

Relationship between group A beta-hemolytic streptococcal tonsillopharyngitis and asthma

Del Carmen Trojavchich M, Crisci CD, Shafa M, Rybicki BA.
Relationship between group A beta-hemolytic streptococcal
tonsillopharyngitis and asthma.
Pediatr Allergy Immunol 2003; 14: 50–54. © 2003 Blackwell Munksgaard

Increasing morbidity due to asthma in children and antimicrobial resistance among human pathogens are both major public-health concerns. Frequent use of antibiotics during childhood might be a factor underlying the rising severity and prevalence of asthma and other allergic disorders. The objective of the study was to determine if pediatric patients with asthma or allergic rhinitis have an altered rate of group A beta hemolytic streptococcal (GABHS) tonsillopharyngeal infection which might support any change in guidelines for antibiotic prescription. A prospective analysis of all patients presenting a clinical feature of GABHS pharyngitis with a sore throat in two pediatric clinics located in Detroit, MI, USA and San Antonio de Areco, Buenos Aires, Argentina. Eligible patients aged between 2 and 18 years were screened for the presence of asthma and/or allergic rhinitis and administered a test (rapid strep test) and throat culture to determine GABHS infection. At the Redford Medical Center, Detroit, 500 patients met the eligibility criteria, with 168 (33.6%) having a positive strep test. At the San Antonio de Areco's Hospital, in a rural area 100 km away from Buenos Aires, 188 patients met the eligibility criteria, with 41 (21.8%) having a positive strep test or GABHS throat cultures. In both the Detroit [odds ratio (OR) = 1.36; 95% confidence interval (CI) 0.72–2.57] and Buenos Aires clinics (OR = 0.50; 95% CI 0.23–1.07), patients with asthma or allergic rhinitis were not at an increased risk for true GABHS tonsillopharyngeal infections when compared with the general pediatric population. These results suggest that children with asthma do not differ from the normal population in their risk of developing GABHS tonsillopharyngeal infection and should not be liberally prescribed antibiotics.

**Maria Del Carmen Trojavchich¹,
Carlos D. Crisci², Mehrdad Shafa³ and
Benjamin A. Rybicki⁴**

¹Department of Pediatrics, San Antonio de Areco General Hospital, Buenos Aires, ²Department of Allergy and Immunology, National University of Rosario, Rosario, Argentina, Departments of ³Pediatrics and ⁴Biostatistics and Research Epidemiology, Henry Ford Health System, Detroit, MI, USA

Key words: streptococcus; infection; asthma; GABHS

María del Carmen Trojavchich, 415 San Martín,
San Antonio de Areco, Buenos Aires, Argentina
Tel.: +54 11 2326 452057
Fax: + 54 11 2326 452881
E-mail: mctroja@areconet.com.ar

Accepted 17 May 2002

Although viruses are the most common causes of childhood throat infections (1), streptococcal pharyngitis is a common illness in children and adolescents (2). The great majority of these infections are caused by group A beta-hemolytic streptococci (GABHS) (3–5).

The signs and symptoms of GABHS tonsillopharyngitis are non-specific, and reliable clinical diagnosis is difficult (3). Throat culture is cost-effective and, if properly obtained and processed, more than 95% accurate. Antigen detection tests (rapid strep tests) are a viable laboratory alternative to throat cultures if these tests are prop-

erly performed and if negative test results are confirmed with traditional throat culture (6).

The incidence of GABHS carriers in a private pediatric practice was shown to be 2.5% among healthy children and 6.9% among children with upper respiratory tract infections (URTI) of confirmed viral etiology (7). In a 1-year multicenter study in general practice, involving 2226 patients, none of them had had sore throats or any other streptococcal illness during the preceding 3 months, the GABHS carrier rate was 10.9% in patients less than or equal to 14 years of age (8). Recurrent GABHS infections occurred

more frequently in the 1990s than the 1970s, affecting more frequently younger children (1–8 years of age, 21.3% recurrence rate) than adolescents (13–19 years, 5% recurrence rate; $p = 0.002$) (9).

