Eradication Therapy for *Helicobacter Pylori* in Idiopathic thrombocytopenic Purpra

Hala M Fahmy[1], Nehad M Twfik [1] , Ahmed Murad Hashem [1] , Maha Gaafar [2]

[1]Department of Internal Medicine ,Faculty of Medicine, Cairo University; Egypt.
[2] Department of clinical and chemical pathology; Faculty of Medicine ; Cairo University;Egypt *
Halafahmy70@yahoo.com

Abstract: Background: Association between *Helicobacter pylori* and idiopathic thrombocytopenic purpura (ITP) has previously been reported. It has also been shown that eradication of *H. pylori* can increase platelet counts in patients with ITP. The aims of this study were to determine the prevalence of *H. pylori* infection in patients with ITP in Egypt, and the effect of bacterial eradication on their platelet counts. **Subjects and methods**: The study included 50 cases of ITP patients 28 females and 22 males with mean age of 33.24 ± 12.44years. 50 healthy individuals who are age and sex matched served as a control group. Testing for *H pylori* infection was done by serological testing for *H.pylori* serum antibodies and *H.pylori* stool antigen test. **Results:** *H. pylori* infection in patients with ITP was significantly higher than in control individuals (82.0% and 46.0%, respectively , $p = 0.000$), no statistical significant difference between *H.pylori* stool Ag and Abs positive and negative ITP patients regarding sex and age , no statistically significant difference between *H.pylori* infected and non infected ITP patients regarding age, sex and disease duration . ITP patients infected with *H pylori* were treated with *H pylori* eradication regimen, Thirty nine *H. pylori* infected ITP patients were successfully eradicated .Of them 26 patients (66.6%) showed complete or partial response regarding improvement of platelet counts, meanwhile 13 patients (33.3%) showed no response . No statistically significant difference between responders and non responders regarding age, sex, duration of disease and steroid treatment before and during the study. **Conclusions**: According to these results and others from different countries where *H. pylori* infection rates are high, patients with ITP should be initially tested for *H. pylori* status, and if present, infection should be eradicated before initiating a drastic conventional ITP treatment .Larger controlled clinical trials are recommended to determine the predictors of response , response rate and durability and optimal time of therapy .
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1. Introduction

Helicobacter pylori is a Gram-negative microaerophilic bacterium that colonizes the human stomach of more than 50% of the world population. It is recognized as the causative agent of active chronic gastritis and is the predominant cause of peptic ulceration, i.e., gastric and duodenal ulcers (1). Additionally, *H pylori* is a cofactor in the development of both adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphomas, and therefore has been designated as a class I carcinogen by the World Health Organization(2). The relationship between *H pylori* infection and idiopathic thrombocytopenic purpura (ITP) is less clear. Eradication of the infection has been reported to produce an increase of the platelet count in some studies, whereas other reports have failed to demonstrate such beneficial effects(3).

The prevalence of *H pylori* infection in adult ITP patients has been systematically reviewed and was not found different from that reported in the general healthy population matched for age and geographical area (4) .

The mechanisms by which *H pylori* may cause ITP was investigated in many studies. Molecular mimicry is one of the most important hypotheses that have been suggested, according to which *H pylori* could induce antibody production in response to antigens that cross react against various platelet glycoprotein antigens. *Takahashi et al.,*showed a decline in platelet-associated Ig G in ITP patients after the eradication of *H pylori* infection as well as the existence of a molecular mimicry between those antibodies and the CagA protein(5).

Also *Franceschi et al.,*demonstrated that CagA antibodies cross-react with a peptide specifically expressed by platelets of patients with ITP ,also *Franceschi et al.,*proposed a possible explanation for the fact that ITP may occur in only a small subset of patients infected by CagA-positive strains(6).

Other putative targets of molecular mimicry are Lewis (Le) antigens, which are expressed by *H pylori* in a strain-specific manner. Gerhard *et al.,*found that Lewis antigens adsorb to platelets and might serve as targets for anti- Lewis antibodies in patients with an appropriate genetic background (7). Another hypothesis suggests that molecular mimicry of cagA or Lewis antigens and platelet antigens may initiate the development of ITP, but with time continued platelet destruction and epitope spreading may lead to the development of chronic thrombocytopenia refractory to eradication of *H pylori*

infection (8) . This model is reminiscent of the role played by *H pylori* in the development of MALT lymphomas, which initially may respond to bacterium eradication but may subsequently develop new mutations leading to autonomous disease.

Furthermore, Semple and colleagues found that the LPS of Gram-negative bacteria can significantly enhance Fc-dependent platelet phagocytosis (9) .These results suggest that infectious agents in combination with antiplatelet antibodies could affect platelet destruction *in vivo*, which may be at least one explanation for why thrombocytopenia worsens in some patients with ITP during infections and, alternatively, resolves in other patients with ITP who are treated with bacterial eradication therapy.

Other studies have shown that some strains of *H pylori* bind von Willebrand factor (VWF) and induce platelet aggregation in the presence of *H pylori* antibodies (10). Activation may promote platelet clearance and antigen presentation, which augments production of antibacterial antibodies. Somatic mutation may lead to the development of antibodies that either recognize bacterially derived factors that bind to platelets or cross react with platelet antigens (8) .

