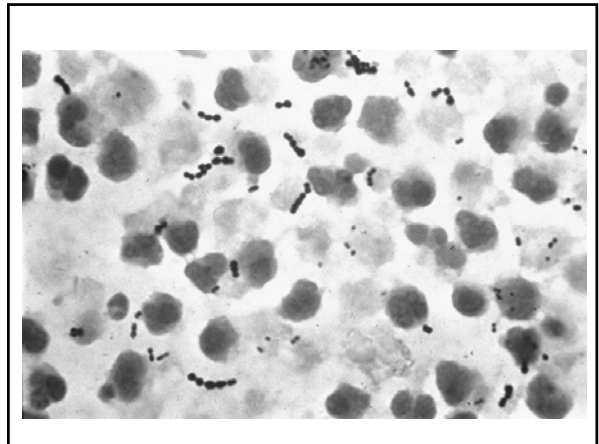
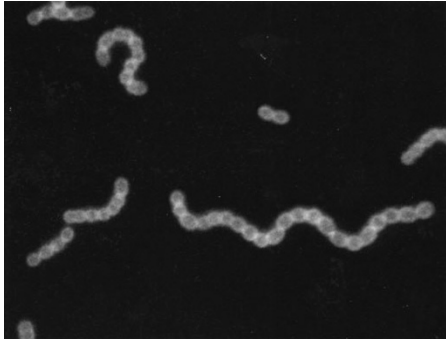


## Streptococci and Enterococci



### Subjects to be Covered

- General description of streptococci and enterococci
- Classification and laboratory identification of the streptococci and enterococci
- Group A  $\beta$  hemolytic streptococci - *Streptococcus pyogenes*
- *Streptococcus pneumoniae*
- Summary

### Species of Streptococci

| Streptococcal Species                    | Sites of Colonization | Sites of Infection  |
|--|-----------------------|---|
| <i>S. pneumoniae</i>                     | Oropharynx, nose      | Lungs, sinuses, middle ear, meninges                        |
| <i>S. pyogenes</i>                       | Oropharynx, rectum    | Pharynx, skin, soft tissue                                  |
| Enterococcal spp.                        | GI tract              | Urinary and biliary tract, cardiac valves                   |
| Nonenterococcal Gp. D                    | GI tract              | Urinary and biliary tract, cardiac valves                   |
| <i>S. agalactiae</i> /Gp. B streptococci | GU tract              | Neonatal infections involving the blood, meninges, GU tract |
| Viridans streptococci                    | Oropharynx            | Cardiac valves, bloodstream                                 |

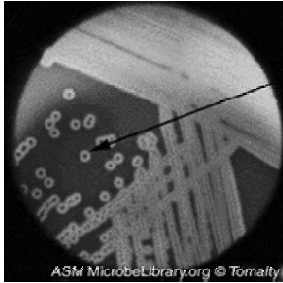
### Streptococci/Enterococci - General Description

- Pyogenic pathogens - nonmotile, catalase negative, Gram positive cocci in chains
- Heterogeneous group that cause a diversity of different diseases
- Enterococci, formerly streptococci, established as separate species based on DNA homology studies

### Classification Systems for Streptococci

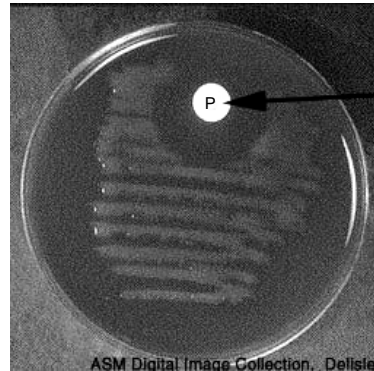
- Hemolysis on blood agar plates
  - *S. pyogenes* is  $\beta$  hemolytic (complete)
  - Viridans streptococci are  $\alpha$  hemolytic (incomplete)
  - Enterococci are  $\gamma$  hemolytic (no hemolysis)
- Lancefield grouping based on group specific carbohydrate antigens. Most  $\beta$  and some  $\alpha$  hemolytic streptococci can be typed by this method
- Biochemical properties
  - Catalase negative, facultative anaerobes

