

# Effectiveness of *Helicobacter pylori* eradication in chronic urticaria: evidence-based analysis using the Grading of Recommendations Assessment, Development, and Evaluation system

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**Current Opinion in Allergy and Clinical Immunology** 2010, 10:362–369

## Purpose of review

Chronic urticaria is a common and often frustrating condition that physicians encounter in the outpatient setting. Its management continues to be a challenge, and an exogenous cause for chronic urticaria is only found rarely. *Helicobacter pylori* has been implicated as a factor for many disorders and proposed as an etiologic factor for chronic urticaria. We aim to provide a comprehensive review of the data on *H. pylori* eradication for treatment of chronic urticaria by utilizing the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to analyze and determine the quality of evidence for this proposed therapy.

## Recent findings

Although *H. pylori* eradication has been recommended as part of routine chronic urticaria management by multiple authors, the trials of *H. pylori* eradication in the treatment of chronic urticaria have yielded conflicting results and suffer from substantial methodological limitations.

## Summary

Our critical appraisal of the 10 trials showing the benefit of *H. pylori* eradication in patients with chronic urticaria leads to an overall very low grade for this intervention. Appraisal of nine studies in which *H. pylori* eradication showed no benefit in the course of chronic urticaria also leads to an overall very low grade. The evidence that *H. pylori* eradication leads to improvement of chronic urticaria outcomes is weak and conflicting; this leads to a weak recommendation for routine *H. pylori* eradication for patients with chronic urticaria. For this reason, a decision to proceed with this management should be considered carefully in the context of relative harms/burdens and benefits, as well as patient values and preferences.

## Keywords

chronic urticaria, evidence-based, Grading of Recommendations Assessment, Development, and Evaluation approach, *Helicobacter pylori*

Curr Opin Allergy Clin Immunol 10:362–369  
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1528-4050

## Introduction

Chronic urticaria is a common condition that physicians encounter in the outpatient setting, though its management continues to be a challenge and is often frustrating for both patients and treating physicians alike. Many etiologic factors have been proposed for chronic urticaria, including chronic infections, though an exogenous cause can only be found rarely. In the last few years, *Helicobacter pylori* infection has been implicated as a potential underlying etiologic factor. Many small trials have focused on *H. pylori* eradication in the treatment of chronic urticaria. These trials have generated conflicting results.

*H. pylori* is a Gram-negative microaerophilic bacterium that colonizes the stomach and duodenum. It was discovered in the stomach lining of humans in the early 1980s and is known to induce chronic inflammation and gastritis. It is a widely prevalent infection in the world, with prevalence ranging from approximately 25% in industrialized nations to 80% in the developing countries [1,2]. Prevalence increases with lower socioeconomic status and with increasing age; however, most infections are acquired during childhood [3–5]. Although it is a very common infection, the vast majority of patients never develop symptoms. However, it is a proven underlying factor in duodenal and gastric ulcers, and the much less

common mucosa-associated lymphoid tissue lymphoma, with eradication resulting in resolution of disease [6]. It is unclear why some infected people develop these illnesses and others do not.

In recent years it has increasingly been suggested that infection with *H. pylori* induces a variety of systemic effects that may lead to extraintestinal and chronic skin disorders such as chronic urticaria. Therefore, eradication of *H. pylori* has been suggested as a treatment for chronic urticaria in cases wherever infection is documented. This has been the basis for several small trials with conflicting results and multiple review articles with differing conclusions [7,8<sup>•</sup>,9,10]. For the purposes of this updated review, we have taken a novel approach to evaluate the quality of evidence through the widely accepted Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to develop clinical practice guidelines and aid in future research.

