

Systematic review and meta-analysis: Effect of *Helicobacter pylori* eradication on chronic spontaneous urticaria

Hyun Jung Kim¹ | Yeon-Ji Kim²  | Ho Jung Lee³ | Jeong Yeon Hong³ |
A Young Park³ | Euy Hyun Chung³ | Sung Yul Lee³ | Jong Suk Lee³ | Young Lip Park⁴ |
Sang Hoon Lee⁴ | Jung Eun Kim³

¹Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea

²Department of Internal Medicine, St. Vincent's Hospital, The Catholic University College of Medicine, Suwon, Korea

³Department of Dermatology, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan, Korea

⁴Department of Dermatology, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Korea

Correspondence

Jung Eun Kim, Department of Dermatology, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, 31, Suncheonhyang 6-gil, Dongnam-gu, Cheonan 31151, Korea.
Email: freesia0210@naver.com

Funding information

the Soonchunhyang University Research Fund.; National Research Foundation of Korea, Grant/Award Number: NRF-2018R1C1B5042271

Abstract

Background: *Helicobacter pylori* (HP) infection is considered to play a role in the pathogenesis of chronic spontaneous urticaria (CSU). However, the efficacy of HP eradication therapy on CSU symptom improvement has not been well established. This meta-analysis was conducted to estimate the association between HP infection and CSU and to evaluate whether HP eradication therapy benefits patients with CSU. **Material and Methods:** In October 2018, we searched databases for studies investigating the efficacy of HP eradication therapy for patients with CSU. Risk ratios (RRs) and 95% confidence intervals (CIs) were pooled using random effects models.

Results: The meta-analysis included 22 studies with a total of 1385 patients with CSU. When comparing the spontaneous remission of urticarial symptom in patients with HP-positive to HP-negative patients, HP-negative patients showed significantly higher spontaneous remission of urticarial symptoms. (risk ratio 0.39; 95% confidence interval: 0.19-0.81). Among HP-positive CSU patients, remission of CSU was more likely shown in HP eradication therapy group compared to untreated group, aside from achieving HP elimination (risk ratio 2.10; 95% confidence interval: 1.20-3.68). However, there was no significant difference in the remission of CSU whether antibiotic therapy was successful in eradication of HP or not (risk ratio 1.00; 95% confidence interval: 0.65-1.54).

Conclusions: The results of this meta-analysis show that HP might be associated with the occurrence and persistence of CSU. The effectiveness of HP eradication therapy in suppressing CSU symptoms was significant. Interestingly, we found that resolution of CSU was not associated with successful eradication of HP infection. CSU Patients who were undergone antibiotic therapy for HP eradication showed significant higher CSU remission with or without HP eradication. Further studies are recommended to evaluate the mechanisms associated with relation of HP with CSU.

KEYWORDS

Helicobacter pylori, meta-analysis, urticaria

1 | INTRODUCTION

Chronic spontaneous urticaria (CSU) is a common skin disease characterized by the development of itchy wheals and/or angioedema with a duration of greater than 6 weeks without identifiable reason.^{1,2} CSU is known to have a substantial impact on the quality of life.^{3,4} Thus, considerable effort has been devoted to the identification of the pathogenesis of CSU; however, it still remains to be fully elucidated.⁵

A possible relationship between CSU and *helicobacter pylori* (HP) infection has often been suggested. Despite a number of studies demonstrating HP as a potential trigger of CSU, other studies have failed to confirm this, even showing that the prevalence of HP infection was similar among CSU patients compared with healthy subjects.⁶⁻⁸ Furthermore, there exists conflicting research about the therapeutic effects of HP eradication in CSU patients. Therefore, the aim of this study was to explore whether HP infection and its eradication affected CSU symptoms using meta-analysis. The allocation diagrams of all the evaluated CSU patients in the study are summarized in Figure 1.

2 | MATERIALS AND METHODS

This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) principles (Table S1).⁹ The study quality was evaluated using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool.¹⁰

2.1 | Literature search

We systematically searched the following literature databases from their dates of inception to October 2018 with no restrictions on language or publication year; MEDLINE, EMBASE, Cochrane Library, SCOPUS, and Web of Science. The keywords/subject headings used were "*Helicobacter pylori*" and "urticaria." The search strategies were developed according to the indices of the various databases and based on a MEDLINE strategy (Table S2). Abstracts were reviewed, and their eligibility for the meta-analysis was determined. In addition to the electronic search via databases, we also searched manually for additional relevant studies from the lists of references on the articles retrieved from the electronic search method.

2.2 | Eligibility criteria and study selection

Two reviewers independently selected studies that met the following inclusion criteria: (a) human studies; (b) urticaria of unknown etiology that lasted for at least 6 weeks in duration; (c) CSU patients who have not achieved remission from conventional urticarial treatments, such as antihistamines or glucocorticoids; (d) assessment of HP infection confirmed by either serology, urea breath test, or upper gastrointestinal (GI) tract endoscopic biopsy; (e) an illustration of the acceptable use of antibiotics known to be active against HP and an evaluation of its effects on CSU symptoms; and, (f) use of appropriate comparison groups (as shown in Figure 1, three comparative analyses were included: analysis

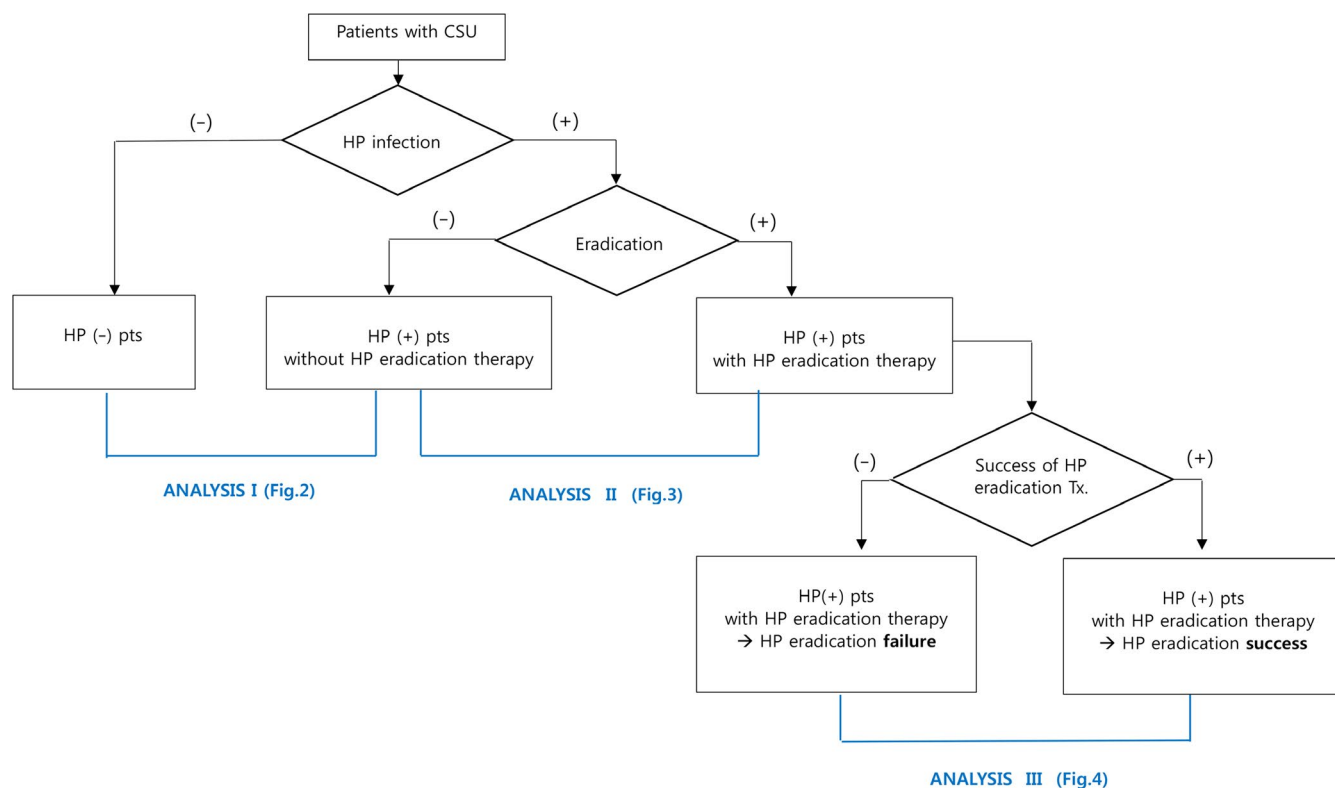


FIGURE 1 Allocation diagrams of the chronic spontaneous urticaria (CSU) patients evaluated

