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Streptococcal group A, C and G pharyngitis in school children: a prospective cohort study in Southern India

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Abstract

Diagnosing streptococcal pharyngitis in children on the basis of clinical appearance and throat culture is complicated by high colonisation rates and by the ability of other pathogens to cause clinically similar disease. To characterise the epidemiology of Lancefield Group A, C and G β-haemolytic streptococcus (GAS, GCS and GGS, respectively) in children, we conducted a 2-year prospective study of 307 school children between 7 and 11 years old. GGS and GAS were commonly identified organisms both for silent streptococcal colonisation and symptomatic sore throat, while GCS was uncommonly found. Streptococcal culture positivity at the time of clinical pharyngitis was estimated to reflect true streptococcal pharyngitis in only 26% of instances, with the frequency varying from 54% for children rarely colonised to 1% for children frequently colonised. Numerous GAS *emm* types were identified, including several types previously associated with severe pharyngitis (e.g. *emm* types 1, 3 and 28). No severe complications were seen in any child. These data suggest that the clinical diagnosis of streptococcal pharyngitis is likely to remain difficult and that treatment decisions will remain clouded by uncertainty. There remains a need for organism-specific rapid point-of-care streptococcal diagnostic tests and tests that can distinguish between streptococcal colonisation and disease.

Introduction

During the first half of the 20th century, acute streptococcal pharyngitis was usually diagnosed on clinical grounds, and severe cases were believed to be caused almost exclusively by what was then known as *Streptococcus hemolyticus*, and which is now known as *Streptococcus pyogenes*, or the Lancefield Group A β-haemolytic streptococcus (GAS). In recent decades, severe GAS pharyngitis has become much less common in the developed world, apparently because of antibiotic treatment and widespread endemic circulation of less pathogenic GAS strains. At the same time, bacteria of other streptococcal groups, including Lancefield Group C and G streptococci (GCS and GGS) have been circulating endemically and have also caused pharyngitis and occasional invasive diseases [1–3]. Throat culture plated on blood agar remains the accepted diagnostic gold standard for these streptococci [4], but positive throat cultures are found not only in pharyngitis [4], but frequently in transient or long-term carriers, rendering isolation an incidental finding in many patients with clinical pharyngitis of other aetiologies. As a consequence, clinical diagnosis of GAS pharyngitis has become less reliable, while GCS and GGS isolations in children with pharyngitis may be of uncertain significance.

This diagnostic uncertainty led us to attempt to estimate, in a prospective cohort of school children in India, the relative frequencies of colonisation with, and pharyngitis caused by, GAS, GCS and GGS, including the probability that a positive GAS, GCS or GGS throat culture in a child presenting with clinical pharyngitis indicates true pharyngitis caused by the isolated organism, rather than pharyngitis of another aetiology coinciding with streptococcal colonisation.

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Methods

Informed consent

Consent forms in Tamil were obtained from parents and assent forms were obtained from all students. The clinical protocol was approved by the Institutional Review Boards of the Christian Medical College (CMC) and of NIAID, NIH.

Determination of asymptomatic GAS, GCS and GGS colonisation

Over a two year period, throat cultures were obtained from 307 children aged 7–11 in classes 2–6 at a village school near Vellore, Tamil Nadu, India, during the first week of each month (except for summer vacation months). Some students in the study withdrew or graduated from school. We maintained a roster of approximately 225–250 children by periodically recruiting additional student volunteers. The number of colonisation visits per child had a median of 8 with 10th and 90th percentiles of 4 and 10, respectively

Detection of incident pharyngitis associated with GAS, GCS or GGS

While at school, the study children were examined weekly, excepting summer and religious holidays, for signs and symptoms of pharyngitis. Sore throat, pain on swallowing, pharyngeal or tonsilar inflammation and pharyngeal exudate indicated suspected streptococcal pharyngitis. Throat cultures were taken from all children presenting with suspected pharyngitis. Children with pharyngitis in association with throat cultures positive for GAS, GCS or GGS were treated for 10 days with the recommended dose per body weight of oral penicillin. Treatment compliance was monitored by the school teachers.

