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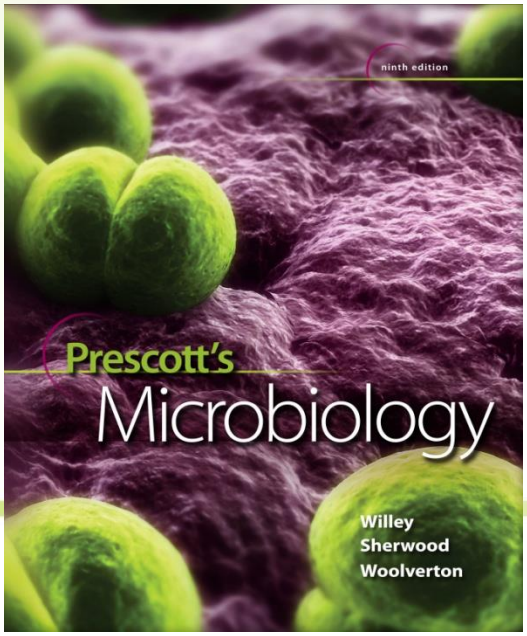


Pathogenicity and Infection

35.1 Pathogenicity and Infectious Disease

1. Compare and contrast competition between microbial species with competition between microbial and human cells
2. Predict the microbial virulence factors and host cell responses that result in disease
3. Relate the infectious disease process to time, identifying events associated with each stage of the process

Pathogenicity and Infectious Disease

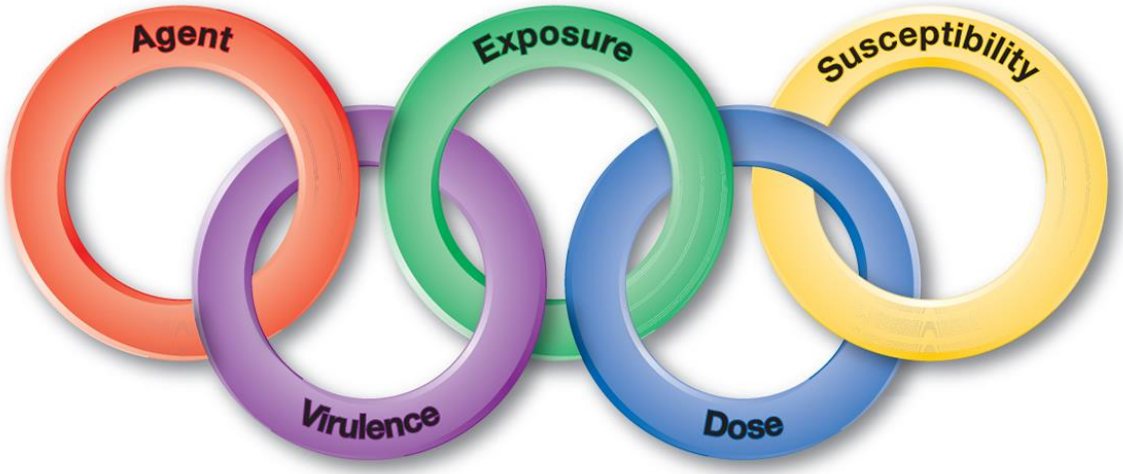
- Host – larger organism that supports the survival and growth of a smaller organism
- Parasites are organisms that
  - live on or within a host organism and are metabolically dependent on the host
  - are any organism that cause disease

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

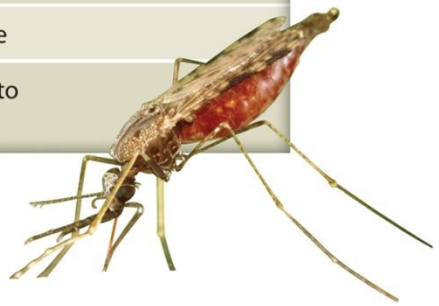
Table 35.1 Infectious Organisms in Nonhuman Reservoirs That May Be Transmitted to Humans

Disease	Etiologic Agent	Usual or Suspected Nonhuman Host	Usual Method of Human Infection
Anthrax	*Bacillus anthracis*	Cattle, horses, sheep, swine, goats, dogs, cats, wild animals, birds	Inhalation or ingestion of spores; direct contact
Babesiosis	*Babesia bovis, B. divergens, B. microti, B. equi*	*Ixodes* ticks of various species	Bite of infected tick
Brucellosis (undulant fever)	*Brucella melitensis, B. abortus, B. suis*	Cattle, goats, swine, sheep, horses, mules, dogs, cats, fowl, deer, rabbits	Milk; direct or indirect contact
Campylobacteriosis	*Campylobacter fetus, C. jejuni*	Cattle, sheep, poultry, swine, pets	Contaminated water and food
Cat-scratch disease	*Bartonella henselae*	Cats, dogs	Cat or dog scratch
Cryptosporidiosis	*Cryptosporidium* spp.	Farm animals, pets	Contaminated water
Encephalitis (St. Louis)	Arboviruses	Birds	Mosquito
Encephalomyelitis (Venezuelan equine)	Arboviruses	Rodents, horses	Mosquito
Encephalomyelitis (Western equine)	Arboviruses	Birds, snakes, squirrels, horses	Mosquito
Giardiasis	*Giardia intestinalis*	Rodents, deer, cattle, dogs, cats	Contaminated water
Hantavirus pulmonary syndrome	Pulmonary syndrome hantavirus	Deer mice	Contact with the saliva, urine, or feces of deer mice; aerosolized viruses
Influenza	Influenza viruses	Water fowl, pigs	Direct contact or inhalation
Listeriosis	*Listeria monocytogenes*	Sheep, cattle, goats, guinea pigs, chickens, horses, rodents, birds, crustaceans	Food-borne
Lyme disease	*Borrelia burgdorferi*	Ticks (*Ixodes scapularis* or related ticks)	Bite of infected tick
Lymphocytic choriomeningitis	Lymphocytic choriomeningitis virus	Mice, rats, dogs, monkeys, guinea pigs	Inhalation of contaminated dust; ingestion of contaminated food
Pasteurellosis	*Pasteurella multocida*	Fowl, cattle, sheep, swine, goats, mice, rats, rabbits	Animal bite
Plague (bubonic)	*Yersinia pestis*	Domestic rats, many wild rodents	Flea bite
Psittacosis	*Chlamydia psittaci*	Birds	Direct contact, respiratory aerosols
Q fever	*Coxiella burnetii*	Cattle, sheep, goats	Inhalation of contaminated soil and dust
Rabies	Rabies virus	Dogs, bats, opossums, skunks, raccoons, foxes, cats, cattle	Bite of rabid animal
Relapsing fever (borreliosis)	*Borrelia* spp.	Rodents, porcupines, opossums, armadillos, ticks, lice	Tick or louse bite
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Rabbits, squirrels, rats, mice, groundhogs	Tick bite

