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# Effect of *Helicobacter pylori* eradication on platelet count in idiopathic thrombocytopenic purpura: a systematic review and meta-analysis

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***Background*: There is a debate in the recent literature about the effect of *Helicobacter pylori* eradication on platelet count in patients with idiopathic thrombocytopenic purpura (ITP). In order to clarify this controversial issue, we performed a systematic review with meta-analysis of the available literature.**

***Methods*: The meta-analytic comparison was focused on the difference in the platelet count increase between the experimental arm (*H. pylori*-infected patients who responded to eradication therapy) and each control arm (*H. pylori*-infected patients who failed to respond to eradication therapy; *H. pylori*-infected patients who did not receive eradication therapy and *H. pylori*-negative patients) and was expressed as weighted mean difference (WMD). Moreover, in order to explain the heterogeneity, a meta-regression model was fitted with arm-level covariates.**

***Results*: Data involving 788 ITP patients were collected from 17 articles (16 studies with a prospective cohort design and 1 randomized trial). There was a statistically significant difference in the increase in platelet count in patients in whom eradication was successful compared with control groups [WMD, $40.77 \times 10^9$/L (95% CI, 20.92–60.63) compared with untreated patients; 52.16 (95% CI, 34.26–70.05) compared with patients who failed eradication and 46.35 (95% CI, 27.79–64.91) compared with *H. pylori*-negative patients]. Moreover, in the meta-regression model, the success of *H. pylori* eradication was highly significant as an explanatory variable for platelet count increase.**

***Conclusions*: Our analysis shows a strict correlation between *H. pylori* eradication and increase in platelet count. However, due to intrinsic limits in the design of the studies analysed, further evidence from randomized clinical trials is required to confirm the effect of eradication treatment on platelet count.**

Keywords: bacterium, therapy, ITP, thrombocytopenia

## Introduction

Recently, it has been suggested that *Helicobacter pylori* may contribute to the pathogenesis of chronic idiopathic thrombocytopenic purpura (ITP), since partial or even complete remission of thrombocytopenia has been reported in some patients after eradication of *H. pylori*.[1–4] A cross molecular mimicry between the highly antigenic *H. pylori* CagA protein and platelet antigens has been indicated by some authors as the possible pathophysiological mechanism of this subset of ITP.[5–7] However, as other studies have failed to demonstrate such a relationship, actually there is a controversy as to whether *H. pylori* eradication in chronic ITP patients is effective in increasing platelet count or not.[8]

Although a number of traditional reviews[2,3,5,8] have been published so far on the association between *H. pylori* and

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thrombocytopenia, none had systematically reviewed the literature data with the aim of comparing the trend of platelet count in *H. pylori*-positive (eradicated or not) and -negative patients. Thus, to clarify this issue, we have conducted a systematic review and meta-analysis of the available literature.

## Methods

### *Literature search*

We first performed an electronic search on chronic ITP and *H. pylori* infection on MEDLINE, EMBASE, SCOPUS and the Cochrane Library without temporal limits using different combinations of the following keywords: '*Helicobacter pylori*', 'infection', 'bacterium', 'thrombocytopenia', 'ITP', 'idiopathic thrombocytopenic purpura', 'immune thrombocytopenic purpura', 'chronic idiopathic thrombocytopenic purpura', 'low platelet count', 'platelet', 'eradication', 'bacterial eradication' and 'therapy'. In addition, the bibliographic references of all retrieved studies and reviews were assessed for additional reports of clinical trials. Unpublished works were identified by searching the abstract books of the most important conferences on digestive, infectious and haematological diseases.

For any publication with missing or incomplete information, we attempted to contact the author(s) (see the Acknowledgements section). We added the data provided by these authors to our tables; thus, in some instances, the results presented in our tables differ from those shown in the published articles.

### *Selection criteria and data collection*

We included in the analysis randomized controlled trials and studies with a prospective cohort design. Case control studies were excluded from the analysis. For inclusion, studies had to enrol a relevant clinical population characterized by: (i) consecutive patients with a diagnosis of chronic ITP; (ii) ITP diagnosed according to the American Society of Hematology guidelines;[9] (iii) *H. pylori* infection documented by the urea breath test; (iv) studies had to report platelet count over the time and to examine the effects of *H. pylori* eradication on platelet count. The extracted data included the total number of ITP patients, the number of *H. pylori*-infected and -uninfected patients; the number of *H. pylori*-infected patients receiving or not receiving eradication therapy and the number of patients with or without response to eradication therapy. In addition, the mean platelet count of this subgroup of patients was recorded. We did not analyse parameters on clinical outcome of ITP patients as these data were not available in the majority of the studies included in the meta-analysis.

Two reviewers (M. F. and M. C.) independently extracted data and resolved disagreements of interpretation by discussion.

### *Quality assessment*

The methodological quality of cohort studies was assessed using an application of the Newcastle–Ottawa quality assessment scale for cohort studies.[10,11] The scale is aimed to assess for selection bias, comparability of cohorts on the basis of the design or analysis, and outcome assessment. The quality of the randomized trial was assessed with a scale developed by Jadad *et al.*[12] This scale evaluates the randomization and double blinding processes, and reports of dropouts and withdrawals; trial scores range from 0 to 5 points.

### *Statistical analysis*

All studies reported two quantities for each arm, the mean platelet count at baseline and at the follow-up (>4 months), along with the two related standard deviations and the number of patients. For the present systematic review, the difference between the two mean counts (after minus before) was preliminarily calculated, along with the standard deviation of this difference. This difference can be viewed as the increase in the mean platelet count during the period of observation. Thereafter, we performed four meta-analytic comparisons focused on the difference in the platelet count increase between: (i) *H. pylori*-infected patients receiving eradication treatment and *H. pylori*-infected patients not receiving eradication treatment, and between *H. pylori*-infected patients who responded to eradication therapy and the following arms: (ii) *H. pylori*-infected patients who failed to respond to eradication therapy; (iii) *H. pylori*-infected patients who did not receive eradication therapy; and (iv) *H. pylori*-negative patients. The effect size of each meta-analytic comparison was expressed as weighted mean difference (WMD). The weight assigned to each study was calculated with the inverse variance method. The statistical target was to demonstrate a higher increase in platelet count in *H. pylori*-infected patients when the eradication treatment was successful; the null hypothesis was an equal platelet count increase in experimental and control arms.

