Principle of Infection

La-or Chompuk, M.D.
Department of pathology
Faculty of Medicine

Infection

• Definition: Invasion and multiplication of microorganisms in body tissues
• No symptom, local cellular injury, localized symptom, dissemination
• Mechanism; competitive metabolism, toxins, intracellular replication, immune response
Classification of infectious agents:
- classification according to structure
- classification according to pathogenesis
- classification according to site of multiplication

Classification according to structure
- Prion - Fungi
- Viruses - Protozoa, metazoa
- Bacteria - Ectoparasite
- Rickettsia, chlamydia, mycoplasma
Classification according to pathogenesis

• Pathogenic agents;
  - Virulence: the degree of pathogenicity of a microorganism
  - Indicated by the severity of disease, the ability to invade tissue
    - high virulence
    - low virulence

• Opportunistic infection

Classification according to site of multiplication

- **obligate intracellular organisms;** Prions, viruses, rickettsiae, chlamydia, some protozoa

- **facultative intracellular organism;** Mycobacteria, Actinomyces, Pseudomonas spp.

- **extracellular organisms;** mycoplasma, fungi, bacteria, metazoa
Pathogenesis of Infectious Disease
- Host
- Pathogen; organism or parasite that cause disease

Host factors:
1. General factors; socioeconomic status, behavior pattern, occupational, and internal factors

2. Natural defense mechanism; skin and normal flora, respiratory tract and mucociliary mechanism, HCl production in stomach, or normal flushing action of urine
3. Inflammation; acute inflammation, phagocytosis, complement, and production of interferon

4. The immune response; HMI and CMI
   HMI: Ag & Ab (B-cell)
   CMI: T- cell, macrophages
   Immunocompetent
   Immunocompromised/ immunodeficiency

Organism factors:
1. Transmission; congenital transfer (Rubella, CMV, HIV, HSV), directly contact, fomite, food and water, airborne, animal, sexual

2. Spread and dissemination; localized and disseminated infection
   - viremia, bacteremia, fungemia, parasitemia
   - sepsis is a serious medical condition characterised by a whole-body inflammatory state caused by infection.
**Definition of sepsis**

- Sepsis is considered present if infection is highly suspected or proven and two or more of the following *systemic inflammatory response syndrome* (SIRS) criteria are met:
  - Heart rate > 90 beats per minute
  - Body temperature < 36 or > 38°C
  - Hyperventilation (high respiratory rate) > 20 breaths per minute or, on blood gas: a PaCO₂ less than 32 mmHg.
  - White blood cell count < 4,000 cells/mm³ or > 12,000 cells/mm³ or greater than 10% band forms (immature white blood cells).

**Septicemia** (blood poisoning; bacteremia with sepsis)

- is the presence of bacteria in the blood (bacteremia) and is often associated with severe disease.
- is a serious, life-threatening infection that gets worse very quickly.
- is considered a subset of sepsis.
- It can arise from infections throughout the body.
Organism factors:

3. Number of organism
   - numerous low virulent organism can cause severe disease

4. Pathogenicity of organism;
   - ability to attach host cells; pili, adhesins, specific receptor

- ability to invade tissue; *S. pyogenase* → hyaluronidase → breakdown ground substance
- toxin production; *C. botulinum* → neurotoxin
- multiplication
- resistance to host defense mechanism
- ability to cause necrosis
- enzyme release; anthrax → enzyme→ vasculitis→ ischemia
- immune evasion
Immune evasion by microbes

- Replicate in sites that are inaccessible to the host response; *S. typhi* in gallbladder
- Varying antigens they express; *influenza virus*
- Escaping killing by phagocytes and complement; *capsule*
- Viruses can produce molecules that inhibit innate immunity; *herpesvirus and poxvirus produce proteins that block complement activation*

### Example: specific attachment to host cells

<table>
<thead>
<tr>
<th>Disease</th>
<th>Organism</th>
<th>Microbial ligand</th>
<th>Target cells/receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td><em>Influenza virus</em></td>
<td>hemagglutinin</td>
<td>Neuraminic acid on Respiratory Epi.</td>
</tr>
<tr>
<td>AIDS</td>
<td><em>HIV</em></td>
<td>Gp 120 protein</td>
<td>CD4 T-cells</td>
</tr>
<tr>
<td>Malaria</td>
<td><em>P. Vivax</em></td>
<td>Merozoite</td>
<td>Duffy Ag on RBC Glycoprotein A, B on RBC</td>
</tr>
<tr>
<td></td>
<td><em>P. falciparum</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Example: specific toxin on vulnerable cells

