Rapid diagnosis of strep pharyngitis: Update for clinicians

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Conflict of Interest

Today’s Webinar is sponsored by Fisher Healthcare and Alere

The presenter has no other affiliations to declare
Segway
Learning Objections:

We will review:

• Signs and symptoms of strep pharyngitis
• Complications of strep pharyngitis
• Role of Strep Score in diagnosis
• Benefits of expedited diagnosis and treatment
• Advantages/Disadvantages of newest “high tech” POC rapid strep tests
Incidence of strep pharyngitis

• In the United States there are 15 million visits to primary care physicians for pharyngitis each year

• 20% to 30% of pharyngeal infections in children are attributed to group A streptococcus (GAS)

• In contrast, only 5% to 15% of throat infections in adults are caused by GAS

• Over 600 million cases of GAS pharyngitis worldwide every year

Pearl!

*Children miss a mean of 1.9 days (range: 0-7 days) of school/day care, and 42% of parents miss a mean of 1.8 days of work. Through extrapolation from this experience, the total cost of group A streptococcal pharyngitis among children in the United States ranges from $224 to $539 million per year.*

Strep pyrogenes (Group A Strep)

Streptococci are catalase-negative and gram positive non-motile, non-sporeforming bacteria

Glossy, grayish-white, translucent colonies, large zone beta hemolysis on blood agar plate

Group A streptococci have several virulence factors and cause a number of diseases
Pathogenesis

Virulence factors of group A streptococci include:

(1) M protein for attachment

(2) a hyaluronic acid capsule that inhibits phagocytosis

(3) other extracellular products, such as pyrogenic (erythrogenic) toxin, which causes the rash of scarlet fever; and

(4) streptokinase, streptodornase (DNase B), and streptolysins

(5) protein F, which is a fibronectin binding protein that allows it to adhere to respiratory epithelial cells.

Pearl!
Not only does Streptococcus pyogenes adhere to its host cells, but it also invades them. Laboratories have shown that “group A streptococci have the potential to invade human epithelial cells at frequencies equal to or greater than classical intracellular bacterial pathogens.” There are two proteins necessary for invasion, which are the M protein and the fibronectin-binding protein.

Cell wall:
Outer layer: Protein and lipoteichoic acid
Middle layer: Group specific carbohydrate
Inner layer: Peptidoglycan
Laboratory Diagnosis

1) Diagnosis is based on cultures from clinical specimens

2) Produces characteristic colonies on blood agar plate with beta (complete, clear) hydrolysis

3) Incubation in Todd-Hewitt broth for few hours increases sensitivity of detection

4) Latex agglutination serologic methods can detect group A antigen, confirmation by PYR test if needed

5) Bacitracin sensitivity presumptively differentiates group A from other β-hemolytic streptococci (B, C, G)

Pearl!
In 1928, Rebecca Lancefield published a method for serotyping *S. pyogenes* based on its M protein. Later, in 1946, Lancefield described the serologic classification of *S. pyogenes* isolates based on their surface T antigen. Four of the 20 T antigens have been revealed to be pili, which are used by bacteria to attach to host cells. Over 220 M serotypes and about 20 T serotypes are known.
Laboratory Diagnosis
Clinical presentation: Strep Pyrogenes

• Can be normal respiratory flora

• **Pharyngitis**

• Scarlet Fever

• Impetigo

• Pneumonia

• Endocarditis

• Septic Arthritis

• Mastoiditis

• Necrotizing fascitis or cellulitis

• Peri-rectal strep cellulitis

**Pearl!**

*A study in Norway assessed transmission of GAS in 110 households that included at least 1 member with symptoms of pharyngitis for less than a week and a positive throat culture for GAS. In 27% of these households, another member developed GAS pharyngitis within 4 weeks of onset of symptoms in the index case. Transmission was more likely to occur in larger households and in those with children.*

Clinical presentation: Strep Pharyngitis

• Associated with crowding and predominates in Winter, Spring and Fall, rare in Summer

• Incubation period of 2 to 5 days

• Symptoms can resolve in a week without treatment

• Frequent history of exposure

• Characterized by sore throat, fever, cervical adenopathy, headache, abdominal pain (does not include cough, rhinorrhea, conjunctivitis, diarrhea, or myalgias)