The heterogeneity in study treatment effect clearly stems from the complex pattern of study design. Indeed, the majority of the studies reported a composition structured on several arms (arms with or without *H. pylori* infection, arms treated with antibiotic therapy in order to eradicate *H. pylori* or without antibiotic treatment and arms with or without *H. pylori* eradication). In order to explain the heterogeneity, a meta-regression model was fitted with arm-level covariates (*H. pylori* yes/no, antibiotic treatment yes/no and successful *H. pylori* eradication yes/no). The dependent variable was the increase in platelet count during the follow-up. Again, the unit of analysis was the arm of each study, included as mean difference and standard error of the difference, summarized by means of the random effects method.[13] All analyses were carried out using Stata version 9.1. The aim of the statistical procedure was to evaluate the modifying effect of the covariates on the increase in platelet count.

### *Assessment of publication bias and heterogeneity*

Graphical funnel plots were generated to visually inspect for publication bias.[14] The statistical methods for detecting funnel plot asymmetry were the rank correlation tests of Begg and Mazumdar[15] and the regression asymmetry test of Egger *et al.*[14]

The heterogeneity of study results was assessed by the Cochran's $Q$[16] and by a test of inconsistency ($I^2$).[17]

## Results

### *Description of studies and methodological quality*

Among the 17 studies considered for this systematic review,[18–34] with information on 788 ITP patients, the prevalence of *H. pylori* infection was 62.7% (494/788 ITP cases). Bacterium eradication consisted of standard therapy including clarithromycin (500 mg twice daily), amoxicillin (1000 mg twice daily) and pantoprazole or omeprazole (20 mg twice daily) for 7–14 days. Standard treatment was able to eradicate bacterium infection in 86.6% (354/409) of treated cases.

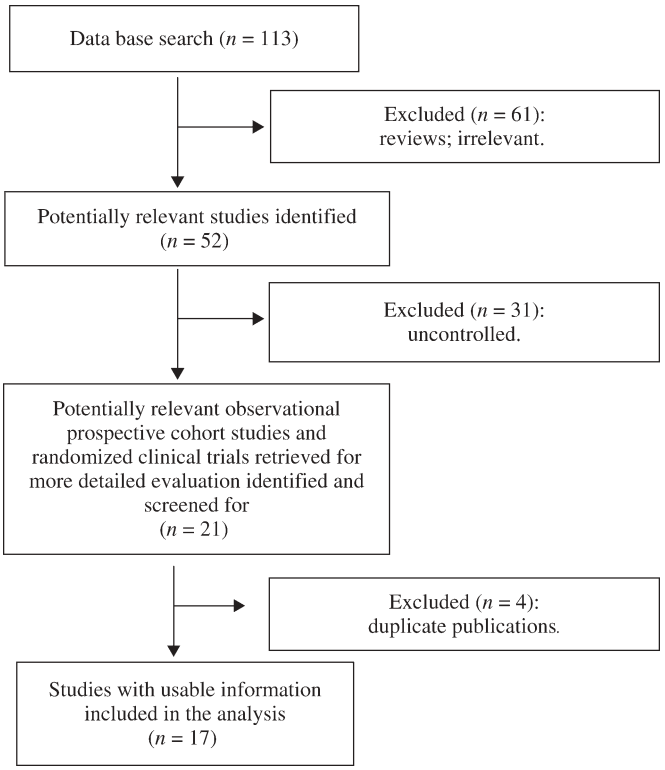


**Figure 1.** Meta-analysis profile summarizing trial flow.

There were 16 prospective cohort studies and one[32] randomized controlled trial. The included studies contained 46 arms. However, four arms were excluded from further evaluation as they have only one patient (variance not calculable).

Figure 1 shows the flowchart of inclusion of studies. Tables 1 and 2 report the studies in detail with data regarding ITP (Table 1) and the platelet response to the eradication treatment (Table 2). Approximately half of the evaluable patients (289/574; 50.3%) received previous treatments for ITP (steroids alone or in combination with other immunosuppressive therapies including splenectomy), while only a minority (86/369; 23.3%) received standard ITP treatment concomitant to the eradication therapy.

According to the Newcastle–Ottawa quality assessment scale, the criteria for selection of patients and comparability of cohorts as well as the outcome evaluation were, with few exceptions, satisfactory [see Table S1, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)].

The Jadad score for the only randomized study was 2; the study reported that patients were randomly assigned by concealed allocation, but no information on the method to generate the sequence of randomization was provided.

### *Results of the meta-analysis*

Figures 2–4 show WMD of platelet count (no. of cells $\times 10^9$/L) and related 95% CI for individual studies in *H. pylori*-infected patients receiving or not receiving eradication treatment and in *H. pylori*-infected patients who responded to eradication therapy compared with each control arm (*H. pylori*-infected patients who failed to respond to eradication therapy; *H. pylori*-infected patients who did not receive eradication therapy and *H. pylori*-negative patients). Visual inspection of figures shows an increase in platelet count in ITP patients receiving eradication treatment compared with untreated patients, and in patients with a favourable response to *H. pylori* eradication therapy in all possible comparisons. Regardless of the outcome of eradication therapy, *H. pylori* treated patients had WMD significantly higher than *H. pylori* untreated patients: 33.95 $\times 10^9$/L (95% CI, 20.48–47.42). Patients in whom eradication was successful had WMD significantly higher than control groups: 40.77 (95% CI, 20.92–60.63) compared with untreated patients; 52.16 (95% CI, 34.26–70.05) compared with patients who failed eradication and 46.35 (95% CI, 27.79–64.91) compared with *H. pylori*-negative patients. The results of these comparisons are summarized in Table 3.

The results of the meta-regression are shown in Table 4. The success in *H. pylori* eradication is highly significant as an explanatory variable, where the outcome is the platelet count increase after treatment. Of note, the intercept is significantly different from zero (higher). This means that even the standard treatment has some success, albeit lower (average increase in platelet count: 15 $\times 10^9$/L) than that observed in *H. pylori*-positive patients after bacterium eradication (average increase 61 $\times 10^9$/L).

### *Publication bias assessment*

Visual examination of the funnel plot (Figure 5) showed no evidence of publication bias, which was confirmed by the Egger test and by the Begg and Mazumdar test.

## Discussion

In this systematic review, we have confirmed the association between *H. pylori* infection and ITP. In fact, the results of our meta-analysis show that eradication of *H. pylori* infection has an important impact on platelet count.

