Do Gastrointestinal Symptoms Accompanying Sore Throat Predict Streptococcal Pharyngitis?

An UPRNet Study

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BACKGROUND. The purpose of this study was to determine whether gastrointestinal (GI) symptoms are more common in streptococcal than nonstreptococcal pharyngitis, and, if so, whether these symptoms are useful diagnostic predictors.

METHODS. Patients aged 4 and older presenting consecutively to one of three family practice clinics and one emergency department with the chief complaint of sore throat were invited to participate in the study. A nurse administered a brief symptom checklist; after documenting clinical signs, the clinician assessed and treated the patient. All patients were screened for group A streptococcus using the Abbott Test Pack Plus. Patients were enrolled from January 1996 through March 1996. Significant associations of signs and symptoms with streptococcal pharyngitis were determined by chi square, likelihood ratios were calculated, and logistic regression was used to compare diagnostic prediction models with and without GI symptoms.

RESULTS. Six hundred fifty-seven consecutive patients with the presenting complaint of sore throat were enrolled in the study. The mean age of the patients enrolled was 19 years; the median age was 14. Thirty-two percent of the children (ages 4 to 18), 23% of the adults (ages 19 to 74), and 29% of all patients had streptococcal pharyngitis. Symptom frequencies for streptococcal and nonstreptococcal pharyngitis, respectively, were: nausea (39% vs 31%, $P = .14$); vomiting (14% vs 7%, $P = .004$); abdominal pain (27% vs 26%, $P = .621$); and any GI symptom (47% vs 41%, $P = .45$). When included in a predictive model with other significant predictors of streptococcal pharyngitis including age, palatal petechiae, absence of cough, and anterior cervical adenopathy, the addition of nausea or vomiting added slight predictive power to the models, but abdominal pain and "any GI symptom" did not.

CONCLUSIONS. Nausea and vomiting are somewhat more common in streptococcal than in nonstreptococcal pharyngitis, but appear to have limited usefulness as clinical predictors of streptococcal pharyngitis.

KEY WORDS. Streptococcal pharyngitis; predictors; gastrointestinal symptoms. *(J Fam Pract 1998; 46:159-164)*

Sore throat is the third most common reason for visiting a physician in the United States, accounting for 35 million (3%) of all office visits per year.[1] Literature on diagnosis and treatment of streptococcal pharyngitis in the age of the throat culture dates back more than 40 years and covers opinions, strategies and protocols of many health professionals.[2-11]

The signs and symptoms of group A beta-hemolytic streptococcal pharyngitis are similar to those of viral pharyngitis, making reliable clinical diagnosis difficult. Diagnosis and treatment of streptococcal pharyngitis is important in avoiding rheumatic fever. Several factors, including season (fall, winter); age (4 to 18 years); presence of fever, tonsillar exudate, and anterior cervical adenopathy; and absence of cough are significantly more common in streptococcal pharyngitis than in viral pharyngitis.[3-5] Because of the low predictive value of individual signs and symptoms, several probability algorithms for diagnosis and testing have been developed.[3-11] However, some clinicians treat

UPRNet is the Upper Peninsula Research Network, a rural primary care research network in Northern Michigan with 15 clinics that cooperate on research projects.

Submitted, revised, September 22, 1997.
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pharyngitis on the basis of clinical findings alone, without laboratory testing, and many base treatment on the results of a rapid assay. Another proven clinical marker for streptococcal pharyngitis could raise diagnostic accuracy enough for clinicians to make treatment decisions for some patients with greater confidence without resorting to testing.

In 1954, Breese and Disney[2] found abdominal pain and vomiting to be weakly predictive of streptococcal pharyngitis. Similar studies published since 1970 make no mention of abdominal pain, nausea, or vomiting as useful clinical predictors for streptococci infection, and gastrointestinal (GI) symptoms have not been included in published prediction algorithms. In a 1992 review, Pichichero[5] lists abdominal pain and vomiting as classic symptoms of streptococcal pharyngitis, but without reference to a primary study.

In our own 1994 unpublished pilot study of 29 consecutive patients presenting with sore throat, 12 (41%) also had nausea. Of these 12, 10 (83%) had a positive streptococcal antigen test result. The other 17 patients did not have nausea, and only 7 (41%) of these had a positive streptococcal test result, indicating a significant association of nausea with streptococcal pharyngitis (P = .02). Because of these promising results, Breese and Disney's results, and common clinical wisdom, we surmised that GI symptoms may be useful clinical predictors of streptococcal pharyngitis. The purpose of this study was to determine whether nausea, abdominal pain, or vomiting are more common in streptococcal than nonstreptococcal pharyngitis and, if so, whether these GI symptoms could be useful clinical predictors in patients presenting with sore throat.

