serologies for hepatitis B and C, Toxoplasma, CMV, syphilis
- G6PD assay
- TB skin test
- pap smear

❑ predictors of progression
- plasma HIV RNA levels, CD4 cell count
- onset of HIV- related symptoms, HLA genes, age, and environmental factors
- after an AIDS diagnosis, survival is usually 1-2 years in an untreated patient due to the opportunistic infections and neoplasms

❑ prevention
- education
- safer sex
- screening blood donations, heat treatment of coagulation factors
- needle exchange programs

❑ prophylaxis
- prevention of neonatal transmission
- post-exposure (e.g. occupational)

Treatment

❑ recent data strongly support the principle that HIV viral replication should be maximally suppressed throughout the course of HIV infection

❑ monotherapy or combination regimens that only partially suppress viral replication allow more rapid selection of resistant variants, and therefore are not used

Table 5. Antiretroviral Therapy
(Recommendations of International AIDS Society, 1997)

Status	Recommendation
Symptomatic HIV disease*	Therapy recommended for all patients
RNA levels above 5 000 to 10 000 copies/mL plasma (regardless of CD_4 cell count)	Therapy recommended for all patients
CD_4 cell count < 500 X 10^6/L	Therapy recommended for all patients
Detectable HIV RNA in plasma	Therapy should be considered
Patients at low risk of disease progression (low plasma HIV RNA level and high CD_4 cell count)	Therapy may be deferred Re-evaluate every 3 to 6 months

*symptomatic HIV disease includes symptoms such as recurrent mucosal candidiasis, oral hairy leukoplakia, and chronic and unexplained fever, night sweats, and weight loss

❑ recommended initial therapy regimens
- 2 nucleoside analogues (e.g. zidovudine + didanosine or lamivudine) and a protease inhibitor
- 2 nucleoside analogues and a non-nucleoside reverse transcriptase inhibitor
- 3 reverse transcriptase inhibitors
- monotherapy is now considered suboptimal

❑ evaluation of treatment on HIV disease
- plasma HIV RNA assays (viral load) are useful for guiding treatment decisions
- effective therapy is indicated by 0.5 log 10 or more (about 3-fold) decline from pre-treatment levels
- "treatment failure" is defined as return of HIV RNA titer or CD4 cell count to pre-treatment levels

❑ modifying an antiviral treatment regimen
- treatment failure and toxicity are indications to change therapy
- may use drugs with greater potency or switch to drugs with different mechanism of action (e.g. adding a protease inhibitor) and those without cross-resistance (e.g. switching nucleoside analogues)
- when changing regimens, at least two antiviral drugs should be changed to minimize the development of resistant virus

- ❑ antiviral medication - nucleoside analogues
  - preferentially incorporated into the growing viral DNA chain thereby terminating its growth and inhibiting reverse transcriptase
  - zidovudine (AZT)
    - thymidine analog
    - dosing: BID-TID, with or without food
    - major toxicities: anemia, neutropenia, nausea, headache, myopathy
    - advantage: can cross the blood brain barrier, effective in decreasing vertical transmission from mother to fetus
    - disadvantage: many treatment experienced patients have developed viral resistance to AZT
  - lamivudine (3TC)
    - dosing: BID, with or without food
    - major toxicities: anemia, nausea, hair loss
    - advantage: when combined with AZT, 3TC can potentially reverse or delay viral resistance to AZT
    - disadvantage: weak antiviral medication; resistance to 3TC alone can develop quickly
  - combivir (AZT+3TC)
    - dosing: BID
    - advantage: increased adherence to antiviral regimen
    - major toxicities: see above for respective toxicities
  - didanosine (ddI)
    - adenosine analog
    - dosing: OD or BID
    - major toxicities: peripheral neuropathy, pancreatitis, nausea, hepatitis, diarrhea
    - disadvantages: must be taken on an empty stomach, therefore, any other drugs requiring an acidic pH to work, like ketoconazole or ciprofloxacin, should be taken at least 2 hours before or after taking ddI
    - ddI can decrease levels of oral ganciclovir
    - advantage: proposed that viral resistance to ddI develops later compared to other nucleoside analogs
  - zalcitabine (ddC)
    - cytosine analog
    - dosing: TID, preferably without food
    - major toxicities: peripheral neuropathy, aphthous mouth ulcers, pancreatitis, rash
  - stavudine (d4T)
    - major toxicities: peripheral neuropathy, hepatitis
    - dosing: BID, with or without food
    - advantage: can cross the blood brain barrier
  - abacavir (1592U89)
    - dosing: BID
    - advantage: potent antiviral drug
    - major toxicities: nausea, vomiting, fever, rash, hypotension
    - deaths reported with rechallenge
- ❑ antiviral medication - protease inhibitors
  - inhibit maturation of infectious virions by inhibiting the cleavage of gag and gag-pol polyproteins
  - immature virions are subsequently cleared by an unknown mechanism
  - combination therapy with protease inhibitors delays disease progression and prolongs life
  - lipodystrophy syndrome: common side-effect associated with the use of protease inhibitors
    - loss of fat from the face, arms and legs
    - thickening of the waist ("protease paunch")
    - "buffalo hump"
    - increased breast size
    - increased triglycerides, decreased HDL and increased LDL cholesterol
    - possible increased risk of cardiac and cerebrovascular diseases
    - increased levels of insulin and insulin resistance
    - some researchers suggest that the syndrome may be related to HIV itself rather than to these drugs
  - saquinavir
    - limited oral bioavailability but new soft-gel capsule (Fortovase) has better bioavailability
    - dosing: TID with food, or up to 2 hr after a fat-containing meal; early results from the TIDBID study, suggest that taking 1600 mg Fortovase twice a day may be as effective as taking 1200 mg three times a day
    - major toxicities: nausea, diarrhea, abdominal discomfort, rash

