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WHAT SHOULD WE DO WITH THAT THROAT SWAB?

Diagnostic Testing for Throat Swabs from Patients with Pharyngitis

NAAT-only Testing—No

- Focusing solely on the detection of GAS in all settings is not optimal patient care

NAAT-only Testing—Yes

- Other testing options are limited
- NAATs are poised to replace antigen detection and culture for the detection of GAS pharyngitis

Pritt BS, Patel R, Kirn TJ, Thomson RB Jr.

Point-Counterpoint: A Nucleic acid amplification test for *Streptococcus pyogenes* should replace antigen detection and culture for the detection of bacterial pharyngitis.

J Clin Microbiol. 2016 Jul 20. pii: JCM.01472-16. [Epub ahead of print]

GAS

- *Streptococcus pyogenes* (β -hemolytic group A streptococci)
 - 25% of cases in adults
 - nearly 40% of cases in children
- Most cases mild and self-limited
- Sequelae
 - Suppurative (invasive infection—peritonsillar abscesses, otitis media, mastoiditis, cervical lymphadenitis, pneumonia)
 - Non-suppurative (rheumatic fever and glomerulonephritis)
- Antibiotics are frequently administered

Antibiotic Treatment

Treat-Yes

- Reducing symptoms and symptom duration
- Prevent rheumatic fever and poststreptococcal glomerulonephritis and other complications
- Minimize spread of infection to others

Treat-NO

- Relatively small effect on reducing symptoms and symptom duration
- Rheumatic fever and poststreptococcal glomerulonephritis are rare in certain populations
- Disruptive to normal microbial flora
- Other adverse events associated with antibiotics

Common Pathogens of Pharyngitis

- Group A Streptococcus
 - 5-15% of acute pharyngitis cases in adults
 - 15-30% of all cases of pharyngitis in children aged 5-15 yrs
- Groups C and G β -hemolytic streptococci
- *Arcanobacterium haemolyticum*
- *Neisseria gonorrhoeae*
- *Corynebacterium diphtheriae*
- *Fusobacterium necrophorum*
- (*Chlamydia pneumoniae*, *Francisella tularensis*, *Mycoplasma pneumoniae*)

- Viral (~50%)
- Epstein-Barr virus (EBV)
- Herpes Simplex virus (HSV) [usually Type 1]
- Cytomegalovirus (CMV) CMV
- HIV

Non-Group A β -hemolytic Streptococci

Groups C and G β -hemolytic streptococci

- “Large colony producers”
 - *S. dysgalactiae* subspecies *equisimilis*
 - *S. equi* subspecies *zooepidemicus*
 - *S. canis*
 - NOT Anginosus group streptococci
- Many healthcare providers consider these organisms to be of significance and base therapeutic decisions on their detection.
- Rare cases of post-streptococcal glomerulonephritis after infection with these species have been reported

Arcanobacterium haemolyticum

- Most often in teenagers and young adults
- Often found to cause a highly suggestive scarlatina-form rash in some patients
- Serious invasive infections have been reported: peritonsillar and pharyngeal abscess, bacteremia and pneumonia.

Fusobacterium necrophorum

- Lemierre’s syndrome: necrotizing tonsillopharyngitis followed by bacteremia, septic thrombophlebitis of the internal jugular vein and septic pulmonary emboli.
- Endemic pharyngitis in adolescents and young adults in the absence of Lemierre’s syndrome at a rate similar to GAS
- Estimated to cause Lemierre’s syndrome at a higher incidence than that at which GAS causes acute rheumatic fever

Looking for *F. necrophorum*

Anaerobic Culture-YES

- Throat infection could be a prelude to Lemierre's syndrome.
- Limited data to support utility

Anaerobic Culture-No

- Too resource intensive for lab
 - Requires additional media
 - Anaerobic isolation and Identification procedures
- Limited data to support utility

Viral Pharyngitis

- Respiratory viruses are the most common cause of pharyngitis in both adult and pediatric populations; however, it is unnecessary to define a specific etiology in patients with pharyngitis due to respiratory viruses because there exists no pathogen-directed therapy for these agents.
- Herpes simplex virus (HSV), human immunodeficiency virus (HIV), and Epstein-Barr virus (EBV) may also cause pharyngitis.
- Because of the epidemiologic and clinical implications of infection due to HSV, HIV, and EBV, circumstances may arise in which it is important to attempt to determine if an individual patient's infection is caused by one of these 3 agents.

