

Alterations of the Oropharyngeal Microbial Flora After Adenotonsillectomy in Children

A Randomized Controlled Trial

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Objectives: To determine whether the oropharyngeal microbial flora changes after adenotonsillectomy (ATY) in children with mild to moderate symptoms of throat infections or adenotonsillar hypertrophy and to relate these findings to recurrence of throat infections.

Design: Randomized controlled trial.

Setting: Twenty-three general hospitals and 3 academic centers.

Patients: Three hundred children aged 2 to 8 years who were selected for ATY because of recurrent throat infections (3-6 episodes per year) or obstructive complaints. Children with a history of 7 or more throat infections in the previous year and those with a high suspicion of obstructive sleep apnea according to current medical practice were excluded.

Interventions: Children were randomly assigned to either ATY or watchful waiting. Oropharyngeal swabs were taken at baseline and at 3 and 12 months after baseline.

Main Outcome Measures: The primary outcome mea-

sure was the prevalence of potentially pathogenic bacteria in the oropharynx at 3 and 12 months. The secondary outcome measure was the association between carriage of group A β -hemolytic streptococci (GABHS) at baseline and at 3 months' follow-up and the number of throat infections during the 12 months of follow-up.

Results: In the ATY group, prevalences of *Haemophilus influenzae*, GABHS, and *Staphylococcus aureus* decreased from 40%, 13%, and 5%, respectively, at baseline to respective levels of 24%, 0%, and 0% at 3 months and 26%, 0%, and 0% at 12 months. In the watchful waiting group, prevalences of *H influenzae*, GABHS, and *S aureus* did not change substantially. In neither the ATY nor the watchful waiting group was carriage of GABHS associated with recurrence of throat infections.

Conclusions: Adenotonsillectomy reduced oropharyngeal carriage of potential respiratory pathogens. Changes in the carriage rate of GABHS, however, had no beneficial effect on recurrence of throat infections.

Arch Otolaryngol Head Neck Surg. 2007;133(10):969-972

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TONSILS AND ADENOIDS ARE the largest components of the Waldeyer ring, the basic function of which is antibody formation.¹ Since tonsils and adenoids are located at the entry of the gastrointestinal and respiratory tracts, they are considered the first line of defense against various microorganisms that enter the body through the mouth or nose.² Adenoids and tonsils are active in young children, and therefore hypertrophy is common.³

Adenotonsillectomy (ATY) is a common therapeutic approach in children with adenotonsillar hypertrophy or recurrent throat infections.^{4,5} Besides viruses, the

most important pathogens causing throat infections are group A β -hemolytic streptococci (GABHS).⁶ Other pathogens that play a role in upper respiratory tract infections are groups C and G β -hemolytic streptococci, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*.⁶⁻¹⁰ The effect of ATY on carriage of these potential pathogens in the pharynx is not well established, nor is the effect of a potential reduction of GABHS on the incidence of throat infections.

The aim of this study was to evaluate alterations in the oropharyngeal microbial flora in children participating in a trial on the effectiveness of ATY. We compared the

culture results of children assigned to ATY with those of children assigned to watchful waiting (WW), and we evaluated the association between carriage of GABHS and recurrence of throat infections.

METHODS

PATIENTS

The present study is part of a randomized controlled trial investigating the effects of ATY in children. The inclusion and exclusion criteria and methods of this trial have been described in detail elsewhere.¹¹ In short, the trial was conducted between March 2000 and February 2003. Participants were recruited by otolaryngologists in 23 general hospitals and 3 academic centers in the Netherlands. Otolaryngologists were asked to refer to the trial center every child aged 2 to 8 years selected for ATY because of recurrent throat infections (≥ 3 episodes per year) or obstructive complaints.