### Analysis using the Grading of Recommendations Assessment, Development, and Evaluation approach

The GRADE system is a detailed and stepwise systematic approach that provides guidance in grading the quality of evidence and the strength of a recommendation for, or against, a particular intervention ([www.gradeworking-group.org](http://www.gradeworking-group.org)) [11,12<sup>•</sup>,13–15]. The overall strength of the recommendation depends on the extent of confidence that desirable effects outweigh undesirable effects. The outcome that is critical to decision making is identified as well the recommended intervention, which should yield greater net benefit than net harm or burden. In this case the assessment entails evaluating the potential benefit of *H. pylori* eradication in chronic urticaria resolution relative to its undesirable consequences such as added cost and harms. There is a clear and transparent separation of the quality of evidence and the strength of recommendations to minimize bias and aid interpretation. This system takes into account four grades in the assessment of the quality of evidence: high, moderate, low, and very low quality (Tables 1–3). Randomized trials are initially given a high-quality grade, whereas observational studies are initially given a low grade. There are explicit and comprehensive criteria in which four qualities are assessed that could potentially move a study into either a higher category or lower category: study design, consistency, directness, and precision. Of these, study design is a critical factor, but not the sole basis of the grade given. When there is high-quality evidence and benefits are shown to outweigh harms, this leads to a strong recommendation and more straightforward clinical decision making. In situations wherein there is only low or very low-quality evidence, greater emphasis may be placed on the ratio of harms to benefits and

**Table 1 Criteria for assigning grade of evidence**

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Type of evidence               | Randomized trial = high<br>Observational study = low<br>Any other evidence = very low                                                                                                                                                                                                                                                                                                                                                        |
| Decrease <sup>a</sup> grade if | Serious or very serious limitation to study quality<br>Important inconsistency<br>Some or major uncertainty about directness<br>Imprecise or sparse data<br>High probability of reporting bias                                                                                                                                                                                                                                               |
| Increase grade if              | Strong evidence of association – significant relative risk of >2 (<0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)<br>Very strong evidence of association – significant relative risk of >5 (<0.2) based on direct evidence with no major threats to validity (+2)<br>Evidence of a dose–response gradient (+1)<br>All plausible confounders would have reduced the effect (+1) |
| Range                          | High-quality evidence<br>Moderate-quality evidence<br>Low-quality evidence<br>Very low-quality evidence                                                                                                                                                                                                                                                                                                                                      |

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<sup>a</sup> Each quality criteria can reduce the quality by one or, if very serious, by two levels.

consideration of patient values and preferences in clinical decision making. We applied this method to the group of studies included in our review to reach our final recommendation.

### Literature review

We identified relevant studies through a search of the medical literature using PubMed, MEDLINE, and the Cochrane registry using a combination of the keywords ‘chronic urticaria,’ ‘chronic idiopathic urticaria,’ and

**Table 2 Grading of recommendations assessment, development, and evaluation summary and definitions**

|                         |                                                                                                                                                                                           |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Outcome of interest     | Complete resolution of urticaria = critical outcome                                                                                                                                       |
| Evidence                | All English-language or translated foreign articles that met our inclusion criteria<br>Case reports and abstracts were excluded                                                           |
| Study design categories | Randomized trials vs. observational                                                                                                                                                       |
| Consistency of results  | Are there differences in the consistency and effect of results (complete urticaria resolution) across studies? Are there differences in definition of response to treatment?              |
| Directness              | Are outcome measures similar to those of interest (complete resolution of urticaria)? Are treatment regimens and duration of treatment similar to those of interest or accepted practice? |
| Precision               | Study is imprecise if it includes relatively few patients with few events (i.e. sparse data), leading to wide estimate of benefits and/or harms                                           |

Table 3 Explanation of the quality of evidence

|          |                                                                                                                                                                                                                                                                                  |
|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| High     | Randomized trials without serious limitations<br>Well performed observational studies with very large effects<br>Future research is very unlikely to change our confidence in the estimate of effect                                                                             |
| Moderate | Randomized trials with serious limitations<br>Well performed observational studies yielding large effects<br>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate                                      |
| Low      | Randomized trials with very serious limitations<br>Observational studies without special strengths or with important limitations<br>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate |
| Very low | Randomized trial with very serious limitations and inconsistent results<br>Observational studies with serious limitations<br>Unsystematic clinical observations (case reports or case series)<br>We are very uncertain about the estimate                                        |

Data obtained from [12\*].

