Thèse d'exercice

Université de Limoges

Faculté de Médecine

Année 2020 Thèse N°

Thèse pour le diplôme d'État de docteur en Médecine

Présentée et soutenue publiquement

Le 29 octobre 2020

Par Thomas Lauvray

Né(e) le 2 août 1992 à Toulouse

Le Traitement d'Helicobacter pylori dans le Purpura Thrombopénique Idiopathique : méta-analyse

Thèse dirigée par Dr Aymeric DALLOCCHIO

Examinateurs :
Pr. **LIENHARDT-ROUSSIE** Anne, Pédiatrie, CHU Limoges.
Pr. **GUIGONIS** Vincent, Pédiatrie, CHU Limoges.
Pr. **JACCARD** Arnaud, Hématologie clinique et thérapie cellulaire, CHU Limoges.
Dr. **DALLOCCHIO** Aymeric, Pédiatrie, CHU Limoges.

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Pour ma Marine.

« J'adore les cas graves, je les attends de pied ferme, je n'ai peur de rien. Je suis un danseur. Je danse avec la Mort, je virevolte autour d'elle. Ma blouse blanche, sa cape noire, nous évoluons dans le même ballet. Le Médecin et la Mort ont toujours formé un joli couple, n'est-ce pas ? »

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Aux membres du Jury :

A notre Maître, Présidente du Jury

Madame Le Professeur ANNE LIENHARDT-ROUSSIE,

Professeur des universités de Pédiatrie.

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Professeur des universités en Pédiatrie.

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Droits d’auteurs

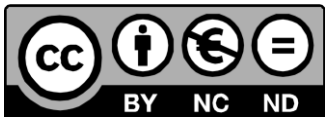

Table des matières

I. Abstract

I.1. Background

Chronic Immune thrombocytopenic Purpura (cITP) is an acquired immune-mediated disease characterized by a prolonged decreased platelet count for more than 6 months. Contradictory results on the effectiveness of *Helicobacter pylori* (HP) eradication in cITP have been published, with varying complete response (CR) rates according to the study. Studies have also shown higher CR rates in adults than in children with cITP after HP treatment.

I.2. Objectives

To determine the efficacy and the safety of a combination of amoxicillin, clarithromycin, and lansoprazole for eradication of Helicobacter pylori in Chronic Immune Thrombocytopenic Purpura.

I.3. Search methods

We searched MEDLINE (from 1950 to September 2020), EMBASE (from 1974 to September 2020), and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify all randomized trials in cITP evaluating a HP eradication treatment. Search method is detailed in Supplementary data 2.

I.4. Selection criteria

Randomized controlled trials (RCTs) comparing a combination of amoxicillin, clarithromycin, and lansoprazole, to placebo, no treatment, or other drugs.

I.5. Data collection and analysis

One review author independently screened results, extracted data, and assessed the risk of bias in the included studies.

I.6. Main results

Four studies with a total of 80 participants were included. There was two pediatric studies and two adult studies. 63 patients were randomized against standard of care without HP eradication treatment, and 17 patients were randomized against proton pump inhibitor monotherapy. There was a majority of female in the patients included (59%). Median age for the two pediatric focused studies was 11 years old, and 60 years old for the two adult studies. Inclusion criteria for included studies were uniform except for the age group.

None of the included studies evaluated overall survival as a primary or secondary outcome.

In a fixed-effect model, the HP eradication treatment versus other treatments improves platelet complete response rate (RR 2.45, 95% CI 1.05 - 5.73, P = 0.04). These results are not confirmed in the pediatric (RR 1.97, 95% CI 0.62 - 6.26, P = 0.25) and the adult subgroups (RR 3.07, 95% CI 0.88 - 10.78, P = 0.08), or in a random-effects model (RR 2.29, 95% CI 0.94 - 5.54, P = 0.07). Results were similar for overall platelet response, 6 months after the intervention, reaching statistical significance in a fixed-effect model (RR 1.87, 95% CI 1.06 - 3.31, P = 0.03) but failing when doing sensitivity analyses (adult subgroup : RR 2.05, 95% CI 0.96 - 4.38, P = 0.06)(pediatric subgroup : RR 1.67, 95% CI 0.71 - 3.94, P = 0.24)(random-effect statistical model : RR 1.53, 95% CI 0.73 - 3.23, P = 0.26). HP eradication treatment compared to no treatment highly improved absolute platelet count difference, 6 months after the intervention (RR 60.10, 95% CI 45.36 - 74.84, P = 0.00001), but results are based on data of a single study. There was no significant difference in total adverse events incidence between the intervention arm and the control arm (RR 3.85, 95% CI 0.80 - 18.44, P = 0.09). Two uncommon severe adverse events were reported : one death because of sepsis in the treatment arm and one severe gastrointestinal bleeding because of profound thrombocytopenia treated by high doses of prednisolone in the control arm. However, there was no significant difference in severe adverse events incidence between the intervention arm and the control arm (RR 1.12, 95% CI 0.16 - 7.78, P = 0.91).

I.7. Authors' conclusions

There was contradictory evidence on the efficacy of HP eradication treatments in chronic ITP, and small randomized controlled trials have failed to evaluate this effect. Compared to no treatment or lansoprazole, despite positive overall platelet response and platelet complete response in the initial analysis, statistical significance was not maintained when performing sensitivity analyses with either age subgroups or random-effect statistical models, which are the most relevant when considering studies composed of a small number of patients. Absolute platelet difference, 6 months after intervention was highly impacted by the HP eradication treatment but data is based on a single adult study. Extreme precaution is warranted considering the high risk of bias of all studies because of the lack of blinding, and supplementary potential bias (selection bias, funding bias). Moreover, the lack of data on overall survival, clinical bleeding events and long-term relapse in the included studies is an additional limitation to evaluate the effect of HP eradication in chronic ITP. The combination of amoxicillin, clarithromycin, and lansoprazole appears to be safe with low total adverse events, and no difference with other treatments regarding serious adverse events. We recommend following National Pediatric and Adult Guidelines until new data is available.

II. Plain language summary

Idiopathic thrombocytopenic purpura (ITP) is an acquired bleeding disorder with the production of anti-platelet auto-antibodies that impair cellular immunity and megakaryopoiesis, leading to profound thrombocytopenia and bleeding symptoms. Helicobacter pylori (HP) eradication treatment is used in patients with Helicobacter pylori associated ITP as an adjunct therapy, and several randomized trials have tried to confirm HP eradication as an effective way to reach that goal, with contradictory results, small cohorts, and low power evidence. This meta-analysis included four trials totaling 80 patients with cITP and compared a HP eradication treatment associating amoxicillin, clarithromycin and lansoprazole with no treatment or proton pump inhibitor monotherapy in children and adults.

Overall survival could not be evaluated for the HP eradication treatment because none of the studies measured overall survival as an outcome. The fact that HP eradication treatment increases the overall platelet response, and the complete response rate remains doubtful. The HP eradication treatment increases the difference in absolute platelet count, 6 months after the intervention, but results are based on a single study. Adverse effects with HP eradication treatment and without were similar. More data is needed to confirm the effect of a HP eradication treatment in chronic ITP. We recommend following National Pediatric and Adult Guidelines until new data is available.

III. Background

III.1. Description of the condition

Idiopathic thrombocytopenic purpura (ITP) is an acquired bleeding disorder, with an incidence of 5 to 10 per 10 000 children per year and 3.3 per 10 000 adults per year (Terrell 2010). Underlying pathophysiology remains incompletely understood, but the core mechanism of ITP revolves around the production of anti-platelet auto-antibodies with impaired cellular immunity and megakaryopoiesis, leading to profound thrombocytopenia and bleeding symptoms (Cines 2002, Figure 5.1.).

The diagnosis of ITP is based principally on the history, physical examination, complete blood count, and examination of the peripheral smear. If ITP remains a diagnosis of exclusion, exhaustive workup is not recommended in both adults and children. In the adult population, testing for HIV and HCV are highly recommended (Neunert 2018).

Classification of acute and chronic ITP is based on the duration of thrombocytopenia. Acute ITP is defined by a thrombocytopenia lasting less than 3 months and spontaneously healing. Persistent ITP may be used for a period of thrombocytopenia of 3 to 12 months. Chronic ITP was defined before 2011 by a thrombocytopenia lasting longer than 6 months but the American Society of Hematology (ASH) guidelines extended the period to longer than 12 months (Neunert 2011).

Guidelines regarding the management of pediatric and adult ITP patients differ (Neunert 2018). These differences are supported by evidence of a more severe form of illness in adults compared to children (lower spontaneous remission rate, higher risk of bleeding events, and increased need for treatment). Adult ITP is generally thought to be more insidious and chronic, as confirmed by several studies on the natural course of adult ITP (Sailer 2006; Schifferli 2018; Stasi 1995). Chronicity in children remains rare, as only 29% of pediatric acute ITP turn into cITP (Schifferli 2018). Viral infection is a common trigger in pediatric acute ITP. ITP affects female and male children alike, contrasting with a high female to male ratio in the adult ITP population (about 2 females for 1 male).

Bleeding symptoms occur in 64% of children with cITP (Schifferli 2018) with a low rate of life-threatening bleeding events compared to the severity of the thrombocytopenia in chronic ITP. Severity and frequency of hemorrhages were found to be linked with a low platelet count. As such, active treatment in adults is reserved to a subgroup with either significant bleeding ; a platelet count < 50 x 10^9/L and comorbid conditions or mandated antiplatelet or anticoagulant therapy ; or with a platelet count < 20 x 10^9/L without any additional risk factors (Provan 2019). Management in pediatric ITP is more conservative as clinical features and symptoms of ITP have more impact on treatment decision than the platelet count. An expectant "watch and wait" policy is recommended if the child has minor or no bleeding at arrival (Provan 2019, Neunert 2019). Bleeding scores (Rodeghiero 2013) should be used for assessing severity of ITP and deciding if active treatment is indicated. However, clinical symptoms of ITP do not consistently predict the risk for life-threatening bleeding such as intracranial hemorrhage.

III.2. Description of the intervention

Available therapies for cITP are primarily aimed at reducing platelet destruction. Corticosteroids and intravenous immunoglobulins are often used as first line therapy. In cITP second line management is mandatory with either repetitive use of first line treatments, splenectomy, or a large specter of immunosuppressive drugs such as rituximab, azathioprine, and cyclosporine (Provan 2019, Neunert 2019). Recently, research on other ways to manage cITP have focused on enhancing thrombopoiesis either by using thrombopoietic platelet growth factors that increase production of platelets by stimulating the thrombopoietin (TPO) receptor or mimicking TPO action.

Helicobacter pylori eradication treatment is used in patients with HP associated ITP as an adjunct therapy. The actual recommended antibiotic regimen when HP antibiotic sensibility is unknown is different in adults

and children. Pediatric ESPGHAN/NASPGHAN guidelines recommend a high dose triple therapy with lansoprazole 30mg twice a day, amoxicillin 1500mg twice a day and clarithromycin 500mg twice a day for 14 days when above 35kg, and adjusted doses to body weight when under 35kg (Jones 2017). In the adult population, French Guidelines from the "Haute Autorité de Santé" for adults recommend a quadruple therapy with proton pump inhibitor, amoxicillin 1000mg twice a day, clarithromycin 500mg twice a day, and metronidazole 500mg twice a day for 14 days, when the antibiotic resistance profile for HP is unknown (HAS 2017).

The studies included in this meta-analysis had different dosages, but all used a combination of amoxicillin, clarithromycin, and lansoprazole. All drugs were given orally. All triple therapies have similar side effects (Schwartz 1998).

III.3. How the intervention might work

Pathogenesis of HP associated ITP is poorly understood. The main hypothesis is that H. pylori cytotoxin-associated gene A (CagA) protein is a cross-reactive antigen, capable of activating B lymphocytes and creating anti-CagA antibodies. These antibodies cross-react and become platelet-associated immunoglobulin G (PAIgG), leading to platelet destruction. By stopping the HP infection in infected patients with ITP, B lymphocytes do not present CagA peptides to T CD4+ lymphocytes and are no more activated. As such, CagA and PAIgG levels decrease (Takahashi 2004).

