β-Hemolytic Streptococcus Testing

Policy Number: **APEA – G2159 – β-Hemolytic Streptococcus Testing**
Initial Presentation Date: 7/01/2020
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**Policy Description**

Streptococcus are Gram-positive, catalase-negative bacteria that are further divided into α-hemolytic, such as *S. pneumoniae* and *S. mutans*; β-hemolytic, such as *S. pyogenes* (Group A), *S. agalactiae* (Group B), and *S. dysgalactiae subsp equisimilis* (Groups C and G); and γ-hemolytic, such as *Enterococcus faecalis* and *E. faecium* (Wessels, 2019). Streptococcal infections can be manifested in a variety of pathologies, including cutaneous infections, pharyngitis, acute rheumatic fever, pneumonia, postpartum endometritis, and toxic shock syndrome to name a few. Streptococcal infections can be identified using bacterial cultures obtained from blood, saliva, pus, mucosal, and skin samples as well as rapid antigen diagnostic testing (RADT) and nucleic acid-based methodologies (Chow, 2018; Wessels, 2019).

Note: For prenatal screening of Group B Streptococcus, please review policy AHS-G2035.

**Related Policies**

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**Indications and/or Limitations of Coverage**

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request.

1. Bacterial culture testing from a throat swab for streptococcal infection for a respiratory illness **MEETS COVERAGE CRITERIA** in the following situations:

   a. Patients have a modified Centor criteria score of 3 or greater (See Note 1 below); OR

   b. Suspected bacterial pharyngitis in the absence of viral features, including cough, oral ulcers, and rhinorrhea; OR

   c. After a negative rapid antigen diagnostic test (RADT) in a symptomatic child or adolescent.
2. Bacterial culture testing for streptococci from a throat swab **DOES NOT MEET COVERAGE CRITERIA** in cases of suspected viral pharyngitis.

3. Rapid antigen diagnostic testing (RADT) for a streptococcal infection **DOES NOT MEET COVERAGE CRITERIA** in the following cases:
   a. As a follow-up test to either a positive or negative bacterial culture test for a streptococcal infection; OR
   b. As a screening method in an asymptomatic patient (except in cases of children under the age of three years who have a mitigating circumstance, including a symptomatic family member); OR
   c. In cases of suspected viral pharyngitis.

4. Blood culture testing for a streptococcal infection **MEETS COVERAGE CRITERIA** in the following situations:
   a. In patients who fail to demonstrate clinical improvement and in those who have progressive symptoms or clinical deterioration after initiation of antibiotic therapy; OR
   b. In cases of suspected prosthetic joint infection.

5. Bacterial culture testing for a streptococcal infection from a skin swab or pus **MEETS COVERAGE CRITERIA** in cases of skin and/or soft tissue infections.

6. Serological titer testing, except in cases of suspected acute rheumatic fever or post-streptococcal glomerulonephritis (PSGN), **DO NOT MEET COVERAGE CRITERIA**.

7. The simultaneous coding for BOTH amplification and direct probes **DOES NOT MEET COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient’s illness.

8. The following tests **DO NOT MEET COVERAGE CRITERIA**:
   a. Panel tests that screen and identify multiple streptococcal strains (S. pyogenes [group A], S. agalactiae [group B], S. dysgalactiae [groups C/G], α-hemolytic streptococcus, and/or γ-hemolytic streptococcus), using either immunoassay or nucleic acid-based assays, such as the Solana Strep Complete Assay and the Lyra Direct Strep Assay; OR
   b. MALDI-TOF identification of streptococcus; OR
   c. Anti-streptolysin O immunoassay (EXCEPT in cases of suspected acute rheumatic fever or post-streptococcal glomerulonephritis (PSGN)); OR
   d. The quantification of any strain of streptococcus using nucleic acid amplification, including PCR; OR
   e. Hyaluronidase activity or anti-hyaluronidase immunoassay (EXCEPT in cases of suspected acute rheumatic fever or post-streptococcal glomerulonephritis (PSGN)); OR
f. Streptokinase activity or anti-streptokinase immunoassay (EXCEPT in cases of suspected acute rheumatic fever or post-streptococcal glomerulonephritis (PSGN)); OR

g. Nicotinamide-adenine dinucleotidase activity or anti-nicotinamide-adenine immunooassay

Note 1: Centor criteria includes tonsillar exudates, tender anterior cervical lymphadenopathy, fever, and absence of cough with each criterion being worth one point (Chow, 2018).

Note 2: For prenatal screening of Group B Streptococcus, please review policy AHS-G2035.

