

The Nature of Disease
Pathology for the Health Professions

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Chapter 4
Infectious Health Problems

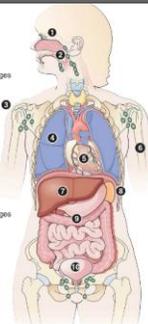
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Overview of Today's Lecture

- Factors in Infection
- Overview of the classes of microorganisms
- Infection and Injury
 - Classes of Microorganisms
 - Bacteria
 - Viruses
 - Rickettsiae, Mycoplasma, Chlamydia
 - Fungi
 - Parasites
 - Communicable Disease
 - Clinical Manifestations
 - Antimicrobial Therapy
- Immunodeficiency

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Review: Innate Antimicrobial Protection

- 
- 1 Eyes
 - Washing and antibiotic activity of tears
 - 2 Lymph nodes
 - Phagocytosis by macrophages
 - Attack by natural killer (NK) cells
 - 3 Skin
 - Physical barrier
 - 4 Respiratory tract
 - Entrapment by mucus
 - Transport to throat by ciliary motion
 - Phagocytosis by alveolar macrophages
 - 5 Blood
 - Phagocytosis by macrophages and granulocytes
 - Digestion by lysozymes
 - Attack by complement proteins
 - 6 Bone marrow
 - Phagocytosis by macrophages and granulocytes
 - Attack by natural killer (NK) cells
 - 7 Liver
 - Phagocytosis by Kupfer cells (macrophages)
 - 8 Spleen
 - Phagocytosis by macrophages
 - Attack by natural killer (NK) cells
 - 9 Digestive system
 - Destruction by gastric acid, bile, and enzymes
 - Competition for nutrients by billions of normal bacteria
 - 10 Urteral tract
 - Flushing and acidity of urine

From: *Pathophysiology: A Clinical Approach*, Braun & Anderson, Lippincott, 2011

Figure 8.1 Innate antimicrobial protective mechanisms. The numbered areas show the functions of various organs and systems that defend against bacteria and other microbes.

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Introduction to Infectious Disease

- **Infectious disease**
 - Transmissible (infectious) agent (**microbes**)
 - Invades through physical barriers (innate defenses)
 - Overcomes innate and adaptive immune defenses of **host**
 - Causes injury and disease (now called a **pathogen**)
- **Endemic rate** – normal expected rate of infection
- **Epidemic** – greater than normal infection rate
- **Commensal relationship** – organism benefits, we are not harmed
- **Parasites** – organisms that need the host to survive

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Microorganism and Human Relationship

- **Mutual relationship**
 - Normal flora
 - Relationship can be breached by injury
 - Leave their normal sites and cause infection elsewhere
- **Opportunistic microorganisms**
 - Normally held in check by immune system/defenses
 - Do not usually cause disease except when a person's decreased immunity/defenses allow it

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Classes of Microorganisms

- Classes of Microorganisms (approx. from smallest to largest)
 - **Prions (mis-folded proteins, PrP)**
 - **Viruses**
 - **Chlamydia (pathogenic bacteria, especially common in STIs)**
 - **Rickettsia (non-motile, gram negative bacteria)**
 - **Mycoplasma (bacterial genus lacking a cell wall)**
 - **Bacteria**
 - **Fungi**
 - **Protozoa (unicellular, eukaryotic, usually motile organisms)**
 - **Helminths (multicellular, parasitic worms)**
 - **Ectoparasites (multicellular, insect-like, invade skin)**

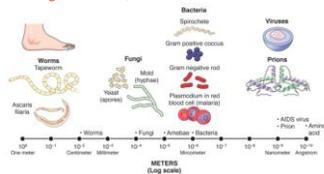


Figure from McConell, *The Nature of Disease*, 2nd ed., Wolters Kluwer, 2014

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Host Reaction to Infectious Organisms