However, some H. pylori strains do not harbor the CagA gene, and CagA-positivity varies depending upon the geographic location. This explains the heterogeneous results in studies testing reactivity between platelet eluates and HP proteins in ITP, and therefore, the unreliable efficacy of HP eradication in ITP (Stein 2001).

III.4. Why it is important to do this review

HP eradication in cITP has become common practice with different protocols in pediatric and adult Hematology Departments to amend cITP evolution and raise platelet count. Several randomized trials have tried to confirm HP eradication as an effective way to reach that goal, with contradictory results, small cohorts, and low power evidence. Considering the lack of conclusive evidence, a meta-analysis combining all previous randomized trials is needed to critically appraise the current data on HP eradication in cITP.

III.5. Objectives

To determine the efficacy and the safety of a HP eradication treatment in chronic ITP patients.

IV. Methods

IV.1. Criteria for considering studies for this review

IV.1.1. Types of studies

Randomized controlled studies. We excluded retrospective or observational case control studies. Quasi-randomized trials, cross-over trials were excluded because of the risk of increasing bias-related issues.

IV.1.2. Types of participants

Adults and children of all age, male and female, with a diagnosis of chronic ITP defined as persistent thrombocytopenia < 150 $x10^9$/L for more than 6 months with no other causes of thrombocytopenia, irrespective of previous therapy, and with a concomitant *Helicobacter pylori* infection.

IV.1.3. Types of interventions

HP eradication with a proton pump inhibitor, amoxicillin, clarithromycin and/or metronidazole versus placebo, other drugs, no treatment, or standard of care.

IV.1.4. Types of outcome measures

IV.1.4.1. Primary outcomes

- Overall survival.
- Complete response defined as platelet count > 150 $x10^9$/L and absence of bleeding, 6 months after intervention.

IV.1.4.2. Secondary outcomes

- Response defined as a platelet count > 30 $x10^9$/L and a greater than 2-fold increase in platelet count from baseline and the absence of bleeding.
- No response defined as a platelet count < 30 $x10^9$/L or a lower than 2-fold increase in platelet count from baseline and the absence of bleeding.
- Absolute platelet count variation at 6 months.
- Clinically significant bleeding events.
- Adverse events.

IV.2. Search methods for identification of studies

Our search strategy followed the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2020), without any restriction on language.

IV.2.1. Electronic searches

IV.2.1.1. Bibliographic databases :

- MEDLINE (via PUBMED) (1950 to September 2020).
- EMBASE (1974 to September 2020).
- Cochrane Central Register of Controlled Trials (CENTRAL).

Detail on search terms is given in Supplementary data 2.

IV.2.1.2. Conference proceedings :

American Society of Hematology (ASH): Blood (2001 to September 2020 electronically), 2017 to 2020 ASH sessions (conference abstracts, posters, and oral presentations).

IV.2.1.3. Databases of ongoing trials :

- The National Research Register Archive (https://webarchive.nationalarchives.gov.uk/20130104163259/http://www.dh.gov.uk/en/Advancedsearch/index.htm).
- Clinical Trials (http://www.clinicaltrials.gov).
- WHO ICTRP Search Portal (https://www.who.int/ictrp/search/en/).

IV.2.2. Searching other resources

We hand-checked references of all identified trials, relevant review articles and current treatment guidelines for further literature.

IV.3. Data collection and analysis

IV.3.1. Selection of studies

Titles and abstracts of studies were screened for eligibility. We obtained a full-text version for assessment when study eligibility was uncertain.

Studies meeting the inclusion criteria were then analyzed for data extraction.

IV.3.2. Data extraction and management

The following data were extracted from the included studies:

- General information: title, authors, journal, contact information, language, year of publication, setting of trial, country.
- Trial data : design, sample size, inclusion and exclusion criteria, randomization, concealment allocation, blinding of participants and personnel, control group, concurrent treatment, lost to follow-up, length of follow-up, funding, conflicts of interest.
- Baseline characteristics of patients : chronic ITP and HP infection diagnosis criteria, age, gender, comorbidity.
- Intervention data : treatment dose and administration, duration of treatment, compliance to treatment, side effects.
- Outcomes : definition of outcomes in the trial, time to assessment, statistical data regarding outcomes.

IV.3.3. Assessment of risk of bias in included studies

Quality of eligible studies was reviewed using the RoB 2 tool (Sterne 2019). A specific RoB 2 tool sheet for cluster-randomized studies was used for one included trial (Brito 2015). For any criterion that was unclear, we contacted the corresponding author of the study. We conducted sensitivity analyses to assess the influence of study quality on the effect of HP eradication in chronic ITP.

IV.3.4. Measures of treatment effect

Dichotomous data was presented as summary risk ratio (RR) with 95% confidence interval (CI). We analyzed continuous data using the mean difference if the criteria for measuring outcomes were all identical, and standardized mean difference when studies used different criteria to measure the same outcome.

IV.3.5. Assessment of heterogeneity

Study heterogeneity was assessed with Review Manager software version 5.4.1.

I^2 and Chi^2 statistical tests were used to test heterogeneity between studies, with $p < 0.05$ considered statistically significant. We performed subgroup analysis to explore the causes of heterogeneity.

IV.3.6. Assessment of reporting biases

The funnel plot for publication bias can be found as Figure 5.2. However, funnel plot asymmetry tests (rank correlation tests of Begg and Mazumdar and Egger's regression asymmetry test) could not be used in this meta-analysis because we included less than 10 studies in this meta-analysis.

IV.3.7. Data synthesis

We conducted the meta-analysis using the Review Manager software version 5.4.1. and pooled data using a fixed-effect model. We ran a sensitivity analysis with a random-effect model to confirm the statistical relevance of the obtained results.

IV.3.8. Subgroup analysis and investigation of heterogeneity

At the protocol stage, we planned to explore heterogeneity with the following subgroup analysis :

- Age under and above 18 years old (pediatric group vs adult group).
- Concurrent therapy.
- Number of previous therapies.
- Patients requiring treatment for bleeding events following ASH guidelines.
- HP eradication therapy dosage.
- Severity of initial thrombocytopenia (between 100 $x10^9$/L and 50 $x10^9$/L, between 50 $x10^9$/L and 20 $x10^9$/L, under 20 $x10^9$/L).

No statistical heterogeneity between studies was found in this meta-analysis, and therefore we did not carry out subgroup analysis for the purpose of heterogeneity testing.

IV.3.9. Sensitivity analysis

At the protocol stage of this meta-analysis, we planned to test for sensitivity to explore effect size differences and validate the robustness of results conclusions. Following sensitivity analysis were performed:

- Age under and above 18 years old (pediatric group vs adult group). Exclusion of studies with high risk of bias for concealment of allocation.
- Exclusion of studies with high risk of bias for blinding of participants and personnel.
- Comparing the effect of intervention after pooling analysis results with a fixed-effect model and random-effect model.
- Exclusion of studies with high risk of bias for generating allocation sequence.
- Exclusion of studies with high risk of bias for allocated intervention.
- Exclusion of studies with high risk of bias for other reasons than the ones above.

V. Results

V.1. Description of studies

V.1.1. Results of the search

Our search in September 2020 resulted in 562 results, and 79 additional references after handsearching American Society of Hematology (ASH) sessions from 2017 to 2020 (conference abstracts, posters and oral presentations). After screening abstracts and titles, we excluded 632 results (553 articles and all 79 additional references from the ASH sessions). Nine full text articles were screened for inclusion criteria. We excluded five additional articles after full text review. Reasons for exclusion are detailed in Characteristics of excluded studies (Supplementary data 1.2.).

V.1.2. Included studies

A total of four studies met the inclusion criteria (Brito 2015; Suzuki 2005; Treepongkaruna 2009; Tsutsumi 2005). Brito 2015 refers to clinical trial NCT01730352. Treepongkaruna 2009 refers to clinical trial NCT00467571. All registered trials were found at http://www.ClinicalTrials.gov. Tsutsumi 2005 and Suzuki 2005 had no trial protocol published. None of the eligible trials studied overall survival as their primary outcome. Treepongkaruna 2009 and Brito 2015 were both multicentric trials (4 centers for both), whereas Tsutsumi 2005 and Suzuki 2005 were monocentric trials. Geographic area for all studies were different, taking place in Japan for Suzuki 2005 and Tsutsumi 2005, Thailand for Treepongkaruna 2009, and Brazil for Brito 2015.

Data for each trial on methods, interventions, participants, and outcomes are detailed in the Characteristics of included studies.

All included studies were parallel open label randomized controlled trials. Two studies had 1:1 randomization (Tsutsumi 2005, Suzuki 2005), one was randomized in blocks of four patients (Brito 2015), and one was randomized in blocks defined by 10 years of age (Treepongkaruna 2009). Patients in the non-eradication arms were treated with HP eradication treatment at 6 months (Treepongkaruna 2009, Suzuki 2005) or if thrombocytopenia persisted (Brito 2015). No supplementary treatment was given (Tsutsumi 2005) for the arm that had been given IPP alone.

Randomized samples ranged from 16 (Treepongkaruna 2009) to 25 patients (Suzuki 2005).

Methods for confirming HP infection differed between studies : Tsutsumi 2005 monitored anti-HP antibody titers, Treepongkaruna 2009 used positive. ^{13}C-Urea Breath Test, Suzuki 2005 used a culture method after gastroscopy, and Brito 2015 confirmed HP infection with both positive ^{13}C-Urea Breath Test and positive monoclonal stool antigen test. Some studies had supplementary exclusion criteria. Brito 2015 also excluded patients with one negative test between the ^{13}C-Urea Breath Test or the Monoclonal antigen stool test, or if only one test was performed. They also excluded patients that were previously treated for HP infection. Treepongkaruna 2009 excluded participants with history of previous HP treatment, patients treated with prednisolone dose above 0.5mg/kg/day at baseline or during study period, or patients treated with other platelet-enhancing therapies than prednisolone. Suzuki 2005 excluded patients with renal failure or severe liver dysfunction, age under 18 or above 75 years old, platelet count below 20 x10^9/L or above 100 x10^9/L.

The HP eradication regimen in all studies used a combination of lansoprazole, amoxicillin and clarithromycin (Brito 2015, Treepongkaruna 2009, Tsutsumi 2005, Suzuki 2005). All drugs were given orally. Brito 2015 gave the HP eradication regimen twice a day for 14 days but did not state the exact dose for each antibiotic. Suzuki 2005 had the following HP eradication treatment : amoxicillin 750 mg, clarithromycin 200 mg, and lansoprazole 30 mg, twice daily for 1 week. Antibiotics in Treepongkaruna 2009 were weight-adjusted : lansoprazole 15 mg (BW<30 kg) or 30 mg (BW>30 kg) twice daily, amoxicillin 25 mg/kg twice daily and clarithromycin 7.5 mg/kg twice daily for 14 days. Tsutsumi 2005 used lansoprazole at 30 mg once a day, amoxicillin at 750 mg twice a day, and clarithromycin at 200 mg twice a day for 7 days in the intervention arm and lansoprazole 30mg once a day, continuously, in the control arm. All studies did not impose limitations on concurrent standard of care for included participants except

Treepongkaruna 2009 where other concomitant therapy than prednisolone for chronic ITP was not allowed. Dosage increase for prednisolone in Treepongkaruna 2009 was allowed if the patient had severe thrombocytopenia under 5 x10^9/L or clinical bleeding, up to a maximum of 0.5mg/kg/day. Standard of care in other studies was poorly described.

HP eradication was confirmed differently between studies. Tsutsumi 2005 monitored anti-HP titer monthly, whereas others used a negative ^{13}C-Urea Breath Test 3 months after completion of treatment (Suzuki 2005), negative ^{13}C-Urea Breath Test 4 weeks after withdrawal (Treepongkaruna 2009), and negative ^{13}C-Urea Breath Test in the second month (4-8 weeks) after the end of the treatment (Brito 2015).

