PATHOGENESIS & VIRULENCE FACTORS

Dr. Orass Madhi

Normal Flora

Microorganisms that are associated with a host, established at a particular anatomical location and don't harm their host

Important part of innate immunity

- Compete for space and nutrients with harm harmful organisms

When displaced from normal site to other areas may cause disease

- Example: ***Staphylococcus aureus*** in nose and throat can enter a wound and cause serious infections

Pathogenicity

Ability of microbes to cause disease in the host it infects

Virulence

Extent of pathogenicity

Capacity to cause disease

- Related to severity of disease in the host

Infectious Disease Caused by Parasites

Infection :-

the state occurring when a parasite is growing and multiplying on or within a host

Infectious disease - a change from a state of health as a result of an infection by a parasitic organism.

- Adverse affect on the function of part or all of the host body as a result of the presence of a parasite or its toxic products

Pathogen - any parasitic organism that produces an infectious disease

Pathogenicity - the ability of a parasitic organism to cause a disease

Latency

When no symptoms present themselves

Intermittent latency

- Herpes simplex virus (HSV)
  - Lies dormant in neural tissue and is induced to replicate by various factors including intense sunlight and stress

Quiescent latency

- Persistence over very long periods of time (many years)
  - Varicella zoster
    - Chickenpox in children
    - Shingles in the elderly

Outcome of Host-Parasite Relationships

The final outcome of host-parasite relationships

- Dependent on three factors:
  - The actual number of parasites in the body
  - How virulent the parasite is
  - How effective the host's resistance is to infection

- Disease often incurred if parasite is particularly virulent, even if the host has high resistance

- Disease also incurred if virulence isn't particularly intense, but the host's resistance is weakened
  - Age
  - Illness
  - Immunosuppressive drugs

What Determines Virulence?

Virulence – a measure of pathogenic intensity determined by three properties of the pathogen:

- **Invasiveness –** organism's ability to penetrate the first line of defense and spread to adjoining tissues in the host
- **Infectivity –** organism's ability to establish a primary site of infection
- **Pathogenic potential –** organism's ability to induce morbid symptoms, determined by toxigenicity

What is toxigenicity?

Refers to organisms ability to produce toxic compounds (toxins) that are harmful and cause disease

Toxins = specific metabolic products of pathogen

- Exotoxins
- Endotoxins
- Leukocidins
- Hemolysins

LD_{50} and ID_{50}

LD_{50}

- Lethal dose 50
- Number of pathogens required to kill 50% of subjects in a given time period

ID_{50}

- Infectious dose 50
- Number of pathogens required to infect 50% of subjects

Components Influencing Infectious Disease

Transmissibility of the pathogen - involves initial transport to the host

---

- **Direct contact** - coughing, sneezing, body contact (shaking hands, kissing)
- **Indirect contact** – deposition into an environmental medium including soil, water, food and bedding
- **Vectors -** living organisms that transmit a pathogen from one host to another
  - Mosquitoes (Malaria, West Nile Virus)
  - Tick (Rocky Mountain spotted fever, Lyme disease)
  - Flea (Plague)

Zoonoses

- Disease which are mainly prevalent in an animal population but can be transferred to humans
  - Rabies
  - Plaque
  - Brucellosis

Methods by which pathogens cause disease:

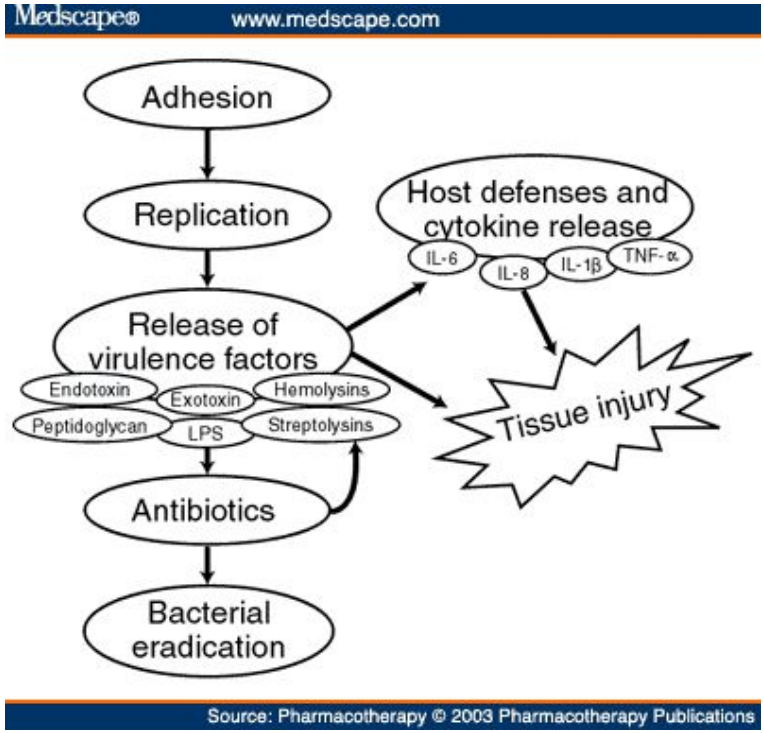
Adhesion.