- Viruses
 - Chronic inflammation
 - Lymphocytes and monocytes
 - Can be cytopathic or cytoproliferative
- Bacteria
 - Suppurative (purulent) inflammation – acute
 - Neutrophil infiltrate at site and in blood (neutrophilia)
 - Exceptions: Chlamydia and Treponema pallidum (syphilis)
 - Exceptions: Mycobacterium tuberculosis -> granulomatous (chronic) inflammation with lymphocytes and monocytes forming nodules
- Fungi
 - Granulomatous inflammation
- Parasitic worms (helminths) – eosinophils
- Protozoa - Variable

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The Natural Course of Infection

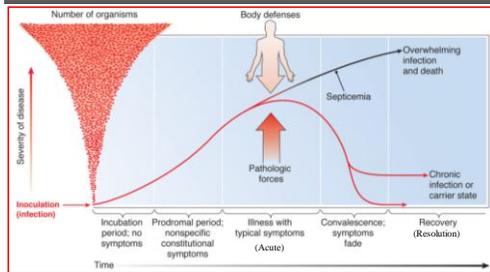


Figure from: McConnell, *The Nature of Disease*, 2nd ed., Wolters Kluwer, 2014

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Examples of Pathogen Defense Mechanisms

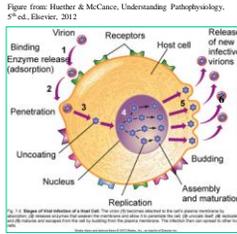
- Bacteria
 - Produce surface coats that inhibit phagocytosis
 - Outer coat gram+ org, waxy coat, LPS
 - Produce toxins (leukocidins) that destroy neutrophils
 - Molecules that destroy Ig's: IgA proteases
- Viruses
 - Many can mutate within cells where they are not available to immune and inflammatory mechanisms
 - Not available to antibodies in circulation
 - Antigenic variations:
 - Antigenic drift – mutation in key surface antigens
 - Antigenic shifts – genetic recombination that changes antigenic properties

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Viral Infections

• Characteristics of viruses:

- **Dependent on host cells for their replication**
- No metabolism
- Simple organism
 - Genetic material
 - Surrounding layer of proteins (capsid)
- Usually a self-limiting infection
- **Spreads cell to cell**
- Virus then uncoats in cytoplasm
- DNA virus replicates in nucleus (except poxviruses)
- RNA virus replicates in cytoplasm (except influenza/retroviruses)
- **Post-infection immunity depends on whether or not virus mutates regularly**



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Acute (Transient) Viral Infections

- **Respiratory-tropic**
 - **Rhinoviruses (100 varieties); common cold**
 - Usually spread by person-to-person contact
 - Respiratory droplet(airborne) transmission is possible
 - Adenoviruses; Tonsillitis, conjunctivitis, bronchiolitis
 - **Respiratory Syncytial Virus (RSV)**
 - Major cause of lower respiratory tract infection in children
 - Bronchiolitis, pneumonia
 - **Influenza (influenza viruses type A and B)**
 - Flu-like symptoms (fever, chills, nasal congestion, cough, myalgia, malaise)
 - Spread mainly by respiratory droplets
 - May cause problems in 'at-risk' segments of the population

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Acute (Transient) Viral Infections

- **Gastrointestinal-tropic (usually fecal contamination)**
 - **Rotavirus**
 - Most common cause of severe diarrhea in infants and young children
 - Fecal-Oral route transmission
 - Vomiting, severe diarrhea, dehydration
 - Common in daycare centers
 - **Norovirus (Norwalk virus)**
 - 90% of non-bacterial gastroenteritis in older children and adults
 - Caused by fecally contaminated food, water
 - Transmission by person-to-person contact or aerosolization
 - **Prevalent in 'close' quarters:** Cruise ships, long-term care facilities, overnight camps, hospitals, prisons, dormitories
 - Nausea, abdominal pain, vomiting, watery diarrhea