HP eradication rate varied between studies. HP eradication was achieved in 90.9% (Brito 2015), 100% (Treepongkaruna 2009), 44.4% (Tsutsumi 2005) and 84.6% (Suzuki 2005).

Four studies with a total of 80 participants were included. 63 patients were randomized against standard of care without HP eradication treatment (Brito 2015, Treepongkaruna 2009, Suzuki 2005), and 17 patients were randomized against proton pump inhibitor monotherapy (Tsutsumi 2005). There was a majority of female in included patients (59%). Median age for the two pediatric focused studies was 11 years old (Brito 2015, Treepongkaruna 2009), and 60 years old for the two adult studies (Suzuki 2005, Tsutsumi 2005). Inclusion criteria for included studies were uniform except for the age group.

No studies evaluated overall survival as a primary outcome. All studies assessed complete response or overall platelet response as primary outcomes. Time points were variable between studies but consistent with a logical timeframe : three and six months (Brito 2015), six months (Suzuki 2005, Treepongkaruna 2009), and finally one, three and six months (Tsutsumi 2005).

Only one study detailed follow-up of non-infected patients (Brito 2015), while most of the studies focused on cITP patients with HP infection (Suzuki 2005, Treepongkaruna 2009, Tsutsumi 2005).

Number of adverse events associated with HP treatment was reported in all studies, but no grade was detailed. There were two severe adverse events : 1 massive gastrointestinal bleeding in the control arm in Treepongkaruna 2009 motivating withdrawal from the study, and 1 death because of sepsis in the intervention arm in Brito 2015.

V.1.3. Excluded studies

Out of the nine full text articles assessed for eligibility, five were excluded. We excluded two publications (Jaing 2003, Sayan 2006) because they did not meet inclusion criteria and were not randomized. Jaing 2003 mentioned "randomization into the study" but treatment allocation was not randomized, therefore not meeting inclusion criteria. Two Chinese studies met inclusion criteria after title and abstract screening but we were unable to access the published article because no contact information was displayed to contact the author (Li 2009, Tang 2013). The second phase after the 6-month time-point in Treepongkaruna 2009, Suzuki 2005, and Brito 2015 was not analyzed because the control arm was exposed to HP eradication treatment.

One additional trial from ClinicalTrials.gov fulfilled the inclusion criteria, however, the trial is recruiting and no results are reported (Bang 2018).

V.2. Risk of bias in included studies

The risk of bias of included studies is detailed in Supplementary data 5.4 and Supplementary data 5.5 and in the Characteristics of included studies.

V.2.1. Allocation (selection bias)

Two studies were judged as having a high risk of inadequate allocation concealment (Brito 2015, Tsutsumi 2005) and two studies as being unclear (Treepongkaruna 2009, Suzuki 2005).

V.2.2. Blinding (performance bias and detection bias)

No included study detailed or mentioned blinding for participants or personnel (Brito 2015, Treepongkaruna 2009, Suzuki 2005, Tsutsumi 2005).

V.2.3. Incomplete outcome data (attrition bias)

When judging studies for incomplete outcome data, we estimated that studies would be at high risk of attrition bias if the loss to follow-up was above 15%. We also verified an intention-to-treat analysis was conducted in all studies and how incomplete data outcome was managed. All studies included reported no loss to follow-up in the randomized cohorts (Brito 2015, Treepongkaruna 2009, Suzuki 2005, Tsutsumi 2005). Death and withdrawal for patients in Brito 2015 and Treepongkaruna 2009 were not included in final statistical analysis and did not respect the intention-to-treat model. When extracting data, we imputed these patients with replacement values, and these values were treated as if they were observed.

V.2.4. Selective reporting (reporting bias)

All studies reported a measure for all outcomes mentioned, and all time points were logical. Two studies were considered unclear for reporting bias because of the absence of published randomized controlled trial protocol (Suzuki 2005, Tsutsumi 2005).

V.2.5. Other potential sources of bias

Sources of funding were not stated for three studies (Brito 2015, Tsutsumi 2005, Suzuki 2005), and as such, were judged as having unclear risk.

V.3. Effects of interventions

Four studies with 80 participants were included. Two studies included adults (Suzuki 2005, Tsutsumi 2005), and two included children (Brito 2015, Treepongkaruna 2009). One compared HP eradication treatment with lansoprazole monotherapy (Suzuki 2005), the three others compared HP eradication treatment with no treatment (Brito 2015, Treepongkaruna 2009, Tsutsumi 2005). Concurrent medical standard of care was prescribed and managed by the investigators following institutional practices or guidelines, except in Treepongkaruna 2009 where other therapies than prednisolone were not allowed.

V.3.1. HP eradication treatment versus no treatment (3 trials)

V.3.1.1. Platelet complete response, 6 months after intervention:

Suzuki 2005, Brito 2015 and Treepongkaruna 2009 provided data on the number of patients with a complete response in the intervention and control arms, for a total of 63 patients. Treatment with amoxicillin, clarithromycin, and lansoprazole results in an increase incidence of platelet complete response, 6 months after intervention (RR 2.83, 95% CI 0.98 - 8.17, P = 0.05). There was no heterogeneity among the analyzed studies (Chi^2 = 2.08, degrees of freedom (df) = 2, P = 0.35; I^2 = 4%) (Supplementary data 5.6.1). However, sensitivity analysis shows no statistical significance when tested for the pediatric subgroup (RR 1.97, 95% CI 0.62 - 6.26, P = 0.25). Same results are found when testing with a random-effect statistical model (RR 2.68, 95% CI 0.82 - 8.78, P = 0.10).

V.3.1.2. Overall platelet response, 6 months after intervention :

All three studies had data regarding overall platelet response 6 months after intervention, for a total of 63 patients. The same phenomenon can be found when evaluating the effect of HP eradication treatment on overall platelet response 6 months after intervention : statistical significance is reached when all patients are pooled (RR 1.87, 95% CI 1.06 - 3.31, P = 0.03) but disappears when a pediatric subgroup analysis is done (RR 1.67, 95% CI 0.71 - 3.94, P = 0.24) and a random-effect statistical model is used (RR 1.53, 95% CI 0.73 - 3.23, P = 0.26). No heterogeneity was found in the analyzed studies (Chi^2 = 4.27, df = 3, P = 0.23, I^2 = 30%) (Supplementary data 5.6.2).

V.3.1.3. Absolute platelet difference, 6 months after intervention :

Suzuki 2005 was the only study to have complete data of platelet count at enrolment and 6 months after intervention. Other studies reported these measures with means and ranges, preventing any statistical analysis. We did not try to estimate the mean and variance because of high probability of estimation error on small samples, and the low power of the statistical tests issued with estimated data (Hozo 2005). HP

eradication treatment compared to no treatment improved absolute platelet count difference, 6 months after intervention (RR 60.10, 95% CI 45.36 - 74.84, P = 0.00001). Switching to a random-effect model did not change the outcome. Heterogeneity was not applicable (single study analyzed) (Supplementary data 5.6.3).

V.3.2. HP eradication treatment versus other treatments (4 trials)

V.3.2.1. Overall Survival :

None of the included studies evaluated overall survival.

V.3.2.2. Platelet complete response, 6 months after intervention:

Data for complete response was available in Suzuki 2005, Tsutsumi 2005, Brito 2015 and Treepongkaruna 2009, for a total of 80 patients. In a fixed-effect model, the HP eradication treatment versus other treatments improves platelet complete response rate (RR 2.45, 95% CI 1.05 - 5.73, P = 0.04). These results are not confirmed in the pediatric (RR 1.97, 95% CI 0.62 - 6.26, P = 0.25) and the adult subgroups (RR 3.07, 95% CI 0.88 - 10.78, P = 0.08), or in a random-effects model (RR 2.29, 95% CI 0.94 - 5.54, P = 0.07). There was no significant heterogeneity in the included studies (Chi^2 = 2.30, df = 3, P = 0.51, I^2 = 0%)(Supplementary data 5.6.4).

V.3.2.3. Overall platelet response, 6 months after intervention :

All four studies had measurements for overall platelet response (80 patients), 6 months after intervention (Suzuki 2005, Tsutsumi 2005, Brito 2015 and Treepongkaruna 2009). The HP eradication treatment raises the overall platelet response rate 6 months after intervention in chronic ITP (RR 1.87, 95% CI 1.06 - 3.31, P = 0.03). No statistical significance is reached in adult (RR 2.05, 95% CI 0.96 - 4.38, P = 0.06) or pediatric subgroups (RR 1.67, 95% CI 0.71 - 3.94, P = 0.24), or when using a random-effects model (RR 1.53, 95% CI 0.73 - 3.23, P = 0.26). There was no significant heterogeneity (Chi^2 = 4.27, df = 3, P = 0.23, I^2 = 30%)(Supplementary data 5.6.5).

V.3.2.4. Total Adverse Events :

Only two studies had non null total adverse events in at least one arm (Brito 2015, Treepongkaruna 2009), including 38 patients in total. There was no significant difference in total adverse events incidence between the intervention arm and the control arm (RR 3.85, 95% CI 0.80 - 18.44, P = 0.09). Moderate heterogeneity with I^2 between 40 and 60% and P value equal to 0.1 was found in analyzed studies (Chi^2 = 2.77, df = 1, P = 0.10, I^2 = 64%)(Supplementary data 5.6.6). No sensitivity analysis was possible because only two studies were compared.

V.3.2.5. Severe Adverse Events :

Two studies had data for severe adverse events, totaling 38 patients (Brito 2015, Treepongkaruna 2009). Two uncommon severe adverse events were reported : one death because of sepsis in the treatment arm (Brito 2015) and one severe gastrointestinal bleeding because of profound thrombocytopenia treated by high doses of prednisolone in the control arm (Treepongkaruna 2009). However, there was no significant difference in severe adverse events incidence between the intervention arm and the control arm (RR 1.12, 95% CI 0.16 - 7.78, P = 0.91). No heterogeneity was found in analyzed studies (Chi^2 = 0.79, df = 1, P = 0.37, I^2 = 0%)(Supplementary data 5.6.7).

VI. Discussion

VI.1. Summary of main results

Compared to no treatment or lansoprazole, HP eradication treatment does not improve overall platelet response and platelet complete response. Statistical significance for better overall platelet response and platelet complete response are only obtained in fixed-effect model statistical analysis when all studies including both pediatric and adult patients are pooled. Statistical significance was not maintained when performing sensitivity analyses with either age subgroups or random-effect statistical models. Because of the absence of data regarding overall survival in the included trials, we could not assess this outcome. The combination of amoxicillin, clarithromycin, and lansoprazole is statistically safe with low total adverse events, and no difference with other treatments regarding serious adverse events.

VI.2. Overall completeness and applicability of evidence

All studies addressed the role of a HP eradication treatment in chronic ITP. Two studies were focused on the pediatric population (Brito 2015, Treepongkaruna 2009) and two studies included adults (Suzuki 2005, Tsutsumi 2005), all studies included patients on and off-treatment for chronic ITP, and one study included ITP with mild thrombocytopenia (initial thrombocytopenia between 150 and 100 $x10^9$/L)(Brito 2015), with diverse clinical situations making this analysis relevant. However small samples prevent the generalization of our findings to a wider population.