Colonization.

Invasion .

Evasion of host defenses.

Toxin releas .



Adhesion

Specific adherence involves complementary chemical interactions between the host cell or tissue surface and the bacterial surface. In the language of medical microbiologist, a bacterial "**adhesin**" attaches covalently to a host "**receptor**" so that the bacterium "docks" itself on the host surface.

- **The adhesins of bacterial cells are**
  - **chemical components of capsules.**
  - **cell walls.**
  - **pili or fimbriae.**

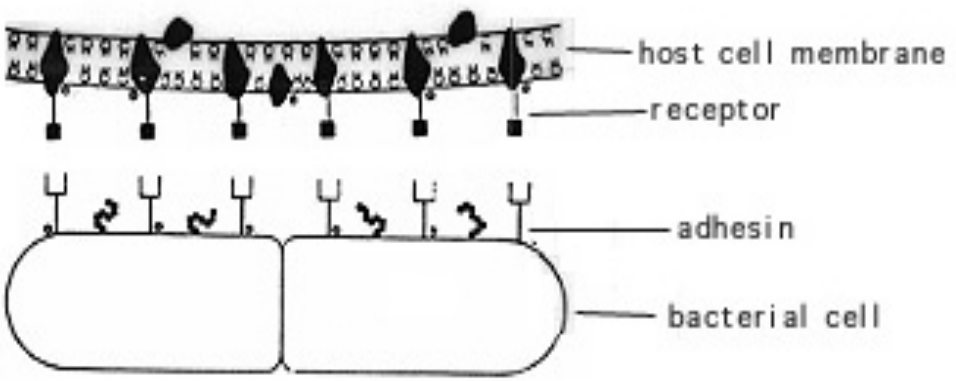
The host receptors are usually glycoproteins located on the cell membrane or tissue surface.

S. pyogenes has surface fimbriae which contain two major components the M protein and lipoteichoic acid for adhesion.

The adhesins of ***E. coli*** are their common pili or fimbriae.. *E. coli* .

Pseudomonas, Vibrio* and *Neisseria possess pili.

pili are the fimbriae used in attachment of *Vibrio cholerae* to the gastrointestinal epithelium.