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Acute (Transient) Viral Infections

• Other transient viral infections

- **Measles (rubeola)**
 - Highly contagious; nasal and oral secretions
 - Characteristic **maculopapular rash** (flat, red area on skin covered with small confluent bumps)
 - **Rash-like Koplick spots** on cheek mucosa
- **Mumps**
 - Contagious (but less than measles)
 - **Tropic for salivary glands, esp. parotid**
- **Rubella (German measles)**
 - Contagious (but less than measles); droplet
 - May be asymptomatic or brief, mild febrile illness
- **Coxsackie (Types A and B)**
 - Type A is tropic for oral mucosa and skin (**hand-foot-and-mouth disease**) ; usually infants/children
 - Type B is tropic for heart, lung, pancreas, and nervous system
 - No vaccine
- **Hepatitis A(HAV)** – epidemic, **fecal-oral transmission**



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Persistent (Chronic) Viral Infections

- **Immune system does not eliminate virus**
 - Latent – recurrent flare-ups
 - Productive – chronic inflammation and tissue injury
 - Transformative – transformation of normal tissue into neoplasm
- **Latent**
 - **Herpes simplex virus (HSV)**
 - type 1 (mainly oral cold sores) and type 2 (mainly genital)
 - Small, painful blisters in skin or mucosa
 - **Tropic for sensory axons; then travels to neuron cell body**
 - No vaccine (acyclovir can limit and lessen symptoms)
 - **Herpes zoster (varicella-zoster) virus** – related to HSV (above)
 - Acute infection is chickenpox (children typically)
 - Usually mild, short-term constitutional symptoms except in immunocompromised
 - **Tropic for neurons, persists, and may reactivate to cause shingles (adults)**
 - **Cytomegalovirus (variant of herpesvirus)**
 - Tropic for blood monocytes; asymptomatic or may mimic infectious mononucleosis
 - Can cross the placenta, be transmitted to newborn through vaginal secretions or milk
 - **Most common opportunistic in AIDS patients**

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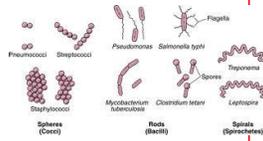
Persistent (Chronic) Viral Infections

- **Productive Virus Infections**
 - Hepatitis B (HBV) (Ch. 12)
 - Hepatitis C (HCV) (Ch. 12)
 - Both: Chronic, productive scarring of liver (cirrhosis)
- **Transformative Virus Infections**
 - **Epstein-Barr Virus (EBV)**
 - Agent of infectious mononucleosis (IM), usually young adults
 - Chronic infection linked to some lymphomas and carcinomas
 - **Human Papilloma Virus (HPV)**
 - Tropic for skin and squamous mucosa
 - Some asymptomatic, some skin warts, anogenital warts, cervical dysplasia/cancer
 - Vaccine available for most types

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Bacteria

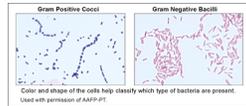
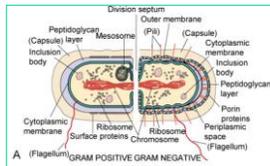
- Single-cell
- Single chromosome, no nucleus (prokaryotic)
- Classified by
 - Shape (cocci, bacilli, coccobacilli)
 - Requirement for oxygen
 - Gram stain (positive or negative)
 - Acid fast (mycobacterium, nocardia)



From: Pathophysiology: A Clinical Approach, Braun & Anderson, Lippincott, 2011

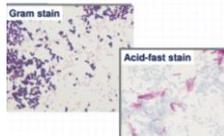
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Bacteria



Color and shape of the cells help identify which type of bacteria are present. Used with permission of AAFP-PT.