‘*H. pylori*’. All relevant English-language publications dating to March 2010 were reviewed. We also included relevant studies from evaluation of bibliographies and references of search articles. For the purpose of inclusion in our review, all studies had to include the following criteria: define chronic urticaria as urticaria lasting more than 6 weeks; attempt to rule out other known causal factors of chronic urticaria by history, physical examination, and laboratory testing; identify *H. pylori* diagnoses method; reveal the antibiotic regimen used in *H. pylori* eradication; and identify follow-up time. Studies and abstracts wherein sufficient information was lacking, or if printed in only another language, or where only a single case report was presented were excluded. We classified included articles as either positive or negative studies based on whether the study results showed a beneficial or no effect on the course of chronic urticaria, respectively. We then evaluated the quality of the body of evidence in each category through the GRADE approach, as described above.

Results

Our search initially produced 106 articles from PubMed, MEDLINE, and the Cochrane registry, using the terms, ‘chronic urticaria’, ‘chronic idiopathic urticaria’ and ‘*H. pylori*’. We identified a total of 19 studies in which *H. pylori* eradication was undertaken in the treatment of chronic urticaria that fit our inclusion criteria, as stated above (Table 4) [10,16–33]. These studies comprised 17 observational (case–control and prospective) studies and two double-blinded, randomized-control trials. Table 4 summarizes the findings and characteristics of each study in detail.

The 19 studies that fit the criteria for inclusion were further divided into two categories, positive and negative, depending on whether they showed a beneficial effect of *H. pylori* eradication on chronic urticaria resolution or no effect on chronic urticaria course, respectively. Ten study results suggested that *H. pylori* eradication was effective in resolving chronic urticaria and nine studies showed no benefit of *H. pylori* eradication in significant improvement or chronic urticaria symptom resolution. The trials in each category were further separated into randomized-controlled trials and observational trials.

Studies suggesting eradication of *Helicobacter pylori* improves chronic urticaria (positive studies)

In each of these 10 trials, a beneficial effect of *H. pylori* eradication in chronic urticaria symptom resolution was claimed (Table 5). There were nine observational studies and only one randomized, double-blinded, placebo-controlled trial (RCT), with each type of study group evaluated separately [16–24]. Based on GRADE criteria, the RCT performed by Gaig *et al.* [16] initially receives a high grade; however, very serious limitations were found in this study ultimately reducing the grade to very low. For example, although randomization was performed, concealment of randomization was not described. Whether patients, caregivers, or collectors and analysts of outcome data were aware of group allocation was not stated. Moreover, there was significant inconsistency in choosing a result range of 70% symptom improvement to complete remission as a measure of *H. pylori* eradication success leading to dilution of the study’s various results and, consequently, indirectness in the outcome of interest being measured. No power analysis was performed to determine appropriate sample size; therefore, the small sample size of 10 patients in the treatment arm and six patients in the placebo arm implies that the study conclusion was vulnerable to small changes in the results of either arm. Finally, although the authors concluded that *H. pylori* eradication was beneficial, the difference was not statistically different ( $P=0.19$ ). An alternative interpretation of these data is that improvement in chronic urticaria could not be demonstrated in this small study.

