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 × 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 reviews2,3,5,8 have been published so far on the association between *H. pylori* and
thrombocytopenia, none had systematically reviewed the literature 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; (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 patients receiving or not receiving eradication therapy and the number of -uninfected patients; the number of ITP patients, the number of

Quality assessment

The methodological quality of cohort studies was assessed using an application of the Newcastle–Ottawa quality assessment scale for cohort studies. 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. 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. 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. The statistical methods for detecting funnel plot asymmetry were the rank correlation tests of Begg and Mazumdar and the regression asymmetry test of Egger et al.

The heterogeneity of study results was assessed by the Cochran’s Q and by a test of inconsistency (I²).

Results

Description of studies and methodological quality

Among the 17 studies considered for this systematic review, 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.

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There were 16 prospective cohort studies and one 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 × 10⁹/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-

Systematic review

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 × 10⁹/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 × 10⁹/L) than that observed in H. pylori-positive patients after bacterium eradication (average increase 61 × 10⁹/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

<table>
<thead>
<tr>
<th>Reference</th>
<th>total</th>
<th>age $^a$</th>
<th>male/female</th>
<th>disease duration $^{a,b}$</th>
<th>previous therapy $^c$</th>
<th>concomitant therapy $^c$</th>
<th>HP-positive</th>
<th>HP-negative</th>
<th>eradication therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>success</td>
<td>failure</td>
<td>untreated</td>
</tr>
<tr>
<td>Gasbarrini et al. $^{18}$</td>
<td>18</td>
<td>45</td>
<td>5/13</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>11/18 (61.1)</td>
<td>7/18 (38.9)</td>
<td>8/11 (72.7) 3/11 (27.3) 0</td>
</tr>
<tr>
<td>Jarque et al. $^{19}$</td>
<td>56</td>
<td>54</td>
<td>18/38</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>40/56 (71.4)</td>
<td>16/56 (28.6)</td>
<td>23/32 (71.9) 9/32 (28.1) 0</td>
</tr>
<tr>
<td>Emilia et al. $^{20}$</td>
<td>30</td>
<td>50.3</td>
<td>13/17</td>
<td>39.6</td>
<td>23/30 (76.7)</td>
<td>NR</td>
<td>13/30 (43.3)</td>
<td>17/30 (56.7)</td>
<td>12/13 (92.3) 1/13 (7.7) 0</td>
</tr>
<tr>
<td>Veneri et al. $^{21}$</td>
<td>35</td>
<td>55</td>
<td>12/23</td>
<td>16.4</td>
<td>9/16 (56.2)$^d$</td>
<td>0/16$^d$</td>
<td>25/35 (71.4)</td>
<td>10/35 (28.6)</td>
<td>15/16 (93.7) 1/16 (6.3) 0</td>
</tr>
<tr>
<td>Kohda et al. $^{22}$</td>
<td>40</td>
<td>52.7</td>
<td>12/28</td>
<td>44.4</td>
<td>27/40 (67.5)</td>
<td>19/40 (47.5)</td>
<td>25/40 (62.5)</td>
<td>15/40 (37.5)</td>
<td>19/19 (100) 0/19 6/25 (24.0)</td>
</tr>
<tr>
<td>Hino et al. $^{23}$</td>
<td>30</td>
<td>54.1</td>
<td>8/22</td>
<td>NR</td>
<td>12/30 (40.0)</td>
<td>7/30 (23.3)</td>
<td>21/30 (70.0)</td>
<td>9/30 (30.0)</td>
<td>18/21 (85.7) 3/21 (14.3) 0</td>
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<tr>
<td>Hashino et al. $^{24}$</td>
<td>22</td>
<td>49.1</td>
<td>4/18</td>
<td>109.8</td>
<td>14/22 (63.6)</td>
<td>8/22 (36.4)</td>
<td>14/22 (63.6)</td>
<td>8/22 (36.4)</td>
<td>13/14 (92.9) 1/14 (7.1) 0</td>
</tr>
<tr>
<td>Ando et al. $^{25}$</td>
<td>61</td>
<td>54.8</td>
<td>12/49</td>
<td>76.3</td>
<td>23/61 (37.7)</td>
<td>NR</td>
<td>50/61 (82.0)</td>
<td>11/61 (18.0)</td>
<td>27/29 (93.1) 2/29 (6.9) 21/50 (42.0)</td>
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<tr>