Excluded were children with (1) a history of 7 or more throat infections in the previous year or 5 or more in each of the 2 preceding years or 3 or more in each of the 3 preceding years (Paradise et al¹² criteria); and/or (2) those with a high suspicion of obstructive sleep apnea (OSA) (Brouillette et al¹³ OSA score > 3.5). These children were excluded because, as our research group showed in a previous study,⁵ of the children currently undergoing ATY in the Netherlands, 35% undergo the operation to treat such severe symptoms, whereas 65% undergo ATY for less frequent throat infections and milder symptoms of adenotonsillar hypertrophy. While frequent throat infections and OSA are generally considered adequate indications for ATY in children,^{12,14} there is no evidence for the benefits of ATY in a large proportion of children currently undergoing this procedure for milder symptoms.^{5,15,16} The primary aim of this trial, therefore, was to assess the effectiveness of ATY in children with mild to moderate symptoms of throat infection or adenotonsillar hypertrophy.¹¹

Children whose parents gave informed consent were randomly assigned to 1 of 2 strategies: ATY within 6 weeks or WW. During the study, parents kept a diary of upper airway complaints in their child, such as sore throat and pain and/or difficulty with swallowing. They also measured their child's temperature daily with a validated infrared tympanic membrane thermometer.¹⁷ Both diary and thermometer data were collected by the study physician during scheduled follow-up visits at 3 and 12 months.

The study protocol was approved by the medical ethics committees of all participating hospitals.

BACTERIOLOGIC PROCEDURE

Throat swabs were taken at inclusion and during the follow-up visits at 3 and 12 months. Samples were obtained under direct light and depression of the tongue to avoid contamination by oral flora. When tonsils were present, their surface was sampled by firmly swabbing the mucosa of the left and the right tonsil with the same cotton swab. If tonsils had been removed, the mucosa of the tonsillar fossae was sampled similarly. The swabs were stabbed into a modified Stuart gel medium and transported to the Clinical Microbiology Laboratory of the University Medical Center Utrecht. Within 24 hours after collection, the samples were inoculated onto 5% sheep blood agar and chocolate agar plates. The plates were incubated both aerobically and under 5% carbon dioxide at 37°C and examined at 24 and 48 hours. Isolates were identified using conventional methods.^{18,19}

The following potentially pathogenic bacteria were identified: GABHS, group C β -hemolytic streptococci, group G β -he-

molytic streptococci, *H influenzae*, *S aureus*, *M catarrhalis*, and *S pneumoniae*.

OUTCOME

The primary outcome of this study was the prevalence of these potentially pathogenic microorganisms in the oropharynx at 3 and 12 months after baseline. Furthermore, positive culture results for GABHS at baseline and at 3 months were related to the incidence of throat infections during the 12 months of follow-up. A throat infection was defined as sore throat and/or pain and/or difficulty with swallowing, as indicated in the diary, in combination with fever (temperature $\geq 38.0^\circ\text{C}$ as measured by the tympanic thermometer).¹¹

STATISTICAL ANALYSIS

The microbial results and use of antibiotics in the ATY and WW groups were compared with χ^2 and Fisher exact tests. Analyses were performed according to the intention-to-treat principle. To study the effect of the microbial findings on recurrence of throat infections in both the ATY and WW group, we compared the median incidence of throat infections during 12 months of follow-up in children with a positive culture for GABHS at baseline or at 3 months vs the median incidence in children with a negative throat culture at these visits. Differences were tested with the Mann-Whitney *U* test, as data were not normally distributed. All analyses were performed with SPSS software, version 12 (SPSS Inc, Chicago, Illinois).

RESULTS

PATIENTS

In total, 300 children were randomized: 151 were allocated to the ATY group, 149 to the WW group. Baseline characteristics did not differ between the 2 groups: the mean age was 54 months; the median number of throat infections in the year before trial entry was 3; and the median OSA score was -1.7 in both groups (**Table 1**).

Fifty children (34%) changed from the WW to the ATY group because of persistent tonsil-related complaints. Seven children in the ATY group (5.5%) did not undergo ATY because their parents declined permission for surgery after randomization to the ATY group.

At baseline, 7 children in the ATY group (5.5%) and 16 in the WW group (13%) ($P = .05$) had used antibiotics in the 2 weeks before their throat culture was taken. At 3 months, these respective figures were $n = 4$ (3.0%) and $n = 6$ (4.5%) ($P = .54$); and at 12 months, $n = 1$ (0.8%) and $n = 4$ (3.6%) ($P = .20$).

