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Brief communication: global temporal trends in the efficacy of clarithromycin-based regimens for the treatment of *Helicobacter pylori* infection

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Abstract

Background: *Helicobacter pylori* eradication rates achieved with clarithromycin-based triple therapies are declining due to antibiotic resistance, but data regarding temporal changes in efficacy with these eradication therapies are scarce.

Objective: To evaluate the efficacy of clarithromycin-based triple eradication regimens over time.

Design: A comprehensive literature review and time-trend analysis.

Data sources and methods: Bibliographies of recently published systematic literature reviews were searched and supplemented with a targeted literature review conducted using Medline and Embase databases and ProQuest from conception to May 2021. Studies reporting *H. pylori* eradication rates of clarithromycin-based triple therapies were included and temporal trends were estimated using a random-effects model.

Results: Eradication rates for triple therapies containing proton pump inhibitors (PPIs), clarithromycin, and amoxicillin showed a significant decline over the past 23 years ($p = 0.0315$). However, this decline was not significant when eradication rates achieved with vonoprazan-based triple therapy were included ($p = 0.3910$).

Conclusion: Vonoprazan-based triple therapy partially mitigated the decline in eradication rates seen with PPI-based triple therapy, likely due to more powerful acid suppression of vonoprazan.

Keywords: clarithromycin resistance, empiric therapy, eradication therapy, first-line regimens, *Helicobacter pylori*

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Background

Helicobacter pylori (*H. pylori*) is the most common chronic bacterial infection, estimated to infect up to half of the world's population, ranging from 20% to 50% in industrialized countries and up to 80% in developing countries.[1] Because of the established role of *H. pylori* in gastroduodenal disease, current clinical guidelines recommend eradication therapy for all patients diagnosed with active infection.[2,3] Careful selection of first-line eradication therapy is important to guarantee high efficacy and limit the risk of antibiotic resistance.[3]

Clarithromycin-based eradication therapies were successfully introduced in the 1990s[4] when their efficacy was at its peak and 7-day omeprazole–clarithromycin–amoxicillin treatment demonstrated an eradication rate of 94%.[5] Up until around the 2000s, reported clarithromycin resistance rates in *H. pylori* were generally at or below 10%.[6] However, between 2001 and 2014,

clarithromycin resistance increased dramatically to over 20% in the United States, Europe, and Asia, with rates as high as 60% reported in some countries.[6,7] In the United States, current resistance rates to clarithromycin, levofloxacin, and metronidazole are all above 30%.[8,9] Infection with a clarithromycin-resistant strain of *H. pylori* has been associated with a sevenfold risk of treatment failure among patients who receive clarithromycin-containing regimens.[9] Published literature suggests that eradication rates achieved with available regimens, particularly those containing clarithromycin, are declining[2,9,10]; however, data regarding changes in the efficacy of clarithromycin-based eradication regimens over time are scarce.

Novel approaches are needed to mitigate the effects of antibiotic resistance and offer effective empiric eradication of *H. pylori* infection. Vonoprazan is a novel potassium-competitive acid blocker[11] that provides more potent and durable acid suppression than traditional proton pump inhibitors (PPIs). Recent trial data suggest that substituting vonoprazan for PPI in clarithromycin-based triple regimens improves eradication rates.[12] We aimed to evaluate the efficacy of clarithromycin-based triple regimens, including vonoprazan-based triple therapy, over time.

Methods

A comprehensive literature review *via* bibliographic searches of three key systematic literature reviews (Rokkas *et al.*,[13] Xin *et al.*,[14] and Therapeutics Initiative of the University of British Columbia[15]) and a targeted literature review using index terms for *H. pylori* (Medical Subject Heading terms: 'H. pylori', 'H pylori', 'Helicobacter pylori' along with 'eradication') was performed. The full search strategy and methodology was previously described by Malfertheiner *et al.*[16] Databases searched from inception through the search date of May 2021 included Embase and MEDLINE *via* ProQuest. This review was not registered with PROSPERO; however, future systematic literature reviews will be registered with PROSPERO. A single reviewer assessed eligibility during title–abstract screening, and inclusion was determined *via* full-text screening according to PICOS criteria. Search results were further limited by interventions to identify prospective randomized studies reporting eradication rates of common triple therapies comprising either a PPI or vonoprazan, together with clarithromycin and amoxicillin.