Clinical Criteria

- Centor Criteria
- Likelihood of a sore throat being due to bacterial infection in adults
 - Tonsillar exudate/swelling
 - Cervical lymphadenopathy
 - Absence of cough
 - Fever
- 3 or 4 of Centor criteria are met, the positive predictive value is 40% to 60%.
- The absence of 3 or 4 of the Centor criteria has a fairly high negative predictive value of 80%.
- Modified criteria=risk based
- Include an age component, along with "tonsillar swelling"
 - Rare in patients under 3 and less common in older adults
- Clinical prediction rules do not differentiate Group A streptococci from viral pharyngitis or non-Group A streptococci
- No significant correlation between clinical symptoms and colony counts

Guidelines

- American College of Physicians, American Academy of Family Physicians, American Society of Internal Medicine, CDC
 - Clinical (Centor) criteria determines use of diagnostic testing
- The Infectious Diseases Society of America and the American Heart Association
 - Bacterial cultures for children and adolescents with negative RADT results
 - No reflex cultures for adults with negative RADT results, given the lower incidence of *S. pyogenes* pharyngitis and rheumatic fever in this population
- American Academy of Pediatrics (AAP)
 - Negative RADT results in children need to be confirmed using throat culture unless physicians can guarantee that RADT sensitivity is similar to that of throat culture in their practice
- CAP requirement
 - MIC.22140 Group A Streptococcus Direct Antigen Detection
 - If group A Streptococcus direct antigen testing is performed, confirmatory testing is performed as appropriate on negative samples.
- Food and Drug Administration (FDA)
 - Culture confirmation of negative results required for some RADTs

RADTs

- Rapid antigen detection tests (RADT)
- Commercially available
- Widely used in point-of-care settings
 - ease of use (CLIA waived test)
 - low cost
 - produce rapid results
- High specificity for detection of *S. pyogenes*
- Low sensitivity
 - ranging from 70 to 90%
 - test sensitivity is dependent on the severity of disease, with poorer sensitivity (47 to 65%) in patients with lower modified Centor scores RADTs fail to detect a significant number of adults with GAS pharyngitis

Culture

Pros

- Considered the gold standard
- Can be used to detect other causes of bacterial pharyngitis

Cons

- Volume
- Must be performed in a clinical laboratory
- Labor-intensive
- 24 to 48 hours to generate a result
 - Untreated patient may experience ongoing symptoms
 - Confirmatory culture may cause clinicians to forgo recommended testing guidelines

GAS in Adolescents and Adults

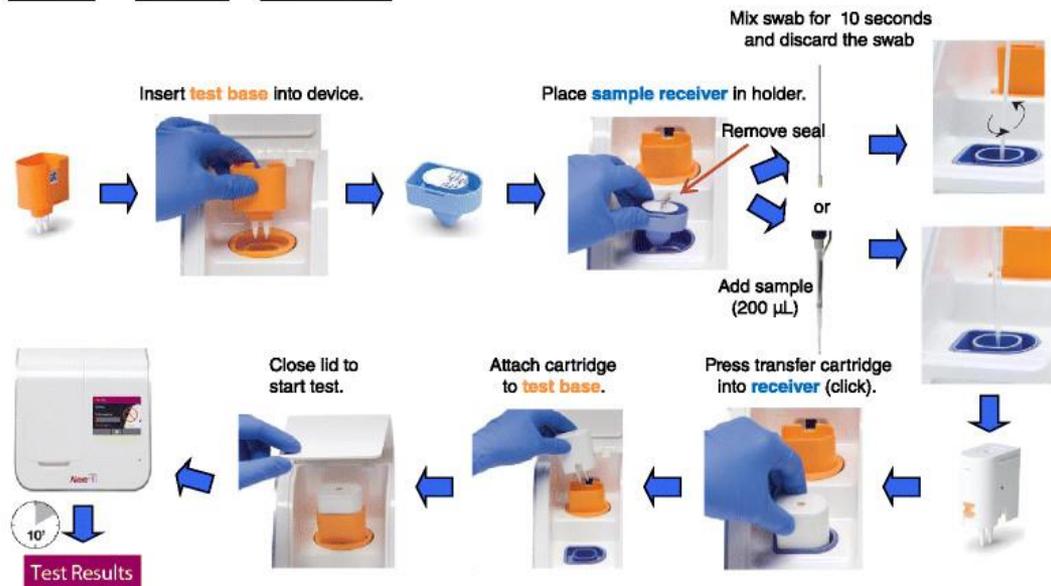
- Assessed the utility of backup cultures in adolescents and adults (>13 years) to test the
- Hypothesis that RADT use alone will miss a substantial number of patients with GAS pharyngitis and associated clinical sequelae that may benefit from treatment.
- Negative RADT and positive GAS culture
- 25,786 patients
- 13.4% RADT positive patients
- 4.8% of negative RADTs were positive for GAS in culture; overall sensitivity for RADTs was 76.3%.