## Beta Hemolysis



Note the clear zone of beta-Hemolysis surrounding the streptococcal colonies when grown on blood agar

ASM MicroLibrary.org © Tomalty



optochin disk

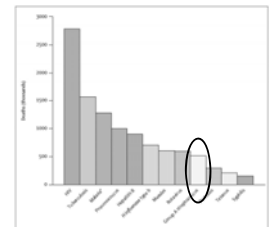
ASM Digital Image Collection, Delisle

## Alpha Hemolysis



## Global Impact of Group A Streptococcus (GAS) Disease

- There are >18 million cases of invasive GAS disease with 517,000 deaths/year
- The poor are disproportionately affected – crowding, hygiene, housing
- > 600 million cases of GAS pharyngitis annually
- Prevalence of rheumatic heart disease 15.6 million with 282,000 new cases/year
- Pyoderma 111 million cases



Estimated global mortality - 2002

Carapetis et al., 2005

## Identification of Streptococci

### CATALASE TEST

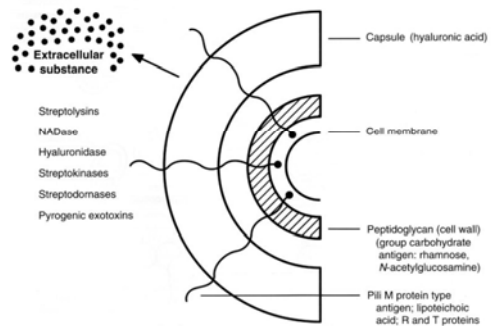
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Streptococcaceae

### Distinguishing tests

|                       | Disks    |            | Ability to Grow in: |              |
|-----------------------|----------|------------|---------------------|--------------|
|                       | Optochin | Bacitracin | 6.5% NaCl           | Bile esculin |
| <i>S. pneumoniae</i>  | S        | R          | -                   | -            |
| <i>S. pyogenes</i>    | R        | S          | -                   | -            |
| <i>E. faecalis</i>    | R        | R          | +                   | +            |
| Nonenterococcal Gp D  | R        | R          | -                   | +            |
| Viridans streptococci | R        | R          | -                   | -            |

## Structural Components of Group A Streptococci



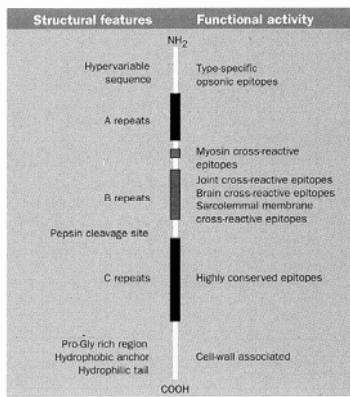
### The Role of M Protein in Disease

- Antigenic variations in M proteins are used to type Group A streptococci (> 80 types)
  - Pharyngitis and impetigo strains differ in gene sequence
- Antibody against M protein is durable and protective but is type-specific
- Strains lacking M protein are avirulent
- M protein is anti-phagocytic, inhibiting activation of complement via the alternate pathway
- M protein positive strains multiply rapidly in fresh human blood
- Vaccine strategies have focused on both the variable and conserved regions of the M protein

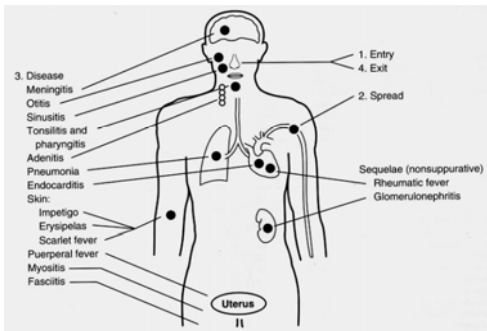
### *Streptococcus pyogenes*

#### Pharyngitis

A 9 year old boy develops fever, chills, a sore throat and swollen glands. On physical examination he is febrile to 103° and has an erythematous (red) pharynx with exudates visible on his posterior pharynx and palatal petechiae. He has enlarged anterior cervical lymph nodes and his WBC count is elevated. The rest of his exam is unremarkable.