<td>Nomura et al. $^{26}$</td>
<td>42</td>
<td>NR</td>
<td>15/27</td>
<td>NR</td>
<td>21/42 (50.0)</td>
<td>NR</td>
<td>28/42 (66.7)</td>
<td>14/42 (33.3)</td>
<td>12/28 (42.9) 16/28 (57.1) 0</td>
</tr>
<tr>
<td>Takahashi et al. $^{27}$</td>
<td>20</td>
<td>51.2</td>
<td>5/15</td>
<td>97.6</td>
<td>13/20 (60.0)</td>
<td>NR</td>
<td>15/20 (75.0)</td>
<td>5/20 (25.0)</td>
<td>13/15 (86.7) 2/15 (13.3) 0</td>
</tr>
<tr>
<td>Sato et al. $^{28}$</td>
<td>53</td>
<td>59.5</td>
<td>16/37</td>
<td>78.5</td>
<td>10/53 (18.9)</td>
<td>27/53 (50.9)</td>
<td>39/53 (73.6)</td>
<td>14/53 (26.4)</td>
<td>27/32 (84.4) 5/32 (15.6) 7/39 (17.9)</td>
</tr>
<tr>
<td>Michel et al. $^{29}$</td>
<td>74</td>
<td>41</td>
<td>24/50</td>
<td>86.4</td>
<td>24/25 (96.0)$^f$</td>
<td>9/25 (36.0)$^f$</td>
<td>16/74 (21.6)</td>
<td>58/74 (78.4)</td>
<td>14/15 (93.3) 1/15 (6.7) 1/16 (6.2)</td>
</tr>
<tr>
<td>Veneri et al. $^{30}$</td>
<td>43</td>
<td>52.1</td>
<td>18/25</td>
<td>NR</td>
<td>14/43 (32.6)</td>
<td>0/21</td>
<td>43/43</td>
<td>0/43</td>
<td>41/43 (95.3) 2/43 (4.7) 0</td>
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<tr>
<td>Stasi et al. $^{31}$</td>
<td>137</td>
<td>51</td>
<td>57/80</td>
<td>24.5</td>
<td>70/137 (51.1)</td>
<td>16/52 (30.8)</td>
<td>64/137(46.7)</td>
<td>73/137 (53.3)</td>
<td>52/52 (100) 0/52 12/64 (18.7)</td>
</tr>
<tr>
<td>Suzuki et al. $^{32}$</td>
<td>36</td>
<td>56.8</td>
<td>14/22</td>
<td>62.7</td>
<td>10/25 (40.0)$^g$</td>
<td>NR</td>
<td>25/36 (69.4)</td>
<td>11/36 (30.6)</td>
<td>11/13 (84.6) 2/13 (15.4) 12/25 (48.0)</td>
</tr>
<tr>
<td>Suvajdzic et al. $^{33}$</td>
<td>54</td>
<td>51</td>
<td>12/42</td>
<td>72</td>
<td>19/30 (63.3)$^b$</td>
<td>0/54</td>
<td>39/54 (72.2)</td>
<td>15/54 (27.8)</td>
<td>23/30 (76.7) 7/30 (23.3) 9/39 (23.1)</td>
</tr>
<tr>
<td>Asahi et al. $^{34}$</td>
<td>37</td>
<td>NR</td>
<td>14/23</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>26/37 (70.3)</td>
<td>11/37 (29.7)</td>
<td>26/26 (100) 0/26 0</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Basal platelet count ($\times 10^9$/L)</th>
<th>Platelet count at the end of follow-up$^a$ ($\times 10^9$/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HP-positive—eradication therapy</td>
<td>HP-positive—eradication therapy</td>
</tr>
<tr>
<td></td>
<td>total</td>
<td>success</td>
</tr>
<tr>
<td>Gasbarrini et al. $^{18}$</td>
<td>95.0 (±28.9)</td>
<td>85.0 (±24.0)</td>
</tr>
<tr>
<td>Jarque et al. $^{19}$</td>
<td>58.4 (±24.5)</td>
<td>57.0 (±22)</td>
</tr>
<tr>
<td>Emilia et al. $^{20}$</td>
<td>52.5 (±25.0)</td>
<td>50.2 (±24.6)</td>
</tr>
<tr>
<td>Veneri et al. $^{21}$</td>
<td>51.9 (±27.2)</td>
<td>51.7 (±27.8)</td>
</tr>
<tr>
<td>Nottola et al. $^{22}$</td>
<td>67.1 (±54.2)</td>
<td>67.1 (±54.2)</td>
</tr>
<tr>
<td>Hino et al. $^{23}$</td>
<td>36.8 (±20.7)</td>
<td>40.5 (±16.3)</td>
</tr>
<tr>
<td>Hashino et al. $^{24}$</td>
<td>58.2 (±30.4)</td>
<td>59.1 (±32.5)</td>
</tr>
<tr>
<td>Ando et al. $^{25}$</td>
<td>56.0 (±24.0)</td>
<td>60.9 (±24.9)</td>
</tr>
<tr>
<td>Nomura et al. $^{26}$</td>
<td>29.0 (±6.0)</td>
<td>27.0 (±5.0)</td>
</tr>
<tr>
<td>Takahashi et al. $^{27}$</td>
<td>39.9 (±26.7)</td>
<td>41.8 (±28.3)</td>
</tr>
<tr>
<td>Sato et al. $^{28}$</td>
<td>54.0 (±17.5)</td>
<td>53.0 (±20.0)</td>
</tr>
<tr>
<td>Michel et al. $^{29}$</td>
<td>32.1 (±14.9)</td>
<td>31.7 (±14.2)</td>
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<td>Veneri et al. $^{30}$</td>
<td>54.3 (±28.7)</td>
<td>55.1 (±26.2)</td>
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<tr>
<td>Stasi et al. $^{31}$</td>
<td>42.0 (±25.0)</td>
<td>42.0 (±25.0)</td>
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<tr>
<td>Suzuki et al. $^{32}$</td>
<td>54.7 (±26.9)</td>
<td>54.7 (±26.9)</td>
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<tr>
<td>Suvajdzic et al. $^{33}$</td>
<td>63.0 (±33.5)</td>
<td>59.2 (±34.2)</td>
</tr>
<tr>
<td>Asahi et al. $^{34}$</td>
<td>35.2 (±13.1)</td>
<td>35.2 (±13.1)</td>
</tr>
</tbody>
</table>