<table>
<thead>
<tr>
<th>Disease</th>
<th>Organism</th>
<th>Toxin</th>
<th>Effect and vulnerable cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholera</td>
<td><em>Vibrio cholerae</em></td>
<td>Cholera toxin</td>
<td>cAMP activation in intestinal epi.</td>
</tr>
<tr>
<td>Diphtheria</td>
<td><em>Corynebacterium diphtheriae</em></td>
<td>Diphtheria exotoxin</td>
<td>Inhibition of protein synthesis in myocardium and nerves</td>
</tr>
<tr>
<td>Tetanus</td>
<td><em>Clostridium tetani</em></td>
<td>Tetanospasmin</td>
<td>Spastic paralysis of skeletal muscle</td>
</tr>
<tr>
<td>Whooping cough</td>
<td><em>Bordetella pertussis</em></td>
<td>Pertussis toxin</td>
<td>Cell death in tracheal epi</td>
</tr>
</tbody>
</table>

### Bacterial toxin

- **Exotoxin:**
  - Enzymes secreted by bacteria
  - Have local effect; *C. difficile* > pseudomembranous colitis
- **Endotoxin:**
  - Lipopolysaccharides from cell walls of GNB; *E. coli*
  - Released on death of the bacterium
  - Activator of complement cascade > inflammation,
    Coagulation cascade > DIC, IL-1 > fever
Summary: how microorganisms cause disease

1. They can contact or enter host cells and directly cause death

2. They may release toxins that kill cells at a distance, release enzymes that degrade tissue components, or damage blood vessels and cause ischemic necrosis

3. They can induce host cellular responses that usually by immune-mediated mechanisms.
   - Immune are necessary to overcome the infection but at the same time may directly contribute to tissue damage.
1. Suppurative Inflammation: Neutrophils

- complication of acute inflammation; liquefactive necrosis with abscess formation
- extracellular organisms; bacteria
  except *S. typhi* – *neutropenia*, *macrophages*
1. Suppurative Inflammation

1.1 acute suppurative; neutrophil infiltrate, necrotic tissue, e.g. S. aureus, Klebsiella spp.

1.2 chronic suppurative; fibrosis, microabscess, and sinus draining e.g. filamentous bacteria or mycelial fungi in Medura foot

Pustule; acute suppurative inflammation
Skin abscess from S. aureus

FIGURE 8-7  Pneumococcal pneumonia. Note the intra-alveolar polymorphonuclear exudate and intact alveolar septa.
2. Chronic inflammation

2.1 chronic inflammation with *lymphocytes* and plasma cells;
- obligate intracellular organisms esp. viruses
- effect of CMI and HMI e.g. chronic hepatitis
- cell necrosis, fibrosis
Viral pneumonia

Syphilitic aortitis; plasma cell infiltrate to vasa vasorum
2. Chronic inflammation

2.2 chronic granulomatous inflammation;
Mycobacteria, fungus

Granulomatous inflammation/ Granuloma: accumulation of activated macrophages called “epitheliod” cells, may fuse to form giant cells.

2.3 chronic inflammation with diffuse proliferation of macrophages; in abnormal CMI patient --- no distinct granuloma, foamy macrophages with numerous organisms

Spectrum of tuberculosis, granulomatous inflammation
2. Chronic inflammation

2.4 combined suppurative & granulomatous inflammation; epithelioid granulomas with central neutrophilic abscess, e.g. deep fungal infection, Lymphogranuloma Venereum, Mellioidosis, Cat-scratch disease
2. Chronic inflammation

2.5 chronic inflammation with *Eosinophils*

- response to multicellular parasites and certain fungi

- **Splendore-Hoepli phenomenon**; radiating or anular eosinophilic deposits of host-derived materials, and possibly of parasite antigens, which form around fungi, helminths, or bacterial colonies in tissue
Strongyloidiasis; eosinophilic infiltration

Strongyloid larva in duodenal tissue
Splendore-Hoepli phenomenon; fungal infection

FIGURE 8–57  Portion of a cysticercus cyst.
3. Cytopathic-Cytoproliferative Inflammation

- these reactions are usually produced by viruses
- cell necrosis or cellular proliferation, usually with sparse inflammatory cells
- some viruses replicate within cells and make viral aggregates that are visible as inclusion bodies (e.g. herpesviruses or adenovirus)
Inclusion bodies of diagnostic use in viral infection

<table>
<thead>
<tr>
<th>Virus</th>
<th>Inclusion body</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV</td>
<td>Intranuclear inclusion surrounded by a halo</td>
</tr>
<tr>
<td>Rabies</td>
<td>Eosinophilic rounded cytoplasmic inclusions (Negri bodies)</td>
</tr>
<tr>
<td>HBV</td>
<td>Ground-glass cytoplasm in hepatocytes</td>
</tr>
<tr>
<td>Molluscum contagiosum (Poxvirus)</td>
<td>Eosinophilic cytoplasmic inclusions</td>
</tr>
<tr>
<td>HSV</td>
<td>Eosinophilic intranuclear inclusion</td>
</tr>
</tbody>
</table>

**FIGURE 8-13** Cytomegalovirus: distinct nuclear and ill-defined cytoplasmic inclusions in the lung.
3. Cytopathic-Cytoproliferative Inflammation

- some viruses induce cells to fuse and form multinucleated cells called polykaryons (e.g. measles virus or herpesviruses)

- focal cell damage in the skin may cause epithelial cells to become detached, forming blisters.
FIGURE 8–11 Measles giant cells in the lung. Note the glassy eosinophilic intranuclear inclusions.