- ritonavir
  - greatest rate of intolerance
  - advantage: ritonavir plus saquinavir combination increases the bioavailability of saquinavir
  - dosing: BID
  - use dose escalation to minimize side-effects
  - major toxicities: nausea, vomiting, diarrhea; elevated triglycerides, creatine kinase, and transaminases
- indinavir
  - dosing: q8h, either 1 hr before or 2 hr after a meal
  - major toxicities: ingrown toenails, nephrolithiasis, abdominal discomfort, asymptomatic hyperbilirubinemia
- nelfinavir
  - dosing: BID-TID, with food
  - major toxicity: diarrhea, urticaria
  - can raise serum levels of soft-gel saquinavir up to 5 x normal level which may increase the side-effects of Fortovase and a change in dose may be necessary

❑ antiviral medication - non-nucleoside reverse-transcriptase inhibitors
- inhibit function of reverse-transcriptase by interacting with the enzyme directly, thereby preventing viral DNA replication
- nevirapine
  - dosing: q12h, with or without food
  - use dose escalation to minimize side-effects
  - major toxicities: fever, nausea, headache, rash, Stevens-Johnson syndrome, hepatitis
  - disadvantages: may interact with rifampin, rifabutin, and birth control pills
- efavirenz
  - dosing: qhs, with or without food (low fat meal)
  - major toxicities (transient): increased depression, dizziness, insomnia, drowsiness, problems concentrating, rash
  - teratogenic in animal models
  - disadvantages: greatly reduces serum levels of saquinavir
- delavirdine
  - dosing: TID, with or without food
  - advantages: increases levels of other protease inhibitors
  - major toxicities: rash, headache, nausea, fever, elevated liver enzymes
  - disadvantages: should be taken at least 1 hr before or 1 hr after taking ddI or any antacid; when taken with saquinavir, may greatly increase serum levels of saquinavir

❑ prophylactic medications for opportunistic infections (see Table 6)

Table 6. Prophylaxis for Opportunistic Infections

Pathogen	Indication	Regimen
Pneumocystis carinii	CD_4 count < 200/mm^3 or fever for 2 weeks	TMP/SMX, aerosol pentamidine or dapsone
M. *tuberculosis*	TB skin test > 5mm or contact with active TB	isoniazid; pyridoxine
Toxoplasma gondii	IgG antibody to toxoplasma and CD_4 count < 100/mm^3	TMP/SMX
S. *pneumoniae*		pneumococcal vaccine
MAC	CD_4 cell count < 75/mm^3	azithromycin clarithromycin rifabutin

Post-Exposure Prophylaxis

❑ occupational exposure
- health-care workers have a 0.3% risk of transmission from a percutaneous needlestick injury from a known HIV+ patient
- prophylaxis with zidovudine has been shown to reduce risk of transmission by nearly 80% in case-control studies
- post-exposure prophylaxis is recommended in situations in which there is definite high risk for transmission
- combination therapy (AZT, 3TC and nelfinavir) may be more effective and should be begun as soon as possible after exposure

- ❑ vertical transmission
  - HIV-infected mothers not on antiretroviral therapy have a 15-35% chance of vertical transmission
  - perinatal prophylaxis with AZT reduces transmission by about 2/3 and is recommended for all HIV-infected women, HIV-infected mothers should be encouraged to bottle-feed
  - current practice in developed countries is to treat infected women with triple combination antiviral therapy
  - delivery by Cesarean section can also decrease the risk of transmission
  - studies ongoing to determine duration and appropriate timing for perinatal prophylaxis

TRANSPLANT OR LEUKEMIA/LYMPHOMA

- ❑ patients are often neutropenic
- ❑ nature of infections depends on the degree and duration of neutropenia, depression of cell-mediated immunity
  - days to weeks post transplant
  - gram positive bacteria (*Staphylococcus, Streptococcus, Listeria*)
  - gram negative bacteria (*Enterobacteriaceae, Pseudomonas, Legionella)*
  - viruses (HSV, VZV, CMV, EBV, hepatitis B, hepatitis C, HIV)
  - months post-transplant
    - fungal infections, (if neutropenic > 21 days), such as histoplasmosis, cryptococcus
    - pneumococcal bacteremia, skin/soft tissue/bone infections, and mycobacteriosis
    - parasites (*Toxoplasma gondii, Strongyloides stercoralis*)
  - empiric treatment (may vary according to sensitivity of local pathogens)
    - cefazolin or piperacillin + tobramycin (first line)
    - ceftazidime + vancomycin (alternative)
    - amphotericin B (if first and second lines fail and TB/MAC not suspected)
  - specific therapy based on sensitivities when available