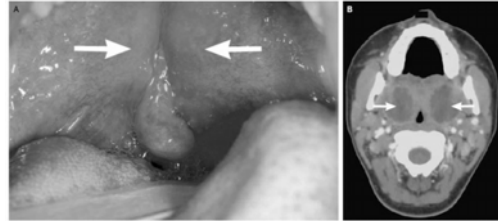
### Diseases Caused by *S. pyogenes*



## Pathogenesis of Streptococcal Pharyngitis

- Bacteria are spread by droplets or nasal secretions. Crowding increases the risk of spread
- Strains rich in both M protein and hyaluronate appear to be more easily transmitted
- Streptococci adhere to epithelial cells using adhesins - protein F1 and lipoteichoic acid
- Colonization of the oropharynx involves the formation of bacterial aggregates or micro-colonies that promote survival
- Susceptibility to infection is determined by the presence of type-specific antibody to M protein

## Peritonsillar Abscess



## Epidemiology of Group A Streptococcal Pharyngitis

- Humans are the natural reservoir
- Primarily seen in 5-15 year olds
- More common in temperate/cold climates
  - Occurs in the winter, early spring
- Different strains (M-protein types) are generally responsible for pyoderma and pharyngitis
- There can be relatively rapid changes in prevalent M type strains in different areas
- Asymptomatic pharyngeal carriage is relatively common

## Diagnosis

- As noted clinical criteria for streptococcal pharyngitis of limited value
- Culture remains the "gold standard" although a positive culture may also reflect colonization
- Rapid streptococcal antigen detection kits based on carbohydrate recognition are highly specific
  - Specific but not sensitive - so treat if positive, confirm if negative
- Streptococcal antibody test (e.g., anti-streptolysin O) reflect past, not present, infection

## Clinical Features of Group A Streptococcal Pharyngitis

- Difficult to distinguish from pharyngitis caused by other pathogens
  - The most common cause of bacterial pharyngitis in children
  - Overall responsible for a small percentage of cases of pharyngitis seen by physicians
- Findings suggestive of GpA strep: sore throat sudden onset, fever, pain with swallowing, headache, lymphadenitis, tonsillar exudates, soft palate petechiae
- Findings not suggestive of GpA strep: conjunctivitis, coryza, cough, diarrhea
- Suppurative sequelae - abscess, sepsis, dissemination

## Nonsuppurative Sequelae of Pharyngitis

- Rheumatic fever: syndromic diagnosis made using the Jones criteria
  - Carditis, polyarthritis, erythema marginatum, subcutaneous nodules, chorea (+ minor criteria)
- Pathogenesis believed to involve "molecular mimicry"
  - Cross reactive epitopes with myosin and M protein
- Glomerulonephritis:
  - Immunologically mediated damage perhaps resulting from streptococcal antigens that cross react with kidney tissue

### Impetigo - Pyoderma

A 3-year old boy presents with a rash on his face. The lesions started as small pustules that progressed to thick "honey"-crusted lesions on his face. There is a large primary lesion by his nose and several satellite lesions on his face. His mother states that he was scratching a mosquito bite there just before the rash started.