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.

$^c$At least 4 months after eradication therapy.

$^d$Data refer to 10 *H. pylori*-negative patients who underwent eradication therapy.

$^e$All patients, *H. pylori*-positive and -negative, were treated with eradication therapy.

$^f$Follow-up data refer to 10 *H. pylori*-negative patients who underwent eradication therapy.
to that found in the healthy population according to the different geographical areas. 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

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**Figure 2.** DerSimonian and Laird meta-analytical WMDs in three studies (identified by first author) reporting platelet count (no. of cells × 10⁹/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 \( t^2 = 129.90 \). (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 \( t^2 = 290.624 \).
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. 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)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies (no. of patients) included in the comparison</th>
<th>WMD (95% CI) in platelet count (no. of cells × 10^9/L)</th>
<th>P value for the WMD test</th>
<th>P value for heterogeneity (χ^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. pylori</em> treated (eradicated and not) versus <em>H. pylori</em> untreated</td>
<td>3 (128)</td>
<td>33.95 (20.48–47.42)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><em>H. pylori</em> eradicated versus <em>H. pylori</em> untreated</td>
<td>3 (114)</td>
<td>40.777 (20.923–60.631)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><em>H. pylori</em> eradicated versus <em>H. pylori</em> treated without eradication</td>
<td>9 (241)</td>
<td>52.163 (34.269–70.058)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>13 (422)</td>
<td>46.351 (27.792–64.910)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Explanatory variables</th>
<th>Coefficient</th>
<th>SE</th>
<th>t</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. pylori</em></td>
<td>−13.279</td>
<td>14.37362</td>
<td>−0.92</td>
<td>0.361</td>
<td>−42.3769</td>
</tr>
<tr>
<td>Anti-<em>H. pylori</em> treatment</td>
<td>3.118287</td>
<td>15.56975</td>
<td>0.2</td>
<td>0.842</td>
<td>−28.401</td>
</tr>
<tr>
<td>Successful anti-<em>H. pylori</em> eradication</td>
<td>56.2282</td>
<td>11.60967</td>
<td>4.84</td>
<td>0.000</td>
<td>32.72566</td>
</tr>
<tr>
<td>Intercept</td>
<td>15.32359</td>
<td>7.148554</td>
<td>2.14</td>
<td>0.039</td>
<td>8.52101</td>
</tr>
</tbody>
</table>

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 (τ^2 = 0); χ^2 (38 d.f.) = 254.818; (P > χ^2 = 0.000). Proportion of variation due to heterogeneity, I^2 = 0.851. Random effects maximum likelihood estimate of between-study variance: τ^2 = 528.3991.

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 draw 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 patients18 and noted the occurrence of molecular mimicry 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.
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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**Supplementary data**

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

**References**