Both *H pylori* infection and ITP are associated with a polarized Th1-type phenotype (11,12). Accordingly, it may be speculated that *H pylori* infection creates an immunological environment that facilitates the onset and/or persistence of ITP (13).

An analysis of 25 reported series world-wide showed that eradication was successful in 671 of 792 (84.7%) patients(14). On the other hand the overall response of 24 Phase II trials with a total of 779 *H. pylori*-positive patients was 53%(14) ranging from 0% in the North American series (15) to 100% in the early Italian series(16).

We therefore conducted a prospective study to assess the prevalence of *H pylori* infection in Egyptian patients with ITP and the efficacy of *H pylori* eradication on the platelets count.

2. Subjects and Methods:

The present study was conducted on 100 subjects classified into two groups as follows;

Group I (ITP patients):-

This group included 50 patients with idiopathic thrombocytopenia, 28 females and 22 males their ages ranged from 19 to 66 years with a mean of 33.24± 12.44years.

Patients with ITP, defined according to the criteria set forth in the American Society of Hematology (ASH) Guidelines (17).Patients were recruited from outpatient clinic and inpatients department of Kasr El-ainy Hospital over a 12 month period (May2011-April 2012).

Inclusion criteria:-

-Age of 18 years and older

-Platelet count of less than 60 X 10^9/L

Exclusion criteria:-

Patients with other possible causes of thrombocytopenia such as

-Pseudothrombocytopenia

-HCV , HBV and HIV infections .

-Lympho proliferative disorders.

-Autoimmune diseases.

-Drug induced thrombocytopenia.

Patients who were treated by immunosuppressive treatments or other drugs for their ITP at the time of inclusion were eligible if the doses of the ongoing medications were stable for at least 4 weeks before inclusion.

Patients were not eligible for the study if they had been treated for *H pylori* within 2 years or if they had been treated with either an antibiotic, proton pump inhibitor or bismuth within the past 4 weeks.

Group II (Control):-

This included 50 healthy individuals who are age and sex matched with group I to serve as a control group.

Verbal consent was provided by all included subjects or their parents according to age.

All enrolled subjects were subjected to full medical history, complete clinical examination, laboratory investigations (complete blood count, platelet count after 3 months, 6 months from *H pylori* eradication, liver enzyme, urea, creatinine and testing for *H pylori* infection by detection of *H.pylori* serum antibodies and *H.pylori* stool antigen .

***H pylori* eradication regimen:**

The 41 Patients infected with *H pylori* were treated by omeprazole 20 mg, clarithromycin 500 mg, and amoxicillin 1000 mg taken together twice a day for 2 weeks. If eradication of *H pylori* was not achieved with the initial regimen, treatment was pursued with alternative regimens. To determine if the *H pylori* eradication regimen could have nonspecific effects on the platelet count, nine ITP patients who are *H pylori* negative were also treated with the same eradication regimen.

Monitoring

- *H. pylori* stool Ag one month after eradication regimen to detect response

-Platelet counts were performed at the time of testing and after 3 and 6 months duration from

H. pylori eradication treatment.

There were two cases lost follow up .

Response criteria

A clinical response was defined by the International Working group on ITP (18)

-*Complete response (CR)* : platelet count of at least 100X10^9/L within 2 months after completion of *H pylori* eradication therapy.

-*Partial response (PR)* : platelet count above 30 x10^9/L and at least a doubling of the initial count.

-*Non responder (NR)* : platelet count below 30 X 10^9/L or when the platelet count did not increase to more than

50% of the pretreatment level with or without maintenance therapy.

According to response the patients group subdivided into responders *(CR + PR)* and non responders *(NR)*.

Sure-Vue *H. pylori* test device (Fisher Scientific Company) :

A rapid test for the qualitative detection of IgG antibodies to *H. pylori* in whole blood, serum and plasma. It is a rapid chromatographic immunoassay aid in the diagnosis of *H. pylori* infection in adults 18 years of age and older. The test was performed according to manufacturer's instructions.

Principle of the test : Purified *H.pylori* antigen is coated on the surface of micro wells. Diluted patient serum is added to wells, and the *H.pylori* IgG specific antibody, if present, binds to the antigen. All unbound materials are washed away. After adding enzyme conjugate, it binds to the antibody-antigen complex. Excess enzyme conjugate is washed off and TMB Chromogenic substrate is added. The enzyme conjugate catalytic reaction is stopped at a specific time. The intensity of the color generated is proportional to the amount of IgG specific antibody in the sample. The results are read by a micro well reader compared in a parallel manner with calibrator and controls.

One step *H. pylori* antigen test device (Atlas Medical, Cambridge):

A rapid test for the detection of *H. Pylori* antigen in stool sample. The test was performed according to manufacturer's instructions.

