

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

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

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 for each episode of strep pharyngitis. 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 - Phoh E, Wessles MR, Goldmann D, et al. Burden and economic cost of group A streptococcal pharyngitis . Pediatrics 2008 Feb;121(2):229-34.

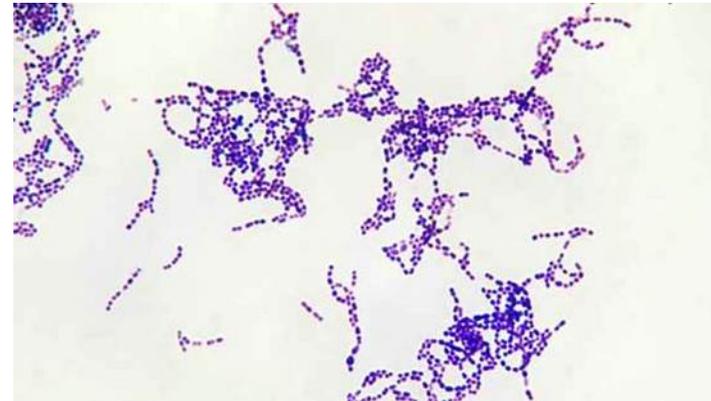


Strep pyogenes (Group A Strep)

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



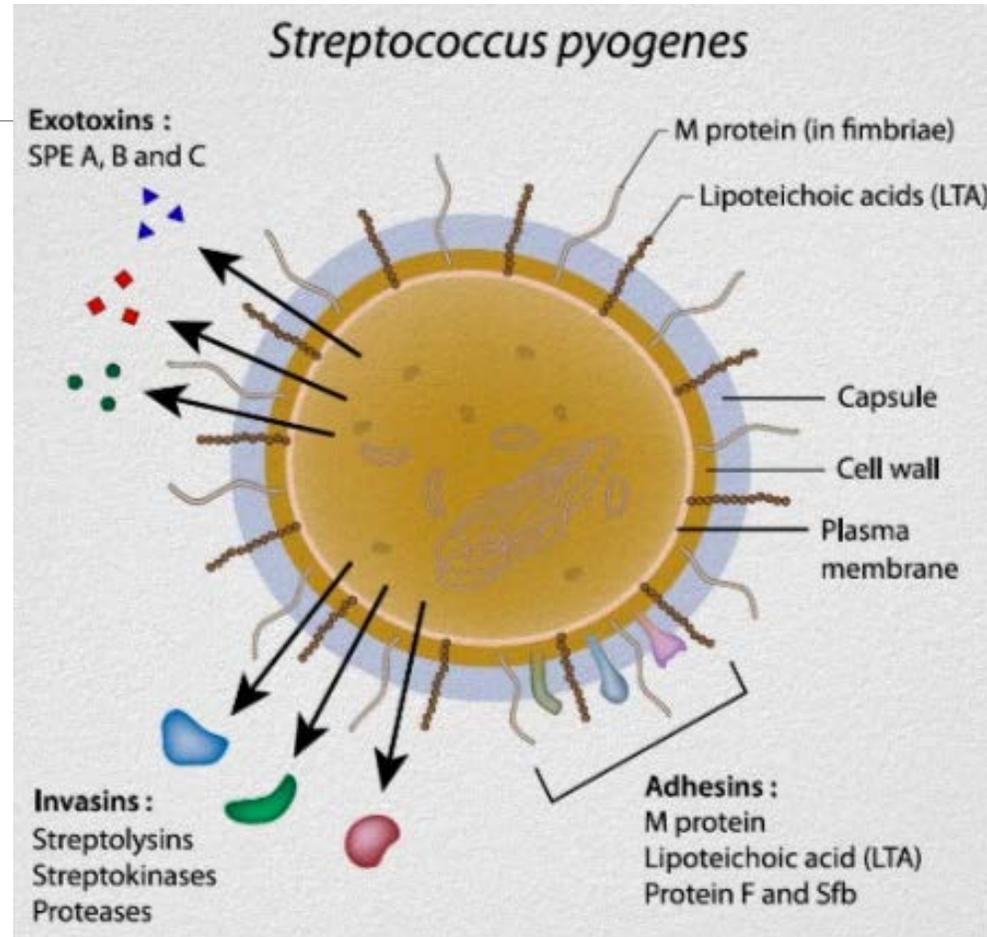
Pathogenesis

Virulence factors of group A streptococci include:

- (1) M protein and Protein F, a fibronectin binding 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
- (4) streptokinase, streptodornase (DNase B), and streptolysins

Cell wall:

- Outer layer: Protein and lipoteichoic acid
- Middle layer: Group specific carbohydrate
- Inner layer: Peptidoglycan



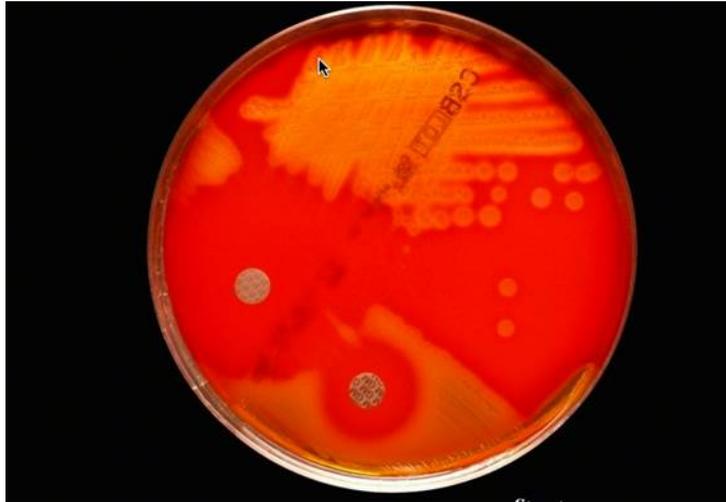
Laboratory Diagnosis

- 1) Diagnosis is based on cultures from clinical specimens
- 2) Requires viable bacteria to grow
- 3) Produces characteristic colonies on blood agar plate with beta (complete, clear) hydrolysis
- 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)

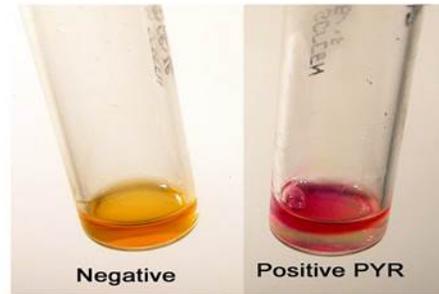
Pearl!

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



PYR Broth Assay



PYR Disk Test



Clinical presentation: Group A Strep

- Can be normal respiratory flora
- **Pharyngitis**
- **Scarlet Fever**
- Impetigo
- Pneumonia
- Endocarditis
- Septic Arthritis
- Mastoiditis
- Necrotizing fasciitis 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

Lindbaek M, Håiby EA, Lermark G, Steinsholt IM, Hjortdahl P. Predictors for spread of clinical group A streptococcal tonsillitis within the household. Scand J Prim Health Care. 2004;22:239-43.

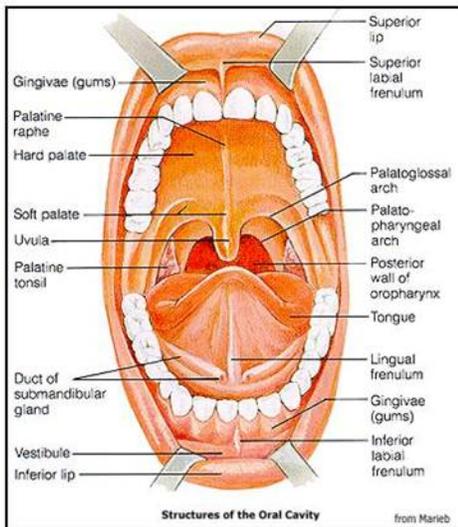
Clinical presentation: Strep Pharyngitis