When WMD in platelet count was compared among the different subgroups of patients, in all the possible comparisons there was a statistically significant difference in the increase in platelet count in patients in whom eradication was successful compared with control groups: 40.77 (95% CI, 20.92–60.63) compared with untreated patients; 52.16 (95% CI, 34.26–70.05) compared with patients who failed eradication and 46.35 (95% CI, 27.79–64.91) compared with *H. pylori*-negative patients. Moreover, using a design similar to an intention to treat analysis, we compared WMD in platelet count for the whole population of *H. pylori*-positive patients receiving eradication therapy (regardless of the outcome of eradication) and in *H. pylori*-positive patients not receiving eradication therapy: patients receiving eradication treatment had an increase in platelet WMD of 33.95 (95% CI, 20.48–47.42) compared with untreated patients.

We also used meta-regression which, like any regression analysis, identifies statistically significant relations between the efficacy of an intervention (the dependant variable) and other factors of interest (the independent variables). Using this approach, we have found that success of *H. pylori* eradication treatment had a significant impact on platelet increase.

From the analysis of Table 1, it emerges that the prevalence of *H. pylori* infection in the ITP population selected was ~63%. However, this finding cannot be added as a proof of the association between ITP and *H. pylori* infection as this rate is similar

**Table 1.** Summary of the literature data: characteristics of patients

| | ITP patients | | | | | | | | HP-positive eradication therapy | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | total | age[a] | male/female | disease duration[a,b] | previous therapy[c] | concomitant therapy[c] | HP-positive | HP-negative | success | failure | untreated |
| Gasbarrini *et al.*[18] | 18 | 45 | 5/13 | NR | NR | NR | 11/18 (61.1) | 7/18 (38.9) | 8/11 (72.7) | 3/11 (27.3) | 0 |
| Jarque *et al.*[19] | 56 | 54 | 18/38 | NR | NR | 0/56 | 40/56 (71.4) | 16/56 (28.6) | 23/32 (71.9) | 9/32 (28.1) | 0 |
| Emilia *et al.*[20] | 30 | 50.3 | 13/17 | 39.6 | 23/30 (76.7) | NR | 13/30 (43.3) | 17/30 (56.7) | 12/13 (92.3) | 1/13 (7.7) | 0 |
| Veneri *et al.*[21] | 35 | 55 | 12/23 | 16.4 | 9/16 (56.2)[d] | 0/16[d] | 25/35 (71.4) | 10/35 (28.6) | 15/16 (93.7) | 1/16 (6.3) | 0 |
| Kohda *et al.*[22] | 40 | 52.7 | 12/28 | 44.4 | 27/40 (67.5) | 19/40 (47.5) | 25/40 (62.5) | 15/40 (37.5) | 19/19 (100) | 0/19 | 6/25 (24.0) |
| Hino *et al.*[23] | 30 | 54.1 | 8/22 | NR | 12/30 (40.0) | 7/30 (23.3) | 21/30 (70.0) | 9/30 (30.0) | 18/21 (85.7) | 3/21 (14.3) | 0 |
| Hashino *et al.*[24] | 22 | 49.1 | 4/18 | 109.8 | 14/22 (63.6) | 8/22 (36.4) | 14/22 (63.6) | 8/22 (36.4) | 13/14 (92.9) | 1/14 (7.1) | 0 |
| Ando *et al.*[25] | 61 | 54.8 | 12/49 | 76.3 | 23/61 (37.7) | NR | 50/61 (82.0) | 11/61 (18.0) | 27/29 (93.1) | 2/29 (6.9) | 21/50 (42.0) |
| Nomura *et al.*[26] | 42 | NR | 15/27 | NR | 21/42 (50.0) | NR | 28/42 (66.7) | 14/42 (33.3) | 12/28 (42.9) | 16/28 (57.1) | 0 |
| Takahashi *et al.*[27] | 20 | 51.2 | 5/15 | 97.6 | 13/20 (65.0) | NR | 15/20 (75.0) | 5/20 (25.0) | 13/15 (86.7) | 2/15 (13.3) | 0 |
| Sato *et al.*[28] | 53 | 59.5 | 16/37 | 78.5 | 10/53 (18.9) | 27/53 (50.9) | 39/53 (73.6) | 14/53 (26.4) | 27/32 (84.4) | 5/32 (15.6) | 7/39 (17.9) |
| Michel *et al.*[29] | 74 | 41 | 24/50 | 86.4 | 24/25 (96.0)[e] | 9/25 (36.0)[e] | 16/74 (21.6) | 58/74 (78.4) | 14/15 (93.3) | 1/15 (6.7) | 1/16 (6.2) |
| Veneri *et al.*[30] | 43 | 52.1 | 18/25 | NR | 14/43 (32.6) | 0/21 | 43/43 | 0/43 | 41/43 (95.3) | 2/43 (4.7) | 0 |
| Stasi *et al.*[31] | 137 | 51 | 57/80 | 24.5 | 70/137 (51.1) | 16/52 (30.8) | 64/137(46.7) | 73/137 (53.3) | 52/52 (100) | 0/52 | 12/64 (18.7) |
| Suzuki *et al.*[32] | 36 | 56.8 | 14/22 | 62.7 | 10/25 (40.0)[f] | NR | 25/36 (69.4) | 11/36 (30.6) | 11/13 (84.6) | 2/13 (15.4) | 12/25 (48.0) |
| Suvajdzic *et al.*[33] | 54 | 51 | 12/42 | 72 | 19/30 (63.3)[g] | 0/54 | 39/54 (72.2) | 15/54 (27.8) | 23/30 (76.7) | 7/30 (23.3) | 9/39 (23.1) |
| Asahi *et al.*[34] | 37 | NR | 14/23 | NR | NR | NR | 26/37 (70.3) | 11/37 (29.7) | 26/26 (100) | 0/26 | 0 |

HP, *Helicobacter pylori*; NR, not reported.
Results are expressed as absolute numbers (%) or means ( ± SE).
[a]Median.
[b]Months.
[c]Previous or concomitant therapy included steroids alone or in combination with other immunosuppressive therapies including splenectomy.
[d]Data refer to the 16 patients who underwent eradication therapy.
[e]Data refer to the 25 (15 *H. pylori*-positive and 10 *H. pylori*-negative) patients treated with eradication therapy.
[f]Data refer to the 25 *H. pylori*-positive patients.
[g]Data refer to the 30 *H. pylori*-positive patients treated with eradication therapy.