Bacteriologic diagnosis

Methodologies standardised by the World Health Organization [4] were employed for bacteriologic testing. β-haemolytic colonies of streptococci from throat cultures were isolated on sheep blood agar plates and grouped into the standard Lancefield Group A, C or G categories by the micronitrous acid-coagglutination method [5]. GAS *emm* types were determined by PCR sequence analysis [6].

Statistical analysis

For each child, the proportions of time colonised over the 2-year study period (C) was defined as the number of GAS- or GCS- or GGS-positive monthly colonisation visits divided by the total number of monthly colonisation visits. For each of the three bacteria, each child was categorised dichotomously as either 'frequently' or 'infrequently' colonised based upon whether that child's colonisation rate, C, was above or below the median C for all children for that organism. For each year of the study, and for both years combined, the probability of causation (PC) of pharyngitis was calculated separately for the two groups of children (frequently and infrequently colonised), based on the rates of pharyngitis episodes that were: (a) associated with isolation of a particular organism (RA) and (b) not associated with isolation of that particular organism (RN), according to the formula PC = (RA–RN)/RA. The rates of pharyngitis episodes for each of the three streptococci were estimated by the number of pharyngitis episodes divided by total time at risk, e.g. RA for GAS was the number of pharyngitis episodes while GAS positive, divided by the person-years of GAS positivity at monthly colonisation visits. An overall PC, for each streptococcus and for all three streptococci combined, was obtained by averaging the PCs for frequently and infrequently colonised children over the 2 years of the study (see supplementary materials for details). A generalised estimating equations approach was used to test for independence of co-colonisation by different streptococci groups [7].

Results

Frequencies of streptococcal colonisation and pharyngitis

Over the 2-year study period, the monthly pharyngeal colonisation surveys indicated that the median colonisation rate for all children combined was 0.13 for GGS, 0.08 for GAS and 0.00 for GCS. Of the 2827 monthly colonisation cultures from the 307 children, there were 433 positive GGS cultures (15.3% of all colonisation visits), 323 GAS positive cultures (11.4% of all colonisation visits) and 82 GCS positive cultures (2.9% of all colonisation visits). A total of 638 cases of pharyngitis were identified in the 307 study children: 111 (17.4%) were GGS positive, 110 (17%) were GAS positive and 30 (4.7%) were GCS positive (Table 1).

PC for GGS pharyngitis

GGS colonisation was detected in 15.3% of visits, associated with a median colonisation rate per child of 0.13 and a combined PC, based upon averaging the PCs for the frequently and infrequently colonised children, of 0.13 (95% CI −0.22 to 0.33, which includes 0 indicating no significant effect). However, the PC varied with median colonisation status. For children infrequently colonised by GGS ($C \leqslant 0.13$) the PC was 0.67 (95% CI 0.40 to 0.84) indicating a high probability that the GGS was causing the pharyngitis in children presenting with both pharyngitis and GGS isolation. On the other hand, for children frequently colonised by GGS ($C > 0.13$) the PC was −0.34 (95% CI −0.96 to −0.06), indicating that for such children, the pharyngitis rate was significantly lower when colonised with GGS compared with when not colonised with GGS.

PC for GAS pharyngitis

The overall GAS-associated PC was 0.32 (95% CI 0.01 to 0.46). For children with infrequent colonisation ($CR \leqslant 0.08$), the PC was 0.69 (95% CI 0.08 to 0.95), whereas for children with frequent colonisation ($CR > 0.08$) the PC was only 0.05 (95% CI −0.28 to 0.23).

