Bacteria Lecture Outline **March 2 and 7, 2001**

I. Extracellular Bacteria Live outside host cells. Fast replicating to avoid elimination.

Innate immune responses

1. Inflammation. Complement activation.
2. Macrophages and neutrophils. Phagocytosis. Mediators released: Cytokines, O_2 radicals, enzymes.

Adaptive immune responses

1. Antibodies play key role in providing opsonization and C' activation.
2. Antibodies can neutralize toxins.
3. Th2 cytokines important for B cell activation.
4. Th1 CKs some role for activating macrophages.

II. Intracellular Bacteria By living inside a host cell they avoid many effective host immune strategies (antibodies, phagocytosis, complement). However these bacteria need to have strategies to escape lysosomes.
Some intracellular bacteria choose to escape from the endosome and replicate in cytoplasm like viruses.
Others stay in protected endosome and alter the endosome in order to prevent fusion with lysosome.
Many intracellular bacteria live in macrophages.

Innate immune responses

Inflammation with activated neutrophils and macrophages during acute infection.

Adaptive immune responses

1. CTLs. Killing infected cells.
2. Th1 cytokine s IFN-γ, TNF-α. Activate macrophages.

Chronic inflammation is elicited if infected macrophages are unable to eliminate bacteria.
2. Antibodies/Th2 cytokines help with protection from reinfection but may be less effective for elimination.

III. Disease examples

Bacterial Pneumonias

1. Tuberculosis. *Mycobacterium tuberculosis* (Mtb) are intracellular bacteria which live in lung macrophages. Infection can be asymptomatic, disseminated or chronic.
Macrophages that kill the Mtb organisms travel to lymph nodes present to T cells start Th1 response. Th1 cells go back to lung to activate more macrophages so that they will kill Mtb. Th1 response controls infection but can also be cause for disease.
Tubercle (granuloma) from Th1 cells along with infected macrophages and epitheloid cells. Tubercles can heal or become fibroid to form scar tissue.
Tb is mostly controlled by improved social conditions, immunizations (BCG), and drug prophylaxis.
Anti Tb drugs are effective but drug resistance is developing.

2. Other bacterial pneumonias.

Streptococcus pneumoniae #1 cause of bacterial pneumonia.
Haemophilus pneumoniae.
Legionella pneumophila--Legionnaire's disease.

Sexually Transmitted Bacterial Diseases

3. Gonorrhea *Neisseria gonorrhea*. Gnococci are extracellular but they attach to mucosal cells and induce an inflammatory response.
Replicates extracellularly but can infect non-ciliated epithelial cells and then connective tissue.
Initially asymptomatic disease can result in pelvic inflammatory disease (PID) and infertility.
Infertility is a from inflammatory damage to Fallopian tubes.

4 Syphilis *Treponema pallidium*. Extracellular. Infections through skin abrasions or mucous membranes.
Primary infection-chancre (lesion) in contact area and then systemic infection.
Infection can become chronic or clinically latent (no evidence of disease). Horizontal and vertical transmission.
Vigorous cell mediated immune response but still ability to persist. Disease is a result of immune response.
Bacteria cell surface covered in antigenically unreactive lipids.

4. Chlamydia. Intracellular. Can cause STD, conjunctivitis of eye, and pneumonias.
STD very similar to gonorrhea. Conjunctivitis can lead to blindness.

Bacterial Diseases of the Gastrointestinal Tract

5. Salmonella Fecal oral food borne disease, where bacteria can live extra/intracellular.
Many species cause same disease. Animal reservoir.
Most species invade epithelial cells infect and cause diarrhea.

6. Pathogenic E. coli. Extracellular replication. Produces entertoxin.

7. Campylobacter. Extracellular. Animal reservoir. Causes diarrhea.
Campylobacter pylori (aka *Helicobacter pylori*) causes gastritis and gastric ulcers.

8. Cholera is caused by *Vibrio cholerae*. Fecal oral transmission, poor sanitation increases transmission. Releases an exotoxin that triggers bloody watery diarrhea..

9. Shigella causes bacillary dysentery. Watery diarrhea.

IV. Pathogenic mechanisms of Bacteria.

1. Direct effects from invading organisms.
Intracellular bacteria multiply in cell and spread to next host cell by rupturing cell.
Extracellular bacteria can attach to mucosal cell surface and cause inflammation.