**Table 2.** Summary of the literature data: platelet response to eradication treatment

| | Basal platelet count ($\times 10^9$/L) | | | | | Platelet count at the end of follow-up[a] ($\times 10^9$/L) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | HP-positive—eradication therapy | | | | | HP-positive—eradication therapy | | | | | |
| Reference | total | success | failure | HP-positive untreated | HP-negative | total | success | failure | HP-positive untreated | HP-negative | Follow-up[b,c,d] |
| Gasbarrini *et al.*[18] | 95.0 (±28.9) | 85.0 (±24.0) | 102.0 (±42.0) | NA | 103.0 (±25.0) | 139.6 (±33.8) | 153.0 (±30.0) | 104.0 (±44.0) | NA | 101.0 (±28.0) | 4 |
| Jarque *et al.*[19] | 58.4 (±24.5) | 57.0 (±22) | 62.0 (±31.0) | NA | 58.0 (±23.0) | 65.0 (±31.8) | 63.0 (±27.0) | 70.0 (±44.0) | NA | 67.0 (±28.0) | 24 |
| Emilia *et al.*[20] | 52.5 (±25.0) | 50.2 (±24.6) | 80 | NA | 41.7 (±14.8) | 127.8 (±92.2) | 132.9 (±94.4) | 67 | NA | 111.4 (±27.2)[d] | 8.3 |
| Veneri *et al.*[21] | 51.9 (±27.2) | 51.7 (±27.8) | 55 | NA | 55.7 (±24.1) | 139.3 (±123.6) | 144.4 (±125.3) | 51 | NA | 104.4 (±37.3)[d] | 11.7 |
| Kohda *et al.*[22] | 67.1 (±54.2) | 67.1 (±54.2) | NA | NR | 59.9 (±40.8) | 120.0 (±50.0) | 118.0 (±50.0) | NA | NR | 45.0 (±20.0) | 14.8 |
| Hino *et al.*[23] | 36.8 (±20.7) | 40.5 (±16.3) | 33.5 (±24.3) | NA | 31.4 (±12.0) | 67.2 (±53.7) | 152.3 (±41.1) | 25.4 (±22.3) | NA | 42.3 (±41.6) | 15 |
| Hashino *et al.*[24] | 58.2 (±30.4) | 59.1 (±32.5) | 47 | NA | 62.6 (±20.4) | 98.6 (±56.5) | 98.8 (±58.8) | 96 | NA | 53.3 (±26.9) | 15 |
| Ando *et al.*[25] | 56.0 (±24.0) | 60.9 (±24.9) | 26.0 (±8.5) | 40.5 (±16.4) | 42.0 (±24.0) | 92.8 (±49.5) | 97.2 (±48.5) | 33.5 (±4.9) | 47.0 (±13) | 55.0 (±35.0) | 11 |
| Nomura *et al.*[26] | 29.0 (±6.0) | 27.0 (±5.0) | 34.0 (±6.0) | NA | 31.0 (±5.0) | 78.0 (±11.0) | 96.0 (±11.0) | 55.0 (±13.0) | NA | 34.0 (±6.0) | NR |
| Takahashi *et al.*[27] | 39.9 (±26.7) | 41.8 (±28.3) | 27.5 (±6.4) | NA | 39.2 (±42.2) | 101.1 (±85.9) | 110.9 (±88.4) | 37.0 (±12.7) | NA | 35.4 (±29.3) | 4 |
| Sato *et al.*[28] | 54.0 (±17.5) | 53.0 (±20.0) | 65.0 (±16.0) | 59.0 (±22.0) | 55.0 (±22.0) | 109.8 (±21.5) | 121.0 (±59.0) | 55.0 (±13.0) | 62.0 (±24.0) | 56.0 (±28.0) | 6 |
| Michel *et al.*[29] | 32.1 (±14.9) | 31.7 (±14.2) | 54 | NR | 25.6 (±17.0)[e] | 66.3 (±97.8) | 64.8 (±101.3) | 88 | NR | 101.7 (±96.6)[e] | 11.5 |
| Veneri *et al.*[30] | 54.3 (±28.7) | 55.1 (±26.2) | 45.9 (±37.5) | NA | NA | 126.1 (±47.8) | 130.3 (±66.7) | 54.3 (±33.9) | NA | NA | 31.2 |
| Stasi *et al.*[31] | 42.0 (±25.0) | 42.0 (±25.0) | NA | NR | 46.0 (±23.0) | 129.4 (±61.0) | 129.4 (±61.0) | NA | NR | NR | 25 |
| Suzuki *et al.*[32] | 54.7 (±26.9) | NR | NR | 48.4 (±22.1) | NR | 114.5 (±90.5) | NR | NR | 48.1 (±26.0) | NR | 6 |
| Suvajdzic *et al.*[33] | 63.0 (±33.5) | 59.2 (±34.2) | 75.3 (±31.1) | 86.5 (±24.1) | 78.1 (±32.1) | 84.1 (±45.2) | 86.1 (±50.4) | 77.4 (±28.0) | 84.8 (±22.5) | 78.0 (±30.7) | 18 |
| Asahi *et al.*[34] | 35.2 (±13.1) | 35.2 (±13.1) | NA | NA | 31.4 (±12.6)[f] | 113.6 (±61.3) | 113.6 (±61.3) | NA | NA | 34.1 (±19.9) | 13 |

HP, *Helicobacter pylori*; NA, not applicable; NR, not reported.
Results are expressed as means (±SE).
[a]Most *H. pylori*-negative patients were treated with immunosuppressive therapy.
[b]Median.
[c]Months.
[d]At least 4 months after eradication therapy.
[e]Data refer to 10 *H. pylori*-negative patients who underwent eradication therapy.
[f]All patients, *H. pylori*-positive and -negative, were treated with eradication therapy.

