Original Investigation

Tonsillar Helicobacter pylori Colonization in Chronic Tonsillitis Systematic Review and Meta-analysis

Michelle S. Hwang, BS; Suzanne N. Forman, BS; Jacob A. Kanter, BA; Michael Friedman, MD

IMPORTANCE Helicobacter pylori colonization contributes significantly to multiple disease states, but its role in the development of tonsillar infection is unclear. Understanding the causes of chronic tonsillitis is important in clinical decision making of this commonly treated disease.

OBJECTIVE To assess the correlation between H pylori colonization of tonsillar tissue in chronic tonsillitis and in noninfectious hyperplastic tonsils.

DATA SOURCES We searched PubMed, MEDLINE, the Cochrane Trial Registry (through June 2014) and relevant article bibliographies.

STUDY SELECTION Systematic review and meta-analysis of studies assessing the correlation between H pylori colonization in tonsillar tissues of patients undergoing tonsillectomy for either chronic tonsillitis or noninfectious causes. Included studies hypothesized that H pylori played a role in the development of chronic tonsillitis. All included studies investigated the presence of H pylori in tonsillar tissue removed for various indications. Included studies must have used an accepted method of testing for H pylori.

DATA EXTRACTION AND ANALYSIS Studies were systematically reviewed by 2 independent reviewers for inclusion. Reported results of H pylori testing between tissues removed for infectious or noninfectious causes were systematically reviewed. The odds ratio of H pylori colonization in tissue removed for chronic tonsillitis compared with tissue removed for noninfectious causes was calculated using a random-effects model.

RESULTS Six studies met inclusion criteria and had suitable data for pooling (n = 436). Of these, 2 studies measured H pylori colonization of tonsillar tissue in pediatric populations. One study analyzed tissue in both adult and pediatric populations. Noninfectious indications for tonsillectomy included sleep apnea or sleep-related breathing disorder, obstruction, carcinoma, and tonsillar hypertrophy. Overall, tonsillar H pylori colonization was found not to be significantly present more often in tissue samples removed secondary to recurrent infection rather than to noninfectious indications. The odds ratio of H pylori colonization in the tonsils of patients with chronic tonsillitis was 1.993 (95% CI, 0.909-4.371) (P = .09).

CONCLUSIONS AND RELEVANCE Helicobacter pylori colonization was not found to be more prevalent on tonsillar tissue with chronic or recurrent infections. The reviewed studies provide no evidence that H pylori infection plays a role in the pathogenesis or development of chronic tonsillitis.


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Helicobacter pylori is a gram-negative, urease-producing bacterium that colonizes gastrointestinal mucosa. It has a well-known role in the pathogenesis of gastric and duodenal ulcers and has also been implicated in gastric cancers, specifically mucosa-associated lymphoid tissue (MALT) lymphoma. The current standard of care for known H pylori infection involves eradication of the bacteria with triple therapy of a proton pump inhibitor and dual antibiotic treatment.

Tonsillar tissue, in the Waldeyer ring, is a component of lymphoid tissue with many studied similarities to the MALT tissue of the stomach. Removal of tonsils via tonsillectomy is a common surgical intervention. Although there is a wide variety of tonsillar disease states, one of the most common indications for tonsillectomy is recurrent tonsillitis, characterized by recurrent infections of the tonsils. Multiple studies have been conducted implicating the oropharynx as a potential reservoir for colonization.3-4 The presence of bacterial colonization on tonsillar tissue may have a role in infection of tonsillar tissues. Multiple studies have reported an association between H pylori colonization and chronic tonsillitis.5-10 However, small sample size and inconsistent methods of detection often limit the statistical power of the studies. The aim of this investigation, therefore, was to assess the association between H pylori colonization in recurrent infection of the tonsils. Understanding the role of H pylori in the pathogenesis of chronic tonsillitis is important because it is a disease that is so often treated in everyday otolaryngologic practice.

Methods

Literature Search
A computerized search to identify literature on the topic of H pylori colonization of tonsils in the setting of chronic tonsillitis was conducted. A comprehensive search of the literature was performed, using PubMed, MEDLINE, and the Cochrane Trial Registry (through June 2014). Search terms included the following keywords: Chronic Tonsillitis; H pylori; H pylori AND tonsils; H pylori AND tonsillitis; H pylori AND chronic tonsillitis; H pylori AND tonsillectomy.