GAS emm types in colonisation and pharyngitis

The *emm* types of the 108 GAS pharyngitis isolates were compared with 302 selected non-pharyngitis isolates from the colonisation surveys; Table 2. Forty-five different GAS *emm* types were isolated from patients with diagnosed GAS pharyngitis; three additional isolates were non-typable and are not counted in Table 2. Each of seven different *emm* types were obtained in four or more pharyngitis episodes, among them types previously identified as pathogenic, e.g. types 1 and 28. Among GAS isolated from colonised children, 66 different *emm* types were identified. A large number of the different *emm* types recovered from colonised

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Table 1. Estimates of the probability of causation (PC) and 95% confidence intervals (CI) for GAS, GCS and GGS, and any of the three streptococci

Student group	Type of visit	Group A *Streptococcus*		Group C *Streptococcus*		Group G *Streptococcus*		Any of the three Streptococci	
		Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos
All students	Colonisation	2504	323	2745	82	2394	433	2012	815
	Pharyngitis	528	110	608	30	527	111	394	244
	PC (95% CI)	0.32 (0.01 to 0.46)		0.87 (0.69 to 0.92)		0.13 (−0.22 to 0.33)		0.26 (0.06 to 0.38)	
Students with high colonisation rates	Colonisation	1144	293	491	82	978	388	732	640
	Pharyngitis	288	85	84	21	260	83	174	168
	PC (95% CI)	0.05 (−0.28 to 0.23)		0.34 (−0.47 to 0.55)		−0.34 (−0.96 to −0.06)		0.01 (−0.28 to 0.21)	
Students with low colonisation rates	Colonisation	1360	30	2254	0	1416	45	1280	175
	Pharyngitis	240	25	524	9	267	28	220	76
	PC (95% CI)	0.69 (0.08 to 0.95)		0.97 (0.92 to 0.99)		0.67 (0.40 to 0.84)		0.54 (0.33 to 0.65)	

PCs are estimated for all 307 students and for students with high and with low colonisation rates. High (low) colonisation was defined as a colonisation rate, C, greater than (less than) the median colonisation rate which was 0.08, 0.00, 0.13 and 0.25 for GAS, GCS, GGS or any the three Streptococci, respectively.
Probability of causation (PC) estimates for pharyngitis based on a weighted combination of 2 × 2 tables stratified by year of study and high/low colonisation rates. See the supplementary materials.

children were not among GAS *emm* types obtained on occasions of pharyngitis in any children.

PC for GCS pharyngitis

GCS, identified in only 2.9% of colonisation visits, was associated with a median colonisation rate of 0.00 and a combined PC of 0.87 (95% CI 0.69 to 0.92). The PC for children with lower GCS colonisation rates (C = 0), was extremely high at 0.97 (95% CI 0.92 to 0.99), whereas for children with higher colonisation rates (C > 0) the PC was only moderately high, 0.34, although statistically insignificant (95% CI −0.47 to 0.55).

PC for any streptococcus

When examining colonisation by any of the three streptococci rather than separately for each single organism (Table 1; final column labelled 'Any streptococcus'), the overall PC was 0.25 (95% CI 0.06 to 0.38).

For children with low colonisation rates (C ⩽ 0.25), the PC was 0.54 (95% CI 0.33 to 0.65) while for children with colonisation rates higher than the median (C > 0.25), the PC was 0.01 (95% CI −0.28 to 0.21).

Streptococcal co-colonisation

It is noteworthy that co-colonisation with more than one streptococcus (Table 3) occurred significantly less commonly than would be expected on the basis of chance alone, consistent with microbial interference or cross-immunity. The magnitude of the effect was substantial, e.g. the odds of GAS colonisation in the presence of GGS was 80% lower than in the absence of GGS ($P < 0.0001$). Similar findings were obtained for the other streptococcal combinations (data not shown).

No cases of acute rheumatic fever, glomerulonephritis, necrotising fasciitis or other severe streptococcal diseases were detected in the population during the 2-year study period.

Discussion

This study of the epidemiology of streptococcal colonisation and of clinical streptococcal pharyngitis in a cohort of school children, allowed estimation of the probability that a case of incident pharyngitis presenting with GAS, GCS or GGS isolation is actually due to the organism isolated. This is a meaningful distinction because acute invasive streptococcal pharyngitis requires antibiotic treatment, whereas antibiotic treatment of asymptomatic streptococcal colonisation is of unproven benefit, and incurs a risk of antibiotic side effects such as allergic reactions. Important aspects of this study include the facts that the prospectively followed childhood study population was 7–11 years old, a key age range for streptococcal pharyngitis, and that the same cohort was the source of streptococcal isolations from both asymptomatically colonised children and from children presenting with pharyngitis.