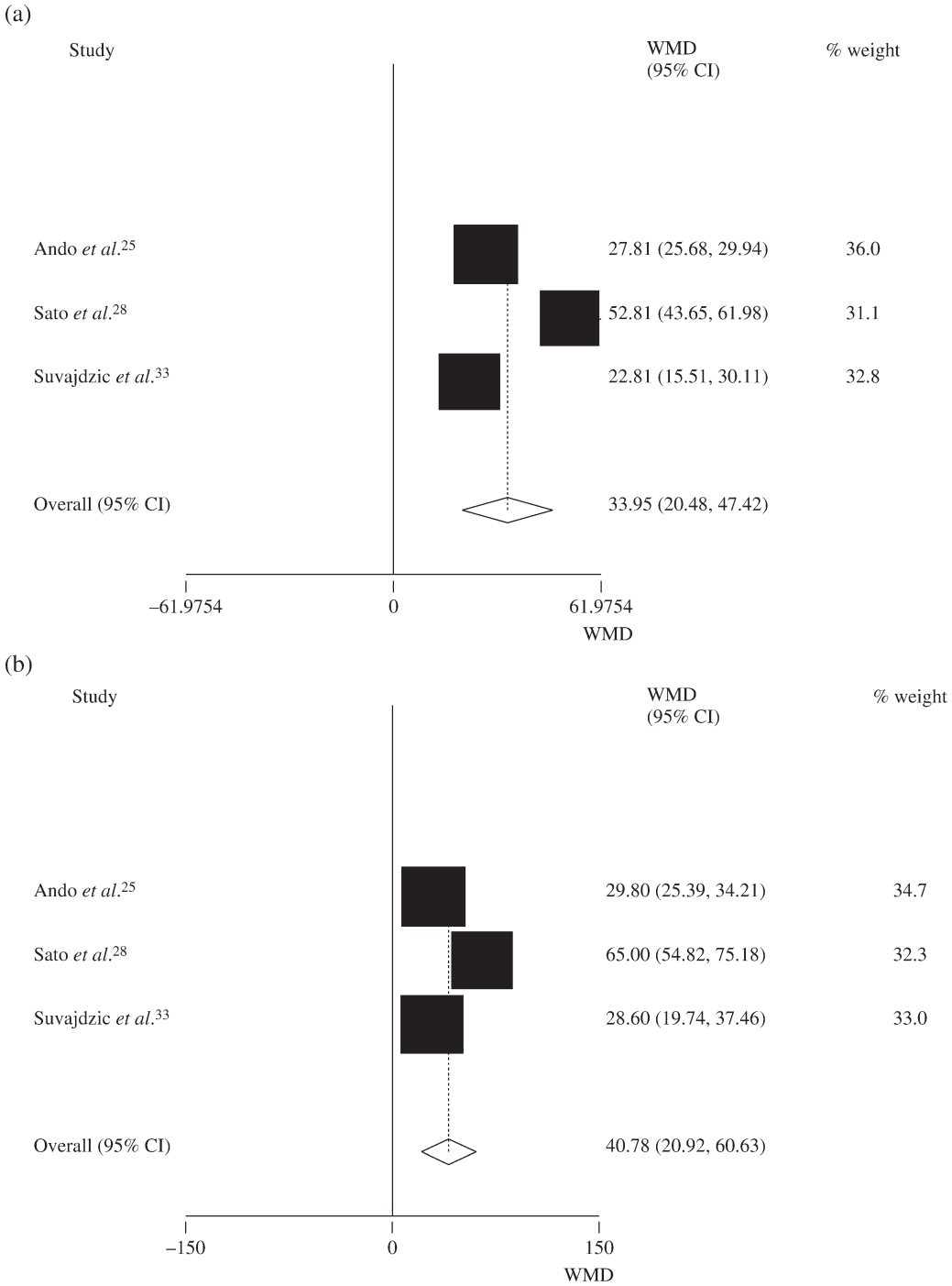


**Figure 2.** DerSimonian and Laird meta-analytical WMDs in three studies (identified by first author) reporting platelet count (no. of cells $\times 10^9$/L) in ITP *H. pylori*-positive patients receiving eradication treatment and in *H. pylori*-positive patients not receiving eradication therapy. (a) Regardless of the outcome of eradication, patients receiving treatment had an increase in platelet count from baseline significantly higher than patients not receiving eradication treatment (overall effect, $z = 4.94$, $P < 0.0001$); test for heterogeneity: $\chi^2 = 29.76$ (d.f. = 2) $P < 0.0001$; $I^2 = 0.966$ (95% CI, 0.910–0.988). Estimate of between-study variance $\tau^2 = 129.90$. (b) Patients in whom eradication was successful had an increase in platelet count from baseline significantly higher than control group (overall effect, $z = 4.03$, $P < 0.0001$); test for heterogeneity: $\chi^2 = 40.54$ (d.f. = 2) $P < 0.0001$; $I^2 = 0.975$ (95% CI, 0.938–0.990). Estimate of between-study variance $\tau^2 = 290.624$.

to that found in the healthy population according to the different geographical areas.[35–37] Another interesting observation is that the antibacterial treatment was highly effective in eradicating *H. pylori* as ~87% of ITP *H. pylori*-infected patients became negative.

Some limitations of this meta-analysis need to be acknowledged. First of all, our conclusions can only be as accurate as the trials upon which they are based. Of note, in this review, we have included only one randomized study and 16 observational cohort studies. Though observational studies may lack the experimental