OROPHARYNGEAL MICROBIAL FLORA

In the ATY group, prevalences of *H influenzae*, GABHS, and *S aureus* decreased from 40%, 13%, and 5% at baseline to 24%, 0%, and 0% at 3 months and 26%, 0%, and 0% at 12 months, respectively. In the WW group, prevalences of *H influenzae*, GABHS, and *S aureus* did not change substantially: 39%, 7%, and 6% at baseline; 38%, 6%, and 7% at 3 months; and 40%, 8%, and 8% at 12 months, respectively (**Table 2**).

OROPHARYNGEAL MICROBIAL FLORA AND THROAT INFECTIONS

In the ATY group, the median number of throat infections during the 12 months of follow-up was 1, both among the children with a positive result of GABHS culture (range, 0-3 infections) and those with negative

GABHS findings at baseline or at 3 months (range, 0-4 infections) ($P = .76$). In the WW group, the median number of throat infections was 1 (range, 0-3 infections) among children with positive GABHS findings and 0 (range, 0-4 infections) among those with negative findings ($P = .86$).

COMMENT

Table 1. Baseline Demographic and Clinical Characteristics of Children Randomly Assigned to Adenotonsillectomy or a Watchful Waiting Strategy^a

Characteristic	Adenotonsillectomy (n = 151)	Watchful Waiting (n = 149)
Male sex	81 (53.6)	66 (44.6)
Age, mean (SD), mo	54 (17.0)	54 (16.2)
Indication considered most important for surgery		
Recurrent throat infections	76 (50.3)	67 (45)
Other indications	73 (48.3)	82 (55.0)
Throat infections in the previous year among 143 children selected for recurrent throat infections, median (range), No.	3 (0-6)	3 (0-6)
Duration of throat infections among 143 children selected for recurrent throat infections, median (range), mo	13 (0-50)	12 (0-60)
OSA score, median (range) ^b	-1.7 (-3.83 to 2.55)	-1.7 (-3.83 to 2.56)
Previous ear, nose, and throat operation		
Adenoidectomy	32 (23.2)	33 (22.1)
Tympanostomy tubes	19 (12.7)	17 (11.4)
Use of antibiotics during the previous 2 wk	7 (5.5)	16 (12.5)

Abbreviation: OSA, obstructive sleep apnea.

^aUnless otherwise indicated, data are reported as number (percentage) of subjects.

^bBrouillette et al¹³ OSA score is calculated using the following equation: $1.42 \times \text{difficulty breathing} + 1.41 \times \text{apnea} + 0.71 \times \text{snoring} - 3.83$. Normal range is -3.83 to 3.5 . A score higher than 3.5 is highly predictive of OSA; a score between -1 and 3.5 indicates possible OSA; and a score lower than -1 indicates no OSA.

To our knowledge, this is the first large randomized controlled trial of ATY in children to evaluate the effect of surgery on the oropharyngeal microbial flora and to relate these findings to clinical effects. It shows that in children undergoing ATY for mild to moderate symptoms of throat infections or adenotonsillar hypertrophy, surgery is associated with a reduction in carriage of potential respiratory pathogens in the oropharynx. A decrease in the carriage rate of GABHS, however, had no beneficial effect on recurrence of throat infections.

In a previous publication, our research group¹⁹ showed that the tonsillar flora of the children selected for ATY and participating in this trial differed only slightly from children without symptoms of tonsillar disease. This suggests that oropharyngeal carriage itself does not play a major role in the susceptibility of children to throat infections.¹⁹

Our results are in agreement with those of others showing reduced oropharyngeal carriage of potential pathogens after tonsillectomy.²⁰⁻²² These studies, however, had smaller sample sizes,^{21,22} shorter follow-up periods,²⁰⁻²² and all lacked a randomly assigned control group.²⁰⁻²²

These results should be interpreted in the light of several limitations. First, children with very frequent (≥ 7 per year) throat infections or OSA were excluded from our trial because these symptoms are generally considered adequate indications for surgery.¹¹ Our results are therefore only generalizable to children with milder symptoms of throat infections or adenotonsillar hypertrophy.