Although a recent anecdotal report showed a greater incidence of GABHS positive throat cultures (73%) in patients with asthma (10), GABHS has been found significantly less often ($p < 0.0005$) in oral washings from asthma and chronic obstructive pulmonary disease (COPD) patients than in healthy control subjects (11). Moreover, children with asthma were not more likely [relative risk (RR) = 0.74; 95% confidence interval (CI) 0.42 to 1.33] to develop group A streptococcal (GAS) invasive disease (12).

Both the outbreaks of rheumatic fever in certain areas of the world (1) and the reported increase in invasive GAS disease in the 1990s (12) encourage early treatment which results in prompt clinical improvement and reduces the risk of transmission. Antibiotics are prescribed frequently because of concerns about serious sequelae such as glomerulonephritis or rheumatic fever although probably only 20% of tonsillopharyngeal infection is due to GABHS (13). Consequently, the use of penicillin therapy in every patient with a sore throat may result in over treatment of 85% of children presented to family physicians with the complaint of a sore throat (6). Moreover, antibiotic treatment might suppress immunologic response and cause an eradication of normal pharyngeal and gastrointestinal flora that normally acts as natural host defenses and promotes immune response development and differentiation (4). In fact, it has been suggested that antibiotics abuse during the first year of life may alter the balance between T helper (Th)-1 and Th-2 cytokines-derived responses towards the Th-2 phenotype, which is associated with asthma and other allergic disorders (14).

The aim of the present multicenter prospective study carried out in the northern and southern hemispheres was to determine if the pediatric patients with asthma and allergic rhinitis have altered rates of GABHS tonsillopharyngeal infection in order to avoid unnecessary antibiotic prescriptions that might contribute to the persistence of their characteristic Th-2 cytokine profile.

Materials and methods

Two pediatric clinic populations recruited during a 1 calendar year (1996) were used in this study. Patients were visited at the Redford Medical Center and the San Antonio de Areco General Hospital.

The Redford Medical Center is in suburban Detroit in southeast Michigan, USA. It is located approximately at 42 degrees parallel north from the Equator. It is a four-pediatrician practice with a total of 18 776 visits in the calendar year.

The city of San Antonio de Areco is 100 km away from Buenos Aires, Argentina, surrounded by farms, and it is located approximately at 35 degrees parallel south from the Equator. It is a one-pediatrician practice, mainly specializing in allergy and immunology, with a total of 3940 visits per year.

All patients aged 2–18 years with a clinical diagnosis of GABHS tonsillopharyngitis, were enrolled. Rapid strep tests (4) and throat cultures were used to confirm GABHS infection. Asthma and allergic rhinitis were diagnosed according to clinical criteria according to international guidelines and consensus (15–17).

Design

The study was cross-sectional.

Variables

Predictor variable = asthma and/or allergic rhinitis.

Outcome variable = strep test/throat culture positive GABHS tonsillopharyngitis

Analytic statistic

Compare strep test/throat culture results in a general population of patients with clinical features of GABHS tonsillopharyngitis vs. patients with asthma and/or allergic rhinitis and clinical features of GABHS tonsillopharyngitis with the chi-square (χ^2) test.

Sample and power

- Two-sided significance level = Type I error = 0.05 (alpha error)
- Power = 80% (beta error)
- Assuming a 30% prevalence of strep test/throat culture positive GABHS tonsillopharyngitis in the general population
- Risk ratio of exposed/unexposed = 1.55
- Sample size = 147 in each group

Odds ratio (OR) and 95% CIs were calculated, for each population (EpiInfo 6). We tested whether the OR estimates between cities were different with a Breslow–Day test for homogeneity (18).

Results

In the Detroit population, 500/18 776 (2.76%) children presented symptoms of pharyngitis, but only 168 of them (33.6%) had either a positive strep test or GABHS throat culture. Cases were evenly distributed between males (50.5%) and females. In the Buenos Aires group, there were 188/3940 (4.77%) patients with pharyngitis; 41 (21.8%) of them had a positive GABHS confirmatory study (Table 1).

In the general pediatric clinic of the USA, 602 (3.21%) patients were diagnosed as having asthma and/or allergic rhinitis, whereas in the pediatric allergy clinic of Argentina 359 (9.11%) had either asthma or allergic rhinitis.