(Continued)

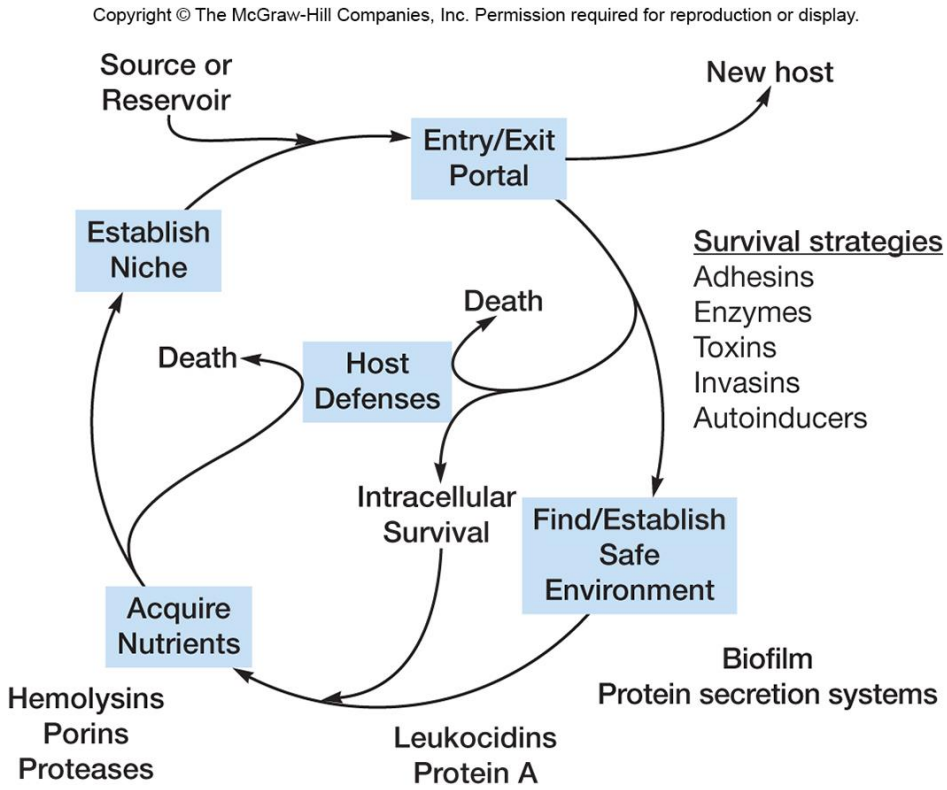
Table 35.1 Infectious Organisms in Nonhuman Reservoirs That May Be Transmitted to Humans (*continued*)

Disease	Etiologic Agent	Usual or Suspected Nonhuman Host	Usual Method of Human Infection
Salmonellosis	*Salmonella* spp. (except *S. typhosa*)	Fowl, swine, sheep, cattle, horses, dogs, cats, rodents, reptiles, birds, turtles	Direct contact; food
SARS	SARS coronavirus	Bats, civets	Contact with infected animal or person
Tuberculosis	*Mycobacterium bovis, M. tuberculosis*	Cattle, horses, cats, dogs	Milk; direct contact
Tularemia	*Francisella tularensis*	Wild rabbits, most other wild and domestic animals	Direct contact with infected carcass, usually rabbit; tick bite, biting flies
Typhus fever (endemic)	*Rickettsia mooseri*	Rats	Flea bite
Yellow fever (jungle)	Yellow fever virus	Monkeys, marmosets, lemurs, mosquitoes	Mosquito



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

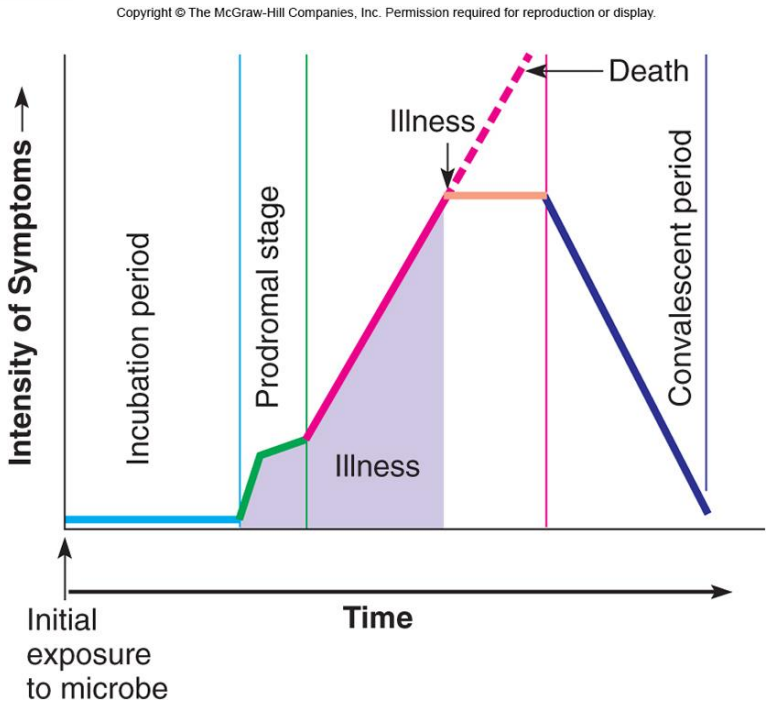
- Some microbes possess toxigenicity
  - ability to produce toxins
- Toxin
  - specific substance that damages host
- Intoxications
  - diseases that result from entry of a specific preformed toxin into host
- Toxemia
  - condition caused by toxins in the blood of host