• In young children (streptococcosis) occurs in outbreaks in daycares

• Varying severity based on host, strep serotype, age – some patients are ill appearing, others have mild illness
Clinical presentation: Strep Pharyngitis

- Varying severity based on host, strep serotype, age – some patients are ill appearing, others with mild illness
- Incubation period of 2 to 5 days
- Characterized by sore throat, fever, cervical adenopathy, headache, abdominal pain (does not include cough, rhinorrhea, conjunctivitis, diarrhea, or myalgias)
- In young children 3 and younger (streptococcosis) occurs in outbreaks in daycares, rhinorrhea common
Sequelae

Purulent sequelae (less than 1%)

- Lymphadenitis
- Peritonsilar abscess
- Streptococcal Toxic Shock Syndrome
- Sepsis
- Erysipelas
- Osteomyelitis
- Peri-rectal strep cellulitis
- Sinusitis
- Otitis Media
Sequela e

Immunogenic Sequelae

• Acute glomerulonephritis

• Rheumatic fever - prevented by antibiotic treatment

• Pandas (Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) (disputed)

In industrial countries Rheumatic Fever is extremely rare!  << 1 per 100,000
Strep pharyngitis: Carriage

• Up to 10-15% of pediatric population may be “carriers” of strep – have no symptoms and are of low risk of transmitting infection to others.

• Can confound diagnosis when other causes of pharyngitis are present i.e. – influenza, mononucleosis,

• Identification: Carriers have no rise in anti-strep titers

• In some circumstances – Carrier state can be eliminated, often temporarily
Diagnosis

Clinical suspicion based on history of exposure, signs and symptoms and Rapid Tests

Rapid Tests can be falsely negative if:
• Taken too early in the course of illness
• Inadequate specimen obtained

False positive if:
• Patient is a carrier
Strep Score

• Originated by Dr. Centor in 1981 to help identify patients likely to have strep pharyngitis

• Based on fever, cervical adenopathy, inflamed throat and absent cough

• Overall a high strep score has poor correlation with culture

• Later modified in 2004 by McIsaac to include age of patient as likelihood of Group A Strep is lower in adults compared to children


## Strep Score: Utility and Controversy

<table>
<thead>
<tr>
<th>Modified Centor Score</th>
<th>Point</th>
</tr>
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<tbody>
<tr>
<td>Temp over 38 °C or 100.4 °F</td>
<td>1</td>
</tr>
<tr>
<td>No Cough</td>
<td>1</td>
</tr>
<tr>
<td>Tender Anterior Cervical Nodes</td>
<td>1</td>
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<tr>
<td>Tonsilar swelling or exudate</td>
<td>1</td>
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<tr>
<td>Age 3 – 14 years</td>
<td>1</td>
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<tr>
<td>Age 15- 44</td>
<td>0</td>
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<td>Age over 44</td>
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<table>
<thead>
<tr>
<th>Total Score</th>
<th>Risk of group A strep infection (%)</th>
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<td>Over 4</td>
<td>51-53</td>
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<tr>
<td>3</td>
<td>28-35</td>
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<tr>
<td>2</td>
<td>11-17</td>
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<tr>
<td>1</td>
<td>5 -10</td>
</tr>
<tr>
<td>0</td>
<td>1 – 2.5</td>
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<tr>
<td>History of Strep exposure</td>
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<td>Absent Myalgia</td>
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<td>&gt;&gt; 51-53</td>
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Strep Score: Clinical Utility

Old days – Culture and treat pending culture

Current strategy 1- Treat patients with a Centor score of 3 or 4 or higher
Current strategy 2 – Test children with Centor score of 2 or above or exposure, treat all with pos Rapid Antigen Detection Test (RADT) and perform backup test.
Current strategy 3 – Perform rapid tests on all children/adults with Modified Centor/Schuman score of 2 or 3 and don’t perform backup culture (except when suspicious or quality of swab suspected)
Current strategy 4 – Rapid test all adults with score 2 and above and treat if positive without backup culture

Pearl!
Practices should determine the correlation of their method of strep detection compared with culture, and determine whether a back up culture should be performed!
Neg RADT: Need for back up Culture

Obtain back up culture, children
- American Academy of Pediatrics
- Infectious Disease Society of America
- American Heart Association

No back up culture, adults
- American Heart Association
- Infectious Disease Society of America
- European Society for Clinical Microbiology and Infectious Diseases
- (Treatment based on severity of disease)

In England, Scotland, Belgium, or the Netherlands, physicians will not use a diagnostic test, and the decision to prescribe antibiotic will depend mainly on the patient’s illness severity.
Advantages of Rapid Diagnosis

• Limits spread within families and schools
• Limits missed school and work days
• Expedites resolution of symptoms, modestly
• Decreases incidence of suppurative complications
• Prevents Rheumatic Heart Disease *, not glomerulonephritis
• Prevents need to contact patients with results, call in prescriptions

Pearl!