2. Exotoxins. Exotoxins are soluble molecules released by pathogen to trigger change in host.
A. Enzymes---hemolysin, phospholipases, hyaluronidase, collagenase.
B. Alter metabolic machinery.
1. Diptheria toxin---blocks protein synthesis.
2. Cholera toxin--causes loss of water from intestinal cells.

C. Hyperactivation. Toxic shock syndrome toxin-1 (TSST-1). Binds to TCR and Class II MHC causing activation of T cells. Known as a **superantigen**.

D. Effects on nerve muscle transmission.
Clostridium tetani and *C.botulinum*. cause Tetanus and Botulism using toxins that block synaptic transmission.

3. Endotoxins. Classic endotoxin is lipopolysaccharide (LPS) on the bacterial cell surface of many bacteria.
LPS receptors on many cell types B cells, macrophages, dendritic cells.
LPS activates these cells nonspecifically and can trigger inflammation which can result in local acute inflammation or a systemic inflammatory response such as fever, shock, or death.

V. Immunopathology.

1. Immune response causes disease.
Inflammation, infected cell lysis, uninfected cells killed, all result in tissue damage.

2. Antigenic mimicry. This is where a protein sequence of a foreign antigen is similar to a self protein which results in unintentional cross reactivity of antibodies or T cell epitopes.
The self proteins become targets of immune response which can result in tissue damage or autoimmune disease. The viral or bacterial antigen acts as a trigger where the infection elicits immune response to self protein. Disease can occur long after infectious agent has been eliminated.

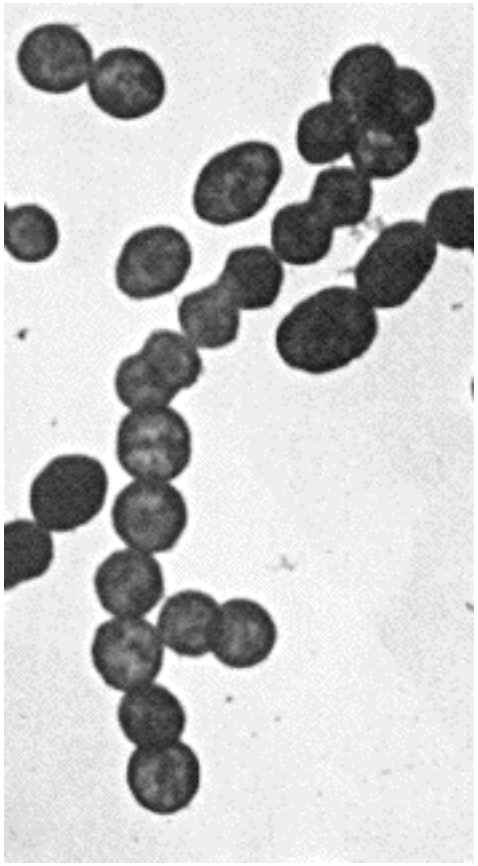
VI. Immune evasion mechanisms for bacteria

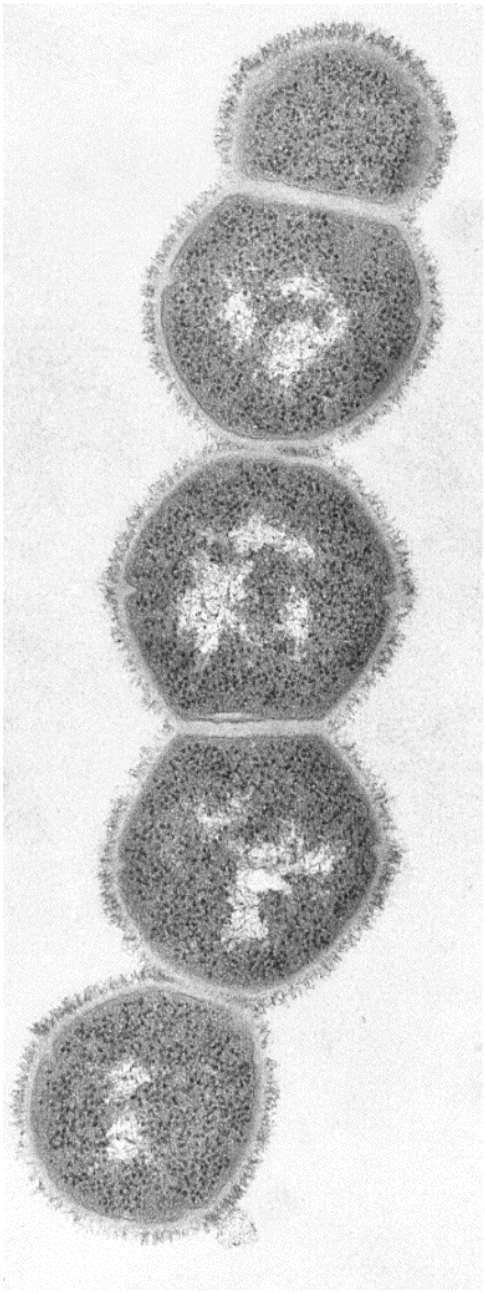
1. IgA specific proteases
2. Antigenic variation
3. Molecules give resistance to phagocytosis.
4. Escape by living inside cells. (especially phagocytic cells)
5. Molecular mimicry. **Pertussis** toxin mimic selectins (a type of CAM) and can block selectin activity and leukocyte recruitment to site of infection.