Course of Infectious Disease

- Infectious disease
  - infection with viruses, bacteria, fungi, protozoa, and helminths
- Signs
  - objective changes in body that can be directly observed
- Symptoms
  - subjective changes experienced by patient
- Disease syndrome
  - set of characteristic signs and symptoms

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



35.2 Virulence

1. Identify and describe the features that allow microorganisms to overcome host resistance and immunity
2. Discuss the strategies microorganisms have evolved to exploit human cells and tissues as resources for their survival
3. Compare the molecular mechanisms by which microorganisms adhere to and invade human cells and tissues
4. Illustrate the mechanisms by which microbial toxins impact human cells
5. Model disease processes and explain virulence

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

Pathogenicity Islands

- Major virulence factors on large segments on chromosomal or plasmid DNA
  - increase bacterial virulence
  - absent in nonpathogenic members
  - common sequence characteristics
    - insertion-like sequences for mobility
    - G + C content different from bacterial genome
    - several open reading frames
  - can be spread through horizontal transfer of virulence genes to bacteria

Table 35.2 Examples of Pathogenicity Islands and the Products They Encode

Organism	Pathogenicity Island[1]	Gene Product	Function
Escherichia coli	cagPI	Type IV secretion proteins	Cytotoxin
Helicobacter pylori	PAI-III	Type 1 pili Secreted protein	Attachment Hemolysin, cytotoxic necrosing factor, uropathogenic protein
Legionella pneumophila	icm/dot	Type IV secretion proteins	Intracellular survival
Rhodococcus equi	PAI-vap	Secreted proteins	Intracellular survival
Salmonella enterica	SPI-1, SPI-2	Type III secretion proteins	Cytotoxin
Shigella flexneri	SHI-1, SHI-2	Type III secretion proteins	Cytotoxin
Staphylococcus aureus	SaPI	Secreted proteins	Superantigens
Vibrio cholerae	VPI	Secreted protein	Toxin
Yersinia pestis	HPI-1	Siderophore synthesis	Iron uptake and storage

1 PI and PAI are both common abbreviations for pathogenicity island.

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

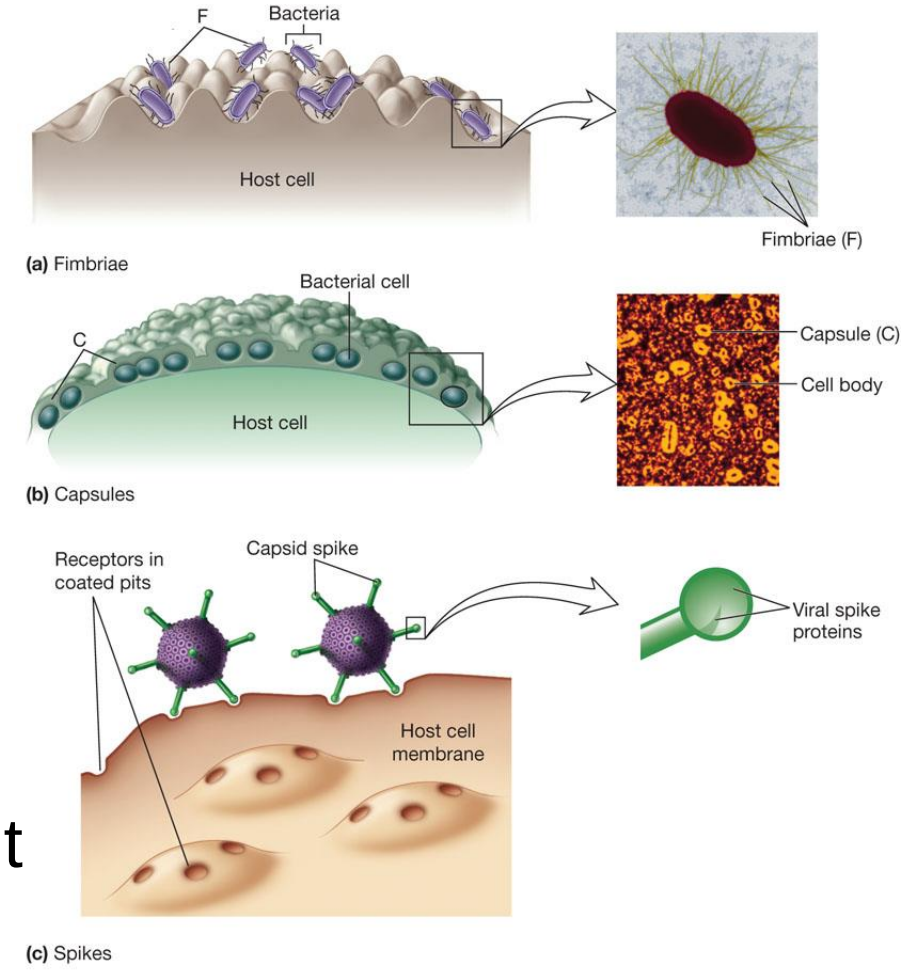
Microbe	Disease	Adhesion Mechanism	Host Receptor
Neisseria gonorrheae	Gonorrhea	Type I fimbriae	Sugar residue on urethral epithelium
Escherichia coli	Diarrhea	Type I fimbriae	Sugar residue on intestinal epithelium
	Hemolytic uremic syndrome	P pili	Sugar residue on kidney cell
	Urinary tract infection	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

Table 35.4 Microbial Virulence Factors Involved in Bacterial Pathogen Invasion and Dissemination