Children who receive the first dose of antibiotic by 5 PM, can return next day if symptom free.

Acute rheumatic fever is no longer a nationally notifiable disease in the United States, and its annual incidence in the continental United States declined in the late 20th century to approximately 0.04–0.06 cases per 1,000 children.
Obtaining the specimen
Non-strep pharyngitis

Group C and G strep
Arcanobacterium haemolyticum
Neisseria gonorrhea
Corynebacterium diptheriae
Fusobacterium necrophorum
Grancisella tularensis
Yersinia pestis
Yersinia enterocolitica
Adenovirus
Herpes simplex
Coxackievirus
Influenza
EBV
HIV
Mycoplasma
Chlamydia
Rapid diagnosis

Over 49 million rapid GAS antigen tests are performed in the USA every year!
Rapid Diagnosis

First rapid strep were latex agglutination assays
Rapid Diagnosis

Optical Immunoassay (OIA)

No longer available, and not Clia 88 waived when it was available
Rapid Diagnosis

Most common today – Lateral flow immunoassay

Cost - $3 per test, Consumers can purchase home kits, Reimbursement $15-$20, 7 minute test

Sensitivities 60- 95%

Limit of detection $10^5$ to $10^7$ cfu/ml

CPT 87880QW
Lateral flow immunoassays

Lateral Flow Assay Architecture

- Analyte
- Antibodies conjugated to Gold Nanoparticles
- Capillary Flow
- Sample Pad
- Conjugate Pad
- Membrane
- Wicking Pad
- Test Line (Antibody) (e.g., anti-IgG Antibody)
- Control Line
- Test Line (Positive)
- Control Line (Valid Test)
Some weak positives difficult to see!
Rapid Diagnosis

Veritor from BD Diagnostics

Cost - $4-6 per test, Reimbursement $15-$20, 7 minute test, Reader costs $300

Limit of detection $10^4$ to $10^5$ cfu/ml

CPT 87880QW
Rapid Diagnosis

Sofia Strep A FIA – Quidel Corporation

Cost - $10 per test, Reimbursement $15-$20, 7 minute test, Reader costs $4500,

Limit of detection $10^3$ to $10^4$ cfu/ml

CPT 87880QW
Rapid Diagnosis

Alere iStrep A - Isothermal PCR

Cost - $26 per test, Reimbursement $48, 8 minute test, Reader Free (600 tests per year)

Limit of detection 10 to $10^2$ cfu/ml

87651QW
Rapid Diagnosis

Alere iStrep A

To perform the assay, the Sample Receiver and Test Base are inserted into the Alere™ i Instrument. The sample is added to the Sample Receiver and transferred via the Transfer Cartridge to the Test Base, initiating bacterial lysis and target amplification.

The reaction tubes in the Test Base contain the reagents required for Group A Strep bacterial lysis and the subsequent amplification of the target nucleic acid and an internal control. Alere™ i Strep A utilizes templates (similar to primers) for the specific amplification of DNA from Group A Strep and a fluorescently-labelled molecular beacon designed to specifically identify the amplified nucleic acid target.
Rapid Diagnosis

Roche Liat POC PCR Rapid Strep

Cost - $26 per test, Reimbursement $48, 20 minute test, Reader $10,000

Limit of detection $10$ to $10^2$ cfu/ml

87651QW
PCR!
## Comparison of high tech strep pocs

<table>
<thead>
<tr>
<th>Strep Test</th>
<th>Cost/Test</th>
<th>Reimbursement</th>
<th>CPT Code</th>
<th>Limit of Detection</th>
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<tr>
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<td>BD Veritor</td>
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<td>$10^4 to $10^5 cfu/ml</td>
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<td>Quidel Sofia</td>
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The Future of Rapid Antigen Tests?
Questions?