The nine observational studies in Table 5 were all characterized by small sample sizes along with significant study limitations that lead to an overall very low grade. This body of evidence consists of widely differing definitions of ‘response to treatment’, including complete response and partial response in some studies; the study by Magen *et al.* [22] used only decrease in symptom scores, leading to resultant uncertainty in the directness of the true outcome that was measured [17,20,21,23,25]. Furthermore, the definitions of ‘complete response’ and ‘partial response’ vary between these studies. This overall heterogeneity in the definitions used leads to

**Table 4 Summary of studies evaluating the effect of *Helicobacter pylori* eradication on the clinical course of chronic urticaria**

| Author                          | Trial type | No. cases | No. controls w/CU | Prevalence (%) | No. completed study | Hp Dx method | Regimen (days)     | No. w/ eradication success (%) | No. remission w/ eradication (%)       | No. remission w/ Rx failure (%) | No. spontaneous remission (%) | Follow-up (months) | CU/HP association? | Origin country |
|---------------------------------|------------|-----------|-------------------|----------------|---------------------|--------------|--------------------|--------------------------------|----------------------------------------|---------------------------------|-------------------------------|--------------------|--------------------|----------------|
| Gaig <i>et al.</i> [16]         | RCT        | 49/88     | 6 (w/ Hp)         | 56             | 16/49               | UBT/UE       | OAC 7              | 9/10 (90)                      | 4/9 CR or 70% improvement 8/14 CR (57) | –                               | 1/6 placebo (20)              | 6 weeks            | YES                | SPA            |
| Tebbe <i>et al.</i> [17]        | OBS        | 17/25     | –                 | 68             | 17/17               | UBT          | A or C (or T +MBO) | 14/17 (82)                     | 0/3                                    | 0/3                             | –                             | 6–10 weeks         | YES                | GER            |
| Wedi and Kapp [18]              | OBS        | 26/35     | –                 | 74             | 21/26               | UE           | OAC 7              | 21/23 (91)                     | 6/14 PR (43) 14/21 (67)                | –                               | –                             | 6–9                | YES                | GER            |
| Di Campli <i>et al.</i> [19]    | OBS        | 23        | 19                | 55             | 18/23               | UBT          | LAC 7              | 16/18 (89)                     | 13/16 (81)                             | 0/2                             | 0/19                          | 3                  | YES                | ITA            |
| Bonamigo <i>et al.</i> [20]     | OBS        | 18        | 18                | 67             | 18/18               | IgG          | OMC ?              | N/A                            | 6/12 CR (50)                           | –                               | N/A                           | N/A                | YES                | BRA            |
| Fukuda <i>et al.</i> [21]       | OBS        | 26/50     | –                 | 52             | 19/26               | IgG/UE       | LAC 7              | 17/19 (89)                     | 3/12 PR (25) 6/17 CR (35)              | –                               | 0/9                           | 6                  | YES                | JPN            |
| Magen <i>et al.</i> [22]        | OBS        | 45/78     | 33 (16 w/ Hp)     | 58             | 45/45               | UBT          | OAC 14             | 39/45 (87)                     | 5/17 PR (29) decrease in UAS           | 0/6                             | no change in UAS              | 16 weeks           | YES                | ISR            |