- 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

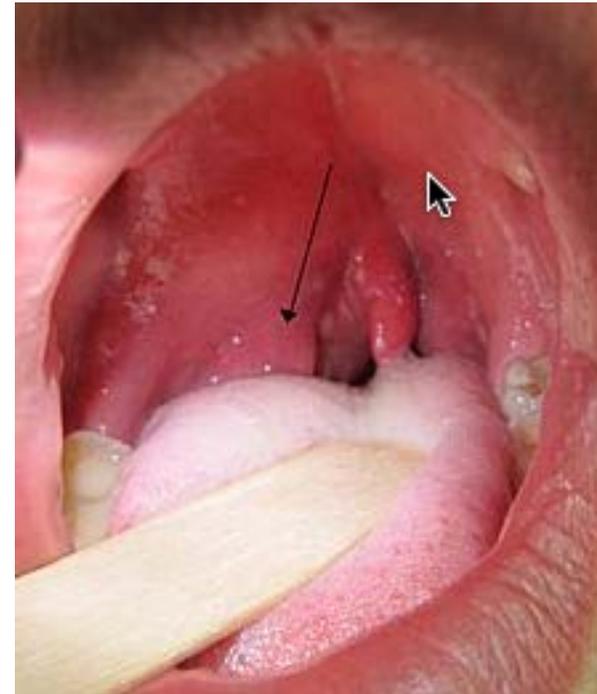




Sequelae

Purulent sequelae (less than 1%)

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



Sequelae

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
- Streptococcus milleri group (SMG) strains present - can express the group A carbohydrate antigen

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

Centor RM, Witherspoon JM, Dalton HP, Brody CE & Link K (1981). The diagnosis of strep throat in adults in the emergency room". Medical Decision Making 1 (3): 239–246.

McIsaac WJ, Kellner JD, Aufricht P, Vanjaka A & Low DE (7 April 2004). Empirical validation of guidelines for the management of pharyngitis in Children and Adults. Journal of the American Medical Association 291 (13): 1587–1595.

Strep Score: Utility and Controversy

Modified Centor Score	Point
Temp over 38 °C or 100.4 °F	1
No Cough	1
Tender Anterior Cervical Nodes	1
Tonsillar swelling or exudate	1
Age 3 – 14 years	1
Age 15- 44	0
Age over 44	-1

Total Score	Risk of group A strep infection (%)
Over 4	51-53
3	28-35
2	11-17
1	5 -10
0	1 – 2.5

Strep Score: Utility and Controversy

Modified Centor/Schuman Score	Point
Temp over 38 °C or 100.4 °F	1
No Cough	1
Tender Anterior Cervical Nodes	1
Tonsillar swelling or exudate	1
Age 3 – 14 years	1
Age 15- 44	0
Age over 44	-1
History of Strep exposure	1
Absent Myalgia	1

Total Score	Risk of group A strep infection (%)
Over 6	>> 51-53
Over 5	> 51-53
Over 4	51-53
3	28-35
2	11-17
1	5 -10
0	1 – 2.5

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.

Neg RADT: Need for back up Culture

Obtain back up culture, children

- American Academy of Pediatrics
- Infectious Disease Society of America
- American Heart Association

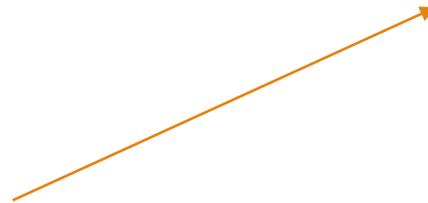
No back up culture, adults

- American Heart Association
- Infectious Disease Society of America

No strep tests at all

- 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 quickly within 24 hours
- Decreases incidence of suppurative complications
- Prevents Rheumatic Heart Disease, not glomerulonephritis
- Prevents need to contact patients with results, call in prescriptions

