Microbial Mechanisms of Pathogenicity

1. **A** An infectious dose of microorganisms penetrates the host's defensive barrier.
2. **B** Microorganisms enter the sterile environment of the host's tissues.
3. **C** They move into a specific target tissue, such as an organ.
4. **D** Here they cause tissue damage, leading to disease.
5. **E** Microorganisms leave the host through a portal of exit to infect another host.
LEARNING OBJECTIVES

Identify the principal portals of entry and exit.
Using examples, explain how microbes adhere to host cells.
Explain how capsules and cell wall components contribute to pathogenicity.
Compare the effects of coagulases, kinases, hyaluronidase, and collagenase.
Describe the function of siderophores.
Provide an example of direct damage, and compare this to toxin production.
Contrast the nature and effects of exotoxins and endotoxins.
Outline the mechanisms of action of A-B toxins, membrane-disrupting toxins, and superantigens.
Classify diphtheria toxin, erythrogenic toxin, botulinum toxin, tetanus toxin, *Vibrio* enterotoxin, and staphylococcal enterotoxin.
**Vocabulary**

**Pathogenicity**: Ability of a pathogen to cause disease by overcoming the host defenses.

**Virulence**: Degree of pathogenicity.

**Attachment is step 1:**

Bacteria use

Viruses use
(Preferred) Portals of Entry

Mucous membranes

- Conjunctiva
- **Respiratory tract**: Droplet inhalation of moisture and dust particles. Most common portal of entry.
- **GI tract**: food, water, contaminated fingers
- **Genitourinary tract**

Skin

- Impenetrable for most microorganisms; can enter through hair follicles and sweat ducts.

Parenteral Route

- **Trauma** (S. aureus, C. tetani)
- **Arthropods** (Y. pestis)
- **Injections**
Numbers of Invading Microbes

**ID$_{50}$**: Infectious dose for 50% of the test population

**LD$_{50}$**: Lethal dose (of a toxin) for 50% of the test population

<table>
<thead>
<tr>
<th><em>Bacillus anthracis</em></th>
<th>ID$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Portal of Entry</strong></td>
<td><strong>ID$_{50}$</strong></td>
</tr>
<tr>
<td>Skin</td>
<td>10–50 endospores</td>
</tr>
<tr>
<td>Inhalation</td>
<td>10,000–20,000 endospores</td>
</tr>
<tr>
<td>Ingestion</td>
<td>250,000–1,000,000 endospores</td>
</tr>
</tbody>
</table>

**Adherence**

**Adhesins**: surface projections on pathogen, mostly made of glycoproteins or lipoproteins. Adhere to complementary receptors on the host cells. Adhesins can be part of:

- **Glycocalyx**: *e.g.* *Streptococcus mutans*
- **Fimbriae** (also pili and flagella): *e.g.* *E. coli*

Host cell receptors are most commonly sugars (*e.g.* mannose for *E. coli*).

**Biofilms** provide attachment and resistance to antimicrobial agents.
Overcoming Host Defenses

- **Capsules**: inhibition or prevention of _______________
- **Cell Wall Proteins**: *e.g.* M protein of *S. pyogenes*
- **Antigenic Variation**: Avoidance of IS, *e.g.* *Trypanosoma* *Neisseria*

- **Penetration into the Host Cell Cytoskeleton**: *Salmonella* and *E. coli* produce **invasins**, proteins that cause the actin of the host cell’s cytoskeleton to form a basket that carries the bacteria into the cell.
Penetration into the Host Cell Cytoskeleton

- Invasins
  - *Salmonella* alters host actin to enter a host cell
- Use actin to move from one cell to the next
  - *Listeria*
Coagulase: Blood clot formation. Protection from phagocytosis (virulent *S. aureus*)

Kinase: blood clot dissolve (e.g.: streptokinase)

Hyaluronidase: (Spreading factor) Digestion of “intercellular cement” \(\Rightarrow\) tissue penetration

Collagenase: Collagen hydrolysis

IgA protease: IgA destruction
Enzymes Used for Penetration

- **Coagulase**: Dissolves clot and releases pathogens.
- **Streptokinase**: Blood clot around pathogen.
- **Hyaluronidase**: Dissolves intracellular cement, allows pathogen to spread to deeper tissues.
How Pathogens Damage Host Cells

1. Use host’s nutrients; *e.g.* Iron
2. Cause **direct damage**
3. Produce **toxins**
4. Induce **hypersensitivity reaction**

**ANIMATION** Virulence Factors: Enteric Pathogens

**ANIMATION** Virulence Factors: Penetrating Host Tissues
Toxins

**Exotoxins:** proteins (Gram- and + bacteria can produce)

**Endotoxins:** Gram- bacteria only. LPS, Lipid A part released upon cell death. Symptoms due to vigorous inflammation. Massive release $\Rightarrow$ endotoxic shock
Vocabulary related to Toxin Production

- **Toxin**: Substances that contribute to pathogenicity.

- **Toxigenicity**: Ability to produce a toxin.

- **Toxemia**: 

- **Toxoid**: 

- **Antitoxin**: 

## Exotoxins Summary

<table>
<thead>
<tr>
<th>Source:</th>
<th>Gram + and Gram -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relation to microbe:</td>
<td>By-products of growing cell</td>
</tr>
<tr>
<td>Chemistry:</td>
<td>Protein</td>
</tr>
<tr>
<td>Fever?</td>
<td>No</td>
</tr>
<tr>
<td>Neutralized by antitoxin?</td>
<td>Yes</td>
</tr>
<tr>
<td>$LD_{50}$:</td>
<td>Small</td>
</tr>
</tbody>
</table>

Circulate to site of activity. Affect body before immune response possible.

