Introduction, Bacterial Classification & Immunology Review
Different from parasites and fungi (eukaryotic)

- **Prokaryotic organisms**
  - *simple* unicellular organisms
  - no nuclear membrane
  - no mitochondria
  - no Golgi bodies
  - no endoplasmic reticulum

- **Complex cell wall**
  - Gram-positive
  - Gram-negative
Microbial Disease

- The relationship between many organisms and their diseases is not simple.
- Most organisms do not cause a single, well-defined disease, although some do e.g., *Treponema pallidum*--syphilis.
- More common for infections to result in many manifestation of disease e.g., *S. aureus*--endocarditis, pneumonia, skin infections, bone infections, sepsis, food poisoning.
Bacterial Classification

• Phenotypic
• Analytic
• Genotypic
Phenotypic Classification

- Microscopic morphology
  - Gram stain, shape *i.e.*, rods (bacillus), spheres (coccis), curved or spiral, size

- Macroscopic
  - Hemolytic properties on agar containing blood, pigmentation of the colonies, size and shape of colonies, smell and color.

- Serotyping
  - Antibody reactivity to specific antigens

- Antibiogram patterns
  - Susceptibility to antibiotics

- Phage typing
  - Susceptibility to viruses that infect bacteria--bacteriophages
Bacterial Morphologies

Cocci
- coccus
- diplococci
- diplococci encapsulated
  - Pneumococcus
- Staphylococci
- streptococci
- sarcina
- tetrad

Others
- enlarged rod
  - Fusobacterium
- Vibrio
- Comma’s form
  - Bdellovibrio
- Club Rod
  - Corynbacteriaceae
- Helical form
  - Helicobacter pylori
- Corkscrew’s form
  - Borrelia burgdorferi
- Filamentous
- Spirochete

Bacilli
- cocco bacillus
- bacillus
- diplobacilli
- palisades
- Streptobacilli

Budding and appendaged bacteria
- hypha
- stalk
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Analytic Classification

- Chromatographic pattern of cell wall mycolic acids
- Lipid analysis
- Proteomic analysis
  - These techniques are labor intensive
  - Require expensive equipment
  - Used primarily in reference laboratories
Genotypic Analysis

• Most precise method for bacterial classification.
  – Ratio of guanine to cytosine
  – DNA hybridization
  – Nucleic acid sequence analysis
• PCR
  – Chromosomal DNA
  – Ribotyping
  – Plasmid analysis
Bacterial Morphology and Cell Wall Structure and Synthesis
Differences between eukaryotes and prokaryotes

- **Eukaryotes** - Greek for true nucleus.
  - 80S Ribosome
  - 60S + 40S

- **Prokaryotes** - Greek for primitive nucleus.
  - 70S Ribosome
  - 50S + 30S

- Peptidoglycan cell wall.
- SEE TABLE 3-1.
Bacterial Ultrastructure - Cytoplasmic Structures

- Bacterial chromosome is a single, double-stranded circle contained in the nucleoid.

- **RIBOSOMES**
  - Plasmids present in most bacteria.
    - confer virulence
    - antibiotic resistance

- **Cytoplasmic membrane**

- **Mesosome**
  - cytoplasmic membrane
  - anchor and pull apart daughter cells
Bacterial Ultrastructure - Cell Wall

Rigid peptidoglycan layers surround the cytoplasmic membranes of most prokaryotes.

- Both Gram positive and negative.

Exceptions are Archaeobacteria organisms and mycoplasmas.
Differences Between Prokaryotes--The Gram Stain
Gram Positive Cell wall
Gram-Negative Cell wall
The Gram Stain

In the late 1800’s, Christian Gram observed that some genera of bacteria retained a iodine-dye complex when rinsed with alcohol, while other genera were easily decolorized with alcohol and could be then visualized by a contrasting counterstain.
This staining procedure defines two bacterial groups: those which retain the primary dyes ("Positive by Gram’s Method" or "Gram-Positive") and those which are easily decolorized ("Negative by Gram’s Method" or "Gram-Negative"). This is the starting point for bacterial identification procedures.
The Gram Stain

The difference in dye retention is dependent on such physical properties as thickness, density, porosity, and integrity of the bacterial cell wall, as well as, to some extent, the chemical composition.

Gram-Positive bacteria have thick, dense, relatively non-porous walls, while Gram-Negative bacteria have thin walls surrounded by lipid-rich membranes.

Some non-bacterial organisms with thick cell walls (e.g., some yeasts) also stain Gram-Positive.