From the included studies, treatment arms for clarithromycin-based triple therapies were extracted and a meta-analysis was conducted to estimate pooled *H. pylori* eradication rates with 95% confidence intervals based on a random-effects model. The meta-analysis was stratified by publication year, and between-group differences were tested using Cochrane's Q-test.

A mixed-effects linear model was constructed with publication year as a predictor. A random intercept was included to account for within-study correlations between treatment arms from the same study. The coefficient 'study year' was used to evaluate the trend in *H. pylori* eradication rates over time. Additional analyses were conducted to include and exclude vonoprazan-based triple therapy.

Results

Overall, 67 study arms with clarithromycin-based triple therapies from 38 trials conducted in East Asian, South Asian, and Western countries including North America were used in the analysis (Figure 1, Table 1). The identified clarithromycin-based triple therapy regimens had the following acid suppression backbones: vonoprazan, rabeprazole, lansoprazole, esomeprazole, omeprazole, and mixed PPI.

Before 2001, *H. pylori* eradication rates averaged around 83%. When considering all clarithromycin-based triple regimens in this study, the pooled *H. pylori* eradication rates over time were comparable to historic rates (82.00% post-2015; $p = 0.3460$), and differences between subgroups were not significant (Table 2).

Since eradication rates are known to be declining globally with PPI-based triple therapies, the impact of vonoprazan-based triple therapy on eradication rate trends was explored by analyzing the eradication rates over time of all clarithromycin-based triple regimens except vonoprazan-based triple therapy. After excluding vonoprazan-based triple therapy, pooled *H. pylori* eradication rates post-2015 for all other clarithromycin-containing triple therapies were significantly lower than historic rates (pre-2001: 83.04% *versus* post-2015: 72.43%; $p < 0.0001$). The

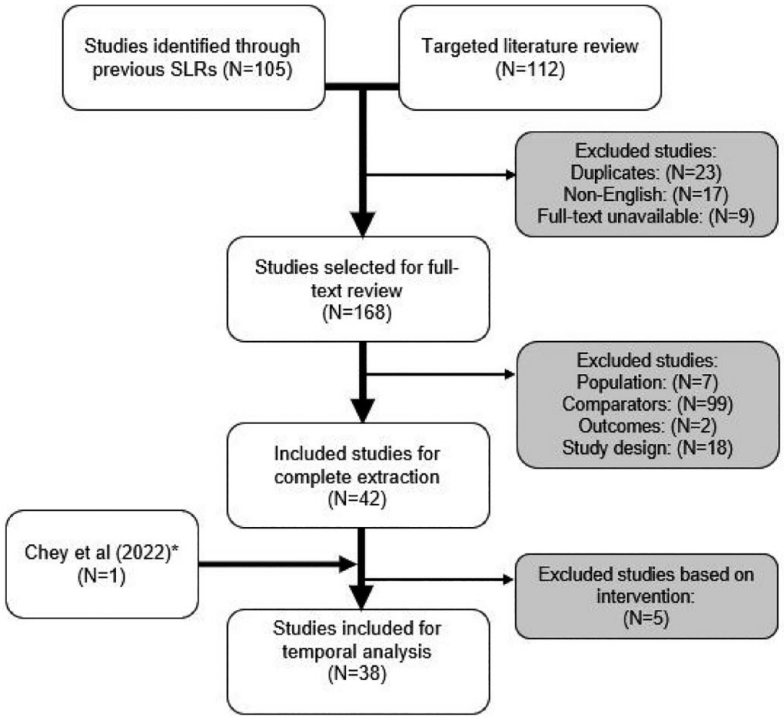


Figure 1. Literature flow diagram.
*The results from the pivotal pHalcon-HP study of vonoprazan were unpublished at the time of the analysis but were included in the model. The subsequent publication of the results included in this analysis is reflected in this diagram as Chey *et al.*[26]

Table 1. Included studies.

