

Robbin's Pathologic Basis of Disease, Chapter 8

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Categories of Infectious Agents

Prions

Protozoa

Viruses

Helminths

Chlamydiae

Ectoparasites

Rickettsiae

Mycoplasma

Bacteria

Fungi

Categories of Infectious Agents

Prions

- "infectious" particles composed of misfolded host protein, PrP
 - not infectious between people
 - an exception is kuru, which people caught from eating the brains of other humans
- Proteolysis resistant protein
- cause variety of spongiform encephalopathies
 - Creutzfeldt-Jakob disease
 - kuru
 - bovine spongiform encephalopathy
- no treatment
- diagnosis obtained pathologically

Categories of Infectious Agents

Viruses

- depend upon metabolism of host cell for replication (obligate intracellular parasites)
- classified by nucleic acid cores (DNA or RNA) and shape of protein capsid
- account for major share of human infections

Bacteriophages, Plasmids & Transposons

Not specifically human pathogens

- mobile genetic elements which encode virulence factors
- infect bacteria and incorporate themselves into the the genome, thus converting nonpathogenic strains into virulent strains
 - E. coli 0157:H7
 - Acquires shiga toxin and causes disease, most often in children

Categories of Infectious Agents

Bacteria

- Prokaryotic -- lack nucleus and contain rigid cell walls
 - gram negative: cell wall of proteoglycan sandwiched between two phospholipid bi-layers
 - gram positive: cell wall of peptidoglycan covering single lipid bilayer
- various shapes -- cocci, bacilli, spiral
- various metabolic lifestyles
 - aerobic -require oxygen environment
 - anaerobic - cannot tolerate oxygen
 - facultative anaerobic - tolerate reduced oxygen levels

Categories of Infectious Agents

Chlamydiae, Rickettsiae & Mycoplasmas

- similar to bacteria in that they divide by binary fission
- unique features
 - mycoplasmas lack a cell wall
 - atypical pneumonia that does respond to antibiotic treatment
 - causes an unfavorable host response
 - chlamydiae lack ATP synthesis
 - rickettsiae are transmitted via insect vectors; are obligate intracellular parasites

Fungi

- contain thick, ergosterol-containing cell walls
- reproduce via budding yeast cells or hyphae tubes
- important opportunistic pathogens in immunocompromised hosts (AIDS and chemotherapy patients)

Protozoa: Malaria, amoeba, giardia, trapanysoma, leishmania, toxoplasma

- motile single-celled organisms
- pliable cell membranes
- complex cytoplasmic organelles

Helminths

- parasitic worms
- exist in either sexual or asexual forms
- most adults produce eggs within human hosts, but do not multiply
- major classes
 - nematodes (roundworms) - not segmented
 - cestodes (flatworms, tapeworms) - gutless, produce ribbons of flat segments attached to head segment
 - trematodes (flukes) - primitive, flat, leaf-like worms

Ectoparasites: Lice, Ticks, Scabies

- are carriers and vectors for other diseases
 - typhus (lice), lime disease (ticks)
- scabies does actually cause illness and is more than simply a vector
 - can be worsened by infection

Acquisition of infectious agents

- Inhalation
- Ingestion
 - Mostly via fecal contamination of water and food
 - Hep A, etc.
 - Can be remedied through adequate food and water sanitation
- Injection, needle, transplant, insect, animal bite
 - Most common are through insect vectors
 - Mosquitoes, lice
 - Yellow fever, malaria etc.
 - Transplantation of infected organs
 - Corneal transplants
 - Blood transfusion
 - Animals bites
 - rabies
- Contact, skin, mucus membrane, sex

- Leprosy is the most important disease transmitted entirely through contact
- CMV, Eb. Barr
- Placental
 - Eb. Barr, CMV, herpes, syphilis,

Host Defense

Barriers:

- Skin: Keratinized layer, pH 5.5, fatty acids
 - Some organisms can penetrate intact skin
 - Hookworm, certain larvae
- GI tract: Mucus, gastric acid, enzymes, peptides (defensin), normal flora, IgA, motility
 - Altering normal flora can cause disease such as in *C. difficile* diarrhea
- Resp: Muco-ciliary blanket and cough, lysozyme, alveolar macrophage
- Urogenital: Flow of urine
- Innate Immune response: phagocytes, complement, toll like receptors
- Acquired immune response: antibody, cytotoxic T-cells