Scientific Background

Bacterial acute pharyngitis is most commonly caused by a Group A Streptococcus (\textit{S. pyogenes} or GAS), accounting for 5-15\% of all acute pharyngitis cases in adults. Group C or Group G Streptococcus (\textit{S. dysgalactiae subsp equisimilis} or GCS/GGS) is believed to be a causative agent in 5-10\% of the cases of pharyngitis; however, “pharyngitis cause group C or G Streptococcus is clinically indistinguishable from GAS pharyngitis” but is more common in young adults and college students (Chow, 2018). “Diagnosis of infection due to group C streptococci (GCS) and group G streptococci (GGS) depends on identification of the organism in a culture from a clinical specimen. In general, a positive culture from a normally sterile site, such as blood, synovial fluid, or cerebrospinal fluid (CSF), can be considered definitive evidence of infection in the setting of a compatible clinical syndrome. The interpretation of positive cultures for GCS or GGS from the pharynx or from cutaneous sites such as open ulcers or wounds is less straightforward since asymptomatic colonization of the upper airway and skin also occurs (Wessels, 2019).” GAS occurs most frequently in the very young and the elderly; although, GAS infections can occur in any age-group. The rates of severe GAS infections have been increasing in the United States as well as in other developed nations (Schwartz, Facklam, & Breiman, 1990).

The Centor criteria can be used to gauge the likelihood of pharyngitis due to a GAS infection. The four components of the Centor criteria are tonsillar exudates, tender anterior cervical lymphadenopathy, fever, and absence of cough with each criterion being worth one point. Patients who score less than three according to the Centor criteria are unlikely to have pharyngitis due to GAS and do not require strep testing or antibiotics; patients scoring \(\geq 3\) can be tested for GAS pharyngitis (Chow, 2018).

GAS is associated with bacterial pharyngitis, scarlet fever, acute rheumatic fever, and post-streptococcal glomerulonephritis. Group A strep pharyngitis presents as a sudden-onset of sore throat with odynophagia and fever; it is commonly referred to as “strep throat”. In children, additional symptoms can include abdominal pain, nausea, and vomiting. Viral pharyngitis, which accounts for more than 80\% of pharyngitis, typically presents with cough, rhinorrhea, hoarseness, oral ulcers, and conjunctivitis unlike GAS pharyngitis. Rare cases of mucopurulent rhinitis caused by GAS has been reported in children under the age of three (CDC, 2018b). Scarlet fever can accompany strep throat. Besides the typical erythematous rash that typically begins on the trunk before spreading outward, scarlet fever can also present as a flushed face, “and the area around the mouth may appear pale (i.e., circumoral pallor).” “Strawberry tongue” can occur due to “yellowish white coating with red papillae”(CDC, 2018e). Scarlet fever is more easily transmitted than asymptomatic carriers through saliva and nasal secretions. Acute Rheumatic Fever (AFR), besides the characteristic fever, can affect the cardiovascular system (carditis and valvulitis), the musculoskeletal system (arthritis), the integumentary system (subcutaneous nodules and erythema marginatum), and the central nervous system (chorea). “Inadequate or lack of antibiotic treatment of streptococcal pharyngitis increases the risk of someone developing acute rheumatic fever. In approximately one-third of patients, acute rheumatic fever follows subclinical streptococcal infections or
infections for which medical attention was not sought (CDC, 2018a).” Post-streptococcal glomerulonephritis (PSGN) presents with edema, hypertension, proteinuria, macroscopic hematuria, lethargy, and, at times, anorexia. “Laboratory examination usually reveals mild normocytic normochromic anemia, slight hypoproteinemia, elevated blood urea nitrogen and creatinine, elevated erythrocyte sedimentation rate, and low total hemolytic complement and C3 complement.” Urine output is usually decreased, and urine examination “often reveals protein (usually <3 grams per day) and hemoglobin with red blood cell casts (CDC, 2018c).”

The virulence factors of GAS include M proteins, a group of more than 80 known proteins that protein the bacteria against phagocytosis; streptolysin O, a thiol-activated cytolyisin; hyaluronidase, which hydrolyzes hyaluronic acid within the host tissue; streptokinase, an enzyme that activates plasmin; nicotinamide-adenine dinucleotidase (NADase), a glycohydrolase of uncertain function; and deoxyribonucleases (DNases) A, B, C, and D. Streptolysin O bind to the eukaryotic membrane's cholesterol to facilitate the characteristic cellular lysis of a GAS infection. Cholesterol and anti-streptolysis O (ASO) antibodies can mitigate streptolysin O damage, and ASO titers often increase following an infection with the peak occurring around four to five weeks post-infection. “Nonsuppurative complications such as rheumatic fever and poststreptococcal glomerulonephritis generally develop during the second or third week of illness... About 80 percent of patients with poststreptococcal glomerulonephritis demonstrate a rise in antistreptolysin titer; however, this assay cannot be used as a measure of severity of glomerular destruction. In patients with suspected glomerulonephritis but with an undetectable ASO titer, prompt testing for other antistreptococcal antibodies such as anti-DNase B (detectable for six to nine months following infection), streptokinase, and anti-hyaluronidase should be performed (Stevens & Bryant, 2018).”