Authors	Year	Country/region	Treatment type	Duration (days)	*N*	ITT (*N*)	ITT (*n*)	ITT (%)	Antibiotic regimen
Alboraie[17]	2015	Kuwait	Omeprazole triple	10	118	118	81	68.6	CLR, AMX
Calvet[18]	2002	Spain	Omeprazole triple	7	171	171	132	77.2	CLR, AMX
Ching[19]	2008	UK	Lansoprazole triple	7	50	50	46	92.0	CLR, AMX
Kim[20]	2012	South Korea	Lansoprazole triple	14	104	104	77	74.0	CLR, AMX
Laine[21]	2003	North America	Omeprazole triple	10	137	137	114	83.2	CLR, AMX
Malfertheiner[22]	2011	France, Germany, Ireland, Italy, Poland, Spain, UK	Omeprazole triple	7	222	222	123	55.4	CLR, AMX
Mantzaris[23]	2002	Greece	Omeprazole triple	10	78	78	61	78.2	CLR, AMX
Murakami[24]	2016	Japan	Vonoprazan triple	7	329	324	300	92.6	CLR, AMX
			Lansoprazole triple	7	321	320	243	75.9	
Maruyama[25]	2017	Japan	Vonoprazan triple	7	72	72	69	95.8	CLR, AMX
			Mixed PPI triple	7	69	69	48	69.6	
Chey[26]	2022	US, Europe	Vonoprazan triple	14	338	338	273	80.8	CLR, AMX
			Lansoprazole triple	14	330	330	226	68.5	

(Continued)

Table 1. (Continued)

Authors	Year	Country/region	Treatment type	Duration (days)	*N*	ITT (*N*)	ITT (*n*)	ITT (%)	Antibiotic regimen
Schwartz[27]	1998	US	Lansoprazole triple	14	47	47	44	93.6	CLR, AMX
Songur[28]	2009	Turkey	Lansoprazole triple	14	104	113	37	32.7	CLR, AMX
Sue[29]	2018	Japan	Vonoprazan triple	7	55	55	48	87.3	CLR, AMX
			Mixed PPI triple	7	51	51	39	76.5	
Suzuki[30]	2020	Japan	Vonoprazan triple	7	167	167	149	89.2	CLR, AMX
Uygun[31]	2007	Turkey	Lansoprazole triple	14	120	120	69	57.5	CLR, AMX
Adachi[32]	2003	Japan	Rabeprazole Triple	5	40	40	36	90.0	CLR, AMX
			Omeprazole triple	5	40	40	30	75.0	
Anagnostopoulos[33]	2004	Greece	Esomeprazole triple	7	52	52	50	96.2	CLR, AMX
			Rabeprazole triple	7	52	52	42	80.8	
Choi[34]	2007	South Korea	Omeprazole triple	7	148	148	96	64.9	CLR, AMX
			Rabeprazole triple	7	140	140	97	69.3	
			Esomeprazole triple	7	148	148	104	70.3	
Dojo[35]	2001	Japan	Omeprazole triple	7	170	89	70	78.7	CLR, AMX
			Rabeprazole triple	7	170	81	65	80.2	
Hawkey[36]	2003	Germany, UK, the Netherlands, Poland, Ireland, Iceland	Rabeprazole triple	7	87	83	70	84.3	CLR, AMX
			Omeprazole triple	7	86	85	61	71.8	
Inaba[37]	2002	Japan	Rabeprazole triple	7	59	59	49	83.1	CLR, AMX
			Lansoprazole triple						
			Omeprazole triple	7	60	60	52	86.7	
Kositchaiwat[38]	2003	Thailand	Rabeprazole Triple	7	54	54	52	96.3	CLR, AMX
			Omeprazole triple	7	54	54	45	83.3	
Lee[39]	2010	China	Esomeprazole triple	7	130	104	88	84.6	CLR, AMX
			Rabeprazole triple	7	126	100	77	77.0	
Liu[40]	2013	Taiwan	Rabeprazole triple	7	222	222	195	87.8	CLR, AMX
			Lansoprazole triple	7	228	228	196	86.0	
Miki[41]	2003	Japan	Lansoprazole triple	7	49	49	39	79.6	CLR, AMX
			Rabeprazole triple	7	48	48	40	83.3	
Miwa[42]	1999	Japan	Omeprazole triple	7	75	75	64	85.3	CLR, AMX
			Lansoprazole triple	7	74	74	62	83.8	
			Rabeprazole triple	7	72	72	63	87.5	
Miwa[43]	1999	Japan	Omeprazole triple	7	76	76	57	75.0	CLR, AMX
			Lansoprazole triple	7	73	73	60	82.2	

(Continued)

Table 1. (Continued)

