

**Title of the study:** Recurrent group A beta-hemolytic streptococcal (GABHS) infections of the throat and the role of tonsillectomy

### **SPECIFIC AIMS**

The logic and the experience of most otolaryngologists favors the notion that by removing a common harbor (tonsils) of GABHS infection, the incidence of recurrent GABHS infection will decrease. No study to date has been able to adequately prove (or disprove) this belief. We will determine whether tonsillectomy is associated with a decreased incidence of subsequent GABHS pharyngitis in children with recurrent GABHS infections, using the resources of the Rochester Epidemiology Project (REP). In addition, we will explore whether specific patient characteristics are associated with a reduction in GABHS infections following tonsillectomy.

Specific Aim 1: Determine whether children with tonsillectomies experienced a lower cumulative incidence of GABHS infection following surgery ("index date") compared to children who did not receive tonsillectomies.

We will test the null hypothesis that children with tonsillectomies have the same cumulative incidence of GABHS infection following the index date compared to children who do not receive tonsillectomies.

Specific Aim 2: Determine whether children with tonsillectomies experienced fewer recurrent GABHS infections following surgery ("index date") compared to children who did not receive tonsillectomies.

We will test the null hypothesis that children with tonsillectomies experience the same number of recurrent GABHS infections following the index date compared to children who do not receive tonsillectomies.

Specific Aim 3: Among the children with recurrent GABHS infections that received a tonsillectomy, determine whether specific patient characteristics are associated with fewer recurrent GABHS infections following tonsillectomy.

Specifically, we will test the null hypotheses in an exploratory analysis that:

- A. Children who have had more GABHS episodes at the time of tonsillectomy will be equally as likely as children with fewer GABHS episodes to experience recurrent GABHS infections following tonsillectomy.
- B. Children who are older at the time of tonsillectomy will be equally as likely as younger children to experience recurrent GABHS infections following tonsillectomy.
- C. Children who have complicated tonsillectomies will be equally as likely as children with uncomplicated tonsillectomies to experience recurrent GABHS infections following tonsillectomy.

## BACKGROUND AND SIGNIFICANCE

Pharyngitis and tonsillitis are among the most commonly diagnosed pediatric illnesses, accounting for approximately 18 million office visits per year<sup>1</sup>. Group A beta-hemolytic streptococci (GABHS) are responsible for approximately 15-30% of all cases of pharyngitis. GABHS infections are of significant concern because of the potential for untreated children to develop severe complications such as peritonsillar abscesses and acute rheumatic fever (ARF). In addition, recent studies have suggested a link between GABHS infection and obsessive/compulsive and tic disorders in certain children,<sup>2,3,4</sup> and a link between GABHS and psoriasis has also been proposed.<sup>5</sup>

In addition to potential complications, approximately 20-30% of children who are diagnosed with GABHS pharyngeal infection experience a second infection within 60 days of the initial episode.<sup>2</sup> Approximately 7% to 9% continue to experience recurrent GABHS infections (more than 3 within a year), and approximately 25% of these children will receive a tonsillectomy to treat their recurrent episodes (preliminary Olmsted County data). Tonsillectomies represent a costly alternative to medical therapy, with an average cost of 4 to 6 thousand dollars per procedure. Recurrent GABHS infections are therefore a significant public health problem, due to the large number of children affected, attendant treatment costs due to lost parental work time and antibiotic prescriptions, potential reactions to antibiotics, potential for complications, and risk for tonsillectomy.

Treatment of GABHS infection routinely involves the use of penicillin (PCN)<sup>6</sup>. However, recent studies on the use of PCN in treating recurrent infections<sup>6,7</sup> or preventing recurrent GABHS infection<sup>8</sup> have questioned the efficacy of this line of therapy. Tonsillectomy has long been considered an alternative to medical therapy in children plagued with recurrent GABHS infection, yet little objective evidence exists to its efficacy in decreasing the incidence of recurrent GABHS infection. A study conducted on a military population between 1949-1954<sup>9</sup> showed no statistical difference in the incidence of GABHS between soldiers with or without tonsils. In contrast, a 1977 Johns Hopkins study<sup>10</sup> demonstrated an increased incidence of GABHS infection in the control population (no tonsillectomy) when compared with their siblings who had undergone tonsillectomy.

