Effectiveness of clinical guidelines for the presumptive treatment of streptococcal pharyngitis in Egyptian children

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Background Primary prevention of acute rheumatic fever requires antibiotic treatment of acute streptococcal pharyngitis. In developing countries, clinicians must rely on clinical guidelines for presumptive treatment of streptococcal pharyngitis since bacterial culture and rapid diagnostic tests are not feasible. We evaluated the WHO Acute Respiratory Infection guideline in a large urban paediatric clinic in Egypt.

Methods Children between 2 and 13 years of age who had a sore throat and pharyngeal erythema were enrolled in the study. Clinical, historical, and demographic information was recorded and a throat culture for group A beta-haemolytic streptococci was done. Sensitivity (\% of true-positive throat cultures) and specificity (\% of true-negative throat cultures) were calculated for each clinical feature. The effect of various guidelines on correct presumptive treatment for throat-culture status was calculated.

Findings Of 451 children with pharyngitis, 107 (24\%) had group A beta-haemolytic streptococci on throat culture. A purulent exudate was seen in 22\% (99/450) of these children and this sign was 31\% sensitive and 81\% specific for a positive culture. The WHO Acute Respiratory Infections (ARI) guidelines, which suggest treatment for pharyngeal exudate plus enlarged and tender cervical node, were 12\% sensitive and 94\% specific; 13/107 children with a positive throat culture would correctly receive antibiotics and 323/344 with a negative throat culture would, correctly, not receive antibiotics. Based on our data we propose a modified guideline whereby exudate or large cervical nodes would indicate antibiotic treatment, and this guideline would be 84\% sensitive and 40\% specific; 90/107 children with a positive throat culture would...
correctly receive antibiotics and 138/344 with a negative throat culture would, correctly, not receive antibiotics.

Interpretation The WHO ARI clinical guideline has a high specificity but low sensitivity that limits the unnecessary use of antibiotics, but does not treat 88% of children with a positive streptococcal throat culture who are at risk of acute rheumatic fever. A modified guideline may be more useful in this population. Prospective studies of treatment guidelines from many regions are needed to assess their use since the frequency of pharyngitis varies.

Lancet 1997; 350: 918-21

Introduction
Antibiotic treatment of acute streptococcal pharyngitis can prevent acute rheumatic fever, but this concept may not receive enough emphasis in less developed countries—even those with adequate primary health-care resources. [1,2] Both group A beta-haemolytic streptococcal pharyngitis and the cardiac sequelae from acute rheumatic fever are major health problems among children of less developed countries. [1,3-5] In Egypt, the incidence of streptococcal pharyngitis is 31 per 100 child-years, and between 0[center dot]4% and 1[center dot]0% of schoolchildren have clinical evidence of cardiac valvular damage probably due to acute rheumatic fever. [6-8]

Studies from the USA and Costa Rica have shown that penicillin treatment of streptococcal pharyngitis decreases the frequency of acute rheumatic fever. [9-11] But it is difficult to differentiate streptococcal pharyngitis from other causes of pharyngitis by clinical signs, [12-15] and laboratory confirmation of streptococcal infection by throat-swab culture or antigen detection is not practicable in most developing countries. [11] Simple clinical guidelines are needed to diagnose streptococcal pharyngitis to aid in primary prevention programmes of acute rheumatic fever. [1] The recommendations from different divisions of the WHO for presumptive therapy of streptococcal pharyngitis in the absence of microbiological data vary. The WHO Cardiovascular Disease Program [16] has a list of signs but does not specify which should be used for management decisions. The WHO Global Acute Respiratory Infections (WHO ARI) treatment programme suggests that, in the absence of other guidelines for children under five, acute streptococcal pharyngitis should be suspected and presumptively treated with penicillin when pharyngeal exudate plus tender, enlarged cervical lymph nodes are found. [17]

An estimated 12 million people have acute rheumatic fever or rheumatic heart disease, and these disorders account for 400 000 deaths per year worldwide and disability in hundreds of thousands of young adults and children. [1] Despite the large number of individuals with acute rheumatic fever and the possibility of prevention, there are few reports from developing countries on the association between clinical signs and group A beta-haemolytic streptococcal cultures. [18,19] We are not aware of prospective evaluations of the WHO ARI guidelines.
We investigated the proportion of children with clinical pharyngitis who had a positive throat culture for group A beta-haemolytic streptococci in an urban clinic in Cairo, Egypt, and assessed associations between clinical features and throat-culture status. We also estimated the effect of the WHO ARI guidelines on presumptive antibiotic treatment. (Table 1)