Product	Organism Involved	Mechanism of Action
Coagulase	*Staphylococcus aureus*	Coagulates (clots) the fibrinogen in plasma. The clot protects the pathogen from phagocytosis and isolates it from other host defenses.
Collagenase	*Clostridium* spp.	Breaks down collagen that forms the framework of connective tissues; allows the pathogen to spread
Deoxyribonuclease	Group A streptococci, staphylococci, *Clostridium perfringens*	Lowers viscosity of exudates, giving the pathogen more mobility
Elastase and alkaline protease	*Pseudomonas aeruginosa*	Cleaves laminin associated with basement membranes
Hemolysins	Staphylococci, streptococci, *Escherichia coli, Clostridium perfringens*	Lyse erythrocytes; make iron available for microbial growth
Hyaluronidase	Groups A, B, C, and G streptococci, staphylococci, clostridia	Hydrolyzes hyaluronic acid, a constituent of the extracellular matrix that cements cells together and renders the intercellular spaces amenable to passage by the pathogen
Hydrogen peroxide (H_2O_2) and ammonia (NH_3)	*Mycoplasma* spp., *Ureaplasma* spp.	Are produced as metabolic wastes. These are toxic and damage epithelia in respiratory and urogenital systems.
Immunoglobulin A protease	*Streptococcus pneumoniae*	Cleaves immunoglobulin A into Fab and Fc fragments
Lecithinase or phospholipase	*Clostridium* spp.	Destroys the lecithin (phosphatidylcholine) component of plasma membranes, allowing pathogen to spread
Leukocidins	Staphylococci, pneumococci, and other streptococci	Pore-forming exotoxins that kill leukocytes; cause degranulation of lysosomes within leukocytes, which decreases host resistance
Porins	*Salmonella enterica* serovar Typhimurium	Inhibit leukocyte phagocytosis by activating the adenylate cyclase system
Protein A Protein G	*Staphylococcus aureus* *Streptococcus pyogenes*	Located on cell wall. Immunoglobulin G (IgG) binds to either protein A or protein G by its Fc end, thereby preventing complement from interacting with bound IgG.
Pyrogenic exotoxin B (cysteine protease)	Group A streptococci *(Streptococcus pyogenes)*	Degrades proteins
Streptokinase (fibrinolysin, staphylokinase)	Groups A, C, and G streptococci, staphylococci	A protein that binds to plasminogen and activates the production of plasmin, thus digesting fibrin clots; this allows the pathogen to move from the clotted area

Invasion

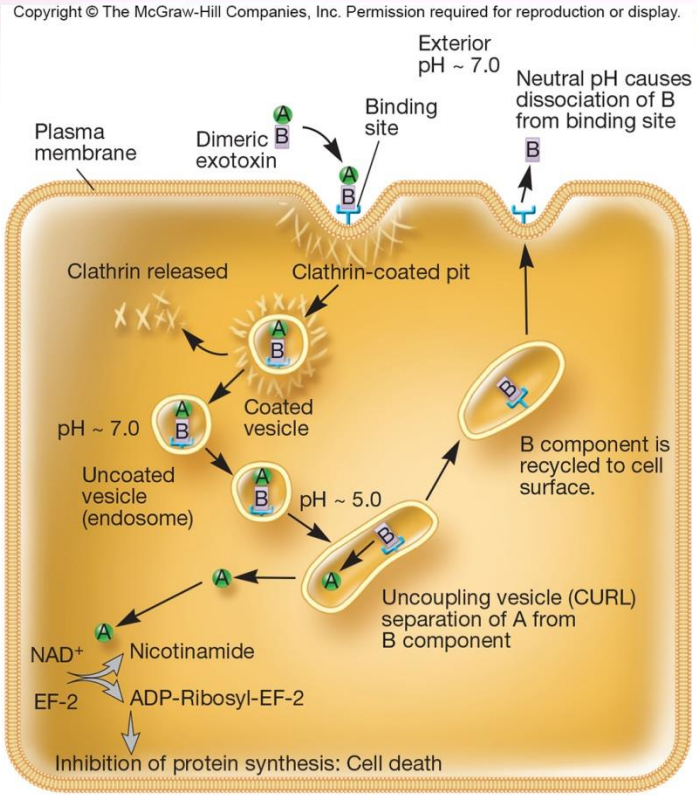
- Once in circulatory system, bacteria have access to all organs and systems
  - ***bacteremia*** – presence of viable bacteria in the blood
  - ***septicemia*** –pathogens or their toxins in the blood
- varies among pathogens
  - e.g., *Clostridium tetani* (tetanus) produces a number of virulence factors 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