Perhaps the best recent evidence for the efficacy of tonsillectomy in the treatment of recurrent throat infection was a randomized trial completed by Paradise et al<sup>11</sup> in 1984. They studied 187 children with recurrent throat infection whose episodes occurred at a high rate (7 in 12 months, 5 per year for 2 years or 3 per year for 3 years). In these children the incidence of throat infection in the first two years following surgery was significantly lower ( $P < 0.05$ ) in the surgical groups than in the corresponding nonsurgical groups. This also held true when looking specifically at post-surgical GABHS infections in the 6-15 year old group but did not reach statistical significance in children between 3-6 years old. These data, however, are difficult to interpret since the patients were not preoperatively required to specifically have recurrent GABHS infections. Thus the efficacy of

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tonsillectomy in preventing recurrent GABHS infections was not specifically addressed. In fact, we were unable to identify either a prospective or retrospective study in the literature which adequately addresses the efficacy of tonsillectomy in preventing recurrent GABHS infection. In addition, it is currently unclear if tonsillectomy is effective in specific subgroups of children, but not in others.

Clearly defining whether tonsillectomy is associated with significantly reducing recurrent streptococcal pharyngitis episodes, or whether it is only effective in specific subgroups of children may have a profound impact on clinical decision making in the treatment of children suffering from recurrent streptococcal infections. In addition, this information will provide preliminary data to further explore the etiology and treatment of recurrent strep infections.

## **PRELIMINARY STUDIES**

Not applicable.

## **RESEARCH DESIGN AND METHODS**

### ***Overview:***

We will conduct a retrospective cohort study of children 4-15 years of age who experienced recurrent GABHS infections as defined by three or more episodes of GABHS tonsillitis/pharyngitis, at least one-month apart, within a 12-month period of time. Children with recurrent GABHS infections who have received a tonsillectomy will be matched according to birth year, gender, and date of the last GABHS infection prior to the tonsillectomy to children with recurrent GABHS infections who have not had a tonsillectomy. The date of the tonsillectomy will serve as the “index” or start date for identifying all subsequent GABHS infections within both groups of children. All GABHS infections will be determined both for children who received a tonsillectomy and for those who did not. We will determine whether children who received a tonsillectomy had fewer GABHS infections and a lower cumulative incidence of GABHS infection following tonsillectomy compared to those who did not receive a tonsillectomy. In addition, we will conduct a nested exploratory analysis among the children who have received tonsillectomies to identify patient characteristics which might be associated with successful tonsillectomies (fewer recurrences of GABHS).

### ***Data Resource***

Epidemiologic research in Olmsted County is possible because the county is relatively isolated from other urban centers and nearly all medical care is delivered to patients in the population by a limited number of local providers. The medical records available at the local health care providers contain details of every inpatient hospitalization, every outpatient visit to the office, clinic, or

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emergency department, as well as every laboratory result and correspondence concerning each patient. The medical records are easily retrievable because the Mayo Clinic has maintained, since the early 1900s, extensive indices based on clinical and histologic diagnoses and surgical procedures. The Rochester Epidemiology Project (AR-30582) has developed a similar index for the records of all other providers of medical care Olmsted County residents. In addition to the Mayo Clinic, these include the Olmsted Medical Center, the Olmsted Medical Center Hospital, and the Rochester Family Medicine Clinic. The result is the linkage of medical records from essentially all sources of medical care available to and utilized by the Olmsted County population.

### ***Identification of Study Subjects:***

Using Medical Index System, we have identified a preliminary count of all children 4 to 15 years old between January 1, 1994 and December 31, 1998 who received three or more primary diagnoses of GABHS pharyngitis or tonsillitis (ICD-9-CM codes 00340111-116 and 34765111 respectively) at least one-month apart, in a 12-month period. We limited our search to children who were residents of Olmsted County between 1994 and 1998 who have not denied research authorization. From this search, we identified a preliminary list of 542 children who meet these initial search criteria. Recurrent GABHS infections will be confirmed during chart abstraction. Infections must be separated by at least one month to be considered recurrent infections. In order to be included in the study, a child must have three or more GABHS infections at least one-month apart within a 12-month period between the ages of 4 and 15 years of life prior to the “index date”. The “index date” is defined as the date of the tonsillectomy for a child in the “exposed” group (as defined below).