### Necrotizing Fasciitis Due to Group A Streptococcus



### Pathogenesis and Epidemiology of Streptococcal Pyoderma

- Primarily seen in 2-5 year olds
- Pyoderma is most commonly encountered in economically disadvantaged populations
  - Influenced by climate and hygiene
- Cutaneous colonization (prior to injury) leads to autoinoculation at sites of injury
- Strains differ from those that cause pharyngitis although pharyngeal carriage of these strains also occurs
- Complications rare: lymphadenitis, immune-complex glomerulonephritis

### Treatment/Prevention of *S. pyogenes* Infection

- The species remains exquisitely sensitive to penicillin
- The use of antibiotics that are protein synthesis inhibitors (e.g. clindamycin) that inhibit protein synthesis may improve outcome
- Soft tissue infections often require surgical debridement
- Intravenous immunoglobulin may also have a beneficial role
- Prophylactic antibiotics
- Vaccines - under investigation

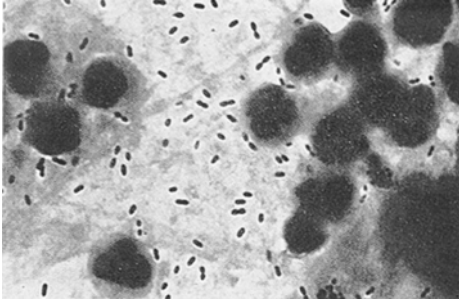
### Streptococcal Toxic Shock Syndrome

- There is concern that the number of severe GAS infections has increased.
- Pyrogenic exotoxins A-C have been implicated.
- Superantigen-mediated disease
- Differs from *S. aureus* TSS because of the frequent presence of infection
- Presentations with necrotizing fasciitis appear to be linked with specific M types

### *Streptococcus pneumoniae*: Clinical Scenario

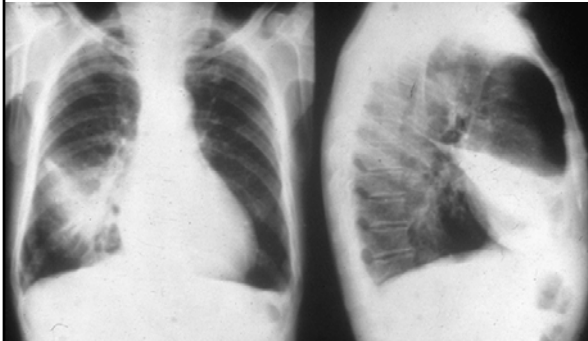
A 33 year old HIV positive male develops the sudden onset of fever with pleuritic chest pain and cough. He begins producing rusty-colored sputum. His CXR reveals a right middle lobe lobar pneumonia and his sputum Gram stain shows numerous neutrophils with Gram positive lancet-shaped diplococci. This is the second such episode in the past year. The patient was recently diagnosed with HIV and has a 10 year history of smoking.

### Sputum Gram Stain

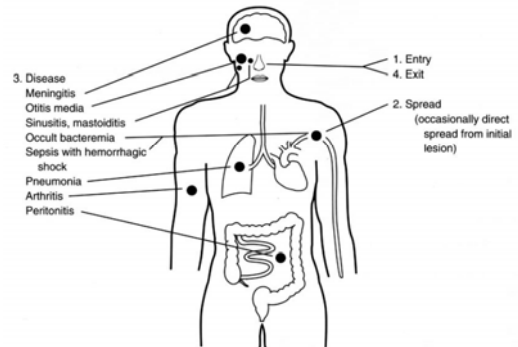


### Epidemiology of Pneumococcal Disease

- Primarily causes disease at the extremes of age (<2 and >65)
- Colonizes the nasopharynx in 5-10% of adults and 20-40% of children
- Transmitted by extensive close contact, increased risk in daycare and military centers, prisons, homeless shelters
- Invasive disease in adults is increased in winter
- Factors that increase the risk of infection: defective antibody or complement formation, antecedent respiratory infection, smoking, HIV infection, COPD
- Mortality remains high despite the availability of effective antibiotics - approximately 17% in bacteremic pneumonias - >65% occurring within 3 days of culture



### Diseases Caused by *S. pneumoniae*



### Description of *Streptococcus pneumoniae*

- Gram positive often lancet-shaped diplococci
- Form  $\alpha$  hemolytic colonies on blood agar plates
- Encapsulated - covalently bound to peptidoglycan
  - 90 serotypes, basis for type-specific immunity
- Naturally competent - i.e. uptake of naked DNA
- Teichoic acid containing phosphorylcholine C-polysaccharide is virtually unique to pneumococci
- Adhesins: choline-binding proteins, pneumococcal surface adhesin A