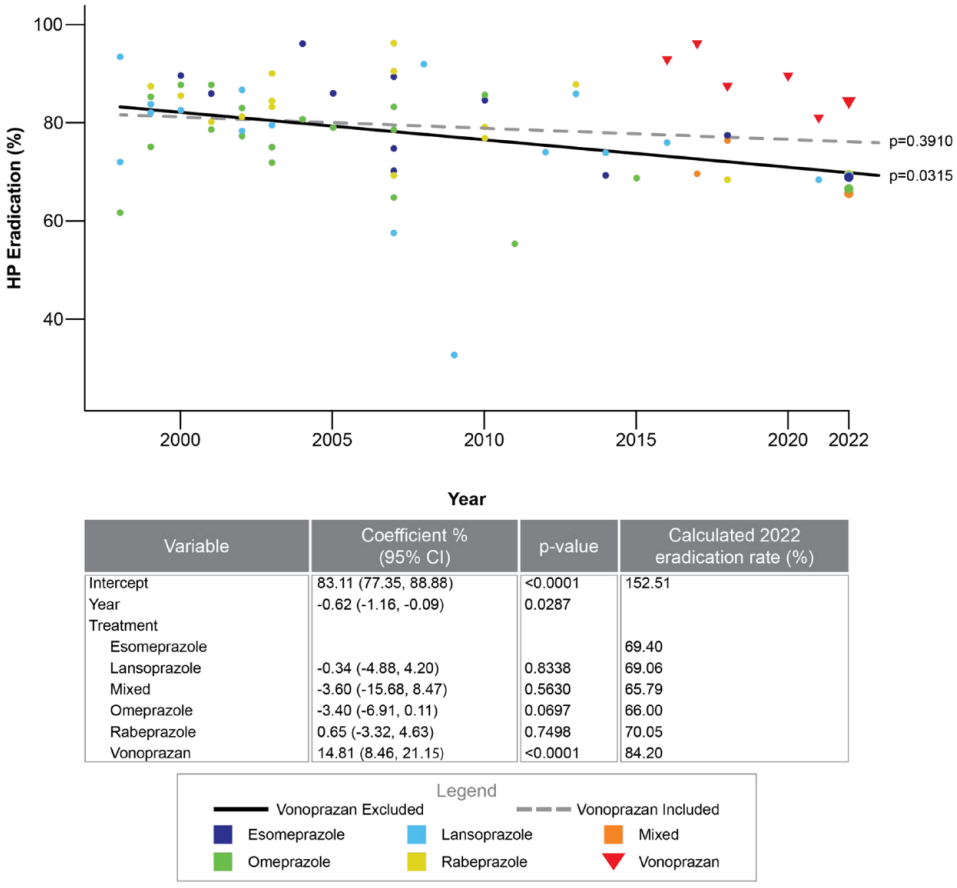
Authors	Year	Country/region	Treatment type	Duration (days)	*N*	ITT (*N*)	ITT (*n*)	ITT (%)	Antibiotic regimen
Miwa[44]	2000	Japan	Lansoprazole triple	7	104	104	86	82.7	CLR, AMX
			Rabeprazole triple	7	104	104	89	85.6	
Murakami[45]	2002	Japan	Lansoprazole triple	7	148	148	116	78.4	CLR, AMX
			Rabeprazole triple	7	48	48	39	81.3	
Nishida[46]	2014	Japan	Esomeprazole triple	7	134	134	93	69.4	CLR, AMX
			Lansoprazole triple	7	134	134	99	73.9	
Ozaki[47]	2018	Japan	Esomeprazole triple	7	71	71	55	77.5	CLR, AMX
			Rabeprazole triple	7	76	76	52	68.4	
Sheu[48]	2005	Taiwan	Omeprazole triple	7	100	100	79	79.0	CLR, AMX
			Esomeprazole triple	7	100	100	86	86.0	
Spinzi[49]	1998	Italy	Lansoprazole triple	7	186	186	134	72.0	CLR, AMX
			Omeprazole triple	7	170	170	105	61.8	
Subei[50]	2007	Africa, the Middle East, and Central and South America	Esomeprazole triple	7s	186	186	139	74.7	CLR, AMX
			Omeprazole triple	7	188	188	148	78.7	
Tulassay[51]	2001	Czech Republic, Hungary, and Poland	Esomeprazole triple	7	222	214	184	86.0	CLR, AMX
			Omeprazole triple	7	224	219	192	87.7	
Van Zanten[52]	2000	Europe and Canada	Esomeprazole triple	7	224	204	183	89.7	CLR, AMX
			Omeprazole triple	7	224	196	172	87.8	
Wu[53]	2007	Taiwan	Esomeprazole triple	7	209	209	187	89.5	CLR, AMX
			Rabeprazole triple	7	211	211	191	90.5	
Zhang[54]	2010	China	Rabeprazole triple	7	120	120	95	79.2	CLR, AMX
			Omeprazole triple	7	120	120	103	85.8	

AMX, amoxicillin; CLR, clarithromycin; ITT, intention to treat; PPI, proton pump inhibitor.