Inclusion and Exclusion Criteria
The meta-analysis was designed to review those studies reporting the presence or absence of H pylori colonization on tonsillar tissue that was removed secondary to recurrent infection. The research inquiry for the study was to assess the correlation between H pylori colonization on posttonsillectomy specimens removed for chronic tonsillitis compared with noninfectious indications (eg, hypertrophy, obstruction). The following inclusion criteria were used:

1. Study must have tested for H pylori specifically in tonsillar tissue. Studies using noninvasive tests like urea breath test, stool antigen test, or serology antibody test were excluded.
2. All studies must have used an accepted method of testing for H pylori, including polymerase chain reaction (PCR), culture, rapid urease test, or Campylobacter-like organism test.
3. All studies must have also tested for presence of H pylori in tonsillar tissue removed for noninfectious causes, including hypertrophy, obstruction, or sleep-related breathing disorder.
4. Studies must have been written in English.

Studies with both pediatric and adult populations were included. We examined reference sections of identified studies for additional relevant articles to review. Case reports, abstracts, and letters to the editor were excluded. Multiple studies published by the same authors or group were analyzed for duplication of patient populations. This analysis was performed by reviewing articles. If missing data were needed, the primary author was contacted. Included studies were reviewed by 2 independent reviewers (M.S.H. and S.N.F.). In cases of disagreement regarding inclusion of an article, a third reviewer (M.F.) was used.

Variations in Testing for H pylori
Multiple mechanisms were used to detect presence of H pylori in the studies included in this meta-analysis. The rapid urease test (RUT), Campylobacter-like organism (CLO) test, culture, and PCR are all accepted ways of testing for H pylori. Both RUT and CLO tests confirm the presence of bacteria based on its production of urease, a characteristic exhibited by Helicobacter. Polymerase chain reaction detection for bacterial DNA and culture for the bacteria itself can also be performed. In gastric reservoirs of H pylori, all methods of testing are widely accepted and accurate, with culturing for bacteria being considered the gold standard for detection. However, Dowett and Kowolik10 noted that testing for presence of oral H pylori is less reliable because oral H pylori may have a coccoid form that is difficult to culture. The oral cavity also has multiple urease-producing species, unlike the stomach, which may cause a higher rate of false-positive results on RUT and CLO tests.11 For the purpose of the present study, results from RUT, CLO, culture, and PCR were all accepted because these are widely reliable tests for gastric H pylori and there is currently no accepted gold standard method of testing for the oral form. Two of the included studies used RUT.12,13 One of those 2 studies used RUT and culture but had no findings on culture, so RUT results were included.12 Four studies used PCR.14-17 Of those 4, 1 study used PCR and CLO17 and 1 study used PCR, culture, and CLO.16 Given the limitations of CLO and culture in the oral cavity, and for increased data homogeneity, PCR results were chosen for inclusion into our study when multiple sets of results were available from 1 study.

Statistical Analysis
Data were retrieved and reviewed systematically. All calculations and plot syntheses were performed using a commercially available statistical software package (Comprehensive Meta-Analysis, version 2; Biostat). The odds ratio (OR) of H pylori colonization in tissue removed for chronic tonsillitis compared with tissue removed for noninfectious causes was calculated using a random-effects model. A forest plot was synthesized. Analysis of publication bias was performed using funnel plot techniques in the Egger weighted-linear regression method. P < .05 was considered statistically significant.
Results

Initial literature search revealed 61 potential articles. Two independent reviewers (M.S.H. and S.N.F.) screened 51 abstracts. Nine articles were excluded for not containing the disease process of interest (4 articles studied otitis media with effusion, 2 studies focused on adenoid tissue, and 3 studies reviewed MALT lymphoma). The remaining 42 full-text articles were reviewed. Once the determined inclusion criteria were applied, and articles without control groups of noninfectious causes for tonsillectomy were excluded, 6 articles were identified to meet parameters (Figure 1). The 6 studies had suitable data for pooling (n = 436). Of these, 2 studies measured *H pylori* colonization of tonsillar tissue in pediatric populations. One study analyzed tissue in both adult and pediatric populations. Included studies presented control group data for presence or absence of *H pylori* in tonsillar tissue that was removed for noninfectious causes. Noninfectious indications for tonsillectomy included sleep apnea or sleep-related breathing disorder, obstruction, carcinoma, and tonsillar hypertrophy. One study provided data as number of biopsies; these data were included in the meta-analysis (Table). All studies included were graded as a 2b based on Center for Evidence-Based Medicine rankings. Publication bias was assessed using the Egger regression intercept (2-tailed, P = .42) and graphically using a precision funnel plot (Figure 2). A non-significant Egger regression intercept was found, decreasing the occurrence of publication bias. No significant heterogeneity was calculated (P = .66), but the calculated I² value was 53.62%, indicating that variability across included studies was likely due to heterogeneity.

