Effects of eradication of Helicobacter pylori infection in patients with immune thrombocytopenic purpura: a systematic review

CRD summary
The review found that detection and eradication of Helicobacter pylori infection should be considered for patients with apparently typical immune thrombocytopenia purpura. The review had limitations, including lack of controlled studies, poor reporting and inappropriate pooling of data. The reliability of the authors’ conclusions is unclear because effect estimates calculated in the review do not appear valid.

Authors’ objectives
To investigate the effects of Helicobacter pylori eradication on the platelet count of adults with immune thrombocytopenic purpura.

Searching
PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic reviews and DARE were searched in April 2008. Search terms were reported. Reference lists of articles retrieved were checked. The search was restricted to full-length papers published in English.

Study selection
Studies that evaluated the effects over time of Helicobacter pylori (H. pylori) eradication on the platelet count of at least 15 adults with immune thrombocytopenia purpura were eligible for inclusion. Studies were required to define immune thrombocytopenia purpura according to the American Society of Hematology guidelines, or to clearly rule out secondary causes of immune thrombocytopenia purpura. H. pylori was required to be diagnosed by a test showing active infection (e.g. C-urea breath test, stool antigen test, gastric biopsy). Studies validating H. pylori solely by serology were excluded.

The studies in the review included participants with immune thrombocytopenia purpura both with and without H. pylori infection; duration of immune thrombocytopenia purpura ranged from 19 months to 10 years (where reported). More than half of the studies were set in Japan. The mean age of participants with H. pylori was 58 years (where stated). More than half the participants received corticosteroids before eradication treatment for H. pylori (where stated). In most studies, eradication treatment consisted of combination therapy of amoxicillin, clarithromycin and a proton pump inhibitor. Co-interventions included conventional immune thrombocytopenia purpura treatments (e.g. corticosteroids, azathioprine, splenectomy).

Outcomes reported in the review were complete response (platelet count over 100x10⁹/L), overall response (platelet count over 30x10⁹/L and at least doubling the baseline count), time to response, response duration, predictors of response, and toxicity. In most studies the first assessment of platelet count was one month after treatment. No studies reported how many platelet counts were used to assess response. Median duration of follow-up for responding patients ranged from four to 43 months (where reported).

Two reviewers independently selected the studies, with disagreements resolved by consensus.

Assessment of study quality
Cohort studies were assessed using the Newcastle-Ottawa Scale, allocating up to 9 points for quality of selection methods, comparability of study groups and outcomes methods. Randomised controlled trials (RCTs) were assessed with the Jadad scale, with up to 5 points according to the adequacy of reported randomisation, double blinding, and withdrawals or drop-outs.

The authors did not state how many reviewers assessed study validity.
Data extraction
Data on response rates were extracted and reported as proportions. Patient-level data were used where available, otherwise group-level data were used. Response rates in primary studies were adjusted to comply with review definitions of platelet response, if necessary. Attempts were made to obtain extra information from primary study authors.

Two reviewers independently extracted the data, with disagreements resolved by consensus.

Methods of synthesis
Studies were combined using the DerSimonian and Laird random-effects model to calculate weighted mean response rates with 95% confidence intervals (CIs). A Freeman-Tukey square-root transformation was conducted to stabilise variance, and was back-transformed after data synthesis. Proportions of 0 and 1 were adjusted as reported to enable inclusion in study weighting. Publication bias was assessed with a funnel plot and Egger test. Heterogeneity was assessed with the Q and $I^2$ tests.

Sensitivity analyses were conducted on baseline platelet count (under or over 30 x 30x10^9/L using individual patient data) and setting (Japan, other). Linear regression was used to analyse the influence of Helicobacter pylori prevalence on outcomes.

Results of the review
Twenty five studies were included in the review (n=1,555 patients; range 15 to 435; 998 patients with Helicobacter pylori, of whom 696 achieved eradication of infection and were evaluable). There was one RCT (n=36 patients), two prospective controlled observational studies (n=172 patients), and 22 case series (20 prospective with 880 patients and two retrospective with 467 patients). The RCT scored 2 points on the Jadad scale; sequence generation was not described. All studies evaluated using the Newcastle Ottawa scale scored at least 5 points and were deemed of acceptable quality.

When all studies were pooled (n=696 patients), the weighted mean complete platelet response rate was 42.7% (95% CI 31.8 to 53.9) and the overall response rate was 50.3% (95% CI 41.6 to 59). There was a high level of statistical heterogeneity ($I^2=86.3%)$. Among patients with a baseline count of less than 30x10^9/L (n=222 patients), the weighted mean complete platelet response rate was 20.1% (95% CI 13.5 to 26.7) and the overall response rate was 35.2% (95% CI 28 to 42.4). No evidence of publication bias was found.

Thirteen studies reported predictors of platelet response to the intervention. The most consistently reported predictor was shorter duration of immune thrombocytopenia purpura (three individual studies). Linear regression of 24 studies found a statistically significant association between background prevalence of Helicobacter pylori infection and response rate (p=0.018).

Other findings were reported in the review

Authors' conclusions
Detection and eradication of Helicobacter pylori infection should be considered for patients with apparently typical immune thrombocytopenia purpura.

CRD commentary
The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies. The search restriction by language and publication status meant that the review was subject to language bias and potential publication bias, but formal testing did not indicate publication bias. Steps were taken to minimise the risk of reviewer error and bias by having more than one reviewer independently select studies, assess study validity and extract the data.

Little or no detail was provided about the design or quality of individual studies (e.g. numbers included in analysis,
nature of control interventions, losses to follow-up, quality scores) and information in the text was not always consistent. It was unclear what proportion of eligible participants were evaluable for outcomes. It was also unclear whether non-controlled studies in the review were assessed using the Newcastle-Ottawa scale (which is designed for controlled studies) and, if not, whether their quality was assessed at all. Differences in study quality did not appear to be taken into account in the interpretation of review findings. The statistical pooling of data did not appear valid, given the extreme heterogeneity between the studies; therefore the overall estimate of effect did not appear statistically or clinically meaningful.

The review had a number of limitations, including a lack of controlled data, poor reporting and inappropriate pooling of data. The reliability of the authors’ conclusions is unclear because effect estimates calculated in the review do not appear valid.

**Implications of the review for practice and research**

**Practice:** The authors stated that *Helicobacter pylori* screening appears worthwhile among patients with immune thrombocytopenia purpura in Japan, and that caution is required in generalising review findings across countries.

**Research:** The authors stated that large RCTs should be conducted to determine: the role of *H. pylori* screening; which patients with immune thrombocytopenia purpura would most benefit from *H. pylori* identification and eradication; precise response rates to treatment; and predictors and duration of response. Prospective studies should also investigate how *H. pylori* causes immune thrombocytopenia purpura; the mechanism of response to eradication; and the association between T-cell abnormalities and response to *H. pylori* eradication.

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