Table 2. Time stratified, pooled HP eradication rates.

Publication year	All clarithromycin regimens			Excluding vonoprazan-based triple therapy		
	Study arms, *N*	HP eradication, % (95% CI)	*p* Value	Study arms, *N*	HP eradication, % (95% CI)	*p* Value
Pre-2001	12	83.04 (77.99, 87.12)	0.3460	12	83.04 (77.99, 87.12)	**<0.0001**
2001–2005	21	82.33 (80.03, 84.42)		21	82.33 (80.03, 84.42)	
2006–2010	16	79.14 (71.21, 85.33)		16	79.14(71.21, 85.33)	
2011–2015	7	75.02 (66.17, 82.18)		7	75.02 (66.17, 82.18)	
Post-2015	11	82.00 (75.18, 87.27)		6	72.43(68.72, 75.85)	

Bold indicates statistical significance of $p < 0.05$.
CI, confidence interval; HP, *Helicobacter pylori; N*, number.



Variable	Coefficient % (95% CI)	p-value	Calculated 2022 eradication rate (%)
Intercept	83.11 (77.35, 88.88)	<0.0001	152.51
Year	-0.62 (-1.16, -0.09)	0.0287	
Treatment			
Esomeprazole			69.40
Lansoprazole	-0.34 (-4.88, 4.20)	0.8338	69.06
Mixed	-3.60 (-15.68, 8.47)	0.5630	65.79
Omeprazole	-3.40 (-6.91, 0.11)	0.0697	66.00
Rabeprazole	0.65 (-3.32, 4.63)	0.7498	70.05
Vonoprazan	14.81 (8.46, 21.15)	<0.0001	84.20

Figure 2. HP eradication rates in clarithromycin-containing triple regimens over time. The annual coefficient represents the slope of eradication rate over time overall. The treatment coefficients represent the difference in eradication rate of the regimen of interest and the reference regimen (esomeprazole) at any point in time. Coefficients are provided in percentage scale. Calculated 2022 eradication rates are based on the year coefficient and treatment coefficient, extrapolated for 2022 based on the model. *p* Values represent the significance in the time trend in eradication rates (i.e. slope of the respective line produced in the linear model).
CI, confidence interval; HP, *Helicobacter pylori*, vonoprazan, vonoprazan-based triple therapy.

results of the mixed-effects linear model (Figure 2) substantiated this negative trend. The negative time trend for eradication rates achieved with PPI triple therapies was statistically significant ($p = 0.0315$), yet once vonoprazan-based triple therapy was included, the trend was no longer significant ($p = 0.3910$).

Overall, significantly lower *H. pylori* eradication rates were observed over time when assessing all clarithromycin-based treatments together (0.62% reduction per year; $p = 0.0287$). Vonoprazan-associated eradication rates were significantly higher than PPI-containing clarithromycin-based triple regimens, including the reference regimen, esomeprazole triple therapy (+14.81%; $p < 0.0001$) (Figure 2). When the results of this model were extrapolated to 2022 for each acid suppression backbone, vonoprazan was associated with an 84.20% eradication rate (i.e. no reduction from historical rate), whereas the PPIs all had estimated eradication rates below or equal to 70% (Figure 2).