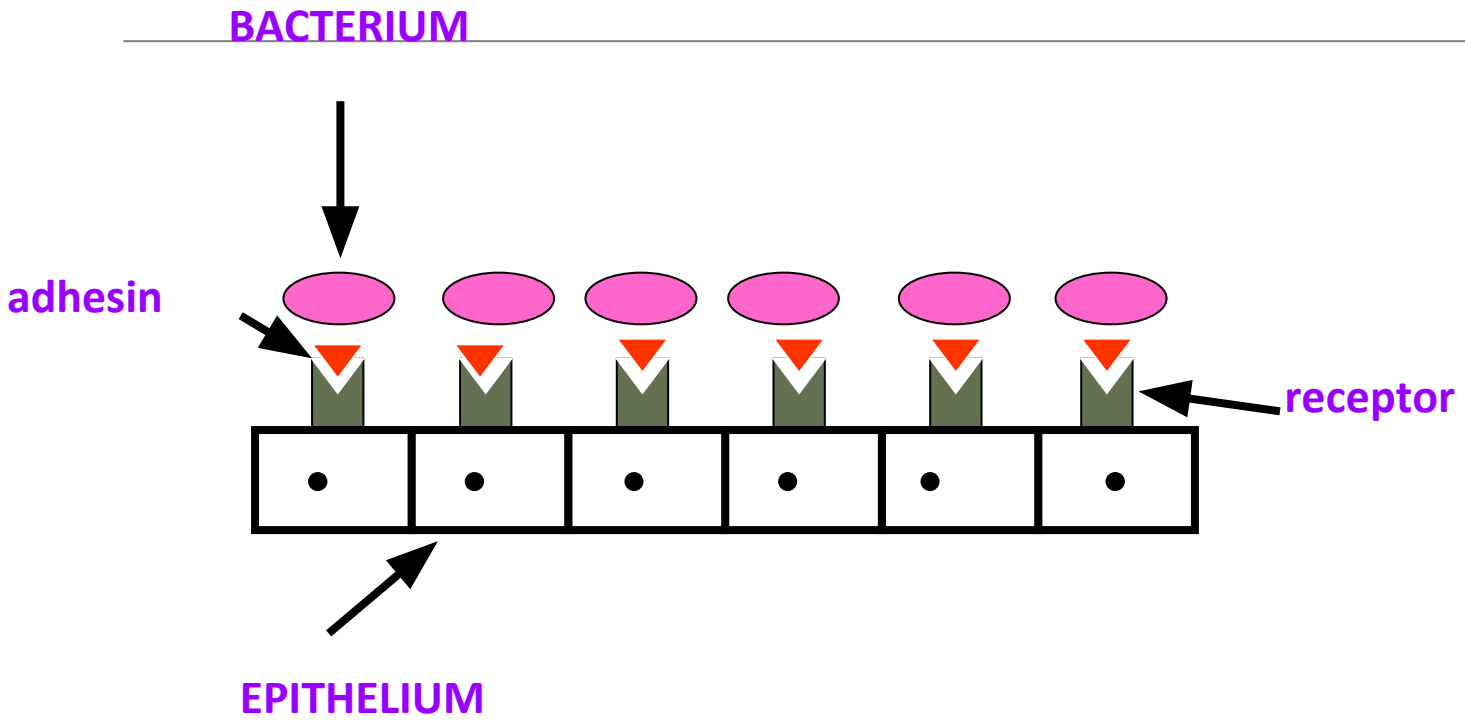


Attachment and colonization (multiplication) by the pathogen

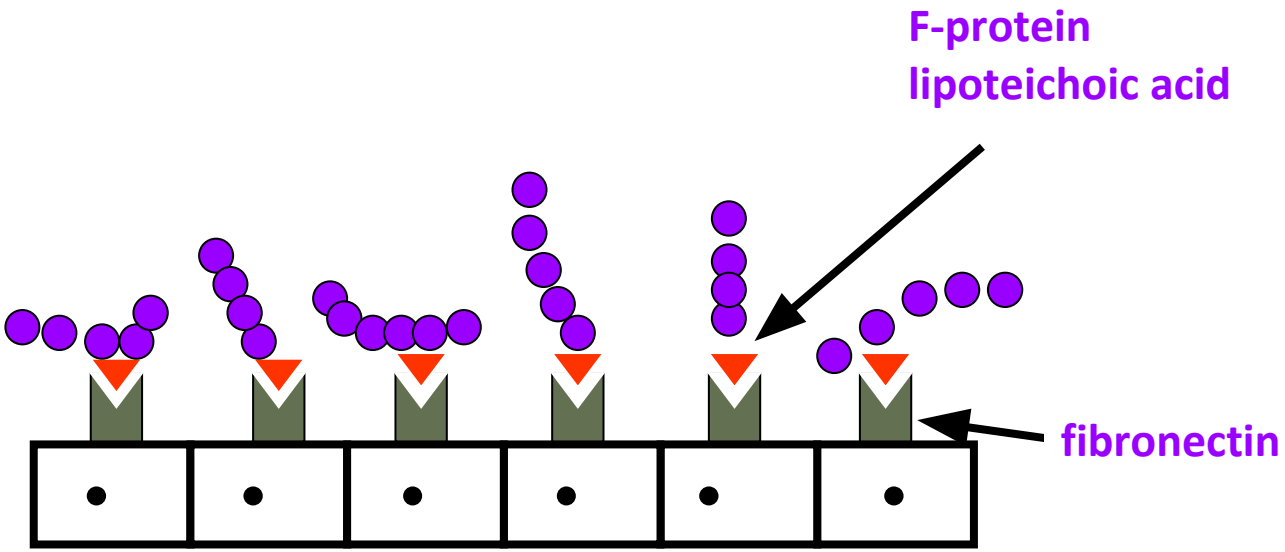
- Pathogen must be able to adhere to and colonize host cells and tissue;
  - this is mediated by special molecules or structures called **adhesins**

- **Examples of adhesins**
  - Filamentous hemagglutinin of *Bordetella pertussis* (binds to cilia of RT)
  - Fimbriae, pili
  - Glycocalyx (dental plaque)
  - Lectin
  - Capsule
  - Slime layer
  - Teichoic and lipoteichoic acids