Acute rheumatic fever (ARF) can occur two to four weeks following GAS pharyngitis. The five major manifestations of ARF are carditis and valvulitis (up to 70% of patients exhibit this condition with ARF), arthritis (up to 66%), CNS system involvement (10-30%), subcutaneous nodules (0-10%), and erythema marginatum (<6%) (A. Steer & Gibofsky, 2018). A diagnosis of ARF is not predicated by confirmation of a preceding GAS infection; however, it is helpful, especially in diagnosing children and young adults with arthritis and/or carditis. Evidence of GAS should include either a positive throat culture, a positive RADT, or an elevated or rising titer of either ASO or anti-DNase B. These two antibodies are used frequently in clinical practice due to their high sensitivity in diagnosing streptococcal infections (A. Steer & Gibofsky, 2018; A. C. Steer, Smeeesters, & Curtis, 2015). A study by Blyth and Robertson demonstrated that the sensitivity of using only a single antibody in the diagnosis of streptococcus ranged from 70.5-72.7%; however, the combination of ASO and anti-DNase B increased the specificity to 88.6% with a sensitivity of 95.5%. The addition of anti-streptokinase (ASK) did not increase either the sensitivity or specificity of testing (Blyth & Robertson, 2006).

A study in Norway in 2013 show that necrotizing soft tissue infections can be caused by GAS or GGS/GCS. The mean annual incidence rate is 1.4 per 100,000. During the time period studied (2000-2009), 61 cases of necrotizing soft tissue infections in Norway were due to GAS while nine cases were due to GCS/GGS. “Our findings indicate a high frequency of streptococcal necrotizing fasciitis in our community. GCS/GGS infections contribute to the disease burden but differ from GAS cases in frequency and predisposing factors.” They note that “the GCS/GGS patients were older, had comorbidities more often and had anatomically more superficial disease than the GAS patients (Bruun et al., 2013).” A review in 2014 also noted the population most affected by GCS/GGS, but they note that “the case fatality in bacteremia has been reported to be 15-18% (Rantala, 2014).”

Group B Streptococcus (GBS) is frequently found in human gastrointestinal tracts and genitalia and can be spread to the upper respiratory tract of newborns. In neonates, a GBS infections can cause bacteremia, pneumonia, meningitis, and sepsis. GBS can also cause complications in pregnancy, such as urinary tract infections and chorioamnionitis. GBS, in pregnant and postpartum women, is of special concern since it is implicated in up to 31% of cases of bacteremia without a focus, 8% of postpartum endometritis, and 2% of pneumonia; moreover,
if left unchecked, GBS can also result in preterm labor and miscarriage. In the adult population at large, GBS infections can be manifest as soft tissue infections, sepsis, and bacteremia (Barshak, 2017; Puopolo, Madoff, & Baker, 2017). “Invasive disease in infants is categorized on the basis of chronologic age at onset. Early-onset disease usually occurs within the first 24 hours of life (range, 0 through 6 days) and is characterized by signs of systemic infection, respiratory distress, apnea, shock, pneumonia, and less often, meningitis (5%–10% of cases). Late-onset disease, which typically occurs at 3 to 4 weeks of age (range, 7 through 89 days), commonly manifests as occult bacteremia or meningitis (approximately 30% of cases); other focal infections, such as osteomyelitis, septic arthritis, necrotizing fasciitis, pneumonia, adenitis, and cellulitis, occur less commonly. Nearly 50% of survivors of early- or late-onset meningitis have long-term neurologic sequelae (encephalomalacia, cortical blindness, cerebral palsy, visual impairment, hearing deficits, or learning disabilities). Late, late-onset disease occurs at 90 days of age and beyond, usually in very preterm infants requiring prolonged hospitalization (Pediatrics, 2018).”