Testing methods for HP infection were diverse : ^{13}C-Urea Breath Test, serologic test for IgG anti-H. pylori antibodies, stool antigen test, or histology and culture of gastric mucosal biopsies. ^{13}C-Urea Breath Test is used in conventional care and is the standard gold standard test in the pediatric test with reliable results, especially post-therapy, with specificity and sensibility exceeding 90% (Patel 2014). Not being invasive is another major advantage in the context of pediatric care. Antigen detection in the stool is a non-invasive technique that has now shown excellent sensibility and specificity, comparable to the ^{13}C-Urea Breath Test (Patel 2014). It is now recommended by the European Helicobacter and Microbiota Study Group as an alternative to the ^{13}C-Urea Breath Test (Malfertheiner 2012). Histology is the gold standard technique for HP infection in the adult population. HP's patchy distribution can cause misdiagnosis, but systematic multiple biopsies have improved the accuracy of the technique. Histology and fluorescent in situ hybridization for 16S rRNA combined have excellent sensitivity and specificity (Patel 2014). Culture is not considered a standard testing method because bacteriological culture is a tedious and time-consuming procedure. Only 50-70% of infected biopsies are positive after culture (Patel 2014). However, Suzuki 2005 and Tsutsumi 2005 had similar infection rates in cITP patients (65-70%) compatible with the prevalence in the Japanese population (Graham 1994). Finally, monitoring IgG anti-HP antibodies is not a gold standard technique and its lack of sensitivity and specificity is source of bias (80-90%, Patel 2014). Moreover, IgG anti-HP antibodies are known to be persistent after HP eradication. This makes it nearly impossible to conclude regarding the cases with persistent IgG anti-HP antibodies (considered as HP eradication failure) and improvement in platelet count in Tsutsumi 2005. The monoclonal stool antigen test

An additional critical bias lies in the fluctuant effectiveness of the HP eradication treatment in all included studies. This could have led to heterogeneity between studies, confirmed in sensitivity analyses of all outcomes with random-effect models.

Different outcomes were analyzed in the included studies. We set overall survival as our primary outcome in our initial research protocol, but as the incidence of mortality in pediatric ITP is low, large cohorts of patients and prolonged follow-up are needed to observe a difference between HP infected and non-infected patients. This primary outcome was not studied by included trials. Data for complete response 6 months after intervention was available in all trials included but lacked for the 12 months follow-up. Late spontaneous complete responses (between 12 and 24 months after diagnosis) have been described (Schifferli 2018), so longer follow-up could have increased the number of responders in both arms and in both pediatric and adult population.

Overall, the effect of HP eradication treatment in cITP cannot be extrapolated to a broader population because of the biases in included studies.

VI.3. Quality of the evidence

All included trials were reported as randomized controlled trials. Allocation concealment was missing for two studies (Brito 2015, Tsutsumi 2005), and not clearly defined in the other two studies (Treepongkaruna 2009, Suzuki 2005). All studies included were open-label with no blinding for participants or personnel. The open-label and inadequate allocation concealment could lead to the existence of selective and performance biases. Overall, we consider that there is “low” level evidence based on this set of data.

VI.4. Potential biases in the review process

Results could have been biased by excluding 2 Chinese randomized controlled studies that met inclusion criteria after title and abstract screening. Both studies totaled 161 pediatric patients which is twice the size of the cohort analyzed in this meta-analysis. We will update our meta-analysis with data from the authors if full articles are retrieved.

Screening, data extraction, and bias judgement was done by a single reviewer, possibly leading to biased decisions on study inclusion.

VI.5. Agreements and disagreements with other studies or reviews

Another meta-analysis (Yu 2011) pooled data from non-randomized studies, comparing a total of 458 cases and 305 controls from 13 studies to evaluate the relationship between HP eradication and ITP remission, resulting in a pooled OR of 6.53 (95%CI = 4.44 - 9.61). The authors concluded that HP infection plays a role in the etiology of ITP and that HP eradication increases platelet count in patients with ITP (Yu 2011, abstract information only). We cannot critic the data used by the authors because the article is unavailable, in Chinese, and no contact information is displayed to ask the authors for additional information. However, potential biases are likely to be increased in meta-analysis of non-randomized trials when evaluating the effect of interventions, and results should be interpreted with caution (Reeves 2019).

VI.6. Authors' conclusions

VI.6.1. Implications for practice

There was contradictory evidence on the efficacy of HP eradication treatments in chronic ITP, and small randomized controlled trials have failed to evaluate this effect. Compared to no treatment or lansoprazole, despite positive overall platelet response and platelet complete response in the initial analysis, statistical significance was not maintained when performing sensitivity analyses with either age subgroups or random-effect statistical models. Absolute platelet difference, 6 months after intervention was highly impacted by the HP eradication treatment but data is based on a single adult study. Extreme precaution is warranted considering the high risk of bias of all studies because of lack of blinding, and supplementary potential bias (selection bias, funding bias). Moreover, the lack of data on overall survival, clinical bleeding events and long-term relapse in the included studies is an additional limitation to evaluate the effect of HP eradication in chronic ITP. The combination of amoxicillin, clarithromycin, and lansoprazole is statistically safe with low total adverse events, and no difference with other treatments regarding serious adverse events. We recommend following National Pediatric and Adult Guidelines until new data is available. A summary table of ASH Guidelines for HP eradication in cITP can be found in Supplementary data : Annexe 6. American Society of Hematology Guidelines (Neunert 2011, Neunert 2019) summary table for the management of ITP.

VI.6.2. Implications for research

The high risk of bias in the included studies could have been avoided by following guidelines issued by the CONSORT Group (Schulz 2010). Future published randomized controlled trials on chronic ITP should follow standardized criteria for reporting outcomes as proposed by international working groups (Rodeghiero 2013). Adverse events need to be detailed and graded for reproducibility. Concurrent treatments, clinical bleeding events, Health-Related Quality of Life questionnaires should become standard available data in all randomized controlled trials evaluating the effect of interventions in adult and

pediatric chronic ITP. Further long-term studies are warranted to know if remission after HP eradication treatment is persistent.

VII. Contributions of authors

Thomas Lauvray : coordinating the review, protocol development, searching for trials, eligibility and quality assessment, data extraction and analysis, drafting of final review.

Aymeric Dallocchio : drafting of final review, providing general advice on the review.

VIII. Declarations of interest

None.

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Included studies :

Brito 2015

Published data only (unpublished sought but not used) [DOI: 10.3109/09537104.2014.911836]

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Supplementary data

Annexe 1. Characteristics of studies

Annexe 1.1. Characteristics of included studies

Annexe 1.1.1. Brito 2015

Methods	Multicenter open-label randomized controlled trial.
Participants	22 participants (11 intervention, 11 control), with cITP (ASH definition), and positive HP infection (13C-urea breath test and monoclonal stool antigen test both positive), < 20 years old.
Interventions	Intervention : HP eradication with "standard" clarithromycin, amoxicillin, and lansoprazole (all twice a day) for 14 days + standard of care. Second line with clarithromycin, furazolidone or doxycycline if needed. Control : Standard of care. Observational group : cITP without HP infection.
Outcomes	- Platelet response : complete response (platelet count >150 $x10^9$ / L), partial response (platelet count <150 $x10^9$ / L and/or platelet increase >20 $x10^9$ / L), no response (platelet count < 50 $x10^9$ / L or platelet increase < 20 $x10^9$ / L), evaluation at 3 and 6 months follow-up. - Adverse events.
Notes	Bleeding events not assessed. Sources of funding not stated.

Annexe 1.1.2. Risk of Bias table for Brito 2015

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote : "The randomization sequence was done in blocks of four patients, and it was generated by the web site ‘‘Randomization.com’’ – http://www.randomization.com by one of the investigators (H.S.H.B.)."
Allocation concealment (selection bias)	High risk	Comment : Allocation concealment not mentioned.
Blinding of participants and personnel (performance bias)	High risk	Comment : No blinding detailed of participants and personnel.
Blinding of outcome assessment (detection bias)	High risk	Comment : No blinding detailed of outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	Quote : "Seventy-one percent of patients completed 12 months of follow-up." Comment : loss to follow-up concerned the non-randomized cohort.
Selective reporting (reporting bias)	Low risk	Comment : Trial protocol published on ClinicalTrials.gov in November 2012 (NCT01730352).
Other bias	Unclear risk	Comment: Sources of funding not stated.

Annexe 1.1.3. Suzuki 2005

Methods	Monocenter open-label randomized controlled trial.
Participants	25 participants (13 intervention, 12 control), with cITP (ASH definition) and positive HP infection (gastroscopy with positive HP culture),18 to 75 years old.
Interventions	Intervention : Amoxicillin 750 mg, clarithromycin 200 mg, and lansoprazole 30 mg, twice daily for 1 week and standard of care. Control : standard of care.
Outcomes	Disease response : CR (platelet count >150×10^3/µl), PR (platelet increase >50 × 10^3/µl), 6 months after eradication therapy Adverse events HP eradication
Notes	Exclusion criteria : platelet counts below 20 × 10^3/µl or above 100 × 10^3/µl, renal failure, or severe liver dysfunction. Sources of funding not stated.

Annexe 1.1.4. Risk of bias table for Suzuki 2005

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote : "randomly assigned by concealed allocation to H. pylori eradication or H. pylori non- eradication group" Comment : Random sequence generation not detailed.
Allocation concealment (selection bias)	Unclear risk	Quote : "randomly assigned by concealed allocation to H. pylori eradication or H. pylori non-eradication group" Comment : No information on how the treatment was concealed.
Blinding of participants and personnel (performance bias)	High risk	Comment : No blinding detailed of participants and personnel.
Blinding of outcome assessment (detection bias)	High risk	Comment : No blinding detailed of outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	Comment : No loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	Comment: Without a trial protocol it is unclear whether any outcomes were measured but not reported based on the results.
Other bias	Unclear risk	Comment: Sources of funding not stated.

Annexe 1.1.5. Treepongkaruna 2009

Methods	Multicenter open-label stratified randomized controlled trial.
Participants	16 participants (7 intervention, 9 control) with cITP and HP infection (13C-urea breath test), 4-18 years old
Interventions	First phase : 6-month follow-up - Intervention : lansoprazole 15 mg (BW<30 kg) or 30 mg (BW>30 kg) twice daily, amoxicillin 25 mg/kg twice daily and clarithromycin 7.5 mg/kg twice daily for 14 days - Control : No treatment. Second phase : 6-month follow-up - Intervention arm : follow-up continued - Control arm : HP eradication treatment
Outcomes	Platelet recovery at 6 months. Platelet recovery rate in all H. pylori-treated patients at 12 months of study. Platelet recovery defined as platelet count > 100 x10^9/L for more than 3 months.
Notes	Other concurrent therapies for chronic ITP except prednisone were not allowed. Side effects for HP treatment not stated. Sources of funding mentioned.

Annexe 1.1.6. Risk of bias table for Treepongkaruna 2009

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote : "stratified randomization by age of 10 years" Comment : randomization generation not stated
Allocation concealment (selection bias)	Unclear risk	Quote : "concealment in an opaque envelope" Comment : Not reported if the envelopes were sealed and sequentially numbered.
Blinding of participants and personnel (performance bias)	High risk	Comment : No blinding of participants and personnel.
Blinding of outcome assessment (detection bias)	High risk	Comment : No blinding of outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	Comment : No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Comment : Trial protocol published on ClinicalTrials.gov in April 2007 (NCT00467571).
Other bias	Low risk	Comment: No other sources of bias identified.

Annexe 1.1.7. Tsutsumi 2005

Methods	Monocenter open-label randomized control trial.
Participants	17 participants (9 intervention, 8 control) with cITP and HP infection (positive anti-HP antibody), from 49 to 89 years old.
Interventions	Intervention : lansoprazole at 30 mg once a day, amoxicillin at 750 mg twice a day, and clarithromycin at 200 mg twice a day for 7 days. Control : lansoprazole 30mg once a day, continuously.
Outcomes	Platelet response : CR (>120×10^9/L), PR (<120×10^9/L), absolute increase (>30×10^9/L increase), 50% increase (between 10×10^9/L and 30×10^9/L increase).
Notes	Sources of funding not stated.

Annexe 1.1.8. Risk of Bias table for Tsutsumi 2005

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment : randomization sequence generation not stated.
Allocation concealment (selection bias)	High risk	Comment : no concealment detailed.
Blinding of participants and personnel (performance bias)	High risk	Comment : No blinding of participants and personnel.
Blinding of outcome assessment (detection bias)	High risk	Comment : No blinding of outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	Comment : No loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	Comment: Without a trial protocol it is unclear whether any outcomes were measured but not reported based on the results.
Other bias	Unclear risk	Comment: Funding sources not stated.