TABLE 1 Characteristics of the 22 studies included in the final analysis

Study	Country	No. of CSU patients	No. of HP (+) patients	HP detection method	Eradication regimen (days)	Spontaneous re-mission of CSU		Complete remission of HP-positive patients		Complete remission of CSU after HP eradication therapy	
						HP (-)	HP (+)	HP eradication Tx. (-)	HP eradication Tx. (+)	Eradicated	Noneradicated
Akashi et al ¹¹	Japan	82	25	HP stool anti-gen (ELISA)	ACL (7)					2/14	1/3
Chiu et al ¹²	Taiwan	25	14	UBT	A or M + CE (7)					7/11	0/3
Choi et al ¹³	Korea	56	30	UBT	AC + PPI (7)					3/27	0/3
Dauden et al ¹⁴	Spain	25		UBT	ACO (7)					1/12	0/3
Di Campli et al ¹⁵	Italy	42	23	UBT	ACL (7)					13/16	0/2
Erel et al ¹⁶	Turkey	38	29	UBT + histol-ogy	ACO (15)					1/25	0/4
Fukuda et al ⁶	Japan	50	26	Serum anti-HP IgG + histol-ogy or UBT or culture	ACL (7)			0/7	6/19	6/17	0/2
Gasbarrini et al ^{17 a}	Italy	42		UBT	ACL (7)					13/16	0/2
Ghaffari et al ^{18 a}	Iran	56	38	UBT + ELISA	AMOB (14)	7/18	0/15				
Ghazzawi et al ⁸	Jordan	100	76	UBT + ELISA	ACP (14)					22/68	2/8
Gonzalez Morales et al ¹⁹	Mexico	20	20	UBT	ACO (14)					9/15	0/5
Hellmig et al ²⁰	Germany		74	UBT		10/51	1/10				
Hook-Nikanne et al ⁷	Finland	231	57	Serum anti-HP IgG, IgA	A or T + ML (7)			5/18	11/35	8/30	3/5
Liutu et al ²¹	Finland	59	43	Serum anti-HP IgG	OA or CAM or OCAM or OAM (14)	3/16	1/11				
Magen et al ²²	Israel	46	29	UBT	ACO (14)	3/17	0/11				
Ozkaya-Bayazit et al ²³	Turkey	35	27	UBT + histol-ogy	ACO (7)	3/8	0/4	0/4	7/23	5/17	2/6
Schnyder et al ²⁴	Switzerland	50	12		AL (14)			1/9	4/11	1/3	3/8
Tebbe et al ²⁵	Germany	25	17	UBT	A or C or T + MBO (14)					8/14	0/3

(Continues)

TABLE 1 (Continued)

Study	Country	No. of CSU patients	No. of HP (+) patients	HP detection method	Eradication regimen (days)	Spontaneous remission of CSU		Complete remission of CSU in HP-positive patients		Complete remission of CSU after HP eradication therapy	
						HP (-)	HP (+)	HP eradication Tx. (-)	HP eradication Tx. (+)	Eradicated	Noneradicated
Valsecchi and Pigatto ²⁶	Italy	125	78		CMO (7)	1/25	1/34	1/34	3/31	3/29	0/2
Wedi et al ²⁷	Germany	100	26	Serum anti-HP IgG, IgA + histology	ACO (7)	6/14	4/18	4/18	15/23	14/21	1/2
Yadav et al ²⁸	India	68	48	Monoclonal fecal antigen assay	ACO (14)					21/46	0/2
Zhelezovet al ²⁹	Russia	36	26		ACO (10)					7/21	3/5

Note: Abbreviations: A, amoxicillin; B, bismuth subsalicylate; C, clarithromycin; CSU, chronic spontaneous urticarial; E, esomeprazole; ELISA, enzyme-linked immunosorbent assay; HP, *Helicobacter pylori*; L, lansoprazole; M, metronidazole; O, omeprazole; P, pantoprazole; T, tetracycline; UBT, urea breath test.

^aAbstract only study.

1—comparison between CSU patients who are HP negative and HP positive; analysis 2—comparison between HP-positive CSU patient who underwent HP eradication therapy and those who did not; analysis 3—among HP-positive CSU patients who underwent HP eradication therapy, a comparison between successful HP eradication therapy and unsuccessful one). Reviews and case reports with fewer than 10 subjects were excluded and studies in which our predefined outcome data (required for analysis) were lacking were also excluded. Studies were not limited by age, sex, or disease severity. If a study was listed more than once, we used the most recent article. All exclusion criteria are listed in Figure S1 in the Supplement.

2.3 | Data extraction

Two reviewers independently extracted all data using a predefined standardized data extraction form. Discrepancies were resolved via discussion. We extracted the following variables: (a) authors; (b) year and language of publication; (c) demographic characteristics of the study population (country, age, sex, number); (d) CSU inclusion criteria and method of assessment of HP infection status; (e) HP eradication regimen; (f) whether or not successful HP eradication was confirmed; and (g) outcome (status regarding complete remission of CSU symptoms).

2.4 | Outcome assessment

We chose complete remission of CSU symptoms as the outcome measure, regardless of whether this was the primary or secondary outcome of an individual study. We compared the improvements in CSU symptoms with respect to whether HP eradication was performed and whether HP eradication was successful. In addition, we subanalyzed the outcomes by the HP eradication regimens and treatment durations.

2.5 | Statistical analysis

We performed pooled analyses using random-effects weighting to analyze the outcomes of multiple studies that were sufficiently similar for the justification of combining the results, which are reported with 95% confidence intervals (CIs). Dichotomous outcomes were statistically analyzed by calculating the risk ratios (RRs). The pooled RR estimates were calculated using the Mantel-Haenszel method. Heterogeneity was assessed by deriving the I^2 statistic, which indicates the proportion of variation in the estimates of trial effects attributable to heterogeneity (rather than sampling error). I^2 values >50% and P -values (χ^2 test) < .10 were taken to reflect substantial heterogeneity among the included studies. In such cases ($I^2 > 50\%$), we planned to explore the characteristics of studies and those of subgroups of the main body of evidence. We drew forest and funnel plots and used Egger's test to assess any potential publication bias. All statistical calculations were performed using STATA MP version 15.0 (Stata Corp).

2.6 | Assessment of bias risk

The risk of bias was assessed using the ROBINS-I tool,¹⁰ which evaluates any biases caused by confounding factors, patient selection, classification of interventions, deviations from intended interventions, missing data, outcome measurements, and selection of reported results. The risk of bias in each domain was categorized as “low”, “moderate”, “serious”, or “critical”.

3 | RESULTS

3.1 | Study identification and characteristics

The database search yielded 1076 abstracts; we removed duplicates and screened the remaining 663 studies. Additional 622 studies were excluded because they did not meet the selection criteria. Among the remaining 41 studies, we identified 22 studies that were relevant, and excluded 19 studies (9 for having inadequate outcome data; 6 for lacking appropriate control groups; and 4 for being laboratory-based studies). The selection process is shown in Figure S1 in the Supplement. Ultimately, 22 studies were included in meta-analysis.

Among the 22^{6-8,11-29} studies, a total of 1385 CSU patients, who were all assessed and diagnosed by dermatologists, were enrolled. The characteristics of the included studies are listed in Table 1. The sample sizes ranged from 20 to 231.

We initially analyzed the spontaneous CSU symptom remission in HP-positive and HP-negative CSU patients and then explored the effects of HP eradication therapy on CSU symptom improvement among HP-positive CSU patients. Finally, we evaluated differences in CSU remission levels according to whether the antibiotic therapy for HP eradication was successful.