**Type of Testing**

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<td>Culture</td>
<td>Cultures can be taken from a swab of the affected tissue when possible, such as the back of the throat and tonsils (1). The cultures are typically grown on a solid, complex rich medium such as Trypticase Soy Agar (TSA) supplemented with 5% sheep blood so that the zone of b-hemolysis can easily be visualized (2). Culture testing can be supplemented with additional conventional identification tests, such as the Lancefield antigen determination test and the PYR test (3).</td>
<td>The CDC considers the throat culture the ‘gold standard’ (4). This testing method can be time-intensive. “Throat culture also can identify other bacteria that cause pharyngitis less commonly than GAS (eg, group C and group G streptococci, <em>Arcanobacterium haemolyticum</em>). However, most laboratories do not routinely identify these pathogens in throat cultures unless specifically requested to do so (5).”</td>
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<td>Serology</td>
<td>Many possible serological tests can be performed, including a measurement of the antibody titers associated with a streptococcal infection. Virulence factors that can be monitored include hyaluronidase, streptokinase, nicotinamide-adenine dinucleotidase, DNase B, and streptolysin O. DNase B and streptolysin O are more frequently used in clinical practice (6).</td>
<td>Anti-streptococcal antibody titers represent past infections and should not be used to routinely diagnose an acute infection (7). Antistreptolysin O (ASO) and/or anti-DNase B (ADB) testing can be used to determine prior streptococcal infection associated with disorders such as rheumatic fever and glomerulonephritis. “An increase in titer from acute to convalescent (at least two weeks apart) is considered the best evidence of antecedent GAS infection. The antibody response of ASO peaks at approximately three to five weeks following GAS pharyngitis, which usually is during the first to third week of ARF, while ADB titers</td>
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<td><strong>Rapid Antigen Diagnostic Testing (RADTs)</strong></td>
<td>RADTs can be performed on a swab at the point of care or can be transported to a lab for testing (9). Numerous RADTs directly detect antigens through an agglutination method or the use of immunoassays, including enzyme-based assays, optical assays, and liposome-based assays that are commercially available (3).</td>
<td>Many RADTs are commercially available but can vary considerably in specificity, sensitivity, and ease of use. “In pediatric patients, if the direct antigen test is negative, and if the direct antigen test is known to have a sensitivity of &lt;80%, a second throat swab should be examined by a more sensitive direct NAAT or by culture as a means of arbitrating possible false-negative direct antigen test results. This secondary testing is not necessarily required in adults. A convenient means of facilitating this 2-step algorithm of testing for Streptococcus pyogenes in pediatric patients is to collect a dual swab initially, recognizing that the second swab will be discarded if the direct antigen test is positive (9).”</td>
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<td><strong>Nucleic Acid Amplification Tests (NAATs)</strong></td>
<td>NAATs amplify DNA or RNA to detect the presence of microorganisms. Some are offered as point-of-care (POC) rapid diagnostic tests while others require special laboratory equipment (9). Some NAATs utilize real-time polymerase chain reaction (rt-PCR), such as the Lyra Direct Strep Assay, while others use a helicase-dependent amplification (HDA)-based methodology like the Solana Strep Complete assay. NAATs are often qualitative but specific NAATs can be quantitative. NAATs can vary in their selectivity, sensitivity, and ability to differentiate between strains of streptococci.</td>
<td>More sensitive than antibody-based testing for streptococcus. Direct NAATs usually require the use of enriched broth cultures. “Negative direct NAAT results do not have to be arbitrated by a secondary test (9).”</td>
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### Clinical Validity and Utility

Rapid in vitro diagnostic tests (RIDT), such as the Alere I Strep A, have been CLIA-waived by the FDA. These tests provide results more quickly than the traditional “gold standard” bacterial culture testing. A 2018 study comparing rapid antigen GAS testing, the Alere I Strep A test—an RIDT using isothermal nucleic acid amplification, and throat cultures. “The sensitivity and specificity of the molecular test were 98% and 100%, respectively, compared with culture. There was a 9% false-positive rate with the rapid antigen-based testing.... The Alere test is sufficiently sensitive and specific for definitive GAS testing in a pediatric urgent care setting (Weinzierl, Jerris, Gonzalez, Piccini, & Rogers, 2018).” In 2016, Cohen et al extensively reviewed the use of rapid antigen detection tests (RADT) for GAS in children. They reviewed 98 unique studies consisting of a total of 101,121 participants and compared both major types of RADTs—enzyme immunoassays (EIA) and optical immunoassays (OIA). “RADT had a summary sensitivity of 85.6%...There was substantial heterogeneity in sensitivity across studies; specificity was more stable. There was no trade-off between sensitivity and specificity.... The sensitivity of EIA and OIA tests was comparable (summary sensitivity 85.4% versus 86.2%)... Based on these results, we would expect that amongst 100 children with strep throat, 86 would be correctly detected with the rapid test while 14 would be missed and not receive antibiotic treatment (J. F. Cohen, Bertille, Cohen, & Chalumeau, 2016).” Another multicenter study using the Alere I Strep A test on cultures obtained from 481 patients of all ages show that the RIDT had 96.0% sensitivity and 94.6% specificity. The authors conclude that this “could provide a one-step, rapid, point-of-care testing method for GAS pharyngitis and obviate backup testing.

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<td><strong>Matrix-Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF)</strong></td>
<td>MALDI-TOF mass spectrometry can be used to quickly identify both gram-negative and gram-positive bacteria once the organism is available in a pure culture on solid medium. The results of the MALDI-TOF test is compared to a known database of spectra of microorganisms for identification (10).</td>
<td>“For less common organisms, the MALDI-TOF result may not be conclusive, and additional bench tests or molecular tests may be required (10).”</td>
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(1) Reference: (AACC, 2015)
(2) Reference: (Gera & McIver, 2013)
(3) Reference: (Spellerberg & Brandt, 2016)
(4) Reference: (CDC, 2018b)
(5) Reference: (Wald, 2018)
(6) Reference: (Stevens & Bryant, 2018)
(7) Reference: (Shulman et al., 2012)
(8) Reference: (A. Steer & Gibofsky, 2018)
(9) Reference: (Miller et al., 2018)
(10) Reference: (Freeman & Roberts, 2018)
on negative results (D. M. Cohen et al., 2015).” This study did note that there are newer tests available that have higher sensitivity, but these tests require more time than the Alere I Strep A method.