Table 1. Frequency of clinical features and association with throat-culture status

Methodstoctoc
Children aged 2-13 who presented with sore throats to the outpatient clinic of the Abu Reesh Children's Hospital, University of Cairo, were eligible for the study. The inclusion criteria were: a history of sore throat; unequivocal erythema of the pharynx; and parental consent for the study. The exclusion criteria were: a history of rheumatic fever; another diagnosis requiring antibiotic treatment, such as otitis media or lower respiratory-tract infection; antibiotic treatment in the previous 7 days; and residence outside Cairo. Children who met the study criteria were referred to one of four paediatricians who verified the entry criteria, obtained and documented informed consent, and recorded demographic, socioeconomic, historical, and clinical data.

We used these definitions of the clinical features: a history of fever was that given by a parent; observed fever was an oral temperature greater than 38[center dot]0[degree sign]C, exudate was white or yellow matter seen on pharynx or tonsils; a tender node was tenderness of an anterior cervical lymph node on palpation confirmed either by a statement from the child or by his or her facial expression; an enlarged node was an anterior cervical lymph node greater than 1[center dot]5 cm; and pain on swallowing was by history.

Throat-swab cultures (Culturette, Baxter, McGaw, IL, USA) were taken by a standard method [20] and delivered to the microbiology laboratory within 4 h. beta-haemolytic colonies identified as Streptococcus pyogenes were grouped (Directigen, BBL Microbiology Systems, Cockeysville, MD, USA) and any group A isolates were deemed a positive culture.

The standard practice in this clinic is to treat pharyngeal erythema or fever with 10 days of oral ampicillin or a single injection of benzathine penicillin. Children with a history of a reaction to penicillin had an intradermal penicillin-sensitivity test. The study was approved by the institutional review board of Johns Hopkins Hospital and by the Ministry of Health, Cairo.

The effect of the different clinical features for presumptive therapy was assessed as the proportion of culture-positive children who would correctly receive antibiotic therapy (% positives treated) and the proportion of culture-negative children who would not receive unnecessary antibiotics (% negatives not treated).
Sensitivity (% of true positives), specificity (% of true negatives), and positive predictive values were calculated for each clinical feature. The chi squared test was used to analyse the associations between sex or clinical features and throat-culture status. [21]

**Results**

451 children were enrolled in the study between October, 1992, and August, 1993. 41% of the children were under 5 years of age and 48% were girls. Overall, 107 (24% [95% CI 20-28%]) children had a positive throat culture for group A beta-haemolytic streptococci. The lowest rate of positive cultures was in children aged between 2 and 3 years and the highest rate was in those between ages 6 and 8 (Figure 1). There was no significant difference in the rates of positive cultures between boys and girls in any age-group. The numbers and percentages of children with specific signs and symptoms are given in the table. The proportion of children with these signs was similar in those older and younger than 5 years of age.

Exudate, tender nodes, and observed temperature greater than 38[°C] each had a high specificity but low sensitivity. By contrast, a large node had a high sensitivity and low specificity. A history of fever had greater than 90% sensitivity for a positive culture and a low specificity (less than 15%), but this common feature was not statistically associated with a positive culture (p>0.09). The sensitivity and specificity of the clinical features were not significantly different between children older or younger than 5 years of age.

The combination of signs recommended by the WHO ARI for presumptive treatment occurred in only 7.5% of all children with pharyngitis and were highly specific (93%) but had a sensitivity of only 12%. The effect on presumptive treatment as suggested by these guidelines or by individual clinical features is shown in Figure 2. The WHO ARI guideline would suggest antibiotic therapy for only 34 children, 13 with group A beta-haemolytic streptococci on culture, and would indicate no treatment for 417 children including 94 who had positive throat-cultures.
Our data suggest a guideline that includes the features of enlarged anterior cervical nodes or pharyngeal exudate—features with high sensitivity and good specificity. This modified guideline would have suggested antibiotic treatment for 296 children including 90 with group A beta-haemolytic streptococci (84% of all culture-positive children correctly treated) and would indicate no treatment for 155 children including 17 with a positive throat culture. 40% of culture-negative children would not receive antibiotics by these criteria. The addition of other features such as no cough, fever, or tender nodes did not substantially improve this modified guideline.