Gram-Positive bacteria which have lost wall integrity through aging or physical or chemical damage may stain Gram-Negative.
The Gram Stain Procedure

• Step 1 - Prepare a Smear

Suspend some of the material to be stained in a drop of water on a microscope slide, spread the drop to about the size of a nickel.

Allow to air dry. Heat fix by gently warming above a flame or other heat source.

Watch what happens to the “Bacteria” at each step
The Gram Stain Procedure

• Step 2 - Apply the Primary Stain

Flood the Smear with **Crystal Violet**

Allow to stand 30 sec to 1 min

Rinse with water to remove excess stain
The Gram Stain Procedure

• Step 3 - Apply the Fixing Agent

  Flood the Smear with **Iodine** solution
  Allow to stand 30 sec to 1 min
The Gram Stain Procedure

• Step 4 - Rinse

Rinse with water to remove excess Iodine
The Gram Stain Procedure

• Step 5 - Decolorize

Drip 95% Alcohol across the slide about 5 sec
The effluent should appear pale or clear
The Gram Stain Procedure

• Step 6 - Rinse

Rinse with water to remove excess alcohol
The Gram Stain Procedure

• Step 7 - Counterstain

Flood the slide with **Safranin** solution
Let stand 30 sec
The Gram Stain

• Step 8 - Rinse, Dry and Observe
  Rinse with water to remove excess stain
  Blot dry
  Observe under Oil Immersion
Examples of Gram Stains

Gram Positive Rods and Cocci

Gram Negative Rods and Cocci
GRAM-POSITIVE
Growth on Blood Agar and Chocolate agar; NO growth on MacConkey Agar

Budding Yeasts
Growth on Sabouraud dextrose Agar with chloramphenicol
Candida albicans

RODS
ACID-FAST(+)
Slow growers
Growth on Lowenstein Jensen Media
Mycobacteria phlei

Large Boxy rods
Bacillus subtilis

ACID-FAST(-)
Slender rods “snapping fission” when grown on Loeffler’s Agar
stain unevenly
Corynebacterium diptheriae

Hemolysis on Blood Agar

Alpha
P disc Sensitive
Streptococcus pneumoniae

Gamma
P disc Sensitive
Enterococcus faecalis
P disc Resistant
Streptococcus mitis

Beta
A disc Sensitive
Streptococcus pyogenes
A disc Resistant
Streptococcus agalactiae

CATALASE (-)
Fermentation
Streptococci
Staphylococci

CATALASE (+)
Fermentation
Mannitol Salt Agar
Staphylococcus aureus
Staphylococcus epidermidis
Gram + Cell Wall

- Thick, multilayered cell wall consisting mainly of peptidoglycan (150-500 Å).
- Similar to the exoskeleton of an insect except it is porous.
Gram + Cell Wall

- Peptidoglycan essential for structure, replication and survival.
- Can interfere with phagocytosis and stimulate innate responses.
- Pyrogenic.
Gram + Cell Wall

- Teichoic acids are water soluble, anionic polymers covalently linked to the peptidoglycan.
- Lipoteichoic acids have a fatty acid and are anchored in the cytoplasmic membrane.
- Both are common surface antigens that distinguish bacterial serotypes and promote attachment to other bacteria and to specific receptors on mammalian cell surfaces.
Gram Negative Cell Wall

- More complex than Gram + cell wall.
- 2 layers external to the cytoplasmic membrane.
  - thin peptidoglycan layer (5-10% of the cell wall by weight).
  - external to the peptidoglycan layer is the outer membrane.
Gram Negative Cell Wall

- **Periplasmic space-**
  - The area between the external surface of the cytoplasmic membrane and the internal surface of the outer membrane.
  - Contains hydrolytic enzymes important to the cell for breakdown of large macromolecules for metabolism.
  - Also contains enzymes associated with pathology e.g., proteases, hyaluronidase, collagenases and β-lactamase.
Gram Negative Cell Wall

- **Outer membrane**-
  - unique to gram negative bacteria.
  - has similar roll as peptidoglycan does in Gram + bacteria.
    - i.e., it maintains the bacterial structure and is permeability barrier to large molecules.
  - Asymmetric.
    - bilayer structure unique among biologic membranes.
      - inner leaflet-phospholipids
      - outer leaflet-LPS which is amphipathic
      - Only place where LPS is found.
      - LPS=endotoxin
The outer membrane is connected to the cytoplasmic membrane at adhesion sites and is tied to the peptidoglycan by lipoprotein.
Porins allow the diffusion of hydrophilic molecules: metabolites and small hydrophylic antibiotics.
Structure and Biosynthesis of the Major Components of the Bacterial Cell Wall

