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Pharyngitis in Low-Resources Settings: A Pragmatic Clinical Approach to Reduce Unnecessary Antibiotic Use

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ABSTRACT

OBJECTIVE. Existing scoring systems for the diagnosis of group A streptococcus pharyngitis are insensitive or inapplicable in low-resources settings. Bacterial cultures and rapid tests can allow for antibiotic prescription abstention in high-income regions. These techniques are not feasible in many low-resources settings, and antibiotics often are prescribed for any pharyngitis episode. However, judicious antibiotics prescription in the community also is of concern in low-income countries. The objective of this study was to develop a clinical decision rule that allows for the reduction of empirical antibiotic therapy for children with pharyngitis in low-resources settings by identifying non–group A streptococcus pharyngitis.

PATIENTS AND METHODS. We prospectively included children with pharyngitis in 3 public hospitals of Brazil during 9 months in 2004. We filled out clinical questionnaires and performed throat swabs. Bilateral $\chi^2$ (2-tailed test) and multivariate analysis were used to determine score categories. The outcome measures were sensitivity, specificity, positive likelihood ratio, and posttest probability of non–group A streptococcus infection with the clinical approach as compared with throat culture.

RESULTS. A total of 163 of the 220 children had non–group A streptococcus pharyngitis (negative culture). We established a 3-questions decision rule (age and viral and bacterial signs) with 3 possible answers. The use of this score would prevent 41\% to 55\% of unnecessary antimicrobial prescriptions. The specificity of the score for non–group A streptococcus pharyngitis was >84\%.

CONCLUSION. Such a clinical decision rule could be helpful to reduce significantly unnecessary antibiotic prescriptions for pharyngitis in children in low-resources settings.
The global burden of antimicrobial resistance is particularly pressing in developing countries. The level of antibiotic resistance is correlated clearly to antibiotic consumption. In Western Europe and North America, modifications of prescribing practice have been attained with diagnosis and prescribing guidelines. These strategies have not been evaluated in developing countries, where health care systems differ greatly from occidental ones, so locally validated interventions are needed. Acute pharyngitis is 1 of the most common childhood illnesses. Viruses are responsible for >80% of them, and group A Streptococcus (GAS) accounts for ~15% of these infections. In cases of GAS as the cause, antibiotics are prescribed frequently. Recent studies underlined the high proportion (20%–50%) of GAS carriers among children, and distinguishing between carriers with viral pharyngitis and real GAS pharyngitis is impossible in general practice.

In low-income regions, there is no access to microbiologic diagnosis of common GAS infections such as pharyngitis. Presumptive diagnosis relies on clinical signs only, although the positive predictive value of clinical signs and symptoms has been shown to be extremely low. The World Health Organization clinical decision rule for streptococcal pharyngitis suggests treating children who are younger than 5 years when pharyngeal exudate plus enlarged, tender cervical nodes are found. The evaluation of this approach was performed in Brazil, Egypt, and Croatia and presented a very low sensitivity (3.6%–8.5%). Some clinical scores, developed in medical settings where microbiology is available in the daily practice, have already been published. Because of the unavailability of microbiologic testing in low-income regions, clinicians often empirically treat all pharyngitis with antibiotics. In these settings, there clearly is a need for modified clinical decision rules with a higher sensitivity and adequate specificity. To our knowledge, only 1 interesting study proposed a clinical decision rule that is designed for the management of streptococcal pharyngitis in low-income regions (Egypt). However, it has not yet been validated clinically, and we have no data so far that it could be applied in other low-income settings.

Bacterial culture and rapid tests are not available for common infections in public hospitals of Brazil (for structural and cost reasons). Like many other public institutions in developing countries, all children with clinical pharyngitis are treated empirically with antibiotics. We developed a clinical decision rule that allows for a reduction in empirical antibiotic therapy for children with pharyngitis in Brazil, as an example of a low-resource settings. We directed our clinical analysis for best identifying non-GAS pharyngitis rather than GAS pharyngitis.

