Antibiotic Stewardship for Community-Acquired Pediatric Pharyngitis: A Pre–Post Intervention Study

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ABSTRACT **Background:** Group A *Streptococcus* (GAS), the predominant bacterial pathogen of pharyngitis, is sometimes difficult to distinguish clinically from viral pharyngitis. Despite the high prevalence of viral pharyngitis in children, antibiotic treatment is common.

Objectives: To investigate the effectiveness of an antibiotic stewardship program (ASP) on antibiotic prescription in children with GAS pharyngitis (GAS-P) at a large pediatric community clinic.

Methods: Antibiotic prescription data were collected from October 2016 to March 2017 (pre-intervention period) and from October 2017 to March 2018 (post-intervention period). The intervention was a one-day seminar for primary care pediatricians on the diagnosis and treatment of GAS-P in children according to national guidelines.

Results: The overall prevalence of testing differed between the two time periods. There was a decrease in children who did not undergo any testing (from 68% to 63%), an increase in streptococcal rapid antigen detection testing (from 28% to 32%), and a slight increase in throat cultures (from 3% to 4%) (P = 0.02). There was no change in the types of antibiotics prescribed before and after the intervention (P = 0.152).

Conclusions: The ASP resulted in a slight reduction in the percentage of children who did not undergo laboratory testing for GAS-P and a slight reduction in the percentage of children who received antibiotic treatment. The ASP did not reduce the use of broad-spectrum antibiotics and macrolides.

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Group A *Streptococcus* (GAS) is the predominant bacterial pathogen of pharyngitis, accounting for approximately one-quarter of cases of pharyngitis that bring children to medical attention [1,2]. Appropriate antimicrobial therapy in GAS pharyngitis (GAS-P) is important for the prevention of acute rheumatic fever (RH); suppurative complications (e.g., peritonsillar abscess, cervical lymphadenitis, mastoiditis, and other invasive infections); the improvement of clinical symptoms and signs; and the reduction of transmission of GAS to family members, classmates, and other close contacts of the patient [3-6]. However, GAS-P is sometimes difficult to distinguish clinically from viral pharyngitis. Antibiotic treatment for children who have viral pharyngitis is ineffective, exposes them to antibiotic side effects, creates unnecessary costs, and contributes to antimicrobial resistance [7]. The guidelines on the diagnosis and treatment of GAS-P in children according to the Infectious Disease Society of America (IDSA) [8], the American Academy of Pediatrics (AAP) [9], and the Israeli Pediatric Association [10] recommend that patients whose clinical presentation is consistent with GAS-P be tested with a streptococcal rapid antigen detection test (RADT) and/or throat culture and antibiotically treated if either is positive. Testing is not recommended for patients whose representation is most consistent with a viral etiology [8-10]. Despite the high prevalence of viral pharyngitis in children, antibiotic treatment is common. Studies evaluating the management of pharyngitis among pediatric providers have identified high rates of antibiotic prescription even for patients with negative GAS tests [11].

We evaluated the impact of a targeted physician educational intervention on the quality and appropriateness of antibiotic prescription for the treatment of GAS-P in a large academic primary care pediatric community clinic.

PATIENTS AND METHODS

SETTING AND DATA SOURCE

Clalit Health Services (CHS) is Israel's largest health fund and serves as both insurer and healthcare provider, insuring 54% of Israel's population and supplying most of the healthcare services within its system. These services include primary, secondary, and tertiary care, as well as pharmacies and paramedical amenities. In CHS, children are predominantly treated at community-based primary healthcare clinics. At our pediatric community healthcare center (PCHC), the staff includes eight board-certified pediatricians who provide acute and preventive care to 9000 children and adolescents aged 1 day to 18 years of age. During the study period, the average number of monthly pediatric patient visits to our PCHC was approximately 7500. All the patients belong to the PCHC as a group. All CHS's primary and secondary care physicians use an advanced electronic medical records system, which feeds into the central database of the organization.

In our study, we included otherwise healthy children and adolescents aged 3 to 18 years. We excluded those who were diagnosed with another bacterial infection during the visit, had a medical condition likely to cause deviation from typical pharyngitis management, were already taking antibiotics, or had been treated for GAS-P within the previous 30 days.