3.2 | Effect of *Helicobacter pylori* infection on CSU symptoms

When HP infection was not treated via eradication therapy, the HP-negative group exhibited significantly greater spontaneous CSU symptom remission than the HP-positive group (RR 0.42; 95% CI 0.20-0.86, $I^2 = 0\%$) (Figure 2).

3.3 | Benefits of *Helicobacter pylori* eradication therapy in terms of CSU symptoms

3.3.1 | *Helicobacter pylori* -treated vs nontreated patients

Helicobacter pylori eradication therapy significantly improved CSU symptoms in HP-positive CSU patients compared with the nontreated patients (RR 2.10; 95% CI 1.20-3.68, $I^2 = 0\%$; Figure 3). Subgroup analysis revealed that patients treated with the standard

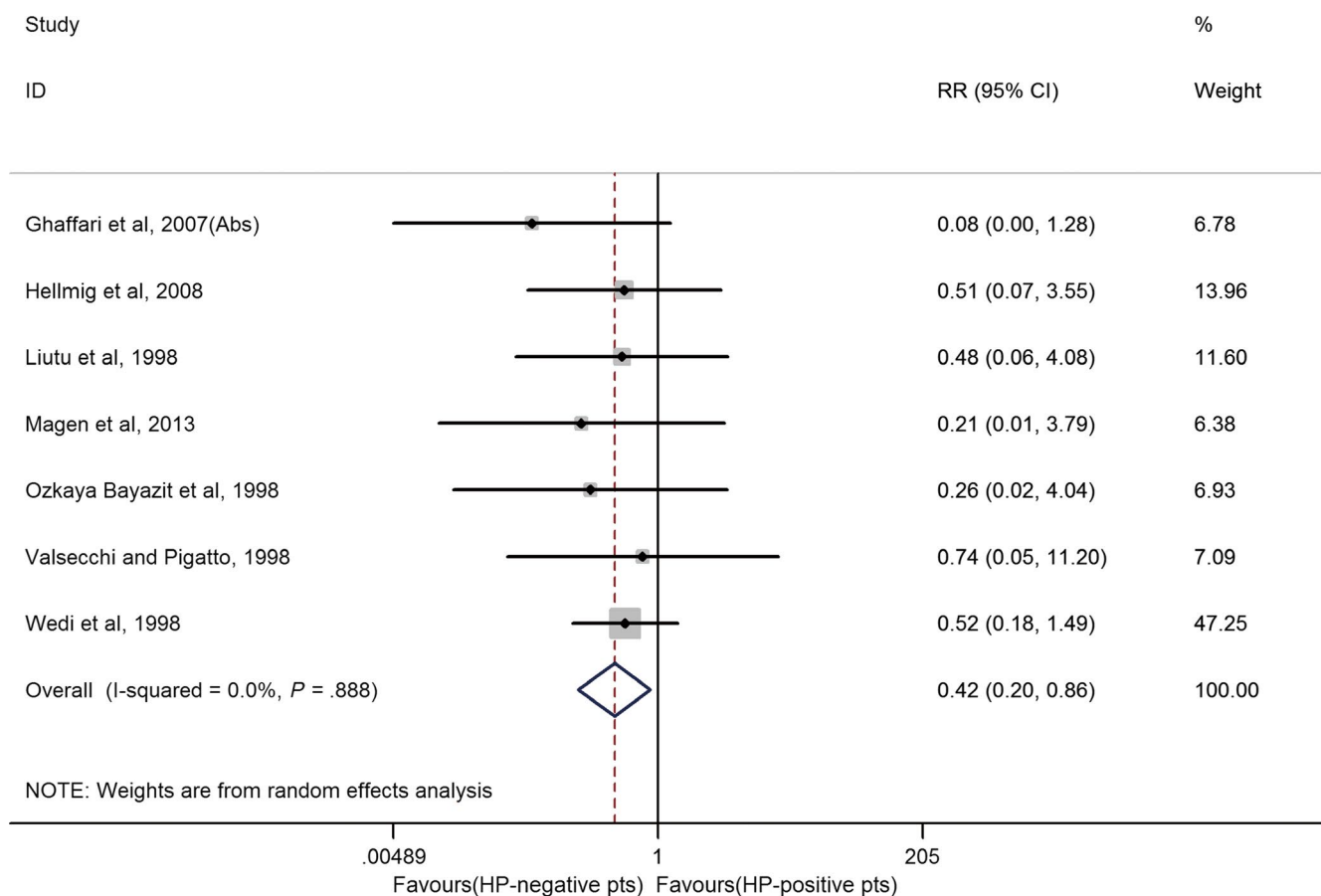


FIGURE 2 Forest plot of chronic spontaneous urticaria (CSU) symptoms according to *Helicobacter pylori* (HP) infection

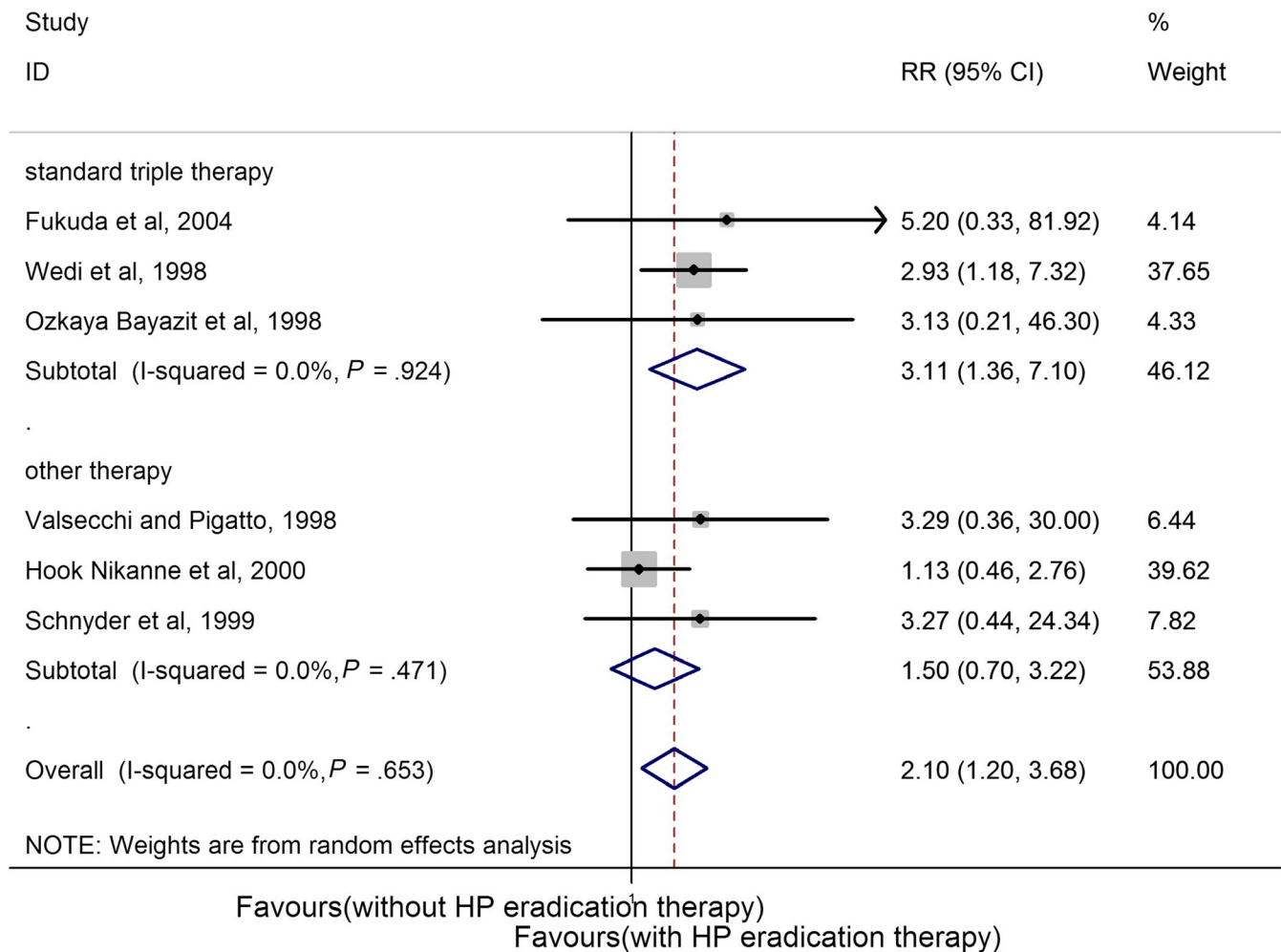


FIGURE 3 Improvement of chronic spontaneous urticaria (CSU) symptoms according to *Helicobacter pylori* (HP) eradication therapy

triple therapy (a proton-pump inhibitor, clarithromycin, and amoxicillin) exhibited significant improvements in CSU symptoms with a RR of 3.11 (95% CI 1.36-7.10, $I^2 = 0\%$), whereas patients treated with other regimens showed RR of 1.50 (95% CI 0.70-3.22, $I^2 = 0\%$).