METHODS

During the study period of January 1996 through March 1996, patients aged 4 and older who reported consecutively to three participating practices of the Upper Peninsula Research Network in Delta County, Michigan, and the local hospital emergency department with the chief complaint of sore throat were invited to participate. After obtaining informed consent, the nurse administered a brief questionnaire asking patients about the duration of the sore throat and whether they had experienced nausea, vomiting, stomach pain, fever, cough, or runny or congested nose with this sore throat. The clinician who treated the patient noted the presence or absence of the following clinical signs: pharyngeal exudate, anterior cervical lymphadenopathy, and petechiae on the throat or palate.

We tested all subjects for streptococci using the Abbott Test Pack Plus Strep A rapid antigen test (Abbott Laboratories, Abbott Park, Ill), following the procedure recommended by the manufacturer. The diagnosis of streptococcal pharyngitis was made by a positive streptococci screen result. Compared with isolation of group A streptococci from throat swabs on a 24-hour sheep blood agar culture, the Abbott Test Pack Plus Strep A is 90% sensitive and 95% specific.[12]

After descriptive data analyses were done, univariate analyses and logistic regression analyses were performed using the Statistical Analysis System (SAS). A separate chi-square test was done for each GI symptom and for "any GI symptoms" (nausea or vomiting or abdominal pain). We also performed chi-square testing to determine the association between other clinical predictors and streptococcal pharyngitis. We treated age as a categorical variable with four groups: ages 4 to 11 years, 12 to 18 years, 19 to 26 years, and 27 years and older. Sensitivity, specificity, likelihood ratios, and their confidence intervals were calculated for each symptom and sign individually.

Using logistic regression we then developed a predictive base model for streptococcal pharyngitis that included all the significant predictors of streptococcal infections, *except* GI symptoms. By adding the GI symptoms one at a time to the base model and comparing each new model with the base model, we determined if any of the GI symptoms added significant predictive power to the base model. We tested statistical significance by the log-likelihood test.

In calculating sample size we assumed a 20% to 30% prevalence of GI symptoms and decided that a difference in rates of GI symptoms in streptococcal pharyngitis compared with nonstreptococcal pharyngitis of 20% would be clinically meaningful. With a two-tailed α of .05 and a power of 90%, 368 patients were needed. We intentionally oversampled in order to have enough power to perform subgroup analyses by age, the results of which are not reported in this paper. We used the Holm-adjusted P value for the four major GI predictors tested, including nausea, vomiting, abdominal pain, and "any GI symptom."[13,14] We did not adjust for multiple testing for the other clinical predictors of streptococcal pharyngitis because we considered that part of the analysis to be exploratory.

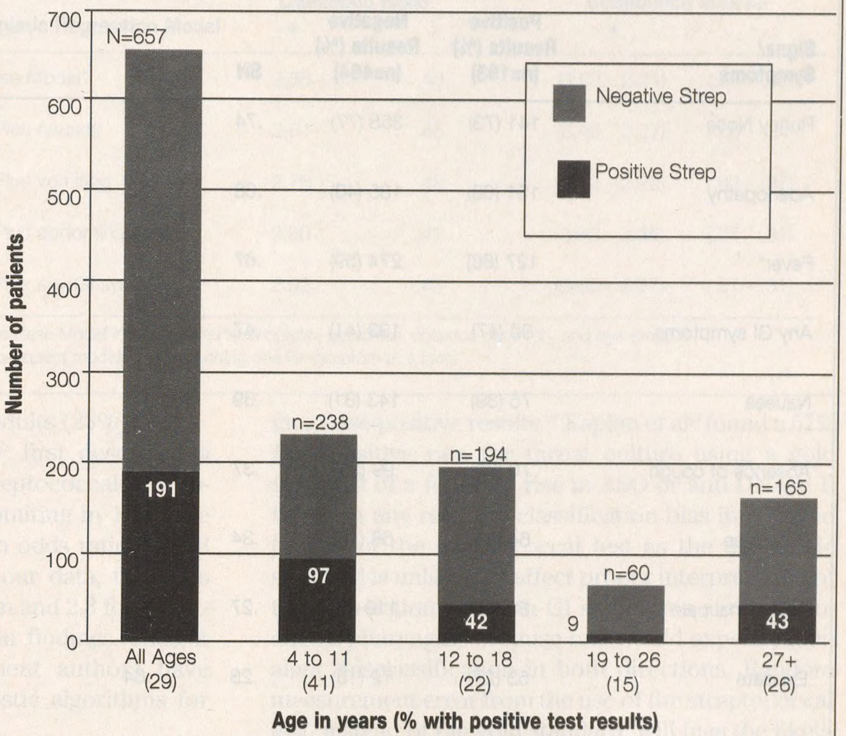
The Michigan State University Committee on Research Involving Human Subjects approved this study protocol.