Spread & Dissemination of Microbes

- Spread enhanced by warm, moist surfaces
- Initial spread via paths of least resistance (i.e. natural tissue planes)
- Lymphatic invasion at site of entry allows quick access to regional nodes, with subsequent entrance to bloodstream
- Viruses spread from cell to cell, but may also be carried in blood to distant sites
- Major manifestations of disease may arise at sites distant to those of site of organism entry
- Placental-fetal route important for congenital infections

How Microorganisms Cause Disease

- Direct cell death following entry or contact
- Kill cells at a distance
 - release of endo or exotoxins
 - release enzymes to degrade tissue

- damage vessels, causing ischemic necrosis
- Induction of host-cellular responses directed against invader may cause secondary damage to host

Modifiers to pathology

- Pathogen:
 - Phase of infection: Primary, secondary or tertiary syphilis
 - Pathogen Dose
 - Virulence
- Host:
 - Age, nutrition, immunity, population experience/genetic selection, route of infection

(Lime Disease Chart)

Mechanisms of Injury

Viral-induced

- Tropism: tendency of viruses to infect certain cells host cells may or may not have specific receptors, virus may or may not be able to replicate within certain cells
- Damage host by entering host and replicating at expense of host, inhibit host DNA, RNA, protein synthesis
- Contain surface proteins which bind to specific host cell receptors and insert into cell membrane impairing cell integrity

Mechanisms of Injury

Viral-induced

- Lyse cells: influenza, polio
- Mediate apoptosis: HIV, adenoviruses
- Cytotoxic T cell response to viral proteins on cell surface: Hepatitis B
- Killing of associated cells: oligodendroglia → neurons, anterior horn cells → skeletal muscle.
- Transformation and proliferation

Mechanisms of Injury

Viral-induced

- Methods of host cell destruction
 - inhibition of DNA, RNA or protein synthesis
 - insertion of viral proteins into host's cell membrane
 - attack of viral-infected host cell by host immune system
- **secondary bacterial infection of viral-damaged host tissue**

(Mechanisms of Viral Injury to Host Cells – Picture)

Acute viral hepatitis – Picture

- T cell mediate cytotoxicity

Chronic viral hepatitis – Picture

- Cell death leads to fibrosis of tissue

Cirrhosis – Chronic hepatitis - Picture

- Final result of hepatitis

Mechanisms of Injury

- *Bacterial-induced*
 - Bacterial endotoxin
 - lipopolysaccharide (LPS) structural component within the outer cell wall of gram-negative bacteria
 - Bacterial exotoxin
 - toxic substances released from various bacteria to act on host cell
 - e.g. *Vibrio cholera*, *Clostridium perfringens*, *E. coli*, *Corynebacterium diphtheriae*
 - **Superantigen:** Massive T-cell stimulation without needing a second syndrome
 - Very similarly to exotoxic shock with release of cytokines etc.
 - TSS?
- Nutrition: giardia, tapeworm, hookworm
- Secondary infection: Scabies
- Vascular injury: Mucormycosis, Filaria, Schistosoma, syphilis
- Mechanical injury: Round worm
- Immune response: Immune complex disease, auto-immune disease,

Host Defense Evasion by Microbes

- Rendering itself inaccessible to host immune response
 - e.g., *Clostridium difficile* in gut lumen; *S. Typhi* in gallbladder; Malaria in liver cells
 - formation of dense fibrous cysts within host, Hydatid cyst
 - Intracellular growth: viruses, TB in macrophages
- Resisting host cell-mediated lysis and phagocytosis
 - carbohydrate capsules of pneumococcus, meningococcus and *Hemophilus* shield bacterial antigens, preventing neutrophilic phagocytosis
 - complement inhibition of host mediated via K-antigen of *E. coli*
- Varying or shedding of microbial antigens
 - many viruses (rhinovirus & influenzae virus) are highly mutagenic, making vaccination difficult to impossible
 - *Borrelia recurrentis* switches its surface antigen before each successive clone is destroyed by the host, causing relapsing fever
- Causing host immunosuppression
 - viruses such as HIV and Epstein-Barr infect lymphocytes, directly damaging immune system
- Protease degradation of antibody; Neisseria, Streptococci.
- Block complement activation: Herpes, polio
- Produce homologues of cytokines and chemokines: IL10 by EBV
- Interference with recognition of infected cells by altering HLA expression: Herpes expresses Class I homologues.
- Viral Latency: herpes, VZV, EBV