| Yadav <i>et al.</i> [23]        | OBS        | 48/68     | 68 (46 w/ Hp)     | 71             | 48/48               | UE           | OAC 14             | 46/48 (96)                     | 21/46 CR (46)                          | 0/2                             | –                             | 3                  | YES                | IND            |
| Abdou <i>et al.</i> [24]        | OBS        | 20/35     | 10 (no CU)        | 57             | 20/20               | SAG          | OAM 14             | N/A                            | 18/46 PR (39) 16/20 (80)               | –                               | –                             | 10 weeks           | YES                | EGY            |
| Sakurane <i>et al.</i> [25]     | OBS        | 28        | –                 | 56             | 15/28               | UE           | LAC 4–14           | 15 (100)                       | 5/15 CR (33)                           | –                               | –                             | 6                  | YES                | JPN            |
| Schnyder <i>et al.</i> [26]     | RCT        | 12/50     | 46                | 24             | 11/12               | UBT          | LA 14              | 3/11 (27)                      | 4/15 PR (27) 1/3 (33)                  | 3/8 (37.5)                      | 19/46 (41)                    | 6                  | NO                 | SUI            |
| Bayazit <i>et al.</i> [27]      | OBS        | 27        | –                 | 77             | 23/27               | UE           | OAC 7              | 17/23 (74)                     | 5/17 (30)                              | 2/6 (33)                        | 1/6 placebo (20) 3/8 (40)     | 6                  | NO                 | TUR            |
| Valsecchi and Pigatto [28]      | OBS        | 78/125    | 34 (w/ Hp)        | 62             | 65/78               | UBT          | OMC 7              | 29/31 (94)                     | 3/29 (10)                              | –                               | 1/34 (3)                      | 12                 | NO                 | ITA            |
| Wustlich <i>et al.</i> [29]     | OBS        | 35        | –                 | –              | 30/35               | UBT/UE       | OA 14              | 24/30 (80)                     | 6/24 CR (25)                           | N/A                             | –                             | 6                  | NO                 | GER            |
| Daudén <i>et al.</i> [30]       | OBS        | 17/25     | 25 (no CU)        | 68             | 15/17               | UBT          | OAC 7              | 12/15 (80)                     | 2/24 PR (8) 1/12 CR (8)                | 0/3                             | –                             | 12                 | NO                 | SPA            |
| Hook-Nikanne <i>et al.</i> [31] | OBS        | 57/231    | 18                | 25             | 35/57               | IgA/IgG      | LAM 7              | 30/35 (86)                     | 2/12 PR (17) 8/30 (27)                 | 3/5 (60)                        | 5/18 (28)                     | 5                  | NO                 | FIN            |
| Erel <i>et al.</i> [32]         | OBS        | 29/38     | –                 | 76             | 29/29               | UE           | OAC 15             | 25/29 (86)                     | 1/25 (4)                               | 0/4                             | –                             | 2                  | NO                 | TUR            |
| Moreira <i>et al.</i> [10]      | OBS        | 15/21     | –                 | 71             | 14/15               | UBT          | OAC 7              | 12/14 (80)                     | 3/12 (25)                              | 0                               | –                             | 6                  | NO                 | POR            |
| Hellmig <i>et al.</i> [33]      | OBS        | 74/106    | 51                | 70             | 43/74               | UBT          | N/A                | 16 confirmed                   | 11/43 (26)                             | –                               | 10/51 (20)                    | >12                | NO                 | GER            |