RESULTS

Six hundred eighty-seven patients were invited to participate in the study, and 657 (96%) patients had complete data. One patient refused to participate and 29 questionnaires were not usable for the following reasons: the patient questions were not complete (3), the clinician questions were not complete (5), the patient did not report a sore throat (9), the patient was younger than 4 years old (6), the results of the streptococcal screen test were missing (4), and data about GI symptoms were missing (2). Most patients (93%) enrolled at the three family practice offices, with the remainder enrolling at the emergency department.

FIGURE

Age Distribution of Patients with Sore Throat and Percentage of Patients with Positive Test Results for Streptococcal Pharyngitis, by Age Group



One hundred ninety-three (29%) of the subjects had streptococcal pharyngitis by antigen test. The age distribution of patients enrolled and the percentage of positive streptococcal test results by age group are shown in the Figure. The mean age of the patients was 19 years, with the majority (72%) being between 4 and 26 years old. Forty-one percent of the children ages 4 to 11 had streptococcal pharyngitis, and the incidence declined with increasing age. The rate of positive tests was 32% at the emergency department and the two local clinics; the rate was 22% at the third clinic located in a smaller town 7 miles away. The mean duration of sore throat was 3.5 days.

Table 1 shows the frequency of symptoms and signs in patients with and without streptococcal pharyngitis, and the sensitivities, specificities, and likelihood ratios of individual symptoms when considered alone. Many of the symptoms are common to both groups. Of the patient-reported symptoms, vomiting (P = .004, Holm-adjusted) and absence of cough (P = .001) were significantly associated with streptococcal pharyngitis on univariate analysis. Nausea (P = .14, Holm-adjusted), abdominal pain (P = .621, Holm-adjusted), and "any GI symptom" (P = .45, Holm-adjusted) were not significantly associated with streptococcal pharyngitis. The clinical signs of exudate, anterior cervical lymphadenopathy, and petechiae were significantly associated with streptococcal infections on univariate analysis (P = .001 for each one). Age group was associated with streptococcal pharyngitis, with younger patients (ages 4 to 11) being more likely to have it (P = .01). The duration of symptoms was not significantly associated with streptococcal pharyngitis.

Logistic regression was used, beginning with the base model, to determine how much predictive power the GI symptoms might contribute to the model (Table 2). Our base clinical predictive model included absence of cough, exudate, petechiae, and

TABLE 1

Frequency of Signs and Symptoms in Patients with Positive and Negative Streptococcal Pharyngitis Screening Test Results (N=657)

Signs/ Symptoms	Positive Results (%) (n=193)	Negative Results (%) (n=464)	SN	SP	Likelihood Ratio (CI) +	Likelihood Ratio (CI) -
Runny Nose	141 (73)	358 (77)	.74	.23	.95 (1.1, .88)	1.1 (1.5, .88)
Adenopathy	131 (68)	185 (40)	.68	.60	1.7 (2.0, 1.5)	.53 (.65, .42)
Fever*	127 (66)	274 (59)	.67	.40	1.1 (1.3, .99)	.81 (1.0, .66)
Any GI symptoms	90 (47)	193 (41)	.47	.74	1.1 (1.3 -.93)	.91 (1.0 - .79)
Nausea	75 (39)	143 (31)	.39	.69	1.2 (1.5 - 1.0)	.88 (.99 - .78)
Absence of cough	70 (36)	99 (21)	.37	.78	1.7 (2.2 - 1.3)	.80 (.89 - .72)
Petechiae	64 (33)	68 (15)	.34	.85	2.3 (3.1 - 1.7)	.77 (.86 - .70)
Abdominal pain	53 (27)	119 (26)	.27	.74	1.1 (1.4 - .81)	.97 (1.1 - .89)
Exudate	53 (27)	72 (15)	.28	.84	1.7 (2.4 - 1.3)	.85 (.93 - .78)
Vomiting	28 (14)	32 (7)	.15	.93	2.1 (3.4 - 1.3)	.91 (.97 - .86)

*Fever reported by patient or parent.
SN denotes sensitivity; SP, specificity; CI, confidence interval.
Note: The formula for the likelihood ratios with confidence intervals (CI) from J Clin Epidemiol 1991;44:763-770.

age group. (Tonsillar exudate, though significant on univariate analysis, was not an independent predictor in the logistic model.) Each GI symptom was added to the base model separately, one at a time. Predictive power of the model significantly increased when nausea ($\chi^2 = 5.34, P < .02$) or vomiting ($\chi^2 = 6.40, P < .02$) was included. The probability of having streptococcal pharyngitis increased 7% with the presence of nausea, and 14% with the presence of vomiting. Abdominal pain or "any GI symptom" did not add predictive power to the base model.