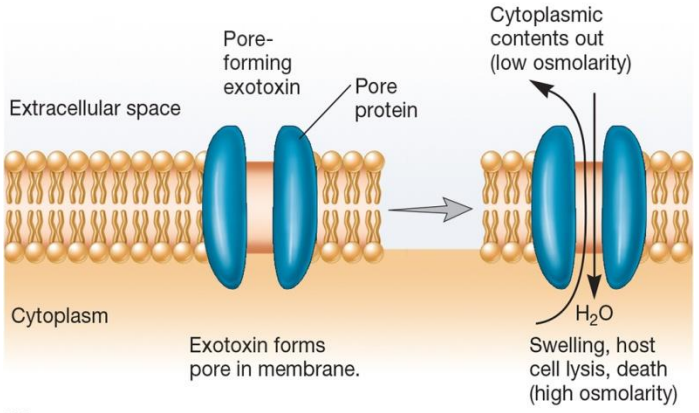
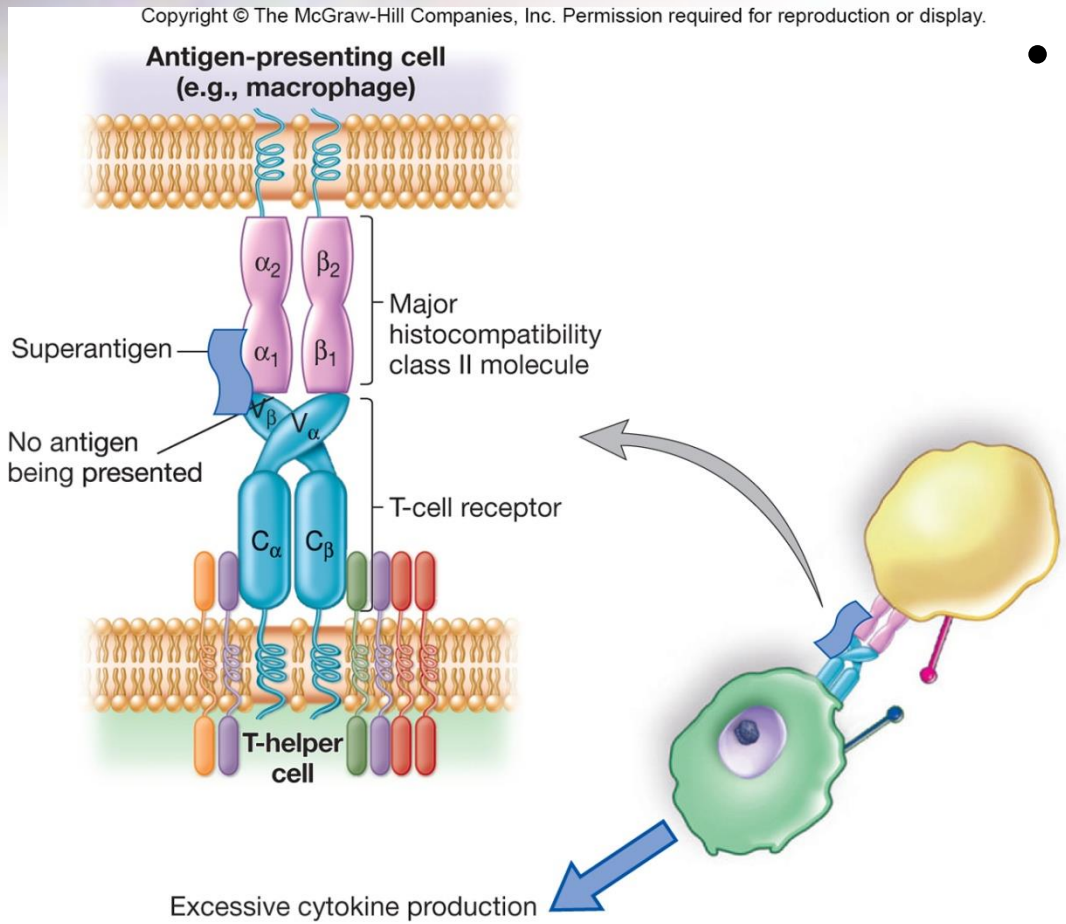


Table 35.5 Exotoxins Produced by Human Pathogens

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

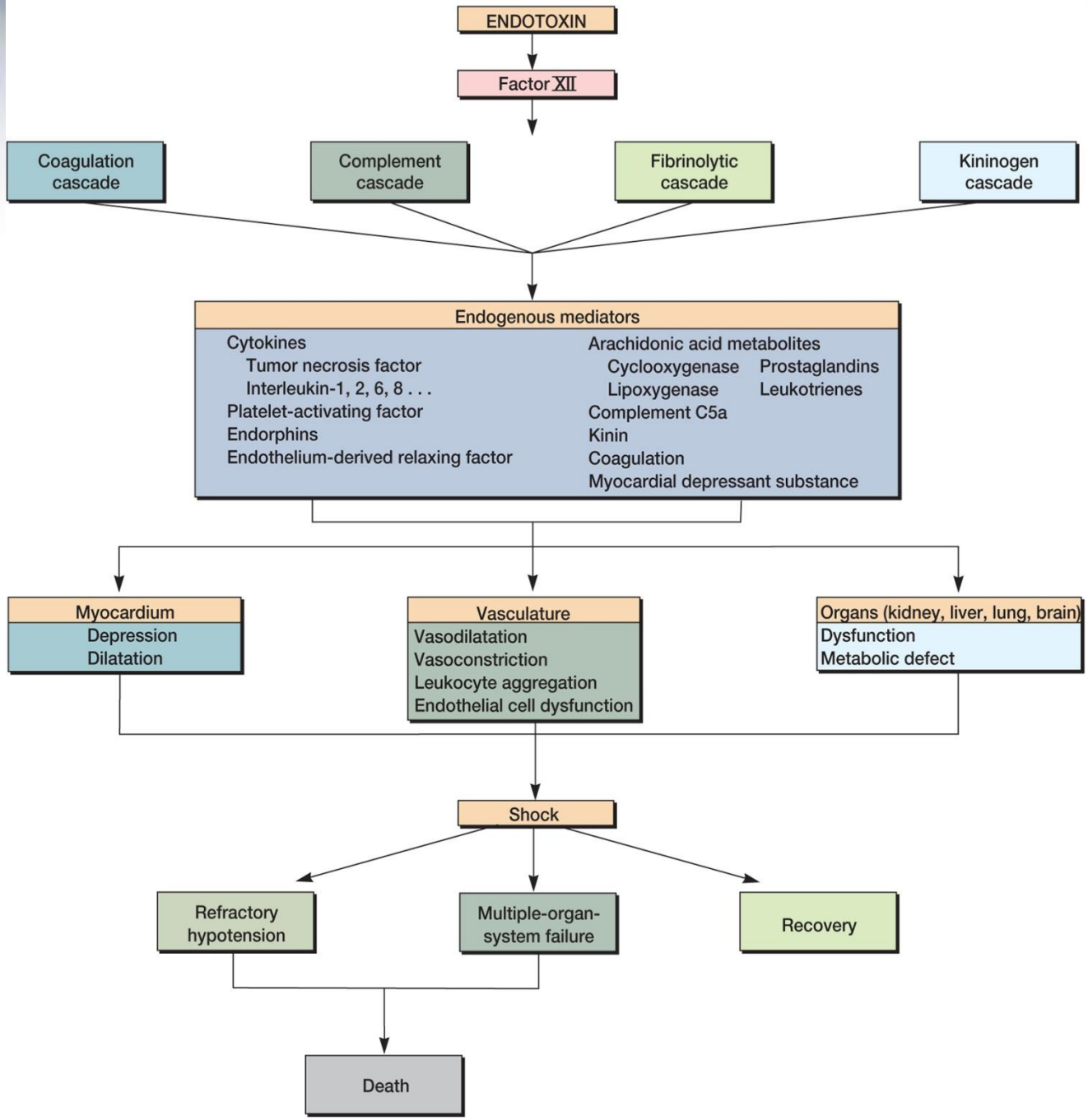


- Stimulate ~30% of T cells of the immune system
  - causes the T cells to overexpress and release cytokines
  - results in failure of multiple host organs allowing time for the microbe to disseminate