3.3.2 | Successful vs failed *Helicobacter pylori* eradication

No significant difference in CSU symptom improvement was evident between initially HP-positive CSU patients who did and did not fail HP eradication despite appropriate HP eradication therapy (RR 1.00; 95% CI 0.65-1.54, $I^2 = 6\%$; Figure 4). Subgroup analysis by eradication regimen revealed no significant differences between the standard triple-therapy group (RR 1.08; 95% CI 0.66-1.77, $I^2 = 0\%$) and the other groups (RR 1.07; 95% CI 0.33-3.46, $I^2 = 44.2\%$). In addition, we divided all trials into two subgroups: treatment regimens with a duration of (a) 7 or 10 days and (b) ≥ 14 days. CSU symptom improvement was more evident, after longer-duration treatment; however, this observation lacked statistical significance (Figure S2).

3.4 | Risk of bias in included studies

The risk of bias was explored using ROBINS-I (Table S3). Nineteen studies were at serious risk for overall bias, and three were at moderate risk.

3.5 | Publication bias

Visual inspection of the funnel plot suggested a degree of asymmetry (Figure S3) and the Egger test revealed significant publication bias ($P = .003$). We performed additional trim and fill analyses to assess the impact of unpublished studies on our results. However, even after the adjustment of the effect size to counter potential publication bias, there was no change in the results. Thus, publication bias may have been present, but likely marginal impact on our study results.

4 | DISCUSSION

Helicobacter pylori is a Gram-negative spiral-shaped bacterium of the gastric epithelium causing chronic gastritis, peptic ulcers, and

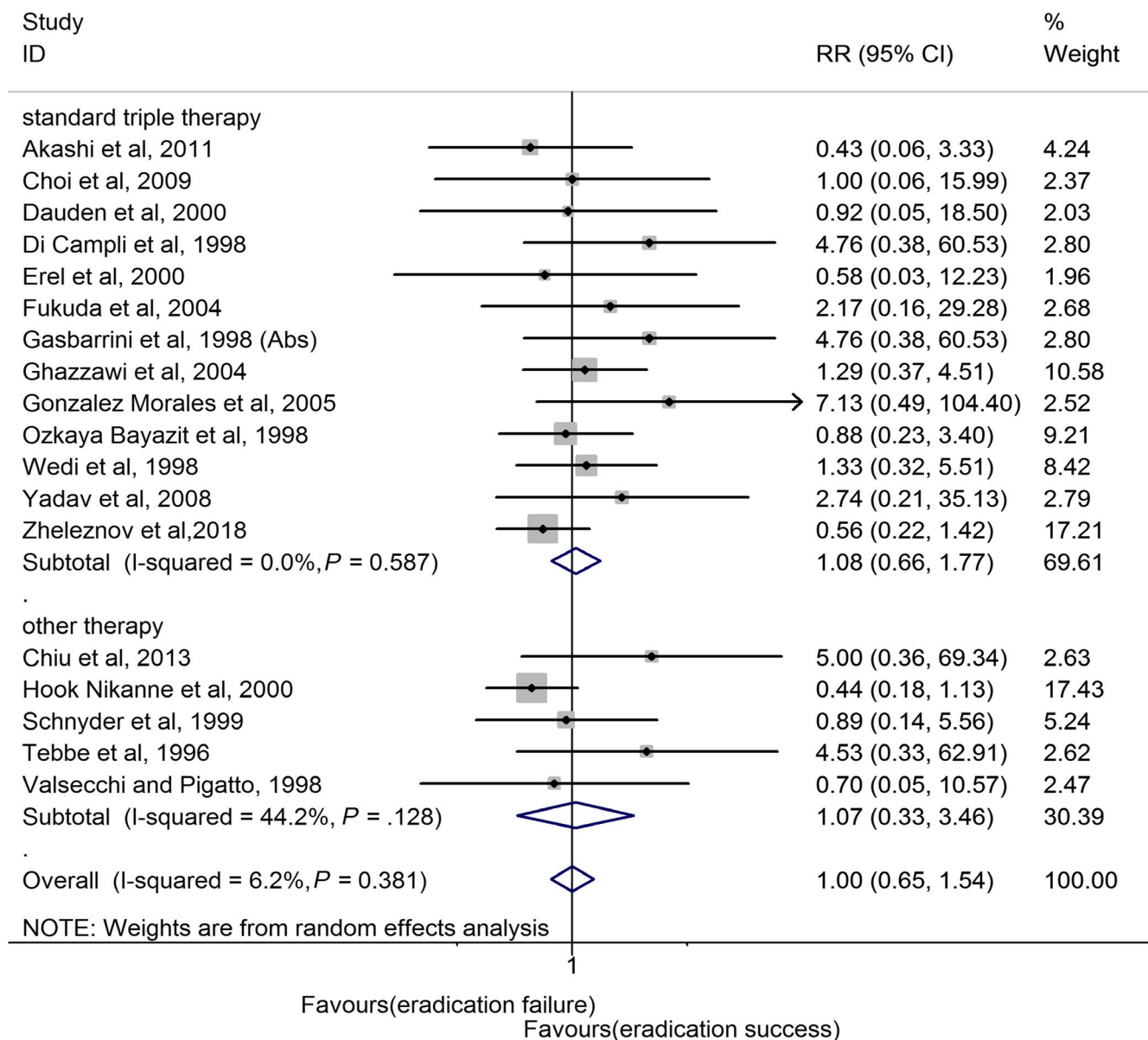


FIGURE 4 Improvement of chronic spontaneous urticaria (CSU) symptoms according to success of HP eradication

gastric cancer.³⁰ Despite decreasing incidence of HP infection in highly industrialized countries, its prevalence remains relatively high in most developing countries and is still a major public health burden worldwide.^{31,32} Recent evidence suggests that HP infection is associated with a variety of skin diseases, including chronic spontaneous urticaria, Henoch-Schonlein purpura, idiopathic thrombocytopenic purpura (ITP), atopic dermatitis, psoriasis, and rosacea.³³ However, dermatologists seem to be unaware of the possible impact of HP on cutaneous pathology; the role of HP in these skin diseases remains contentious. To date, whether there is an association between HP infection and CSU remains unclear.^{6-8,12,27} The findings of our meta-analysis revealed that HP eradication therapy significantly improved CSU symptoms in HP-positive CSU patients. Notably, CSU resolution was not necessarily associated with the success of HP eradication. In the absence of eradication therapy, the HP-negative

group exhibited a significantly higher CSU remission rate than the HP-positive group.

The direct effects of HP, including immunoglobulins, HP virulence genes, autoimmune reactions, have been considered in CSU development. Immunoglobulin (Ig) G, IgA, and IgE antibodies against HP antigens were detected in some studies.³⁴⁻³⁶ The release of proinflammatory cytokines, granulocyte attraction, as well as B- and T-cell-mediated responses, is elevated in HP-positive patients, which may all contribute to the development of urticarial lesions.¹⁵ Moreover, HP virulence genes, such as *cagA*, *vacA*, and *nap*, induce proinflammatory responses and may facilitate CSU development by triggering systemic immune responses.^{37,38} Autoimmune reactions reflecting inappropriate immune responses to HP antigen may also influence the development of CSU.³⁹ Several studies have described associations between HP infection and autoimmune diseases such as ITP,

thyroid autoimmunity, rheumatoid arthritis, and inflammatory bowel disease.⁴⁰⁻⁴³ Moreover, enhanced gastric permeability may also play a role; CSU is associated with a pseudo-allergy to food and increased permeability of the gastric mucosa, since damage caused by HP may give rise to inappropriate immunorecognition of food allergens.^{6,44} Zheleznov et al²⁹ reported significant differences in urticarial symptom improvement between those in whom erosions did and did not heal. Gastric mucosal inflammation itself may possibly be relevant.

