35

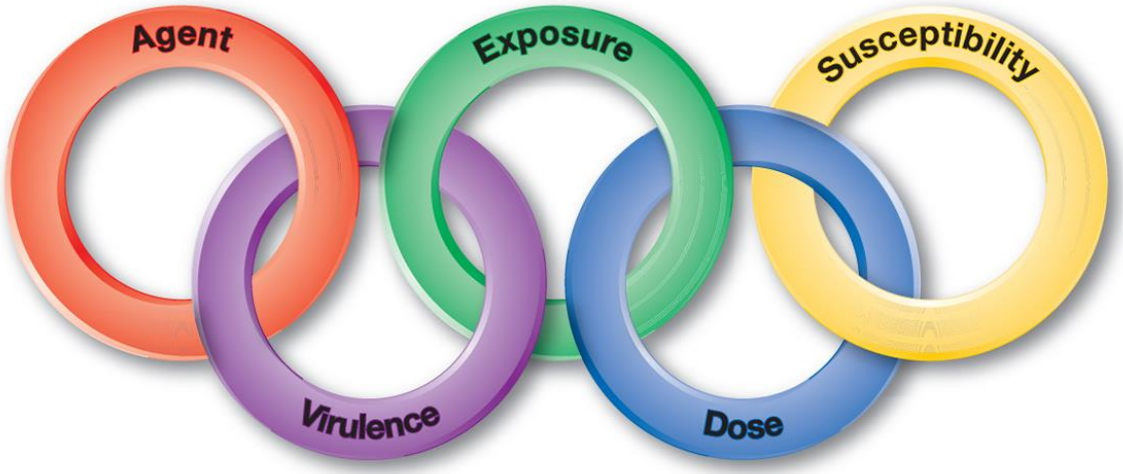
Pathogenicity and Infection

Pathogenicity and Infectious Disease

- Infection
  - a parasite growing and multiplying within/on a host
  - may or may not result in overt infectious disease
- Pathogen
  - any parasitic organism causing infectious disease
  - ***primary (frank) pathogen*** – causes disease by direct interaction with healthy host
  - ***opportunistic pathogen*** – may be part of normal flora and causes disease when it has gained access to other tissue sites or host is immunocompromised
- Pathogenicity
  - ability of parasite to cause disease

The Chain of Infection

- Chain of events for a successful infection
  - agent identity
  - virulence of agent
  - dose of agent
  - means of exposure to agent
  - susceptibility of host to agent

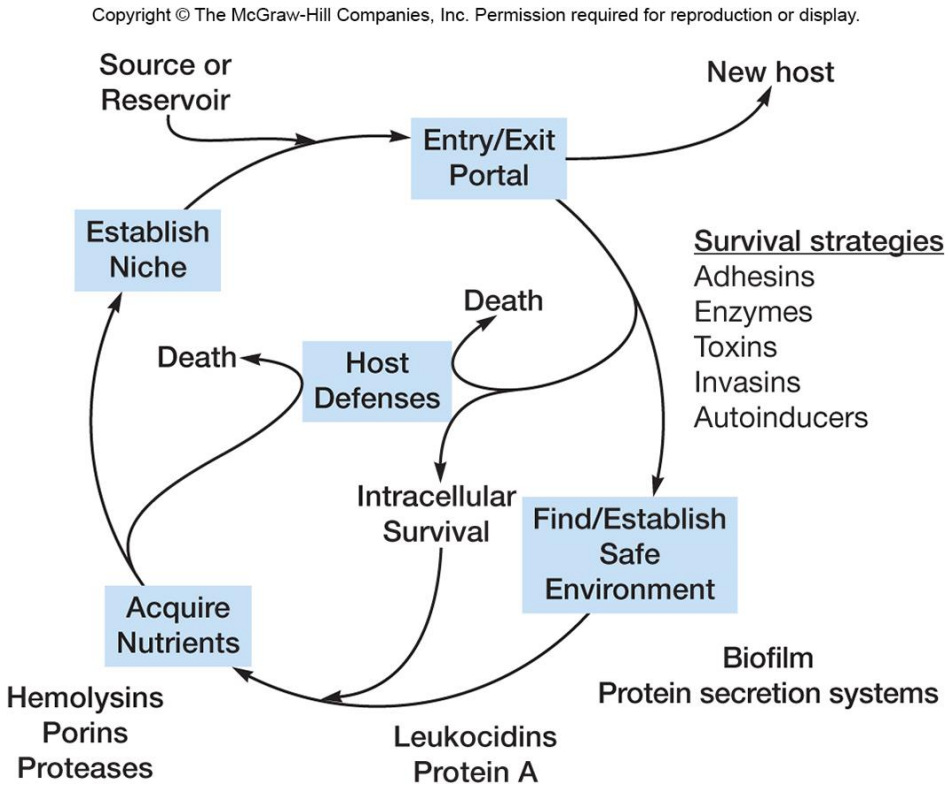


Sources of Pathogens

- Can be animate (other humans or animals)
  - **infections passed from animal to human** are termed ***zoonoses***
  - many examples of zoonoses exist (see tables on next two slides)
- **Can be inanimate** (water, soil, food)
- **Reservoir** = natural environmental location in which the pathogen normally resides