Exotoxins with special action sites: **Neuro-**, and **enterotoxins**
### Toxin Examples

<table>
<thead>
<tr>
<th>Portal of Entry</th>
<th>ID(_{50})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum (in mice)</td>
<td>0.03 ng/kg</td>
</tr>
<tr>
<td>Shiga toxin</td>
<td>250 ng/kg</td>
</tr>
<tr>
<td>Staphylococcal enterotoxin</td>
<td>1350 ng/kg</td>
</tr>
</tbody>
</table>

Which is the least potent toxin?
1. Botulinum
2. Shiga
3. Staph
Type of Exotoxins:

A-B Exotoxins

**Fig 15.5**

1. Bacterium produces and releases exotoxin.

2. B (binding) component of exotoxin attaches to host cell receptor.

3. A-B exotoxin enters host cell by endocytosis.


5. A-B components of exotoxin separate. The A component alters cell function by inhibiting protein synthesis. The B component is released from the host cell.
Membrane-Disrupting Toxins

Lyse host’s cells by

1. Making protein channels into the plasma membrane, *e.g.* *S. aureus*

2. Disrupting phospholipid bilayer, *e.g.* *C. perfringens*

*Examples:*

**Leukocidin:** PMN and MΦ destruction

**Hemolysin** (*e.g.*: Streptolysin) : RBCs lysis ⇒

get at?
Superantigens

Special type of Exotoxin
Nonspecifically stimulate T-cells.
Cause intense immune response due to release of cytokines from host cells.
Fever, nausea, vomiting, diarrhea, shock, and death.
### Representative Examples of Exotoxins

<table>
<thead>
<tr>
<th>Bacterial Species</th>
<th>Exotoxin</th>
<th>Lysogeny</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. diphtheriae</em></td>
<td>A-B toxin</td>
<td>+</td>
</tr>
<tr>
<td><em>S. pyogenes</em></td>
<td>Membrane-disrupting erythrogenic toxin</td>
<td>+</td>
</tr>
<tr>
<td><em>C. botulinum</em></td>
<td>A-B toxin; neurotoxin</td>
<td>+</td>
</tr>
<tr>
<td><em>C. tetani</em></td>
<td>A-B toxin; neurotoxin</td>
<td></td>
</tr>
<tr>
<td><em>V. cholerae</em></td>
<td>A-B toxin; enterotoxin</td>
<td>+</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>Superantigen</td>
<td>+</td>
</tr>
</tbody>
</table>

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Endotoxins

- Bacterial cell death, antibiotics, and antibodies may cause the release of endotoxins.

- Endotoxins cause **fever** (by inducing the release of interleukin-1) and **shock** (because of a TNF-induced decrease in blood pressure).

- TNF release also allows bacteria to cross BBB.

- The **LAL assay** (*Limulus* amoebocyte lysate) is used to detect endotoxins in drugs and on medical devices.
# Endotoxin Summary

<table>
<thead>
<tr>
<th>Source:</th>
<th>Gram –</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relation to microbe:</td>
<td>Present in LPS of outer membrane</td>
</tr>
<tr>
<td>Chemistry:</td>
<td>Lipid A component of LPS</td>
</tr>
<tr>
<td>Fever?</td>
<td>Yes</td>
</tr>
<tr>
<td>Neutralized by antitoxin?</td>
<td>No</td>
</tr>
<tr>
<td>$LD_{50}$:</td>
<td>Relatively large</td>
</tr>
</tbody>
</table>
Inflammation Following Eye Surgery

- Patient did not have an infection
- The LAL assay of solution used in eye surgery
- What was the cause of the eye inflammation?
- What was the source?

Clinical Focus, p. 440
Pathogenic Properties of Viruses

Evasion of IS by
- Growing inside cells
- Rabies virus spikes mimic Ach
- HIV hides attachment site → CD4 long and slender

Visible effects of viral infection = Cytopathic Effects
1. cytocidal (cell death)
2. noncytocidal effects (damage but not death)
Pathogenic Properties of Fungi

- Fungal waste products may cause symptoms
- Chronic infections provoke allergic responses
- Proteases
  - *Candida, Trichophyton*
- Capsule prevents phagocytosis
  - *Cryptococcus*

### Fungal Toxins

- **Ergot toxin**
  - *Claviceps purpurea*
- **Aflatoxin**
  - *Aspergillus flavus*
Pathogenic Properties of Protozoa & Helminths

- Presence of protozoa
- Protozoan waste products may cause symptoms
- Avoid host defenses by
  - Growing in phagocytes
  - Antigenic variation
- Presence of helminths interferes with host function
- Helminths metabolic waste can cause symptoms

Wuchereria bancrofti
Portals of Exit

- Respiratory tract: Coughing and sneezing
- Gastrointestinal tract: Feces and saliva
- Genitourinary tract: Urine and vaginal secretions
- Skin
- Blood: Biting arthropods and needles or syringes
Microbial Mechanisms of Pathogenicity - Overview

Foundation Fig 15.9

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
Cytotoxic effects

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

Adherence

The End