### ***Identification of “Exposed” Group (patients with a tonsillectomy):***

In a preliminary analysis, we have identified 129 children in our study cohort who received a tonsillectomy between January 1990-April 2001 by cross-referencing the data file of potential study subjects (n=542) with the surgical retrieval database to identify children who have had a tonsillectomy at any time at a hospital in Olmsted County. The medical charts of the children with a tonsillectomy will be reviewed to confirm that these children had three or more GABHS infections at least one-month apart within a 12-month period between age 4 and the date of their tonsillectomy in order to be included in the “exposed” group.

### ***Identification of “Unexposed” Group (patients without a tonsillectomy):***

The “unexposed” group will consist of children in the recurrent GABHS study population who have not received a tonsillectomy. Children who have had a tonsillectomy will be matched (1 exposed : 1 unexposed) according to birth year, gender, and date of the last GABHS infection prior to the tonsillectomy (within 3 months before) to children who have not had a tonsillectomy. The matches will be identified using an optimal matching algorithm applied to the values of each matching factor<sup>13</sup>. The list of exposed and unexposed children will be randomly ordered prior to applying the algorithm and one unexposed child matched to each

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exposed child will be selected. Children will be matched on time of last GABHS infection prior to the tonsillectomy to alleviate the bias of potentially having a shorter lead-in time until the next recurrent infection following the tonsillectomy.

**Data Collection:**

Once exposed and unexposed children have been identified, the complete inpatient and outpatient medical records of each subject will be reviewed to confirm each diagnosis of GABHS infection occurring between age 4 and age 15. The date of each GABHS diagnosis will be recorded, and we will note whether each GABHS diagnosis was confirmed by a laboratory test. GABHS is rarely diagnosed without laboratory confirmation; therefore, we expect the vast majority of our GABHS episodes to have positive laboratory test records.

Date of tonsillectomy among our exposed children will be confirmed from Mayo and Olmsted Medical Group records. Variables thought to influence the risk of recurrent GABHS infection include age, sex, tonsillar hypertrophy, number and ages of siblings, complications of medical and surgical treatments, complications of GABHS infections, pre-existing medical conditions (such as Down's syndrome and congenital heart disease), and antibiotic use.

Trained nurse abstractors will collect all data and record abstracted information on data abstraction forms (note appendix 1). In preparation for computer entry, the consistency, clarity and completeness of data recording shall be verified by the principal investigator. All data shall be entered with built-in edit checks into a SASGEN data entry system and stored in a SAS data file for analysis

**Statistical Analyses:**

Specific Aim 1: *Determine whether children with tonsillectomies experienced a lower cumulative incidence of GABHS infection following surgery ("index date") compared to children who did not receive tonsillectomies.*

Overall patient follow-up will be calculated from the "index date" to the date of the last recurrent GABHS infection or last follow-up, prior to age 15. The "index date" has been defined for each set of matched exposed and unexposed children as the date of the tonsillectomy for the exposed child in each matched set. The cumulative incidence of recurrent GABHS infection following the "index date" will be estimated using the Kaplan-Meier method. The association between having a tonsillectomy (exposed vs. unexposed) and time until first recurrent GABHS infection following the "index date" will be evaluated based on fitting a stratified Cox proportional hazards model. Each matched set of exposed and unexposed children will be treated as a separate stratum. Multivariable models will be fit to assess this association after adjusting for potential confounders such as tonsillar hypertrophy. Risk ratios (for exposed versus unexposed) and corresponding 95% confidence intervals will be calculated based on the parameter estimates from the Cox proportional hazards models.