DISCUSSION

In our sample, vomiting was somewhat more common in streptococcal than nonstreptococcal pharyngitis. Nausea showed a trend but did not reach statistical significance when adjusted for multiple testing. Abdominal pain and "any GI symptom" were not associated with streptococcal pharyngitis. However, the GI symptom rates between streptococcal and nonstreptococcal pharyngitis did not differ markedly even for nausea or vomiting. In our series, nausea was reported in 39% of streptococcal pharyngitis cases and in 31% of nonstreptococcal pharyngitis cases, a rather small difference. For vomiting, the figures are 14% and 7%, respectively. But vomiting is reported infrequently, so this symptom has limited diagnostic value. The modeling did show small but significant improvements in predictive power with the addition of nausea or vomiting. That these improvements are clinically meaningful is doubtful because the likelihood ratios of diagnostic models did not improve with the addition of any of the GI symptoms. However, our models would need to be validated or refuted on other samples of patients with pharyngitis in other locations with different prevalences of streptococcal pharyngitis. The literature on group A streptococcal pharyngitis indicates a peak incidence in adults of 5% to 9% and 28% to 30% in children presenting with sore throat; our rates were somewhat higher in children (32%) and much higher in adults (23%).[15]

TABLE 2

Likelihood Ratios for Logistic Regression Models to Predict Streptococcal Pharyngitis

Logistic Regression Model	Likelihood Ratio +	Likelihood Ratio -	Confidence Interval +	Confidence Interval -
Base Model*	2.86	.43	(3.53 - 2.31)	(.58 - .32)
Plus nausea	2.81	.45	(3.48 - 2.27)	(.60 - .34)
Plus vomiting	2.76	.48	(3.42 - 2.22)	(.62 - .37)
Plus abdominal pain	2.90	.42	(3.60 - 2.35)	(.57 - .31)
Plus any GI symptoms	2.92	.43	(3.60 - 2.37)	(.57 - .31)

*The Base Model includes lymphadenopathy, petechiae, absence of cough, and age group. Subsequent models include adding one GI symptom at a time.

Although Breese and Disney[2] first described a positive association between streptococcal pharyngitis and abdominal pain and vomiting in 1954, the association was quite weak, with odds ratios of 1.3 and 1.8, respectively. Based on our data, the odds ratios were 1.1 for abdominal pain and 2.3 for vomiting, which is quite similiar to their findings. Thus, it is not surprising that subsequent authors have ignored GI symptoms in diagnostic algorithms for pharyngitis.

There are potential weaknesses in our study design. First, the offices that enrolled patients used tympanic thermometers, but because of the thermometers' known inaccuracies,[16-19] we could not analyze temperature data with any confidence. However, frequency of patient or parent report of fever was not significantly different in the two groups of patients with sore throat.

Second, we used streptococcal antigen tests rather than throat cultures to diagnose streptococcal pharyngitis. To check our false-negative rate, blood agar throat cultures were done on 271 consecutive study patients whose streptococcal test results were negative. In only four cases was the culture positive for group A beta-hemolytic streptococci when the streptococcal screen result was negative, giving a false-negative rate of 1.5% compared with throat culture (95% confidence interval, 0.1 to 2.9). The false-positive rate for streptococcal antigen screen results is known to be very low. Moreover, some argue that streptococcal antigen tests are better diagnostic tests for acute streptococcal pharyngitis than throat cultures because they are less likely than cultures to give false-positive results.[20] Kaplan et al[21] found a 57% false-positive rate for throat culture using a gold standard of a four-fold rise in ASO or anti-DNAse B titers. At any rate, the classification bias introduced by use of the streptococcal test as the diagnostic standard is unlikely to affect proper interpretation of the association between GI symptoms and streptococcal pharyngitis because one would expect equivalent misclassification in both directions. Random measurement error from the use of the streptococcal test, instead of the gold standard, will bias the likelihood ratios toward 1.0, thus potentially underestimating the predictive value of GI symptoms for streptococcal pharyngitis.

Although vomiting and nausea are slightly more common in streptococcal pharyngitis than in nonstreptococcal pharyngitis, the association is weak, and these symptoms have minimal diagnostic value in the evaluation of sore throat.

ACKNOWLEDGMENTS

Sincere thanks to the American Academy of Family Physicians and its Foundation, the Michigan Academy of Family Physicians Foundation, and the Blue Cross/Blue Shield Foundation of Michigan for their financial support of the project.

The authors would like to thank Patti Cain, Research Assistant, for her work on the project. Thank you to Dr John Sesney and Teresa Ettenhofer for their assistance in completing the project. We appreciate the cooperation and efforts of the Doctor's Park Family Physicians Group and their lab, the Emergency Department at St Francis Hospital, the St Francis Hospital Lab, and the Order of St Francis Family Health Centers in Escanaba and Gladstone, Michigan.

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