

Platelet count response to *H. pylori* treatment in patients with immune thrombocytopenic purpura with and without *H. pylori* infection: a systematic review

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ABSTRACT

Eradication of *H. pylori* improves thrombocytopenia in some patients with immune thrombocytopenic purpura by mechanisms that remain obscure. Platelet count responses may occur independently of *H. pylori* infection as a result of the immune modulating effects of macrolide antimicrobials or the removal of other commensal bacteria. We performed a systematic review of the literature to determine the effect of *H. pylori* eradication therapy in patients with immune thrombocytopenic purpura by comparing the platelet response in patients who were, and who were not infected with *H. pylori*. MEDLINE, EMBASE, Cochrane central registry and abstracts from the American Society of Hematology (from 2003) were searched in duplicate and independently without language or age restrictions. Eleven studies, 8 from Japan, were included enrolling 282 patients with immune thrombocytopenic purpura who received eradication therapy; 205 were *H. pylori*-positive and 77 were *H. pylori*-negative. The odds of achieving a platelet count response following eradication therapy were 14.5 higher (95% confidence interval 4.2 to 83.0) in patients with *H. pylori* infection (51.2% vs. 8.8%). No study reported bleeding or quality of life. Adverse events were reported in 12 patients. *H. pylori* eradication therapy was of little benefit for *H. pylori*-negative patients. These findings strengthen the causal association between *H. pylori* infection and immune thrombocytopenia in some patients. Randomized trials are needed to determine the applicability of *H. pylori* eradication therapy across diverse geographical regions.

Key words: helicobacter, autoimmunity, purpura, platelets.

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Introduction

A causal link between *H. pylori* infection and immune thrombocytopenic purpura (ITP) is suggested by clinical studies demonstrating a platelet count response in approximately 50% of patients following *H. pylori* eradication.¹⁻³ However, eradication therapy may result in the improvement of thrombocytopenia by mechanisms independent of *H. pylori* including the immune modulating effects of the treatment itself⁴ or the removal of other commensal bacteria. In support of these hypotheses is a recent meta-analysis showing an increase in platelet count following treatment in some patients with ITP

regardless of the outcome of eradication therapy.² Furthermore, in certain geographical regions, the prevalence of *H. pylori* infection among patients with ITP is no different than the general population⁵ suggesting that the association between *H. pylori* and ITP is not certain. Understanding the mechanism of the platelet count response following *H. pylori* treatment may help explain pathophysiology and determine whether or not uninfected patients stand to benefit from treatment. To determine the independent effect of *H. pylori* eradication therapy on platelet count response, we performed a systematic review of all studies reporting treatment responses compared to *H. pylori*-negative controls.

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Design and Methods

Literature Search

The electronic databases of MEDLINE, EMBASE and the Cochrane central registry were searched in duplicate and independently using the subject headings *Purpura*, *Thrombocytopenic*, *Idiopathic*, *Purpura*, *Thrombocytopenic*, and the keywords *idiopathic thrombocytopenic purpura*, *thrombocytopenic purpura*, *immune thrombocytopenia*, and *ITP*, combined with the subject headings *Helicobacter pylori*, *Helicobacter Infections* and the keywords *Helicobacter pylori*, *helicobacter infections* and *H. pylori*. Abstracts from the American Society of Hematology (2003 to 2007) were searched in duplicate electronically using the term *pylori*. Experts were canvassed for additional references and relevant bibliographies were searched by hand. No age or language restrictions were applied. Articles were included if they enrolled patients with ITP and described the platelet count response following *H. pylori* eradication for both infected and uninfected patients. Eradication therapy had to include at least one antibiotic and a proton pump inhibitor. Studies that selected only *H. pylori*-positive patients and case reports of fewer than 5 patients were excluded.

Study quality

The quality of included studies was assessed independently by two reviewers with expertise in methodology. Reviewers assessed each study for the presence or absence of 4 key design features derived from the specifications for reporting meta-analyses of observational studies⁶ and from a quality assessment tool for non-randomized studies⁷: (i) prospective data collection; (ii) enrolment of consecutive patients unselected for *H. pylori* infection status; (iii) a clearly stated duration of follow-up; and (iv) a description of losses to follow-up. Disagreements were resolved by consensus. Funnel plots relating sample size to treatment effect expressed as the log of the odds ratio (OR) were examined for evidence of publication bias.

Analysis

Platelet count response, bleeding and quality of life were captured. We used two definitions of overall response – the definitions from primary reports (which varied) and a standardized definition of a platelet count rise to at least $30 \times 10^9/L$ within six months (reported in most studies). Group level proportions for overall, partial and complete response following eradication therapy were derived for *H. pylori*-positive, eradicated, non-eradicated and negative patients. Age, duration of ITP, time to response and duration of response were derived by weighted means adjusted for sample size; when means and standard deviations were not reported for these variables, they were imputed from quartiles assuming a normal distribution. The comparison of proportion of responders between the *H. pylori*-positive and negative groups was performed using an exact test (two-tailed) for stratified data,⁸ and the common OR was reported with exact 95% confidence intervals (CI) to account for small sample sizes. Unweighted chance-cor-

rected kappa was used to assess agreement between reviewers for study selection.⁹ This systematic review had no external source of funding. The authors had complete access to all study data, and all have seen and approved this manuscript.

Results

Article selection

The initial literature search yielded 266 citations. Titles were screened for relevance and duplicates leaving 165 citations. Of those, 76 did not meet eligibility criteria leaving 90 articles which underwent detailed review. Finally, 11 articles were included (Figure 1). Agreement on article selection was moderate ($k=0.48$) and discrepancies, which were often due to uncertainty about the inclusion of *H. pylori*-negative patients, were resolved by consensus.

Study characteristics

Of 11 studies, 8 were from Japan and one was from each of Italy, USA and Canada (Table 1). Median prevalence of *H. pylori* infection from studies from Japan was 73% (first, third quartile 70%, 81%) compared with 22%¹¹ and 18%¹⁵ as reported in the 2 studies from North America, and 51%¹⁰ in the study from Italy. Most studies defined ITP as thrombocytopenia in the absence of any other cause and consistent with the American Society of Hematology guidelines;²¹ 8 of 11 studies required a bone marrow examination showing normal or increased megakaryocytes. The platelet count values for inclusion were heterogeneous from study to study, ranging from $\leq 50 \times 10^9/L$ ¹² to $\leq 120 \times 10^9/L$,^{11,16,19} and with an overall mean ($\pm SD$) baseline platelet count of $43 \pm 28 \times 10^9/L$. The definitions of platelet count responses were variable.

Patient characteristics

In total, 355 patients with ITP (68.2% female) with a

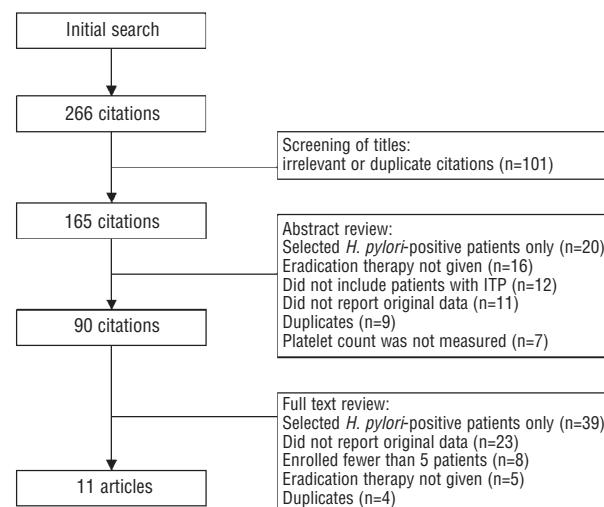


Figure 1. Results of study search and selection.

Table 1. Characteristics of *H. pylori* eradication studies that met inclusion criteria (n=355 patients) and the criteria used to define platelet count responses.

Study	Country	N.	Inclusion PLT count	<i>H. pylori</i> prevalence	Complete response	Partial response	Overall response	Response assessment
Emilia 2007 ¹⁰	Italy	75	PLT <100 for 6 months	51%	PLT >150	PLT 40-149, and doubling from baseline	PLT >40 and doubling	3 months
Michel 2004 ¹¹	USA	74	PLT < 60	22%	PLT >150	PLT >50, and doubling from baseline	PLT >50, and doubling	3 months
Asahi 2006 ¹²	Japan	37	PLT < 50 for 3 months	70%	NR	NR	PLT >100	6 months
Inaba 2005 ¹³	Japan	35	PLT < 100 for 6 months	71%	NR	NR	PLT >100, and increase by 30	6 months
Hino 2003 ¹⁴	Japan	30	PLT < 100	70%	NR	NR	Significant increase	3 months
Jackson 2008 ¹⁵	Canada	22	PLT < 120	18%	PLT >150	PLT >30	PLT >30	2 months
Takahashi 2004 ¹⁶	Japan	20	PLT <120	75%	PLT >120	PLT Increase by 20	Increase by 20	4 months
Ando 2004 ¹⁷	Japan	20	PLT < 100	85%	PLT >120	PLT 90-120	PLT >90	1 month
Kato 2004 ¹⁸	Japan	20	PLT < 100	85%	PLT >150 or increase by 100	Increase by 70-100	Increase by 70-100	
Morimoto 2007 ¹⁹	Japan	15	PLT < 120	80%	PLT >120	PLT increase by 20	Increase by 20	4 months
Ohguchi 2005 ²⁰	Japan	7	PLT < 100	32%	NR	NR	Significant increase	6 months

PLT: platelet count ($\times 10^9/L$); NR: not reported.

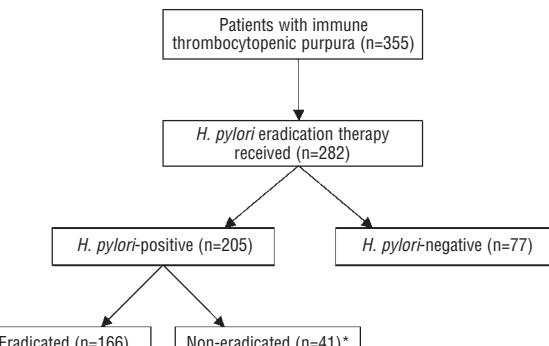
mean age of 51.6 ± 17.1 years were enrolled. None were children. Mean prior duration of ITP was 61.5 months and 47 (13.2%) patients had undergone splenectomy. Mean duration of follow-up was 34.5 ± 23.9 months. Of 355 patients, 282 received eradication therapy as part of the study design; 205 (72.7%) were *H. pylori*-positive and 77 (27.3%) were *H. pylori*-negative. *H. pylori* was successfully eradicated in 166 (81.0%) infected patients (Figure 2).

H. pylori diagnosis and treatment

The urea breath test was used to diagnose *H. pylori* in all studies except one¹⁵ in which fecal antigen testing was used. Additional tests for *H. pylori* included serology (n=5 studies) and tissue culture (n=1). Treatment consisted of amoxicillin 750 to 1500 mg twice daily, clarithromycin 200 to 400 mg twice daily, and a proton pump inhibitor for seven days in all studies except one¹¹ in which the duration of therapy was 14 days.

Response

The overall platelet count response (as variably defined in primary reports) for *H. pylori*-positive (n=205), eradicated (n=166) and negative (n=77) patients was 53.1%, 53.6% and 6.5% respectively (Table 2). The OR (OR; positive vs. negative) was 24.0, exact 95% CI 7.1 to 125.1. Using the homogeneous definition of a platelet count increase to $30 \times 10^9/L$ or higher by six months,^{10-13,15,18} overall platelet count response was 51.2%, 52.5% and 8.8% for positive (n=125), eradicated (n=115) and negative (n=57), respectively; OR (positive vs. negative) 14.5, 95% CI 4.2 to 83.0 (Figure 3). Complete platelet count response (platelet count greater than $150 \times 10^9/L$) was not significantly different between *H. pylori*-positive and negative patients (OR 3.4, 95% CI 0.7 to 22.4), although only 4 studies report-



* Data on platelet count response are reported for 12 non-eradicated patients

Figure 2. Patients who received *H. pylori* eradication therapy.

ed this outcome. A comparison of partial response was not possible since the definition varied too widely between studies. Relapses were reported in 3 *H. pylori*-positive responders, and one *H. pylori*-negative responder.

We performed a descriptive sensitivity analysis using only those studies that enrolled consecutive patients whose infection status was not known until after the effect of treatment had been assessed (n=4 studies). Three of those studies, one from Canada¹⁵ and 2 from Japan,^{12,13} showed a positive effect of treatment in infected compared with uninfected patients [3/4 (75%) vs. 3/18 (17%); 16/26 (62%) vs. 0/11 (0%); and 11/25 (44%) vs. 0/10 (0%)]. In contrast, the American study by Michel¹¹ showed no significant difference between groups [1/15 (6.7%) vs. 0/10 (0%)].