*Specific Aim 2: Determine whether children with tonsillectomies experienced fewer recurrent GABHS infections following surgery (“index date”) compared to children who did not receive tonsillectomies.*

The association between having a tonsillectomy and number of recurrent GABHS infections following the “index date” will be evaluated using the Anderson-Gill (AG) method to model multiple ordered events within a stratified Cox model and obtain robust variance estimates<sup>15</sup>. Each matched set of exposed and unexposed children will be treated as a separate strata. The AG method will be implemented using the counting process style of data input, such that each child is represented as a series of observations with time intervals of (entry time, 1<sup>st</sup> infection], (1<sup>st</sup> infection+30 days, 2<sup>nd</sup> infection], ..., (m<sup>th</sup> infection+30 days, last follow-up]. Since, by definition, recurrent GABHS infections need to be at least one-month (30 days) apart, discontinuous risk intervals will be created by incorporating a 30-day lag between the time intervals. Multivariable models will be fit to assess this association after adjusting for potential confounders such as tonsillar hypertrophy. Risk ratios (for exposed versus unexposed) and corresponding 95% confidence intervals will be calculated based on the parameter estimates and robust standard errors from the Cox proportional hazards models.

*Specific Aim 3: Among the children with recurrent GABHS infections that received a tonsillectomy, determine whether specific patient characteristics are associated with fewer recurrent GABHS infections following tonsillectomy.*

Within the subset of children that received a tonsillectomy, Cox models will be fit to evaluate the association between patient characteristics (e.g. number of prior recurrent GABHS infections, age, complicated tonsillectomy) and time to first recurrent GABHS infection and number of subsequent recurrent GABHS infections following the tonsillectomy. The AG method described above will be utilized to model the multiple ordered events represented by the subsequent GABHS infections following the tonsillectomy. Risk ratios and corresponding 95% confidence intervals will be calculated for each patient characteristic based on the parameter estimates from the Cox proportional hazards models.

The statistical analyses will be performed using S-Plus<sup>15</sup>. All calculated p-values will be two-sided and p-values less than 0.05 will be considered statistically significant.

### ***Statistical Power Considerations:***

The following calculations are based on assuming a two-sided alternative hypothesis, a type I error level of 5%, and a sample size of 129 exposed children matched 1:1 with 129 unexposed children.

The two reported power calculations focus on assessing the power to address Specific Aims 1 and 2. Because the endpoint of Aim 2 (total number of subsequent GABHS infections) is an extension of Aim 1 (time to the development of the first GABHS infection) with some additional statistical complexity, the power calculation focused on Aim 1.

***Specific Aim 1:** Determine whether children with tonsillectomies experienced a lower cumulative incidence of GABHS infection following surgery (“index date”) compared to children who did not receive tonsillectomies.*

In the randomized trial completed by Paradise et al <sup>11</sup> in 1984, 23% of the children that underwent a tonsillectomy experienced a GABHS infection in the following year. Based on a preliminary screen of the subsequent GABHS infections that have been diagnosed in the 129 children in the proposed exposed group, 39% have had at least one GABHS infection following their tonsillectomy (39%=50 total “events”). Table 1 summarizes the minimal detectable risk ratio (exposed vs. unexposed) for the risk of developing a subsequent GABHS infection for a varying number of events among subjects in the unexposed group. Depending on the total number of events, the study will have an 80% chance of detecting a risk ratio (exposed vs. unexposed) of at least 1.6 based on a log-rank test<sup>14</sup>. Given that the analysis will involve a matched comparison of exposed versus unexposed subjects, the minimum detectable risk ratio with 80% power may actually be less than 1.6.

**Table 1.** Minimum detectable risk ratio for the risk of developing a subsequent GABS infection among exposed and unexposed subjects.

Anticipated number of subjects with a subsequent GABHS infection after the “index” date (“events”)		Total number of “events”	Minimum detectable risk ratio with 80% power
Among the Exposed (n=129)	Among the Unexposed (n=129)		
50 (39%)	65 (50%)	115	1.69
	77 (60%)	127	1.64
	90 (70%)	140	1.61

***Specific Aim 3:** Among the children with recurrent GABHS infections that received a tonsillectomy, determine whether specific patient characteristics are associated with fewer recurrent GABHS infections following tonsillectomy.*