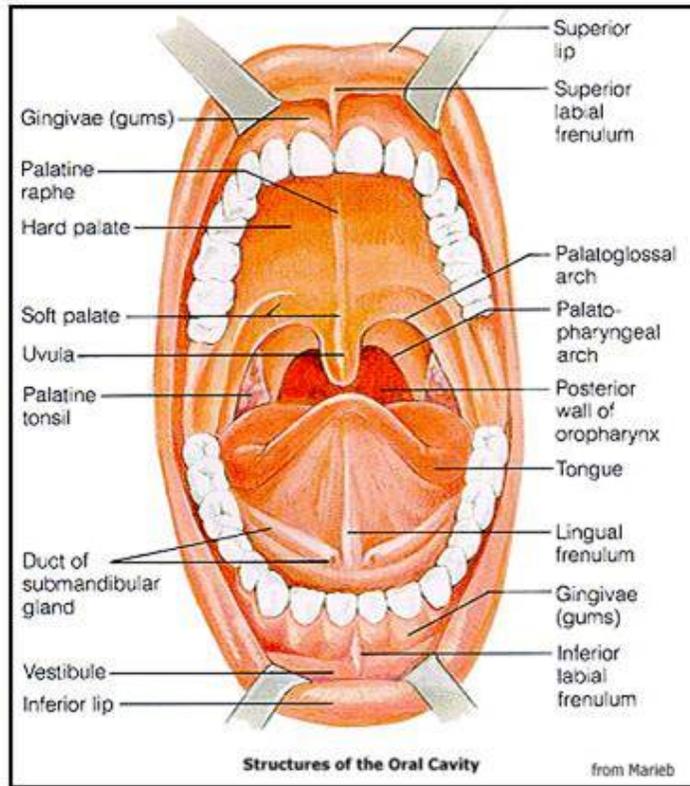
Pearl!

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

All patients were symptom free next day!

Schwartz RH, Kim D, Martin M, et al. A Reappraisal of the Minimum Duration of Antibiotic Treatment Before Approval of Return to School for Children With Streptococcal Pharyngitis. *Pediatr Infect Dis J.* 2015 Dec;34 (12):1304 -2

Obtaining the specimen



Non-strep pharyngitis

Group C and G strep

Arcanobacterium haemolyticum

Neisseria gonorrhoea

Corynebacterium diphtheriae

Fusobacterium necrophorum

Francisella tularensis

Yersinia pestis

Yersinia enterocolitica

Adenovirus

Herpes simplex

Coxsackievirus

Influenza

EBV

HIV

Mycoplasma

Chlamydia

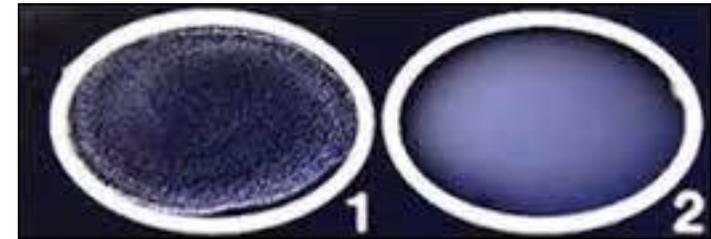
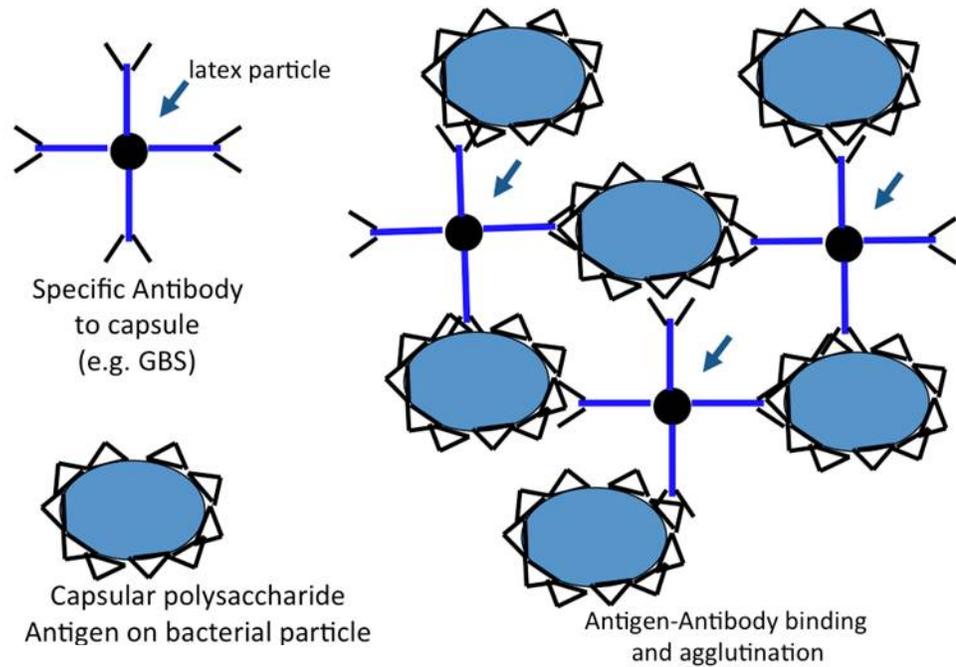
Rapid diagnosis