There are several hypotheses on the mechanisms of antibiotics with respect to the eradication of HP and improvement of CSU. First, the antibiotics used for HP eradication may have corrected both HP itself and also the associated gut dysbiosis. Several studies^{45,46} demonstrated that HP-positive samples exhibited decreased gastric microbiotic diversity; this suggests that HP infection may likely trigger dysbiosis of the gut microbiota, which in turn affects the immune system, potentially initiating the development of CSU. Various skin diseases such as acne, atopic dermatitis, and psoriasis are considered as examples of dysbiosis^{47,48} and oral probiotics improved skin symptoms in several studies.^{49,50} Intestinal microbiota is considered to modulate skin dyshomeostasis via gut-skin axis,⁵¹ possibly by inducing systemic immunity to gut bacteria and migration of such bacteria to the skin via the bloodstream.^{52,53} Second, if the HP population is reduced via antimicrobial treatment, CSU remission may be induced even if HP eradication is incomplete. The severity of CSU symptoms may vary by the extent of HP infection.⁵⁴ Even if HP is eradicated, bacteria may not disappear completely; small amounts may remain and regrow at a later time.⁵⁴ The test used to detect eradication does not guarantee full and complete elimination of all bacteria. Third, the host immune response to high-dose proton-pump inhibitors (PPIs) in HP eradication regimens must be considered. PPIs may directly affect the immune response via the inhibition of gastric acid production.⁵⁵⁻⁵⁸ It has been shown that exposure to acid enhances the expression of adhesion molecules and cytokines, such as IL-8 and IL-1 β , which in turn increases the inflammation and thus possibly recruiting immune cells.^{59,60} Therefore, acid reduction via PPIs may reduce these responses and also minimize food allergen stimulation caused by acid-induced damage to the gastric mucosa.⁶¹

Subgroup analysis revealed that patients treated with the standard triple therapy showed significant improvements in CSU symptoms compared with nontreated HP-positive patients, whereas patients treated with other regimens did not show significant improvements. Thus, antibiotic combinations that include clarithromycin and amoxicillin, which are both components of the standard triple therapy, may more effectively improve CSU symptoms.⁶² Although the detailed mechanisms remain unclear, the results suggest that the antibiotics of the standard triple-therapy regimen afford secondary benefits, such as eradication of certain non-HP bacteria.

Chronic spontaneous urticaria could be a considerable burden to patients and clinicians, because it is sometimes extremely difficult to treat, and a cause is often not identified, even after a thorough examination. Our study suggests that clinicians, after considering other potential triggers of CSU, need to consider diagnostic workup for HP, and if present, appropriate HP eradication therapy should be considered.

Our study has several limitations. First, substantial between-study heterogeneity was evident in terms of both CSU treatments and HP eradication regimens. Second, despite the geographical variance of HP-related disease with respect to public sanitation conditions, we lacked data to perform such subgroup analyses. Third, CSU development is influenced by age, sex, and systemic disease status. Fourth, our sample size was small. In the near future, well-designed trials with a large number of patients varying in ethnicity are required. Randomized controlled trials are also needed to further explore the effects of HP eradication therapy on CSU symptoms.

Our findings suggest that HP infection may underpin CSU development and that antibiotic therapy potentially eradicating HP may improve CSU symptoms in HP-positive CSU patients. The underlying pathogenic mechanism requires further study, as does the utility of HP eradication in CSU patients.

ACKNOWLEDGEMENTS

This work was financially supported by the National Research Foundation of Korea (grant no. NRF-2018R1C1B5042271) and the Soonchunhyang University Research Fund.

CONFLICT OF INTEREST

No potential conflicts of interest are disclosed.

ORCID

Yeon-Ji Kim  <https://orcid.org/0000-0001-9823-577X>

REFERENCES

- Cooper KD. Urticaria and angioedema: diagnosis and evaluation. *J Am Acad Dermatol*. 1991;25(1):166-176.
- Greaves MW. Chronic urticaria. *N Engl J Med*. 1995;332:1767-1772.
- Kang MJ, Kim HS, Kim HO, Park YM. The impact of chronic idiopathic urticaria on quality of life in Korean patients. *Ann Dermatol*. 2009;21:226-229.
- Guillet G, Becherel PA, Pralong P, et al. The burden of chronic urticaria: French baseline data from the international real-life AWARE study. *Eur J Dermatol*. 2019;29:49-54.
- Pawlowski R, Wytrychowski K, Panaszek B. Eradication of *Helicobacter pylori*, as add-on therapy, has a significant, but temporary influence on recovery in chronic idiopathic urticaria: a placebo-controlled, double blind trial in the Polish population. *Postepy Dermatol Alergol*. 2018;35:151-155.
- Fukuda S, Shimoyama T, Umegaki N, Mikami T, Nakano H, Munakata A. Effect of *Helicobacter pylori* eradication in the treatment of Japanese patients with chronic idiopathic urticaria. *J Gastroenterol*. 2004;39:827-830.
- Hook-Nikanne J, Varjonen E, Harvima RJ, Kosunen TU. Is *Helicobacter pylori* infection associated with chronic urticaria? *Acta Derm Venereol*. 2000;80:425-426.
- Ghazzawi IM, Obidat NA. The role of *Helicobacter pylori* infection in the pathogenesis of chronic urticaria. *Pak J Med Sci*. 2004;20:101-104.

9. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine*. 2009;6:e1000097.
10. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
11. Akashi R, Ishiguro N, Shimizu S, Kawashima M. Clinical study of the relationship between *Helicobacter pylori* and chronic urticaria and prurigo chronica multiformis: effectiveness of eradication therapy for *Helicobacter pylori*. *J Dermatol*. 2011;38:761-766.
12. Chiu YC, Tai WC, Chuah SK, et al. The clinical correlations of *Helicobacter pylori* virulence factors and chronic spontaneous urticaria. *Gastroenterol Res Pract*. 2013;2013:436727.
13. Choi JH, Ahn IS, Lee HB, Kim HO, Park CW, Lee CH. A study of an autologous serum skin test and *Helicobacter pylori* infection in patients with chronic idiopathic urticaria. *Korean J Dermatol*. 2009;47:798-802.
14. Dauden E, Jimenez-Alonso I, Garcia-Diez A. *Helicobacter pylori* and idiopathic chronic urticaria. *Int J Dermatol*. 2000;39:446-452.
15. Di Campli C, Gasbarrini A, Nucera E, et al. Beneficial effects of *Helicobacter pylori* eradication on idiopathic chronic urticaria. *Dig Dis Sci*. 1998;43:1226-1229.
16. Erel F, Sener O, Erdil A, et al. Impact of *Helicobacter pylori* and *Giardia lamblia* infections on chronic urticaria. *J Invest Allergol Clin Immunol*. 2000;10:94-97.
17. Gasbarrini A, Franceschi F, Di Campli C, et al. *Helicobacter pylori* eradication ameliorates idiopathic chronic urticaria. *Gastroenterology*. 1998;114:A129.
18. Ghaffari J, Farid R, Nazari Z, Jabbar Azad F. Treatment of *Helicobacter pylori* infection on idiopathic chronic urticaria. *Allergy*. 2007;62:167-551.
19. Gonzalez Morales JE, Leal Villareal L, Castillo Salazar Nde J, Gonzalez Martinez A, Garcia ME. Correlation between chronic idiopathic urticaria and infection due to *H pylori*. *Rev Alerg Mex*. 2005;52:179-182.
20. Hellmig S, Troch K, Ott SJ, Schwarz T, Folsch UR. Role of *Helicobacter pylori* infection in the treatment and outcome of chronic urticaria. *Helicobacter*. 2008;13:341-345.
21. Liutu M, Kalimo K, Leino R, Uksila J, Kalimo H. Chronic urticaria and *Helicobacter pylori* infection. *J Dermatolog Treat*. 2009;9:31-33.
22. Magen E, Mishal J. Possible benefit from treatment of *Helicobacter pylori* in antihistamine-resistant chronic urticaria. *Clin Exp Dermatol*. 2013;38:7-12.
23. Özkaya-Bayazit E, Demir K, Özgüroğlu E, Kaymakoglu S, Özarmağan G. *Helicobacter pylori* eradication in patients with chronic urticaria. *Arch Dermatol*. 1998;134:1165-1167.
24. Schnyder B, Helbling A, Pichler WJ. Chronic idiopathic urticaria: natural course and association with *Helicobacter pylori* infection. *Int Arch Allergy Immunol*. 1999;119:60-63.
25. Tebbe B, Geilen CC, Schulzke JD, Bojarski C, Radenhausen M, Orfanos CE. *Helicobacter pylori* infection and chronic urticaria. *J Am Acad Dermatol*. 1996;34:685-686.
26. Valsecchi R, Pigatto P. Chronic urticaria and *Helicobacter pylori*. *Acta Derm Venereol*. 1998;78:440-442.
27. Wedi B, Wagner S, Werfel T, Manns MP, Kapp A. Prevalence of *Helicobacter pylori*-associated gastritis in chronic urticaria. *Int Arch Allergy Immunol*. 1998;116:288-294.
28. Yadav MK, Rishi JP, Nijawan S. Chronic urticaria and *Helicobacter pylori*. *Indian J Med Sci*. 2008;62:157-162.
29. Zheleznev S, Urzhumtseva G, Petrova N, et al. Gastritis can cause and trigger chronic spontaneous urticaria independent of the presence of *Helicobacter pylori*. *Int Arch Allergy Immunol*. 2018;175:246-251.
30. Roesler BM, Rabelo-Goncalves EM, Zeitune JM. Virulence factors of *Helicobacter pylori*: A review. *Clin Med Insights Gastroenterol*. 2014;7:9-17.
31. Eusebi LH, Zagari RM, Bazzoli F. Epidemiology of *Helicobacter pylori* infection. *Helicobacter*. 2014;19(suppl 1):1-5.
32. Hooi J, Lai WY, Ng WK, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. *Gastroenterology*. 2017;153:420-429.
33. Guarneri C, Lotti J, Fioranelli M, Rocchia MG, Lotti T, Guarneri F. Possible role of *Helicobacter pylori* in diseases of dermatological interest. *J Biol Regul Homeost Agents*. 2017;31:57-77.
34. Bakos N, Fekete B, Prohaszka Z, Fust G, Kalabay L. High prevalence of IgG and IgA antibodies to 19-kDa *Helicobacter pylori*-associated lipoprotein in chronic urticaria. *Allergy*. 2003;58:663-667.
35. Liutu M, Kalimo K, Uksila J, Savolainen J. Extraction of IgE-binding components of *Helicobacter pylori* by immunoblotting analysis in chronic urticaria patients. *Int Arch Allergy Immunol*. 2001;126:213-217.
36. Hizal M, Tuzun B, Wolf R, Tuzun Y. The relationship between *Helicobacter pylori* IgG antibody and autologous serum test in chronic urticaria. *Int J Dermatol*. 2000;39:443-445.
37. Supajatura V, Ushio H, Wada A, et al. Cutting edge: VacA, a vacuolating cytotoxin of *Helicobacter pylori*, directly activates mast cells for migration and production of proinflammatory cytokines. *J Immunol*. 2002;168:2603-2607.
38. Tsai CC, Kuo TY, Hong ZW, et al. *Helicobacter pylori* neutrophil-activating protein induces release of histamine and interleukin-6 through G protein-mediated MAPKs and PI3K/Akt pathways in HMC-1 cells. *Virulence*. 2015;6:755-765.
39. Appelmelk BJ, Simoons-Smit I, Negrini R, et al. Potential role of molecular mimicry between *Helicobacter pylori* lipopolysaccharide and host Lewis blood group antigens in autoimmunity. *Infect Immun*. 1996;64:2031-2040.
40. Choi YM, Kim TY, Kim EY, et al. Association between thyroid autoimmunity and *Helicobacter pylori* infection. *Korean J Intern Med*. 2017;32:309-313.
41. Hou Y, Sun W, Zhang C, et al. Meta-analysis of the correlation between *Helicobacter pylori* infection and autoimmune thyroid diseases. *Oncotarget*. 2017;8:115691-115700.
42. Ishikawa N, Fuchigami T, Matsumoto T, et al. *Helicobacter pylori* infection in rheumatoid arthritis: effect of drugs on prevalence and correlation with gastroduodenal lesions. *Rheumatology (Oxford)*. 2002;41:72-77.
43. Luther J, Dave M, Higgins PD, Kao JY. Association between *Helicobacter pylori* infection and inflammatory bowel disease: a meta-analysis and systematic review of the literature. *Inflamm Bowel Dis*. 2010;16:1077-1084.
44. Buhner S, Reese I, Kuehl F, Lochs H, Zuberbier T. Pseudoallergic reactions in chronic urticaria are associated with altered gastroduodenal permeability. *Allergy*. 2004;59:1118-1123.
45. Andersson AF, Lindberg M, Jakobsson H, Backhed F, Nyren P, Engstrand L. Comparative analysis of human gut microbiota by bar-coded pyrosequencing. *PLoS ONE*. 2008;3:e2836.
46. Maldonado-Contreras A, Goldfarb KC, Godoy-Vitorino F, et al. Structure of the human gastric bacterial community in relation to *Helicobacter pylori* status. *ISME J*. 2011;5:574-579.
47. Campanati A, Gesuita R, Giannoni M, et al. Role of small intestinal bacterial overgrowth and *Helicobacter pylori* infection in chronic spontaneous urticaria: a prospective analysis. *Acta Derm Venereol*. 2013;93:161-164.
48. Ojetti V, De Simone C, Aguilar Sanchez J, et al. Malabsorption in psoriatic patients: cause or consequence? *Scand J Gastroenterol*. 2006;41:1267-1271.
49. Horii Y, Kaneda H, Fujisaki Y, et al. Effect of heat-killed *Lactobacillus brevis* SBC8803 on cutaneous arterial sympathetic nerve activity, cutaneous blood flow and transepidermal water loss in rats. *J Appl Microbiol*. 2014;116:1274-1281.
50. Ogawa M, Saiki A, Matsui Y, et al. Effects of oral intake of heat-killed *Lactobacillus brevis* SBC8803 (SBL88) on dry skin conditions:

- a randomized, double-blind, placebo-controlled study. *Exp Ther Med*. 2016;12:3863-3872.
51. Salem I, Ramser A, Isham N, Ghannoum MA. The gut microbiome as a major regulator of the gut-skin axis. *Front Microbiol*. 2018;9:1459.
52. O'Neill CA, Monteleone G, McLaughlin JT, Paus R. The gut-skin axis in health and disease: a paradigm with therapeutic implications. *BioEssays*. 2016;38:1167-1176.
53. Samuelson DR, Welsh DA, Shellito JE. Regulation of lung immunity and host defense by the intestinal microbiota. *Front Microbiol*. 2015;6:1085.
54. Abdou AG, Elshayeb EI, Farag AG, Elnaidany NF *Helicobacter pylori* infection in patients with chronic urticaria: correlation with pathologic findings in gastric biopsies. *Int J Dermatol*. 2009;48:464-469.
55. Biswas K, Bandyopadhyay U, Chattopadhyay I, Varadaraj A, Ali E, Banerjee RK. A novel antioxidant and antiapoptotic role of omeprazole to block gastric ulcer through scavenging of hydroxyl radical. *J Biol Chem*. 2003;278:10993-11001.
56. Untersmayr E. Acid suppression therapy and allergic reactions. *Allergo J Int*. 2015;24:303-311.
57. Larussa T, Suraci E, Leone I, et al. Short-term therapy with celecoxib and lansoprazole modulates Th1/ Th2 immune response in human gastric mucosa. *Helicobacter*. 2010;15:449-459.
58. Cortes JR, Rivas MD, Molina-Infante J, et al. Omeprazole inhibits IL-4 and IL-13 signaling signal transducer and activator of transcription 6 activation and reduces lung inflammation in murine asthma. *J Allergy Clin Immunol*. 2009;124(607-610):610.e601.
59. Rafiee P, Theriot ME, Nelson VM, et al. Human esophageal microvascular endothelial cells respond to acidic pH stress by PI3K/AKT and p38 MAPK-regulated induction of Hsp70 and Hsp27. *Am J Physiol Cell Physiol*. 2006;291:C931-945.
60. Souza RF, Huo X, Mittal V, et al. Gastroesophageal reflux might cause esophagitis through a cytokine-mediated mechanism rather than caustic acid injury. *Gastroenterology*. 2009;137:1776-1784.
61. Tobey NA, Hosseini SS, Argote CM, Dobrucali AM, Awayda MS, Orlando RC. Dilated intercellular spaces and shunt permeability in nonerosive acid-damaged esophageal epithelium. *Am J Gastroenterol*. 2004;99:13-22.
62. Strzepa A, Lobo FM, Majewska-Szczepanik M, Szczepanik M. Antibiotics and autoimmune and allergy diseases: causative factor or treatment? *Int Immunopharmacol*. 2018;65:328-341.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Kim HJ, Kim Y-J, Lee HJ, et al.

Systematic review and meta-analysis: Effect of *Helicobacter pylori* eradication on chronic spontaneous urticaria.

Helicobacter. 2019;00:e12661. <https://doi.org/10.1111/hel.12661>

SUPPLEMENTAL TABLES

eTable I. Preferred Reporting Items for Systematic Reviews and Meta-analyses 2009 checklist

Section/Topic	No.	Checklist item	Reported on page no.
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	#1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; and systematic review registration number.	#4, #5
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	#6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	#6
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	#6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	#7, #8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	#6, #7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	#7
Study selection	9	State the process for selecting studies (e.g., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	#7, #8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	#8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	#8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	#9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	#8, #9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	#8, #9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	#9
Additional	16	Describe methods of additional analyses (e.g., sensitivity or	#8, #9

analyses		subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	#9, #10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	#10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	#11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	#10, #11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	#10, #11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	#11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).	#10, #11
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	#12, #14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	#14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	#15
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	#17

eTable II. Search strategy on MEDLINE, EMBASE, Cochrane Library, SCOPUS, and Web of Science

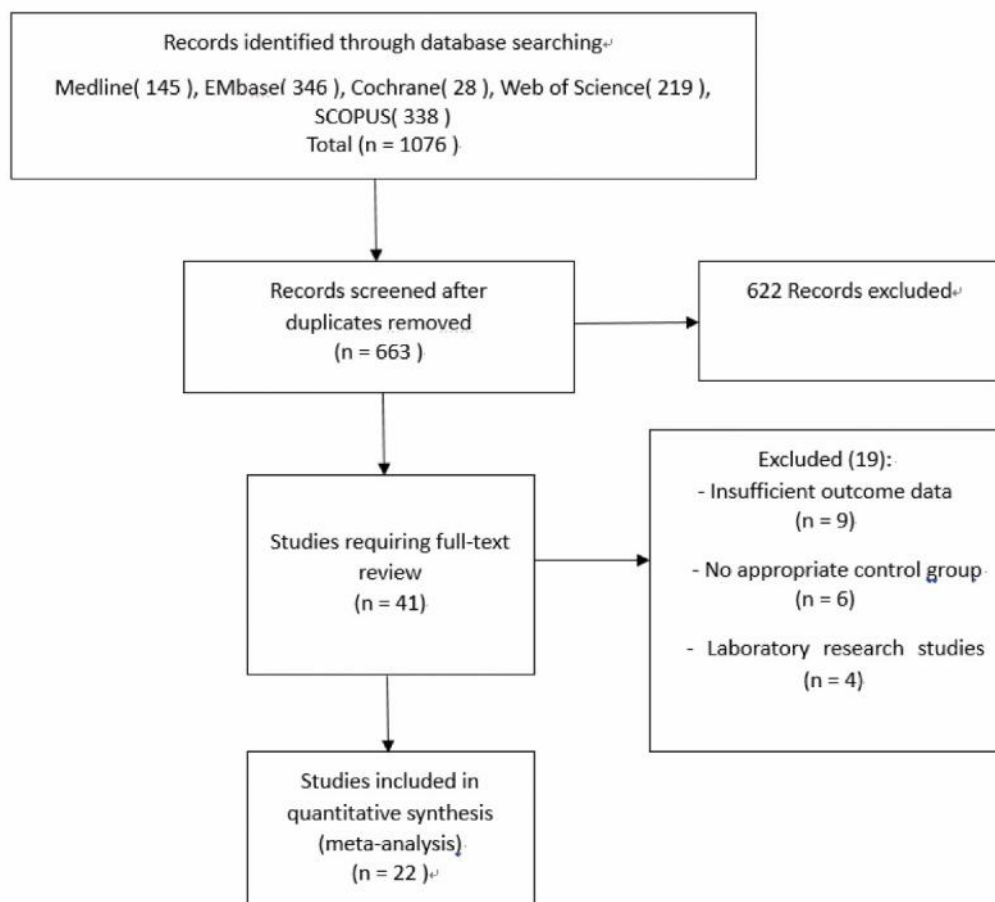
Search strategy	No. of Result
MEDLINE	
1. urticaria[TIAB] OR Urticarias[TIAB] OR hives[TIAB] 14226	
2. "Urticaria"[Mesh] 15307	
3. 1 OR 2 21742	
4. (Helicobacter[TIAB] AND (Infections[TIAB] OR pylori[TIAB] OR Infection[TIAB])) OR "H.pylori"[TIAB] 40747	145
5. "Helicobacter pylori"[Mesh] OR "Helicobacter Infections"[Mesh] 35504	
6. 4 OR 5 44090	
7. 3 AND 6 193	
8. 7 NOT "review"[Publication Type] OR "review literature as topic"[MeSH Terms] 145	
EMBASE	
1. urticaria:ab,ti OR Urticarias:ab,ti OR hives:ab,ti 22082	
2. 'urticaria'/exp 41809	
3. 1 OR 2 45702	
4. (Helicobacter:ab,ti AND (Infections:ab,ti OR pylori:ab,ti OR Infection:ab,ti)) OR "H.pylori":ab,ti 55991	346
5. 'helicobacter pylori'/exp OR 'helicobacter infection'/exp 62005	
6. 4 OR 5 68090	
7. 3 AND 6 514	
8. 7 NOT 'review'/it 408	
9. 8 NOT 'nonhuman'/de 346	
Web of Science	
1. TOPIC: (urticaria OR Urticarias OR hives) OR TITLE: (urticaria OR Urticarias OR hives) 19100	
2. TOPIC: ((Helicobacter AND (Infections OR pylori OR Infection)) OR "H.pylori") OR TITLE: ((Helicobacter AND (Infections OR pylori OR Infection)) OR "H.pylori") 65757	219
3. 1 and 2 256	
4. 3 Refined by: [excluding] DOCUMENT TYPES: (REVIEW) 219	
SCOPUS	
1. TITLE-ABS-KEY (urticaria OR urticarias OR hives) 44845	
2. INDEXTERMS (urticaria) 35024	
3. 1 OR 2 44845	
4. TITLE-ABS-KEY((helicobacter AND (infections OR pylori OR infection)) OR "H.pylori") 612995	338
5. INDEXTERMS ("Helicobacter pylori" OR "Helicobacter Infections") 55089	
6. 4 OR 5 61299	
7. 3 AND 6 446	
8. 7 AND (EXCLUDE (DOCTYPE , "re")) 338	
Cochrane Library	
1. (Urticaria OR Urticarias OR hives) :ti,ab,kw 2398	
2. MeSH descriptor:[Urticaria] explode all trees 675	
3. 1 OR 2 2510	
4. (Helicobacter AND (Infections OR pylori OR Infection)) OR "H.pylori":ti,ab,kw 4569	28
5. MeSH descriptor:[Helicobacter pylori] explode all trees 1914	
6. MeSH descriptor:[Helicobacter Infections] explode all trees 2014	
7. 4 OR 5 OR 6 4569	
8. 3 AND 7 28	
9. 8/Trials 28	
No. of all results	1,076
No. of redundant results	413
No. of final results	663

eTable III. Risk of bias judgments of included studies (risk of bias in seven different domains according to the Risk Of Bias In Non-randomized Studies of Interventions-I tool)