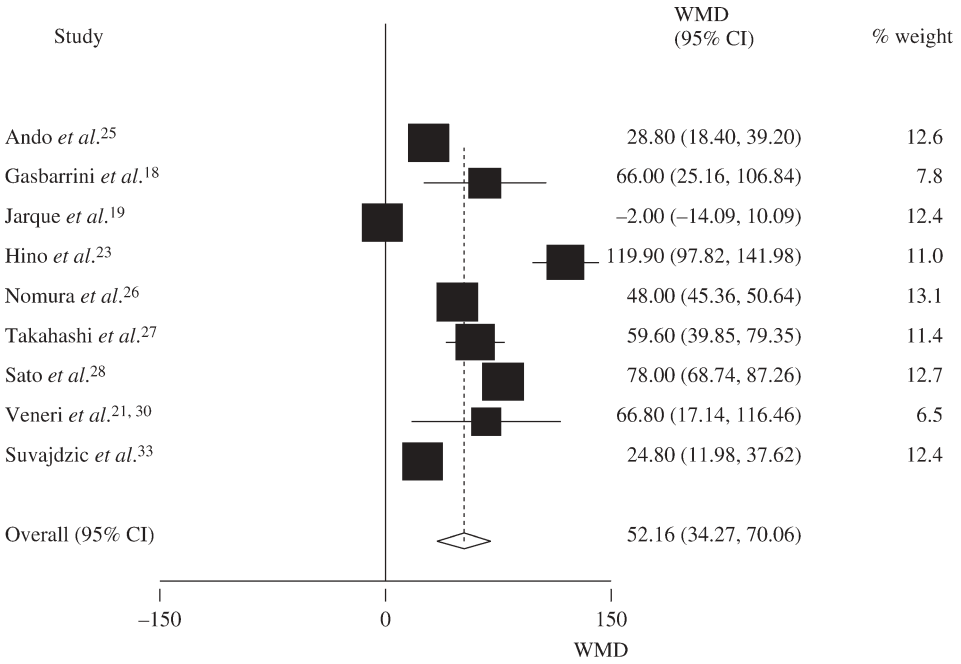


**Figure 3.** DerSimonian and Laird meta-analytical WMDs in nine studies (identified by first author) reporting platelet count (no. of cells $\times 10^9$/L) in ITP *H. pylori*-positive patients in whom eradication was successful and in *H. pylori*-positive patients in whom eradication was not successful. Patients in whom eradication was successful had an increase in platelet count from baseline significantly higher than control group (overall effect, $z = 5.71$, $P < 0.0001$). Test for heterogeneity: $\chi^2 = 174.77$ (d.f. = 8) $P < 0.0001$; $I^2 = 0.959$ (95% CI, 0.939–0.973). Estimate of between-study variance $\tau^2 = 632.159$.

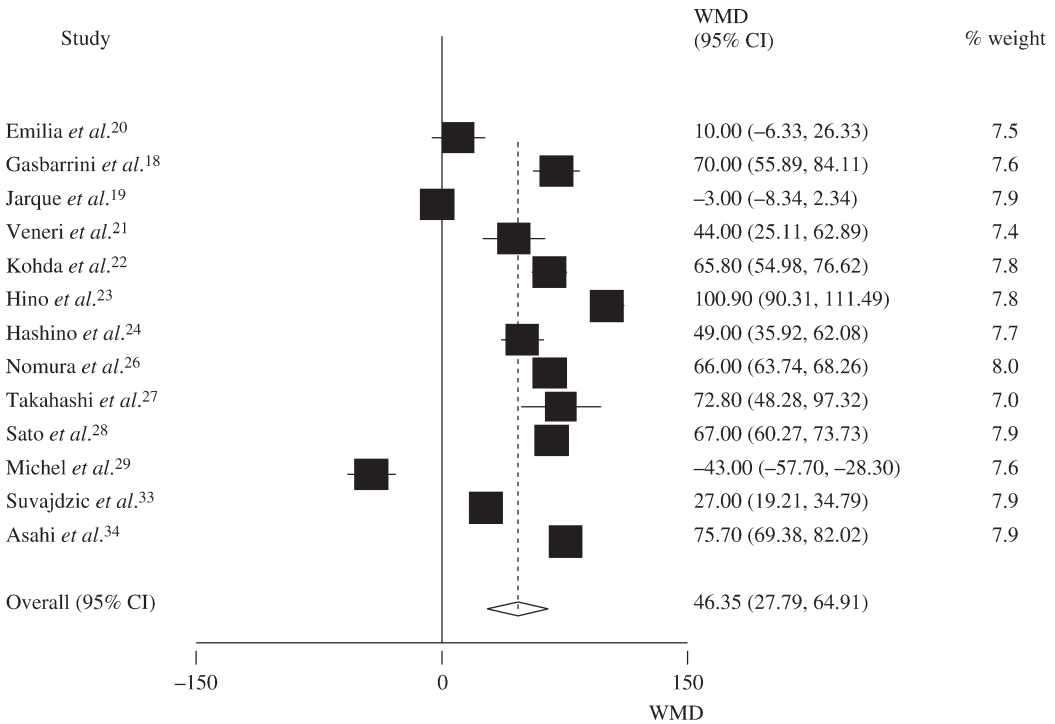


**Figure 4.** DerSimonian and Laird meta-analytical WMDs in 13 studies (identified by first author) reporting platelet count (no. of cells $\times 10^9$/L) in ITP *H. pylori*-positive patients in whom eradication was successful and in *H. pylori*-negative patients. Patients in whom eradication was successful had an increase in platelet count from baseline significantly higher than control group (overall effect, $z = 4.90$, $P < 0.0001$). Test for heterogeneity: $\chi^2 = 930.58$ (d.f. = 12) $P < 0.0001$; $I^2 = 0.988$ (95% CI, 0.985–0.990). Estimate of between-study variance $\tau^2 = 1100$.

element of a random allocation to an intervention, they can be regarded as a useful tool in order to assess the effectiveness of an intervention in a community as opposed to the special setting of controlled trials.[38] In the same way, although meta-analyses restricted to randomized clinical trials are usually preferred to meta-analyses of observational studies, the number of published

**Table 3.** DerSimonian and Laird pooled WMDs comparison between different subgroups of ITP patients (in all possible comparisons, an increase in platelet count from baseline was observed in *H. pylori* eradicated patients compared with controls)

| Comparison | No. of studies (no. of patients) included in the comparison | WMD (95% CI) in platelet count (no. of cells $\times 10^9$/L) | *P* value for the WMD test | *P* value for heterogeneity ($\chi^2$) |
|---|---|---|---|---|
| *H. pylori* treated (eradicated and not) versus *H. pylori* untreated | 3 (128) | 33.95 (20.48–47.42) | <0.0001 | <0.0001 |
| *H. pylori* eradicated versus *H. pylori* untreated | 3 (114) | 40.777 (20.923–60.631) | <0.0001 | <0.0001 |
| *H. pylori* eradicated versus *H. pylori* treated without eradication | 9 (241) | 52.163 (34.269–70.058) | <0.0001 | <0.0001 |
| | 13 (422) | 46.351 (27.792–64.910) | <0.0001 | <0.0001 |

**Table 4.** Meta-regression on WMD in platelet counts, random effects model

| Explanatory variables | Coefficient | SE | *t* | *P* value | 95% CI | |
|---|---|---|---|---|---|---|
| *H. pylori* | −13.279 | 14.37362 | −0.92 | 0.361 | −42.3769 | 15.81891 |
| Anti-*H. pylori* treatment | 3.118287 | 15.56975 | 0.2 | 0.842 | −28.401 | 34.63761 |
| Successful anti-*H. pylori* eradication | 56.2282 | 11.60967 | 4.84 | 0.000 | 32.72566 | 79.73075 |
| Intercept | 15.32359 | 7.148554 | 2.14 | 0.039 | 0.852101 | 29.79508 |

The continuous dependent variable was the WMD in platelet counts (count at the discharge minus count at the admission into hospital). The model was fitted with three arm-level, binary covariates, *H. pylori* (yes/no), antibiotic anti-*H. pylori* treatment (yes/no) and successful *H. pylori* eradication (yes/no). An increase in platelet count was predicted by successful (*H. pylori* eradicating) treatment, whereas the simple presence of *H. pylori*, or the simple anti-*H. pylori* treatment (unlinked to successful outcome), exerted no significant effect on platelet count. Number of studies = 42; fit of model without heterogeneity ($\tau^2 = 0$): $\chi^2$ (38 d.f.) = 254.818; ($P > \chi^2 = 0.000$). Proportion of variation due to heterogeneity, $I^2 = 0.851$. Random effects maximum likelihood estimate of between-study variance: $\tau^2 = 528.3991$.