In this study, the antibiotic prescription practice as per recommendation guidelines for the treatment of GAS-P was examined before and after the educational intervention, held in September 2017. The study covered two winter seasons when GAS-P morbidity was maximal: pre-intervention from 1 October 2016 to 30 March 2017, and post-intervention from 1 October 2017 to 30 March 2018. The educational intervention consisted of a 1-day seminar on the diagnosis and treatment of GAS-P based on the principles of the AAP, IDSA, and Israeli Pediatric Association guidelines. A written summary of the recommendations was distributed to the participants. The physicians were not aware that they were participating in a research study, but rather in a project to improve the judicious use of antibiotics. Antibiotic prescription data were collected from the computerized records of the PCHC for all visits by patients aged 3 to 18 years of age who were diagnosed with GAS-P during the study period. We compared the appropriateness of antibiotics use for GAS-P before and after the educational intervention. All eight board-certified pediatricians from our center who treated children with pharyngitis/tonsillitis participated in the seminar.

We identified appropriate antibiotic treatment as the first-line antimicrobial agent stipulated by the judicious use of antimicrobial agents for pediatric GAS-P as per local and international guidelines.

STATISTICAL ANALYSIS

We reported descriptive findings using proportions and means with standard deviations, before and after the educational intervention. We used Student's *t*-tests to compare continuous variables as appropriate, and Pearson's chi-square test to compare categorical variables.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Clalit Health Services (approval number 0080-17-COM2).

Table 1. Prescribed antibiotics for children diagnosed with pharyngitis before and after the intervention, by streptococcal testing status

	Winter 2016-2017 (n=1657)				Winter 2017-2018 (n=1710)				
	Total	Prescribed antibiotics		*P**	Total	Prescribed antibiotics		*P***	*P****
		Yes (n=845)	No (n=812)	< 0.001		Yes (n=848)	No (n=862)	< 0.001	0.02
No testing	1125 (68%)	476 (56%)	649 (80%)		1074 (63%)	467 (55%)	607 (70%)		
Rapid test only	465 (28%)	332 (39%)	133 (16%)		554 (32%)	347 (41%)	207 (24%)		
Throat culture only	50 (3%)	26 (3%)	24 (3%)		62 (4%)	26 (3%)	36 (4%)		
Both tests	17 (1%)	11 (1%)	6 (1%)		20 (1%)	8 (1%)	12 (1%)		

All values are presented as n (%)

******P*-value based on chi-square, to assess whether there was an association between prescribed antibiotics and the type of testing performed before intervention

*****P*-value based on chi-square, to assess whether there was an association between prescribed antibiotics and the type of testing performed after the intervention

******P*-value based on chi-square, to assess whether there was an association between the type of testing performed and the time of the study (pre- vs. post-intervention)

RESULTS

PATIENT CHARACTERISTICS AND TEST RESULTS

There were 1657 children diagnosed with GAS-P during the pre-intervention period, and 1710 in the post-intervention period. The mean age of the children was the same in both time periods (8.6 ± 3.9) ($P = 0.90$). There were slightly more female patients in both the pre-intervention and the post-intervention periods (54% and 52%, respectively) ($P = 0.24$).

Testing differed between children who were prescribed antibiotics and those who were not, in both time periods ($P < 0.001$). In the pre-intervention period, among children who were prescribed antibiotics, 56% did not undergo any testing, compared to 80% of the children who had no testing and who were not prescribed antibiotics. The most substantial difference in testing was due to increased rapid testing in children who were prescribed antibiotics compared to those who did not (39% vs. 16%, respectively) [Table 1]. These findings were similar in the post-intervention period ($P < 0.001$). The overall prevalence of testing differed between the two time periods, with a decrease in children who did not undergo any testing (68% to 63%) along with an increase in streptococcal RADT (28% to 32%) and a slight increase in throat cultures (3% to 4%) ($P = 0.02$).

ANTIBIOTIC TYPES PRESCRIBED

We found virtually no difference in the types of antibiotics prescribed by pediatricians before and after the intervention ($P = 0.152$) [Table 2]. Prior to the intervention, 49% of children with GAS-P had not been prescribed antibiotics; 47% were prescribed amoxicillin; and the rest (4%) were prescribed azithromycin, amoxicillin-clavulanic acid, or another type of antibiotic (ceftriaxone, cephalexin, co-trimoxazole, and roxithromycin). Following the intervention, 50% of children with GAS-P were prescribed antibiotics: 47% were prescribed amoxicillin and the remainder (3%), azithromycin, amoxicillin-clavulanic acid, or another type of antibiotic (ceftriaxone, cephalexin, co-trimoxazole, and roxithromycin).

