# *Helicobacter pylori* eradication: a novel therapeutic option in chronic immune thrombocytopenic purpura

Vanaja Sivapathasingam, Michael P Harvey and Robert B Wilson


## ABSTRACT

**Objective:** To determine whether *Helicobacter pylori* eradication is an effective treatment for Australian patients with chronic immune thrombocytopenic purpura (ITP).

**Design, setting and patients:** Retrospective analysis of clinical records of a consecutive series of ITP patients referred to a gastrointestinal surgeon in a tertiary referral hospital for laparoscopic splenectomy between August 2005 and November 2007.

**Main outcome measures:** Platelet response (measured at least 3-monthly) following successful *H. pylori* eradication therapy (confirmed by urea breath test 4 weeks later).

**Results:** Of 16 patients, seven were *H. pylori*-negative and underwent laparoscopic splenectomy. Nine were *H. pylori*-positive and successfully underwent *H. pylori* eradication therapy; five of the nine had an initial platelet response. Four patients had platelet counts $> 100 \times 10^9$/L (reference range, 140–450 $\times 10^9$/L) and were off all immunosuppression at 9 months; three had a sustained response beyond 12 months. One patient had an initial response at 3 months ($15 \times 10^9$/L to $208 \times 10^9$/L), but relapsed 4 months after *H. pylori* eradication and underwent splenectomy with platelet count recovery. The remaining four patients showed no platelet response and subsequently underwent splenectomy.

**Conclusion:** Larger prospective studies are needed to fully ascertain the role of *H. pylori* in Australian patients with ITP. However, *H. pylori* eradication is simple and safe. *H. pylori* screening and eradication should be considered before immunosuppression or splenectomy.


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Immune thrombocytopenic purpura (ITP) is the most common autoimmune-mediated haematological disorder, characterised by antibodies against platelet surface antigens.[1] Its aetiology, pathogenesis and molecular receptor targets remain unclear. It has been associated with HIV infection and hepatitis C.[1]

*Helicobacter pylori* is a causative agent in a spectrum of gastrointestinal diseases, including peptic ulcer disease, gastric cancer and MALToma (mucosa-associated lymphoid tissue lymphoma). There is growing evidence of an association between *H. pylori* eradication and platelet recovery in patients with ITP.[2-6] The evidence is strongest in Japan, where *H. pylori* eradication is now recommended as an initial treatment for infected ITP patients.[7] Screening and eradication may be a simpler and safer therapeutic option than immunosuppression or splenectomy in certain ITP patients.[8,9] Most studies of *H. pylori* and ITP are from Japan, Spain and Italy; however, the British Society for Haematology now recommends *H. pylori* screening and eradication as a treatment in ITP (evidence level, III).[10] To date, there have been no published reports of such therapy in Australian patients. Local experience is important, given the potential regional variation in strains of *H. pylori*.

## METHODS

Sixteen consecutive patients (age range, 24–79 years) with ITP were referred to a single gastrointestinal surgeon (R B W) for laparoscopic splenectomy at a tertiary hospital between August 2005 and November 2007. All patients had been diagnosed with ITP following investigations by a haematologist, including abdominal computed tomography scan, bone marrow biopsy, HIV and hepatitis serological testing, and antibody testing for other autoimmune disorders such as rheumatoid arthritis, antiphospholipid syndrome and systemic lupus erythematosis.

We began routine testing for *H. pylori* in patients with ITP referred for splenectomy in August 2005. Testing was via gastroscopy, serological testing or urea breath test.[11] Patients were treated with standard triple therapy, comprising clarithromycin 500 mg, amoxycillin 1000 mg and oral esomeprazole 20 mg, all twice daily for 1 week. One patient was treated with metronidazole instead of amoxycillin due to penicillin allergy. Eradication was confirmed by urea breath test, with titres of isotope $^{14}C$ < 50 disintegrations/min 4 weeks after completion of triple therapy indicating a negative result. Patients who had previously undergone successful *H. pylori* eradication therapy were not treated again.

Platelet counts were measured at least 3-monthly after *H. pylori* eradication. ITP patients who were *H. pylori*-negative or whose platelet counts did not rise after *H. pylori* eradication underwent splenectomy.