Pneumococcus. Utilizes receptor for platelet activating factor-mimics adhesion that is increased by CKs.

Bacteria: *Streptococcus pyogenes*

S. pyogenes is a very common bacterial pathogen that causes a wide range of diseases.
Phagocytic cells serve as a major barrier if bacteria cross skin or mucosal epithelial barrier.
S. pyogenes owes its major success as a pathogen to its ability to colonize and rapidly multiply and spread in its host while evading phagocytosis and confusing the immune system.
S. pyogenes is identifiable as a spherical cell 0.6-1.0 um in diameter and occurs as pairs or as short chains in clinical specimens. It is usually grown in the laboratory with the supplementation of blood or human serum.





Diseases from Streptococcus pyogenes infection

1. Streptococcal pharyngitis. Strep throat.
All age groups are susceptible but severe epidemics are most common in school age children and concentrated adults such as military training facilities. The disease is spread from person to person via droplets of saliva or nasal secretions. The symptoms include sore throat with malaise, fever and headache. Diagnosis is made clinically and on isolation of the bacteria from a throat swab.

2. Scarlet fever
This disease results from the release of toxic substances by S. pyogenes. If it occurs, it is usually associated with Streptococcal throat infections. It is associated with a rash which appears as a diffuse red blush with many points of deeper red. Diagnosis is again made clinically and on isolation by throat swab.

3. Skin infections such as: **Streptococcal pyoderma**- a localized purulent (pus producing) skin infection It begins as a flat sore on the skin which then becomes fluid filled and develops pus and crusting.
Streptococcal cellulitis is an acute spreading infection of the skin and underlying tissue and may follow burns, wounds or mild trauma.

4. Streptococcal Gangrene (The Flesh-eating Bacterial Disease)
This is a rare infection of the skin and deeper tissues characterized by extensive and rapidly spreading death of tissue and underlying structures. It is by no means a new entity and was described in China as early as 1924. Characteristically, it begins at a site of trivial or even inapparent trauma. It begins as an area of mild redness on the skin, but over the next 2-3 days undergoes a marked change. The inflammation becomes more pronounced, the skin becomes dusky and then purplish, and then bloody blisters develop in the skin. Unless appropriate medical treatment is undertaken the process may quickly march over large areas of the body. The patient is very ill and death rates are high even with appropriate medical treatment.
Treatment includes appropriate surgery and removal of all dead tissue and antibiotic therapy.

5. Streptococcal Toxic Shock Syndrome (STSS)
In most cases the initial focus of infection is the skin and soft tissues. The illness is similar to the flesh eating bacteria however the patient will also develop shock and failure of multiple organs including: kidneys; heart; lungs; liver and brain. Treatment involves intensive care, surgical care and antibiotics.

6. Rheumatic fever. A possible consequence of Streptococcal sore throat or other Streptococcus pyogenes infections is acute rheumatic fever. This disease is characterized by inflammation of the heart, joints, tissue underlying the skin, and central nervous system. It may damage the heart permanently. It is likely to be a result of either toxic effects of Streptococcal products, or antibodies produced by us to fight the bacteria which actually start to attack the parts of our own body-called an autoimmune phenomena. Affected individuals take life-long antibiotic therapy to prevent further attacks.

Mechanisms of Immune Evasion (Virulence Determinants)

1. Evasion of phagocytosis.
2. Antigenic variation. M protein on surface has 50 diff types.
3. Toxins.
4. Cross-reactive antibodies that can cause autoimmune response.