Methods

Patients

All children (0–15 years) who attended the emergency department of 3 public hospitals of Brazil (Academic hospital of Brasília, Regional Hospital of the south wing of Brasília, and Medical Unit of São Sebastião, with 250, 180, and 40 beds, respectively) with signs and symptoms of acute pharyngitis from February 1 to October 31, 2004, were enrolled prospectively in the study. This study was approved by the ethical board of all participant hospitals. Exclusion criteria were current antimicrobial treatment or refusal to participate in the study. A written informed consent was obtained from the children’s parents or guardian. A predesigned questionnaire that comprised general data (date of birth, gender, antimicrobial treatment in the past 6 months, and the prescribed treatment for current episode), demographic information (number of children living under the same roof), and description of infection was used for data collection. Signs and symptoms of pharyngitis were derived from the practice guidelines of the Infectious Diseases Society of America and included the presence of (1) conjunctivitis, coryza, cough, diarrhea, and viral-like exanthema, features suggestive of viral cause and defined as viral signs; or (2) fever >38.5°C, tender cervical node, headache, petechia on the palate, abdominal pain, and sudden onset (<12 hours), features suggestive of GAS as causative agent and defined as bacterial signs. The pediatricians filled out the questionnaire, measured the weight and height, and collected the throat secretion samples using sterile cotton-tipped swabs. Physicians were trained to standardize the swabbing technique.

Laboratory Analysis

The swabs were plated on 5% sheep blood agar plates that were incubated at 37°C for 24 to 48 hours. GAS were identified by a β hemolysis on blood agar, colony morphology, Gram stain, catalase reaction, sensitivity to 0.04-U bacitracin disk, latex agglutination (SlideX, strepto A, Biomérieux, France), and a commercially available method following the manufacturer’s recommendations (MicroScan, Dade Behring, São Paulo, Brazil).

Statistical Analysis

We used the data that were collected in this study to develop the clinical decision rule. The association of clinical findings with negative throat culture was assessed with the use of a bilateral χ² (2-tailed test). Continuous variables also were assessed using a t test analysis (Gaussian distribution). The 3 more significant items (age, viral signs, and bacterial signs) were retained for multivariate analysis (using SPSS 11.0; SPSS, Chicago, IL). The weighting of each question was based on the β value of the regression coefficients and optimized for
best results with our data. The outcome measures were sensitivity, specificity, positive likelihood ratio, and posttest probability of non-GAS infection with the clinical approach as compared with throat culture.

RESULTS

General Data

A total of 220 patients were included during the study period. The mean ± SD age was 6.6 ± 2.8 years, and 56% were male. An antimicrobial treatment had been prescribed in the past 6 months for 80 (36%) patients. Most (90%) of them had received benzathine penicillin or amoxicillin. The mean number of children who lived under the same roof was 2.2 (range: 1–8 children). Among the 220 patients, 163 (74%) had no GAS isolated from their throat, whereas 57 (26%) had a pharyngeal positive culture. A GAS-positive culture was recovered in 0%, 18%, and 33% of children who were 0 to 36 months of age, 37 to 59 months of age, and older than 59 months, respectively ($P = .003$). All children were treated empirically with antibiotics independent of the bacteriologic result. Most (83%) received intramuscular benzathine penicillin. Other treatments included amoxicillin (9%), macrolides (3%), cephalaxin (3%), and amoxicillin with clavulanate (2%).

Clinical Decision Rule

The 3 questions (age, viral signs, and bacterial signs) of our decision rule had a $\beta$ value of the regression coefficients of 2.8, 0.8, and 1.0, respectively. The scoring system is presented in Table 1, and the decision rule to apply according to the score is shown in Table 2.

The classification of our children in our study according to this clinical approach and the result of the throat culture is shown in Table 3. A cutoff of 8 was chosen as having the optimal risk/benefit ratio. The discriminative ability of the model at the cutoff value $\geq 8$ was calculated according to sensitivity, specificity, positive likelihood ratio, and posttest probability in Table 4.

We designed 2 different decision rules depending on the accessibility to microbiologic diagnosis. A clinical score $\geq 8$ suggests a symptomatic treatment with an 84% specificity for non-GAS pharyngitis. Those children had a likelihood ratio for non-GAS pharyngitis of 2.6, which give a posttest probability for non-GAS pharyngitis of 88%. Nine (16%) of 57 children with a score $\geq 8$ nevertheless had a GAS-positive culture. The clinical characteristics of these children are shown in Table 5. In medical settings where bacteriologic diagnosis is unavailable, the application of that recommendation would have reduced the antibiotic prescription by 41%.