Annexe 1.2. Characteristics of excluded studies

Annexe 1.2.1. Bang 2018

Reason for exclusion	Ongoing trial, no published data.

Annexe 1.2.2. Jaing 2003

Reason for exclusion	Prospective trial. No randomization.

Annexe 1.2.3. Li 2009

Reason for exclusion	Whole article not available online. No response from author for access. Chinese article.

Annexe 1.2.4. Sayan 2006

Reason for exclusion	Prospective trial. No randomization.

Annexe 1.2.5. Tang 2013

Reason for exclusion	Whole article not available online. No response from author for access. Chinese article.

Annexe 2. Searching strategy table

Database	Search Strategy	Results
PUBMED	#1 : Purpura, Thrombocytopenic, Idiopathic [Mesh] #2 : Thrombocytopeni* [Title/Abstract] AND Immun* [Title/Abstract] #3 : ITP #4 : #1 OR #2 OR #3 #5 : "Helicobacter pylori"[Mesh] #6 : Helicobacter [Title/Abstract] #7 : Helicobacter infection [Title/Abstract] #8 : #5 OR #6 OR #7 #9 : Amoxicillin [Title/Abstract] #10 : Clarithromycin [Title/Abstract] #11 : Bismuth [Title/Abstract] #12 : Metronidazole [Title/Abstract] #13 : ((((lansoprazole[Title/Abstract]) OR (esomeprazole[Title/Abstract])) OR (omeprazole[Title/Abstract])) OR (pantoprazole[Title/Abstract])) OR (rabeprazole[Title/Abstract]) #14 : "Proton Pump Inhibitors"[Mesh] #15 : (treat*) AND (helicobacter) [Title/Abstract] #16 : Placebo [Title/Abstract] #17 : #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 #18 : #4 AND (#8 OR #15)	562
EMBASE	#1 : Purpura, Thrombocytopenic, Idiopathic [Emtree] #2 : (Thrombocytopeni$):ti,ab AND (Immun$):ti,ab #3 : ITP #4 : #1 OR #2 OR #3 #5 : "Helicobacter pylori"[Emtree] #6 : (Helicobacter):ti,ab #7 : (“Helicobacter infection”):ti,ab #8 : #5 OR #6 OR #7 #9 : (Amoxicillin):ti,ab #10 : (Clarithromycin):ti,ab #11 : (Bismuth):ti,ab #12 : (Metronidazole):ti,ab #13 : (((((lansoprazole):ti,ab) OR ((esomeprazole):ti,ab)) OR ((omeprazole):ti,ab) OR ((pantoprazole):ti,ab)) OR ((rabeprazole):ti,ab) #14 : "Proton Pump Inhibitors"[Emtree] #15 : ((treat*) AND (helicobacter)):ti,ab #16 : (Placebo):ti,ab #17 : #9 ~ #16 OR #18 : #4 AND (#8 OR #15)	980
COCHRANE	#1 : (Purpura, Thrombocytopenic, Idiopathic):ti,ab,kw OR (Thrombocytopeni* AND immun*):ti,ab,kw OR (ITP):ti,ab,kw	560

	#2 : ("Helicobacter infection"):ti,ab,kw OR (Helicobacter):ti,ab,kw #3 : (amoxicillin):ti,ab,kw OR (metronidazole):ti,ab,kw OR (clarithromycin):ti,ab,kw OR (bismuth):ti,ab,kw OR (placebo):ti,ab,kw #4 : (lansoprazole):ti,ab,kw OR (omeprazole):ti,ab,kw OR (esomeprazole):ti,ab,kw OR (rabeprazole):ti,ab,kw OR (pantoprazole):ti,ab,kw #5 : ("proton pump inhibitor"):ti,ab,kw OR (treat* AND helicobacter):ti,ab,kw #6 : #3 OR #4 OR #5 #7 : #1 AND (#2 OR #6)	

Annexe 3. Statistical data for included studies

First author, year	Number of positive HP in cITP patients	Randomization : - Intervention arm - Control Arm	Patients per arm	M/F	Mean age (in years) +/- SD	Platelet at inclusion (x10^9/L) +/- SD	Platelet at 6 months (x10^9/L) +/- SD	CR	Response (CR + PR)	Adverse Events
Suzuki, 2005	25	Eradication	13	5/8	57,4 +/- 15,0	54,7 +/- 26,9	114,5 +/- 90,5	4	6	0
		Observation	12	5/7	56,2 +/- 7,8	48,4 +/- 22,1	48,1 +/- 26,0	0	0	NR
Tsutsumi, 2005	17	Eradication	9	2/7	60,3 +/- 9,3	5,38 +/- 0,93	Missing data	4	6	0
		PPI	8	3/5	63,2 +/- 11,7	5,38 +/- 1,49	Missing data	2	5	NR
Treepongkaruna, 2009	16	Eradication + PD	7	3/4	11,0 +/- missing data	16,0 +/- missing data	Missing data	0	1	Missing data
		PD	9	4/5	10,8 +/- missing data	25,0 +/- missing data	Missing data	1	1	1 (withdrawn for massive GE bleeding)
Brito, 2015	22	Eradication +/- PD	11	6/5	12,7 +/- missing data	35,0 +/- missing data	128 +/- 73	6	7	5 minor SE and 1 death (sepsis)
		No HP treatment +/- PD	11	5/6	10,5 +/- missing data	47,0 +/- missing data	63 +/- 44	2	4	NR

Annexe 4. Data and analyses :

Annexe 4.1. HP eradication treatment versus no treatment.

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect estimate
1.1 Complete response at 6 months	3	63	Risk Ratio (M-H, Fixed, 95% CI)	2.83 [0.98, 8.17]
1.1.1 Adult population	1	25	Risk Ratio (M-H, Fixed, 95% CI)	8.36 [0.50, 140.56]
1.1.2 Pediatric population	2	38	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [0.62, 6.26]
1.2 Platelet response at 6 months	3	63	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [1.16, 6.16]
1.2.1 Adult population	1	25	Risk Ratio (M-H, Fixed, 95% CI)	12.07 [0.75, 193.73]
1.2.2 Pediatric population	2	38	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.71, 3.94]
1.3 Absolute platelet difference, 6 months after intervention	1	25	Mean Difference (IV, Fixed, 95% CI)	60.10 [45.36, 74.84]

Annexe 4.2. HP eradication treatment versus other.

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect estimate
2.1 Complete response at 6 months	4	80	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [1.05, 5.73]
2.1.1 Adult population	2	42	Risk Ratio (M-H, Fixed, 95% CI)	3.07 [0.88, 10.78]
2.1.2 Pediatric population	2	38	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [0.62, 6.26]
2.2 Platelet Response at 6 months	4	80	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.06, 3.31]
2.2.1 Adult population	2	42	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.96, 4.38]
2.2.2 Pediatric population	2	38	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.71, 3.94]
2.3 Total Adverse Events	2	38	Risk Ratio (M-H, Fixed, 95% CI)	3.85 [0.80, 18.44]
2.4 Severe Adverse Events	2	38	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.16, 7.78]

Annexe 5. Figures.

Annexe 5.1. Pathogenesis of ITP and epitope spreading

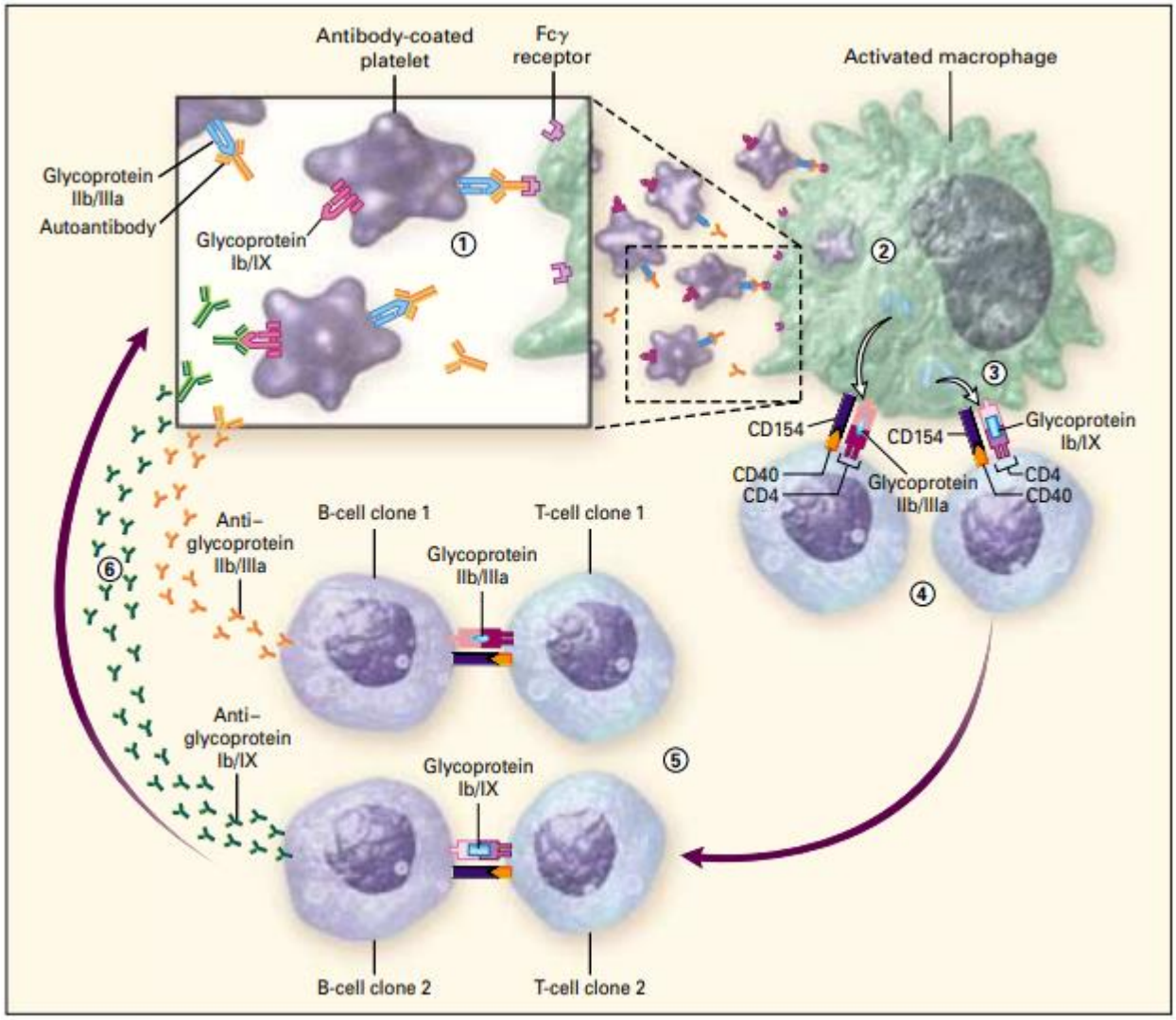
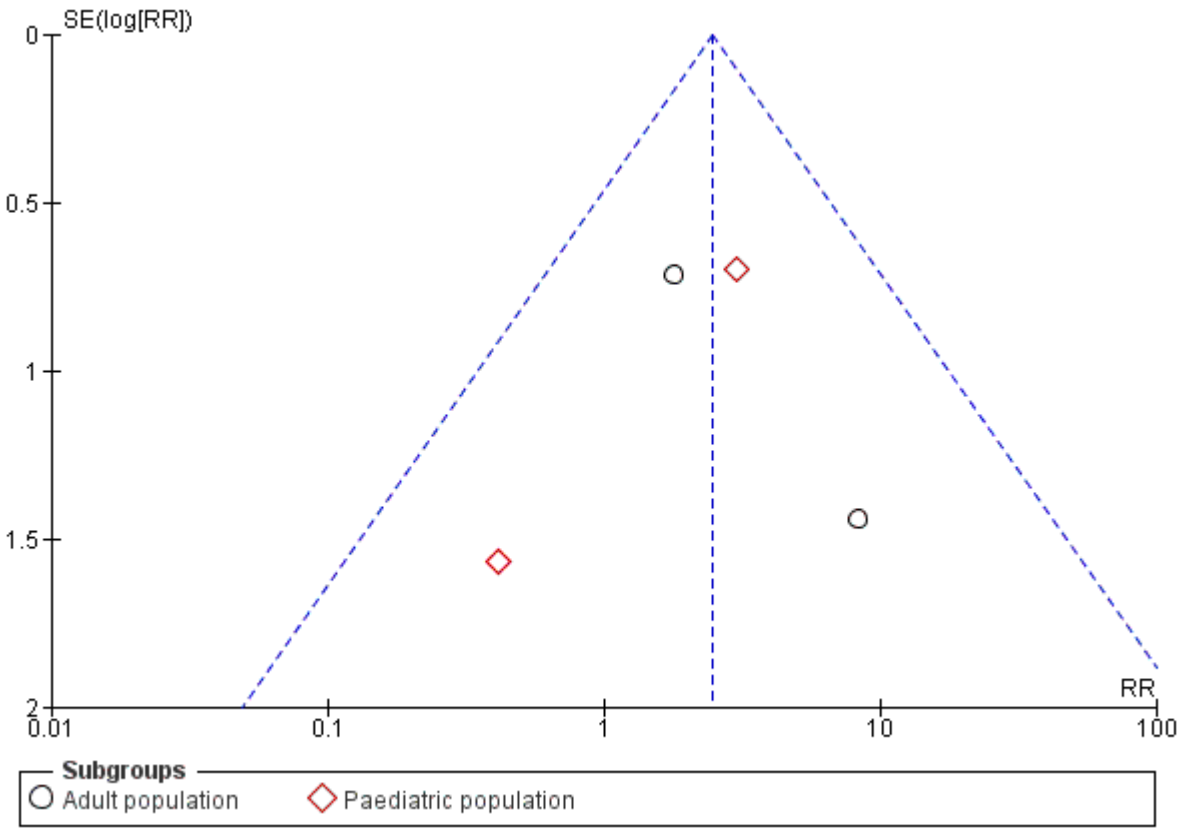
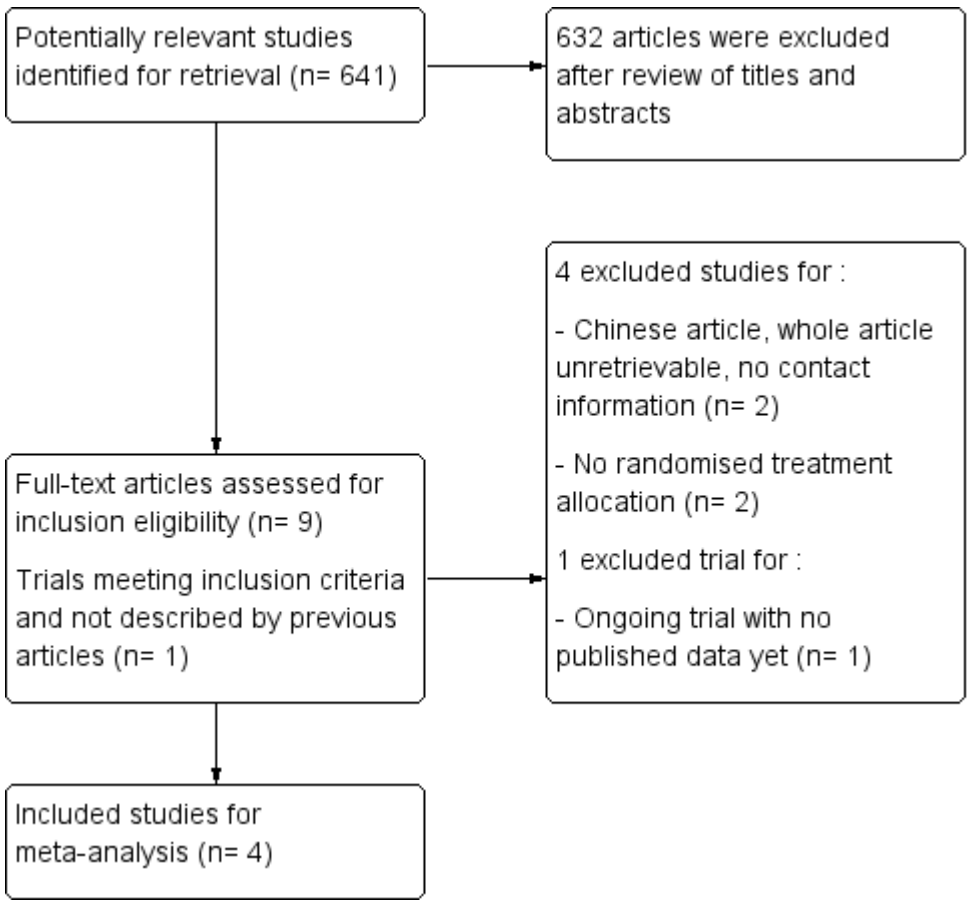


