

# Diagnostic Accuracy of Group A *Streptococcus* Rapid Antigen Detection Test on Middle Ear Fluid in Children With Acute Otitis Media With Spontaneous Perforation

## A Prospective Multicenter Evaluation

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**Abstract:** Group A *Streptococcus* is one of the leading causes of otorrhea. The performance of rapid antigen tests in 256 children with otorrhea showed excellent sensitivity, 97.3% (95% confidence interval: 90.7%–99.7%), and specificity, 100% (95% confidence interval: 98.0%–100%). In a period of increasing invasive and noninvasive group A *Streptococcus* infections, an early diagnosis could be useful.

**Key Words:** group A streptococcus, rapid antigen detection test, middle ear fluid, otorrhea, spontaneous perforation

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Spontaneous perforation of the tympanic membrane (SPTM) accounts for approximately 7% of acute otitis media (AOM) cases.<sup>1</sup> Several studies have shown that group A *Streptococcus* (GAS), which represents 12% to 17% of cases, is more often involved in children  $\geq 3$  years old.<sup>2–4</sup> Moreover, when GAS is isolated from middle ear fluid (MEF), co-infections and recurrent AOM are less frequent than in SPTM due to *Haemophilus influenzae* infection.<sup>5,6</sup>

To describe the bacteriologic spectrum of AOM with SPTM, we conducted an observational study from 2015 to 2018, as described elsewhere.<sup>5</sup> Because our results showed that GAS ranked first in infections in children older than 3 years of age, it seemed potentially relevant to perform and evaluate a GAS rapid antigen detection test (RADT) on MEF in addition to otorrhea culture.<sup>5</sup> RADTs have been developed for GAS pharyngitis and are the cornerstone of management of sore throat in many countries. Although this use is off-label, the diagnostic accuracy of GAS RADTs in extrapharyngeal infections (perineal infections, blistering dactylitis, pleural fluid) was assessed in several studies and seemed comparable to that found for pharyngitis.<sup>7–10</sup> However, to our knowledge, the performance of RADTs in children with SPTM was never evaluated.

The present study aimed to assess the diagnostic accuracy of a GAS RADT compared with culture of MEF in children with AOM with SPTM.

## MATERIALS AND METHODS

From March 2019 to March 2023, children 3 months to 15 years old with SPTM were prospectively and consecutively enrolled by 17 pediatricians throughout France. Detailed study methods were previously described. Briefly, after written informed consent was obtained, an MEF swab was used for the GAS RADT (StreptAtest Exacto Pro, Biosynex, Ilkirch-Graffenstaden, France), an immunochromatographic test provided free of charge by the French National Health Service. RADTs were performed according to manufacturer instructions, at the point of care, by the clinician in charge, with blinding to reference standard test results. A second MEF specimen was obtained with cotton-tipped wire swabs, immediately placed in transport medium (Copan Venturi Transystem, Brescia, Italy), and transported within 48 hours to one of the 2 centralized microbiology laboratories participating in the study (Robert Debré Hospital, Paris, France or National Centre for Pneumococci at CHI Créteil Hospital, Créteil, France).<sup>5</sup> *Streptococcus pneumoniae*, nontypable *H. influenzae* (NTHi), *Moraxella catarrhalis* and GAS in culture were considered significant as otopathogens.<sup>11</sup> Microbiologists assessing culture results were blinded to RADT results.

The diagnostic accuracy of the GAS RADT was evaluated by computing sensitivity, specificity and predictive values estimates, with bacterial otorrhea culture results as the reference standard. We also assessed whether patient clinical characteristics (ie, age, otitis-prone children, unilateral otorrhea, duration of otorrhea before sampling) were associated with the presence of GAS in culture. Otitis-prone children was defined as children with 3 separate AOM infections within a 6 months or 4 AOM infections within a 12-month time.<sup>12</sup> Categorical variables were compared by  $\chi^2$  or Fisher exact test. We used the Cuzick test for trend from 2019 to 2023.