A, amoxicillin; B, bismuth; BRA, Brazil; C, clarithromycin; CR, complete response; CU, chronic urticaria; EGY, Egypt; FIN, Finland; GER, Germany; HP, *Helicobacter pylori*; IND, India; ISR, Israel; ITA, Italy; JPN, Japan; L, lansoprazole; M, metronidazole; N/A, not available; O, omeprazole; OBS, observation study (case-control or prospective); POR, Portugal; PR, partial response; RCT, randomized placebo-controlled trial; SAG, stool antigen; SPA, Spain; SUI, Switzerland; T, tetracycline; TUR, Turkey; UAS, urticaria activity score; UBT, urea breath test; UE, upper endoscopy; w/, with.

**Table 5 Application of the Grading of Recommendations Assessment, Development, and Evaluation system of findings for studies with results favoring eradication of *Helicobacter pylori* in treatment of chronic urticaria**

| Study authors/references                           | Design                               | Limitations in study design (bias)                                                                                                                                                       |                  |                  |                         |               |
|----------------------------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------|-------------------------|---------------|
| Gaig <i>et al.</i> [16]                            | Randomized<br>Double-blinded placebo | Vague concealment and blinding<br>Results did not reach statistical significance<br>High dropout rate (16/49 completed study)<br>Small control group (six patients)<br>Follow-up 6 weeks |                  |                  |                         |               |
| Tebbe <i>et al.</i> [17]                           | Prospective                          | Did not account for antihistamines/steroids<br>Included partial response<br>Follow-up 6–10 weeks                                                                                         |                  |                  |                         |               |
| Wedi and Kapp [18]<br>Di Campli <i>et al.</i> [19] | Prospective<br>Prospective           | No additional limitations<br>Did not account for antihistamines/steroids<br>Follow-up 12 weeks                                                                                           |                  |                  |                         |               |
| Bonamigo <i>et al.</i> [20]                        | Case–control                         | Used serology for diagnosis (IgG)<br>Included partial response                                                                                                                           |                  |                  |                         |               |
| Fukuda <i>et al.</i> [21]                          | Case–control                         | High dropout rate (19/26)<br>Included partial response                                                                                                                                   |                  |                  |                         |               |
| Magen <i>et al.</i> [22]                           | Case–control                         | Did not account for antihistamines<br>Follow-up 16 weeks                                                                                                                                 |                  |                  |                         |               |
| Yadav <i>et al.</i> [23]                           | Case–control                         | Inclusion, and definition, of partial response vague<br>Follow-up 12 weeks (statistical analyses performed)                                                                              |                  |                  |                         |               |
| Abdou <i>et al.</i> [24]                           | Case–control                         | Did not account for antihistamines/steroids<br>Follow-up 10 weeks                                                                                                                        |                  |                  |                         |               |
| Sakurane <i>et al.</i> [25]                        | Prospective                          | Treatment success/failure not acknowledged<br>High dropout rate (13/28)<br>Does not account for antihistamines/steroids<br>Included partial response                                     |                  |                  |                         |               |
|                                                    |                                      |                                                                                                                                                                                          |                  |                  |                         |               |
| Study design                                       | Number of studies                    | Study limitations (bias)                                                                                                                                                                 | Inconsistency    | Indirectness     | Imprecision/sparse data | Overall grade |
| GRADE summary                                      |                                      |                                                                                                                                                                                          |                  |                  |                         |               |
| Randomized, double-blinded placebo [16]            | 1                                    | Very serious                                                                                                                                                                             | Yes <sup>a</sup> | No               | Yes                     | Very low      |
| Observational [17–25]                              | 7                                    | Very serious <sup>b</sup>                                                                                                                                                                | Yes              | Yes <sup>c</sup> | Yes                     | Very low      |

<sup>a</sup> Results varied between 70% improvement of symptoms in some patients to complete remission in others.

<sup>b</sup> Statistical analyses are not performed in most observational studies, unless otherwise specified, and all studies contain small sample sizes.

<sup>c</sup> Definition of response to treatment is variable, and treatment regimens are not uniform and/or the standard of care.

inconsistency in the results reported. Consequently, there are widely differing estimates of the true magnitude of effect. *H. pylori* eradication therapy has on chronic urticaria resolution. For example, in one study [25] when ‘partial response’ is not included as a surrogate success marker, the success rate actually falls to 33%. In this case, the results and conclusion obtained may have been due to chance alone, and symptom resolution may well have occurred spontaneously irrespective of the eradication therapy, leading to the opposite ‘no benefit seen’ result. Follow-up time of less than 6 months was felt to be inadequate to rule out chronic urticaria symptom relapse and was also a source of potential bias reflected in beneficial outcomes seen more in the positive studies. Along with individual sparse data leading to imprecision and wide estimate of effect, lack of statistical data analyses in most studies and high dropout rates were also noted. These confounders make deducing a conclusion from these data difficult. In addition, there are serious questions regarding lack of accounting for concurrent treatment and dosing with antihistamines and

corticosteroids, which could have produced perceptible chronic urticaria symptom resolution [17,19,22,24,25].

#### **Studies showing eradication of *Helicobacter pylori* has no effect on chronic urticaria (negative studies)**

In each of these nine trials no benefit was demonstrated in chronic urticaria symptoms when *H. pylori* eradication therapy was performed (Table 6). These articles included eight observational studies and one RCT [10,26–33]. Unfortunately, the RCT in this category suffers from the same limitations as the RCT in the positive category, with lack of explanation of concealment, allocation, and blinding [26]. Furthermore, the results of this study are uncertain because the overall prevalence of *H. pylori* in their study population was low (24%) when compared with other published studies, which may be, in part, due to the demographics of the selected population in Switzerland where the trial was performed. This, in part, may have led to their very small patient sample size of 11 patients. Conceivably as a result of their nonstandard treatment regimen, this study also included a very low