Cell wall components are prefabricated precursors and subunits of the final structure are assembled on the inside and then brought to the surface.
PEPTIDOGLYCAN

- Peptidoglycan is a rigid mesh made up of ropelike linear polysaccharide chains made up of repeating disaccharides of N-acetylglucosamine (GlcNAc, NAG, G) and N-acetylmuramic acid (MurNAc, NAM, M).
- Tetrapeptide attached to MurNAc.
PEPTIDOGLYCAN SYNTHESIS

1. INSIDE:
   Soluble substrates are activated and peptidoglycan units are built.

2. MEMBRANE:
   Activated units are attached and assembled on the undecaprenyl phosphate membrane pivot.

3. OUTSIDE:
   The peptidoglycan units are attached to, and cross-linked into, the peptidoglycan polysaccharide.

START

1. UTP
   - UDP-GlcNAc
   - UDP-MurNAc
   - 1 Ala
   - 1 Glu
   - 1 Lys
   - D-Ala-D-Ala

2. UDP-MurNAc
   - GlcNAc-MurNAc-PP
   - (AA)₅
   - pentaglycine

3. UDP-MurNAc-(AA)₅
   - GlcNAc-MurNAc-PP
   - (AA)₅
   - APP-MurNAc-GlcNAc

4. MurNAc-PP
   - MurNAc-GlcNAc-MurNAc
   - (AA)₃

5. 1(Gly tRNA)₅
   - P-enolpyruvate
   - UDP-GlcNAc

6. GlcNAc-MurNAc-PP
   - (AA)₅
   - 1UDP-GlcNAc
   - MurNAc-PP
   - MurNAc-GlcNAc-MurNAc

7. MurNAc-GlcNAc-MurNAc
   - (AA)₄
   - D-Ala (Gly)₅ + D-Ala

8. MurNAc-GlcNAc-MurNAc
   - (AA)₄

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PEPTIDOGLYCAN SYNTHESIS

Transpeptidation Reaction

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The number of cross-links and the length of the cross-links determine the rigidity of the peptidoglycan mesh.
LPS

- Consists of three structural sections:
  - Lipid A
  - Core polysaccharide
  - O-antigen
- Lipid A is responsible for the endotoxin activity of LPS.
  - Phosphorylated glucosamine disaccharide backbone.
  - Connect LPS molecules into aggregates.
LPS

- **Core**
  - Polysaccharide is a branched polysaccharide of 9-12 sugars.
  - Essential for LPS structure
- **O-Antigen**
  - Attached to core
  - Long, linear polysaccharide consisting of 50-100 repeating saccharide units of 4-7 sugars per unit.
LPS

LPS structure used to classify bacteria. Lipid A is identical for related bacteria is similar for all gram-negative Enterobacteriaceae. The core region is the same for a species of bacteria. The O antigen distinguishes serotypes (stains) of a bacterial species e.g., *E. coli* O157:H7.
LPS

- Powerful nonspecific stimulator of the immune system.
- Activate B cells (non specifically) and induce macrophages, dendritic, and other cells to release IL-1, IL-6, and TNF-α.
- Induce shock if reaches blood stream at elevated levels.
  - Disseminated Intravascular Coagulation.
Nature of Infection

- Plays a critical role in the interactions between *Acquired* and *Adaptive* immunity
  - *Intracellular* pathogens
  - *Extracellular* pathogens
  - Dose
  - Route
Infection-Immunity-Pathogenicity

- Only rarely is the infectious disease the direct and invariable consequence of an encounter between host and pathogen.

- Rather, it is the eventual outcome of complex interactions between them.
Intracellular Bacteria

• Routs of Infection
  – Directly into the blood e.g., *Rickettsia* sp.
  – Mucosa e.g., *M. tuberculosis* and *L. pneumophila*
  – Intestine e.g., *S. enterica* and *L. monocytogenes*
Fate of Bacteria

• Removed nonspecifically by mucociliary movements and gut peristalsis

• Destroyed by professional phagocytes without SPECIFIC attention of the immune system

• Cells surviving these nonspecific mechanisms colonize deeper and stably infect a suitable niche.
Intracellular lifestyle represents the distinguishing feature of intracellular bacteria.

Invasion of host cells is not restricted to these pathogens.

Transient trespassing through epithelial cells is a common invasion mechanism of BOTH intracellular and extracellular pathogens.
Hallmark 2

• T cells are the central mediators of protection

• These T cells do not interact with microbes directly

• Interact with the infected host cell.