Host response to microbes

- Cytopathic/cytoproliferative
 - More about this later.
- Suppurative/acute inflammation
- Necrotizing inflammation
- Chronic inflammation and granuloma
- Neoplastic

(CMV Lung Infection – Picture)

Inflammatory Responses to Infection

- *Suppurative Inflammation*
 - characterized by increased vascular permeability and neutrophilic infiltration
 - common in infections with gram-positive cocci and gram-negative rods
 - mass infiltration of neutrophils results in pus
- *Necrotizing Inflammation (Acute) – Pictures?*
 - characterized by rapid and severe tissue damage and cell death from release of potent toxins
 - infection of anaerobes and aerobes
 - sometimes the infection progresses so fast, there is not chance for a host response
 - host inflammatory response often not seen due to speed of process (*Clostridium perfringens/gas gang green*)
 - lesion resembles ischemic necrosis (loss of nuclei with preservation of cellular outline)
- *Mononuclear and Granulomatous Inflammation (Chronic)*
 - mononuclear cell infiltrates occur in response to viruses, intracellular bacteria, spirochetes, parasites and helminths
 - infiltrates consist of either lymphocytes, plasma cells, macrophages or eosinophils, depending upon type of organism present
 - *Granuloma – Picture*
 - Caused by fusion of certain cells to create giant cells
- *Cytopathic-Cytoproliferative Inflammation*
 - viral-mediated damage to individual cells without host response
 - examples:
 - viral inclusion bodies within nuclei of host cells (herpes, CMV)
 - fusion of host cells forming multinucleate cells (measles)
 - dysplastic changes in host epithelial cells and lymphocytes (human papilloma virus)
 - *Transformed cells: (EBV) – Picture*
 - Large cytoplasm
 - Large nucleus

(Mono Cells: EBV infection – Picture referred to above)

Inflammatory Responses to Infection

- *Chronic Inflammation and Scarring*
 - final common pathway of certain infections, in absence of complete healing
 - examples:
 - “pipe-stem” fibrosis of liver due to schistosome eggs
 - fibrous constrictive pericarditis due to tuberculosis (common cause)
 - *Liver Fibrosis - Picture*

Viral Infections

- Transient infections
- Chronic latent infections
- Chronic productive infections
- Transforming infections
-

Viral Infections

Transient Infections

- Only once: mumps, polio, West Nile, hemorrhagic fever.
- Repeatedly: Influenza
- Other transient viral infections:
 - e.g., measles
 - exception- sub-acute sclerosing pan-encephalitis.
- Host response: Cell mediate immunity for termination of infection; Antibody response for prevention of re-infection.

Viral Infections

Chronic Latent Infections

- Herpes simplex:
 - Primary infection
 - Periodic reactivation, e.g. cold sore
 - Immune deficiency – disseminated infection

- Eczema herpeticum, encephalitis, hepatitis, bronchopneumonia.
- HSV 2: Infection in new born
- Other examples: CMV, VZV

Viral meningitis – Picture

Herpes meningoencephalitis – Picture

- Tissue necrosis

CMV infection

- Congenital infection:
 - encephalitis, hepatitis, pneumonitis
- Perinatal infection:
 - usually mild affecting liver, lung, skin
- CMV mononucleosis:
 - Primary infection in adult
- CMV infection in immunosuppressed,
 - e.g., HIV: retinitis, pneumonia, enteritis

Chronic Productive infection

- Hepatitis B virus:
 - 5-10% of adults and up to 90% neonates
 - Chronic infection, hepatitis, scarring, cirrhosis, hepatocellular carcinoma
- Hepatitis C virus:
 - 80-85% infections become chronic leading to cirrhosis and cancer.
 - 1% of the US adult population are infected with Hepatitis C

Transforming infections

- EBV, HPV, HTLV-I
- EBV: usually self limited mononucleosis
 - X-linked immunodeficiency (Duncan Disease)
 - Small population of infected B-lymphocytes persists:
 - proliferation on immunosuppression
 - 8:14 translocation: Burkitt's lymphoma