Discussion

We found that the clinical features of children with sore throats in a Cairo paediatric clinic have a wide range of sensitivity and specificity in predicting a throat-culture positive for group A beta-haemolytic streptococci, and are similar to results of studies of children in the USA. [15] The clinical features that correctly indicate antibiotic therapy for a high proportion of culture-positive children also lead to inappropriate treatment of a high proportion of culture-negative children (Figure 2). The local practice of antibiotic treatment for all children with pharyngitis and fever will include most culture-positive children but also results in unnecessary therapy for 80% of children who are negative for group A beta-haemolytic streptococci. Although this approach may reduce the incidence of acute rheumatic fever, [11] it has the disadvantage of substantial over-use of antibiotics and the consequent risk of increasing resistance to penicillin in S pneumoniae, Haemophilus spp, and other colonising organisms.

The WHO ARI criteria had the highest positive predictive value, but also missed 88% of the culture-positive children who should have been treated. According to these criteria, a very small fraction of culture-negative children would be treated and inappropriate use of antibiotics is limited. However, the very low sensitivity of these criteria suggests that they will not substantially decrease the incidence of acute rheumatic fever in areas where the disorder is common. Therefore, it may be more useful to assess clinical guidelines by correct treatment for throat-culture status than by the customary sensitivity and specificity analyses. Our suggestion of a modified guideline that includes the features of enlarged anterior cervical nodes or pharyngeal exudate seems to balance both goals of presumptive antibiotic treatment for culture-positive children and limitation of inappropriate treatment of culture-negative children. These data will be analysed to establish whether a scoring system will give better results. We believe the modified guideline, if validated in other studies, would be simple to use—which is essential for primary health-care interventions.
In our study, the proportion of children with a sore throat and a positive throat culture was 24%, which is similar to that in other studies. [15] We recognise that a throat culture positive for group A beta-haemolytic streptococci in a child with pharyngitis may indicate only colonisation without streptococcal disease and therefore not at risk of acute rheumatic fever. [22] However, clinical management recommendations in industrialised countries advise antibiotic treatment of symptomatic children who have a positive throat culture or antigen test, [23] although 30-40% of these may be only colonised. [22] In our analyses, we used the same assumption of presumptive therapy for all positive throat cultures.

Large numbers of people develop rheumatic carditis in less developed regions of the world, and the availability of resources and programmes for primary prevention is variable. Clinicians and policy-makers should determine locally appropriate approaches to this clinical problem. [24] If a validated clinical guideline is developed, a policy of presumptive antibiotic treatment of pharyngitis may be useful in some settings-similar to treatment advised by WHO and UNICEF for cough and fast breathing (presumed bacterial pneumonia), fever (malaria), and dysentery (Shigellosis). [25] Because specific identification of streptococci before antibiotic treatment of pharyngitis is not practicable in most developing countries, policy-makers should consider either a policy of treatment for all pharyngitis cases [11] or pick a constellation of clinical features that allows presumptive treatment of a high proportion of people with positive throat cultures. The prevalence of streptococcal pharyngitis and acute rheumatic fever differs between countries and guidelines need to be evaluated in prospective studies.

Contributors

Mark Steinhoff contributed to all aspects of the study and had main responsibility for writing the article. Nagwa Khallaf coordinated the study and supervised the data collection. Mohammed Khalek supervised the clinical data collection. Hala Hamza, Azza Orabi, Hala Fouad, and Ahmed Ayadi enrolled the patients and recorded the clinical data. Moamena Kamel was responsible for the microbiology laboratory. All authors contributed to writing the paper.

Acknowledgments

We thank Mona Wassif and her staff in the Department of Microbiology in Abu Reesh Hospital and Mohsen El Said, Training Coordinator, National ARI program. Leon Gordis, Robert Black, Michael Gerber, Sandy Gove, and Edward Kaplan made helpful suggestions on the manuscript. This document was prepared under subcontract to Clark Atlanta University as funded by USAID/Cairo Contract #263-0203.

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