- 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

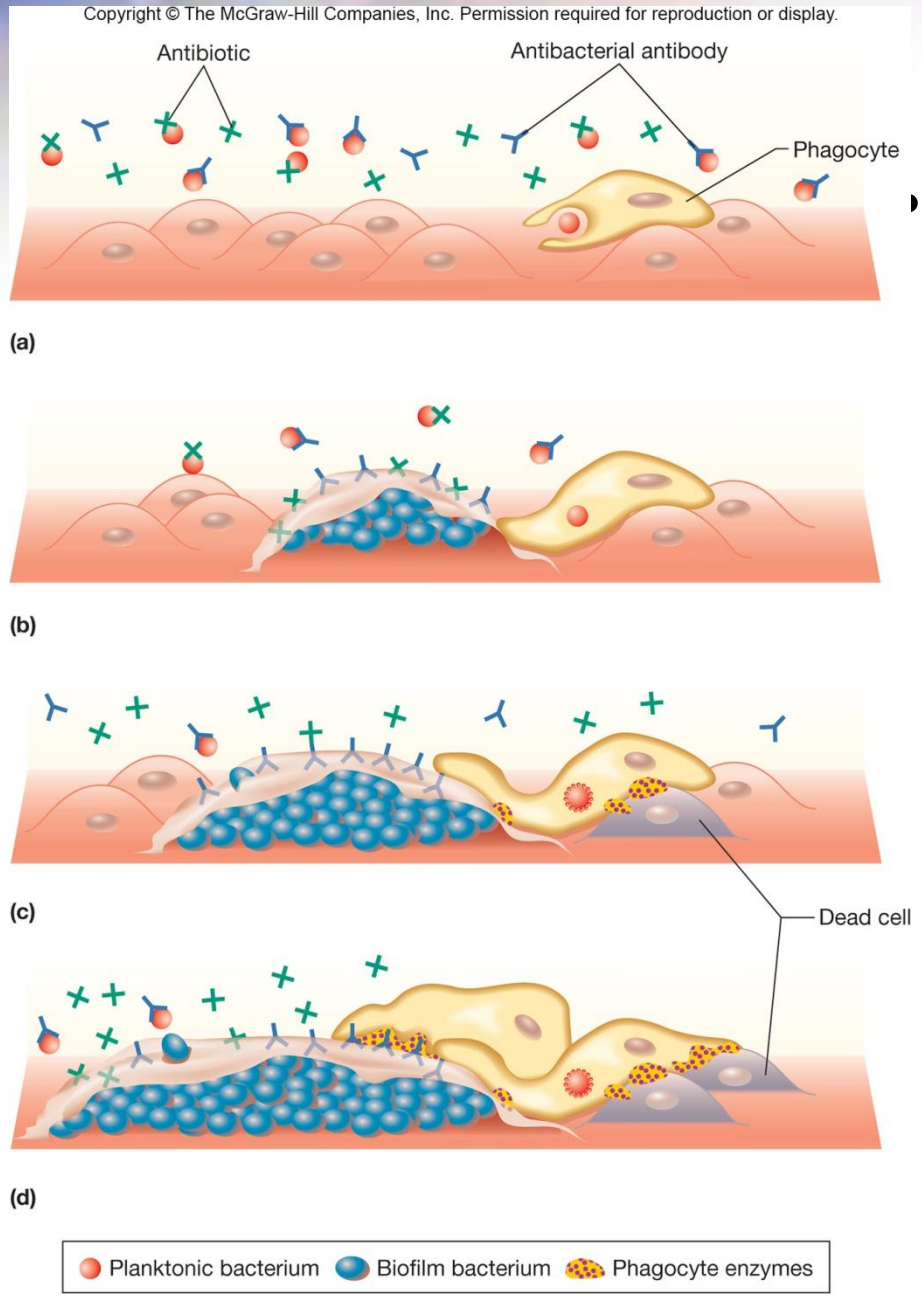
Endotoxins

- 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

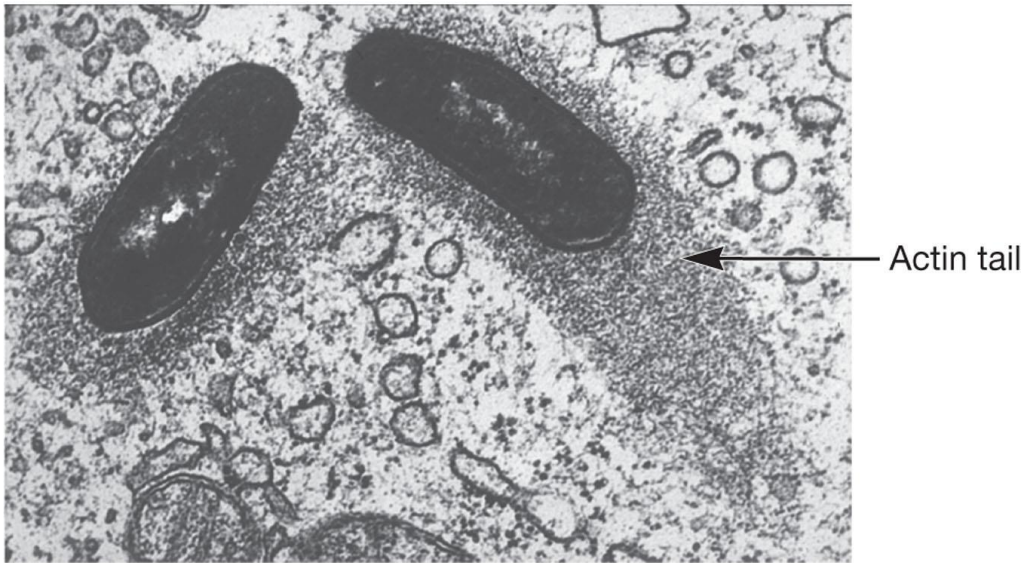
- Most microbes eliminated before they can cause disease due to immune system
- Successful pathogen evades immune system
- Numerous mechanisms for both viral and bacterial pathogens