Bacterial Infections: Gram positive

- Local destruction: Follicular abscess, necrotizing fasciitis
 - Eyelash sty
- Massive T-Cell activation: Toxic shock syndrome
 - Super antigens
- Autoimmune: Rheumatic fever, Glomerulonephritis
- Exotoxins: Diphtheria
- Listeria: Food poisoning, abortion, immunosuppressed
 - Not pathogenic to normal adults
 - Disseminated infection can cause abortion and disease in immunosuppressed people
- Anthrax: Cutaneous, pulmonary, gastro-intestinal
- Nocardia: Immunodeficient hosts

Pneumonia - Picture

Broncho-pneumonia – Picture

- Usually tissue destruction

Lobar pneumonia – Picture

- Consolidation of one lobe of the lung
- Full recovery, not really associated with tissue destruction unlike in broncho-pneumonia

Bacterial Infections: Gram negative

- Neisserial infections:
 - Meningitidis: 10% colonized, multiple serotypes, complement deficiency (c5-9)
 - **Most rapidly fatal infection to normal healthy people (6 hrs from contraction)**
 - Waterhouse-Friderichsen syndrome
 - N. gonorrhoeae
- Bordetella pertussis: Ciliated cells, exotoxin, secondary infection, lymphocytosis
- Pseudomonas: cystic fibrosis (patients with this disease have chronic infection), burns, neutropenia, mucopolysaccharide capsule and biofilm (antibiotics don't penetrate this capsule), exotoxin, vasculitis

Pseudomonas vasculitis - Picture

Legionnaires' Disease

- Caused by gram-negative bacillus, *legionella pneumophila*
- Require special culture media for growth
- Organisms resistant to chlorine
- Grow and spread via aerosolization within cooling systems
 - Important nosocomial infection
 - Copper pipe/ionization of water is needed to get rid of this in the environment
- Cause limited fever in healthy individuals
- Cause severe pneumonia (Legionnaires' Disease) in smokers, elderly and immunocompromised patients

Bacterial Infections: Gram negative

- *Yersinia pestis*: Western US, rodents
 - Bubonic (only spread via vectors), Pneumonic (can spread from person to person in this form), Septicemic
 - Pneumonic plague is the most infection of infectious diseases
 - You probably only need to inhale one organism
 - Leprosy is the least
 - Requires years of contact with an infected person

Anaerobic bacteria

- Clostridia: potent exotoxins
 - *C. perferingens*
 - *C. tetani*
 - *C. botulinum*
 - *C. difficile*: pseudomembranous colitis in antibiotic treated patients (nosocomial)
 - *Picture*
 - Alcohol hand wipes will not kil *C. difficile*. You have to wash your hands with soap and water.

Helicobacter pylori – Stomach – Picture

- Cause stomach ulcers

- Warren and Marshall won the Nobel Prize =)

Mycobacteria

- Mycobacterium tuberculosis
- Mycobacterium leprae
 - As said above, is the least infectious organism
- Mycobacterium avium
- Mycobacterium intracellulare
 - Mycobacterium avium intracellulare complex (MAC) in AIDS patients (*picture*)
 - Doesn't really hurt them, but grows abundantly
 - Can grow in hot tubs and can cause disease if inhaled

Mycobacterium tuberculosis infection – Pictures

- Phagocytized by alveolar macrophages
 - Sent throughout the body and can cause other disease at a later time
 - Progressive primary TB (miliary TB)
 - Secondary tuberculosis
 - Localized caseating lesions
 - Leads to progressive secondary TB → miliary TB
- Delayed hypersensitivity
 - Local destruction and fibrosis
- Lesion
 - Giant cells, inflammation etc.

Obligate intracellular bacteria

- Chlamydia trachomatis:
 - multiple serotypes
 - Trachoma – ocular infection (major cause of blindness)
 - Genital infection: PID and sterility; co-infection with N. gonorrhoeae, Dx by PCR (can't culture them)
 - Lymphogranuloma venereum
 - Always treat the individual for both Chlamydia and Gonorrhoea since they are usually contracted together.
- Rickettsiae: lice and ticks, typhus and spotted fevers

- *Vasculitis – picture*
- Ehrlichia: tick, granulocytic and monocytic ehrlichiosis

Spirochetes

- Treponema pallidum: Veneral syphilis
 - *Manifestations of syphilis – picture*
 - Neurosyphilis: people have illusions of grandeur =)
 - Gummas: can affect many organs, and are similar to tuberculosis lesions
 - Congenital syphilis: not treatable, physical features such as frontal bossing
- Borrelia recurrentis: Louse and tick
- Borrelia burgdorferi: Tick
 - *How did lyme disease get it's name?*