Infectious Process

- A pathogen must contact a host AND survive within it to cause a disease. To survive, it needs
  - a suitable environment
  - a source of nutrients
    - in competition with eukaryotic host cells
  - Protection from harmful elements
    - ***virulence factors*** allow a pathogen to outcompete host cells and resist their defenses

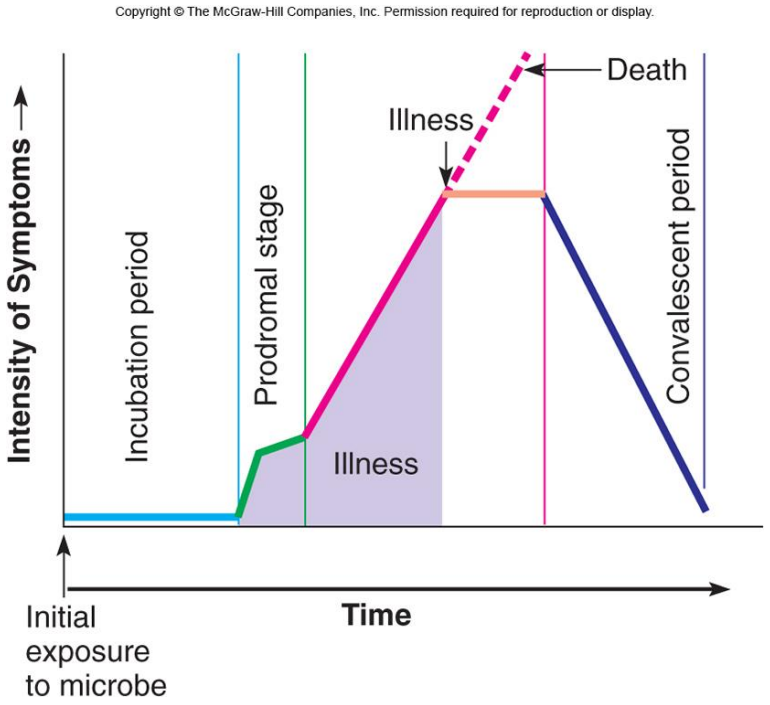


Toxigenicity

- Some microbes possess toxigenicity
  - ability to produce toxins
- Toxin
  - specific substance that damages host
- Intoxications
  - diseases that result from entry of a specific preformed toxin into host
- Toxemia
  - condition caused by toxins in the blood of host

Course of Infectious Disease

- incubation period
  - period after pathogen entry, before signs and symptoms
- prodromal stage
  - onset of signs and symptoms
  - not clear enough for diagnosis
- period of illness
  - disease is most severe, signs and symptoms
- convalescence
  - signs and symptoms begin to disappear



Virulence

- Degree or intensity of pathogenicity
- Virulence factors
  - determine the degree to which the pathogen causes damage, invasion, infectivity
- Determined in part by pathogen's ability to survive outside host

Virulence Factors

- Animal model systems may be used to determine role of virulence factor in disease process
- Determined by characteristics of the pathogen
  - adherence and colonization
  - invasion