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

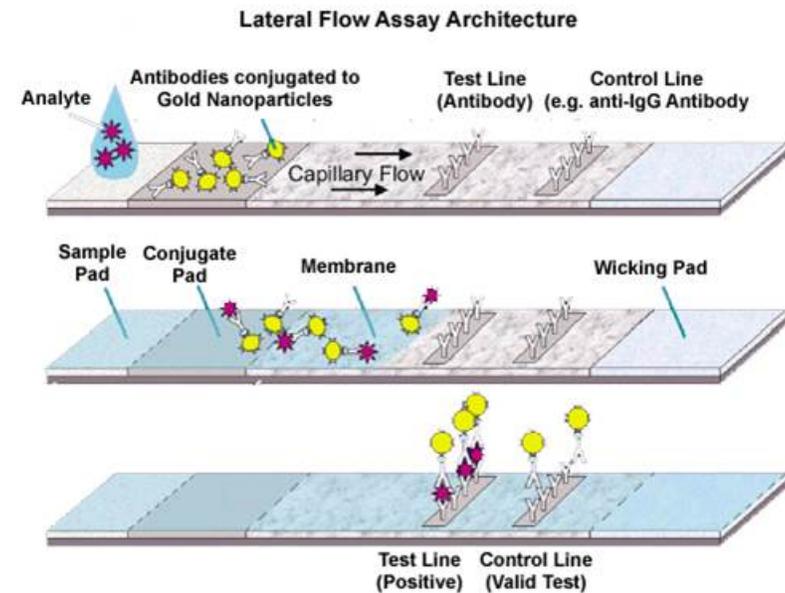
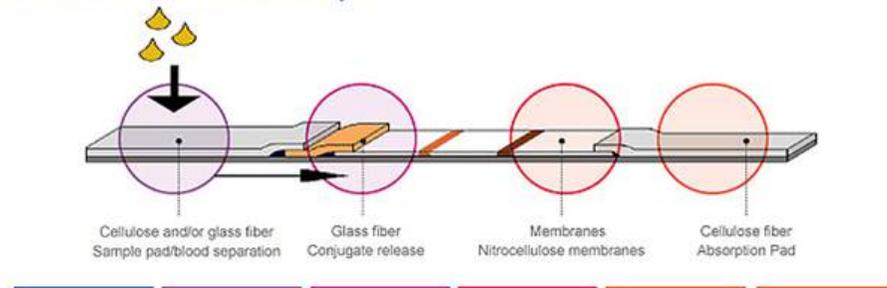
Cost - \$3 per test, Consumers can purchase home kits, Reimbursement \$15-\$20 , 7 minute test