We found that the PC of pharyngitis, i.e. the estimated probability that a particular streptococcus isolated from a child with clinical pharyngitis actually caused that episode of pharyngitis, was low overall (26%), and that it depended strongly upon the individual child's historical colonisation rates for the specific bacteria isolated (GAS, GCS or GGS). For infrequently colonised children, as opposed to frequently colonised children, there was

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Table 2. A comparison of the *emm* types of GAS isolated from 108 patients with pharyngitis to the 302 GAS types isolated from the monthly throat culture surveys of the study population, excluding those volunteers with pharyngitis at the time of the survey. (Only 302 of the 323 GAS from the GAS carriers were available for *emm* analysis.)

emm type	No. GAS from pharyngitis	No. of GAS from carrier survey	*emm* type	No. GAS from pharyngitis	No. of GAS from carrier survey	*emm* type	No. GAS from pharyngitis	No. of GAS from carrier survey
28	9	15	97	2	5	69	0	5
1	5	8	102	2	1	65	0	4
15	4	1	103	2	7	86	0	3
44	4	6	105	2	4	88	0	3
49	4	14	109	2	1	8	0	2
80	4	5	110	2	6	9	0	3
st2147	4	9	st212	2	0	11	0	2
3	3	2	4	1	9	12	0	2
25	3	1	58	1	3	22	0	2
42	3	10	67	1	4	stD633	0	2
53	3	7	68	1	3	54	0	1
55	3	6	73	1	1	56	0	1
63	3	14	74	1	9	60	0	1
75	3	6	81	1	14	70	0	1
100	3	0	106	1	0	92	0	1
118	3	12	122	1	7	93	0	1
st11014	3	2	st854	1	10	104	0	1
st1731	3	10	st1389	1	4	113	0	1
36	2	1	st1759	1	0	stKNB1	0	1
39	2	2	stD432	1	2	stKNB3	0	1
71	2	5	stKNB2	1	2	stKNB4	0	1
77	2	8	82	0	10	stKNB5	0	1
85	2	6	57	0	7	stKNB6	0	1
89	2	4						
						Total	108	302

a higher probability that an episode of pharyngitis was actually caused by a streptococcus isolated from the throat at the time of pharyngitis presentation. In other words, isolation of a streptococcus from the pharyngitic throat of such an historical 'non-carrier' is more likely to represent an acute invasive streptococcal infection requiring antibiotic treatment, and less likely to represent coincidental streptococcal colonisation associated with pharyngitis of another cause. These data do not specifically

Table 3. Carriage and pharyngitis visits classified by colonisation status by culture of GAS, GCS and/or GGS organisms

GAS	GCS	GGS	Colonisation visits	(% of all visits)	Pharyngitis visits	(% of all visits)
–	–	–	2012	71.2	394	61.6
+	–	–	307	10.9	103	16.1
–	+	–	72	2.5	29	4.5
–	–	+	413	14.6	107	16.7
+	+	–	3	0.1	1	0.2
+	–	+	13	0.5	6	0.9
–	+	+	7	0.2	0	0.0
+	+	+	0	0.0	0	0.0

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show that streptococcal colonisation prevents pharyngitis, but they do indicate that if clinicians were able to identify historical carriers and non-carriers of streptococci at the time of presentation with pharyngitis, diagnosis and treatment could be optimised. However, while feasible in a study such as ours, identifying streptococcal carriage is not practical in a real-world clinical setting with current diagnostic tests.

A further unresolved problem in diagnosis and treatment is that the epidemiology of non-GAS streptococci such as GCS and GGS is less well understood, and may vary from place to place. GGS has been associated with invasive disease in other studies [3, 8]. In India, it is frequently recovered from children with and without pharyngitis [3], as reported in our study, in which its role in both colonisation and pharyngitis was similar to that of GAS. There is an extensive literature on GCS as an important cause of both pharyngitis [1, 3] and systemic infection [9], but in our study GCS was far less common than GAS or GGS, and thus despite an overall PC of 0.87, GCS pharyngitis was not a major problem. Nevertheless, in our study population, isolation of GCS from a child with acute pharyngitis would mandate antibiotic treatment.