Table 35.3 Examples of Microbial Attachment Mechanisms

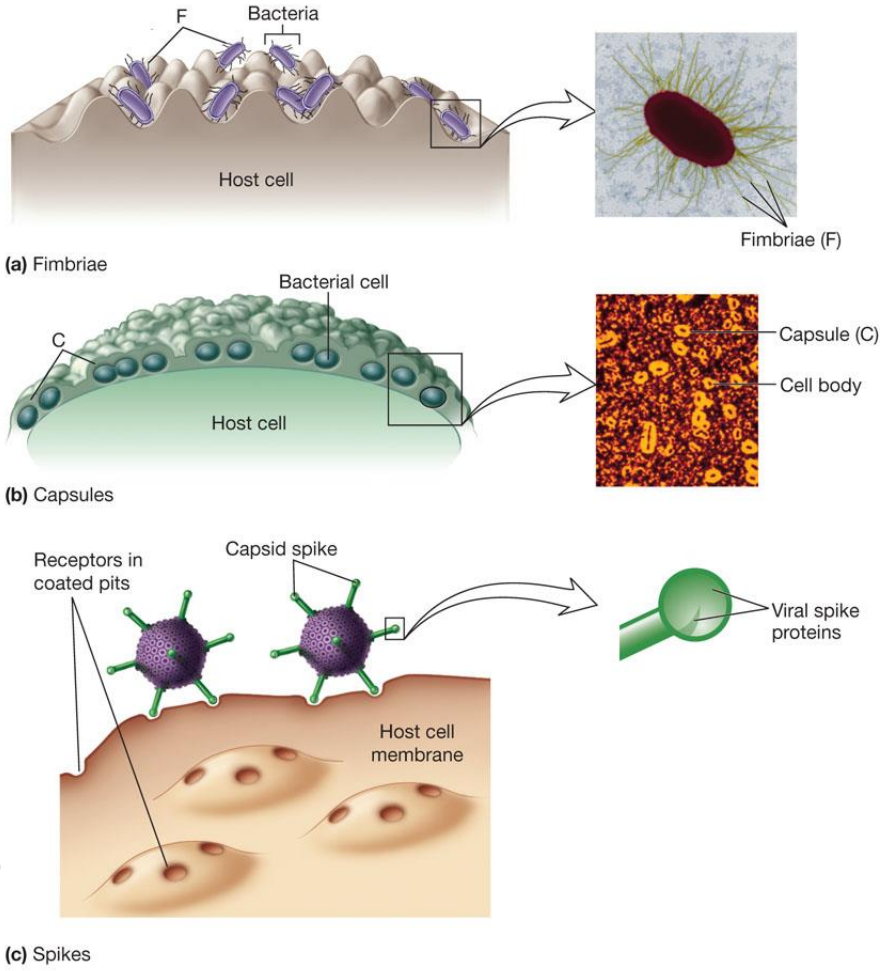
Microbe	Disease	Adhesion Mechanism	Host Receptor
Neisseria gonorrheae	Gonorrhea	Type I fimbriae	Sugar residue on urethral epithelium
Escherichia coli	Diarrhea	Type I fimbriae	Sugar residue on intestinal epithelium
	Hemolytic uremic syndrome	P pili	Sugar residue on kidney cell
	Urinary tract infection	Type I fimbriae	Sugar residue on urethral epithelium
Treponema pallidum	Syphilis	Outer membrane protein	Protein residue on mucosal cell
Mycoplasma pneumoniae	Pneumonia	Membrane protein	Protein residue on lung cell
Streptococcus pyogenes	Sore throat	Protein F	Protein residue on upper respiratory tract cell
Streptococcus mutans	Dental caries	Sugar residue	Salivary glycoprotein on tooth
Influenza virus	Influenza	Hemagglutinin spike protein	Protein residue on upper respiratory tract cell
HIV-1	AIDS	gp120 protein	CD4 receptor on T cells
Polio virus	Poliomyelitis	Capsid protein VP1	CD 155 protein on intestinal and nerve cells

Adherence and Colonization

- First step in disease is entrance and attachment
- Portal of entry
  - skin, respiratory, gastrointestinal, urogenital systems, or conjunctiva of eye
  - vector borne, sexual contact, blood transfusion, or organ transplant
- Adherence
  - mediated by special molecules called adhesins
- Colonization
  - a site of microbial reproduction on or within host
  - does not necessarily result in tissue invasion or damage

Attachment and Colonization

- Adherence structures
  - pili, fimbriae (adhesion molecules on bacterium's cell surface) bind complementary receptor sites on host cell surface
- Colonization
  - a site of microbial reproduction on/in host
  - does not necessarily result in tissue damage



Invasion

- Infectivity - ability to create a discrete point of infection
- Invasiveness - ability to spread to adjacent tissues
- Penetration can be active or passive
  - active occurs through lytic substances which
    - attack the extracellular matrix and basement membranes of integuments and intestinal linings
    - degrade carbohydrate-protein complexes between cells
    - disrupt host cell surface
  - passive (e.g., skin lesions, insect bites, wounds)
    - spread to deeper tissues involves production of specific products and/or enzymes that promote spreading

Invasion

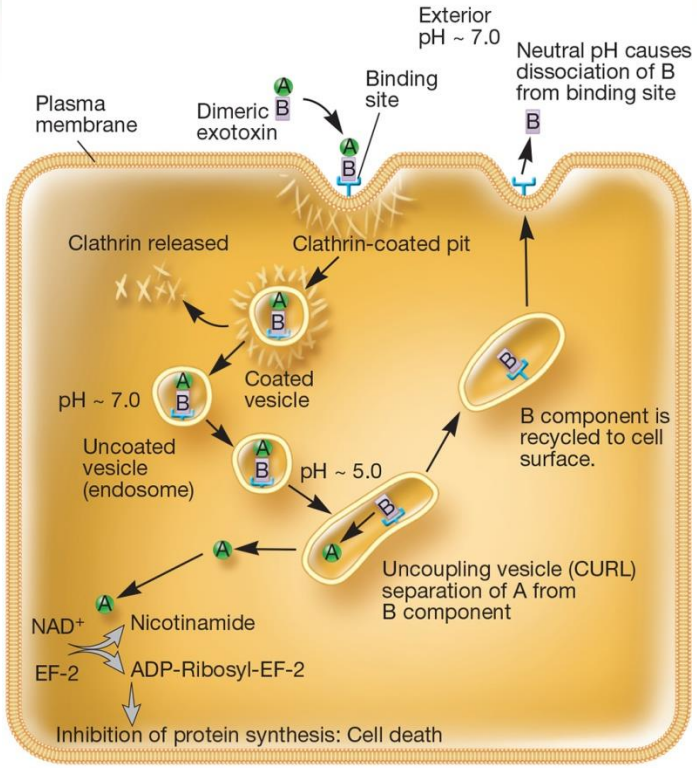
- Once in circulatory system, bacteria have access to all organs and systems
  - ***bacteremia*** – presence of viable bacteria in the blood
  - ***septicemia*** –pathogens or their toxins in the blood
- varies among pathogens
  - e.g., *Clostridium tetani* (tetanus) produces a number of virulence factors but is non-invasive
  - e.g., *Bacillus anthracis* (anthrax) and *Yersinia pestis* (plague) also produce many virulence factors and are highly invasive
  - e.g., *Streptococcus* spp. span the spectrum of virulence factors and invasiveness