FIGURE 8–9 Herpesvirus blister in mucosa. See Figure 8–13 for viral inclusions.
FIGURE 8-12 High-power view of cells from the blister in Figure 8–9 showing glassy intranuclear herpes simplex inclusion bodies.

Tzanck test

HSV: intranuclear inclusion, multinucleation
3. Cytopathic-Cytoproliferative Inflammation

- some viruses can cause epithelial cells to proliferate (e.g. venereal warts caused by human papillomavirus or the umbilicated papules of molluscum contagiosum caused by Poxviruses)
HPV: Koilocyte

Poxvirus: Molluscum contagiosum
3. Cytopathic-Cytoproliferative Inflammation

- Viruses can cause dysplastic changes and contribute to the development of malignant neoplasms;
  - EBV: Burkitt lymphoma
  - HBV and HCV: Hepatocellular carcinoma
  - HPV: Squamous cell carcinoma of cervix, penis
Hepatocellular carcinoma; HBV/HCV

Squamous cell carcinoma of penis/ cervix
HPV
4. Necrotizing inflammation

- *Clostridium perfringens* and other organisms that secrete powerful toxins can cause rapid and severe necrosis.

- *Clostridia* are often opportunistic pathogens that are introduced into muscle tissue by penetrating trauma or infection of the bowel in a neutropenic host.

Gas gangrene
*Clostridium perfringens*
4. Necrotizing inflammation

- *Entamoeba histolytica* causes colonic ulcers and liver abscesses characterized by extensive tissue destruction with liquefactive necrosis and without a prominent inflammatory infiltrate.
4. Necrotizing inflammation

- By entirely different mechanisms, viruses can cause widespread and severe necrosis of host cells, with inflammation, as exemplified by total destruction of the temporal lobes of the brain by herpesvirus or the liver by HBV.

Herpes encephalitis
5. Chronic inflammation and scarring

- chronic HBV infection; cirrhosis of liver
- sometimes the exuberant scarring response is the major cause of dysfunction (e.g., the “pipe-stem” fibrosis of the liver or fibrosis of the bladder wall caused by schistosomal eggs or the constrictive fibrous pericarditis in tuberculosis)
HBV, liver cirrhosis

Schistosomal periportal fibrosis
FIGURE 8–10 *Schistosoma haematobium* infection of the bladder with numerous calcified eggs and extensive scarring.

### Summary: tissue responses to infection

<table>
<thead>
<tr>
<th>Type of inflammation</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exudative inflammation</td>
<td>Pyogenic bacteria</td>
</tr>
<tr>
<td>Necrotizing inflammation</td>
<td>GNB, amebiasis</td>
</tr>
<tr>
<td>Granuloma</td>
<td>Mycobacteria, fungi</td>
</tr>
<tr>
<td>Histiocytic inflammation</td>
<td>Rhodococci, Legionella, Whipple’s disease, MAC</td>
</tr>
<tr>
<td>Eosinophilic inflammation</td>
<td>Fungi, parasites</td>
</tr>
<tr>
<td>Cytopathic change</td>
<td>Viruses</td>
</tr>
</tbody>
</table>
Clinical evaluation:
1. Clinical history
   - Prevalence of infectious disease
   - Assessment of immune status
   - Exposure to animals
   - Travel history

Prevalence of infectious disease
   - Community-acquired infection
   - Hospital-acquired infection/Nosocomial infection
     - Increased susceptibility
     - Used of invasive procedure
     - Numerous source of infection
     - Use of antibiotic
   - Opportunistic infections
2. Physical examination
3. Investigation
   - Microbiological tests
   - Immunological tests
   - Histological examination of tissue specimens
   - Immunohistochemistry, PCR, DNA probe, DNA microarray
<table>
<thead>
<tr>
<th>TABLE 8-9 Special Techniques for Diagnosing Infectious Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram stain</td>
</tr>
<tr>
<td>Acid-fast stain</td>
</tr>
<tr>
<td>Silver stains</td>
</tr>
<tr>
<td>Periodic acid–Schiff</td>
</tr>
<tr>
<td>Mucicarmine</td>
</tr>
<tr>
<td>Giemsa</td>
</tr>
<tr>
<td>Antibody probes</td>
</tr>
<tr>
<td>Culture</td>
</tr>
<tr>
<td>DNA probes</td>
</tr>
</tbody>
</table>

References: