Chapter 15

Microbial Mechanisms of Pathogenicity
I. Entry of a Microorganism into the Host

A. Portals of Entry

1. Mucous Membranes
   - Conjunctiva, respiratory, gastrointestinal, and genitourinary tracts
   - Important way is by inhaling droplets of moisture that contain microorganisms.
     - Example: TB – respiratory tract very common portal
   - Food, water, and contaminated fingers can introduce microorganisms via gastrointestinal tract.
   - Most organisms introduced via the genitourinary tract are done so via sexual contact.

2. Skin
   - Since most organisms cannot penetrate the skin they do so via cuts, bites, injections, surgery, hair follicles, or some fungi can infect the skin itself.
   - When microorganisms are introduced through the skin it is called parenteral route
# Table 15.1: Portals of Entry for the Pathogens of Some Common Diseases

<table>
<thead>
<tr>
<th>Portal of Entry</th>
<th>Pathogen*</th>
<th>Disease</th>
<th>Incubation Period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mucous Membranes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Pneumococcal pneumonia</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td><em>Mycobacterium tuberculosis</em>†</td>
<td>Tuberculosis</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td><em>Bordetella pertussis</em></td>
<td>Whooping cough (pertussis)</td>
<td>12–20 days</td>
</tr>
<tr>
<td></td>
<td><em>Influenza virus (Influenzavirus)</em></td>
<td>Influenza</td>
<td>18–36 hours</td>
</tr>
<tr>
<td></td>
<td><em>Measles virus (Morbillivirus)</em></td>
<td>Measles (rubeola)</td>
<td>11–14 days</td>
</tr>
<tr>
<td></td>
<td><em>Rubella virus (Rubivirus)</em></td>
<td>German measles (rubella)</td>
<td>2–3 weeks</td>
</tr>
<tr>
<td></td>
<td><em>Epstein-Barr virus (Lymphocryptovirus)</em></td>
<td>Infectious mononucleosis</td>
<td>2–6 weeks</td>
</tr>
<tr>
<td></td>
<td><em>Varicella-zoster virus (Varicellovirus)</em></td>
<td>Chickenpox (varicella)</td>
<td>14–16 days</td>
</tr>
<tr>
<td></td>
<td><em>Histoplasma capsulatum</em> (fungus)*</td>
<td>(primary infection)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Histoplasmosis</td>
<td>5–18 days</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td><em>Shigella spp.</em></td>
<td>Shigellosis (bacillary dysentery)</td>
<td>1–2 days</td>
</tr>
<tr>
<td></td>
<td><em>Brucella spp.</em></td>
<td>Brucellosis (undulant fever)</td>
<td>6–14 days</td>
</tr>
<tr>
<td></td>
<td><em>Vibrio cholerae</em></td>
<td>Cholera</td>
<td>1–3 days</td>
</tr>
<tr>
<td></td>
<td><em>Salmonella enterica</em></td>
<td>Salmonellosis</td>
<td>7–22 hours</td>
</tr>
<tr>
<td></td>
<td><em>Salmonella typhi</em></td>
<td>Typhoid fever</td>
<td>14 days</td>
</tr>
<tr>
<td></td>
<td><em>Hepatitis A virus (Hepatovirus)</em></td>
<td>Hepatitis A</td>
<td>15–50 days</td>
</tr>
<tr>
<td></td>
<td><em>Mumps virus (Rubulavirus)</em></td>
<td>Mumps</td>
<td>2–3 weeks</td>
</tr>
<tr>
<td></td>
<td><em>Trichinella spiralis</em> (helminth)*</td>
<td>Trichinellosis</td>
<td>2–28 days</td>
</tr>
</tbody>
</table>

*All pathogens are bacteria, unless indicated otherwise. For viruses, the viral species and/or genus name is given.*

†These pathogens can also cause disease after entering the body via the gastrointestinal tract. Hepatitis B virus can also cause disease after entering the body via the genitourinary tract.

‡These pathogens can also cause disease after entering the body via the parenteral route.
<table>
<thead>
<tr>
<th>Portal of Entry</th>
<th>Pathogen*</th>
<th>Disease</th>
<th>Incubation Period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mucous Membranes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td><em>Neisseria gonorrhoeae</em></td>
<td>Gonorrhea</td>
<td>3–8 days</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td></td>
<td>Syphilis</td>
<td>9–90 days</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td></td>
<td>Nongonococcal urethritis</td>
<td>1–3 weeks</td>
</tr>
<tr>
<td>Herpes simplex virus type 2</td>
<td></td>
<td>Herpes virus infections</td>
<td>4–10 days</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV)†</td>
<td></td>
<td>AIDS</td>
<td>10 years</td>
</tr>
<tr>
<td>Candida albicans (fungus)†</td>
<td></td>
<td>Candidiasis</td>
<td>2–5 days</td>
</tr>
<tr>
<td><strong>Skin or Parenteral Route</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td></td>
<td>Gas gangrene</td>
<td>1–5 days</td>
</tr>
<tr>
<td>Clostridium tetani</td>
<td></td>
<td>Tetanus</td>
<td>3–21 days</td>
</tr>
<tr>
<td>Rickettsia rickettsii</td>
<td></td>
<td>Rocky Mountain spotted fever</td>
<td>3–12 days</td>
</tr>
<tr>
<td>Hepatitis B virus (Hepadnavirus)†</td>
<td></td>
<td>Hepatitis B</td>
<td>6 weeks–6 months</td>
</tr>
<tr>
<td>Rabiesvirus (Lyssavirus)</td>
<td></td>
<td>Rabies</td>
<td>10 days–1 year</td>
</tr>
<tr>
<td>Plasmodium spp. (protozoan)</td>
<td></td>
<td>Malaria</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

*All pathogens are bacteria, unless indicated otherwise. For viruses, the viral species and/or genus name is given.

†These pathogens can also cause disease after entering the body via the gastrointestinal tract. Hepatitis B virus can also cause disease after entering the body via the genitourinary tract.

††These pathogens can also cause disease after entering the body via the parenteral route.
I. Entry of a Microorganism into the Host

• B. Preferred Portal of Entry – have to be able to survive and multiply even if they are introduced.
  – *Salmonella typhi* – Preferred is GI tract, harmless on skin
  – Streptococci – Preferred is respiratory tract, harmless if swallowed.

• C. Numbers of invading Microbes – Need to have a certain dose (ID or infectious dose)
  – Shigella ID$_{50}$ = 1 bacterium
  – Salmonella ID$_{50}$ = 20,000 bacteria
I. Entry of a Microorganism into the Host

• D. Adherence
  – 1. Surface projections on a pathogen called adhesins (ligands) adhere to complementary receptors on the host cells.
    • *Streptococcus mutans* – Attached to the surface of teeth by glycocalyx. Forms a biofilm that causes tooth decay.
    • *Treponema pallidum* – Uses tapered end as a hook to attach to host cells. Causes syphilis.
    • *Neisseria gonorrhoeae* – Has fimbriae containing adhesins that permit attachment to certain cells in genitourinary tract. Causes gonorrhea.
Figure 15.1 - Overview

(a) Surface molecules on a pathogen, called adhesins or ligands, bind specifically to complementary surface receptors on cells of certain host tissues.

(b) *E. coli* bacteria (yellow-green) on human bladder cells.

(c) Bacteria (yellow) adhering to human skin.
I. Entry of a Microorganism into the Host
II. How Bacterial Pathogens Penetrate Host Defenses

• A. Capsules
  – 1. Prevent them from being phagocytized, however, antibodies can be made by host to capsules which could then be phagocytized.
    • *Klebsiella pneumoniae* – causes pneumonia
    • *Hemophilis influenza* – causes pneumonia and meningitis
    • *Streptococcus pneumoniae* – causes pneumonia
II. How Bacterial Pathogens Penetrate Host Defenses

• B. Components of the Cell Wall
  – 1. Proteins facilitate adherence or prevent phagocytosis.
    • *Streptococcus pyogenes* – M protein, increases virulence by initiating attachment to epithelial cells.
    • *Mycobacterium tuberculosis* – Has a waxy cell wall, so resists digestion by phagocytes.
II. How Bacterial Pathogens Penetrate Host Defenses