Due to the time constraints of clinical laboratories and the variability of RADTs, nucleic acid amplification test (NAAT) use has been increasing in clinical settings. The FDA has approved multiple NAATs for the detection of Streptococcus. The Lyra Direct strep assay is an FDA-approved, NAAT that uses real-time PCR to qualitatively detect the presence of GAS and GGS/GCS in throat swab samples. It should be noted, though, that this assay does not distinguish between GGS and GCS. A study by Boyanton et al. evaluated the efficacy of the Lyra Direct method as compared to the traditional, time-consuming culture test for GAS and GGS/GCS. The sample sizes were not large (n = 19 for GAS and n = 5 for GGS/GCS out of a total of 161 samples submitted); however, the Lyra Direct strep assay did correctly detect “all b-hemolytic streptococci...” and “in batch mode, the Lyra assay reduced intra-laboratory turnaround time by 60% (18.1 h versus 45.0 h) but increased hands-on time by 96% (3 min 16 s versus 1 min 40 s per specimen) (Boyanton, Darnell, Prada, Hansz, & Robinson-Dunn, 2016).” The authors note that the RADTs “have largely augmented bacterial culture (the gold standard). However, the performance of commercially available [RADTs] varies greatly depending upon the manufacturer, methodology used (i.e., optical immunoassay, immunochromatographic, or enzyme immunoassay), and the patient population (i.e., pediatric versus adult) being tested. Due to these limitations, nucleic acid amplification tests (NAATs) are being implemented in clinical laboratories (Boyanton et al., 2016).” The Solana method is also an FDA-approved NAAT, but it uses a rapid helicase-dependent amplification (HDA) methodology. Solana is available for either GAS testing or as a panel testing for GAS, GCS, and GGS. A study by Uphoff and colleagues compared the Solana GAS testing to that of conventional culture testing. Their research used 1082 throat swab specimen. The traditional culture tested positive in 20.7% of the samples as compared to 22.6% positive values in the HDA-based methodology. The Solana assay in their results had 98.2% sensitivity and 97.2% specificity. “In 35 min, the HDA method provided rapid, sensitive GAS detection, making culture confirmation unnecessary (Uphoff et al., 2016).” Recently, another study compared an HDA-based method to the Simplex GAS Direct PCR-based method, which is another FDA-approved diagnostic test. The Simplex GAS Direct method does not require initial DNA extraction from the sample, a potential time-saving benefit. The study used 289 throat swabs. The HDA-based method “compared to Simplexa qPCR had sensitivity, specificity, positive predictive value and negative predictive value of 93.1% vs 100%, 100% vs. 100%, 100% vs. 100% and 98.31% vs. 100% respectively... Simplexa qPCR has improved performance and diagnostic efficiency in a high-volume laboratory compared to [HDA-based method] for GAS detection in throat swabs (Church, Lloyd, Larios, & Gregson, 2018).”

The Solana® Strep Complete Assay by Quidel received FDA clearance in 2016. According to Quidel’s FDA application, it is defined as “a rapid in vitro diagnostic test, using isothermal amplification technology (helicase-dependent amplification, HDA) for the qualitative detection and differentiation of Streptococcus pyogenes (Group A □-hemolytic Streptococcus) and Streptococcus dysgalactiae (pyogenic Group C and G □-hemolytic Streptococcus) nucleic acids isolated from throat swab specimens obtained from patients with signs and symptoms of pharyngitis, such as sore throat (Lollar, 2016).” This test must be performed using Quidel’s Solana proprietary equipment. According to the 510(k) application, the Solana Strep Complete Assay panel has a clinical sensitivity and specificity for GAS of 98.8% and 98.9%, respectively, as compared to the Lyra Direct Strep Assay’s reported 96.5% sensitivity and 98.0% specificity for GAS. The Lyra Direct Strep Assay is a real-time PCR-based assay that cannot differentiate between the pyogenic strains of streptococci. Concerning the pyrogenic GCS/GGS, the Solana Strep Complete Assay panel has a clinical sensitivity of 100% with a specificity of 99.5% as compared to Lyra Direct Strep Assay’s reported 95.7% sensitivity and 98.3% specificity for GCS/GGS strains. The reported testing time also varies between the two assays with Solana requiring 25 minutes versus 60-70 minutes for the Lyra Direct Strep Assay (Lollar, 2016).