Table 2. Type of antibiotic prescribed for children diagnosed with pharyngitis before and after the intervention, by testing status

Antibiotic type	Winter 2016–2017 (n=1657)	Winter 2017–2018 (n=1710)	*P*-value
Amoxicillin	770 (47%)	793 (47%)	0.152
Azithromycin	57 (3%)	40 (2%)	
Other*	18 (1%)	15 (1%)	
None	812 (49%)	862 (50%)	

All values are presented as n (%)

P-value was assessed using the chi-square test

*Ceftriaxone, cephalexin, co-trimoxazole, or roxithromycin

DISCUSSION

Our study provides a true depiction of pediatrician-prescribed antibiotics for GAS-P among children and adolescents treated by primary care pediatricians at a large academic PCHC. After the educational intervention, there was a reduction in the percentage of children who had no test for GAS-P diagnoses (from 68% to 63%), and among those who had no test for diagnosis, there was a reduction in the percentage of children who eventually were not treated with antibiotics (from 80% to 70%). The percentage of children who underwent RADT before and after the educational intervention was similar (28% and 32%, respectively), as well as a similar percentage of children who underwent RADT and who were treated with antibiotics before and after the educational intervention (39% and 41%, respectively). However, there was an increase in the number of children who underwent RADT and were not treated with antibiotics before and after the educational intervention (16% and 24%, respectively). The rate of using throat culture only, or using both RADT and throat culture for diagnosis of GAS-P, and the distribution of prescribed antibiotics were not statistically different before and after the educational intervention.

We assumed that some of the clinicians did not adhere strictly to the ASP and were more likely to prescribe an antibiotic if the patient had a rash that might be compatible with scarlet fever, in case of tonsillar exudate, or on weekends when the lab was unavailable.

Most cases of pharyngitis (70–80%) in children are secondary to viruses (e.g., influenza, parainfluenza, rhinovirus, adenovirus, human coronavirus, respiratory syncytial virus, coxsackie, Epstein-Barr virus, cytomegalovirus, herpes viruses). If signs and symptoms are suggestive of viral infection, RADT or bacterial culture is not recommended [12]. GAS is responsible for 15–30% of pharyngitis visits [12,13]. Rare bacterial causes of pharyngitis that require antibiotics include group G and C *Streptococcus* (similar presentation to GAS but with no risk for RF), *Fusobacterium* (Lemieree's syndrome), *Arcanobacterium* (a rare cause of pharyngitis in adolescents), and *Neisseria gonorrhea* (in sexually active adolescents) [12]. Unnecessary antibiotic use contributes to unwanted side effects such as allergic reactions and diarrhea and may increase antibiotic resistance [7]. Nonetheless, 50–60% of patients diagnosed with pharyngitis receive an antibiotic prescription [2,12].

About 21% of the general pediatric population are carriers (3–26%) and they are not associated with acute RF and do not typically transmit infection [12]. Antimicrobial therapy is not indicated for most chronic streptococcal carriers.

Different clinical scoring systems have been proposed to assess the probability that a patient has GAS-P [14]. The most popular are the Centor criteria and the McIssac score [14,15]. Like the Centor algorithm, a higher McIssac composite score means a greater risk of GAS infection [14]. In addition, children younger than 3 years of age should not be routinely tested because the prevalence of GAS infection is low, and they are not at risk for acute RF [8-10].

The IDSA [8] and the Israeli Pediatric Association [10] guidelines do not endorse the use of clinical decision rules as the sole means to diagnose GAS. They recommend performing RADTs and/or throat cultures because clinical features cannot differentiate GAS-P from viral pharyngitis on its own. They also recommend performing a throat culture for children and adolescents with negative RADT results. The European Society for Clinical Microbiology and Infectious Diseases 2012 guidelines state that RADTs are unnecessary for patients with Centor score from zero to two but can be considered for those with Centor score from three to four. They do not recommend routine backup throat culture for individuals with negative RADT results [16].

Fewer than 50% of physicians use RADTs to assist in the diagnosis of GAS [17]. Kose and colleagues [18] reported that antibiotic prescription rates for children fell by 41% after pediatricians were given the results of RADTs. Randomized control trials confirmed that physicians who used RADTs prescribed antibiotics at lower rates than physicians who did not [19].

There is substantial evidence that most physicians do not use or follow any published guidelines for diagnosing and treating pharyngitis. Less than 1% of physicians clearly document using a clinical decision rule in their exam notes [20].