Patients with asthma and/or allergic rhinitis consulted more frequently for sore throats than normal children, both in the Detroit clinic (8.3% vs. 2.5%) and the in San Antonio de Areco clinic (26.2% vs. 2.6%), with a highly significant relative risk (RR = 5.99; 95% CI 5.05–7.12) for the whole population.

Patients with asthma and/or allergic rhinitis from Detroit did not show a significantly higher incidence of positive GABHS culture [OR = 1.36; 95% CI 0.72–2.57] when compared with those without these diagnoses (Table 2). Children with asthma and/or allergic rhinitis from Buenos Aires tended to have a lower number of confirmed GABHS pharyngitis when compared with the general pediatric population

(OR = 0.50; 95% CI 0.23–1.07). The relative estimates from the two cities were not statistically significantly different from each other ($p = 0.63$). Neither relative risk by itself was statistically significant at the 0.05 alpha level, nor was the pooled OR estimates significantly different from 1 (OR = 0.70; 95% CI 0.45–1.09) (Table 3).

Discussion

In this prospective series of pediatric patients, we attempted to elucidate the relationship between GABHS infection and asthma.

The percentage of children without asthma or allergic rhinitis that consulted with a clinical feature of tonsillopharyngitis was very similar for both studied populations (2.5% and 2.6% for Detroit and Areco clinics, respectively) as was the rate of positive GABHS culture (33% and 27.5%, respectively). These figures are equivalent to those reported at different geographic areas. In Rochester, USA, Pichichero et al. (7) reported a 4.4% incidence of GABHS carriers among children with URTI including sore throat of presumed viral etiology, with a rate of 30% of positive strep test in those cases suspected of GABHS etiology (4). In a prospective study, during a 1-year period, 1116 children with acute tonsillopharyngitis were examined by a group of Swiss pediatricians (2). The throat swab cultures were positive in 29.6% of the cases. In a total of 133 patients who were visited by general practitioners in Bergen (Norway) for a sore throat, the

Table 1. Comparative incidence of tonsillopharyngitis, asthma and/or allergic rhinitis, and confirmed GABHS infection in children attending a general pediatric clinic in the northern hemisphere (Detroit) and a pediatric allergy clinic in the southern hemisphere (Areco)

	Redford Medical Center, Detroit, Michigan, USA	San Antonio de Areco Buenos Aires, Argentina
Total visits per year in 1996	18 776	3940
Pharyngitis	500 (2.76%)	188 (4.77%)
Asthma and/or allergic rhinitis	602 (3.21%)	359 (9.11%)
GABHS confirmed pharyngitis	168 (33.6%)	41 (21.8%)

Table 3. Incidence of strep test positive GABHS tonsillopharyngitis in pediatric patients with and without asthma and/or allergic rhinitis presented with clinical features of GABHS pharyngitis

	Strep test (+)	Strep test (–)	Odds ratio (95% confidence interval)
Asthma/allergic rhinitis	35	109	OR = 0.70;
General population	174	379	CI = 0.45–1.09

Chi-square (χ^2) test (Mantel–Hensel correction) = 2.79; $p = 0.095$.

Table 2. Incidence of GABHS culture positive (GABHS+) pharyngitis in pediatric patients with and without asthma and/or allergic rhinitis presented with clinical features of GABHS tonsillopharyngitis in Detroit and Buenos Aires

Population	Patients with asthma or allergic rhinitis		Patients without asthma or allergic rhinitis		Odds ratio (95% confidence interval)
	Cases	GABHS+ n (%)	Cases	GABHS+ n (%)	
Detroit	50	20 (40)	450	148 (33)	1.36 (0.72–2.57)*
S. A. de Areco	94	15 (16)	94	26 (27.5)	0.50 (0.23–1.07)†

*Chi-square (χ^2) test (Mantel–Hensel correction) = 1.02; $p = 0.31$.

†Chi-square (χ^2) test (Mantel–Hensel correction) = 3.75; $p = 0.052$.

prevalence of streptococcal infection was 29% (5).