The pooled data demonstrated that *H pylori* does not have a significant role in chronic tonsillitis compared with noninfectious indications for tonsillectomy. Using a random-effects model, the overall OR of *H pylori* colonization on tonsillar tissue removed for chronic tonsillitis was 1.993 (95% CI, 0.909-4.371) (P = .09) (Figure 3).

One study had significant findings (OR, 77.057 [95% CI, 4.359-1362.155]; P = .003) using RUT, but it also simultaneously reported no growth on any samples by culture. Given the difficulties in testing for oropharyngeal *H pylori*,

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**Figure 1. Flowchart of Literature Review**

61 Records identified through database searching

51 Records screened after article duplicates removed

42 Full-text articles assessed for eligibility

36 Full-text articles excluded

9 Records excluded for not containing the disease process of interest

21 Incomplete or missing data

6 Did not meet other inclusion criteria

9 Nonrelevant articles

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**Table. Evidence Table Showing Methods and Results of Included Studies**

<table>
<thead>
<tr>
<th>Source</th>
<th>Patient Population</th>
<th>PCR, culture, CLO</th>
<th>Patient Diagnoses</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nártová et al, 2014</td>
<td>89 Adult patients diagnosed as having either chronic tonsillitis or OSAS</td>
<td>PCR</td>
<td>60 Patients with chronic tonsillitis; 29 patients with OSAS</td>
<td>48 Patients with chronic tonsillitis (80%) were <em>H pylori</em> positive; 24 with OSAS (83%) were <em>H pylori</em> positive</td>
</tr>
<tr>
<td>Lukeš et al, 2014</td>
<td>56 Adult patients diagnosed as having chronic tonsillitis, tonsillar carcinoma, or OSAS</td>
<td>PCR</td>
<td>20 Patients with chronic tonsillitis; 23 with tonsillar carcinoma; 13 with OSAS</td>
<td>14 Patients with chronic tonsillitis (70%) were <em>H pylori</em> positive; 17 with tonsillar carcinoma (74%) were <em>H pylori</em> positive; 9 with OSAS (69%) were <em>H pylori</em> positive</td>
</tr>
<tr>
<td>Güçlü et al, 2013</td>
<td>49 Patients (12 adult, 37 pediatric) with obstruction or infection</td>
<td>PCR, culture, CLO</td>
<td>24 Pediatric patients with infection; 12 adult patients with infection; 13 pediatric patients with obstruction</td>
<td>By PCR: 2 pediatric infection (8%), 1 adult infection (8%), and 0 pediatric obstruction samples were <em>H pylori</em> positive; by culture: no samples were positive for <em>H pylori</em>; by CLO: 2 samples showed growth, but it was not reported if it was from the infection or obstruction group</td>
</tr>
<tr>
<td>Lin et al, 2010</td>
<td>94 Adult patients with chronic tonsillitis or SRBDs</td>
<td>Pronto Dry (RUT) test (MIC France)</td>
<td>44 Patients with chronic tonsillitis; 50 patients with SRBDs</td>
<td>21 Patients with chronic tonsillitis (48%) were <em>H pylori</em> positive; 12 with SRBDs (24%) were <em>H pylori</em> positive</td>
</tr>
<tr>
<td>Jelavic et al, 2007</td>
<td>77 Pediatric patients with chronic tonsillitis or tonsillar hypertrophy</td>
<td>RUT and culture</td>
<td>31 Patients with chronic tonsillitis; 46 patients with tonsillar hypertrophy</td>
<td>By RUT: 14 chronic tonsillitis (45%) and 0 hypertrophy (0%) samples were <em>H pylori</em> positive; by culture: no growth on any sample</td>
</tr>
<tr>
<td>Bulut et al, 2006</td>
<td>71 Pediatric patients diagnosed as having RAT or ATH</td>
<td>PCR and CLO</td>
<td>118 Tonsillar tissue samples from 71 patients: 43 with RAT; 75 with ATH</td>
<td>By PCR: 14 patients with RAT (33%) and 15 with ATH (20%) samples were <em>H pylori</em> positive; by CLO: 5 patients with RAT (12%) and 11 with ATH (15%) were <em>H pylori</em> positive</td>
</tr>
</tbody>
</table>