Fungal infections

- Candida: oral thrush, vaginitis; dissemination in immunosuppressed
- Cryptococcus: meningoenephalitis can affect healthy people but mostly immunosupressed
- Histoplasma: Ohio River Valley
 - Causes a primary lesion and has a process similar to tuberculosis
- Aspergillus: Immunosuppressed, vasculitis, aspergilloma, allergic reactions
 - Can grow in cavities created by tuberculosis
- Rhizopus, Avsidia, Cunninghamella and Mucor:
 - diabetes, neutropenia, corticosteroids
 - *Rhinocerebral mucormycosis – picture (hyphae shown in vessel wall)*
 - In people with **diabetic ketoacidosis**, affects the nose and spread to the vasculature and eventually can spread to the brain
 - Can cause venous thrombosis in the head

Protozoa

- Plasmodia: malaria

- Babesia: similar to malaria, endemic in USA, tick, splenectomized-fatal parasitemia
- Leishmania: visceral (genital wasting etc.), cutaneous (via bites of sand flies), mucocutaneous; Iraq and Afghanistan (think soldiers)
- Trypanosoma:
 - African-sleeping sickness
 - Chagas Disease:
- Cryptosporidium: water borne/contamination of drinking water
 - Is not killed by chlorine, but only by sand filtration (when this fails boil the water)
- Pneumocystis: Immunosuppressed host
- Entamoeba histolytica, Giardia lamblia, Toxoplasma

Chagas Disease

- Trypanosoma cruzi: Humans and domestic animals
 - Fecal matter inoculation through bite of “kissing bug”
 - not actually from the bug itself but when you crush it after it bites you =)
 - Acute phase: myocarditis due to inflammatory response
 - Chronic phase in about 20%, over 5-15 years: Damage due to immune response to small numbers of parasites.
 - Dilated cardiomyopathy with mural thrombi, arrhythmia
 - Dilatation of esophagus and colon due to damage to innervation
 - Infection of myenteric plexus
 - Transmission through blood transfusion from donors with chronic disease.

Pneumocystis carinii

Pneumocystis Pneumonia – many pictures

Diffuse infiltrate on CXR

Alveoli filled with foamy, amorphous material containing organisms and debris

Often see concurrent CMV infection

Cryptosporidium

Caused by protozoan parasite, *Cryptosporidium parvum*

Long known as cause of diarrhea in cattle

Causes debilitating, chronic diarrhea in AIDS patients
May cause mild, transient diarrhea in healthy individuals
Organisms killed by sand filtration, NOT chlorine
Epidemics occur with breakdown of city water filtration systems
Organisms disrupt microvilli, enter cytoplasm of epithelial cells and cause malabsorption
Organisms shed in stool and reenter water supply

Metazoa

- Hook worm, Pin worm, Strongyloides
- Tape worms and Fasciola
- Hydatid disease
- Trichonosis
- Schistosomiasis
- Filariasis
- Onchocerca

Strongyloidosis

- Strongyloides stercoralis:
 - Endemic in south eastern USA
 - Larvae enter through skin
 - Adult worm in upper intestine
 - **Hyperinfection in immunocompromised host (especially those on steroids)**
 - **Secondary bacterial infection due to penetration of intestinal wall by larvae which move to other tissues**
 - ***Strongyloides – picture of above***

Hydatid disease

- Echinococcus granulosus
 - Adult worm in dogs
 - Sheep usual intermediate host,
 - In human cases, cysts in liver, lung and other organs in order of frequency
 - Scolices of new worms develop in the cysts

Trichinosis

- *Trichinella spiralis*
 - Larvae in pork
 - Larvae grow into adult worms in intestine and release new larvae that invade blood stream
 - Larvae can cause myocarditis, encephalitis
 - Usually larvae encyst in skeletal muscle.

Trichinosis – picture (worms shown in intestines)

Onchocerca volvulus – picture

- Worms are released into other tissues - this is an important cause of blindness
- Antibiotic treatment will stop the cycle of release of larvae

Visceral larva migrans (not in book)

- Animal parasites, dog and cat-*Toxocara*
- Ingestion of embryonated eggs in soil, usually children
- Larvae in tissues, lungs, eye, liver, skin
 - Migrans – worms migrate throughout the body
- Intense eosinophilic response.
- Hypergammaglobulinemia, increased IgE and high titers of isoheamagglutinins (Blood group A, B)