In medical settings where limited bacteriologic diagnosis is available, a score $< 8$ can be refined into 2 distinct situations. In case of a score result from 5 to 7, an antibiotic treatment would be recommended if the culture were positive for GAS. Only 16% of the children of our population would fall into this intermediate category

### Table 1: Scoring System

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age?</td>
<td>$\geq 35$ mo</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>36–59 mo</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>$\geq 60$ mo</td>
<td>2</td>
</tr>
<tr>
<td>Viral signs?</td>
<td>No sign</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1 sign</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>$\geq 2$ signs</td>
<td>10</td>
</tr>
<tr>
<td>Bacterial signs?</td>
<td>No sign</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>1 sign</td>
<td>$-2$</td>
</tr>
<tr>
<td></td>
<td>$\geq 2$ signs</td>
<td>$-4$</td>
</tr>
</tbody>
</table>

Viral signs were defined as conjunctivitis, coryza, cough, diarrhea, and viral-like exanthema. Bacterial signs were defined as tender cervical node, headache, petechia on the palate, fever $>38.5^\circ C$, abdominal pain, and sudden onset (<12 hours). The total score will be determined by summing the values attributed to age and presence or absence of viral and bacteriological signs and will determine the therapeutic option as shown in Table 2.

### Table 2: Treatment Decision Rule According to Total Clinical Score in 2 Different Situations of Availability of Microbiological Resources

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Microbiological Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 8$</td>
<td>Symptomatic</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>$&lt; 8$</td>
<td></td>
<td>Antibiotic</td>
</tr>
<tr>
<td>$\geq 8$</td>
<td>No</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>$5–7$</td>
<td>Yes</td>
<td>Antibiotic if positive culture</td>
</tr>
<tr>
<td>$&lt; 5$</td>
<td>No</td>
<td>Antibiotic</td>
</tr>
</tbody>
</table>

Bacterial diagnosis is unavailable

Limited bacteriological diagnosis is available

### Table 3: Classification of Pharyngitis According to the Total Score, Throat Culture Result (GAS Negative or GAS Positive), and Age

<table>
<thead>
<tr>
<th>Total Score</th>
<th>No. of Cases (%)</th>
<th>Throat Culture</th>
<th>Age, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GAS Negative</td>
<td>GAS Positive</td>
</tr>
<tr>
<td>$\geq 8$</td>
<td>76 (34)</td>
<td>67</td>
<td>9</td>
</tr>
<tr>
<td>$5–7$</td>
<td>35 (16)</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>$&lt; 5$</td>
<td>109 (50)</td>
<td>74</td>
<td>35</td>
</tr>
<tr>
<td>Total</td>
<td>220 (100)</td>
<td>163</td>
<td>57</td>
</tr>
</tbody>
</table>

The number of children with positive and negative GAS culture and the age repartition are shown for 3 different score results.

---

**Note:** The table and text content are cut off and not fully visible due to the image constraints. For a complete understanding, please refer to the full document or online source.
TABLE 4  Accuracy of the Clinical Diagnosis for the Identification of Non-GAS Pharyngitis With a Cutoff of ≥8

<table>
<thead>
<tr>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>LHR+ (95% CI)</th>
<th>Posttest Probability (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.41 (0.33–0.48)</td>
<td>0.84 (0.75–0.94)</td>
<td>2.6 (1.5–4.9)</td>
<td>0.88 (0.79–0.95)</td>
</tr>
</tbody>
</table>

Sensitivity is defined as the proportion of children who do not have non-GAS pharyngitis and a score of ≥8. Specificity is the proportion of children who do not have non-GAS pharyngitis and have a score of <8. The positive likelihood ratio (LHR+) expresses the ratio of the probability that a score result would be expected in children with non-GAS pharyngitis as opposed to children with GAS-positive culture. The pretest probability is 0.74 (163 of 220). The posttest probability is the proportion of children who have that particular score result and non-GAS pharyngitis. Those results are expressed with a 95% confidence interval (CI).

TABLE 5  Children Who Would Not Have Been Treated With Antibiotic if the Clinical Decision Rule Had Been Used

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Viral Signs</th>
<th>Bacterial Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Cough</td>
<td>Fever ≥38.5°C and tender cervical node</td>
</tr>
<tr>
<td>4</td>
<td>Cough</td>
<td>Fever ≥38.5°C and petechia</td>
</tr>
<tr>
<td>5</td>
<td>Coryza and cough</td>
<td>Headache, sudden onset (&lt;12 h)</td>
</tr>
<tr>
<td>6</td>
<td>Coryza and cough</td>
<td>Absent</td>
</tr>
<tr>
<td>6</td>
<td>Coryza and cough</td>
<td>Headache, fever &gt;38.5°C, tender cervical node, abdominal pain, and sudden onset (&lt;12 h)</td>
</tr>
<tr>
<td>7</td>
<td>Coryza and cough</td>
<td>Absent</td>
</tr>
<tr>
<td>8</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>8</td>
<td>Coryza and cough</td>
<td>Fever ≥38.5°C and tender cervical node</td>
</tr>
<tr>
<td>9</td>
<td>Coryza and cough</td>
<td>Fever ≥38.5°C</td>
</tr>
</tbody>
</table>