**Table 6 Application of the Grading of Recommendations Assessment, Development, and Evaluation system of findings for studies with results not favoring eradication of *Helicobacter pylori* in treatment of chronic urticaria**

| Study authors/references          | Design                               | Limitations in study design (bias)                                                                                                    |  |  |  |  |
|-----------------------------------|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|--|--|--|--|
| Schnyder <i>et al.</i> [26]       | Randomized<br>Double-blinded placebo | Vague concealment and blinding<br>Low eradication success rate<br>Nonstandard treatment regimen<br>Small patient sample size          |  |  |  |  |
| Ozkaya-Bayazit <i>et al.</i> [27] | Prospective                          | Did not account for antihistamines/steroids<br>Follow-up not clearly stated<br>Low eradication success rate                           |  |  |  |  |
| Valsecchi and Pigatto [28]        | Case-control                         | Did not account for antihistamines/steroids                                                                                           |  |  |  |  |
| Wustlich <i>et al.</i> [29]       | Prospective                          | Nonstandard treatment regimen<br>Included partial response (statistical analyses performed)                                           |  |  |  |  |
| Daudén <i>et al.</i> [30]         | Case-control                         | Included partial response                                                                                                             |  |  |  |  |
| Hook-Nikanne <i>et al.</i> [31]   | Case-control                         | Did not account for antihistamines/steroids<br>High dropout rate (22/57)<br>Follow-up 5 months<br>Used IgA/IgG serology for diagnoses |  |  |  |  |
| Erel <i>et al.</i> [32]           | Prospective                          | Follow-up 2 months                                                                                                                    |  |  |  |  |
| Moreira <i>et al.</i> [10]        | Prospective                          | Small patient sample size (14 patients)                                                                                               |  |  |  |  |
| Hellmig <i>et al.</i> [33]        | Case-control                         | High dropout rate (31/74)<br>Eradication success rate not clear (only 16/43 confirmed)<br>Antibiotic regimen not specified            |  |  |  |  |

  

| Study design                            | Number of studies | Study limitations (bias)  | Inconsistency | Indirectness     | Imprecision/sparse data | Overall grade |
|-----------------------------------------|-------------------|---------------------------|---------------|------------------|-------------------------|---------------|
| GRADE summary                           |                   |                           |               |                  |                         |               |
| Randomized, double-blinded placebo [26] | 1                 | Very serious              | No            | Yes              | Yes <sup>a</sup>        | Very low      |
| Observational [27–34]                   | 8                 | Very serious <sup>b</sup> | Yes           | Yes <sup>c</sup> | Yes                     | Very low      |

<sup>a</sup>Prevalence of *H. pylori* in study population is very low at 24%.

<sup>b</sup>Statistical analyses are not performed in most observational studies unless otherwise specified, and all studies contain small sample sizes.

<sup>c</sup>Definition of response to treatment is variable, and treatment regimens are not uniform and/or the standard of care.

*H. pylori* eradication success rate of 27%. Therefore, it is very difficult to eliminate an association of *H. pylori* and chronic urticaria based on these data. These very serious study design limitations decrease the assigned grade from an initial high to very low.

The eight negative result observational studies all consisted of small sample sizes along with significant heterogeneity and many of the same issues also present in the positive study category [10,27–33]. High dropout rates in some studies [31,33] and very small patient sample sizes led to generation of sparse data; these were among the most conspicuous methodological limitations. In this group, statistical analyses of data were not performed in the majority of the studies, excluding two articles from Wustlich *et al.* [29] and Erel *et al.* [32]. The study by Hook-Nikanne *et al.* [31] used IgA/IgG serologies for *H. pylori* diagnoses, which may have overestimated the prevalence of *H. pylori* in their study population as serological testing has lower specificity and utility in identifying active infection and confirming eradication when compared with properly performed urea breath testing and the fecal antigen test [31,34–36]. Again, similar to the *positive* studies, uncertainty about the directness of outcomes measured was also evident. Definitions of response to treatment varied, with the