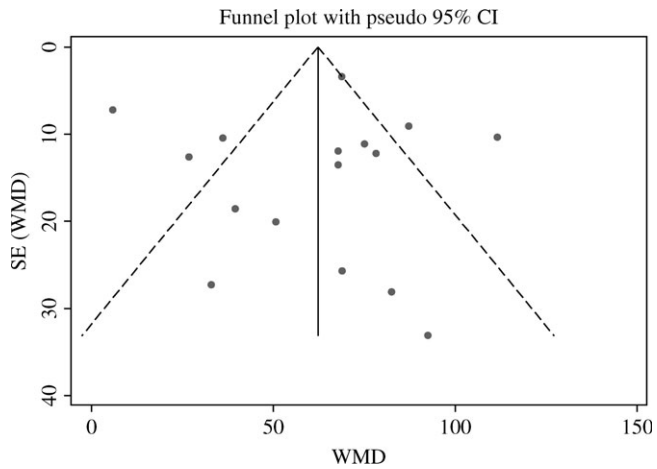


**Figure 5**. Begg's funnel plot with pseudo 95% for subgroups of studies reporting the outcome in *H. pylori*-infected patients who responded to eradication therapy. For each study, the natural logarithm of the WMD is plotted against its standard error. The funnel plot suggests no significant asymmetry, indicating no evidence of substantial publication bias.

meta-analyses in relation to observational studies has increased considerably in the last years.[39,40] This is not surprising, since in several instances the available clinical evidence relies upon observational studies rather than on randomized trials.

There was a significant heterogeneity in the studies analysed. The statistical heterogeneity was addressed by using a random effect model. Moreover, in order to explain the heterogeneity, a meta-regression model fitted with arm-level covariates was used.

Publication bias is a significant threat to the validity of meta-analysis. In the present meta-analysis, evidence of publication bias with graphical and statistical methods was not detectable for the outcome of interest. The absence of evidence of publication bias suggests that the conclusions we can drawn from these data are realistically robust.

After the first report by Gasbarrini *et al.*[18] several other authors have documented a correlation between *H. pylori* infection and many cases of ITP as the bacterium eradication was accompanied by a rise of platelet count. By contrast other authors did not confirm these positive results.[41] A difference in bacterial strains or genetic differences among the population of the various studies were advocated by some authors to explain the discrepancy of platelet response observed in the literature.[42,43] However, a number of studies have documented an association between *H. pylori* infection and a subset of ITP. In fact, Takahashi *et al.*[27] showed that platelet-associated immunoglobulins G from 12 out of the 18 ITP patients evaluated recognized the highly antigenic *H. pylori* CagA protein and that cross-reactive antibody levels decreased following *H. pylori* eradication in patients who showed a complete response. Franceschi *et al.*[44] reported follow-up data from eight previously reported ITP patients[18] and noted the occurrence of molecular mimicry

mechanisms between the CagA antigen and a similar platelet peptide of 55 kDa and the disappearance of anti-CagA antibodies in all eight platelet responders eradicated for *H. pylori*. Thus, these data suggest that cross-reacting autoantibodies against CagA may play a pathogenic role in at least some patients with ITP. Another point supporting the autoimmune hypothesis of ITP associated with *H. pylori* infection is that some authors have studied the presence of autoantibodies against platelets in ITP *H. pylori*-infected patients and have found that bacterial eradication and platelet recovery were accompanied by the disappearance of autoantibodies in most cases.[22,34]

In accordance with these findings, the results of this meta-analysis suggest a correlation between *H. pylori* infection and ITP with a positive effect of bacterium eradication on platelet count.

However, due to intrinsic limits in the design of the studies analysed, further evidence from randomized clinical trials comparing standard ITP therapy with standard ITP therapy plus eradication of *H. pylori* is required to confirm the effect of eradication treatment on platelet count.

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## Transparency declarations

None to declare.

## Supplementary data

Table S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

## References

**1.** Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med* 2002; **346**: 995–1008.

**2.** Franchini M, Veneri D. *Helicobacter pylori* infection and immune thrombocytopenic purpura: an update. *Helicobacter* 2004; **9**: 342–6.

**3.** Fujimura K. *Helicobacter pylori* infection and idiopathic thrombocytopenic purpura. *Int J Hematol* 2005; **81**: 113–8.

**4.** Emilia G, Luppi M, Torelli G. Infectious agents and human immune diseases: lessons from *Helicobacter pylori*. *Am J Med* 2005; **118**: 420–1.

**5.** Franchini M, Veneri D. *Helicobacter pylori* infection and immune thrombocytopenic purpura. *Haematologica* 2003; **88**: 1087–91.

**6.** Huber MR, Kumar S, Tefferi A. Treatment advances in adult immune thrombocytopenic purpura. *Ann Hematol* 2003; **82**: 723–7.

**7.** Kurtoglu E, Kayacetin E, Ugur A. *Helicobacter pylori* infection in patients with autoimmune thrombocytopenic purpura. *World J Gastroenterol* 2004; **10**: 2113–5.

**8.** Jackson S, Beck PL, Pineo GF *et al*. *Helicobacter pylori* eradication: novel therapy for immune thrombocytopenic purpura? A review of the literature. *Am J Hematol* 2005; **78**: 142–50.

**9.** George JN, Woolf SH, Raskob GE *et al*. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 1996; **88**: 3–40.

**10.** Wells GA, Shea B, O'Connell D *et al*. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. http://www.ohri.ca/programs/clinical_epidemiology/nosgen.doc (30 October 2006, date last accessed).

**11.** Tleyjeh IM, Tlaygeh HM, Hejal R *et al*. The impact of penicillin resistance on short-term mortality in hospitalized adults with pneumococcal pneumonia: a systematic review and meta-analysis. *Clin Infect Dis* 2006; **42**: 788–97.

