Chapter 14: Principles of Disease

1. Important Disease Concepts

2. Disease Transmission
1. Important Disease Concepts
Important Disease Terminology

Pathology
- the study of disease (state of ill health)

Infectious Disease
- disease due to a transmissible microbial agent

Symptoms
- what the patient experiences (subjective)

Signs
- what the health care provider observes (objective)

Syndrome
- a set of multiple signs or symptoms that characterize specific condition or disease
Classifying Diseases

Not all diseases are infectious (e.g., cancer, genetic conditions), but those that are can be further classified as follows:

Communicable Diseases

• capable of being spread from one host to another
• a disease that is *easily* spread is **contagious**

Non-communicable Diseases

• NOT spread directly from one host to another
• e.g., tetanus
Koch’s Postulates

In the late 19th century, Robert Koch established the following principles to identify the microbial source of disease:

1) same pathogen must be present in every case of the disease

2) pathogen must be isolated from diseased host and grown in pure culture

3) pathogen must cause the associated disease following inoculation into healthy test subject

4) pathogen must be isolated from test subject and shown to be identical to the original pathogen
Application of Koch’s Postulates

The following must be shown to “finger” the pathogen:

1) suspect pathogen is isolated from ill subject, identified & cultured

2) test subject is inoculated with pathogen & manifests the same illness

3) same pathogen is isolated from test subject

**If these 3 things are demonstrated, pathogen is guilty!**
Exceptions 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** OK 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…
Stages of Disease Development

- Incubation period (no signs or symptoms)
- Prodromal period (mild signs or symptoms)
- Period of illness
- Period of decline
- Period of convalescence

Most severe signs and symptoms

Signs and symptoms
Disease Development

Disease development refers to the characteristic stages of the disease process:

Incubation Period
• period of time from the onset of infection to the first appearance of signs or symptoms of disease
• can be short, long, variable

Prodromal Period (“optional”)
• initial appearance of mild symptoms (aches, malaise)
• not seen with every infectious disease
Period of Illness

- when symptoms and signs are most severe
- e.g., fever, chills, sore throat, swollen lymph nodes

Period of Decline

- when symptoms and signs of illness diminish
- patient is vulnerable to secondary infections

Period of Convalescence

- recovery of strength, return to pre-disease state
- despite lack of symptoms or signs, disease can still be communicable
2. Disease Transmission
Reservoirs of Infection

A reservoir of infection is a continual source of pathogen from which it can spread:

- in between “outbreaks” the pathogen must exist somewhere (unless it’s been eradicated entirely)

- common reservoirs of infection include:

  The host species (e.g., humans)
  - some hosts serve as carriers (show no signs of illness)

  Non-host animal species (e.g., insects, rodents)

  Non-living material (e.g., soil or water)
Modes of Disease Transmission

Transmission of a pathogen occurs in 3 basic ways:

1) **Contact** Transmission
   - spread of pathogen by direct or indirect casual contact

2) **Vehicle** Transmission
   - spread of pathogen through physical media such as water, air or food

3) **Vector** Transmission
   - animals that spread disease to a different species
Contact Transmission

Direct Contact Transmission

• transmission by direct contact between a source of the pathogen and a susceptible host

• commonly called “person to person” transmission

Indirect Contact Transmission

• transmission to susceptible host through a nonliving object (e.g., cups, utensils, syringes, bedding)

• such “intermediate” materials are called fomites

Droplet Transmission

• transmission over short distances (< 1 meter) through tiny droplets produced by sneezing, coughing, talking
Vehicle Transmission

**Waterborne Transmission**
- transmission through contact or ingestion of water contaminated with the pathogen
- typically due to contamination with sewage

**Foodborne Transmission**
- transmission through ingestion of contaminated food
- due to undercooking, improper storage of food

**Airborne Transmission**
- transmission through airborne particles that travel >1 m
- droplets, dust, airborne spores
Vector Transmission

Transmission through animal vectors occurs in 2 basic ways:

**Mechanical Transmission**

- physical transport of the pathogen on the external structures of an animal
- e.g., legs of a fly that has landed on fecal matter

**Biological Transmission**

- pathogen survives *within* host animal to be spread by biting, defecation or vomiting
- e.g., mosquitoes that spread *Plasmodium vivax*
Nosocomial Infections

Infections that occur in a health care environment (e.g., hospital, nursing home):

**Nosocomial infections are the 8th leading cause of death in the United States!**

So why are hospitals such dangerous reservoirs of infection?
Factors in Nosocomial Infection

Microorganisms in the hospital environment

- most nosocomial pathogens are bacterial
- resistant strains are selected for due to the wide use of antibiotics

Compromised state of hospital patients

- bodily defenses of patients are weakened due to illness, injury, surgery, IVs, catheters (parenteral entry)

Multiple modes of transmission

- direct transmission through hospital personnel, patients
- indirect transmission through fomites (needles, catheters)
- vehicle transmission (through air mainly)
Key Terms for Chapter 14

• symptoms, signs, syndrome
• prodromal
• reservoir of infection
• contact, vehicle & vector transmission
• mechanical vs biological transmission
• nosocomial

Relevant Chapter Questions
rvw: 1, 2, 4-6, 9, 12, 15          MC: 4-10
Chapter 15: Mechanisms of Pathogenicity

1. How Bacteria Enter Host
2. How Bacteria Damage Host
3. Viral Pathogenesis
1. How Bacteria Enter Host
Important Concepts

Pathogen
• a disease-causing organism (or virus)

Infection
• growth of a pathogen in host tissue

Virulence
• the degree to which a pathogen causes disease

Portal of Entry/Exit
• tissue through which a pathogen enters or exits a host (i.e., a human body)
Portals of Entry

Bacteria can enter the body of a human host through several “portals” or types of tissue:

1) Skin
   • the toughest barrier to get through

2) Mucous membranes
   • moist surfaces with mucus coating
   • the linings of the respiratory, digestive & genito-urinary tracts

3) Parenteral entry
   • direct entry into internal tissues
   • i.e., through cuts, punctures or other injuries
The Effect of Numbers

For each pathogen at a particular portal of entry there is a numerical “threshold” required for an infection to occur:

- below the threshold the immune response will control and eliminate the pathogen
- above the threshold growth (infection) occurs
- threshold depends on tissue, individual host

Useful concept:

$\text{ID}_{50}$ – infectious dose for 50% of population
- unique for each pathogen, type of host, portal of entry
Preferred Portals

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!***
Adherence to Host Cells

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

- complementary interactions between a type of adhesin on pathogen and “receptor” on specific host cells
- host cells with appropriate “receptor” are found in preferred portal thus making entry much more likely

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

Most human infections involve heterogeneous microbial aggregates called biofilms which have some unique properties:

- biofilms form via bacteria on solid yet moist surfaces (e.g., teeth, prosthetics, food processing equipment)
- secretion of additional glycocalyx material creates a gelatinous extracellular matrix
- provides protection from disinfectants, immune cells, etc, which do not penetrate biofilms very well

**pathogenic cells in a biofilm are much harder to kill than isolated cells**
Penetration of Host Defenses

Following adhesion, bacteria have a variety of ways to *penetrate* host tissues *avoid destruction* by the immune system:

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

2) Cell Wall
   - the cell walls of some bacteria also resist phagocytosis (and may have adhesins for attachment)

3) Antigenic Variation
   - some bacteria are able to periodically change the molecules on their surface to avoid immune detection
4) Enzymes

- a variety of enzymes are released by bacteria to increase their virulence:

Coagulases – cause blood to clot, isolating bacteria from immune cells

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

Hyaluronidase – breaks down hyaluronic acid, an important component of connective tissue, allowing tissue penetration

Collagenase – breaks down collagen in connective tissue

IgA proteases – destroy IgA type antibodies
2. How Bacteria Damage Host
Siderophores & Iron

