Chapter 15: Microbial Mechanisms of Pathogenicity

1. Characteristics of Infectious Disease
2. How Pathogens Cause Disease
3. Virulence Factors
1. Characteristics of Infectious Disease

“The patient in the next bed is highly infectious. Thank God for these curtains.”
Signs & Symptoms, etc

**Signs** – what the health care provider observes or measures (objective)

**Symptoms** – what the patient experiences (subjective)

*Some diseases may be asymptomatic (no symptoms) and/or subclinical (no signs).*

**Syndrome** – multiple signs or symptoms that characterize a disease state

**Pathogenicity** – the ability of a microbial pathogen to cause disease

**Virulence** – the degree or severity of disease
Disease Classification...

**Infectious** – caused directly by a microbial pathogen

**Communicable** – capable of spread to others, directly or indirectly

**Contagious** – easily spread from person to person

**Iatrogenic** – unintended illness caused by a medical procedure

**Nosocomial** – acquired in a healthcare facility (e.g., hospital)
Factors Contributing to Nosocomial Infection

Microorganisms in the hospital environment

- most nosocomial pathogens are bacterial, many being drug-resistant due to antibiotic use

Weakened state of patients

- immune defenses are weakened due to illness, injury, surgery, etc

Ease of transmission

- hospital personnel, fomites (needles, catheters, etc), airborne transmission
Disease Classification

**Zoonotic** – transferred from animals to humans (e.g., malaria)

**Acute** – rapid onset, short duration (e.g., a cold or flu)

**Chronic** – active over a long period of time (e.g., hepatitis C)

**Latent** – extended periods of normalcy, potential to reactivate
**Periods of Disease**

**Incubation Period** – from onset of infection to first signs/symptoms

**Prodromal Period** – initial, general signs & symptoms

**Period of Illness** – signs & symptoms characteristic of disease, most severe period

**Period of Decline** – signs & symptoms diminishing

**Period of Convalescence** – signs & symptoms gone, return to “normal” state
2. How Pathogens Cause Disease
Koch’s Postulates

Proposed by Robert Koch in 1894.

- essentially a test or trial to determine the microbial cause of a disease

- used to identify pathogens causing anthrax (*Bacillus anthracis*) and tuberculosis (*Mycobacterium tuberculosis*)

1. The suspected causative agent must be absent from all healthy organisms but present in all diseased organisms.

2. The causative agent must be isolated from the diseased organism and grown in pure culture.

3. The cultured agent must cause the same disease when inoculated into a healthy, susceptible organism.

4. The same causative agent must then be reisolated from the inoculated, diseased organism.
Limitations to Koch’s Postulates

It would be nice if every suspected microbial pathogen was subject to “trial” by this method, however, this is not always possible because:

- many pathogens cannot be successfully cultured
  - pure “live” pathogen cannot be produced for inoculation into a test subject
- many pathogens only infect humans
  - it is not ethical to use human test subjects!

Does this mean that a pathogen cannot be identified without obtaining a pure culture?

Not necessarily, circumstantial evidence can be enough...
Portals of Entry

Following exposure, pathogens can enter the body of a human host through several “portals” or types of tissue:

1) Skin
   - the toughest barrier

2) Mucous membranes
   - the linings of the respiratory, digestive & genito-urinary tracts

3) Parenteral entry
   - through cuts, punctures, etc
The Importance of Numbers

Two important numerical concepts are the median infectious dose ($ID_{50}$) and median lethal dose ($LD_{50}$), which lead to infection or death, respectively, in 50% of test subjects.
Each type of pathogen has a “preferred” portal of entry, i.e., a tissue through which infection occurs most effectively:

* e.g., *Bacillus anthracis* (cause of anthrax)

\[
\text{ID}_{50} \text{ for skin}^{*} = 10-50 \text{ endospores} \\
\text{ID}_{50} \text{ for respiratory tract} = \sim 10,000 \text{ endospores} \\
\text{ID}_{50} \text{ for gastrointestinal tract} = \sim 500,000 \text{ endospores}
\]

Preferred portal of entry for *B. anthracis* = skin!
Adhesion

Entry into the host at the preferred portal typically involves adhesion between specific molecules on the surface of the pathogen and certain host cells:

- can involve a type of adhesin on pathogen and “receptor” on specific host cells or attachment via capsule, slime layer or biofilm

![Diagram of adhesion process](https://example.com/adhesion_diagram.png)
If an infection is to occur, adhesion will be followed by invasion of the surround tissues or cells, depending on the pathogen.

- this frequently involves enzymes or toxins produced by the pathogen

Contact with stomach acid keeps the mucin lining the epithelial cell layer in a spongy gel-like state. This consistency is impermeable to the bacterium *H. pylori*.

The bacterium releases urease, which neutralizes the stomach acid. This causes the mucin to liquefy, and the bacterium can swim right through it.
Infection

If the pathogen succeeds in reproducing in the region of invasion, it is now an infection.