## RESULTS

Clinical characteristics of the patients and their responses to treatment are summarised in Box 1.

Nine of 16 patients tested positive for *H. pylori* and all had successful eradication therapy. Of these, five patients showed an initial platelet response, and three of these showed a long-term (> 12 months) response and did not require immunosuppression or splenectomy (Box 2). Only one of these patients had initial severe ITP (platelet count, $4 \times 10^9$/L [reference range, 140–450 $\times 10^9$/L]). Two of three patients who tested positive for anticardiolipin or antinuclear antibodies also tested positive for *H. pylori* and did not have a sustained platelet response to *H. pylori* eradication.

Five patients who were *H. pylori*-positive (and the seven who were *H.pylori*-negative) had laparoscopic splenectomies between November 2005 and December 2007. There were no conversions to open surgery. Two patients who underwent splenectomy later relapsed, requiring recommencement of immunosuppression; both had achieved successful *H. pylori* eradication before splenectomy.

## DISCUSSION

This study found that *H. pylori* eradication was of long-term benefit in three of nine patients with ITP who were *H. pylori*-positive, leading to a sustained platelet

**1 Clinical characteristics of patients with immune thrombocytopenic purpura (ITP) referred for splenectomy, 2005–2007**

| Pt no. | Age, sex | Comorbidity* | Hp testing† | Serology‡ | ITP duration | Past treatment§ | Platelet count, $\times 10^9$/L (RR, 140–450 $\times 10^9$/L) Min | Referral | 3 mo | 6 mo | 9 mo | 12 mo | 15 mo | Current status |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Helicobacter pylori*-positive | | | | | | | | | | | | | | |
| 1 | 72, M | HT, GORD, GI bleed | CLO + | SLE –, RF – | > 2 y | Nil | 30 | 30 | 70 | 99 | — | 126 | 161 | Stable, no concurrent therapy |
| 2¶ | 60, M | AMI, HT, GORD | CLO + | nd | 2 y | Nil | 58 | 67 | 106 | 142 | 196 | 203 | 182 | Stable, no concurrent therapy |
| 3 | 42, F | GORD, uterine polyps | IgG + | ACA –, B2GA – | 22 y | Pred, az, rtx, dnzl | 4 | 24 | 223 | 237 | 204 | 194 | 177 | Stable, no immunosuppressants |
| 4 | 45, F | — | IgG + | ACA + (30), ANA + (40 titre), B2GA + (63), ENA –, dsDNAa – | 1 y | Pred, IgG | 4 | 15 | 280 | 34 | 30 | LS | 480 | Initial response to eradication, relapse after 3 mo requiring steroids. Stable, no immunosuppressants post-LS |
| 5 | 79, M | HT, diabetes, TIA, CRF | IgG + (130) | ACA –, B2GA – | 2 y | Pred | 7 | 40 | 105 | 74 | 108 | 37 | — | Relapsed after 9 mo; steroids recommenced |
| 6** | 26, M | Shingles | UBT + | B2GA –, dsDNAa –, RF –, ACA –, ENA –, ANA + (80) | 1 y | Pred | 18 | 95†† | — | LS | — | — | — | Stable, no immunosuppressants post-LS |
| 7** | 54, F | HT | IgG + (247) | ANA + (160 titre), ACA –, LA – | 16 mo | Pred, danocrine | 19 | 33†† | 19 | LS | | 148 | 34 | Relapsed post-LS; pred, dnzl recommenced |
| 8** | 75, M | AMI, CABG, HT, HC | IgG + | na | 15 y | Pred, IgG | 29 | 20–30†† | LS | | | 100 | 105 | Stable, no steroids |
| 9 | 24, F | — | IgG + | ANA + (320 titre), ENA –, dsDNAa –, ACA – | 6 mo | Pred, IgG | 2 | 20†† | LS | 200 | 34 | — | — | Relapsed post-LS, required steroids. Splenunculus identified, splenunculectomy performed |
| *H. pylori*-negative | | | | | | | | | | | | | | |
| 10 | 47, F | HT | IgG – | ANA –(1280 titre), ENA +, SSA +, dsDNAa – | 13 mo | Pred, az, dnzl | 49 | 64 | LS | 233 | — | — | — | Stable, no immunosuppressants post-LS |
| 11 | 41, F | GORD | IgG – | ACA – | 8 mo | Pred, az, dnzl | 11 | 4†† | LS | 408 | — | — | — | Stable, no immunosuppressants post-LS |
| 12 | 24, M | Asthma | IgG – | *Mycoplasma* antibody +, ACA –, B2GA –, LA – | 12 mo | Pred | 16 | 58†† | LS | 422 | — | — | — | Stable, no immunosuppressants post-LS |
| 13 | 23, F | Immune neutropenia, asthma | IgG – | na | 1 y | Pred, az, GCSF | 34 | 60 | LS | 422 | 37 | — | — | Relapsed; steroid recommenced |
| 14 | 40, F | — | IgG – | ANA (40), ENA –, ACA –, dsDNAa –, RF – | 13 mo | Pred | 24 | 44 | LS | 604 | — | — | — | Stable, no immunosuppressants post-LS |
| 15 | 72, F | Diabetes, HT | IgG – | B2GA – | 2 mo | Pred, az, dnzl | 27 | 70†† | LS | — | 427 | — | — | Stable, no immunosuppressants post-LS |
| 16 | 25, F | Infertility, GORD | CLO – | ACA –, LA –, B2GA – | 2 mo | Pred, az, dnzl | 40 | 40 | LS | — | — | 435 | — | Stable, no immunosuppressants post-LS |

Pt = patient. RR = reference range. Hp = *Helicobacter pylori*. nd = not done. na = not available. — = no result. LS = laparoscopic splenectomy.

* GORD = gastro-oesophageal reflux disease. GI = gastrointestinal. HT = hypertension. HC = hypercholesterolaemia. AMI = acute myocardial infarction. TIA = transient ischaemic attack. CRF = chronic renal failure. CABG = coronary artery bypass grafting. † CLO = *Campylobacter*-like organism test. IgG = Hp IgG (RR, < 20 U/mL). UBT = urea breath test (RR, $^{14}C$ < 50 disintegrations/min). ‡ SLE = systemic lupus erythematosis. RF = rheumatoid factor (RR, < 21 IU/mL). ACA = anticardiolipin antibody (RR, < 20 U/mL). ANA = antinuclear antibody (RR, < 40 U/mL). B2GA = β2 glycoprotein antibody (RR, < 20 U/mL). ENA = extractable nuclear antigen. dsDNAa = anti-double-stranded DNA antibody (RR, 0–7 kIU/L). SSA = Sjögren syndrome antibody. LA = lupus anticoagulant. § pred = prednisolone. az = azathioprine. rtx = rituximab, CD20 monoclonal antibody. dnzl = danazol. GCSF = granulocyte colony-stimulating factor.

¶ Pt began clopidogrel therapy following coronary artery stenting, but stopped it when platelet count fell, before Hp eradication. Platelet count continued to rise following Hp eradication and clopidogrel was recommenced, with no effect on platelet count. ** Pt had successful Hp eradication achieved with no platelet response at the time of referral by the respective haematologists. †† Platelet count boosted by increasing steroid therapy before surgical referral. ◆

response. Two other patients had a short-term response. *H. pylori* eradication appeared to be least successful in the context of severe ITP that had already been extensively treated. To our knowledge, this is the first published study of *H. pylori* eradication therapy in Australian ITP patients.

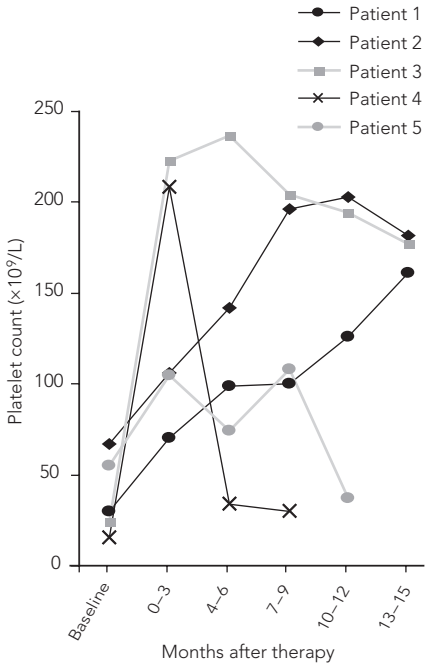
The association between ITP and *H. pylori* was first reported in 1998.[12] Possible aetiological links include molecular mimicry and cross-reactivity of bacterial and platelet antigens, in association with host factors such as specific human leukocyte antigen (HLA) class II alleles.[13,14] A recent Italian study found that the HLA-DRB1*11, -DRB1*14 and -DQB1*03 alleles occur significantly more often in *H. pylori*-infected ITP patients and indicate a higher probability of platelet response to eradication therapy.[15] ITP patients who had successful *H. pylori* eradication showed significantly decreased serum platelet-associated IgG levels, suggesting that removal of the *H. pylori* antigenic stimulus leads to platelet recovery.[9]