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

- iron is a very essential and limiting trace nutrient for all living cells

- siderophores bind and essentially steal extracellular iron from host, damaging it indirectly

- special receptors on the surface of the bacterium bind iron-siderophore complexes and internalize them for bacterial use

**iron supplements can actually worsen a bacterial infection**
Direct Damage to Host

Bacteria can also cause direct damage to host cells in 2 basic ways:

1) Use of host cells for nutrition
   • lipids, protein and carbohydrate components of host cells are used directly as a source of energy, carbon, nitrogen, etc…
   • can even occur in host cells following phagocytosis!

2) Production of metabolic wastes
   • release of waste products of bacterial metabolism can be directly harmful to host cells
Bacterial Toxins

The most significant source of host damage is due to the release of poisonous toxins:

**Exotoxins**

- proteins produced inside certain bacteria and released into host tissues
- can inhibit various process such as protein synthesis, neural transmission, fluid and salt balance...
- can spread throughout body of host via blood, lymph

**Endotoxins**

- lipid A from the outer membranes of Gram- bacteria
- induce potent physiological responses in host

**LD_{50} of toxins = lethal dose for 50% of population**
Types of Exotoxins

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

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

(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.

  - **Staphylococcal enterotoxin:**
    *Staphylococcus aureus*
  - **Erythrogenic toxins:**
    *Streptococcus pyogenes*,
    “scarlet fever”
A-B Exotoxins

A-B toxins are proteins with an “A” part that causes the damage and a “B” part that binds to host “receptor”

e.g. **Diphtheria toxin:**
inhibits protein synthesis
* *(Corynebacterium diphtheriae)*

**Botulinum toxin:**
inhibits nerve impulses
* *(Clostridium botulinum)*

**Tetanus toxin:**
inhibits nerve impulses
* *(Clostridium tetani)*

**Cholera toxin:**
disrupts enteric fluid balance
* *(Vibrio cholerae)*
Exotoxins, Plasmids & Viruses

In many cases bacteria acquire genes coding exotoxins from viruses or plasmids:

- viruses can transfer exotoxin genes by transduction
  - usually by specialized transduction via lysogenic bacteriophages
  - e.g., diphtheria, cholera, pyrogenic & botulinum toxins

- bacteria can acquire plasmids containing exotoxin genes by transformation or conjugation
  - e.g., tetanus toxin & S. aureus enterotoxins

**transfer of exotoxin genes by these methods can convert benign strains into virulent strains**
Endotoxin

Endotoxin is the lipopolysaccharide (LPS) portion of the Gram- outer membrane (specifically, lipid A)

- endotoxin is released when a Gram- cell dies or to a lesser degree when it divides

Endotoxin release triggers physiological responses in the host which can be lethal

- the endotoxin (lipid A) itself does NOT damage the host, it is the host’s response to endotoxin that results in tissue damage, even death!
Physiological Responses to Endotoxin

Fever (resetting body “thermostat” to a higher temperature):
  • phagocytes encountering endotoxin release the cytokine IL-1 & trigger the fever response via the hypothalamus

Shock (severe lowering of blood pressure):
  • due to release of the cytokine Tumor Necrosis Factor (TNF) which increases the permeability of capillaries, fluid loss

**these responses help to fight infection, but can go too far**
Summary of Bacterial Pathogenesis

Bacterial virulence depends on:

- adherence & high numbers to facilitate entry into host
- the ability to penetrate host, survive host defenses
- the degree of damage to host tissues

**spread to other hosts also depends on portals of exit**
Key Terms for Chapter 15

- pathogen, infection, virulence
- portals of entry/exit, parenteral
- adhesin, invasin, ID_{50}, LD_{50}
- biofilm, antigenic variation
- siderophore, exotoxin, endotoxin
- superantigen, A-B toxin

Relevant Chapter Questions
rvw: 1, 2, 4-7, 9-11    MC: 1-3, 5, 6, 10