Helicobacter pylori infection and immune thrombocytopenic purpura

*Helicobacter pylori* is a recently re-discovered Gram-negative bacterium which has revolutionized the understanding of the pathogenesis of peptic ulcer disease and hence its treatment.1 *H. pylori* is etiologically related to many digestive tract diseases including peptic ulcer disease, chronic active gastritis, primary low-grade B cell gastric lymphoma and gastric carcinoma.2,3 The seroprevalence of *H. pylori* has also been investigated in many other diseases and a positive correlation has been found in an increasing number of conditions outside the digestive tract, such as cardiovascular, respiratory, neurological, skin and autoimmune disorders.4,5 These last include rheumatoid arthritis, autoimmune thyroiditis and autoimmune neutropenia. The interaction between *H. pylori* and the immune system was also confirmed by recent studies that reported an association between *H. pylori* infection and idiopathic thrombocytopenic purpura (ITP) and, in many cases, a significant increase in platelet count after bacterial eradication.4,7 The relationship between infection with *H. pylori* and the development of ITP opens a new exciting and controversial area of investigation with important implications for both pathogenesis and patients' management. However, the data reported in literature are limited4,24 and mostly regard single case reports or small series of patients so that the evi-
Evidence of a link between \textit{H. pylori} and ITP remains speculative. The aim of this concise review was to consider the studies so far published on \textit{H. pylori} infection and ITP in order to evaluate the seroprevalence of \textit{H. pylori} infection and the response to eradication treatment in ITP patients and to clarify, if possible, the role of this bacterium in the pathogenesis of immune thrombocytopenic purpura.

Source of materials

This review collects the studies so far published in the medical literature on ITP and \textit{Helicobacter pylori} infection. MedLine reports from January 1998 to June 2003 were searched via PubMed using the following terms: ‘thrombocytopenia’, ‘autoimmune thrombocytopenic purpura’, ‘immune thrombocytopenic purpura’, ‘idiopathic thrombocytopenic purpura’, and ‘ITP’. All these terms were searched for alone and in combination with ‘therapy’, ‘infection’, ‘\textit{Helicobacter pylori} infection’, ‘\textit{Helicobacter pylori} infection’, and ‘\textit{H. pylori} infection’. This search generated 31 references, 16 of which reported bacterial seroprevalence and the results of eradication treatment in adult ITP patients infected by \textit{H. pylori}. These studies are listed chronologically in Table 1.

Prevalence of \textit{Helicobacter pylori} infection in ITP patients

It is well known that seroprevalence of \textit{H. pylori} infection in otherwise healthy individuals varies greatly from country to country, that it has decreased over the last decades in industrialized countries and that it increases with age.

Table 1 summarizes the clinical data from the medical literature on ITP patients and \textit{H. pylori} infection, including the seroprevalence. Although