Staining: Differential Stains



Figures from: Pathophysiology: A Clinical Approach, Braun & Anderson, Lippincott, 2011

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Bacterial Virulence & Toxins

- Bacterial toxin production
 - Exotoxins
 - Proteins and Enzymes released during growth
 - Enzymatically inactivate or modify key cellular components
 - Diphtheria toxin; inhibits cellular protein synthesis
 - Botulism toxin; decreases release of acetylcholine causing flaccid paralysis
 - Tetanus toxin; decreases release of glycine/GABA causing spastic paralysis
 - Immunogenic
 - Antitoxin production
 - Can produce antibodies against exotoxins
 - Some vaccines available
 - Endotoxins
 - Lipopolysaccharides (LPS) contained in the cell walls of gram-negative organisms released during cell destruction
 - Pyrogenic (fever-producing) effects; endotoxic/septic shock

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Bacterial Virulence

- **Bacteria in blood**
 - Presence = bacteremia
 - Growth = septicemia (sepsis)
 - failure of immune system to check bacterial growth
- **Invasion of blood by bacteria**
 - A result of a failure of the body's defense mechanisms
 - By **gram-negative bacteria**
 - Endotoxins released in the blood
 - release of vasoactive peptides and cytokines
 - produce widespread vasodilation leading to **septic (endotoxic) shock**

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Bacteria - Cocci

- **Gram positive cocci**
 - Most are aerobic
 - Usually cause acute, intense, pyogenic infections
 - Staphylococci (grow in tight clusters), e.g., *S. aureus*
 - Streptococci (grow in twisted chains)
 - Identified by
 - Antigenic properties into groups (A, B, D, etc.)
 - Character of hemolysis they cause (green (α), clear (β), none)
 - Examples:
 - *Streptococcus pneumoniae* (pneumococcus) causes lobar pneumonia
 - *Streptococcus pyogenes*
- **Gram negative cocci**
 - *Neisseria* are only important ones; *N. meningitidis*
 - Causes life-threatening meningitis, especially in children

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Streptococcal Diseases

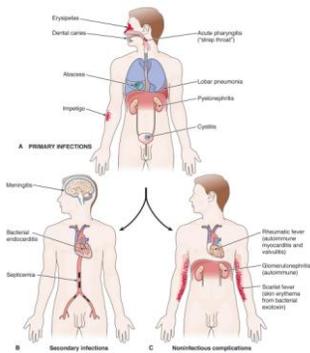


Figure from: McConnell, *The Nature of Disease*, 2nd ed., Wolters Kluwer, 2014

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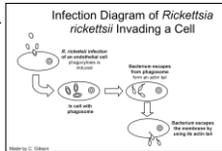
Bacteria - Bacilli

- **Gram positive bacilli**
 - Illnesses caused are typically species-specific
 - Examples:
 - Corynebacterium Diphtheriae (diphtheria)
 - Listeria monocytogenes (food borne infections)
 - Bacillus anthracis (anthrax)
 - Clostridium (C. difficile, C. perfringens, C. tetani, C. botulinum)
- **Gram negative bacilli**
 - **Intestinal infections**
 - H. pylori, E. coli, Salmonella, Shigella, Vibrio cholera
 - **Respiratory infections**
 - H. influenza, Legionella pneumophila, Bordatella pertussis, Psuedomonas aeruginosa

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Rickettsiae, Mycoplasmas, and Spirochetes

- Have characteristics of both bacteria and viruses
- **Rickettsiae**
 - Obligate intracellular parasites
 - Also gram-negative bacteria
 - Target human endothelium
- **Mycoplasmas**
 - Lack cell wall
 - Survive on surface of host cells
 - Commonly found in human urogenital & respiratory tracts
- **Spirochetes**
 - Gram negative, flagellated, thin, motile, corkscrew shaped
 - Example: Borrelia Burgdorferi (Lyme disease)