Among responders, the mean time to response was 2.7 weeks (range 1-6),^{10-12,15-17} and the mean duration of response was 19.9 months (range 7-60) measured to the end of follow-up.^{10-13,15,17-18}

Of 12 patients whose infection could not be eradicated with treatment, 3 (25.0%, 95% CI 5% to 57%) achieved a platelet count response.^{10,15-16} The median platelet count increase by group could not be derived because of insufficient data from primary reports, and an analysis by severity of thrombocytopenia was not possible with the study-level data available for this review. None of the studies reported bleeding or quality of life measures. A response to eradication therapy correlated with a reduction in platelet associated IgG levels in 3 studies,^{13,16,19} and in one study¹² suppression of B cells secreting anti-glycoprotein IIb-IIIa antibody was demonstrated in responders by 24 weeks.

Adverse events

Diarrhea (n=6 patients), taste disturbance (n=3), constipation (n=1), vomiting (n=1) and skin rash (n=1) were reported among treated patients.^{11,13-14} There were 2 deaths reported,¹⁰ neither were related to ITP or to *H. pylori* treatment.

Study quality

Data collection was prospective for all studies, however only one study¹³ met all methodological quality criteria (Table 3). Duration of follow-up was often not explicitly stated and reporting of losses to follow-up was inadequate; however, the data accounted for virtually all patients enrolled. Four studies^{11-13,15} entered consecutive patients with ITP without knowledge of *H. pylori* status; whereas 7 studies identified patients' infection status prior to treatment.^{10,14,16-20} Funnel plots relating sample size to OR were asymmetric suggesting that publication bias may have been present; however small studies with large effect sizes were not overrepresented.

Discussion

H. pylori is a commensal gram-negative microaerophilic bacterium that colonizes the human stomach. It is recognized as the causative agent of active chronic gastritis and peptic ulcer disease²² and is associated with the development of adenocarcinoma and mucosa-associated lymphoma.²³ The association with ITP was first noted by Gasbarrini who described a platelet count improvement in 8 of 11 patients following eradication of *H. pylori* with disappearance of platelet autoantibodies in 6 of these 8

Table 2. Platelet count responses among patients with immune thrombocytopenic purpura given *H. pylori* eradication therapy.

Response (number of studies)	<i>H. pylori</i> infection status			
	Positive	Negative	p value ^a	Odds ratio (95% CI)
All studies				
Overall response (n=11)	109/205 (53.2%)	5/77 (6.5%)	<0.001	24.0 (7.1, 125.1)
Complete response (n=6)	41/106 (38.7%)	4/43 (9.3%)	0.012	5.7 (1.4, 30.1)
Partial response (n=6)	14/106 (13.2%)	1/43 (2.4%)	0.071	21.0 (0.9, 588.0)
Homogeneous outcome criteria^b				
Overall (n=6)	64/125 (51.2%)	5/57 (8.8%)	0.001	<14.5 (4.2, 83.0)
Complete (n=4)	26/74 (35.1%)	4/36 (11.1%)	0.148	3.4 (0.7, 22.4)
Partial (n=4)	11/74 (14.9%)	1/36 (2.8%)	0.135	16.5 (0.7, 554.9)

^aExact test (two-tailed) for stratified data; ^bOverall response: achievement of a platelet count of $30 \times 10^9/L$ or higher by 6 months; complete response: platelet count $150 \times 10^9/L$ or higher; partial response was variably defined.

Study	<i>H. pylori</i> -positive	<i>H. pylori</i> -negative	OR; Exact 95% CI
Emilia 2007 ¹⁰	24/38	0/5	∞ [1.78, ∞)
Asahi 2006 ¹²	16/26	0/11	∞ [3.95, ∞)
Inaba 2005 ¹³	11/25	0/10	∞ [1.77, ∞)
Michel 2004 ¹¹	1/15	0/10	∞ [0.04, ∞)
Jackson 2008 ¹⁵	3/4	3/18	15.00 [0.74, 837.60]
Kato 2004 ¹⁸	9/17	2/3	0.56 [0.01, 13.17]
Total	64/125	5/57	14.51 [4.17, 83.01]

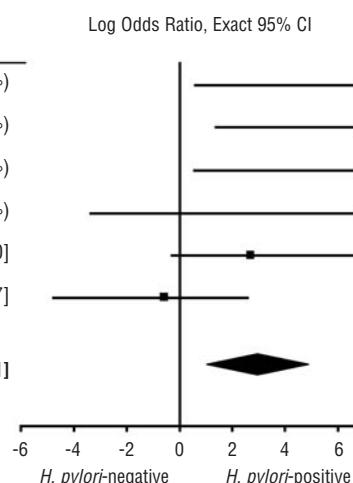


Figure 3. Pooled odds ratio (OR) of *H. pylori* eradication therapy on overall platelet count response (platelet count greater than $30 \times 10^9/L$ by 6 months) in *H. pylori*-positive and *H. pylori*-negative patients with immune thrombocytopenic purpura.