A recent study by Helmig and Gertsen evaluated the accuracy of PCR-based testing for GBS in pregnant women. Their study used rectovaginal swabs from 106 women in gestational weeks
For each, both a GBC culture and a PCR-based molecular GBS test (Xpert GBS of Cepheid Ltd) were performed. Only one PCR test yielded no result, so the invalid PCR-based test rate is <1%. 25/106 of the GBS cultures tested positive as compared to 27/105 of the PCR-based test. The specificity of the PCR-based test was 97.5% with a 100% sensitivity and a 92.6% positive predictive value. The authors conclude that “the PCR test has sufficient accuracy to direct intrapartum antibiotic prophylaxis for GBS transmission during delivery (Helmig & Gertsen, 2017).” A preliminary study in France of 1416 mothers with newborns compared swab cultures and GBS PCR assay for their predictive value of early-onset bacterial sepsis (EOS) in newborns since GBS is the most common cause of EOS. The results show that “the diagnostic values of the two tests highlighted a nonsignificant superiority of intrapartum GBS PCR assay” but that “the negative predictive value was improved with intrapartum PCR assay (negative likelihood ratio [LR]: 0.3 [0.1-0.9] vs. 0.6 [0.4-1.1]).... These results suggest that the intrapartum GBS PCR assay offers a better predictive value of GBS EOS that the usual vaginal culture swab at the 9th month but requires confirmation by large studies (Raignoux et al., 2016).”

Guidelines and Recommendations

Centers for Disease Control and Prevention (CDC)

Group B Streptococcus (Verani, McGee, & Schrag, 2010): The CDC recommends the algorithm in the figure below concerning GBS screening in pregnant women. According to their website, the CDC updated their recommendations on 7/23/2018, “All pregnant women should get a group B strep (GBS) test when they are 35–37 weeks pregnant. Babies can get very sick and even die if their mothers pass GBS bacteria to them during childbirth (CDC, 2018d).” For more information on the Avalon policy concerning prenatal screening, please refer to AHS-G2035.

Acute Pharyngitis (CDC, 2018b): Most cases of acute pharyngitis are viral. Only 20-30% of sore throats in children and 5-15% in adults are due to GAS. History and clinical examination can be used to diagnosis viral pharyngitis when clear viral symptoms (e.g., cough, rhinorrhea, hoarseness, oral ulcers, conjunctivitis) are present; these patients do not need testing for group A strep. However, clinical examination cannot be used to differentiate viral and group A strep
pharyngitis in the absence of viral symptoms, even for experienced clinicians. The diagnosis of
group A strep pharyngitis is confirmed by either a rapid antigen detection test (RADT) or a
throat culture. RADTs have high specificity for group A strep but varying sensitivities when
compared to throat culture. Throat culture is the gold standard diagnostic test (CDC, 2018b).

**Scarlet Fever** (CDC, 2018e): Scarlet fever (scarlatina) consists of an erythematous rash caused
by GAS and can occur along with acute pharyngitis. “The differential diagnosis of scarlet fever
with pharyngitis includes multiple viral pathogens that can cause acute pharyngitis with a viral
exanthema. Clinicians need to use either a rapid antigen detection test (RADT) or throat culture
to confirm scarlet fever with pharyngitis. RADTs have high specificity for group A strep but
varying sensitivities when compared to throat culture. Throat culture is the gold standard
diagnostic test. Clinicians should follow up a negative RADT in a child with symptoms of scarlet
fever with a throat culture. Clinicians should have a mechanism in place to contact the family
and initiate antibiotics if the back-up throat culture is positive” (CDC, 2018e).

**Post-Streptococcal Glomerulonephritis (PSGN)** (CDC, 2018c): PSGN is primarily due to a GAS
infection, but rare cases of GCS-induced PSGN have been reported. Clinical features include
edema, hypertension, proteinuria, macroscopic hematuria, and lethargy. “The differential
diagnosis of PSGN includes other infectious and non-infectious causes of acute
glomerulonephritis. Clinical history and findings with evidence of a preceding group A strep
infection should inform a PSGN diagnosis. Evidence of preceding group A strep infection can
include isolation of group A strep from throat or skin lesions or elevated streptococcal
antibodies” (CDC, 2018c).

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**2017 Institute for Clinical Systems Improvement (ICSI) (Short et al., 2017)**

In 2017, the ICSI updated their guidelines titled *Diagnosis and treatment of respiratory illness in children and adults*. They give the following consensus recommendation: “It is the consensus of the ICSI work group to NOT test for Group A Streptococcal (GAS) pharyngitis in patients with modified Centor criteria scores less than three or when viral features like rhinorrhea, cough, oral ulcers and/or hoarseness are present. Testing should generally be reserved for patients when there is a high suspicion for GAS and for whom there is intention to treat with antibiotics (Short et al., 2017).” The Centor criteria include age of patient, physical state of the tonsils and lymph nodes, temperature, and presence or absence of cough (Walker & Habboushe, 2018).