In this study, the clinical picture of GAS pharyngitis was typical of the mild illnesses commonly seen in the modern era, which is often indistinguishable on clinical grounds from illnesses due to viruses and other bacteria, including GCS and GGS. Nevertheless, there is increasing evidence to support treating all such patient with antibiotics [10], particularly as GCS and GGS organisms may have some of the same genetic virulence factors as GAS, and because in some settings invasive GCS and GGS diseases may be increasing [11, 12]. However, high streptococcal colonisation rates in asymptomatic children with low to intermediate risks of pharyngitis, as we found in our study, would inevitably lead to significant over-treatment of colonised children who do not have, and may not otherwise develop, streptococcal pharyngitis. In our study population, treating all patients presenting with culture-positive pharyngitis would result in unnecessary antibiotic therapy in an estimated 74% of presenting cases. The physician must therefore decide to treat or not to treat on the basis of experience, the clinical and bacteriologic information and the epidemiological setting.

Various clinical criteria have been found to be of some use in diagnosis of streptococcal pharyngitis [13], but their value may be relevant to particular populations and epidemiologic settings [14]. Measurement of ASO or anti-DNAase B is most helpful in retrospective diagnosis, and may not be widely available in resource poor settings. Rapid antigen detection tests can be of value, but may be less reliable in children [15], do not distinguish between colonisation and disease, and are generally unavailable in resource poor settings where disease is most likely to occur. Tests that could distinguish between colonisation and invasive disease by any streptococcus are therefore needed, e.g. tests that could detect streptococcal antigens or genes as well as host responses to streptococcal invasion.

Our study also supports existence of an epidemiologic pattern of GAS that is increasingly being documented in other locales: highly diverse *emm* types isolated from both asymptomatically colonised children and from children with acute pharyngitis, and no pronounced *emm* type pattern distinguishing the two groups (Table 2). While some *emm* types previously associated with severe diseases were among the most common causes of pharyngitis in our study (e.g. types 1, 3 and 28), other known pathogenic types were rarely detected in association with pharyngitis (e.g. types 12 and 49). A longer period of observation would be needed to determine if any of the 'carrier-only' *emm* types could cause GAS infections in the study population. Such findings are in contrast to data from most of the 20th century, during which time epidemic GAS pharyngitis tended to be linked to only a few M types. For example, in a 1962–1963 outbreak, there were 961 cases of GAS pharyngitis in a U.S. community of 15 825 persons, 62% of which were caused by 6 M types and 30% of those by type 12 [16].

Also in contrast to many GAS data from the past, in our study we did not identify any serious complications such as acute rheumatic fever or glomerulonephritis. The shift in recent decades from GAS pharyngitis associated with severe complications to milder endemic pharyngitis of diverse streptococcal aetiology, has been accompanied by a marked decrease in the incidence of acute rheumatic fever and acute glomerulonephritis [17–19]. Nevertheless, in the modern era clusters of post-streptococcal pharyngitis complications associated with only a limited number of GAS M types still do occur [20, 21], e.g. the thousands of cases of scarlet fever in mainland China and Hong Kong in 2011, 50% of which were due to *emm* type 12, and the remainder to *emm* type 1 and several others [21]. Thus, we appear to be in a period of transition in the epidemiologic patterns and clinical appearance of streptococcal disease [22].

As long ago as 1934, Frederick Griffith (1879–1941) suggested that urban crowding and other environmental and host factors were creating pressures of herd immunity that might well cause streptococci to become 'differentiated' into many attenuated 'serologic races' [23], a notion that still seems reasonable, and which today might be tested by epidemiologic studies in diverse populations. Such studies would need to examine circulation of and disease caused by GAS, as well as other streptococci, circulation of specific strains, colonisation *vs.* acute disease, the possible effects of bacterium-specific immunity and cross-immunity on colonisation and disease, including host susceptibility factors and determinants of invasiveness.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S095026881800064X

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