patients.²⁴ The association between platelet count improvement and *H. pylori* eradication has since been corroborated in other studies.¹⁻³ However, an independent effect of *H. pylori* treatment has been hypothesized, since 1) macrolide antibiotics including clarithromycin (universally included in eradication regimens) possess anti-inflammatory properties which may improve platelet autoreactivity in ITP by blocking the production of proinflammatory cytokines;⁴ and 2) antimicrobials used for *H. pylori* treatment may eradicate other commensal bacteria that stimulate cross reactive platelet antibodies. Using treated, *H. pylori*-negative patients as controls, this systematic review confirms that the effect

of *H. pylori* treatment is indeed due to eradication of the bacteria and not to the treatment itself. Platelet responses were only rarely observed in uninfected patients and in patients whose infection could not be eradicated, at a rate similar to that of spontaneous remissions expected in this patient population.^{25,26}

The methods that we adopted and the results that we produced in this systematic review are different from other reviews on this topic (Table 4). For one, we used treated, *H. pylori*-negative patients as controls. This design allowed us to assess the effect of eradication therapy, independent of *H. pylori* infection, and to determine whether or not uninfected patients might also

Table 3. Key features of study design.

Study	Study design	Consecutive patients* enrolled	Duration of follow-up clearly stated	Losses to follow-up
Jackson 2008 ¹⁵	Prospective cohort	Yes	No	None described
Emilia 2007 ¹⁰	Prospective cohort	No	Yes	None described
Morimoto 2007 ¹⁹	Prospective cohort	No	No	None described
Asahi 2006 ¹²	Prospective cohort	Yes	No	None described
Takahashi 2004 ¹⁶	Prospective cohort	No	No	None described
Inaba 2005 ¹³	Prospective cohort	Yes	Yes	One patient withdrawn
Ohguchi 2005 ²⁰	Unable to assess	No	No	None described
Michel 2004 ¹¹	Prospective cohort	Yes	Yes	None described
Ando 2004 ¹⁷	Prospective cohort	No	Yes	None described
Kato 2004 ¹⁸	Prospective cohort	No	Unable to assess	None described
Hino 2003 ¹⁴	Prospective cohort	No	No	None described

**H. pylori* infection status was not known until after eradication therapy was administered.²

Table 4. Comparison of reviews of *H. pylori* eradication in patients with immune thrombocytopenic purpura.

Study	N*	Controls	Outcome	Results	Interpretation
Arnold [#]	282	Treated, HP-negative	Platelet count response (>30×10 ⁹ /L lasting 6 months or more)	Exact odd ratio (HP-positive vs. HP-negative) = 14.5 (95% CI 4.2 to 83.0)	The odds of responding to HP eradication therapy was 14.5 times higher in patients with ITP who were HP-positive, compared with those who were HP-negative.
Stasi ¹	866	None	Platelet count response [doubling of baseline and >100×10 ⁹ /L (complete) or >30×10 ⁹ /L (overall)]	Overall response = 50.3% (95% CI, 41.6% to 59.0%)	Of HP-positive ITP patients who received eradication therapy, 50% achieved a platelet count response.
Franchini ²	409	Untreated; HP-positive, eradicated; HP-positive, non-eradicated; and HP-negative [†]	Difference in platelet count level	Weighted mean difference (treated vs. untreated) = 34×10 ⁹ /L (95% CI, 20-47)	HP-positive ITP patients who received eradication therapy had a platelet count level that was 34×10 ⁹ /L higher than those who did not receive eradication therapy.
Jackson ³	234	None	Platelet count response (variably defined)	Response = 52%	Of HP-positive ITP patients who received eradication therapy, 52% achieved a platelet count response.

*N = treated patients; [†]*H. pylori*-negative patients did not receive eradication therapy in the review by Franchini; [#]Arnold DM, Kelton JG. Current options for the treatment of idiopathic thrombocytopenic purpura. *Semin Hematol.* 2007 Oct;44(4 Suppl 5):S12-23.

benefit from treatment. The review by Franchini used as controls, untreated *H. pylori*-positive patients, eradicated and non-eradicated *H. pylori*-positive patients, and untreated *H. pylori*-negative patients;² whereas other reviews did not include a control group.^{1,3} Second, our review used comparative statistical methods (exact OR) to determine the effect of treatment on the proportion of responders; whereas Franchini reported the difference in platelet count levels between groups,² and other reviews described the number of responders among treated *H. pylori*-positive patients.^{1,3} The review by Stasi did describe 41 treated, *H. pylori*-negative patients, none of whom showed a platelet count recovery.¹