Exotoxins

- Soluble, heat-labile, proteins
- Secreted into surroundings as pathogen grows
- Most exotoxin producers are Gram-negative
- Often travel from site of infection to other tissues or cells where they exert their effects
- Usually synthesized by specific bacteria that have toxin genes in their plasmids or prophage DNA
- Among the most lethal substances known
- Are highly immunogenic
- Stimulate production of neutralizing Ab (antitoxins)
- Chemically inactivated to form immunogenic toxoids
  - e.g., tetanus toxoid

Types of Exotoxins

- AB exotoxins
  - composed of two subunits
    - A subunit – responsible for toxic effect
    - B subunit – binds to specific target cell
- Specific host site exotoxins
- Membrane-disrupting exotoxins
- Superantigens



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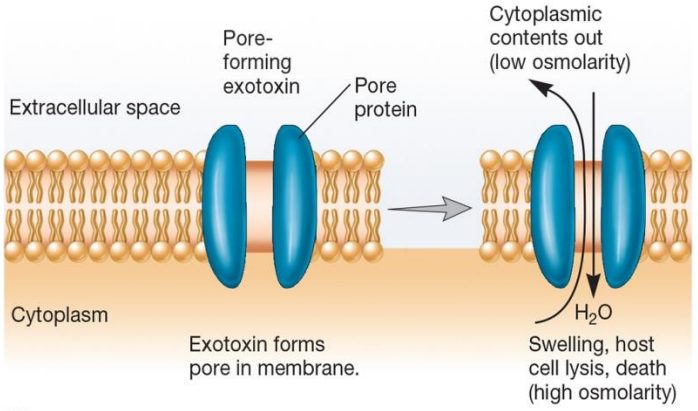

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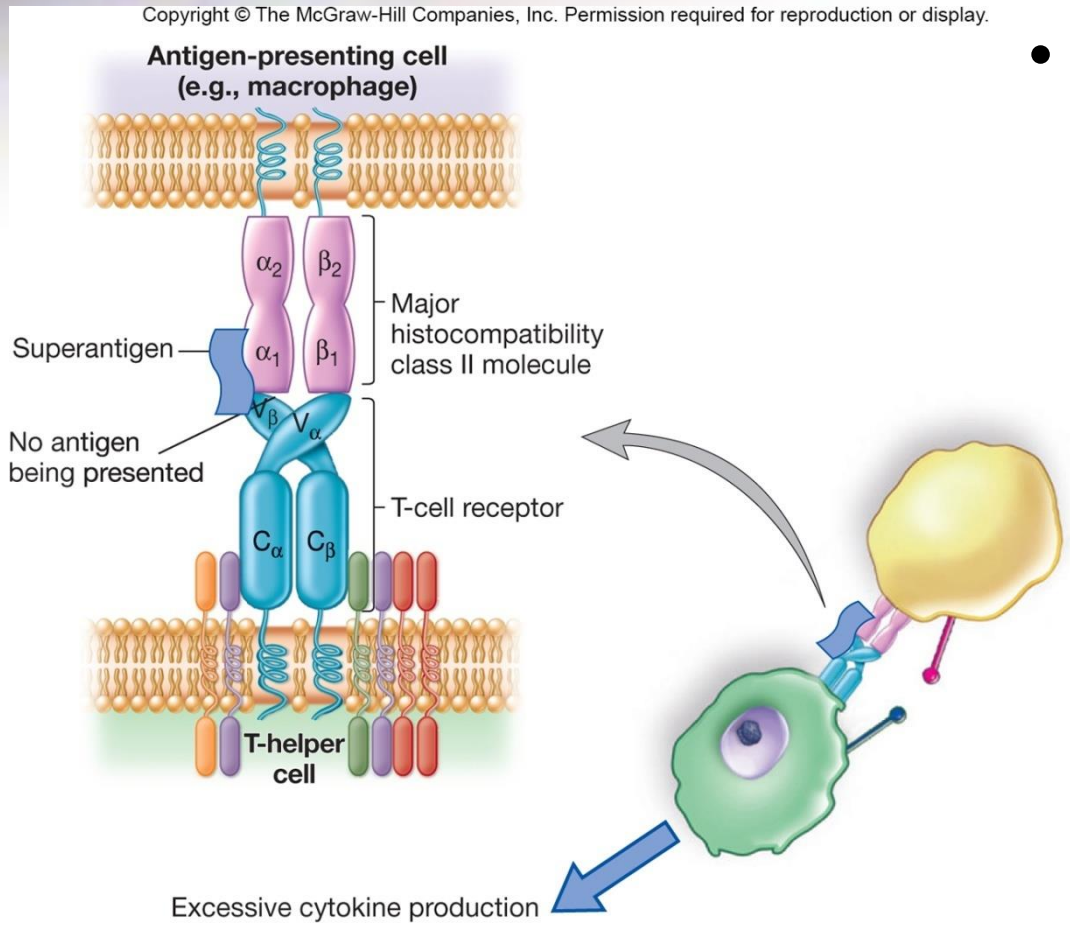
Table 35.5 Exotoxins Produced by Human Pathogens