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

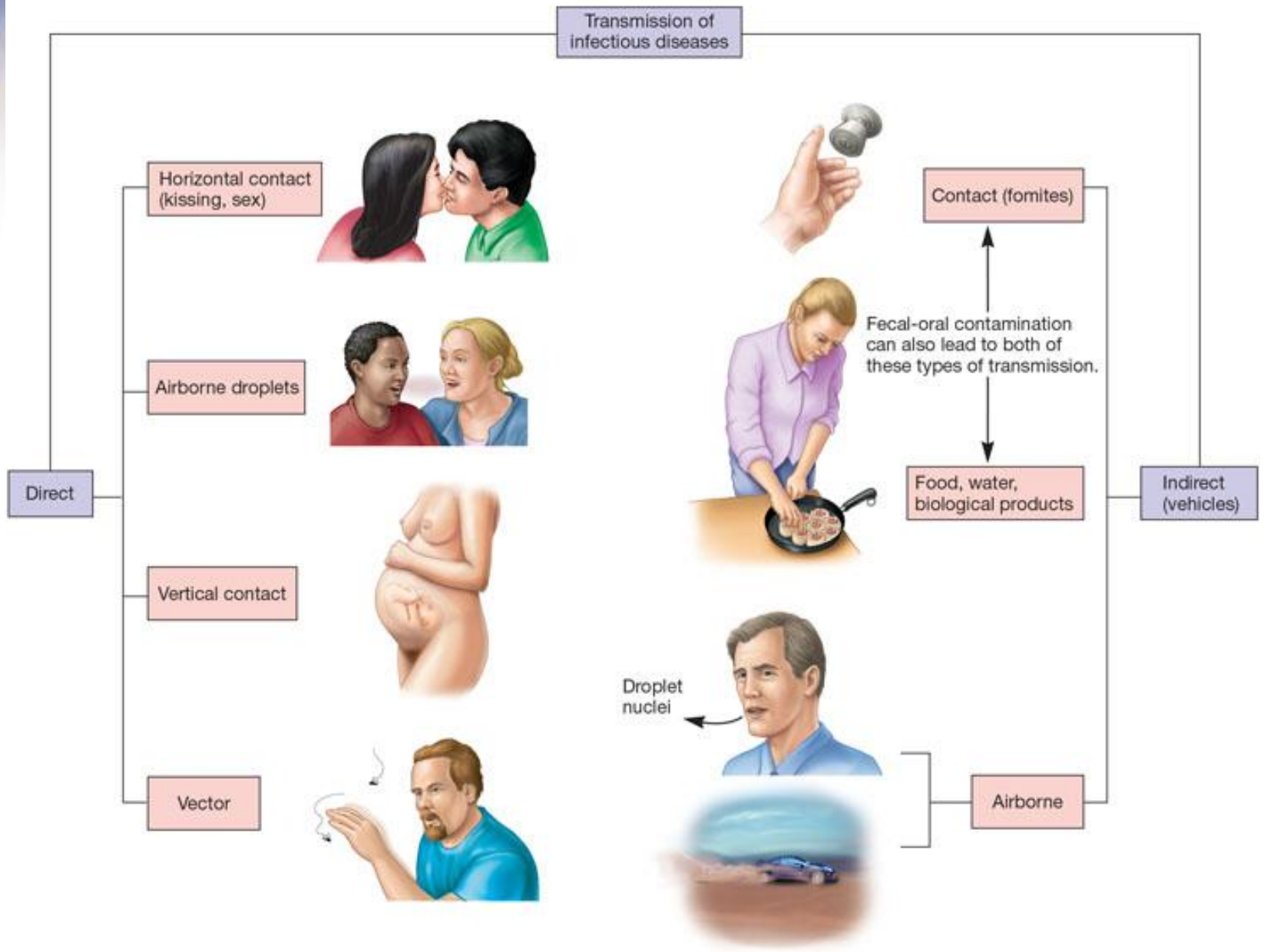


35.3 Exposure, Transmission, and Host Factors

1. List and describe the means by which microorganisms access humans to cause disease
2. Correlate initial microbial numbers and replication rates to infection and lethality
3. Synthesize a concept map of the infectious process

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



(a)

Pathogen Transmission

- Five main modes of transmission
  - airborne
  - contact
  - vehicle
  - vector borne
  - vertical

Airborne Transmission

- Pathogen suspended in air and travels ≥1 meter
- Droplet nuclei
  - small particles (1–4 μm diameter)
  - can remain airborne for long time
  - can travel long distances
  - usually propelled from respiratory tract of source organisms by sneezing, coughing, or vocalization
- Dust particles also important route of airborne transmission