Figure 5.1. The factors that initiate autoantibody production are unknown. Most patients have antibodies against several platelet-surface glycoproteins at the time the disease becomes clinically evident. Here, glycoprotein IIb/IIIa is recognized by autoantibody (orange, inset), whereas antibodies that recognize the glycoprotein Ib/IX complex have not been generated at this stage (1). Antibody-coated platelets bind to antigen-presenting cells (macrophages or dendritic cells) through Fcg receptors and are then internalized and degraded (2). Antigen-presenting cells not only degrade glycoprotein IIb/IIIa (light blue oval), thereby amplifying the initial immune response, but also may generate cryptic epitopes from other platelet glycoproteins (light blue cylinder) (3). Activated antigen-presenting cells (4) express these novel peptides on the cell surface along with costimulatory help (represented in part by the interaction between CD154 and CD40) and the relevant cytokines that facilitate the proliferation of the initiating CD4-positive T-cell clones (T-cell clone 1) and those with additional specificities (T-cell clone 2) (5). B-cell immunoglobulin receptors that recognize additional platelet antigens (B-cell clone 2) are thereby also induced to proliferate and synthesize anti–glycoprotein Ib/IX antibodies (green) in addition to amplifying the production of anti–glycoprotein IIb/IIIa antibodies (orange) by B-cell clone 1 (6) (Cines 2002).

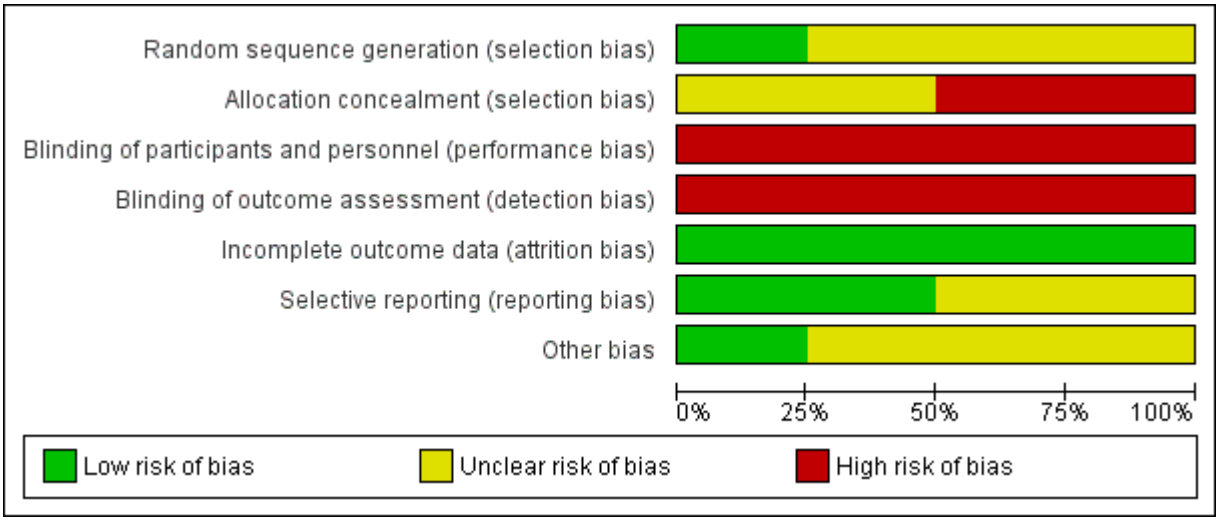
Annexe 5.2. Funnel plot of comparison: HP eradication treatment versus other treatments, complete response at 6 months.



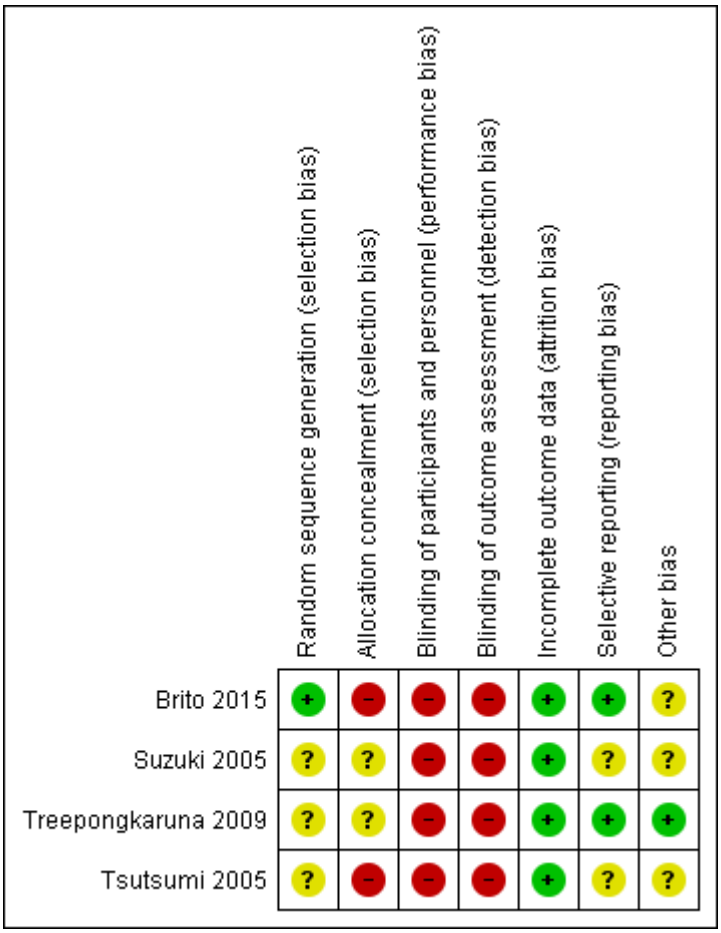
Annexe 5.3. Flow diagram of search process.



Annexe 5.4. Risk of bias graph: review authors' judgement about each risk of bias item presented as percentages across all included studies.

