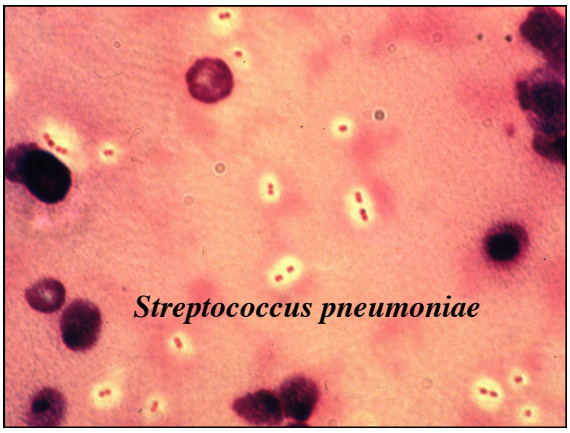
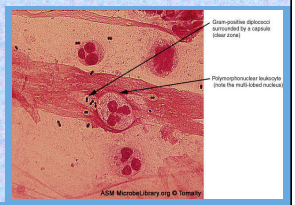
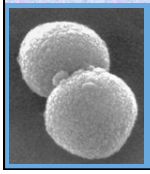
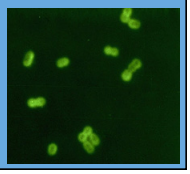


Characteristics of *Streptococcus pneumoniae*

- ***Streptococcus pneumoniae*** **(pneumococcus or diplococcus): Gram+, non-motile, coccus with polysaccharide capsule.**
- **Occurs as paired organisms (diplococci) in tissue.**
- **Performs α-hemolysis (greening) on blood agar.**
- **Over 90 antigenic strains. Strains determined by chemical composition of capsule.**





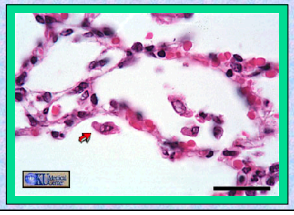


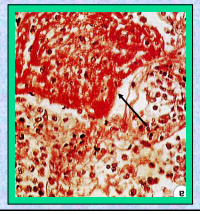
Diseases Caused by *Streptococcus pneumoniae*

- **~300,000 cases of pneumonia per year.**
- **Other Diseases:**
  1. **Otitis Media: ear infections (~6,000,000 cases/year).**
  2. **Sinusitis: inflammation of sinuses.**
- **Complications:**
  1. **Bacteremia with organisms lodging in heart valves (endocarditis) or in pericardium (pericarditis). Both cause heart damage.**
  2. **Meningitis: ~2% patients with serious pneumonia and bacteremia develop meningitis. Fatality rate ~25%.**

What is Pneumonia?

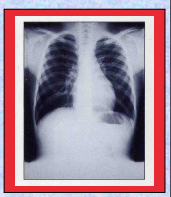
- **Pneumonia: consolidation of the alveoli. Air spaces fill with bacteria, inflammatory cells, and clotted fluid. Oxygen exchange compromised.**
- **Organisms causing pneumonia vary depending on age.**
  - **Infants/children get pneumonia from virus (respiratory syncitial virus and influenza virus).**
  - **Adults get pneumonia from bacteria (*Streptococcus pneumoniae, Klebsiella pneumoniae, Mycoplasma pneumoniae, Haemophilus influenzae, Legionella pneumophila).***

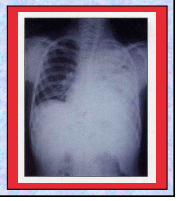




Streptococcal Pneumonia

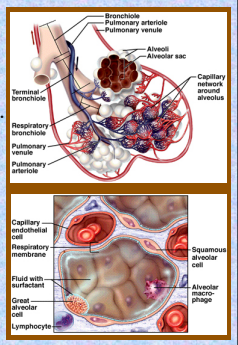
- **~65% of adult pneumonia (normal individuals) caused by *Streptococcus pneumoniae*.**
- **80% of lobar pneumonia (infection found in a single lobe of lung) due to *Streptococcus*.**
- **~30% have *S. pneumoniae* as normal flora.**
- **Opportunistic pathogen causing disease after respiratory epithelium damage.**
  - **With healthy individual, ~100,000 bacteria/ml is infective dose.**
  - **Individuals with underlying disorder (viral infection), infective dose drops to 10 pneumococci.**
- **Incubation period is short, 1-3 days.**
  - **Onset: single, body-shaking chill followed by development of fever, chest pain, coughing, and rust-colored sputum.**
  - **Shortness of breath and cyanosis (dusky-colored skin due to poor oxygen uptake) develop.**
  - **Without treatment, disease lasts 7-10 days. No permanent lung damage.**
  - **5-10%of cases are fatal.**





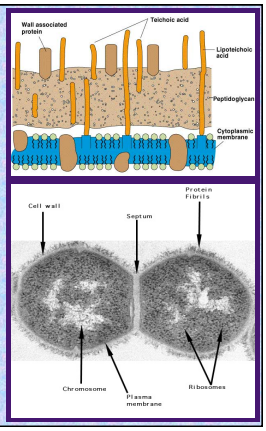
The Infection Process

- **Pneumococci: non-invasive pathogens (except severe cases). Bacteria infect and grow in alveoli.**
- **Interaction between cell wall components and pulmonary epithelium increases vascular permeability.**
- **Alveoli fill with fluid and phagocytic cells.**
- **Pneumococci occasionally invade endothelial cells.**
  - **Increased vascular permeability and leakage into alveoli exposes endothelial cells.**
  - **Pneumococci bind to endothelium and enter by endocytosis.**
  - **Vacuole crosses cell to release bacteria into blood stream.**
- **With bacteremia, risk of meningitis increases.**
  - **Pneumococci adhere to cerebral capillaries.**
  - **Bacteria use endocytosis to enter cerebrospinal fluid.**
  - **Inflammation of meninges results.**