However, children with asthma and or allergic rhinitis were visited for a sore throat more frequently than normal children, both at the Detroit clinic (8.3%) and at the San Antonio de Areco clinic (26.2%). This observation might be explained by the well-known role of URTI as a trigger of asthma exacerbations (19). In fact, the relative incidence of both pharyngitis and asthma increased during the same months and cold weather in our group of patients, both in the northern and southern hemispheres (data not shown). The greater incidence of tonsillopharyngitis in children with asthma observed in San Antonio de Areco might be attributed to the fact that this office is headed by a specialist in allergy and immunology who may have to treat a greater percentage of patients with persistent asthma.

The rate of positive GAHBS culture (40% for Detroit and 16% for Areco clinics) was similar to that found in the general pediatric population. In fact, in the rural environment of San Antonio de Areco, 100 km away from Buenos Aires, surrounded by farms, a positive GABHS throat culture was less likely to occur in patients with asthma or allergic rhinitis presenting pharyngitis, although the relative risk estimate did not reach statistical significance ($p = 0.052$).

One of the mechanisms evoked to explain the increasing prevalence of asthma and allergy among children is the 'hygiene' hypothesis. This hypothesis is based on the concept that certain viral and bacterial infections, which induce a strongly polarized Th-1-type response and a long-lasting memory immunity, are in early life able to reverse or prevent the biased Th-1/Th-2 balance in individuals prone to atopy and asthma. Possibly also non-pathogenic residents of the intestinal mucosa are involved in the proper maturation of the immune system (20).

As the asthma prevalence follows the geographic and temporal trend of antibiotic use into clinical medicine, widespread use of antibiotics during the first year of life may have led to an increased risk of asthma and allergy (21). Wheezing has been associated with an increasing number of antibiotic courses early in life. Repeated episodes of fever and antibiotic treatment were strongly associated with the prevalence of asthma at school age (22, 23). Also non-pulmonary treatment indication has been associated with later wheezing (24). Treatment with oral antibiotics in the first 2 years of life has been identified as a statistically significant predictor of subsequent atopic disease (25).

A retrospective cohort study evaluating asthma medication and antibiotic use by children and adults with asthma and the prescribing of these medications by primary-care physicians showed that high bronchodilator users and long-term users of anti-inflammatory agents received more antibiotics per person per year than low users (26). Moreover, antibiotics are often prescribed to patients who are admitted to hospital with acute asthma although their exacerbation is often precipitated by a viral upper respiratory infection and in spite of the lack of strong evidence to support the use of antibiotics in acute asthma (27).

Our findings suggest that the concurrent diagnosis of asthma or allergic rhinitis should not be a routine indication for antibiotic treatment in those patients with tonsillopharyngitis, as only a small percentage of them showed positive strep test and GABHS throat culture, which did not significantly differ from that of the general pediatric population.

Acknowledgments

The authors would like to thank John A. Anderson, MD, Head of the Division of Allergy and Clinical Immunology, Henry Ford Health System, for reviewing this paper. This study was partially supported by an Internal Educational Grant from the Division of Allergy and Clinical Immunology, Henry Ford Health System.

References

1. PARADISE JL. Etiology and management of pharyngitis and pharyngotonsillitis in children: a current review. *Ann Otol Rhinol Laryngol* 1992; 155 (Suppl.): 51-7.
2. EGGENBERGER K, CHRISTEN JP, DELARUE C, et al. Streptococcal pharyngitis-tonsillitis in Swiss children. Diagnosis and management. *Paediatrician* 1980; 9: 295-308.
3. DOUGLAS RM, MILES H, HANSMAN D, FADEJEVS A, MOORE B, BOLLEN MD. Acute tonsillitis in children: microbial pathogens in relation to age. *Pathology* 1984; 16: 79-82.
4. PICHICHERO ME. Group A streptococcal tonsillopharyngitis. cost-effective diagnosis and treatment. *Ann Emerg Med* 1995; 25: 390-403.
5. MELAND E, DIGRANES A, SKJAERVEN R. Assessment of clinical features predicting streptococcal pharyngitis. *Scand J Infect Dis* 1993; 25: 177-83.
6. PICHICHERO ME. Culture and antigen detection tests for streptococcal tonsillopharyngitis. *Am Fam Physician* 1992; 45: 199-205.
7. PICHICHERO ME, MARSOCCI SM, MURPHY ML, HOEGER W, GREEN JL, SORRENTO A. Incidence of streptococcal carriers in private pediatric practice. *Arch Pediatr Adolesc Med* 1999; 153: 624-8.
8. HOFFMANN S. The throat carrier rate of group A and other beta hemolytic streptococci among patients in general practice. *Acta Pathol Microbiol Immunol Scand (B)* 1985; 93: 347-51.