Toxin	Organism	Gene Location	Toxin Type	Mechanism of Action
Edema factor (EF) Lethal factor (LF) Protective antigen (PA)	*Bacillus anthracis*	Plasmid	Tripartite AB	EF causes edema. LF is a cytotoxin. PA is a B component.
Pertussis toxin	*Bordetella pertussis*	Chromosome	AB	↓ATP, ↑ cAMP alters cell function, leading to death.
Botulinum toxin	*Clostridium botulinum*	Prophage	AB	Blocks neurotransmitter release, leading to paralysis
CPE enterotoxin	*Clostridium perfringens*	Chromosome	Cytotoxin	Hemolysis
Tetanospasmin	*Clostridium tetani*	Plasmid	AB	Blocks neurotransmitter, leading to spastic paralysis
Diphtheria toxin	*Corynebacterium diphtheriae*	Phage	AB	Alters translation, leading to protein synthesis inhibition
Enterotoxin Shiga-like toxin	*Escherichia coli* *E. coli* O157:H7	Plasmid Phage gene integrated into chromosome	AB AB	↑cAMP, leading to water secretion from cell Inhibits protein synthesis leading to death
Cytolysin	*Salmonella* spp.	Chromosome	Cytotoxin	↑cAMP, leading to water secretion from cell
Shiga toxin	*Shigella dysenteriae*	Chromosome	AB	Inhibits protein synthesis, leading to death
Exfolative toxin Toxic shock syndrome toxin-1 Panton-Valentine leukocidin	*Staphylococcus aureus*	Chromosome Chromosome Phage	Protease Superantigen Cytotoxin	Skin peeling Cytokine-induced shock Necrotizing pneumonia
Streptolysin O Erythrogenic toxin	*Streptococcus pyogenes*	Chromosome Phage	Cytolysin Superantigen	Hemolysis Cytokine-induced shock
Cholera toxin	*Vibrio cholerae*	Phage	AB	↑cAMP, leading to water secretion from cell

Superantigens



- Stimulate ~30% of T cells of the immune system
  - causes the T cells to overexpress and release cytokines
  - results in failure of multiple host organs allowing time for the microbe to disseminate

- Example is staphylococcal enterotoxin B

Endotoxins

- Lipopolysaccharide (LPS) in Gram-negative cell wall can be toxic to specific hosts
  - called endotoxin because it is an endogenous (part) of the bacterium and released when organism lyses
    - some is also released during multiplication
  - toxic component is the lipid portion, lipid A

Endotoxins

- Heat stable
- Toxic (nanogram amounts)
- Weakly immunogenic
- Generally similar, despite source
- Cause general system effects
  - fever, weakness, diarrhea, inflammation, intestinal hemorrhage, and fibrinolysis, the enzymatic breakdown of fibrin, the major protein component of blood clots

