Clinical Policy Title: Molecular tests for group A streptococcus

Clinical Policy Number: 18.01.04

Effective Date: July 1, 2016
Initial Review Date: February 17, 2016
Most Recent Review Date: March 15, 2017
Next Review Date: March 2018

Policy contains:
- Group A streptococcus (GAS).
- Pharyngitis.

Related policies:
None.

ABOUT THIS POLICY: AmeriHealth Caritas Louisiana has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Louisiana’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas Louisiana when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Louisiana’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Louisiana’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Louisiana will update its clinical policies as necessary. AmeriHealth Caritas Louisiana’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Louisiana considers the use of molecular testing for group A streptococcus (group A strep, or GAS) clinically proven, and, therefore, medically necessary for suspected cases of the condition.

Limitations:
None.

Alternative covered services:

Rapid strep and throat culture.

Background
GAS bacteria are spread through contact with droplets from an infected person's cough or sneeze, and live in a person's nose and throat. In developed countries, 15 percent of school-age children and 4 percent to 10 percent of adults will have a GAS episode of pharyngitis every year (Shulman, 2012).

Most GAS infections cause relatively mild (noninvasive) illnesses such as strep throat, scarlet fever, and impetigo (a skin infection). More than 10 million noninvasive GAS infections (primarily throat and superficial skin infections) occur annually in the United States. Occasionally, these bacteria can cause severe and even life-threatening (invasive) diseases. Cases of invasive GAS infections, such as necrotizing fasciitis and streptococcal toxic shock syndrome, occur less frequently but are associated with higher rates of death.

Acute GAS pharyngitis has certain characteristic epidemiological and clinical features. The disorder is primarily a disease of children 5 to 15 years of age, and, in temperate climates, it usually occurs in the winter and early spring. Patients with GAS pharyngitis commonly present with sore throat (generally of sudden onset), pain on swallowing, and fever. Headache, nausea, vomiting, and abdominal pain may also be present, especially in children. On examination, patients have tonsillopharyngeal erythema, with or without exudates, often with tender, enlarged anterior cervical lymph nodes (lymphadenitis). Other findings may include a beefy, red, swollen uvula; petechiae on the palate; excoriated nares (especially in infants); and a scarlatiniform rash. However, none of these findings are specific for GAS pharyngitis. Conversely, the absence of fever or the presence of clinical features such as conjunctivitis, cough, hoarseness, coryza, anterior stomatitis, discrete intra-oral ulcerative lesions, viral exanthema, and diarrhea strongly suggests a viral rather than a streptococcal etiology.

The traditional throat culture test to diagnose GAS typically takes two to three days for results to be returned from labs. The rapid strep test, in which the throat and tonsils are swabbed to collect bacteria, can produce results in 10 to 15 minutes, improving the chances for effectiveness to rapidly commence.

Diagnosis of GAS pharyngitis has traditionally been made by swabbing the throat and testing for GAS pharyngitis by rapid antigen detection test (RADT) and/or culture.

- 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 low in adults with acute pharyngitis.

- Anti-streptococcal antibody titers are not recommended in the routine diagnosis of acute pharyngitis as they reflect past but not current events (Shulman, 2012).

The clinical significance of the number of GAS colonies on the throat culture plate is problematic. Although patients with true acute GAS pharyngitis are likely to have more strongly positive cultures than patients who are streptococcal carriers (i.e., individuals with chronic GAS colonization of the pharynx), there is too much overlap in this regard to permit accurate differentiation on this basis alone using RADTs. A major disadvantage of throat cultures is the delay (overnight or longer) in obtaining results. RADTs have been developed for the identification of GAS pharyngitis directly from throat swabs, with
shorter turnaround time. A meta-analysis of 48 studies found sensitivity of RADTs has been only 86 percent (including considerable variability between studies), falling short of qualifying as an accurate tool to diagnose GAS pharyngitis (Lean, 2014). In November 2014, Roche Diagnostics received approval from the U.S. Food and Drug Administration (FDA) for the cobas® Liat® system, a molecular test and the first to provide a result in 15 minutes. In April 2015, Alere received similar approval for its Alere™ i Strep A Rapid Molecular Test, which is designed to detect GAS bacteria in throat swab specimens in under eight minutes.

**Searches**

AmeriHealth Caritas Louisiana searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on February 1, 2017. Search terms were: “Alere i Strep A Rapid Molecular Test,” “cobas Liat,” and “group A streptococcus.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

A 2012 practice guideline from the Infectious Disease Society of America included recommendations for rapid diagnosis of GAS pharyngitis, but made no mention of use of polymerase chain reaction (PCR) molecular testing. The guideline also recommended confirming negative results in children, most often with a culture (Shulman, 2012).

An Institute for Clinical Systems Improvement guideline cited a 2003 study (Uhl, 2003) of PCR testing that renders a culture not necessary, although the PCR testing requires 30 to 60 minutes to perform, and longer for lab results to be obtained. The 2013 guideline concludes the PCR test can replace rapid antigen testing and cultures for GAS (Snellman, 2013).
A 2014 meta-analysis of 48 studies compared sensitivity and specificity of diagnosing GAS pharyngitis using either optical immunoassay (19 studies) or molecular (six studies) techniques. Molecular techniques were found to be superior to optical immunoassay in sensitivity (0.92 vs. 0.86) and specificity (0.99 vs. 0.94). In addition, findings from studies of the molecular technique varied less than did findings from the optical immunoassay studies (Lean, 2014). Of the six studies using molecular techniques, one of the more recent was a 2011 trial of 306 patients that used GAS PCR assay including DNA, had a sensitivity of 96.0, and had specificity of 98.6 percent (Slinger, 2011).