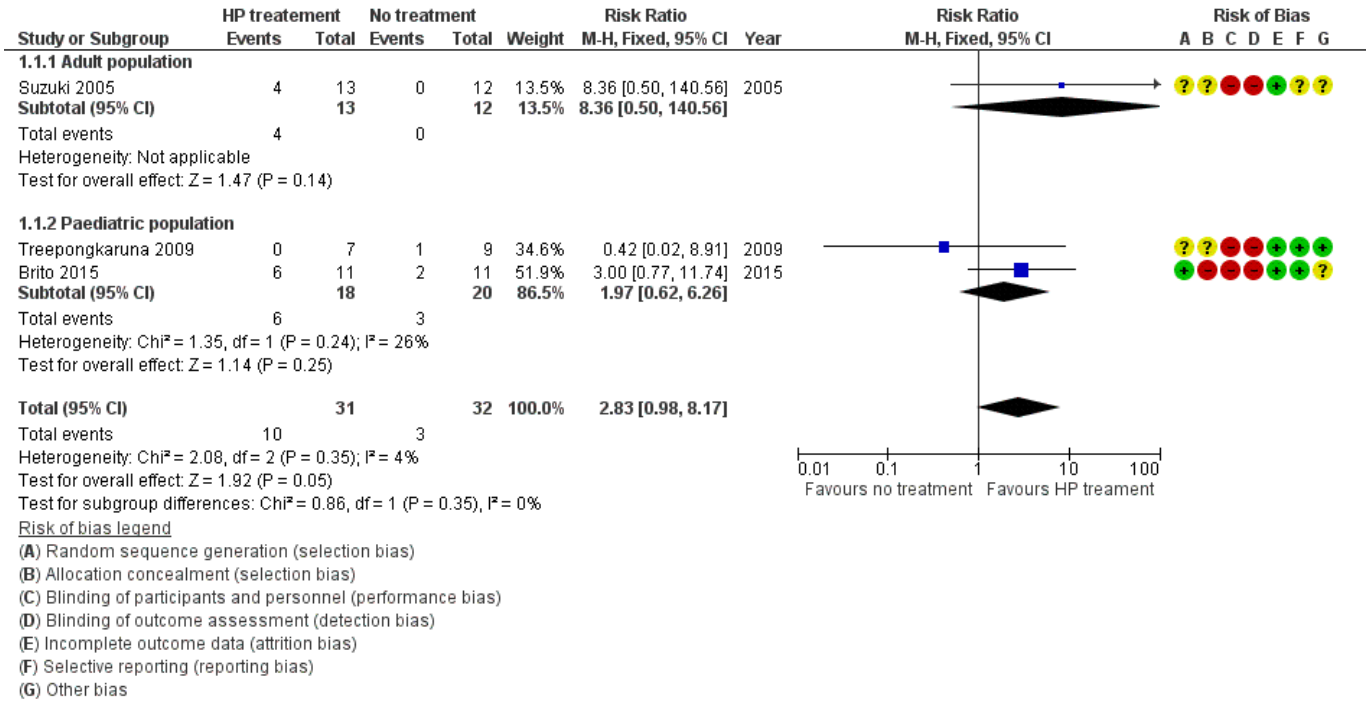


Annexe 5.5. Risk of biais summary: review authors' judgement about each risk of bias for each included study.

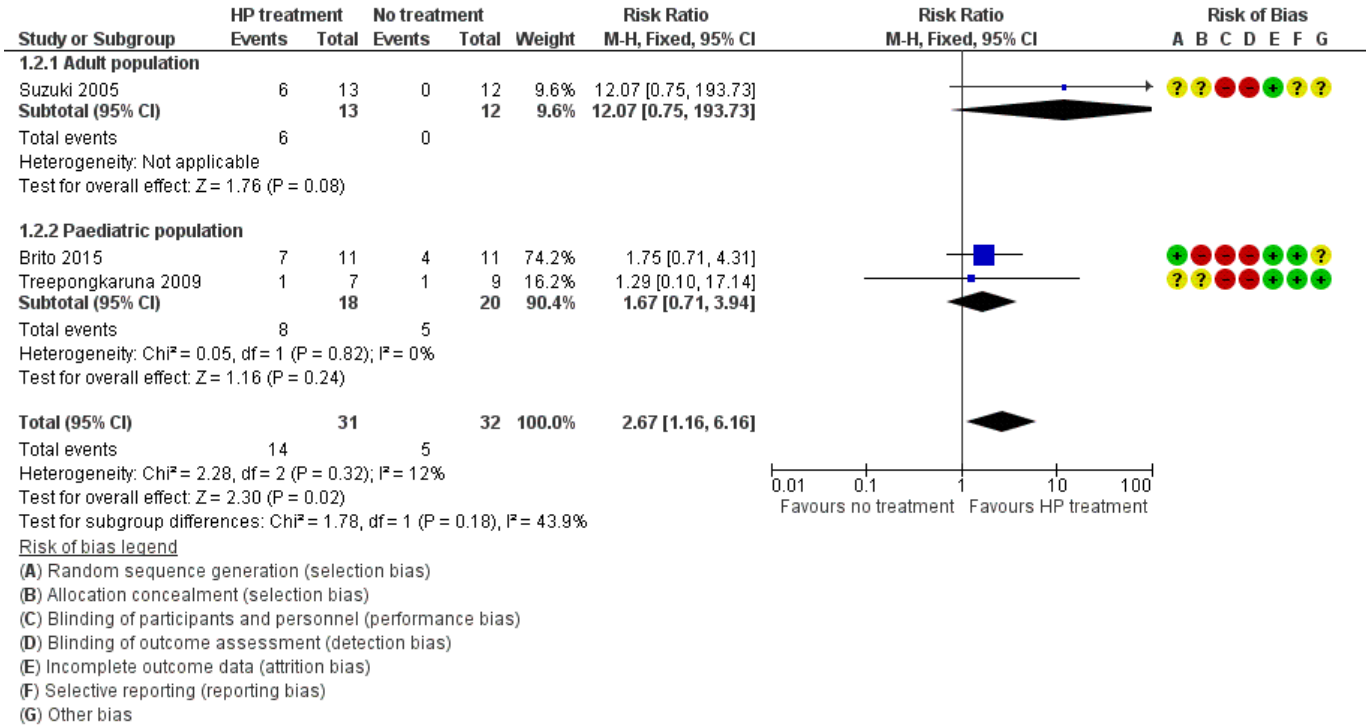


Annexe 5.6. Forest plots of comparison

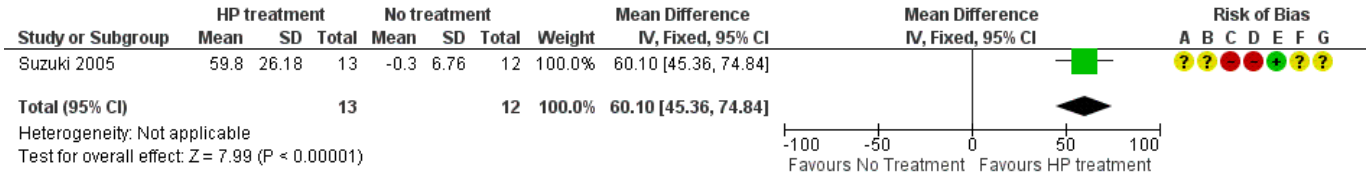
Annexe 5.6.1. Forest plot of comparison: HP eradication treatment versus no treatment, Complete response at 6 months (Analysis 1.1).



Annexe 5.6.2. Forest plot of comparison: HP eradication treatment versus no treatment, Platelet response at 6 months (Analysis 1.2).

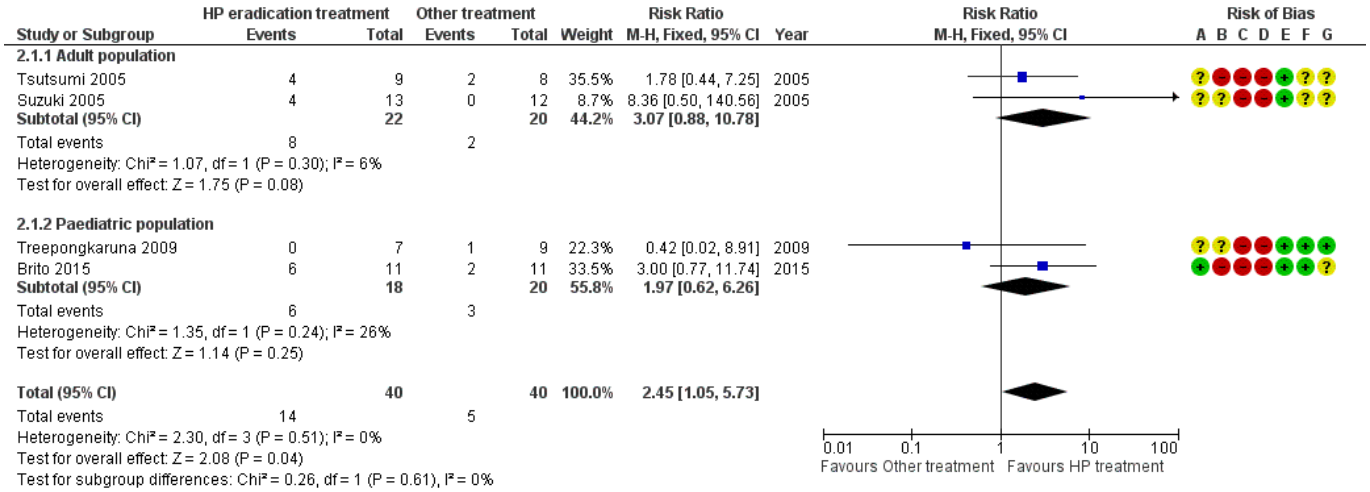


Annexe 5.6.3. Forest plot of comparison: HP eradication treatment versus no treatment, Absolute platelet difference, 6 months after intervention (Analysis 1.3).



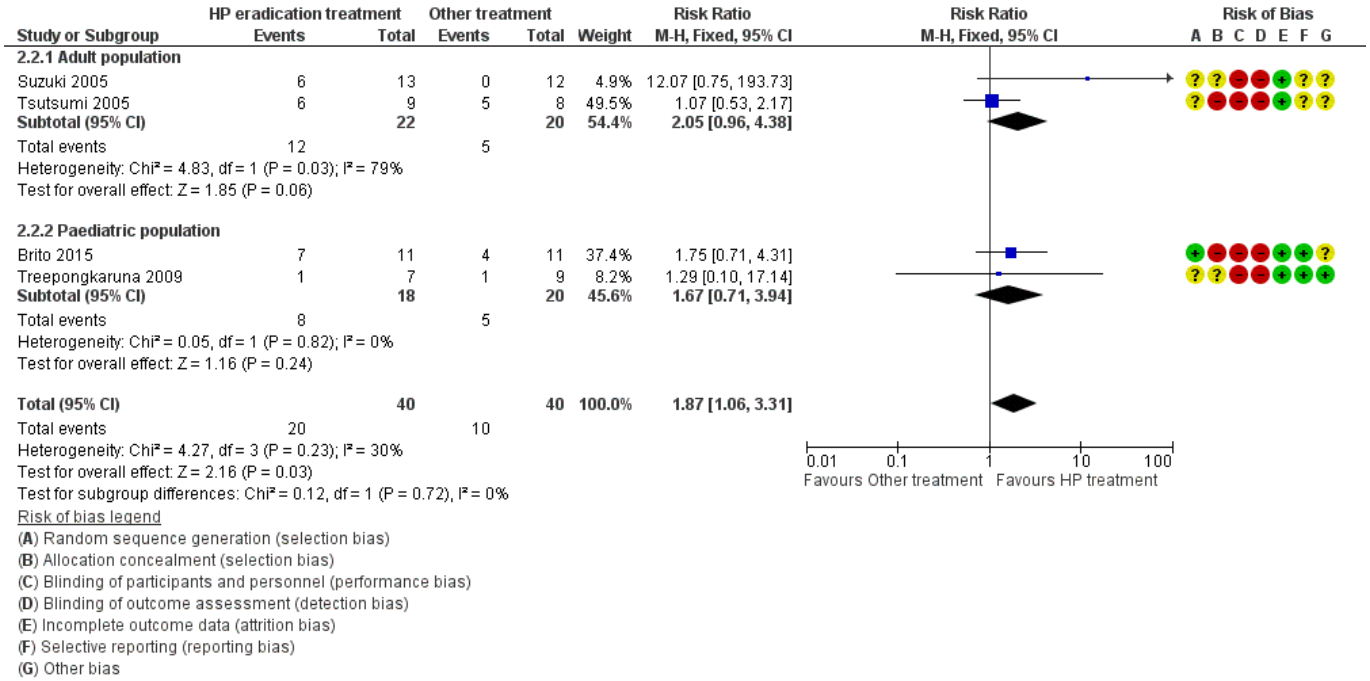
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Annexe 5.6.4. Forest plot of comparison: HP eradication treatment versus other treatments, Complete response at 6 months (Analysis 2.1).