Sensitivities 60- 95%

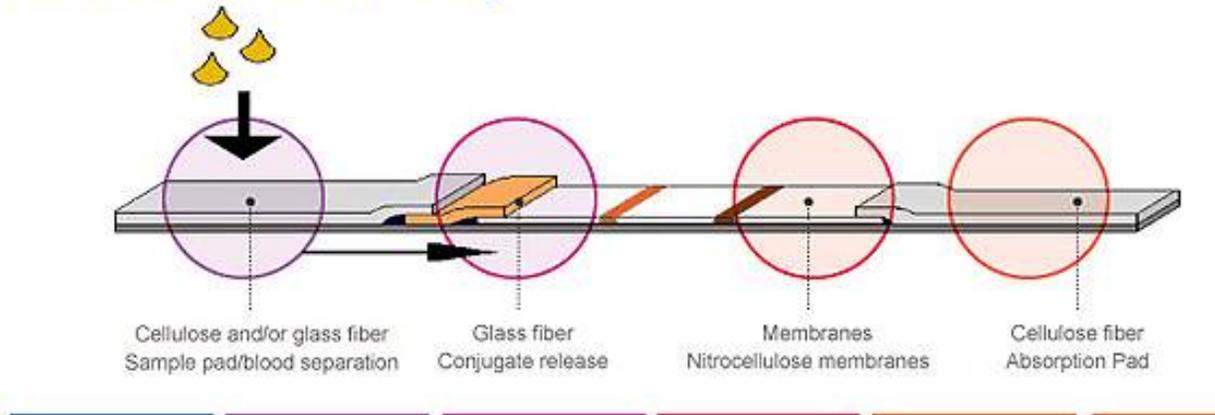
Limit of detection 10^5 to 10^7 cfu/ml

CPT 87880QW

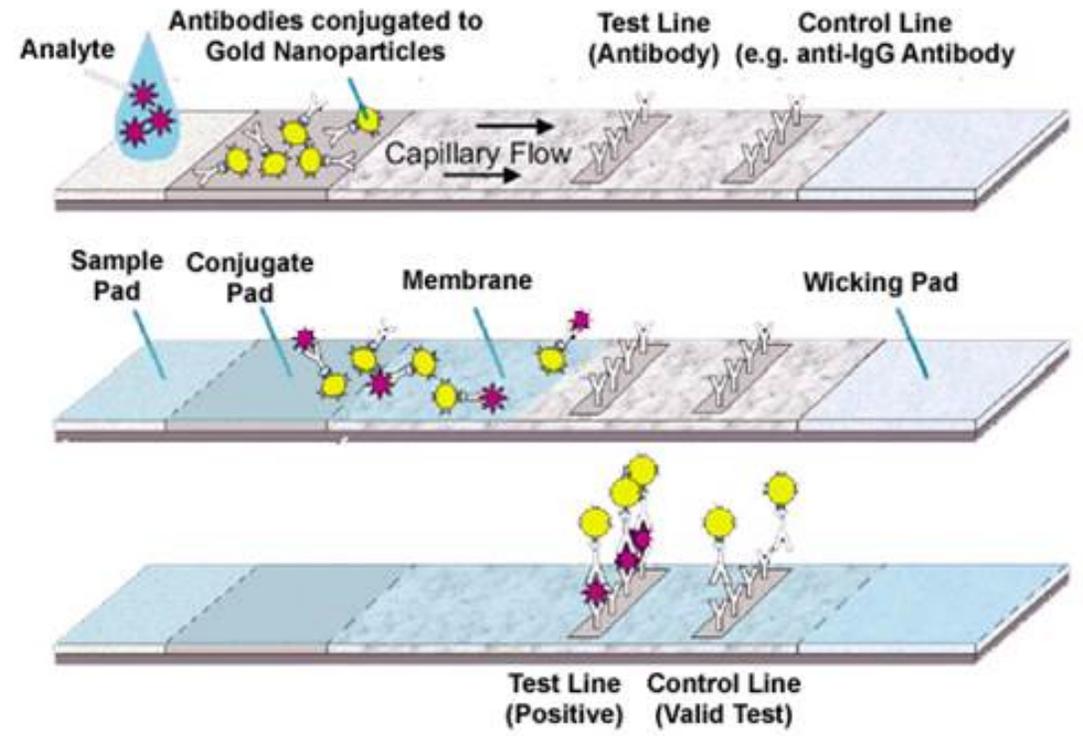
Lateral flow immunoassays



Lateral flow immunoassays



Lateral Flow Assay Architecture



Some weak positives difficult to see!