• C. Enzymes
  – 1. Substances that break cells open, dissolve materials between cells, form or dissolve blood clots, and other functions. Examples:
    • Coagulase – Clot the fibrinogen in blood. Protects the bacterium from phagocytosis and other host defenses.
      – *Staphylococcus aureus* – Actually report out organisms as coagulase positive or coagulase negative Staph.
    • Hyaluronidase – Hydrolyzes a type of polysaccharide that holds certain cells, particularly connective tissue, together. Responsible for tissue blackening in wound infections.
      – Strep and Clostridium
    • Collagenase – Also breaks down connective tissue, attacks collagen.
      – *Clostridium perfringens*, cause of gas gangrene. Allows bacterium to spread.
III. How Bacterial Pathogens Damage Host Cells

A. Direct Damage by Toxins. Two main types: exotoxins and endotoxins.

(a) Exotoxins are produced inside mostly gram-positive bacteria as part of their growth and metabolism. They are then secreted or released following lysis into the surrounding medium.

(b) Endotoxins are part of the outer portion of the cell wall (lipid A; see Figure 4.13c) of gram-negative bacteria. They are liberated when the bacteria die and the cell wall breaks apart.
III. How Bacterial Pathogens Damage Host Cells

• A. Direct Damage by Toxins: exotoxins
  – 1. Exotoxins – Proteins (mainly enzymatic) that are poisonous that destroy part of the cell (especially cell membrane, ~40%) or inhibit certain metabolic functions (e.g., protein synthesis).
  • Some are the most lethal substances known. Diseases are caused by very minute amounts. Most genes for production carried on plasmids or phages.
III. How Bacterial Pathogens Damage Host Cells

• 1. Exotoxins
  – a. Cytotoxins – affect cells
    • Diphtheria Toxin (Corynebacterium diphtheriae) - inhibits protein synthesis in eukaryotes.
    • Erythrogenic Toxins (Strep pyogenes) – causes scarlet fever. Damage blood capillary plasma membranes under the skin and produce a red rash.
Proposed action of diphtheria toxin

1. Bacterium produces and releases exotoxin.

2. B (binding) component of exotoxin binds to host cell receptor, and exotoxin enters cell.

3. A (active) component of exotoxin alters cell function by inhibiting protein synthesis. B component is released from the cell.
III. How Bacterial Pathogens Damage Host Cells

• 1. Exotoxins
  – b. Neurotoxins – affect nerve cells
    • Botulism Toxin *(Clostridium botulinum)* –
      – Acts at neuromuscular junction and prevents transmission of impulses by inhibiting release of neurotransmitter acetylcholine. Causes flaccid paralysis in which muscle tone is lacking.
    • Tetanus Toxin *-Clostridium tetani* –
      – Reaches central nervous system and binds to nerve cells that control the inhibition of contraction skeletal muscles. Result is uncontrollable muscle contraction. Example: ‘Lock jaw’.
III. How Bacterial Pathogens Damage Host Cells

1. Exotoxins
   
   - c. Enterotoxins – affect lining of gastrointestinal tract.
     
     - Vibrio Enterotoxin - *Vibrio cholerae* – Binds to plasma membranes of epithelial cells in small intestine leading to massive fluid and electrolyte loss. Normal muscular contractions are disturbed, leading to severe diarrhea accompanied by vomiting.
     
     - Staphylococcal Enterotoxin - *Staphylococcus aureus* – affects intestines similar to vibrio toxin. Also produces another type associated with toxic shock syndrome.
       
       - Both are examples of a superantigen that produce a very intense immune response.
III. How Bacterial Pathogens Damage Host Cells