GAS in Adolescents and Adults

- 726 patients
 - absence of cough was noted in 67.6%
 - tender or swollen anterior cervical lymphadenopathy in 51.3%
 - tonsillar swelling or exudate in 47.0%
 - fever in 13.8%
 - 55% of the patients had modified Centor scores ≥ 2
- 77% of cultures had $\geq 2+$ growth
 - disagreement with previous studies suggesting that GAS RADTs are subject to spectrum bias (ie, greater likelihood of a false-negative RADT result when low quantities of bacteria are present)
- 29 patients with negative RADTs had peritonsillar abscesses, 2 patients with rheumatic fever

Rapid POCT Molecular Testing

Alere i



cobas Liat



<https://usdiagnostics.roche.com/en/instrument/cobas-liat.html#how-it-works>

<http://www.alere-i.com/en/index/alere-i-system/how-to-use.html>

GAS NAAT

Pros

- Easy to perform
- Can be performed in many locations
- Sensitive
- Faster TAT compared to bacterial culture
- Rapid and easy-to-use commercial formats
- Timely results to patients
- Definitive and actionable results =streamlined testing

Cons

- Not always interfactable=increased workflow
- Cost of reagents/instrument
- Inability to detect potential pathogens other than GAS.

Cost

- Cost to the laboratory will increase with NAAT and/or comprehensive testing
- Cost to the healthcare system may decrease with better patient management and public health.

Literature Review

- Reliance on clinical presentation alone results in overtreatment, but reliance on rapid antigen testing results in undertreatment.
- Causes of acute pharyngitis other than GAS have been largely ignored when addressing patients presenting with acute pharyngitis.
- Disease frequency, severity and serious sequelae suggest the following approach.
 - Pediatric patients need GAS testing.
 - Adolescents and young adults need, GAS, Groups C and G, and *A. hemolyticum* culture, with testing for *F. necrophorum* to follow as soon as an acceptable test is developed.
- Rigorous outcome studies are needed to demonstrate the benefit of antimicrobial treatment of Group C and G streptococcal, *F. necrophorum*, and *A. haemolyticum* infections.

Moving Forward

- Rapid, syndromic based testing approach to acute pharyngitis, analogous to those that have been implemented for patients with respiratory symptoms, diarrheal illnesses and meningitis/encephalitis
 - 1. Etiologic diagnosis is always known.
 - 2. Therapy is directed, not empiric, favoring antimicrobial stewardship.
 - 3. Complications are prevented, e.g., those following *A. haemolyticum* and *F. necrophorum* infections.
 - 4. Epidemiology is robust, enhancing community and healthcare prevention.
 - 5. Clinical acumen is improved as etiologic answers are known not assumed.
 - 6. Sexually transmitted diseases are identified and contained by education and contact tracing.
- Patient (or parent) collected throat swab (Mayo model)
- Link the filling of a prescription with positive results (Mayo model)

Syndromic Based Testing for Pharyngitis

Etiologies	Pharyngitis GAS PCR	Pharyngitis Culture-Based	Pharyngitis Molecular Syndromic
GAS	X	X	X
Gr C and G Streptococci		X	X
<i>A. haemolyticum</i>		X	X
<i>F. necrophorum</i>		X	X
<i>N. gonorrhoeae</i>		X	X
<i>C. trachomatis</i>			X
HIV			X
Enteroviruses			X
HSV			X
<i>M. pneumoniae</i>			X
<i>C. diphtheriae</i>			X
Respiratory Viruses			X

Summary

- One size does not fit all
- Move in the direction that benefits patient care