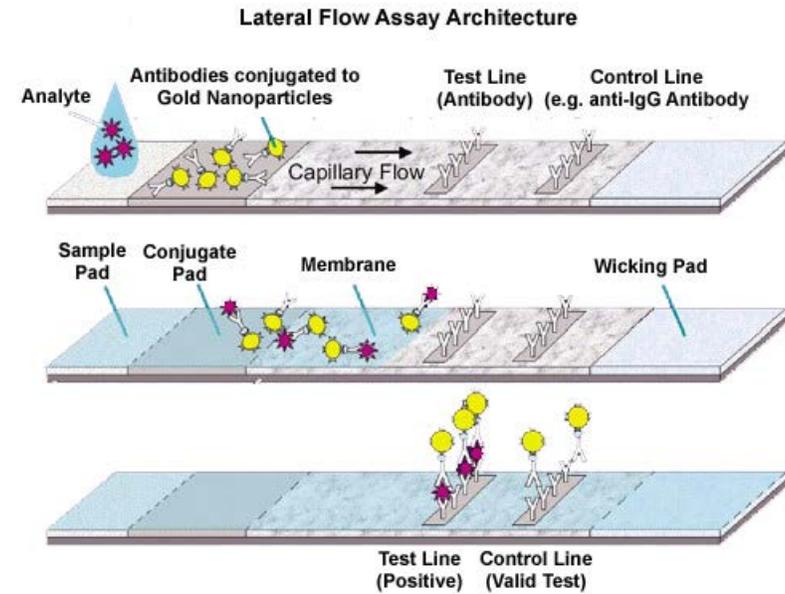
Rapid Diagnosis

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



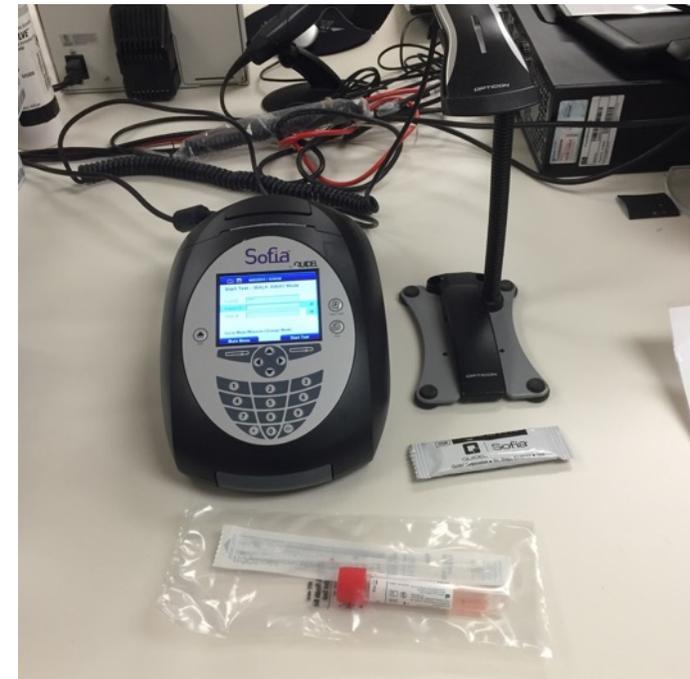
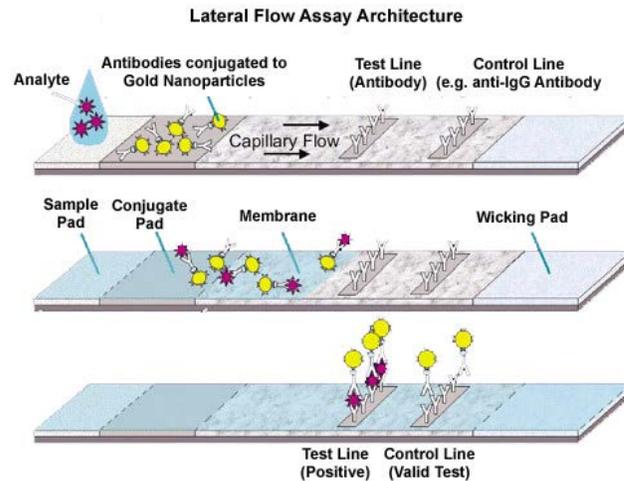
Rapid Diagnosis