Several mechanisms have been proposed to explain the association between *H. pylori* and ITP. For one, antibodies against *H. pylori*, specifically against CagA protein have been shown to cross react with platelet antigens^{16,27} causing accelerated platelet clearance. This hypothesis may explain the observed variability in treatment effect by country since CagA-positive strains of *H. pylori* are more prevalent in Japan than in North America.²⁸ Other proposed mechanisms are modulation of host immunity following colonization by *H. pylori* to favor the emergence of autoreactive B-1 cells²⁹ and the enhancement of phagocytic capacity of monocytes together with low levels of the inhibitory Fcγ receptor IIIB following *H. pylori* infection.³⁰

Our findings raise questions that merit further research. For instance, we found that the rate of complete response (platelet count greater $150 \times 10^9/L$) was low in both *H. pylori*-positive and negative patients following eradication therapy (35.1% vs. 11.1%, respectively) suggesting that while treatment may improve platelet counts, it may not reverse the autoimmune process. Also, extended follow-up is needed to address the durability of the platelet count response. Finally, we, like others, observed regional differences in the proportion of *H. pylori*-positive responders with the highest rates from Japan¹² and Italy¹⁰ [16/26 (62%) and 24/38 (63%), respectively], and the lowest rate from North America¹¹ [1/15 (7%)]. While differences in the prevalence of CagA-positive strains may explain some of this variability,³¹ additional prospective studies with sufficient power and geographical representation are needed.

Strengths of this review were the inclusion of controlled studies only, allowing for the determination of the treatment effect with respect to controls; the use of standardized outcome criteria for defining platelet count response, limiting ascertainment bias; and the use of exact statistical tests to account for small sample sizes and large variability. Exact statistical methods involve synthesizing the evidence over studies based on the available data without requiring point estimates to be computed for each study. As opposed to standard meta-analytic methods, exact methods are most suitable when data are sparse and are particularly useful when estimates of effect cannot be derived from individual studies because of small sample sizes.

None of the primary reports were randomized trials,

thus measured and unmeasured bias including concomitant treatments and variable platelet count inclusion thresholds confound our results. Pooling results of such non-randomized trials is subject to bias; however we felt that studies using the same definition of platelet count response were sufficiently homogeneous. Furthermore a sensitivity analysis based only on studies of consecutive patients, where investigators were effectively blinded to *H. pylori* infections status, showed similar results. Our results are also limited by the lack of individual patient data and the lack of detailed reporting of prior ITP treatments, demographic data and outcome responses in some studies. The data from primary reports did not support an analysis by severity of thrombocytopenia (mild vs. severe), as these groups were generally not reported separately. While in practice, patients with mild thrombocytopenia often do not require any treatment, the goal of this review was to show a biological effect compared with controls; thus even patients with mild thrombocytopenia (baseline platelet count for the cohort was $43 \times 10^9/L$) contribute meaningfully to the data.

Although empiric *H. pylori* eradication therapy in ITP is appealing because of its simplicity and low toxicity, our data suggest that treatment should be reserved for *H. pylori*-positive patients only. High response rates and high prevalence of the infection in certain countries like Japan support routine screening for *H. pylori* in those regions. Even in countries like the US and Canada where prevalence is low, screening may be justified since some (albeit few) patients may respond to treatment, which is brief and well tolerated. Nevertheless, the efficacy and cost effectiveness of screening in North America remains uncertain. Randomized trials in unselected patients from diverse geographical regions are needed to confirm our findings and to determine the durability of the platelet count response.

Authorship and Disclosures

DMA: conception and design of the study, acquisition of data from original reports, interpretation of the data, drafting the manuscript and final approval; AB: acquisition of data from original reports, interpretation of the data, revision of the manuscript and final approval; IN: acquisition of data, interpretation of the data, revision of the manuscript and final approval; RS: conception of the study, acquisition of data from original reports, interpretation of the data, revision of the manuscript and final approval; MK: acquisition of data, interpretation of the data, revision of the manuscript and final approval; YL: data analysis and interpretation, revision of the manuscript and final approval; JGK: conception of the study, acquisition of data, interpretation of the data, revision of the manuscript and final approval; MAC: conception and design of the study, interpretation of the data, drafting the manuscript and final approval.

The authors reported no potential conflicts of interest.

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