A recent trial found that 25.7 percent of 101 children with sore throat tested positive for GAS using the Alere i strep A test, compared to just 0.7 percent of those without sore throat, leading to the conclusion that clinician judgment and Center score without such an adjunctive test were not sufficiently accurate for prescribing antibiotics (Orda, 2016a). An accompanying article by the same team of Australian researchers calculated positive and negative etiological predictive values of 88 percent to 100 percent and 97 percent to 99 percent for swab samples from children with and without sore throat, using Alere TestPack +Plus Strep A. The team stated the traditional culture for streptococcus was “impracticable” because of the lengthy time awaiting a result (Orda, 2016b).

The Alere i strep A test was compared to a bacterial culture in 481 children and adults. The Alere test had a 96.0 percent and 94.6 percent sensitivity and specificity compared to bacterial culture, which rose to 98.7 percent and 98.5 percent when adjudicated by PCR. The 13 subjects with no GAS growth nevertheless had positive results from the Alere i strep A test and PCR (Cohen, 2015).

The cobas Liat strep A assay was used to detect strep A bacteria in 427 patients (over 95 percent of whom were age 21 and younger), as was the RADT. Sensitivity and specificity results were roughly equivalent, i.e., 97.7 percent and 93.3 percent for cobas Liat and 97.7 percent and 84.5 percent for RADT (Wang, 2016).

A Mayo Clinic study of 198 specimens tested for Streptococcus pyogenes (a type of group A bacteria) compared the cobas Liat group A strep test to the (traditional) LightCycler PCR assay; both found 84 samples were positive and 114 were negative (Uhl, 2016). Two staff members of the Mayo Clinic, where nucleic acid amplification tests for Streptococcus pyogenes (flesh-eating bacteria within group A) have been used for over a decade, contend that these tests should replace the traditional antigen detection and culture for detecting bacterial pharyngitis, based on existing evidence (Pritt, 2016).

Relative efficacy of cobas Liat and Alere i strep A tests have yet to be assessed. However, these were compared for detection of influenza A and B viruses. The sensitivities to the A and B viruses for Alere were 71.3 percent and 93.3 percent, and 100 percent for both using the cobas Liat test. Specificities were 100 percent for both viruses for both tests. The lower sensitivity numbers for Alere for detecting influenza A virus were due to low-positive samples below the test’s detection limit (Nolte, 2016). Results for some other molecular-based methods of testing for GAS, not yet approved by the FDA, have been reported. In one case, the Simplexa™ group A strep direct assay had sensitivity and specificity of 97.4 percent and 95.2 percent in 1,352 samples tested for GAS pharyngitis (Tabb, 2015). A study of 796
swabs using illumigene group A streptococcus DNA amplification assay documented the detection of GAS in all 74 direct culture-positive specimens and 100 of 102 extracted culture-positive specimens (Anderson, 2013).

Policy updates:

A total of two practice guidelines/other and 11 peer-reviewed references have been added to this policy, many of them published recently. A total of one practice guidelines/other and 15 peer-reviewed references have been removed, many of which are more than a decade old.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Wang, 2016</td>
<td><strong>Key points:</strong></td>
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<tr>
<td></td>
<td>• Throat specimens from 427 patients tested with cobas Liat Strep A assay and RADT.</td>
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<td></td>
<td>• Sensitivity and specificity of cobas Liat test were 97.7% and 93.3% to reference culture.</td>
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<tr>
<td></td>
<td>• Sensitivity and specificity of cobas Liat test were 97.7% and 84.5% vs. RADT.</td>
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<td>• Sensitivity and specificity equal, cobas Liat had 15-minute turnaround time.</td>
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<td>Uhl, 2016</td>
<td><strong>Key points:</strong></td>
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<td>• LightCycler PCR assay and Liat strep A assay used for 198 specimens.</td>
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<td>• Each method produced 84 positive results and 114 negative results.</td>
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<td></td>
<td>• Sensitivity and specificity of Liat strep A assay were 100.0% and 98.3%.</td>
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<tr>
<td>Orda, 2016b</td>
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<td>• Test of 101 children ages 3–15 with and without sore throat for Strep A.</td>
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<td>• Positive and negative etiological predictive values were 88%–100% and 97%–99%.</td>
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<td>• Traditional cultures are “impracticable” because of 1–2 day wait for results.</td>
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<td>Cohen, 2015</td>
<td><strong>Key points:</strong></td>
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<td>• Multicenter prospective trial of 481 children and adults to detect GAS.</td>
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<td>• Sensitivity/specificity of Alere i are 96.0% and 94.6% compared to bacterial culture.</td>
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<td>• Rates increased to 98.7% and 98.5% when adjudicated by PCR.</td>
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<td>• Thirteen subjects with no GAS growth had positive results from Alere i test.</td>
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<td>Lean, 2014</td>
<td><strong>Key points:</strong></td>
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<td>• Meta-analysis of 48 studies of RADT for GAS pharyngitis.</td>
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<td>• Nineteen optical immunoassay (OI) trials compared to six molecular trials.</td>
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<td>• Sensitivity and specificity of molecular (0.92% and 0.99%) greater than OI (0.86% and 0.94%).</td>
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<td>• Sensitivity and specificity variation among trials lower in molecular group.</td>
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References
Professional society guidelines/other:


Peer-reviewed references:


**CMS National Coverage Determinations (NCDs):**
No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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