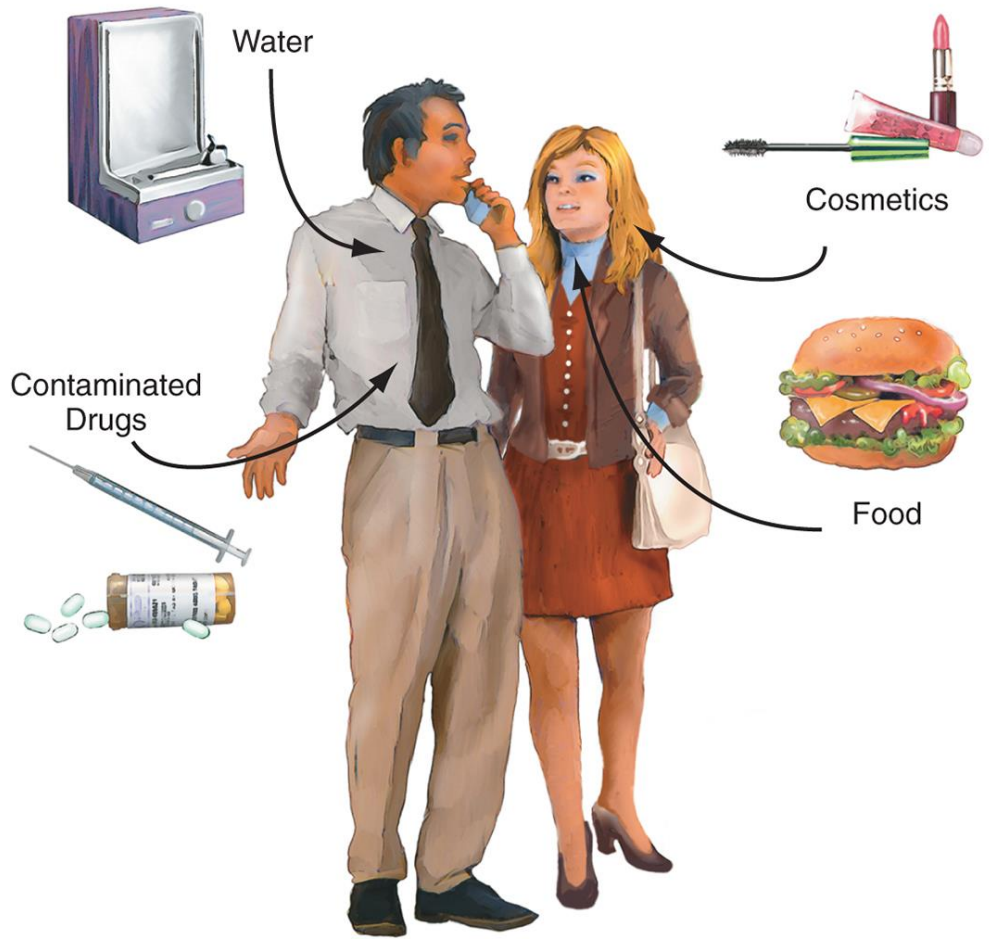
(b)

CDC/James Gathany

Contact Transmission

- Coming together or touching of source/reservoir and host
- Direct contact (person-to-person)
  - physical interaction between source/reservoir and host
  - e.g., kissing, touching, and sexual contact
- Indirect contact
  - involves an intermediate (usually inanimate)
  - e.g., eating utensils, bedding
- Droplet spread
  - large particles (>5 μm) that travel <1 meter

Vehicle Transmission



- Vehicles
  - inanimate materials or objects involved in pathogen transmission
- Common vehicle transmission
  - single vehicle spreads pathogen to multiple hosts
  - e.g., water and food
- Fomites
  - common vehicles such as surgical instruments, bedding, and eating utensils

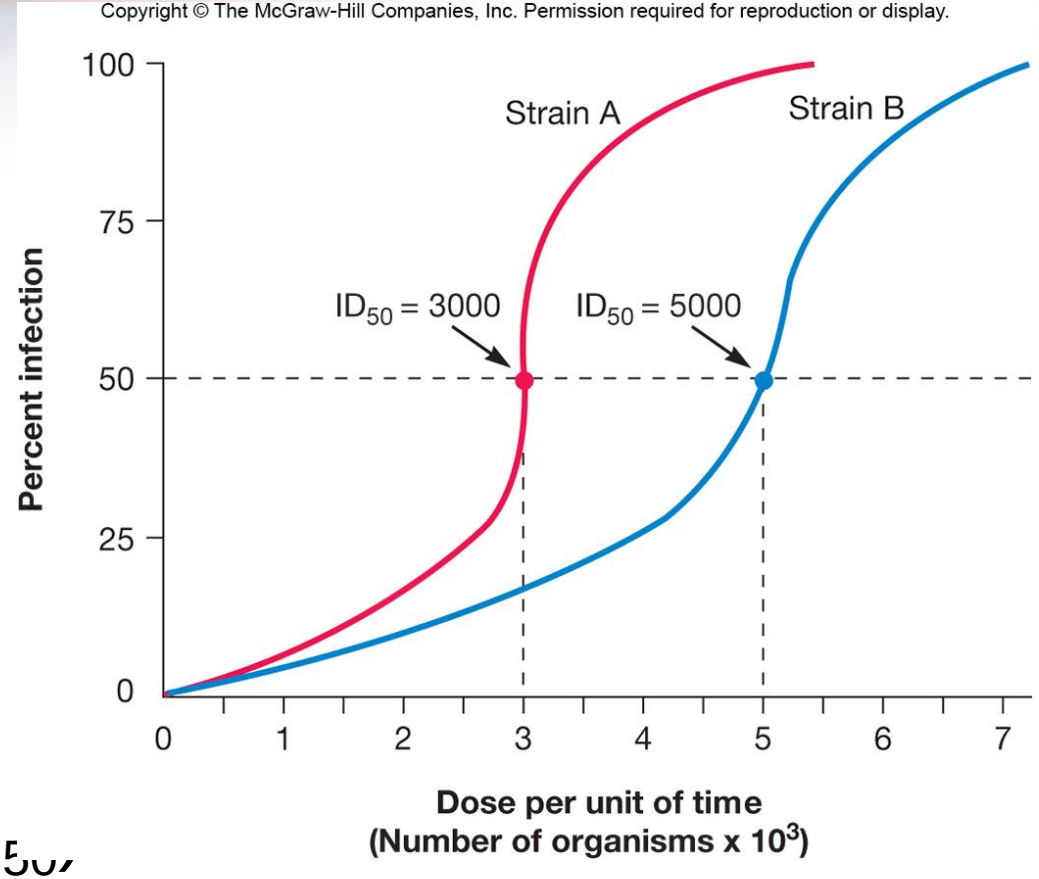
Vector-Borne Transmission

- External (mechanical) transmission
  - passive carriage of pathogen on body of vector
  - no growth of pathogen during transmission
- Internal transmission
  - carried within vector
  - harborage transmission – pathogen does not undergo changes within vector
  - biologic transmission – pathogen undergoes changes within vector

Vertical Transmission

- Occurs when the unborn child acquires a pathogen from an infected mother
- Not as common as horizontal transmission
- Babies born with an infectious disease are said to have a congenital infection
- Examples include
  - gonorrhea (especially in the eyes)
  - herpes
  - german measles
  - toxoplasmosis

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