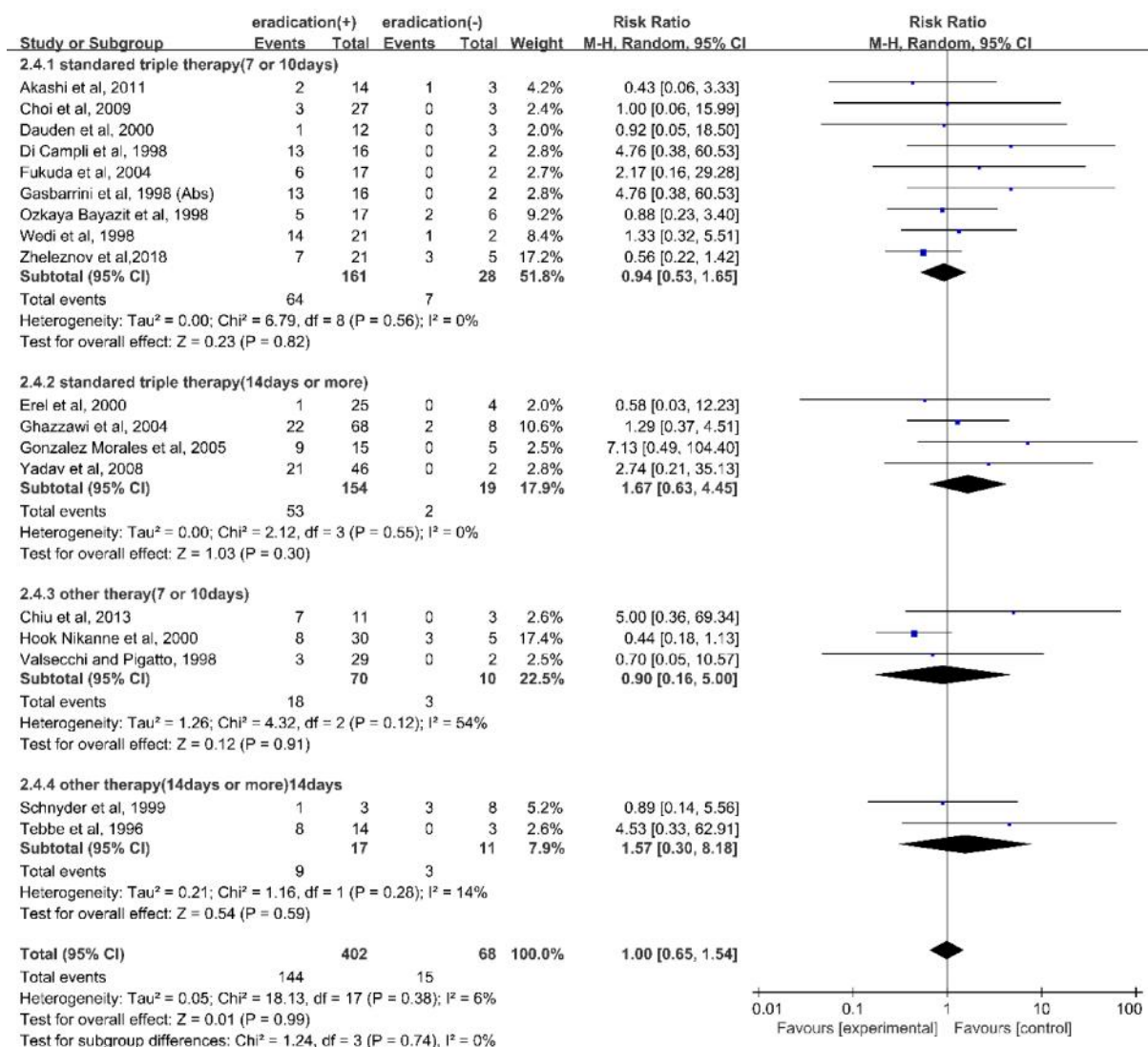
Study	Confounding	Selection of participants	Classification of interventions	Deviation from intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall
Akashi et al, 2011	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Chiu et al, 2013	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Choi et al, 2009	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Dauden et al, 2000	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Di Campli et al, 1998	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Erel et al, 2000	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Fukuda et al, 2004	Serious	Moderate	Low	Moderate	Moderate	Serious	Moderate	Serious
Gasbarrini et al, 1998	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Ghaffari et al, 2007	Serious	Moderate	Low	Moderate	Moderate	Serious	Moderate	Serious
Ghazzawi et al, 2004	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Gonzalez Morales et al, 2005	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Hellmig et al, 2008	Serious	Moderate	Low	Moderate	Moderate	Serious	Moderate	Serious
Hook-Nikanne et al, 2000	Serious	Moderate	Low	Moderate	Moderate	Serious	Moderate	Serious
Liutu et al, 1998	Serious	Moderate	Low	Moderate	Moderate	Serious	Moderate	Serious
Magen et al, 2013	Moderate	Moderate	Low	Moderate	Moderate	Serious	Moderate	Serious
Ozkaya Bayazit et al, 1998	Serious	Moderate	Low	Moderate	Moderate	Serious	Moderate	Serious
Schnyder et al, 1999	Serious	Moderate	Low	Moderate	Moderate	Serious	Moderate	Serious
Tebbe et al, 1996	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Valsecchi and Pigatto, 1998	Serious	Moderate	Low	Moderate	Moderate	Serious	Moderate	Serious
Wedi et al, 1998	Moderate	Moderate	Low	Moderate	Moderate	Serious	Moderate	Serious
Yadav et al, 2008	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Zheleznov et al, 2018	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious

[Reprinted from "ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions.", by Sterne, et al., 2016, BMJ, 355, pp.i4919. Copyright 2016 by the British Medical Association. Reprinted with permission].

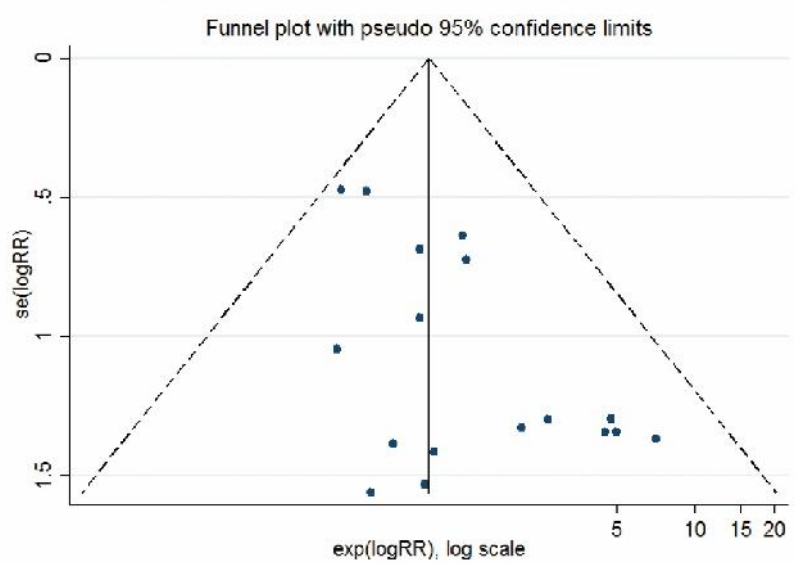
SUPPLEMENTAL FIGURE LEGENDS



eFigure 1. Flow diagram of studies in analysis.



eFigure 2. Forest plot showing subgroup analysis in *Helicobacter pylori* eradication therapy group according to treatment regimens and durations. RR, relative risk; CI, confidence interval.



eFigure 3. Funnel plot of included studies for meta-analysis. *RR*, relative risk.