• 1. Exotoxins
  – d. Membrane Disrupting Toxins
    • Leukocidins – Destroy neutrophils and macrophages. Produced by staphylococci and streptococci.
    • Hemolysins – Lyse red blood cells. *Clostridium perfringens* and streptococci.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Bacterium</th>
<th>Type of Exotoxin</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulism</td>
<td><em>Clostridium botulinum</em></td>
<td>A-B</td>
<td>Neurotoxin prevents the transmission of nerve impulses; flaccid paralysis results.</td>
</tr>
<tr>
<td>Tetanus</td>
<td><em>Clostridium tetani</em></td>
<td>A-B</td>
<td>Neurotoxin blocks nerve impulses to muscle relaxation pathway; results in uncontrollable muscle contractions.</td>
</tr>
<tr>
<td>Diphtheria</td>
<td><em>Corynebacterium diphtheriae</em></td>
<td>A-B</td>
<td>Cytotoxin inhibits protein synthesis, especially in nerve, heart, and kidney cells.</td>
</tr>
<tr>
<td>Scalded skin syndrome</td>
<td><em>Staphylococcus aureus</em></td>
<td>A-B</td>
<td>One exotoxin causes skin layers to separate and slough off (scalded skin).</td>
</tr>
<tr>
<td>Cholera</td>
<td><em>Vibrio cholerae</em></td>
<td>A-B</td>
<td>Enterotoxin causes secretion of large amounts of fluids and electrolytes that result in diarrhea.</td>
</tr>
<tr>
<td>Traveler’s diarrhea</td>
<td>Enterotoxigenic <em>Escherichia coli</em> and <em>Shigella spp.</em></td>
<td>A-B</td>
<td>Enterotoxin causes secretion of large amounts of fluids and electrolytes that result in diarrhea.</td>
</tr>
<tr>
<td>Gas gangrene and food poisoning</td>
<td><em>Clostridium perfringens</em> and other species of <em>Clostridium</em></td>
<td>Membrane-disrupting</td>
<td>One exotoxin (cytotoxin) causes massive red blood cell destruction (hemolysis); another exotoxin (enterotoxin) is related to food poisoning and causes diarrhea.</td>
</tr>
<tr>
<td>Antibiotic-associated diarrhea</td>
<td><em>Clostridium difficile</em></td>
<td>Membrane-disrupting</td>
<td>Enterotoxin causes secretion of fluids and electrolytes that results in diarrhea; cytotoxin disrupts host cytoskeleton.</td>
</tr>
<tr>
<td>Food poisoning</td>
<td><em>Staphylococcus aureus</em></td>
<td>Superantigen</td>
<td>Enterotoxin causes secretion of fluids and electrolytes that results in diarrhea.</td>
</tr>
<tr>
<td>Toxic shock syndrome (TSS)</td>
<td><em>Staphylococcus aureus</em></td>
<td>Superantigen</td>
<td>Toxin causes secretion of fluids and electrolytes from capillaries that decreases blood volume and lowers blood pressure.</td>
</tr>
</tbody>
</table>
III. How Bacterial Pathogens Damage Host Cells

2. Endotoxins: lipopolysaccharides (LPS) in cell wall, lipid A portion.
   - a. Are actually part of the outer portion (lipopolysaccharide) of the cell wall of gram-negative bacteria. Exert effect when bacteria die and substances are liberated.
III. How Bacterial Pathogens Damage Host Cells

2. Endotoxins
   b. All gram-negative endotoxins produce the same symptoms:
      • Fever and chills by IL1 release by macrophage.
      • Stimulate macrophage to release cytokines with symptoms of weakness, generalized aches, clot formation with disseminated intravascular coagulation (DIC), and in some cases shock with low blood pressure (TNF damages capillaries) and even death.
   – See Table 15.3 for exotoxin and endotoxin comparison
<table>
<thead>
<tr>
<th>Property</th>
<th>Exotoxin</th>
<th>Endotoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial source</strong></td>
<td>Mostly from gram-positive bacteria</td>
<td>Gram-negative bacteria</td>
</tr>
<tr>
<td><strong>Relation to microorganism</strong></td>
<td>Metabolic product of growing cell</td>
<td>Present in LPS of outer membrane of cell wall and released with destruction of cell or during cell division</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td>Proteins, usually with two parts (A-B)</td>
<td>Lipid portion (lipid A) of LPS of outer membrane (lipopolysaccharide).</td>
</tr>
<tr>
<td><strong>Pharmacology (effect on body)</strong></td>
<td>Specific for a particular cell structure or function in the host (mainly affects cell functions, nerves, and gastrointestinal tract)</td>
<td>General, such as fever, weaknesses, aches, and shock; all produce the same effects</td>
</tr>
<tr>
<td><strong>Heat stability</strong></td>
<td>Unstable; can usually be destroyed at 60–80°C (except staphylococcal enterotoxin)</td>
<td>Stable; can withstand autoclav ing (121°C for 1 hour)</td>
</tr>
<tr>
<td><strong>Toxicity (ability to cause disease)</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Fever-producing</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Immunology (relation to antibodies)</strong></td>
<td>Can be converted to toxoids to immunize against toxin; neutralized by antitoxin</td>
<td>Not easily neutralized by antitoxin; therefore, effective toxoids cannot be made to immunize against toxin</td>
</tr>
<tr>
<td><strong>Lethal dose</strong></td>
<td>Small</td>
<td>Considerably larger</td>
</tr>
<tr>
<td><strong>Representative diseases</strong></td>
<td>Gas gangrene, tetanus, botulism, diphtheria, scarlet fever</td>
<td>Typhoid fever, urinary tract infections, and meningococcal meningitis</td>
</tr>
</tbody>
</table>
III. How Bacterial Pathogens Damage Host Cells