| Abbreviations: ATH, adenotonsillar hypertrophy; CLO, Campylobacter-like organism test; *H pylori*, Helicobacter pylori; OSAS, obstructive sleep apnea syndrome; PCR, polymerase chain reaction; RAT, recurrent adenotonsillitis; RUT, rapid urease test; SRBDs, sleep-related breathing disorders. |
as previously discussed, studies were assessed and divided by means of testing. When the 2 studies that used RUT were excluded,\textsuperscript{12,13} the remaining 4 studies using PCR displayed nonsignificant findings (OR, 1.317 [95% CI, 0.734-2.362]; \(P = .44\)).

Because both adult and pediatric populations were included in this meta-analysis, subgroup analysis was also performed to see whether \textit{H pylori} colonization had an effect in chronic tonsillitis in adults. When all studies that included pediatric populations were excluded,\textsuperscript{12,16,17} the pooled data from the remaining 3 studies had an OR of 1.402 (95% CI, 0.596-3.297) (\(P = .44\)).

**Discussion**

The goal of this study was to conduct a meta-analysis on published studies to determine whether \textit{H pylori} colonization plays a role in the pathogenesis of infectious disease processes of the tonsils. \textit{Helicobacter pylori} is a recognized pathogen of gastric mucosa and has been implicated in disease processes ranging from ulcers to lymphoma. Within the aerodigestive tract, tonsillar tissue has many established similarities to gastric mucosal lymphoid tissue. Therefore, it is reasonable that \textit{H pylori} colonization may play a role in infection of the tonsils. However, current clinical practice does not address this potential relationship, and treatment of \textit{H pylori} has never been implicated as a means of noninterventional treatment of chronic tonsillitis, despite multiple studies that have sought to establish \textit{H pylori} colonization in the setting of tonsillar infection.

Six studies had data suitable for inclusion in our quantitative analysis. All studies presented clear data that tested for the presence or absence of \textit{H pylori} in tonsillar tissues removed either for infectious or noninfectious causes. Given our inclusion criteria, included studies used multiple methods of testing for \textit{H pylori} and also tested in adult and pediatric populations, so the random-effects model was applied. This allows our study to account for variance in protocol and patient population.

In posttonsillectomy tissue, our analysis revealed that \textit{H pylori} did not significantly colonize the tonsils more in chronic tonsillitis compared with noninfectious disease processes (eg, obstruction, hypertrophy). The strength of these findings was supported by the fact that when the data were stratified by method of detection, with PCR being considered the better means of testing for oropharyngeal \textit{H pylori}, the pooled data still showed no significant results. When studies on pediatric populations were excluded, \textit{H pylori} was not found to colonize adult tissue samples with chronic tonsillitis more often. Our data therefore suggest that \textit{H pylori} does not play a significant role in the infectious process leading to recurrent infections of the tonsils. Treatment for \textit{H pylori} with antibacterial medication or proton pump inhibitors, therefore, is not warranted as a clinical consideration in treating chronic tonsillitis.

Limitations to this study include the need for studies using an accepted means of testing for \textit{H pylori} in tonsillar tissues. Although the various methods currently used are highly sensitive in gastric mucosa, a means of detecting oropharyngeal \textit{H pylori} has yet to be standardized. The heterogeneity in study population and methodology may have contributed to the nonsignificant results. This study also does not make conclusions about whether \textit{H pylori} is a factor in all tonsillar disease process as a group. More studies that compare \textit{H pylori} in all diseased tonsillar tissue with normal tissue may be needed.

**Conclusions**

Given the frequency with which tonsillectomies are performed secondary to recurrent infection or chronic tonsillitis, it is important to understand the various factors that may
Tonsillar Helicobacter pylori colonization in tonsillitis

ARTICLE INFORMATION
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Author Contribution: Ms Hwang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hwang, Forman, Friedman. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Hwang, Forman, Friedman. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Hwang, Forman. Administrative, technical, or material support: Friedman. Study supervision: Friedman.

Conflict of Interest Disclosures: None reported.

REFERENCES