Pneumonia

- Pneumonia: intense inflammation.
- *S. pneumoniae:* no toxins, invasins, or bacterial activities responsible for pathology.
  - *S. pneumoniae* cell wall: Gram+ cell wall with thick peptidoglycan.
    - Teichoic and lipoteichoic acids (cell markers) modified by phosphorylcholine.
    - Phosphorylcholine important because choline adheres to choline-binding receptors present on most human cells. (Reason for variety of diseases.)
  - Surface proteins: more than 500 including:
    - Penicillin binding proteins.
    - IgA protease (inactivates antibody class, IgA).
    - Protective Antigen: inhibits complement opsonization (C3b).
    - CbpA(choline binding protein A): major adhesin. Binds carbohydrates on pulmonary epithelium.



Initiation of Inflammation

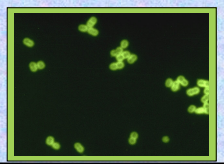
- Pneumococcal cell wall, cell membrane, and surface proteins are inflammatory stimuli.
  - Mouse models: cell wall components (no living bacteria) create symptoms of pneumonia.
- Cell wall components activate:
  - Complement cascade: Chemotactic factors produced.
  - Coagulation cascade: promotes clot formation.
  - Cytokine production by alveolar macrophage: Interleukin-1 and tumor necrosis factor produced.
- Phosphorylcholine in cell wall binds to platelet activating factor receptor (on phagocytes and endothelial cells) and C-reactive protein. Binding prevents activities to inhibit/clear pathogen.

The Anti-Phagocytic Capsule of *Streptococcus pneumoniae*

- Capsule: loose layer of polysaccharides or proteins that envelop bacteria. May be covalently linked to cell wall or just loosely bound. Capsule is penetrated by cell wall teichoic acid, plasma membrane lipoteichoic acid, flagella and pili. Interface with external environment but usually not essential.
- Capsule of *Streptococcus pneumoniae*: formed of polysaccharides, primary virulence factor. Prevents phagocytosis by alveolar macrophage, neutrophils, and monocytes.
- Exact chemical nature important for preventing phagocytosis. Different "strains" have varying levels of virulence determined by molecules that make capsule. Strains without capsule don't cause disease.
- >90 different capsules identified. Antibody against specific capsule polysaccharides is protective.
- Vaccine composed of capsule material from 23 virulent strains of *Streptococcus pneumoniae* is available.

Virulence Factor: The Anti-phagocytic Capsule of *Streptococcus pneumoniae*

- Polysaccharides of capsule are not toxic and not inflammatory (don't activate inflammation). Only interaction with defense systems is causing activation of immune response (antibodies against capsule polysaccharides).
- Mechanisms of virulence:
  - Anti-phagocytosis: smooth nature of the capsule prevents phagocytes from adhering. No phagocytosis.
  - Opsonins bind but capsule physically prevents interaction of opsonins with receptors on phagocytic cells.
  - Capsule prevents complement-mediated lysis.



Resolution of Pneumonia

- Pneumonia symptoms due to inflammation and inability of phagocytes and complement to kill the pneumococcus.
- Immune responses (7-10 days) produce antibody directed against capsule polysaccharides. Antibodies bind to capsules and opsonize bacteria. Allows phagocytes to bind and kill bacteria.
- Little damage to cells during pneumonia, with bacteria removed, inflammation ends.
  - Complement components are inactivated.
  - Clotted material is dissolved.
  - Macrophage phagocytize any residual material.
  - Coughing clears lungs.
  - Few lasting effects on lung function.

Treatment of Pneumonia

- *Streptococcus pneumoniae* has 5 penicillin binding sites.
  - Penicillin drug of choice for treating pneumonia.
  - Penicillin cross-linking of polysaccharides in last step of peptidoglycan synthesis. Defective cell wall leads to hypotonic lysis.
- Antibiotic resistance to penicillin and other antibiotics is occurring.
  - Antibiotic resistant strains of *S. pneumoniae* first encountered in 1970's in New Guinea and South Africa. Not taken seriously because horizontal gene transfer was thought to be very rare. Development of pneumococcus resistant to multiple drugs was thought to be a random occurrence.
  - Multiple antibiotic resistance strains of *S. pneumoniae* now found world-wide.
  - Rapid increase since 1995.

Penicillin Resistance in *Streptococcus pneumoniae*

- **Incidence of penicillin resistance in US increased from <0.02 in 1987 to 3% in 1994 to 30% in some communities by 1998. Incidence is 80% in regions of some countries.**
- **Multi-drug resistance also increased.**
- **Appearance of multi-drug resistance in *Streptococcus pneumoniae* was one indicator that resistance plasmids were transferred between unrelated bacteria.**

Proportion of *Streptococcus pneumoniae* isolates that were non-susceptible to penicillin (PNSP) in surveillance areas in the United States, 1997*

Site	No. of isolates in area hospitals	Proportion of isolates that were PNSP+
California	182	15.4%
Connecticut	603	18.1%
Georgia	843	34.6%
Maryland	557	15.3%
Minnesota	435	21.8%
Oregon	178	18.0%
Tennessee	439	38.3%

*** Data Source: Morbidity and Mortality Weekly Report, August 6, 1999 / 48(30); 656-661.**