The power estimates for this aim vary depending on the prevalence of each patient characteristic that will be evaluated. The power calculations assume that 50 of the 129 patients in the exposed group will have at least one GABHS infection following their tonsillectomy (i.e. number of “events”). Table 2 summarizes the minimal detectable risk ratio (patient characteristic, present vs. absent) for the risk of developing a subsequent GABHS infection based on the log-rank test <sup>14</sup>. Depending on the prevalence of the patient characteristic, the study will have an 80% chance of detecting a risk ratio of at least 2.2. Given that some of the patient characteristics will be analyzed as continuously scaled

cohort

variables rather than as dichotomized variables, the power may be improved for some of these patient characteristics. While the power to detect small differences is low, this aim is exploratory in nature, and we expect our analyses to provide us with some suggestion of factors that may be associated with poor tonsillectomy outcomes. Such factors will then be further explored in future studies.

**Table 2.** Minimum detectable risk ratio for the risk of developing a subsequent GABS infection among 129 exposed subjects with 50 anticipated events.

Prevalence of the patient characteristic	Minimum detectable risk ratio with 80% power
50%	2.20
40%	2.24
30%	2.37
20%	2.84

***Timeline:***

Approximately one year will be required for complete chart review. Data editing will be completed 2 months following completion of data abstraction, and analyses will be completed 8 months after editing. A draft manuscript will be completed within two months of completed data analysis.

***Strengths and Limitations:***

The proposed study has a number of strengths. First, the question of whether tonsillectomy is truly efficacious for treating and preventing recurrent streptococcal pharyngeal infections has plagued pediatricians and otolaryngologists for years. This study will provide important information about whether tonsillectomy is associated with decreased GABHS infections among children with medically documented recurrent GABHS infections. In addition, it is unknown whether tonsillectomy might actually be an effective treatment in some children, but not others based on specific characteristics. Such information is essential for clinical decision making in treating children with recurrent streptococcal tonsillitis and pharyngitis.

Second, this study takes advantage of the population-based medical data available through the Rochester Epidemiology Project resources. The unique strengths of this resource have been previously established<sup>16</sup>. This linked medical records system allows us access to accurate and detailed clinical and laboratory data over many years, which are not typically available in other databases or research settings. This resource also allows us to efficiently examine long-term outcomes of tonsillectomy retrospectively in a well-defined population in a relatively short period of time, while a prospective study would require years to collect complete data.

The primary limitation of this study is due to its retrospective nature. This study relies on complete and accurate recording of pertinent information in the medical

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record. We expect the record to be reasonably complete and accurate for the data elements most essential to testing our study hypotheses (such as occurrence of tonsillectomy and occurrence of GABHS infection). However, other elements, such as complete medication usage, may be less complete. In addition, as the study is retrospective, we are unable to randomly assign children to different treatment groups (such as tonsillectomy vs medical management). Certain factors other than recurrent GABHS infections may therefore predispose children to having a tonsillectomy vs medical management, and these third variables may confound any associations between tonsillectomy and reduced GABHS infections. We are therefore collecting information on such variables, and will control for these potential confounders in our analysis. There may be more subtle factors which we are unable to control for. Our data however, will provide preliminary information to support the feasibility and importance of performing a randomized clinical trial to examine the efficacy of tonsillectomy in treating recurrent GABHS infections. Finally, Olmsted County is predominantly white and middle class, and our findings may not be directly applicable to other populations or locales.

## **HUMAN SUBJECTS**

This project does not involve experimentation on human subjects, and is limited only to a retrospective review of medical records. The data will be analyzed anonymously and the usual policies and safeguards enforced by the Department of Health Sciences Research will be used to protect the confidentiality of the patient record. Data on individual patients will not be released, and all results will only be published in aggregate. Medical records of children whose parents have not provided MN research authorization will not be reviewed. Additionally, no data will be compared between health care institutions participating in the REP. We have chosen to study children, as these are the individuals at highest risk of both recurrent GABHS infections and tonsillectomy.

## **GENDER/MINORITY MIX**

All children between 4 and 15 years of age between January 1, 1994 and December 31, 1998 will be considered for this study. We expect our study population to reflect the underlying demographic composition of Olmsted County. According to 2000 census data, we therefore expect that approximately 50% of the children in our study will be girls, and about 11% will belong to racial or ethnic minority groups.

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