Second, 50 children (34%) changed from the WW to the ATY group, whereas 7 children in the ATY group (5.5%) did not undergo ATY. Since we found that ATY reduced oropharyngeal carriage of potentially pathogenic bacteria, our intention-to-treat analytic strategy may

Table 2. Potential Bacterial Pathogens Isolated From the Oropharynx in Children in the Adenotonsillectomy and Watchful Waiting Groups^a

Potential Bacterial Pathogen	Baseline			3 Months			12 Months		
	ATY (n=134)	WW (n=143)	P Value	ATY (n=120)	WW (n=125)	P Value	ATY (n=107)	WW (n=104)	P Value
Group A BHS	17 (12.7)	10 (7.0)	.11	0	8 (6.4)	.005	0	8 (7.7)	.003
Group C BHS	1 (0.7)	1 (0.7)	>.99	0	0		0	0	
Group G BHS	1 (0.7)	3 (2.1)	.62	0	0		0	2 (1.9)	.24
<i>Haemophilus influenzae</i>	54 (40.3)	56 (39.2)	.85	29 (24.2)	47 (37.6)	.02	28 (26.2)	42 (40.4)	.03
<i>Moraxella catarrhalis</i>	8 (6.0)	8 (5.6)	.89	11 (9.2)	10 (8.0)	.74	7 (6.5)	0	.01
<i>Staphylococcus aureus</i>	7 (5.2)	9 (6.3)	.70	0	9 (7.2)	.003	0	8 (7.7)	.003
<i>Streptococcus pneumoniae</i>	3 (2.2)	2 (1.4)	.68	1 (0.8)	2 (1.6)	>.99	0	2 (1.9)	.24
None	60 (44.8)	70 (49.0)	.49	87 (72.5)	60 (48.0)	<.001	74 (69.2)	48 (46.2)	.001

Abbreviations: ATY, adenotonsillectomy; BHS, β -hemolytic streptococci; WW, watchful waiting.

^aUnless otherwise indicated, data are reported as number (percentage) of subjects. Because 2 or more types of potentially pathogenic bacteria were isolated in some children, the totals are greater than 100%.

have resulted in an underestimation of the number of potentially pathogenic bacteria in the WW group. We therefore also performed a per-protocol analysis including only the children who were compliant to the randomization; ie, children who changed from the WW group to the ATY group or from the ATY group to the WW group were excluded. The results of this analysis, however, did not differ substantially from those of the intention-to-treat analysis.

In conclusion, ATY was associated with a reduction of oropharyngeal carriage of potential respiratory pathogens. Changes in the carriage rate of GABHS, however, had no beneficial effect on recurrence of throat infections.

Submitted for Publication: October 19, 2006; final revision received January 22, 2007; accepted February 7, 2007.

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Author Contributions: Dr Schilder had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Rovers, van Staaïj, van den Akker, Hoes, and Schilder. *Acquisition of data:* Rovers, van Staaïj, van den Akker, and Schilder. *Analysis and interpretation of data:* Le, Rovers, Hoes, and Schilder. *Drafting of the manuscript:* Le, Rovers, and Schilder. *Critical revision of the manuscript for important intellectual content:* Rovers, van Staaïj, van den Akker, Hoes, and Schilder. *Statistical analysis:* Rovers, van Staaïj, and Hoes. *Obtained funding:* Hoes and Schilder. *Administrative, technical, and material support:* van den Akker. *Study supervision:* Rovers, Hoes, and Schilder. **Financial Disclosure:** None reported.

Funding/Support: This study was funded by a grant from the Dutch Health Care Insurance Board (OG-99-060), Dieren, the Netherlands.

Additional Contributions: We thank the participants and their parents and our colleagues and nurses in the participating hospitals; Nelly van Eden provided secretarial support and Frank Leus, data management.

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