Discussion

Lack of antibiotic stewardship, short treatment durations, differing usage and policies by geography, and increased, and often inappropriate, use of macrolides have all been possible contributors to increased clarithromycin resistance and decreased effectiveness of clarithromycin-based

H. pylori eradication regimens.[55,56] Guidance from both Europe and North America recommends against first-line empiric *H. pylori* treatment with clarithromycin containing PPI-based triple therapy because of antibiotic resistance and the risk of potential treatment failure.[2,10] Nevertheless, a recent review of real-world evidence in North America suggests the PPI-based triple therapies are still commonly used.[57] Recent evidence suggests that triple therapy with the potassium-competitive acid blocker vonoprazan is an effective treatment for *H. pylori*, offering high rates of eradication, even among patients infected with clarithromycin-resistant *H. pylori*.[26]

The results of this analysis confirmed that *H. pylori* eradication rates for PPI-based clarithromycin-based triple therapies have continued to decline over time. Inclusion of vonoprazan-based triple therapy partially mitigated the observed decline in eradication rates. Higher eradication rates observed with vonoprazan-based triple therapy[26] in comparison to the historical eradication rates of PPI-based triple regimens suggest that vonoprazan-based triple therapy may be less impacted by increasing clarithromycin resistance.

Vonoprazan acts on H+, K+-ATPase in parietal cells in an acid-independent manner, providing a rapid antisecretory effect that is maintained over 24 h.[58] Moreover, vonoprazan demonstrated superior acid suppression compared to lansoprazole, with a more rapid and sustained acid-inhibitory effect.[59] Acid suppression and maintenance of an intragastric pH between 6 and 8 is essential to optimal antibiotic action, particularly for amoxicillin, which is acid labile and requires bacterial replication for its antimicrobial effects.[60,61] Thereby, the efficacy of vonoprazan-based triple therapy may be driven, at least in part, by potent acid suppression and the related effectiveness of amoxicillin, limiting the impact of clarithromycin resistance.

In a recent network meta-analysis which provided an indirect comparison of available *H. pylori* eradication regimens, vonoprazan-based triple therapy showed the highest relative efficacy, ranking higher according to surface under the cumulative rank than bismuth quadruple therapy and all PPI-based triple therapy regimens (regardless of individual PPI backbone).[16] Interestingly, vonoprazan dual therapy with amoxicillin ranked second only to vonoprazan-based triple therapy *versus* individual PPI triple therapies, providing further evidence that the more durable and potent acid suppression provided by vonoprazan may support maintained stability and optimal effectiveness of amoxicillin compared to PPIs.

The interpretation of the results of this temporal analysis is limited by the amount of available published evidence for vonoprazan-based triple therapy, since it has only recently become available in the United States. It was not feasible to correct for the heterogeneity of dosage and duration of treatment in multivariable models due to the limited amount of data. Among the studies analyzed, amoxicillin dosage was largely comparable between vonoprazan studies and other studies from 2015 onward.

Conclusion

Overall, the temporal decline in effectiveness of clarithromycin-based triple therapies may be mitigated by the advent of triple therapies with more potent acid suppression.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Steven F. Moss: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

William D. Chey: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Patrick Daniele: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing.

Corey Pelletier: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Gabriel Tremblay: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Elizabeth Hubscher: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Peter Malfertheiner: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

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Competing interests
Dr. Moss has been a consultant for Takeda, has served on advisory boards for RedHill Biopharma and Phathom Pharmaceuticals regarding novel H. pylori therapies, and is a consultant for and has received research support from American Molecular Laboratories regarding molecular diagnostics for *H. pylori*.

Dr. Chey reported being a Board member of the American College of Gastroenterology, GI on Demand, International Foundation of Functional GI Disorders, and the Rome Foundation; compensation as a consultant from AbbVie, BioAmerica, Ironwood Pharmaceuticals, QOL Medical, Nestle, Phathom Pharmaceuticals, RedHill Biopharma, Salix/Valeant, Takeda, Urovant, and Vibrant; grant/research support from BioAmerica, Commonwealth Diagnostics International, QOL Medical, Salix, and stock options in Dieta, Kiwi Bioscience, Isothrive, and Modify Health; and patents relating to methods and kits for identifying food sensitivities and intolerances, digital manometry, and a rectal expulsion device.

Dr. Malfertheiner has served as a speaker for Aboca, Bayer, Biocodex, Biohit, Malesci, Menarini, Luvos, and Mayoly-Spindler, a consultant for Aboca, Bayer, Danone, and an advisory board member for Bayer, Danone, Imevax, and Phathom.

Dr. Pelletier, Dr. Jacob, and Dr. Leifke are employees of Phathom Pharmaceuticals.

Dr. Tremblay and Dr. Hubscher are employees of Cytel, Inc, which served as a consultant on this project. Mr. Daniele was an employee of Cytel at the time of writing.

Availability of data and materials
All data relevant to the study are included in the article.

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