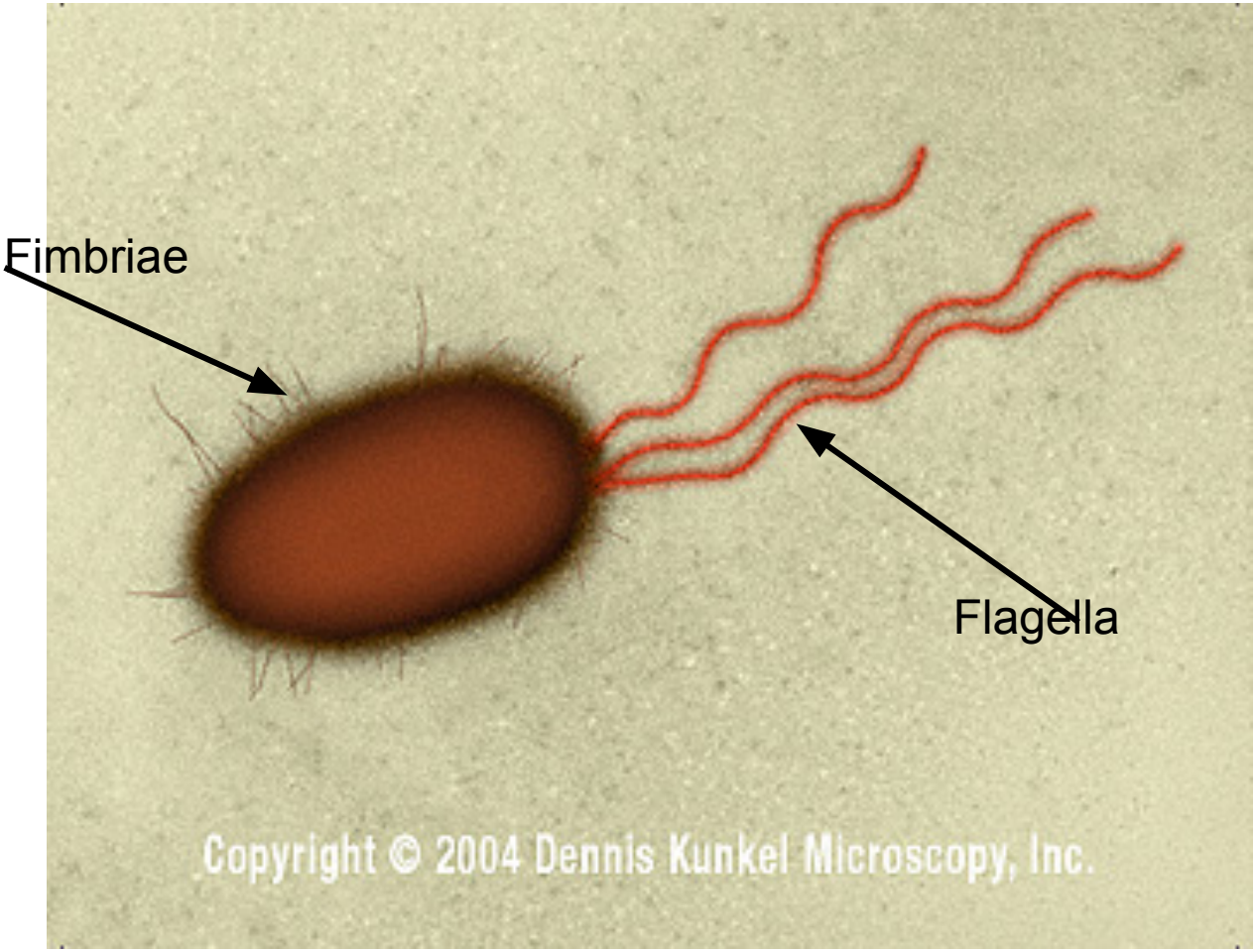
Adhesion



S. pyogenes

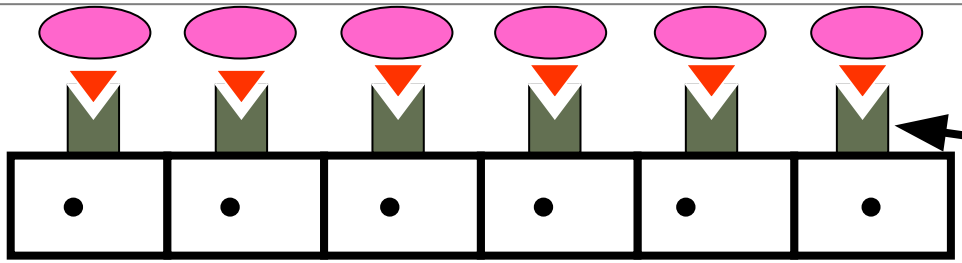


E. coli


Fimbriae
Flagella
Copyright © 2004 Dennis Kunkel Microscopy, Inc.