Figures from: howweb.uwax.edu

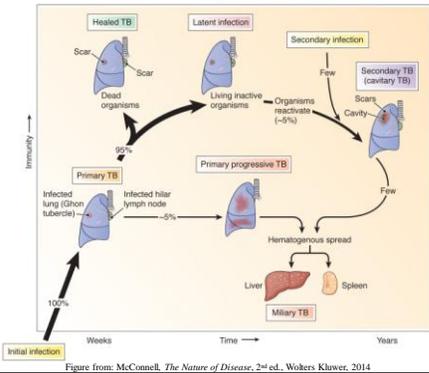
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Mycobacteria Cause Chronic Infection

- Mycobacteria are aerobic, acid-fast, comma shaped
- M. tuberculosis, M. lepreae (leprosy), M. avium (common in AIDS opportunistic infection), M. bovinum
- **Mycobacterium Tuberculosis**
 - Tuberculosis (TB) is a major, chronic, progressive, and communicable disease
 - Lungs most commonly affected; vertebrae & meninges also
 - Distinctive **granulomatous inflammation**
 - Monocyte and lymphocyte infiltration
 - Caseous necrosis with crumbly, cheese-like necrotic tissue
 - Incidence has declined in US except in certain target populations
 - poor, crowded, debilitated, and aged at risk
 - immunocompromised, DM, chronic lung diseases, malnutrition, alcoholism

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Pathogenesis of Tuberculosis

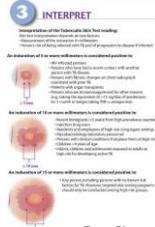


Pathology of Tuberculosis

- **1^o TB**
 - Small focus of granulomatous inflammation
 - Scarring causes **calcified, necrotic lesions, Ghon tubercles, in lungs (primary infection site)**
 - When Ghon tubercles also appear in hilar LN -> Ghon complex
- **1^o progressive TB (only about 5% of clinical cases)**
 - Typically seen in **children and target population**
 - Bacterial spread is more extensive than primary TB
 - May 'seed' other organs through blood (miliary TB)
 - **NO caseating granulomas (Why?)**
- **2^o TB (reactivation TB; about 95% of clinical cases)**
 - Characterized by **caseating granulomatous inflammation** since this occurs in previously sensitized individuals
 - Fewer granulomas, but they are typically larger
 - Lesions **typically seen in apex of lung**
 - **May cavitate into airways and facilitate spread through coughing**

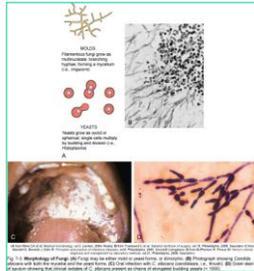
Diagnosis and Treatment of TB

- **Typically mild clinical onset with fever, night sweats, mild malaise, weight loss, and poor appetite**
 - If neglected, causes wasting ('consumption')
 - If progresses, productive cough perhaps with blood
- **Test is the Purified Protein Derivative (PPD)**
 - **Skin test for infection, not disease**
 - After 2 weeks post infection, positive test
 - Almost all negative tests have not been infected
 - 48-72 hours after PPD injection (on volar surface of forearm)
 - **Must be induration (hard, tense), not just erythematous, to be positive**
 - 5-10 mm: high risk for development of active TB
 - 10-15 mm: increased risk for development of active TB
 - > 15 mm: unlikely to develop to active TB



Fungal Infection

- Characteristics of **fungi**
 - Relatively **large microorganisms**
 - Thick rigid **cell walls without peptidoglycans (resist penicillin and cephalosporins)**
 - **Eukaryotic (nucleated)**
 - Exist as
 - **single-celled yeasts**; facultative anaerobes
 - **multi-celled molds**; aerobic
 - Sometimes both (dimorphic fungi)
 - Reproduce by simple division or budding



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Infection and Injury - Fungal Infection