FEBRILE NEUTROPENIA

- ❑ most commonly due to chemotherapy-induced marrow suppression
- ❑ other potential causes of neutropenia
  - bone marrow injury (drugs, radiation, chemicals, congenital, hereditary, autoimmune mechanisms, viral or bacterial infection, malignancy)
  - drugs: procainamide, propranolol, chloramphenicol, penicillins, sulfonamides, rifampin, vancomycin, etc...
  - maturational defects (vitamin B_{12} deficiency, folate deficiency, AML)
  - peripheral blood abnormalities (severe infections, protein calorie malnutrition, hypersplenism, complement-mediated)
  - extravascular abnormalities (consumption by severe infection or anaphylaxis, rheumatic disorders, drugs)
- ❑ risk of bacterial infection increases significantly if peripheral neutrophil count falls below 1.0×10^9/L but is greatly increased with levels below 0.5×10^9/L, duration of neutropenia > 10 days or hematologic malignancies
- ❑ infecting organisms may be normally nonpathogenic flora for the given anatomic site
- ❑ the usual signs and symptoms of infection may be diminished or absent in neutropenia because leukocytes that mediate much of the inflammatory response to infection are absent
- ❑ changing epidemiology of infections in febrile neutropenics
  - recent in serious Gram positive infections
- ❑ history
  - recent medication/drug use
  - recurrent infections, travel, disease exposure
- ❑ physical
  - complete skin inspection including visible evaluation for perirectal abscess; however AVOID rectal exam
  - ecthyma gangrenosum; emboli of Gram negative bacilli (e.g. *Pseudomonas aeruginosa*)
  - oral cavity examination in diabetics (mucormycosis)
  - fungal colonization (oropharynx, rectum, vagina)
  - mental status, meningeal signs, focal deficits
  - new heart murmurs
  - signs of respiratory infection
- ❑ labs
  - CBC with differential
  - urine R&M, C&S
  - blood cultures (x 2)
  - CXR

- sputum Gram stain and C&S, acid-fast stain
- C&S and Gram stain of skin lesions
- lumbar puncture if indicated clinically

❑ treatment
- may vary with local organisms and sensitivity patterns
- if no documented organism, can start empiric treatment IV antibiotics to cover Gram negative and positive organisms
- initial: piperacillin and tobramycin or ceftazidine monotherapy
- if high incidence of Gram positive organisms in the hospital population, add cloxacillin, cefazolin, or vancomycin
- if no improvement after 4 days and all cultures negative add amphotericin B to cover possible fungal pathogens

FEVER OF UNKNOWN ORIGIN

❑ definition: documented fever for at least 3 weeks, with temperature > 38.3ºC and of undetermined etiology after 1 week of investigation in hospital

❑ etiologies
- infectious
- neoplastic
- collagen vascular disease
- miscellaneous e.g. drug induced, granulomatous disease
- undiagnosed
- note: undiagnosed etiology does not imply a worse prognosis

❑ infectious causes
- infective endocarditis
- intra-abdominal infections
- osteomyelitis
- infected peripheral blood vessels
- TB
- UTI

❑ neoplastic causes
- solid tumours (kidney, hepatoma)
- lymphoreticular malignancy (Hodgkin's, non-Hodgkin's lymphoma)

❑ hematologic disorders
- adult-onset Still's disease
- temporal arteritis/polymyalgia rheumatica
- vasculitic syndromes (PAN, Wegener's)
- seropositive diseases (SLE, rheumatoid arthritis)

❑ miscellaneous
- factitious fever
- drug fever (antibiotics, barbiturates, antiarrhythmics, phenytoin)
- sarcoidosis
- IBD

❑ clinical approach
- history
- including travel, occupation, hobbies, exposure to animals
- known infectious contacts, drug use, family history, previous surgery
- physical
  - confirm actual fever and assess fever pattern (sometimes just circadian temperature elevation i.e. in the evening)
  - complete physical, always examine skin, eyes, lymph nodes, abdomen, chest, heart, MSK, oral cavity
- investigations
  - CBC and smear, ESR
  - lytes and LFTs
  - blood C&S, urine C&S, U/A
  - CXR (rule out pneumonia, TB, neoplasm etc...)
  - abdominal U/S
- further investigation depends on results of initial tests
  - liver biopsy
  - bone marrow examination
  - temporal artery biopsy if ESR elevated
  - CT chest and abdomen
  - gallium scan
  - GI endoscopy
  - 2D-Echo, transesophageal echocardiology