Linder and co-authors [21] noted that physicians prescribed antibiotics in 53% of an estimated 7.3 million annual visits of children aged 3 to 17 years for sore throat and non-recommended antibiotics to 27% of children who received an antibiotic. The prescription of antibiotics decreased from 66% of visits in 1995 to 54% of visits in 2003 ($P = 0.01$ for trend). The decrease was attributed to a decrease in the prescribing of recommended antibiotics (49% to 38%; $P = 0.002$). Physicians performed a Group A beta-hemolytic *Streptococcus* (GABHS) test in 53% of visits. They performed a GABHS test in 51% of visits for sore throat at which they prescribed an antibiotic. They concluded that GABHS throat testing was not associated with a lower overall antibiotic prescribing rate (48% tested vs 51% not tested; $P = 0.40$), but testing was associated with a lower rate of antibiotic prescription rate for children with a diagnosis of pharyngitis, tonsillitis, and streptococcal sore throat (57% tested vs. 73% not tested; P=0.001) [21].

In another study, Linder and colleagues [20] noted that the major problem in the testing and treatment of pharyngitis in adults was not which clinical guideline to follow, but that clinicians usually did not follow any guideline. They suggested performing interventions that would concentrate on an area where the guidelines agree: avoiding testing and antibiotic prescribing to patients at low risk for streptococcal pharyngitis.

In our study, the ASP for GAS-P did not significantly reduce antibiotic treatment. This finding might be due to a combination of factors, including poor clinician follow-up of clinical guidelines, parental pressure for antibiotic treatment and refusal to delay therapy, and poor parental understanding of the risk of antibiotic resistance.

The recommended treatment for GAS-P is a 10-day narrow-spectrum antibiotic (penicillin or amoxicillin) [8-10]. However, approximately 10% of all U.S. patients reported having had an allergic reaction to a penicillin-class antibiotic in the past [https://www.cdc.gov/antibiotic-use/clinicians/penicillin-allergy.html]. Even so, many patients who reported penicillin allergies did not have true immunoglobulin E-mediated reactions. When evaluated, less than 1% of the population is truly allergic to penicillin [22]. Penicillin allergy can lead to high utilization of broader spectrum antibiotics, such as cephalosporins, as a first-line alternative. Another alternative therapy often includes azithromycin or clindamycin [23].

Antibiotic stewardship encompasses a few critical issues including diagnosing appropriately; initiating indicated antibiotics on time; identifying the best drug, dose, and duration to treat the infection effectively; and preventing unnecessary antibiotic overuse [24]. A few obstacles were identified regarding outpatient ASPs, including time, financial support, the development of meaningful reports, and administrative aid. The promotion of appropriate antibiotic prescribing in outpatient clinics necessitates time and resource funding by administrative leaders [25].

STUDY LIMITATIONS

There were several limitations to our study. First, the retrospective nature of the study relied on clinician documentation. Second, our data were limited to what was available in the electronic medical records so we could not relate to additional factors that were not documented (parental request for antibiotics, undocumented anamnesis, or physical examination findings that might have influenced antibiotic selection). Third, we had no available data regarding the individual physician's prescription patterns before and after the intervention. Fourth, our study was conducted in an accredited center, which has high levels of teaching and auditing. This environment may indicate better management of patients and proper guideline adherence compared to non-accredited centers. Fifth, our study was based on a single academic community clinic and the results may not reflect the practice in other community clinic settings (such as small clinics with one or two physicians, or large non-academic group practices). Sixth, the study period was relatively short. Multi-center and longer duration studies might reflect more accurately what happens in real life.

Our data demonstrate that the implementation of an ASP yielded a slight reduction in the percentage of children who were laboratory tested for GAS-P and a lower percentage of children who received antibiotic treatment. The ASP did not reduce the use of broad-spectrum antibiotics and macrolides.

We suggest conducting periodic ASPs at healthcare centers on the recommended management of children and adolescents with a suspected diagnosis of GAS-P. Such programs should include a session on the clinical guidelines for diagnosis and treatment of GAS-P, as well as examples from daily, routine scenarios on the subject. The participating physicians should know in advance that the program's goal is to work according to the guidelines and that the results will be tested over a prolonged period. The head of the PCHC should inform the physicians periodically of the results of the intervention program until the program's goals are achieved.

In our opinion, periodic ASPs may increase the adherence to the recommended guidelines and may prevent unnecessary antibiotic overuse. They may enable appropriate diagnosis and timely initiation of the appropriate antibiotic, while reducing the risk of adverse effects. These measures yield the most efficacious and professional treatment for the patient and reduce unnecessary cost and time as well as discomfort for the patient and family members.

CONCLUSIONS

The ASP resulted in only a slight reduction in the percentage of children who did not undergo laboratory testing for GAS-P, and a slight reduction only in the percentage of antibiotic prescriptions. The ASP did not reduce the use of broad-spectrum antibiotics and macrolides. We recommend six monthly ASP programs for pediatricians with performance testing over a prolonged period until the program's goals are achieved.

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