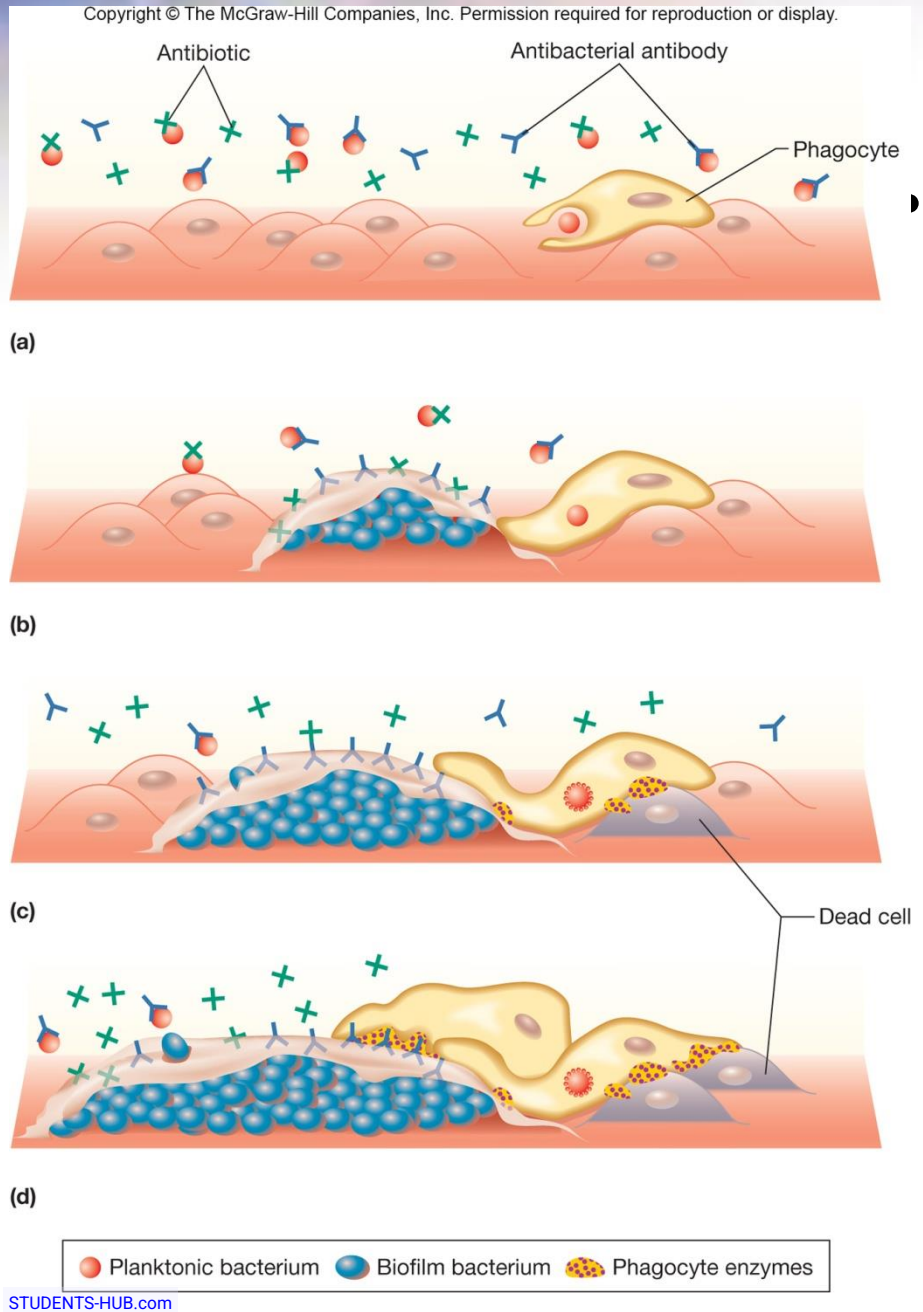
Endotoxins

- Bring about these effects indirectly
  - endotoxin interacts with host molecules and cells, activating host systems
    - coagulation, complement, fibrinolytic, and kininogen system
  - e.g., interaction with macrophages → release of endogenous pyrogen (induces fever)
  - e.g., binding to LPS-binding protein → release of cytokines
    - tumor necrosis and others lead to septic shock

Mycotoxins

- Secondary metabolites of fungi
  - common contaminants of food crops
  - *Aspergillus flavus* and *A. parasiticus* produce carcinogenic aflatoxin
  - *Stachybotrys* produce tissue-damaging satratoxins
  - *Claviceps purpurea* (ergot) produce hallucinogen lysergic acid (LSD)

Biofilm Development



- Biofilm growth is physiologically different from planktonic growth
  - may cause chronic infection
  - increases virulence
  - become less sensitive to antibiotics
  - make cells in biofilm more resistant to host defense ("frustrates" phagocytes)