However, response rates have varied. A literature review of 13 major studies published between 1998 and 2004 revealed an overall platelet response rate of 52% following *H. pylori* eradication therapy when used as an adjunct to standard ITP therapy or in otherwise untreated cases.[5] Another review concluded that 58% of 482 patients with ITP were *H. pylori*-positive and, of these, more than 50% showed a significant platelet response to successful *H. pylori* eradication.[13] Long-term follow-up studies, including one with a median follow-up of 31 months, have also shown good results.[2,16,17] A large retrospective analysis in Japan yielded a platelet response rate as high as 63%, with remission sustained after 12 months, even among patients whose ITP was refractory to splenectomy.[7] A small randomised controlled trial, also in Japan, showed a significant increase in platelet count in the group who had successful eradication therapy.[3] Some studies showed that platelet recovery was better in less severe or recent-onset ITP,[18,19] or in the absence of concurrent steroid therapy.[20]

In contrast, several studies have refuted a significant association between *H. pylori* and ITP.[21-23] For example, a prospective study in the United States found that only one of 14 patients who responded to *H. pylori* eradication had a rise in platelet count.[21]

There is substantial variability in ITP response to *H. pylori* eradication in different countries.[5,18,20,24] This may be due to variations in bacterial virulence factors, such as CagA expression or host immunological class II HLA factors.[2,24] Most Japanese *H. pylori* strains are CagA-positive, unlike most American strains.[9] Patients infected with CagA-positive strains (as measured by anti-CagA IgG antibodies) are thought to have increased platelet response to *H. pylori* eradication compared with those who are CagA-negative or who have low serum titres of CagA antibodies.[3,5] Serum levels of anti-CagA IgG may be used as a predictor of response to *H. pylori* treatment.[2,25]

**2 Pattern of platelet response to successful *Helicobacter pylori* eradication in five patients with immune thrombocytopenic purpura who responded (reference range, 140–450 × $10^9$/L)**




The prevalence of *H. pylori* infection in ITP patients varies from 22% in a US study[21] to 47% in a study from the United Kingdom and Italy[19] to 71% in a Spanish study.[23] In a comparison of *H. pylori* and ITP data from the UK and Italy, the prevalence of *H. pylori* infection in patients with ITP appeared to be similar to that in the general population.[19] The prevalence of *H. pylori* infection in the general Australian population is 25%–38%,[26] but its prevalence in Australians with ITP is yet to be determined. In our series, 56% of ITP patients were *H. pylori*-positive.

The results in this small series support a role for *H. pylori* eradication in the treatment of patients with ITP in Australia. *H. pylori* screening and eradication should be considered in patients presenting with ITP, given the low cost and potential for avoidance of immunosuppression and splenectomy. Larger prospective studies are needed to fully ascertain the role of *H. pylori* in Australian patients with ITP.

## COMPETING INTERESTS

None identified.

## AUTHOR DETAILS

**Vanaja Sivapathasingam,** BSc(Med), MB BS(Hons), Basic Surgical Trainee,[1] and currently Ear, Nose and Throat and Head and Neck Surgery Trainee[2]
**Michael P Harvey,** PhD, FRACP, FRCPA, Haematologist[1]
**Robert B Wilson,** BSc, MB BS(Hons), FRACS, Upper Gastrointestinal Surgeon[1]
1 Liverpool Hospital, Sydney, NSW.
2 Monash Medical Centre, Melbourne, VIC.
*Correspondence:* Rbwilson52@hotmail.com

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