inclusion of partial response to treatment and resultant decreased certainty in the reported outcome [29,30]. In a study by Hellmig *et al.* [33], only 11 of 43 patients showed symptom resolution; however, confirmation of *H. pylori* eradication was performed in only 16 of the 43 patients. This leaves some doubt in the negative conclusion and possibly a higher success rate than reported. Based on these limitations, the overall grade for this body of evidence is very low.

## Discussion

We utilized the GRADE approach to provide an updated review and evaluate the strength of evidence for *H. pylori* eradication therapy in the treatment of chronic idiopathic urticaria. Our assessment found significant methodological shortcomings in each of the 10 trials showing benefit and an overall very low grade for these data. We also found considerable limitations in the nine studies in which *H. pylori* eradication showed no benefit in the course of chronic urticaria, again with an overall very low grade. There were two randomized placebo-controlled trials; however, methodological limitations and small size obfuscates interpretation of the findings of these studies. There was significant heterogeneity seen across all studies with regard to method of diagnosis,

antibiotic treatment regimen, and follow-up time, as well as significant variation in the accepted definition of response to treatment. The extensive differences in the treatment regimens used in the trials could possibly be due to country of origin, as accepted guidelines and resources differ in various nations. The studies published to date have been in non-US populations, which not only could have contributed to variation in outcomes but also limit applicability to patients with chronic urticaria in the United States. Finally, nearly all of the studies included small patient sample sizes leading to diminished confidence in the reported results. Taken in the context of these substantial limitations, the overall grade for the quality of the available evidence for, or against, *H. pylori* eradication in the treatment of chronic urticaria is very low. For this reason, the extent of effect for this therapy is unclear, leading to a weak recommendation.

Our approach differs from previous review articles by proponents of this therapy such as Federman *et al.* [9] and Wedi and coworkers [7,8], who grouped and then re-analyzed the data from these trials. The GRADE system of analysis is a widely endorsed grading system that minimizes bias and allows consistency and transparency [12]. We believe the application of statistical analyses across a large number of studies with heterogeneous populations and variance in the measured outcomes entails introducing bias and may lead to potentially erroneous conclusions. We performed a comprehensive assessment of each trial for, and conversely against, this therapeutic intervention from an objective standpoint. We further assigned value to the group of studies based on their design and limitations, and collectively to each body of evidence based on the merits of the published studies. In this way the conclusion reached is based primarily on methodological quality.

## Conclusion

Large, randomized, double-blinded, controlled trials that are methodologically sound are needed to establish the therapeutic utility of *H. pylori* eradication in patients with chronic urticaria. Based on our critical appraisal, the evidence that routine *H. pylori* eradication in patients with chronic urticaria improves outcomes is of low quality. In view of this, and the uncertainty of the balance between harms/burdens and benefits, this therapeutic intervention is associated with a weak recommendation.

Patient values and preferences merit consideration in determining whether to proceed with assessment and treatment for *H. pylori* in patients with chronic urticaria. This consideration includes the contention that colonization has been suggested to offer health benefits that may be impeded by empiric eradication in an otherwise asymptomatic patient [37–39].

Potential limitations in this study include the exclusion of non-English-language articles and abstracts, wherein sufficient information was lacking to meet our initial inclusion criteria. Also, we acknowledge that in strictly choosing complete symptom resolution as our critical outcome, we may have not acknowledged the possibility that in some patients with chronic urticaria partial symptom resolution is of value. However, this does not necessarily reflect causality or a specific association between chronic urticaria with *H. pylori*. Any endorsement of this therapy should consider the high prevalence of *H. pylori* infection in the population, and the overall cost burden of additional testing, antibiotic therapy, and confirming eradication along with medication side effects and a possible increase in bacterial resistance.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 406).

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