The study was approved by Saint Germain en Laye Hospital Ethics Committee and registered at ClinicalTrials.gov (NCT04807660). Data were entered by using 4D software (v17), Le Pecq, France and statistical analyses involved using Stata/SE v15 (StataCorp, College Station, TX). All tests were 2-sided, and the level of significance was set at  $P < 0.05$ . No formal sample calculation was performed for this exploratory study; we estimated that including about 250 children would provide sufficient precision. We followed Standards for Reporting of Diagnostic Accuracy Studies 2015 for reporting.<sup>13</sup>

## RESULTS

From March 2019 to March 2023, we enrolled and sampled 256 children with acute SPTM (mean age  $28.3 \pm 23.5$  months; girls 46.2%). Table (Supplemental Digital Content 1, <http://links.lww.com/INF/F145>) presents patient characteristics in the overall population and according to age and presence of GAS in MEF. The proportion of otitis-prone children was greater before than after 3 years of age (20.7% vs. 4.5%;  $P = 0.002$ ). Among the culture proven bacterial infections, in the overall population, among the positive samples, the first bacterial species implicated in MEF was GAS (75/141, 53.2%), followed by NTHi (51/141, 36.2%) and *S. pneumoniae* (30/141, 21.3%). Co-infection of GAS with NTHi accounted for 5.0% of cases (7/141). The proportion of GAS infection significantly increased from 43.8% (14/32) in 2019 to 63.4% (16/26) in 2023 ( $P = 0.04$ ). No clinical variable was associated with the presence of GAS.

Table 1 shows the performance of the GAS RADT compared with bacterial culture. RADT sensitivity was 97.3% (95% confidence interval [CI]: 90.7%–99.7%) and specificity 100% (95% CI: 98.0%–100%). The positive and negative predictive values were 100% (95% CI: 95.1%–100%) and 98.9% (95% CI: 96.1%–99.9%), respectively.

## DISCUSSION

To the best of our knowledge, this is the first prospective study to assess in a large cohort the diagnostic accuracy of a GAS RADT in children with SPTM. Among the positive samples, GAS was the first bacterial species isolated in the

overall population (53.2%). The GAS RADT had high sensitivity (97.3%, 95% CI: 90.7%–99.7%) and specificity (100%, 95% CI: 98.0%–100%) compared with bacterial culture as the reference standard.

In a recent Cochrane review, the sensitivity and specificity of a GAS RADT in children with sore throat was 85.6% (95% CI: 83.3%–87.6%) and 95.4% (95% CI: 94.5%–96.2%).<sup>14</sup> The excellent performance of a GAS RADT in SPTM is probably due to the ease of otorrhea sampling, which does not require the child's cooperation compared with throat sampling in children with pharyngitis. Furthermore, otorrhea sampling is not painful. Unlike in the throat, in the external auditory canal, GAS is not a common host, and the positivity of a RADT or culture allows for affirming the responsibility of GAS in the otorrhea episode.

Although other pathogens involved in otorrhea (NTHi, *S. pneumoniae*, *M. catarrhalis*) are often resistant or intermediately resistant to amoxicillin, the vast majority of *Streptococcus pyogenes* strains remain susceptible to penicillin with very low minimum inhibitory concentrations. Confirming the presence of GAS at the point of care allows for prescribing narrow-spectrum antibiotics, such as amoxicillin, with low impact in terms of selective pressure, and possibly at lower doses.<sup>15</sup> However, GAS strains with reduced susceptibility to  $\beta$ -lactams have been reported and justified surveillance and vigilance.<sup>16</sup> Of note, we did not identify any clinical parameter significantly associated with the presence of GAS in MEF culture. Furthermore, the frequency of GAS in otorrhea increased after the relaxation of nonpharmaceutical interventions introduced to mitigate the COVID-19 pandemic.

In the current context of rising rates of invasive and noninvasive GAS infections, an early diagnosis of GAS is of paramount clinical importance. Our findings, which support the off-label use of a RADT, may play a crucial role in accurately detecting GAS in extrapharyngeal sites.<sup>17</sup>

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**TABLE 1.** Performance of the Group A *Streptococcus* Rapid Antigen Detection Test From Middle Ear Fluid Collected by Healthcare Workers, Compared With Bacterial Culture (N = 256 Children)

RADT result	GAS Culture+	GAS Culture–	Total
RADT+	73	0	73
RADT–	2	181	183
Total	75	181	256

GAS prevalence: 29.3 (95% CI: 23.8–35.3).

RADT performance: Sensitivity: 97.3% (95% CI: 90.7%–99.7%), specificity: 100% (95% CI: 98.0%–100%), positive predictive value: 100% (95% CI: 95.1%–100%) and negative predictive value: 98.9% (95% CI: 96.1%–99.9%).

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