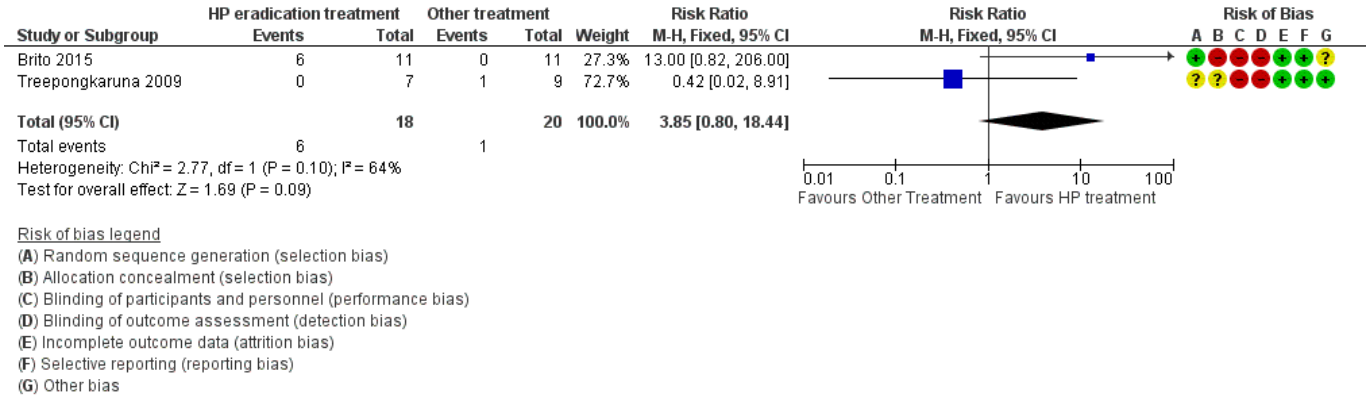


Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

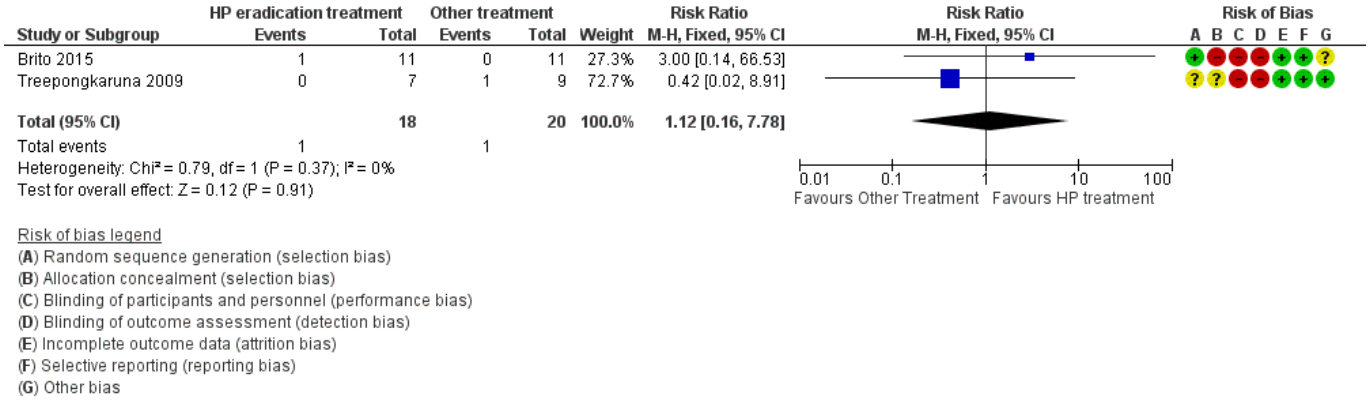
Annexe 5.6.5. Forest plot of comparison: HP eradication treatment versus other treatments, Platelet Response at 6 months (Analysis 2.2).



Annexe 5.6.6. Forest plot of comparison: HP eradication treatment versus other treatments, Total Adverse Events (Analysis 2.3).



Annexe 5.6.7. Forest plot of comparison: HP eradication treatment versus other treatments, Severe Adverse Events (Analysis 2.4).



Annexe 6. American Society of Hematology Guidelines (Neunert 2011, Neunert 2019) summary table for the management of ITP :

ITP in adults :

Case 1 : Newly diagnosed ITP in adults

First-line treatment of adult ITP

4.3.A. We suggest:

- Longer courses of corticosteroids are preferred over shorter courses of corticosteroids or IVIg as first-line treatment (grade 2B).
- IVIg be used with corticosteroids when a more rapid increase in platelet count is required (grade 2B).
- Either IVIg or anti-D (in appropriate patients) be used as a first-line treatment if corticosteroids are contraindicated (grade 2C).
- If IVIg is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary (grade 2B).

Treatment of patients who are unresponsive to or relapse after initial corticosteroid therapy

4.4.A. We recommend:

- Splenectomy for patients who have failed corticosteroid therapy (grade 1B).
- Thrombopoietin receptor agonists for patients at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy (grade 1B).

4.4.B. We suggest:

- Thrombopoietin receptor agonists may be considered for patients at risk of bleeding who have failed one line of therapy such as corticosteroids or IVIg and who have not had splenectomy (grade 2C).
- Rituximab may be considered for patients at risk of bleeding who have failed one line of therapy such as corticosteroids, IVIg, or splenectomy (grade 2C).

Laparoscopic versus open splenectomy and vaccination prior to splenectomy

4.5.A. We recommend:

- That for medically suitable patients, both laparoscopic and open splenectomy offer similar efficacy (grade 1C).

Management of secondary ITP, H. pylori-associated

7.3.A. We recommend:

- That eradication therapy be administered for patients who are found to have H pylori infection (based on urea breath tests, stool antigen tests, or endoscopic biopsies) (grade 1B).

7.3.B. We suggest:

- Screening for H pylori be considered for patients with ITP in whom eradication therapy would be used if testing is positive (grade 2C).

Case 2: treatment of adult ITP after splenectomy

Treatment of ITP after splenectomy

5.1.A. We recommend:

- Against further treatment in asymptomatic patients after splenectomy who have platelet counts > 30 x 109/L (grade 1C).

ITP in children :

Case 1 : Newly diagnosed ITP in children

Initial management of ITP

1.2.A. We recommend:

- Children with no bleeding or mild bleeding (defined as skin manifestations only, such as bruising and petechiae) be managed with observation alone regardless of platelet count (grade 1B).

Initial pharmacologic management of pediatric ITP

1.3.A. We recommend:

- For pediatric patients requiring treatment, a single dose of IVIg (0.8-1 g/kg) or a short course of corticosteroids be used as first-line treatment (grade 1B).
- IVIg can be used if a more rapid increase in the platelet count is desired (grade 1B).
- Anti-D therapy is not advised in children with a hemoglobin concentration that is decreased due to bleeding, or with evidence of autoimmune hemolysis (grade 1C).

1.3.B. We suggest:

- A single dose of anti-D can be used as first-line treatment in Rh-positive, non splenectomized children requiring treatment (grade 2B).

Case 2: Children who are treatment non-responders

Appropriate second-line treatments for pediatric ITP

2.1.A. We suggest:

- Rituximab be considered for children or adolescents with ITP who have significant ongoing bleeding despite treatment with IVIg, anti-D, or conventional doses of corticosteroids (grade 2C).
- Rituximab may also be considered as an alternative to splenectomy in children and adolescents with chronic ITP or in patients who do not respond favorably to splenectomy (grade 2C).
- High-dose dexamethasone may be considered for children or adolescents with ITP who have significant ongoing bleeding despite treatment with IVIg, anti-D, or conventional doses of corticosteroids (grade 2C).
- High-dose dexamethasone may also be considered as an alternative to splenectomy in children and adolescents with chronic ITP or in patients who do not respond favorably to splenectomy (grade 2C).

Splenectomy for persistent or chronic ITP or ITP unresponsive to initial measures

2.2.A. We recommend:

- Splenectomy for children and adolescents with chronic or persistent ITP who have significant or persistent bleeding, and lack of responsiveness or intolerance of other therapies such as corticosteroids, IVIg, and anti-D, and/or who have a need for improved quality of life (grade 1B).

2.2.B. We suggest:

- Splenectomy or other interventions with potentially serious complications be delayed for at least 12 months, unless accompanied by severe disease defined by the International Working Group as unresponsive to other measures or other quality of life considerations (grade 2C).

H. pylori testing in children with persistent or chronic ITP

2.3.A. We recommend:

- Against routine testing for H pylori in children with chronic ITP (grade 1B).

Serment d’Hippocrate

En présence des maîtres de cette école, de mes condisciples, je promets et je jure d’être fidèle aux lois de l’honneur et de la probité dans l’exercice de la médecine.

Je dispenserai mes soins sans distinction de race, de religion, d’idéologie ou de situation sociale.

Admis à l’intérieur des maisons, mes yeux ne verront pas ce qui s’y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les moeurs ni à favoriser les crimes.

Je serai reconnaissant envers mes maîtres, et solidaire moralement de mes confrères. Conscient de mes responsabilités envers les patients, je continuerai à perfectionner mon savoir.

Si je remplis ce serment sans l’enfreindre, qu’il me soit donné de jouir de l’estime des hommes et de mes condisciples, si je le viole et que je me parjure, puissé-je avoir un sort contraire.

Le Traitement d’Helicobacter pylori dans le Purpura Thrombopénique Idiopathique : méta-analyse

Le traitement d'éradication d'Helicobacter pylori (HP) est utilisé comme traitement complémentaire chez les patients atteints conjointement de PTI et d’une infection à Helicobacter pylori. Plusieurs essais randomisés ont tenté de confirmer l'éradication d’HP comme un moyen efficace d’obtenir une rémission complète du PTI, avec des résultats contradictoires, des petites cohortes et un faible niveau de preuve. Cette méta-analyse inclus quatre essais cliniques avec un total de 80 patients pédiatriques et adultes atteints de PTI chronique. Elle compare l’évolution du PTI après une trithérapie associant amoxicilline, clarithromycine et lansoprazole, ou une monothérapie par inhibiteur de pompe à protons, ou en l’absence de traitement spécifique anti-HP. La survie globale n'a pas pu être évaluée pour le traitement d'éradication d’HP car aucune des études n'a mesuré la survie globale comme critère principal. Selon notre méta-analyse, le traitement d'éradication d’HP augmente la réponse plaquettaire globale et le taux de réponse complète mais les résultats sont critiquables. Le traitement d'éradication d’HP augmente la différence de numération plaquettaire avant et 6 mois après le traitement, mais les résultats se basent sur une seule étude. Les effets indésirables avec et sans traitement d'éradication d’HP sont similaires. Des données supplémentaires sont nécessaires pour confirmer l'effet du traitement d'éradication d’HP dans le PTI chronique. Nous recommandons de suivre les recommandations nationales pédiatriques et adultes jusqu'à ce que de nouvelles données soient disponibles.

Mots-clés : PTI, randomisation, réponse complète, numération plaquettaire

Helicobacter pylori treatment for immune thrombocytopenic purpura : a meta-analysis

Idiopathic thrombocytopenic purpura (ITP) is an acquired bleeding disorder with the production of anti-platelet auto-antibodies that impair cellular immunity and megakaryopoiesis, leading to profound thrombocytopenia and bleeding symptoms. Helicobacter pylori (HP) eradication treatment is used in patients with Helicobacter pylori associated ITP as an adjunct therapy, and several randomized trials have tried to confirm HP eradication as an effective way to reach that goal, with contradictory results, small cohorts, and low power evidence. This meta-analysis included four trials totaling 80 patients with cITP and compared a HP eradication treatment associating amoxicillin, clarithromycin and lansoprazole with no treatment or proton pump inhibitor monotherapy in children and adults. Overall survival could not be evaluated for the HP eradication treatment because none of the studies measured overall survival as an outcome. The fact that HP eradication treatment increases the overall platelet response, and the complete response rate remains doubtful. The HP eradication treatment increases the difference in absolute platelet count, 6 months after the intervention, but results are based on a single study. Adverse effects with HP eradication treatment and without were similar. More data is needed to confirm the effect of a HP eradication treatment in chronic ITP. We recommend following National Pediatric and Adult Guidelines until new data is available.

Keywords : ITP, randomization, complete response, platelet count