**12.** Jadad AR, Moore RA, Carroll D *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12.

**13.** Dersimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–88.

**14.** Egger M, Davey Smith G, Schneider M *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–34.

**15.** Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088–11.

**16.** Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954; **10**: 101–29.

**17.** Higgins J, Thompson S, Deeks J *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–60.

**18.** Gasbarrini A, Franceschi F, Tartaglione R *et al*. Regression of autoimmune thrombocytopenia after eradication of *Helicobacter pylori*. *Lancet* 1998; **352**: 878.

**19.** Jarque I, Andreu R, Llopis I *et al*. Absence of platelet response after eradication of *Helicobacter pylori* infection in patients with chronic idiopathic thrombocytopenic purpura. *Br J Haematol* 2001; **115**: 1002–3.

**20.** Emilia G, Longo G, Luppi M *et al*. *Helicobacter pylori* eradication can induce platelet recovery in idiopathic thrombocytopenic purpura. *Blood* 2001; **97**: 812–4.

**21.** Veneri D, Franchini M, Gottardi M *et al*. Efficacy of *Helicobacter pylori* eradication in enhancing platelet count in adult patients with idiopathic thrombocytopenic purpura. *Haematologica* 2002; **87**: 1777–9.

**22.** Kohda K, Kuga T, Kogawa K *et al*. Effect of *Helicobacter pylori* eradication on platelet recovery in Japanese patients with chronic idiopathic thrombocytopenic purpura and secondary autoimmune thrombocytopenic purpura. *Br J Haematol* 2002; **118**: 584–8.

**23.** Hino M, Yamane T, Park K *et al*. Platelet recovery after eradication of *Helicobacter pylori* in patients with idiopathic thrombocytopenic purpura. *Ann Hematol* 2003; **82**: 30–2.

**24.** Hashino S, Mori A, Suzuki S *et al*. Platelet recovery in patients with idiopathic thrombocytopenic purpura after eradication of *Helicobacter pylori*. *Int J Hematol* 2003; **77**: 188–91.

**25.** Ando K, Shimamoto T, Tauchi T *et al*. Can eradication therapy for *Helicobacter pylori* really improve the thrombocytopenia in idiopathic thrombocytopenic purpura? Our experience and literature review. *Int J Hematol* 2003; **77**: 239–44.

**26.** Nomura S, Inami N, Kanazawa S. The effects of *Helicobacter pylori* eradication on chemokine production in patients with immune thrombocytopenic purpura. *Eur J Haematol* 2004; **72**: 304–5.

**27.** Takahashi T, Yujiri T, Shinohara K *et al*. Molecular mimicry by *Helicobacter pylori* CagA protein may be involved in the pathogenesis of *H. pylori*-associated chronic idiopathic thrombocytopenic purpura. *Br J Haematol* 2004; **124**: 91–6.

**28.** Sato R, Murakami K, Watanabe K *et al*. Effect of *Helicobacter pylori* eradication on platelet recovery in patients with chronic idiopathic thrombocytopenic purpura. *Arch Intern Med* 2004; **164**: 1904–7.

**29.** Michel M, Cooper N, Jean C *et al*. Does *Helicobacter pylori* initiate or perpetuate immune throbocytopenic purpura? *Blood* 2004; **103**: 890–6.

**30.** Veneri V, Krampera M, Franchini M. High prevalence of sustained remission of idiopathic thrombocytopenic purpura after *Helicobacter pylori* eradication: a long-term follow-up study. *Platelets* 2005; **16**: 117–9.

**31.** Stasi R, Rossi Z, Stipa E *et al*. *Helicobacter pylori* eradication in the management of patients with idiopathic thrombocytopenic purpura. *Am J Med* 2005; **118**: 414–9.

**32.** Suzuki T, Matsushima M, Masui A *et al*. Effect of *Helicobacter pylori* eradication in patients with chronic idiopathic thrombocytopenic purpura—a randomized controlled trial. *Am J Gastroenterol* 2005; **100**: 1265–70.

**33.** Suvajdzic N, Stankovic B, Artiko V *et al*. *Helicobacter pylori* eradication can induce platelet recovery in chronic idiopathic thrombocytopenic purpura. *Platelets* 2006; **17**: 227–30.

**34.** Asahi N, Kuwana M, Suzuki H *et al*. Effects of a *Helicobacter pylori* eradication regimen on anti-platelet autoantibody response in infected and uninfected patients with idiopathic thrombocytopenic purpura. *Haematologica* 2006; **91**: 1436–7.

**35.** Russo A, Eboli M, Pizzetti P *et al*. Determination of *Helicobacter pylori* seroprevalence among Italian blood donors. *Eur J Gastroenterol Hepatol* 1999; **11**: 867–73.

**36.** Graham DY, Malaty HM, Evans DG *et al*. Epidemiology of *Helicobacter pylori* in a asymptomatic population in the United States. Effect of age, race and socioeconomic status. *Gastroenterology* 1991; **100**: 1495–501.

**37.** Everhart JE, Kruszon-Moran D, Perez-Perez GI *et al*. Seroprevalence and ethnic differences in *Helicobacter pylori* infection among adults in the United States. *J Infect Dis* 2000; **181**: 1359–63.

**38.** Moayyedi P. Meta-analysis: can we mix apples and oranges? *Am J Gastroenterol* 2004; **99**: 2297–301.

**39.** Stroup DF, Berlin JA, Morton SC *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008–12.

**40.** Lau J, Ioannidis JP, Schmid CH. Summing up evidence: one answer is not always enough. *Lancet* 1998; **35**: 123–7.

**41.** Franchini M, Veneri D. *Helicobacter pylori*-associated immune thrombocytopenia. *Platelets* 2006; **17**: 71–7.

**42.** Takahashi T, Yujiri T, Tanizawa Y. *Helicobacter pylori* and chronic ITP: the discrepancy in the clinical responses to eradication therapy might be due to differences in the bacterial strains. *Blood* 2004; **104**: 594.

**43.** Veneri D, Gottardi M, Guizzardi E *et al*. Idiopathic thombocytopenic purpura, *Helicobacter pylori* infection and HLA class II alleles. *Blood* 2002; **100**: 1926–7.

**44.** Franceschi F, Christodoulides N, Kroll MH *et al*. *Helicobacter pylori* and idiopathic thrombocytopenic purpura. *Ann Intern Med* 2004; **140**: 766–7.