Sofia Strep A FIA – Quidel Corporation

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

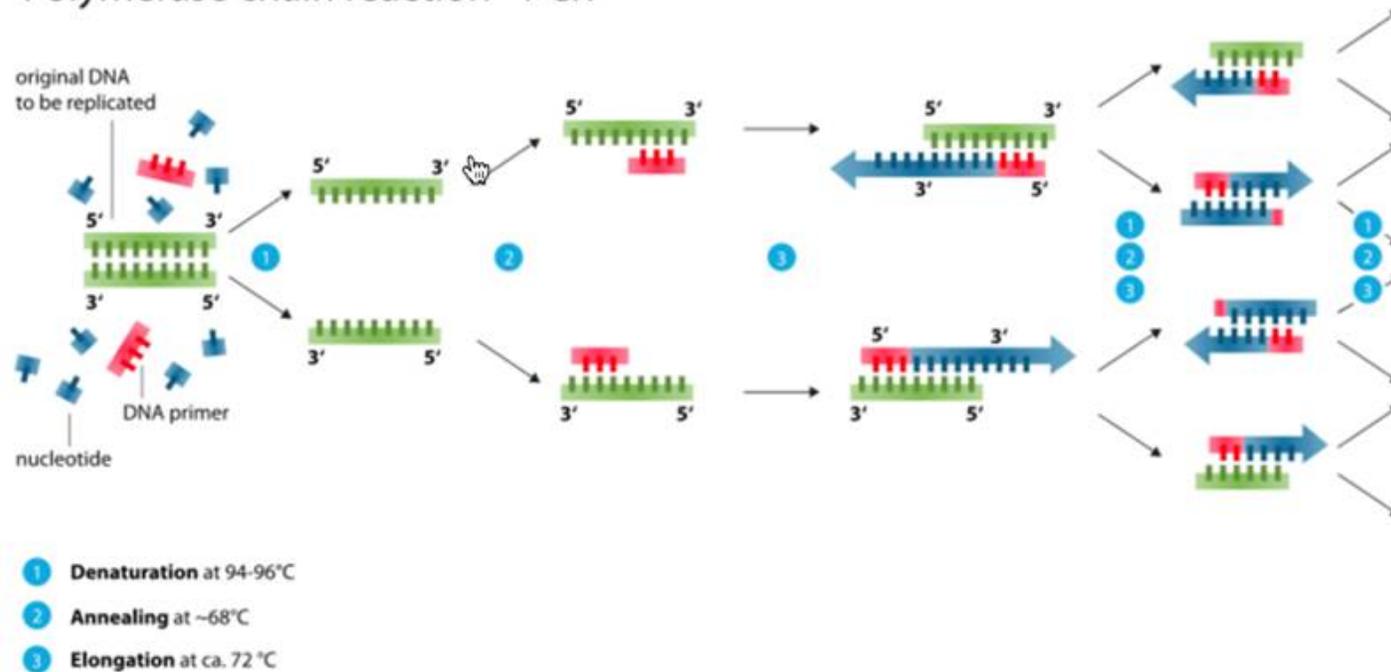
Limit of detection 10^3 to 10^4 cfu/ml

CPT 87880QW



PCR !

Polymerase chain reaction - PCR



PCR Cycles	Target Copies
1	2
2	4
3	8
4	16
5	32
6	64
7	128
8	256
9	512
10	1024
15	32,768
20	1,048,576
25	33,554,432
30	1,073,741,842

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 10² 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 10² cfu/ml

87651QW



Comparison of high tech strep POCs

Strep Test	Cost/Test	Reimbursement	CPT Code	Limit of Detection
Lateral Flow	\$3	\$15-20	87880QW	10 ⁵ to 10 ⁷ cfu/ml
BD Veritor	\$6	\$15-20	87880QW	10 ⁴ to 10 ⁵ cfu/ml
Quidel Sofia	\$10	\$15-20	87880QW	10 ³ to 10 ⁴ cfu/ml
Alere	\$26	\$48	87651QW	10 to 10 ² cfu/ml
Roche	\$26	\$48	87651QW	10 to 10 ² cfu/ml

Rapid Strep Package Inserts

“All negative test results should be confirmed by bacterial culture because negative results do not preclude infection with Group A Streptococcus and should not be used as the sole basis for treatment!”

“Therefore, when a patient suspected of having GAS pharyngitis has a negative rapid streptococcal test, a throat culture should be obtained to ensure that the patient does not have GAS infection. “

“All negative test results should be confirmed by bacterial culture because negative results do not preclude Group A Strep infection and should not be used as the sole basis for treatment. “

Rapid Strep Package Inserts

- Package inserts verbiage says ***SHOULD, which to most mean “recommended” not “required”***
- It is a clinical decision (provider, not lab) to confirm negative results with culture
- Labs should discuss concerns with the labs regulatory agency