- **Pathogenicity**
 - Adapt to host environment
 - Wide temperature variations, digest keratin, low oxygen
 - Suppress the immune defenses
 - Usually controlled by phagocytes, T lymphocytes
- Diseases caused by fungi are called **mycoses**
 - Superficial, deep, endemic (dimorphic fungi), or opportunistic
- Fungi that invade the skin, hair, or nails are known as **dermatophytes (superficial mycoses)**
 - The diseases they produce are called **tineas (ringworm)**
 - Tinea capitis, tinea pedis, and tinea cruris
- Deep fungal infections are life threatening and are commonly opportunistic (e.g., with antibiotics or pH changes).
- *Changes that alter normal flora promote fungal infections

From: www.ringwormtreatment.com



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Infection and Injury - Fungal Infection

- **Candida albicans**
 - Usually superficial as commensals on skin and mucous membranes
 - **Candidiasis or moniliasis**
 - Spread from superficial structures more serious
 - *Aspergillus* is another commensal that can become dangerous in immunocompromised individuals
- **Deep mycoses**
 - B. dermatitis – **Blastomycosis** (endemic)
 - Coccidioids – **Coccidiomycosis** (SW US)
 - Histoplasma – **Histoplasmosis** (bat guano)
 - *Pneumocystis jirovecii* only occurs in immunocompromised individuals



Figure 5-8 Oral candidiasis. These candida lesions can be seen in immunocompromised patients. (Image from: Stedman's Medical Dictionary, 2008. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)
From: Pathophysiology: A Clinical Approach, Braun & Anderson, Lippincott, 2011

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Clinical Models – Tinea (Fungus)

- Group of fungal skin diseases that occur in several locations
 - Feet (tinea pedis)
 - Nails (tinea unguium)
 - Scalp (tinea capitis)
 - Groin (tinea cruris)
 - Skin (tinea corporis/ringworm, tinea versicolor)
- Pathophysiology
 - Major route of transmission is by direct contact with infected reservoir
 - Some predisposing factors
 - Exposure to moist conditions
 - Genetic predisposition
 - Immunocompromise
 - Sharing of hygiene facilities with infected individuals
 - Fungus (dermatophyte) attaches to keratinized cells and causes thickening
 - May be complicated by bacterial superinfection or invasive dermatophyte invasion



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Infection and Injury - Parasitic Infection

- Parasite – organism that benefits at host's expense
- Major classes of parasites
 - Unicellular, nucleated, motile protozoa
 - include malaria, amoebae, flagellates
 - Cases of Primary Amoebic Meningoencephalitis in 2013 caused by *Naegleria fowleri*
 - Large worms (helminths)
 - Flatworms (flukes), roundworms (nematodes), tapeworms (cestodes)
 - Ectoparasites – life on surface of host: lice, scabies,
- More common in developing countries
- Spread human to human via vectors
- Usually ingested
- Tissue damage
 - May be direct or secondary to infestation itself with toxin damage
 - May be from consequences of inflammatory/immune response

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Protozoa

- Malaria (*Plasmodium* spp.; most common protozoan infection worldwide)
 - Vector is mosquito
 - Invade/destroy RBCs
- Leishmaniasis (*Leishmania* spp.)
 - Chronic, inflammatory disease
 - Infects WBC; skin, mucous membranes, viscera
 - Vectors are sandflies
- Trypanosomiasis (*Trypanosoma* spp.)
 - Infects blood
 - Vectors are several types of insects
 - African sleeping sickness; Chagas disease (cats are reservoir)
- Amebiasis (*Entamoeba histolytica*)
 - Consumption of fecally contaminated food
 - Intestine (diarrhea), portal blood to form amebic abscesses, brain and lung
- Giardiasis (*Giardia lamblia*; most common protozoan infection in US)
 - Ingesting fecally contaminated water or produce (chlorination not effective)
 - Acute or chronic diarrhea when symptomatic
- Cryptosporidiosis (*Cryptosporidium*; also called microsporidiosis)
 - In soil, food, water, fecally contaminated surfaces
 - diarrhea in immunocompromised