Local
- confined to region near portal of entry

Focal
- spreads to other areas of the body

Systemic
- spreads throughout the body

A primary infection can lead to secondary infection by a different opportunistic pathogen.
Transmission of the pathogen to other individuals occurs through characteristic portals of exit.

- e.g., coughing, fecal material, secretions
3. Virulence Factors
As mentioned earlier, cell surface molecules that facilitate adhesion to host cells – **adhesins** – are a type of virulence factor that promotes infection and disease.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease</th>
<th>Adhesin</th>
<th>Attachment Site</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>Strep throat</td>
<td>Protein F</td>
<td>Respiratory epithelial cells</td>
</tr>
<tr>
<td><em>Streptococcus mutans</em></td>
<td>Dental caries</td>
<td>Adhesin P1</td>
<td>Teeth</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>Gonorrhea</td>
<td>Type IV pili</td>
<td>Urethral epithelial cells</td>
</tr>
<tr>
<td>Enterotoxigenic <em>E. coli</em> (ETEC)</td>
<td>Traveler's diarrhea</td>
<td>Type 1 fimbriae</td>
<td>Intestinal epithelial cells</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>Cholera</td>
<td>N-methylphenylalanine pili</td>
<td>Intestinal epithelial cells</td>
</tr>
</tbody>
</table>
Exoenzymes that Enhance Virulence

Glycohydrolases such as hyaluronidase – break down connective tissue carbohydrates such as hyaluronic acid

Collagenase – breaks down collagen in connective tissue
**Coagulases** – cause blood to clot, isolating bacteria from immune cells

**Kinases** – phosphorylate fibrin in blood clots causing clot to break down, infection to spread

**Nuclease**s – degrade nucleic acids, host cell DNA in particular

**Phospholipases** – break down phospholipids in host cell membranes
**Exotoxins**

- proteins produced inside certain bacteria (usu. Gram-positive) and released into host tissues to inhibit various cellular processes

**Exotoxins**

- Bacteria secrete exotoxins, in this case a cytotoxin.
- Cytotoxin kills host’s cells.

**Endotoxin**

- Dead Gram-negative bacteria release endotoxin (lipid A) which induces effects such as fever, inflammation, diarrhea, shock, and blood coagulation.

**Endotoxin**

- lipid A from LPS in the outer membranes of Gram-negative bacteria
Types of Exotoxins

Membrane-disrupting toxins

• disrupt the lipid bilayer (e.g., *Staphylococcus aureus*) or create a channel (e.g., *Clostridium perfringens*) resulting in lysis of host cell

Superantigens

• trigger intense and dangerous immune response by the non-specific activation of helper T cells

**Toxic Shock Syndrome** toxin: *(Staphylococcus aureus)*  
**Pyrogenic** toxins: *(Streptococcus pyogenes, “scarlet fever”)*
A-B Exotoxins

- proteins with an enzymatic “A” subunit that causes the damage and a “B” subunit that binds to host “receptor”
- “A” subunit is released from acidic phagolysosome (vacuole)
Examples of Exotoxins

**Diphtheria toxin:**
inhibits protein synthesis in respiratory epithelial cells
(*Corynebacterium diphtheriae*)

**Cholera toxin:**
disrupts Cl⁻ and Na⁺ balance, cells lose water by osmosis > diarrhea
(*Vibrio cholerae*)
**Botulinum toxin:** prevents muscle contraction, leads to inability to breathe, death by suffocation (*Clostridium botulinum*)

*botulinum toxin* (flaccid paralysis: stops muscle contraction)

**Tetanus toxin:** inhibits signals that relax muscle contraction, prevents muscle relaxation (*Clostridium tetani*)

tetanus toxin (spastic paralysis: stops uncontrollable muscle contraction)
Evading Host Defenses

Microbes have a variety of ways to avoid destruction by the immune system once they have invaded the body:

**Capsules**
- a dense glycocalyx that provides protection from phagocytosis by host immune cells

**IgA protease**
- breaks down IgA antibodies
More on Evading Host Defenses

Cell Wall components

- the cells walls of some bacteria (e.g., *Bacillus anthracis*) may also resist phagocytosis

Antigenic Variation

- some microbes are able to periodically change the molecules on their surface to avoid immune detection
- e.g., *Neisseria gonorrhoeae* (gonorrhea), *Borrelia burgdorferi* (Lyme disease), *Trypanosoma brucei* (sleeping sickness)
Siderophores & Iron

Most bacteria secrete proteins referred to as siderophores that bind iron:

- iron is an essential and limiting trace nutrient for all cells
- siderophores bind and essentially steal iron from host
- special receptors on the bacterium bind iron-siderophore complexes and internalize them

**Iron supplements may worsen a bacterial infection.**
Key Terms for Chapter 15

- symptoms, signs, syndrome, pathogen, virulence
- infectious, communicable, contagious, iatrogenic, nosocomial
- zoonotic, acute, chronic, latent
- portals of entry/exit, parenteral
- adhesin, LD$_{50}$, ID$_{50}$, mutualism, commensalism, parasitism
- siderophore, exotoxin, endotoxin, superantigen
- antigenic variation