<table>
<thead>
<tr>
<th>Authors</th>
<th>Total number</th>
<th>Infected (%)</th>
<th>Bacterial eradication (%)</th>
<th>Platelet response (%)*</th>
<th>Median follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gusbamini et al. (1998)</td>
<td>18</td>
<td>11 (61.1)</td>
<td>8 (72.7)</td>
<td>8 (100.0)</td>
<td>4.0</td>
</tr>
<tr>
<td>Garcia Perez et al. (1999)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>32.0</td>
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<tr>
<td>Grimaz et al. (1999)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>21.0</td>
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<tr>
<td>Tohda et al. (2000)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6.0</td>
</tr>
<tr>
<td>Emilia et al. (2001)</td>
<td>30</td>
<td>13 (43.3)</td>
<td>12 (92.3)</td>
<td>6 (50.0)</td>
<td>8.3</td>
</tr>
<tr>
<td>Soldinger et al. (2001)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3.0</td>
</tr>
<tr>
<td>Jarque et al. (2001)</td>
<td>56</td>
<td>40 (71.4)</td>
<td>23/32 (71.9)†</td>
<td>3 (13.1)</td>
<td>24.0</td>
</tr>
<tr>
<td>Kumagai et al. (2001)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>32.0</td>
</tr>
<tr>
<td>Venere et al. (2002)</td>
<td>35</td>
<td>25 (71.4)</td>
<td>15/16 (93.7)‡</td>
<td>11 (73.3)</td>
<td>11.7</td>
</tr>
<tr>
<td>Emilia et al. (2002)</td>
<td>7</td>
<td>3 (42.9)</td>
<td>3 (100.0)</td>
<td>2 (66.7)</td>
<td>—</td>
</tr>
<tr>
<td>Kohda et al. (2002)</td>
<td>48</td>
<td>27 (56.2)</td>
<td>19/19 (100.0)§</td>
<td>12 (63.2)</td>
<td>14.8</td>
</tr>
<tr>
<td>Mukai et al. (2002)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>Michel et al. (2002)</td>
<td>51</td>
<td>15 (29.4)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hino et al. (2003)</td>
<td>30</td>
<td>21 (70.0)</td>
<td>18 (69.7)</td>
<td>10 (66.6)</td>
<td>15.0</td>
</tr>
<tr>
<td>Hashino et al. (2003)</td>
<td>22</td>
<td>14 (63.6)</td>
<td>13 (92.9)</td>
<td>5 (38.5)</td>
<td>15.0</td>
</tr>
<tr>
<td>Ando et al. (2003)</td>
<td>61</td>
<td>50 (82.0)</td>
<td>27/29 (93.1)¶</td>
<td>16 (59.2)</td>
<td>11.0</td>
</tr>
<tr>
<td>Total</td>
<td>365</td>
<td>226 (61.9)</td>
<td>145/165 (87.9)</td>
<td>80 (55.2)</td>
<td>14.0</td>
</tr>
</tbody>
</table>

*Complete or partial response. †Bacterial eradication was obtained in 23 of 32 treated patients (71.9%). ‡Bacterial eradication was obtained in 15 of 16 treated patients (93.7%). §Bacterial eradication was obtained in 19 of 19 treated patients (100.0%). ¶Bacterial eradication was obtained in 27 of 29 treated patients (93.1%).
the studies reported so far are few and regard small series of patients, most of the authors found a high prevalence of *H. pylori* infection in ITP patients. However, since the majority of previous studies involving a relatively large number of patients were conducted in Italy and Japan, in which the prevalence of *H. pylori* infection in the healthy population is high (>70% over the age of 50 years), the prevalence of *H. pylori* infection in ITP patients in these countries may not be different from the prevalence in the healthy population. Only one French study recorded a low prevalence (29%) of *H. pylori* infection in ITP patients, similar to that found in control subjects. Although this may reflect the great variability in the rate of infection in different areas, we must highlight that the authors chose the serologic antibody method to detect *H. pylori* infection. This assay does not necessarily indicate an active *H. pylori* infection, since antibody titer may remain positive for years after successful treatment, and is a more laborious and less reliable assay than the urea breath test, which was the method used in almost all the other reported studies. On the whole, even considering the study by Michel et al., 226 out of the 365 ITP patients studied (62%) so far have been found to have *H. pylori* infection. The data must be interpreted cautiously because of the variability in the rate of *H. pylori* infection in different areas and generations. In fact, in our opinion, for meaningful results, the seroprevalence in ITP patients must be compared with that in healthy populations in different geographical areas, corrected for age distribution. Individual cohorts should have their own regional, age-matched controls, although most of the previous studies did not have adequate controls.