9. PICHICHERO ME, GREEN JL, FRANCIS AB, et al. Recurrent group A streptococcal tonsillopharyngitis. *Pediatr Infect Dis J* 1998; 17: 809–15.
10. VAZQUEZ NAVA F, CASADOS ROBLEDOS JS, BELTRAN GUZMAN FJ. Oropharyngeal bacterial flora in asthmatic and healthy subjects. *Rev Alerg Mex* 1998; 45: 31–5.
11. SACHS AP, VAN DER WAAIJ D, GROENIER KH, KOETER GH, SCHIPHUIS J. Oropharyngeal flora in asthma and in chronic obstructive pulmonary disease. Indigenous oropharyngeal microorganisms in outpatients with asthma or chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1993; 148: 1302–7.
12. LAUPLAND KB, DAVIES HD, LOW DE, SCHWARTZ B, GREEN K. Invasive group A streptococcal disease in children and association with Varicella-Zoster virus infection. *Pediatrics* 2000; 105: 60.
13. BISNO AL, GERBER MA, GWALTNEY JM, KAPLAN EL, SCHWARTZ RH. Diagnosis and management of group A streptococcal pharyngitis: a practice guideline. *Clin Inf Dis* 1997; 25: 83–574.
14. COOKSON WOCM, MOFFATT MF. Asthma, an epidemic in absence of infection? *Science* 1997; 275: 41–2.
15. INTERNATIONAL RHINITIS MANAGEMENT GROUP. International consensus report on diagnosis and management of rhinitis. *Allergy* 1994; 49 (Suppl. 19): 1–34.
16. INTERNATIONAL RHINITIS MANAGEMENT GROUP. International consensus report on diagnosis and management of rhinitis. *Allergy* 1992; 47 (Suppl. 13): 1–61.
17. Global strategy for asthma management and prevention. In: WHO/NHLBI Workshop Report. National Institutes of Health, National Heart, Lung and Blood Institutes, 1995.
18. REIS IM, HIRJI KF, AFIFI AA. Exact and asymptotic tests for homogeneity in several 2 x 2 tables. *Stat Med* 1999; 18: 893–906.
19. PATTEMORE PK, JOHNSTON SL, BARDIN PG. Viruses as precipitants of asthma symptoms. I. Epidemiology. *Clin Exp Allergy* 1992; 22: 325–36.
20. VON HERTZEN LC. Puzzling associations between childhood infections and the later occurrence of asthma and atopy. *Ann Med* 2000; 32: 397–400.
21. DROSTE JH, WIERINGA MH, WEYLER JJ, NELEN VJ, VERMEIRE PA, VAN BEVER HP. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? *Clin Exp Allergy* 2000; 30: 1547–53.
22. VON MUTIUS E, ILLI S, HIRSCH T, LEUPOLD W, KEIL U, WEILAND SK. Frequency of infections and risk of asthma, atopy and airway hyperresponsiveness in children. *Eur Respir J* 1999; 14: 4–11.
23. WICKENS K, PEARCE N, CRANE J, BEASLEY R. Antibiotic use in early childhood and the development of asthma. *Clin Exp Allergy* 1999; 29: 766–71.
24. WIST M, HOELSCHER B, FRYE C, WICHMANN HE, DOLD S, HEINRICH J. Early antibiotic treatment and later asthma. *Eur J Med Res* 2001; 28, 263–71.
25. FAROOQI IS, HOPKIN JM. Early childhood infection and atopic disorder. *Thorax* 1998; 53: 927–32.
26. GLAUBER JH, FUHLBRIGGE AL, FINKELSTEIN JA, HOMER CJ, WEISS ST. Relationship between asthma medication and antibiotic use. *Chest* 2001; 120: 1485–92.
27. GRAHAM V, LASSERSON T, ROWE BH. Antibiotics for acute asthma (Cochrane Review). *Cochrane Database Syst Rev* 2001; 3: CD002741.