Resisting Host Defenses

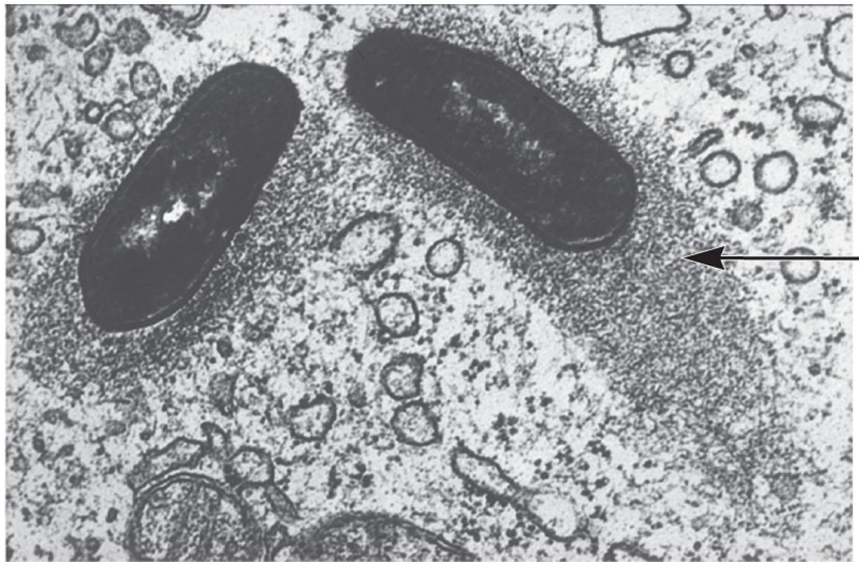
- Most microbes eliminated before they can cause disease due to immune system
- Successful pathogen evades immune system
- Numerous mechanisms for both viral and bacterial pathogens

Resisting Host Defenses

- Infection of immune system cells, diminishing function
- Fuse with adjacent cells to prevent exposure to antimicrobial proteins in host
- Capsules prevent phagocytosis
- Mutations change antigenic sites or alter expression of antigens
  - through downregulation or phase variation
- Produce substances that resemble host tissue
- Produce proteases that degrade host proteins
- Special proteins that interfere with host defenses

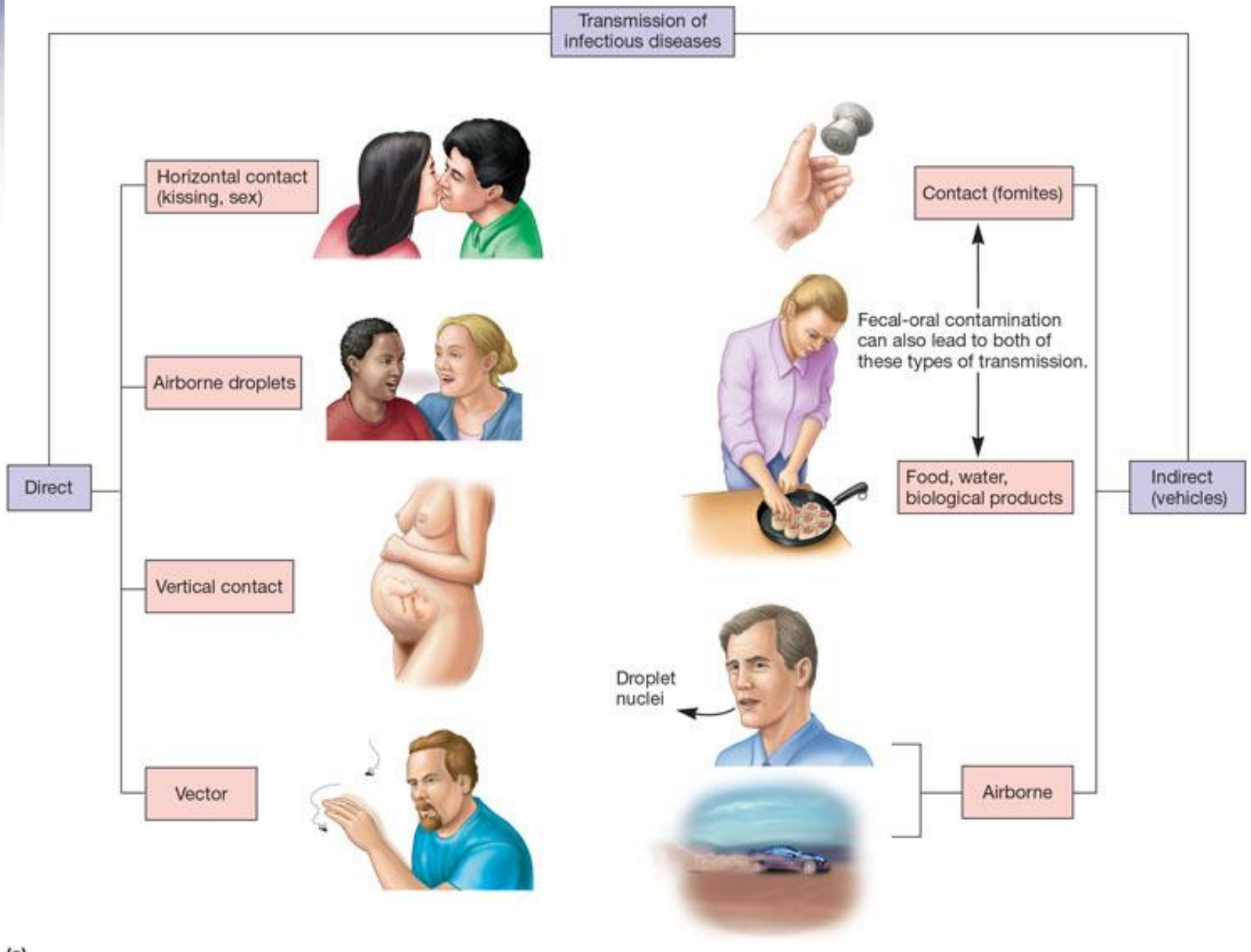
Resisting Host Defenses

- Production of decoy proteins to bind available neutralizing antibodies
- Lengthened O-chains to prevent host detection or lysis
- Some survive inside host cells
  - eject themselves from cell to cell using host actin