**Pathogenesis of ITP associated with Helicobacter pylori infection**

We recently reported some other proof of the importance of *H. pylori* infection in the pathogenesis of ITP in a subset of adults. In fact, we found a difference in HLA class II allele patterns between ITP patients with or without *H. pylori* infection. Patients with ITP had a lower frequency of HLA-DRB1*11 and -DQB1*03 alleles than did healthy controls. Analyzing the ITP patients with respect to *H. pylori* infection, we observed that this low frequency was a typical feature of *H. pylori*-negative patients. Although this finding may contribute to stratifying different subgroups of ITP patients with probably different pathogenesises of thrombocytopenia and, finally, different responses to eradication treatment, it does not clarify the pathophysiology of immune thrombocytopenia associated with *H. pylori* infection. Some authors studied the presence of autoantibodies against platelets in ITP *H. pylori*-infected patients and found that bacterial eradication and platelet recovery were accompanied by the disappearance of autoantibodies in most cases. These results provide further support to the autoimmune hypothesis of ITP associated with *H. pylori* infection in which there would be a cross mimicry between *H. pylori* and platelet antigens. Michel and colleagues investigated this possible molecular mimicry by testing platelet eluates from *H. pylori*-positive patients with ITP for *H. pylori* antibodies, but none of the 3 patients investigated was found to be positive. However, this series seems too small to exclude a possible cross-reactivity between *H. pylori* antibodies and platelet–membrane antigens. Finally, another possible pathogenetic mechanism is the occurrence of a B-cell clonal expansion. In fact, on the basis of previous observations of the association between gastric extranodal marginal zone B-cell lymphoma and *H. pylori* infection and the regression of some cases after bacterial eradication, we cannot exclude a similar mechanism also for *H. pylori*-associated ITP. Thus, chronic *H. pylori* infection could stimulate the emergence of autoreactive clonal B cells producing platelet-reactive antibodies.

**Effect of Helicobacter pylori eradication on platelet count in ITP patients**

The first observations of a positive association between *H. pylori* infection and ITP and that eradication of the bacterium was accompanied by an increase in platelets in most cases were made by Gasbarrini and colleagues in 1998. Since then, many other authors have verified and, in the majority of cases, confirmed this intriguing preliminary observations. Table 1 lists these studies, analyzing platelet response after bacterial eradication. We do, however, advise caution in interpreting these data, since the patients enrolled in the studies, the bacterial eradication protocols, the evaluation of platelets response and the follow-up periods differed greatly from study to study and make comparisons of the results difficult. In spite of this caveat, it is clear that the majority of patients in whom *H. pylori* infection was eradicated subsequently had a platelet increase. In fact, 80 out of the 145 patients (55.2%) who became *H. pylori*-negative obtained a complete or partial platelet response. Among the studies including the largest series of patients, only Jarque and colleagues observed a very low platelet response (13%) after eradication of *H. pylori* infection in 56 adult patients with chronic ITP. Recently, we demonstrated that also *H. pylori*-positive ITP patients who relapse after steroid therapy and those with severe (<30 × 10^9/L) platelets, refractory ITP requiring continuous immuno-suppressive therapy may be rescued with this bacterial eradication treatment. In fact, 17 H. pylori eradication significantly increased the platelet count in 6 out of 9 such patients (66.7%) and dra-
matically improved these patients’ quality of life, liberating them from immunosuppressive therapy. Another important finding, which indirectly confirms the etiologic role of *H. pylori* in a subset of ITP patients, is that in the majority of the studies reported, platelet count did not differ before and after treatment in those patients in whom the bacterium was not eradicated. However, the data so far published indicate that bacteri(al eradication resolves the majority but not all cases of *H. pylori* positive ITP. The variability in the response rate to treatment, which could depend on an interaction between genetic host factors (HLA) and bacterial factors (strains), will be clarified when the pathogenesis of this condition becomes completely understood.

**Conclusions**

The data so far reported confirm the existence of an association between *H. pylori* infection and idiopathic thrombocytopenic purpura. The pathogenesis of ITP associated with *H. pylori* is still not well defined, but it seems that genetic host factors (i.e., the HLA class II system) and bacterial factors (i.e., the variability of *H. pylori* strains) may both play important roles. These factors may also account for the variability in the response to eradication treatment observed in ITP *H. pylori*-infected patients.

Although the data are still limited, there are clear indications that eradication of *H. pylori* has a beneficial effect on platelet recovery in ITP patients. In our opinion, these positive results justify placebo-controlled trials on larger numbers of patients.

Until the results of such trials are available, we advise investigation for *H. pylori* and bacterial eradication in all patients with chronic ITP found to have the infection, since this management may be sufficient to avoid the toxicity and disadvantages of long-term immunosuppressive treatments.

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**References**


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