Discussion

The prevalence of pharyngitis associated with GAS-positive culture was similar (26%) to previous reports. Therefore, at least 74% of the children were treated unnecessarily with antibiotics. The presence of GAS in the throat sample depended on the age of the children. As shown previously, the incidence of GAS pharyngitis was lower in children who were younger than 5 years than in older children. However, a significant proportion of children had a GAS-positive culture in the 37- to 59-month age group. This would lead us to propose a lower age limit (3 years) for considering a GAS cause for pharyngitis as chosen for the Canadian sore throat score and in contrast with the 5-year cutoff chosen by the Infectious Diseases Society of America. In children who were younger than 36 months, no GAS was isolated in our study. This result differs from other studies that showed the presence of GAS in the throat of children who were younger than 3 years. However, the proportion of GAS infections (or colonization?) in children who are younger than 3 years is lower and is well correlated to age in this young age group. Epidemiologic variations over time and location also have been demonstrated with GAS. We assume, until validation and with the present epidemiology, that the absence of GAS in children who were younger than 3 years in our data could justify the symptomatic treatment of all of these children.

A 41% to 55% sparing of antibiotic prescriptions by use of our clinical decision rule would represent a significant impact given the high prevalence of pharyngitis in children. As in most cases, the children were given a benzathine penicillin G shot; this would also mean a significant reduction of the pain associated with this treatment and a decrease of the financial cost related to the antibiotic injection.

The posttest probability for non-GAS pharyngitis was high (corresponding to a theoretical positive predictive value of 88.1%), even without taking into account the GAS carriers among these children. The use of that pragmatic approach in our population would have resulted in antibiotic abstinence for 9 (16%) children with pharyngitis that was associated with a GAS-positive culture. However, this seems acceptable because, first, 16% is lower than the general pediatric GAS carriage rates (20%–50%). Second, the sensitivity of throat culture is limited to a maximum of 90% in study settings (this could be lower in the day-to-day medical practice), and the culture does not distinguish between carriage and infection. Serologic examinations were not performed in this study, and we do not know whether these 9 children were infected by GAS or only carriers. In an additional validation study, the capacity of this scoring system to discriminate between carriage and infection will be investigated in the patients with high score and positive culture. The true specificity of our clinical decision rule could be underestimated in the present study if such patients were carriers.

Rheumatic fever still is highly prevalent in many developing countries (one third of the Brazilian heart surgeries in 2004). In pediatric patients, the efficacy of primary prevention of rheumatic fever by antibiotic treatment of GAS pharyngitis has not been demonstrated firmly. Some studies showed a positive effect of this prevention, but design flaws and use of atypical populations limit the applicability of these studies to children in developing countries. However, a careful attitude has been favored and antimicrobial treatment of GAS pharyngitis probably can be justified in countries with a high prevalence of rheumatic fever. Nevertheless, the hypothetical prevention of rheumatic fever has to be balanced against the development of antimicrobial resistance and its consequences.

Another scoring system was constructed for use in children from Cairo (Egypt). The use of this score would have allowed for a 37.5% reduction of unnecessary antibiotic therapy with 9% of missed streptococcal cases in the study population of Cairo. When we applied this Egyptian score to our Brazilian children population,
we obtained only a 20% reduction of unnecessary antibiotic therapy with 12.5% missed streptococcal cases. This variability could be attributable to epidemiologic differences between Cairo and Brazil. However, a scoring system directed for best sensitivity to non-GAS pharyngitis with an acceptable specificity theoretically could be more efficient in terms of antibiotic reduction.

There are several limitations to our study. First, the number of included children was small. Second, this clinical decision rule has to be validated on a large population of children who attend different medical settings. Third, the acceptability of this scoring system by the general physician and pediatricians has to be evaluated in the daily practice. The validation also should include bacterial serology and viral culture and serologies to improve distinction between carriage and infection.

CONCLUSIONS
This clinical decision rule for pharyngitis management was constructed on the basis of the reality of public pediatric practice in Brazil, which could be representative of many emerging countries of the developing world. Clinically based and locally designed guidelines in such setting could be a potent incentive for physicians to modify their prescribing practice.

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