Pathogen Transmission

- Initial transmission of pathogen to host
  - evidence suggests correlation between mode of transmission and degree of virulence
    - direct contact → less virulent
    - vector-borne → highly virulent in human host; relatively benign in vector
    - greater ability to survive outside host → more virulent
- Transmission from host to host
- Transmission alone not enough for infection to occur
  - Tropism - pathogen must make contact with appropriate host tissue
    - determined by specific cell surface receptors



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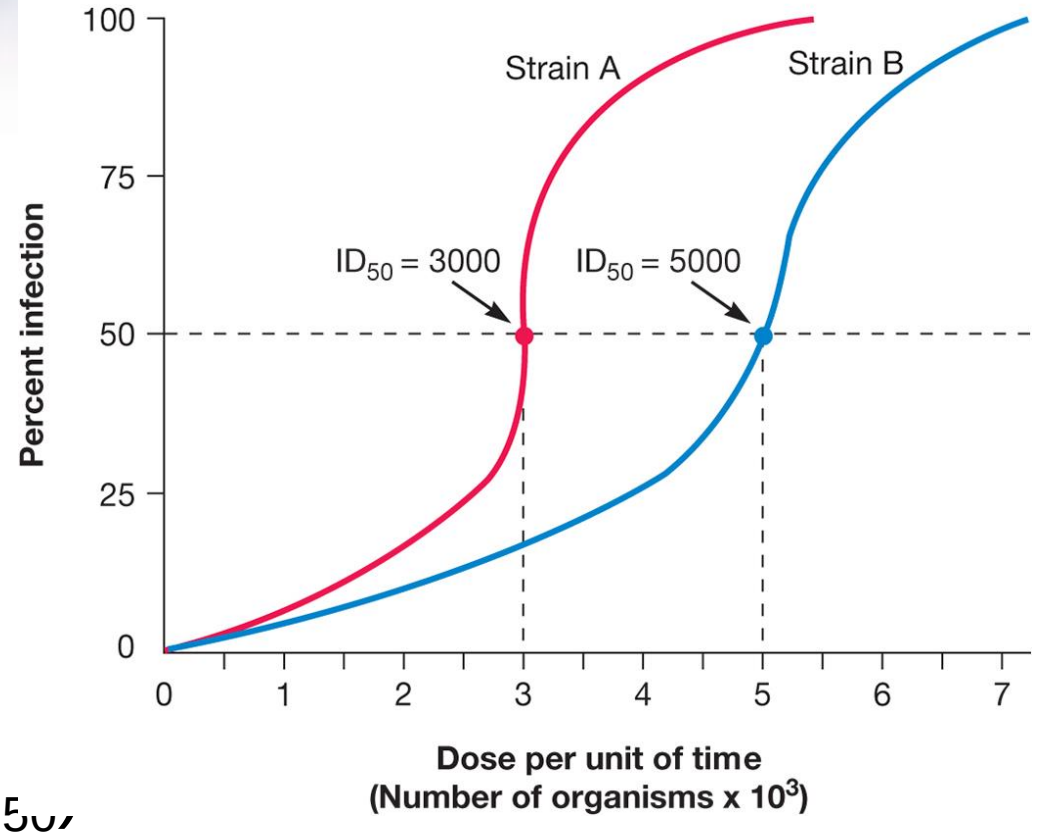
Infectious Dose



- Infectious dose 50 (ID_{50})
  - number of pathogens that will infect 50% of an experimental group of hosts in a specified time
  - varies with pathogen
  - handwashing reduces number of pathogens

Infectious Dose

- Lethal dose 50 (LD_{50})
  - dose that kills 50% of experimental animals within a specified period
- Cytopathology – cellular changes
  - Can be used to observe cells in tissue culture for death rates rather than entire organisms
- Examining virulence factors and their release

Growth Rate

- Pathogen must find most favorable conditions in the host
  - extracellular pathogens
    - grow outside cells in blood, tissue fluids
  - intracellular pathogens
    - grow and multiply within cells
    - facultative intracellular pathogens
      - grow within or outside cells
    - obligate intracellular pathogens
      - only grow when inside cells

Host Susceptibility

- Two main factors
  - defense mechanisms of host (discussed in Chs. 33 and 34)
  - pathogenicity of pathogen
- Nutrition, genetic predisposition, and stress also play a role in host susceptibility to infection