• In contrast, antibodies that recognize microbial antigens directly are of exquisite importance for defense against extracellular bacteria.
• Infections are accompanied by delayed-type hypersensitivity (DTH).
• DTH expresses itself after local administration of soluble antigens as a delayed tissue reaction
• DTH is mediated by T cells and effected by macrophages.
IFNγ, IL-2, LTα, GM-CSF + other cytokines (Cell-mediated)

IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13 + other cytokines (Antibody-mediated)

Bendtzen 1999
Tuberculin Test

Figure 3.1 Giving the Mantoux tuberculin skin test.
Hallmark 4

• Tissue reactions against intracellular bacteria are granulomatous.

• Rupture of a granuloma promotes bacterial dissemination and formation of additional lesions.

• In contrast, tissue reactions against extracellular bacteria are purulent and lead to abscess formation or systemic reactions.
Intracellular bacteria express little or no toxicity for host cells by themselves.

Pathology is primarily a result of immune reactions, particularly those mediated by T-lymphocytes.

In contrast, extracellular bacteria produce various toxins, which are directly responsible for tissue damage.
Hallmark 6

• Intracellular bacteria coexist with their cellular habitat for long periods.

• A balance develops between persistent infection and protective immunity, resulting in long incubation time and in chronic disease.

• Infection is clearly dissociated from disease.

• In contrast, extracellular bacteria typically cause acute diseases, which develop soon after their entry into the host and are terminated once the immune response has developed.
Two Types of Intracellular Bacteria

• Facultative

• Obligate
Major infections of humans caused by facultative intracellular bacteria

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease</th>
<th>Preferred target cell</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycobacterium tuberculosis/M. bovis</em></td>
<td>Tuberculosis</td>
<td>Macrophages</td>
</tr>
<tr>
<td><em>Myocabacterium leprae</em></td>
<td>Leprosy</td>
<td>Macrophages</td>
</tr>
<tr>
<td><em>Salmonella enterica</em> serovar Typhi</td>
<td>Typhoid fever</td>
<td>Macrophages</td>
</tr>
<tr>
<td><em>Brucella sp.</em></td>
<td>Brucellosis</td>
<td>Macrophages</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>Legionnaire’s disease</td>
<td>Macrophages</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Listeriosis</td>
<td>Macrophages</td>
</tr>
<tr>
<td><em>Francisella tularensis</em></td>
<td>Tularaemia</td>
<td>Macrophages</td>
</tr>
</tbody>
</table>
## Major infections of humans caused by obligate intracellular bacteria

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease</th>
<th>Preferred target cell</th>
</tr>
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<tbody>
<tr>
<td>• <em>Rickettsia rickettsii</em></td>
<td>Rocky Mountain spotted fever</td>
<td>Endothelial cells, smooth muscle cell</td>
</tr>
<tr>
<td>• <em>Rickettsia prowazekii</em></td>
<td>Endemic typhus</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>• <em>Rickettsia typhi</em></td>
<td>Typhus</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>• <em>Rickettsia tsutsugamushi</em></td>
<td>Scrub typhus</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>• <em>Coxiella burnetii</em></td>
<td>Q-fever</td>
<td>Macrophages, lung parenchyma cells</td>
</tr>
<tr>
<td>• <em>Chlamydia trachomatis</em></td>
<td>Urogenital infection, conjunctivitis, trachoma,</td>
<td>Epithelial cells</td>
</tr>
<tr>
<td></td>
<td>lymphogranuloma venerum</td>
<td></td>
</tr>
<tr>
<td>• <em>Chlamydia psittaci</em></td>
<td>Psittacosis</td>
<td>Macrophages, lung parenchyma cell</td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>Pneumonia, coronaryheart disease (?)</td>
<td>Lung parenchyma cells</td>
</tr>
</tbody>
</table>
Trachoma
Mechanisms of Immune Evasion

- Easy way—avoid the immune system entirely...how?
- MIMs (Microbial Immunomodulatory Molecules)
Bacterial Invasion

- Invasive bacteria actively induce their own uptake by phagocytosis in normally nonphagocytic cells.
  - Establish a protective niche.
  - Avoid immunity.
  - Multiply.
  - Active process.
  - Opposite to phagocytosis by phagocytes which is active.
A Zipper mechanism

Yersinia
Invasin-mediated entry

Listeria
Internalin-mediated entry
InLB (bacterial attached or free)

B Trigger mechanism

Salmonella

Shigella

Legend:
- Type III secretion apparatus
- Actin
- Arp2/3 complex
- Rho GTPases
- Rho GTPases
- Bacterial proteins
Zipper Mechanism