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Helminths (worms)

- *Peripheral blood eosinophilia is a hallmark
- Roundworms (nematodes)
 - Filariasis
 - Vector is mosquito
 - Infects Lymphatics and subcutaneous tissue
 - Lymphedema, usually of scrotum and legs (elephantiasis)
 - Intestinal roundworms (Usually tropical areas; oral-fecal contamination; intestine)
 - Ascariasis (*Ascaris* spp.) – intestinal bleeding/obstruction, anemia (feed on blood),
 - Hookworms – intestinal bleeding, anemia
 - Pinworm – common pediatric infection in US; intestine, perianal area
 - Trichinosis – eating inadequately cooked pork; spread to muscle (pain, fever)
- Flatworms (flukes, trematodes)
 - Infect blood vessels, GI tract, lungs, or liver
 - Schistosomiasis – most common of all worm infections; snail vector
 - Tapeworms (cestodes)
 - 3 stages: eggs, larvae, adult
 - Intestinal infection
 - Adults are named for their intermediate host, e.g., fish, beef, pork; larvae are in muscle
 - When intermediate host is eaten (undercooked), larvae develop
 - Echinococcosis (hydatid disease)

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Sexually Transmitted Infections (STIs)

- Infections communicated by sexual contact
- Can be cause by any type of microorganism
 - Viruses, e.g., genital and anorectal warts by HPV, genital herpes, HIV
 - Bacteria, e.g., syphilis, gonorrhea, Chlamydia, Mycoplasma
 - Parasites, e.g., trichomoniasis (amebic), scabies (skin mites), lice (pediculosis)
- Some non-STI infections can be transmitted sexually, e.g., viral hepatitis
- Problematic because many cases are asymptomatic and this increases the risk of transmission
- Safe-sex practices can prevent STIs
- Chlamydia (*C. trachomatis*) is most common STI in the world
- Chlamydia and gonorrhea (*N. gonorrhoeae*) are the most common causes of STI-related infertility

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Infection and Injury – Countermeasures; Antimicrobials

- Antimicrobials (antibiotics)
 - Usually products of fungi or bacteria that inhibit growth of bacteria
 - Bacteriocidal (kill) vs. bacteriostatic (inhibit growth)
 - General mechanisms of most antibiotics
 - Inhibit synthesis of cell wall and other proteins
 - Damage cytoplasmic membrane
 - Alter metabolism of nucleic acid, inhibition of DNA synthesis
 - Modify energy (folic acid) metabolism
- Antimicrobial resistance mechanisms
 - Genetic mutations transmitted to other bacteria by plasmid exchange
 - Inactivation and/or breakdown of antibiotic
 - Multidrug transporters in bacterial cell membrane inhibit uptake
 - Multiple antibiotic-resistance bacteria (e.g., MRSA, VISA, VRSA, etc.)
 - Major problem in hospitals
 - Inadequate patient compliance with antibiotic regimen
 - Overuse/over-prescribing of antibiotics by healthcare professionals

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Infection and Injury – Countermeasures; Vaccines

- Vaccines
 - Biologic preparations of weakened or dead pathogens
 - Stimulate cellular or humoral immunity against virus
 - Live, attenuated strains; not enough virus to cause disease (except in immunocompromised individuals)
 - Heat killed virus; outer protein coat stays intact to promote immune response
 - Recombinant viral protein
 - Long lasting immunity (artificial, active)
 - Primary response is short-lived;
 - Booster increases secondary response
 - CDCP schedules @ <http://www.cdc.gov/vaccines/schedules/index.html>
 - Vaccines against bacterial exotoxins are called 'toxoids', e.g., DPT
 - Reluctance to vaccinate
 - Most objections are based on incomplete or incorrect information
 - Complications are rare
 - Removal of thimerosal (Hg containing) from most vaccines in 2001 has lessened the risk and increased the favorable perception about vaccines

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