**2012 Infectious Diseases Society of America (IDSA)(Shulman et al., 2012)**

The 2012 IDSA’s *Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis* report includes detailed recommendations concerning Group A Streptococcal (GAS) infections. Recommendation #1 (strong recommendation; high level of evidence) states: “Swabbing the throat and testing for GAS pharyngitis by rapid antigen
detection test (RADT) and/or culture should be performed because the clinical features alone do
not reliably discriminate between GAS and viral pharyngitis except when overt viral features
like rhinorrhea, cough, oral ulcers, and/or hoarseness are present. In children and adolescents,
negative RADT tests should be backed up by a throat culture. Positive RADTs do not
necessitate a back-up culture because they are highly specific.” Also, with a strong
recommendation and moderate level of evidence, they state, “Routine use of back-up throat
cultures for those with a negative RADT is not necessary for adults in usual circumstances,
because of the low incidence of GAS pharyngitis in adults and because the risk of subsequent
acute rheumatic fever is generally exceptionally low in adults with acute pharyngitis.” However,
they do state that if a physician so desires, he or she ”may continue to use conventional throat
culture or to back up negative RADTs with a culture”. With a strong recommendation and high
level of evidence, they do not recommend using anti-streptococcal antibody titers to diagnose
an infection since the titers can reflect previous infections and not necessarily a current event.
In recommendation #4 (strong recommendation; high level of evidence), the IDSA does not
recommend taking a culture of a patient exhibiting signs of a viral infection in either adults or
children. With a strong recommendation, but moderate level of evidence, they state, “Diagnostic studies for GAS pharyngitis are not indicated for children <3 years old and the incidence of streptococcal pharyngitis and the classic presentation of streptococcal pharyngitis are uncommon in this age group.” They do give an exception to children <3 years old if they have mitigating circumstances, including an older sibling with a GAS infection. With respect to follow-up testing, they do not recommend repeat culture or RADT testing post-treatment “but may be considered in special circumstances” (strong recommendation, high level of evidence). In recommendation #7 (strong recommendation; moderate level of evidence), the IDSA says that “diagnostic testing or empiric treatment of asymptomatic household contacts of patients with acute streptococcal pharyngitis is not routinely recommended (Shulman et al., 2012).”

2011 Pediatric Infectious Diseases Society (PIDS) and Infectious Diseases Society of America (IDSA) (Bradley et al., 2011)

The 2011 joint PIDS-IDSA guidelines concerning pediatric community-acquired pneumonia (CAP) recommended (strong recommendation; moderate-quality evidence) that “blood cultures should not be routinely performed in nontoxic, fully immunized children with CAP managed in the outpatient setting” and that “blood cultures should be obtained in children who fail to demonstrate clinical improvement and in those who have progressive symptoms or clinical deterioration after initiation of antibiotic therapy”. Concerning inpatient services, they recommend (strong recommendation; low-quality evidence) that “blood cultures should be obtained in children requiring hospitalization for presumed bacterial CAP that is moderate to severe, particularly those with complicated pneumonia”; however, “in improving patients who otherwise meet criteria for discharge, a positive blood culture with identification or susceptibility results pending should not be routinely preclude discharge of that patient with appropriate oral or intravenous antimicrobial therapy. The patient can be discharged if close follow-up is assured (weak recommendation; low-quality evidence)”. For pneumococcal bacteremia, they do not recommend repeated blood cultures to document resolution (weak recommendation; low-quality evidence), but they do recommend “repeated blood cultures to document resolution of bacteremia...caused by S. aureus, regardless of clinical status (strong recommendation; low-quality evidence)”. With respect to sputum gram stain and culture, “sputum samples for culture and Gram stain should be obtained in hospitalized children who can produce sputum” (weak recommendation; low-quality evidence). They do not recommend using urinary antigen detection testing “for the diagnosis of pneumococcal pneumonia in children; false-positive tests are common (strong recommendation; high-quality evidence) (Bradley et al., 2011).”

2012/2013 IDSA (Osmon et al., 2013)

In 2012 (published in 2013), the IDSA issued Diagnosis and Management of Prosthetic Joint Infection. With a B-III recommendation, “blood cultures for aerobic and anaerobic organisms should be obtained if fever is present, there is an acute onset of symptom, or if the patient has a condition or suspected condition or concomitant infection or pathogen...that would make the presence of a bloodstream infection more likely.” They also recommend (B-II) to perform “at least 3 and optimally 5 or 6 periprosthetic intraoperative tissue samples or the explanted prosthesis itself should be submitted for aerobic and anaerobic culture at the time of surgical debridement or prosthesis removal to maximize the chance of obtaining a microbiologic diagnosis.” They consider a prosthetic joint infection to be two or more intraoperative positive cultures of the same organism or a “combination of preoperative aspiration and intraoperative cultures” of the same organism. It should be noted that their table of possible bacterial infections does include β-hemolytic streptococci.