1. Contact and adherence
2. Phagocytic cup formation
3. Phagocytic cup closure and retraction, and actin depolymerization.
Trigger Mechanism—Require a Type III Secretory System (TTSS)

- **1-Pre interaction stage.**
  - TTSS assembled
- **2-Interaction stage.**
  - Injection of material via needle.
- **3-Formation of the macropinocytic pocket.**
- **4-Actin depolymerization and closing of the macropinocytic pocket.**
Following Internalization…

• Bacteria that replicate inside the internalization vacuole have developed an impressive array of survival strategies.
  – Adapt to and eventually resist the hostile conditions.
  – Alter the dynamics of the vacuolar compartment.
  – Combinations of the two e.g., Salmonella
Following Internalization…

- Some bacteria later ‘escape’ the vacuole, replicate in the cytosol, and move by recruiting and polymerizing actin.
- Facilitates transmission to other cells.
## Extracellular bacteria

<table>
<thead>
<tr>
<th>Species</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>N. gonorrhoeae</em></td>
<td>urethritis, cervicitis, salpingitis, genital ulcer</td>
</tr>
<tr>
<td><em>N. meningitidis</em></td>
<td>meningitis, arthritis, pneumonia, genital ulcer</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>meningitis, sepsis, arthritis, whooping cough</td>
</tr>
<tr>
<td><em>H. ducreyi</em></td>
<td>meningitis, sepsis, arthritis, whooping cough</td>
</tr>
<tr>
<td><em>B. pertubis</em></td>
<td>meningitis, sepsis, arthritis, whooping cough</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>meningitis, sepsis, arthritis, whooping cough</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>meningitis, sepsis, arthritis, whooping cough</td>
</tr>
<tr>
<td><em>V. cholera</em></td>
<td>meningitis, sepsis, arthritis, whooping cough</td>
</tr>
<tr>
<td><em>H. pylori</em></td>
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</tr>
<tr>
<td><em>T. pallidum</em></td>
<td>meningitis, sepsis, arthritis, whooping cough</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>meningitis, sepsis, arthritis, whooping cough</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>meningitis, sepsis, arthritis, whooping cough</td>
</tr>
<tr>
<td><em>S. pyogenes</em></td>
<td>meningitis, sepsis, arthritis, whooping cough</td>
</tr>
</tbody>
</table>
OBJECTIVES

• 1. The general nature of immune responsiveness.
  – Memory
  – Specificity
    • Innate immunity
    • Acquired Immunity

• 2 Infection and Immunity

• 3. The anatomic basis of immune responsiveness.
Where things happen

<table>
<thead>
<tr>
<th>Primary lymphoid organs</th>
<th>Secondary lymphoid organs and tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymus</td>
<td>Waldeyer’s ring (lymph nodes, tonsils, and adenoids)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Bronchus-associated lymphoid tissue</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Lymph nodes</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>Spleen</td>
<td>Spleen</td>
</tr>
<tr>
<td>Peyer’s patches</td>
<td>Peyer’s patches</td>
</tr>
<tr>
<td>Mesenteric lymph nodes</td>
<td>Mesenteric lymph nodes</td>
</tr>
<tr>
<td>Lamina propria</td>
<td>Lamina propria</td>
</tr>
<tr>
<td>Urogenital lymphoid tissue</td>
<td>Urogenital lymphoid tissue</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Lymph nodes</td>
</tr>
</tbody>
</table>

But...
MALT: Mucosa Associated Lymphatic Tissue
(here, more specifically called BALT: Bronchial Associated Lymphatic Tissue)

lumen of trachea

epithelium
cartilage
Mounting a Response
Mounting a Response
The Largest Immune Organ
Additional Barriers

- Eyes
  - Washing of tears
  - Lysozyme
- Respiratory tract
  - Mucus
  - Ciliated epithelium
  - Alveolar macrophages
- Skin
  - Anatomic barrier
  - Antimicrobial secretions
- Genitourinary tract
  - Washing of urine
  - Acidity of urine
  - Lysozyme
  - Vaginal lactic acid
- Digestive tract
  - Stomach acidity
  - Normal flora
  - Bile
Mounting a Response
Mounting a Response

Figure 2. The lymph node.
Mounting a Response

Diagram showing the interaction between DC, MHC-I/MHC-II, TCR, CD4/CD8, processed antigen, and T cell.
Clonal Expansion

The activated T cell
increases in size and
divides by mitosis.

Clone of competent
T cells is produced.

T cells differentiate,
becoming various types
of T cells.

Activated T cell

Helper T cells

Cytotoxic T cells

Memory T cells
Distribution of Activated/Primed Lymphocytes