B. Plasmids, Lysogeny, and Pathogenicity

1. Plasmids: Small, circular, double-stranded DNA molecules that are not connected to the main bacterial chromosome.
   - These molecules are responsible for resistance of some organisms to antibiotics, toxins, capsules, and fimbriae – all factors in pathogenicity.
   - Can pass on resistance to other organisms. Becoming very important in emerging diseases.

2. Bacteriophages inserted into the bacteria change the properties of the cell. New factors, such as toxins or capsules, can be coded for by the virus’s DNA.
   - Examples: Diphtheria, staph enterotoxin, botulism, *Strep pneumo* capsule.
IV. Pathogenic Properties of Nonbacterial Microorganisms

• A. Viruses
  – 1. Viral Mechanisms for Evading Host Defenses
     • Can grow inside cell where immune system can’t reach
     • Gain entrance to cell because they have attachment site for receptors on the cell surface.
       – HIV actually attacks the immune system T cells via CD4 receptors
IV. Pathogenic Properties of Nonbacterial Microorganisms

• A. Viruses
  – 2. Cytopathic Effects (CPE) of Viruses
    • Examples: Stopping of mitosis, lysosome lysis, formation of inclusion bodies (aid in ID), cell fusion (syncytium), antigenic changes (triggers immune response), chromosomal changes (oncogene, gene disruption), and transformation (loss of contact inhibition).

(a) Inclusion body due to rabies
(b) syncytium due to measles
IV. Pathogenic Properties of Nonbacterial Microorganisms

• B. Fungi, Protozoa, and Helminths
  – 1. Fungi
    • a. Capsules
IV. Pathogenic Properties of Nonbacterial Microorganisms

• B. Fungi, Protozoa, and Helminths
  – 1. Fungi
    • b. Proteases
      – *Candida albicans* and *Trichophyton* secrete proteases that allow them to modify host cell membranes so they can attach.
    • c. Toxins: aflatoxin (mutagen) (*Aspergillus flavus*), ergot (resembles LSD) (*Claviceps purpurea*), amanitin (*Amanita phalloides* - deathcap)
IV. Pathogenic Properties of Nonbacterial Microorganisms

• B. Fungi, Protozoa, and Helminths
  – 2. Protozoa
    • *Plasmodium* - Causes malaria: Invades host cells and reproduces, causes them to rupture.
    • *Toxoplasma* – Enters phagocytic cells and actually grow in the phagocytic vacuole.
    • *Giardia lamblia* – Attach to host cells and digest the cells and tissue fluids.
    • *Giardia lamblia* and *Trypanosoma* – Evasion of immune system. Change surface antigens frequently while growing in the host so the host’s antibodies don’t kill them.
IV. Pathogenic Properties of Nonbacterial Microorganisms

• B. Fungi, Protozoa, and Helminths
  – Helminths
    • *Wucheria bancrofti* – Parasite blocks lymphatic circulation leading to accumulation of lymph and eventually grotesque swelling of legs and other body parts (elephantiasis).

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*Wucheria bancrofti* in blood

WHO/TDR/Stammers
V. Summary of Microbial Mechanisms of Pathogenicity

**Fig 15.9** Microbial mechanisms of pathogenicity

- **Portals of Entry**
  - Mucous membranes
  - Respiratory tract
  - Gastrointestinal tract
  - Genitourinary tract
  - Conjunctiva
  - Skin
  - Parenteral route

- **Number of Invading Microbes**

- **Penetration or Evasion of Host Defenses**
  - Capsules
  - Cell wall components
  - Enzymes
  - Antigenic variation
  - Invasins
  - Intracellular growth

- **Damage to Host Cells**
  - Siderophores
  - Direct damage
  - Toxins
  - Exotoxins
  - Endotoxins
  - Lysogenic conversion
  - Cytopathic effects

- **Portals of Exit**
  - Generally the same as the portals of entry for a given microbe

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