2014 IDSA (Stevens et al., 2014)

The 2014 update of the IDSA’s guidelines concerning skin and soft tissue infections included a recommendation (strong; moderate-quality evidence) of “Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether
Staphylococcus aureus and/or β-hemolytic Streptococcus is the cause, but treatment without these studies is reasonable in typical cases.” They make a similar recommendation in the cases of pus from carbuncles and abscesses as well as pyomyositis; however, they do not recommend (strong, moderate) a “Gram stain and culture of pus from inflamed epidermoid cysts”. As for erysipelas and cellulitis, “cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended (strong, moderate) …cultures of blood are recommended (strong, moderate), and cultures and microscopic examination of cutaneous aspirates, biopsies, or swabs should be considered in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites (weak, moderate).”


The ACOG issued Committee Opinion #485 in 2011 (and reaffirmed in 2016) concerning the prevention of GBS in newborns. They recommend “universal screening for GBS…at 35-37 weeks of gestation” in order to determine if intrapartum antibiotic prophylaxis is required to protect the newborn. They do have a “permissive statement for limited role of nucleic acid amplification tests for intrapartum testing for GBS.” They recommend using rectovaginal swab specimens at 35-37 weeks, but the updated recommendation does allow for “identification options expanded to include use of chromogenic media and nucleic acid amplification tests.”

State and Federal Regulations, as applicable

The FDA approved the Lyra Direct Strep Assay (k133833) on 04/16/2014 and reclassified it on 07/11/2014. It is a “Real-Time PCR in vitro diagnostic test for the qualitative detection and differentiation of Group A □-hemolytic Streptococcus (Streptococcus pyogenes) and pyogenic Group C and G β -hemolytic Streptococcus nucleic acids isolated from throat swab specimens obtained from patients with signs and symptoms of pharyngitis, such as sore throat. The assay does not differentiate between pyogenic Groups C and G β-hemolytic Streptococcus (Hojvat, 2014).” The FDA has also approved the Solana Strep Complete Assay by Quidel that is “an in vitro diagnostic test for the detection of Group A, C and G beta- hemolytic Streptococcus in throat swab specimens from symptomatic patients” on 10/25/2016 (K162274) (FDA, 2016).

On 03/06/2019, the FDA approved GenePOC’s Strep A assay to be performed using GenePOC’s Revogene instrument as a “single-use test for qualitative detection of Streptococcus pyogenes (group A Streptococcus-GAS) nucleic acids from throat swab specimens obtained from patients with signs and symptoms of pharyngitis (FDA, 2019).”

A search of “Strep A” on the FDA Medical Devices Database (Devices@FDA) on 06/22/2018 yielded 178 results. A similar search of “Strep B” on 06/22/2018 yielded 20 results (FDA, 2018).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Applicable CPT/HCPCS Procedure Codes

<table>
<thead>
<tr>
<th>Code Number</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>83789</td>
<td>Mass spectrometry and tandem mass spectrometry (eg, MS, MS/MS, MALDI, MS-TOF, QTOF), non-drug analyte(s) not elsewhere</td>
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<td>Code</td>
<td>Description</td>
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<tr>
<td>86060</td>
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<tr>
<td>86063</td>
<td>Antistreptolysin 0; screen</td>
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<tr>
<td>86215</td>
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<tr>
<td>86317</td>
<td>Immunoassay for infectious agent antibody, quantitative, not otherwise specified</td>
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<tr>
<td>86318</td>
<td>Immunoassay for infectious agent antibody, qualitative or semiquantitative, single step method (eg, reagent strip)</td>
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<tr>
<td>87040</td>
<td>Culture, bacterial; blood, aerobic, with isolation and presumptive identification of isolates (includes anaerobic culture, if appropriate)</td>
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<td>87070</td>
<td>Culture, bacterial; any other source except urine, blood or stool, aerobic, with isolation and presumptive identification of isolates</td>
</tr>
<tr>
<td>87071</td>
<td>Culture, bacterial; quantitative, aerobic with isolation and presumptive identification of isolates, any source except urine, blood or stool</td>
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<tr>
<td>87077</td>
<td>Culture, bacterial; aerobic isolate, additional methods required for definitive identification, each isolate</td>
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<tr>
<td>87081</td>
<td>Culture, presumptive, pathogenic organisms, screening only</td>
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<td>Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; Streptococcus, group A</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group A, amplified probe technique</td>
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<td>87802</td>
<td>Infectious agent antigen detection by immunoassay with direct optical observation; Streptococcus, group B</td>
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</table>
Infectious agent antigen detection by immunoassay with direct optical observation; Streptococcus, group A

Evidence-based Scientific References


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**Policy Implementation/Update Information**

7/1/20  New Policy

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.