### Pathogenesis of Pneumococcal Pneumonia (1)

- Nasopharyngeal colonization involves two phenotypes opaque and transparent (the latter can persist)
  - Specific PSA-A and glycoconjugate receptors
- The capsule is antiphagocytic. Anticapsular antibody is protective. Colonization can lead to formation of type-specific antibody
- Respiratory infection develops as a result of aspiration of nasopharyngeal secretions
- Pneumococci adhere to alveolar type II cells and initiate an inflammatory response

## Pathogenesis of Pneumococcal Pneumonia (2)

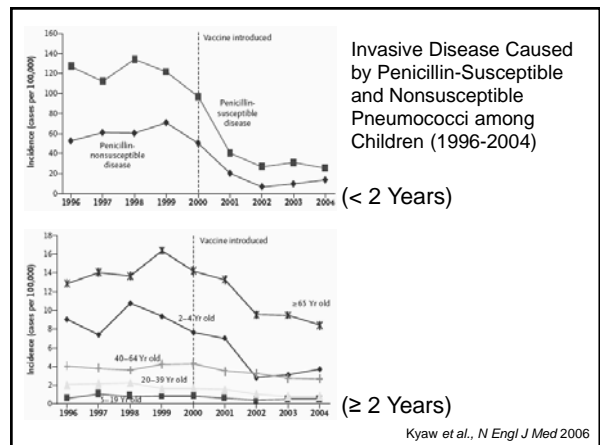
- The **cell wall**, rather than the capsule is responsible for the inflammatory response
- Congestion: induction of fluid accumulation, IL-1 release
- Red hepatization: migration of PMNs, leakage of RBCs, tissue factor expression, increased procoagulant activity
- Gray hepatization: Macrophage recruitment, fibrin deposition.
- Resolution of pneumonia starts with development of anticapsular antibody
- If the infection is not contained, the pneumococcus can spread to other sites such as joints or the meninges

## Prevention of Pneumococcal Disease

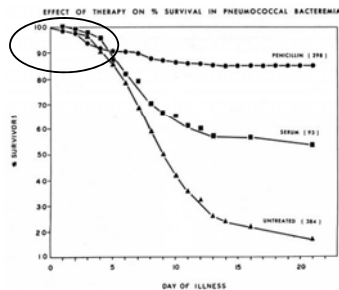
- Rationale: Early South African vaccine studies, Austrian bacteremia data, emerging antimicrobial resistance
- Types of vaccines
  - Polysaccharide (23 types) - T cell independent
  - Polysaccharide protein conjugate vaccine (7 types) T cell dependent, more effective in infants  $\leq 2$  years of age

## Treatment of Pneumococcal Infections

- Strains have become increasingly resistant to penicillin as well as to other antimicrobial agents
- Need to test for antimicrobial susceptibility and, in settings where there is a high incidence of penicillin resistance, use other agents as initial empirical therapy.



## Impact of Therapy on Survival in Pneumococcal Pneumonia



## Summary (1)

- Streptococci are a diverse group of species that cause a variety of different diseases
- *S. pyogenes* are primarily responsible for cutaneous and pharyngeal infections. More severe disease is associated with toxin producing strains and particular M serotypes
  - The M protein, the hyaluronate capsule, and the pyrogenic exotoxins are the most important virulence determinants
- Development of a vaccine has been hampered by the large number of M serotypes and the concern about epitopes that cross react with human tissue

## Summary (2)

- *S. pneumoniae* is among the most common causes of pneumonia, otitis and meningitis
- Capsules are antiphagocytic and capsular antibody induces protection against subsequent infection
- Peptidoglycan is largely responsible for the brisk inflammatory response induced during infection
- Antimicrobial resistance has become a serious concern in the management of these infections