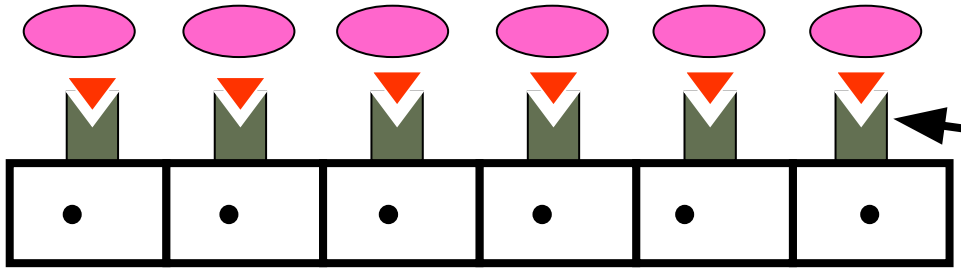
E. coli fimbriae

Type 1



mannose

P



galactose
- glycolipids
- glycoproteins

Invasion and Evasion of Host Defense Mechanisms

Invasion of the pathogen

- Requires penetration of the host's epithelial cells or tissues
- Invasiveness = features that enable pathogens to escape immune detection/defenses and cause overt infection

Portals of Entry

Each infectious organism has its own portal of entry and portal of exit from the host

Entry:

- Respiratory tract via nose and throat
  - M tuberculosis can survive in dried sputum for weeks
- Gastrointestinal tract via mouth
  - S. typhi multiply only In cells of intestinal mucosa
- Skin and mucus membranes
- Genitourinary system (STD)
- Blood (insects, transfusions, needles)

Exit: Usually the same as the portals of entry

- **Passive mechanisms of entry involve:**

  - **Breaks, lesions, or ulcers in the mucous membranes**
  - **Wounds, abrasions, or burns on the skin surface**
  - **Arthropod vectors that penetrate when feeding**
  - **Tissue damage caused by other organisms**
  - **Endocytosis by host cells**
  - **Gaining of access to deeper tissues**
  - **Penetration into the circulatory system**

Growth and multiplication of the pathogen:-

pathogen must find an appropriate environment

- **pH**
- **Oxygen tension**
- **Nutrient availability (including specialized growth factors)**
- **Intracellular growth**
  - ***Mycobacterium tuberculosis* in alveolar macrophages**
- **Extracellular growth**
  - **Pyogenic infections – pus formation in extracellular spaces (*Streptococcus pyogenes*)**

Dissemination by Evasion

Pathogens spread throughout the host tissue and sometimes even gain entry into lymphatic capillaries and then eventually into the circulation

- Localized infection = limited
- Systemic dissemination = multiple organs

Enhanced by microbial products and enzymes (virulence factors)

Capsules and fimbriae – antiphagocytic, requires antibodies for opsonization

Leukocidins - extracellular enzymes that kill phagocytic leukocytes by causing degranulation of lysosomes

Hemolysins - extracellular enzymes that kill erythrocytes by forming a pore (iron released)

- **Streptolysin O – inactivated by oxygen, beta hemolysis when incubated anaerobically (S. pyogenes)**
- **Streptolysin S – not oxygen sensitive, beta hemolysis under aerobic conditions**
  - **If phagocytosed, acts as a leukocidin and kills macrophages**

Coagulase – clots fibrinogen in plasma, protecting pathogen from phagocytosis and other host defenses

Collagenase – Degrades collagen in connective tissue promoting the spread of the pathogen

Deoxyribonuclese – reduces viscosity of exudates, improving pathogen mobility

Elastase – degrades laminin in ECM

Exotoxin B – aka pyrogenic exotoxin b – protease

Hydrogen peroxide and ammonia – damage to respiratory and urogenital systems

Hyaluronidase – degrades hyaluronic acid in intercellular ground substances holding cells together – increases mobility

IgA protease – Degrades antibody (IgA isotype) into Fab and Fc fragments

Lecithinase – degradation of lecithin in PM (phosphatidylcholine)

Protein A – binds IgG at Fc, prevents C' activation

Streptokinase (fibrinolysin, staphylokinase)– binds plasminogen and induces production of plasmin, and digestion of fibrin clots – increasing mobility of pathogen from clotted areas