***Principle*:** The one step *H. pylori* antigen test device is a qualitative, lateral flow immunoassay for the detection of *H. pylori* antigens in human stool specimens. In this test, the membrane is pre coated with anti-*H. pylori* antibodies on the test line region of the test. During testing, the diluted specimen reacts with the particle coated with anti-*H.pylori* antibodies. The mixture migrates upward on the membrane by capillary action to react with anti-*H. pylori* antibodies on the membrane and generate a colored line. The presence of this colored line in the test region indicates a positive result, while its absence indicates a negative result. To serve as a procedural control, a colored line will always appear in the control line region indicating that proper volume of specimen has been added and membrane wicking has occurred.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD) or as median (range). Chi-square test or Fischer exact tests were used for analysis of categorical data; the t test was used to compare groups in which the data involved continuous variables. A 2-tailed P value (probability of chance) was as follows:

$P < 0.05$ was considered significant.

$P > 0.05$ was considered non significant.

$P < 0.01$ was considered highly significant

3.Results

The present study was conducted on 100 subjects classified into two groups as follows:

(Group I) included 50 ITP patients, patient characteristics are shown in table (1).

(GroupII) included fifty healthy individuals, who are age and sex matched with group I to serve as a control group

Comparison between cases and control as regard *H.pylori* results is showed in table (2).

Table 1; Shows the characteristics of ITP patients

Patients characteristics	
Age (ys)	33.24± 12.44 (19-66)
Sex (%)	22(44%) Male 28(46%) Female
Disease duration (ys)	4.1± 5.2
Number of previous treatment medications no 1 2 3 and more	 1(2%) 12(24%) 32(64%) 5(10%)
Prednisone treatment during study (%)	26(52.0%)

Table 2; Comparison between cases and control as regard *H.pylori* results

***H.pylori* infection**	**Cases**	**Controls**	***P value***
Positive stool Ag	31(62.0%)	18(36.0%)	0.009
Positive serum Abs	34 (68.0%)	12(24.0%)	0.000
stool Ag & serum Abs	41(82.0%)	23(46.0%)	0.000

This table shows a highly significant statistical difference between cases and controls as regard *H.pylori* stool antigen (*P value*= 0.009), *H.pylori* serum Abs (*P value*= 0.000) and *H.pylori* infection (*P value*= 0.000)

Table 3; Comparison between males and females as regards *H.pylori* stool Ag & serum Abs in ITP patients.

Item	Females (28)	Males (22)	*P* value
Positive Stool antigen	15(53.57%)	16(72.72%)	0.166
Positive Serum Abs	17(60.7%)	17(77.27%)	0.212

This table shows no statistical significant difference between males and females as regards *H.pylori* stool antigen and serum Abs positivity in ITP patients.

Table 4; Comparison between *H.pylori* Ag & Abs positivity and negativity as regards the age of ITP patients.

Stool Ag / Item	Positive	Negative	*P* value
Age	33.68 ± 13.11	30.95 ± 10.78	0.449
Serum Abs / Item	**Positive**	**Negative**	**P value**
Age	33.26 ± 13.33	31.63 ± 11.83	0.678

This table shows a comparison between *H.pylori* stool Ag and Abs positivity and negativity regarding age in ITP patients, it shows that there is no statistical significant difference regarding age (*P* value = 0.449).

Table 5; Comparison between *H.pylori* infected ITP patients regarding age ,sex and disease duration.

Item	ITP patients		
	***H.pylori* positive N=41**	***H.pylori* negative N=9**	***P* value**
Age (mean) years	33.98±12.6	31.25±11.6	0.354
Duration (years)	4.5±5.2	3.00±3.7	0.227
Sex Males/ Females	20:21 (48.8 : 51.2%)	2:7 (22.2 : 77.8%)	0.146

This table shows no statistically significant difference between *H.pylori* infected and non infected ITP patients regarding age, sex and disease duration .

Thirty nine *H.pylori* infected ITP patients were successfully eradicated , only 2(9.5%) of 41 were not due to drug intolerance.

Table 6; Comparison between responders and non-responders in relation to ITP treatment prior to study after 6 month from *H.pylori* eradication.

Response	Treatments prior to study				Total N=39
	None N=1	1 drug N=12	2drugs N=23	3or more N=3	
Responders	1 2.56%	7 17.94%	17 43.58%	1 2.56%	26 66.66%
Non-responders	0 0.0%	5 12.82%	6 15.38	2 5.12%	13 33.33%

Table 7; Comparison between responders and non responders in relation to age, sex, duration and type of treatment before and during the study in ITP patients 6 months from *H.pylori* eradication .

Item	Responders N =26	Non-responders N=13	*P* value
Age (years)	32.30±10.88	34.93±1077	0.480
Duration (years)	3.2±2.2	4.7±3.83	0.37
Sex Males(20) Females(19)	 14 (70.0 %) 12(63.1%)	 6(30.0%) 7(36.8%)	0.345
Treatment with prednisone Yes (19) No (20)	 14(73.7%) 12 (60%)	 5(26.3%) 8(40%)	0.364

This table shows no statistically significant difference between responders and non responders regarding age, sex, duration and steroid treatment during the study in ITP patients 6 months from *H.pylori* eradication .

4. Discussion

Helicobacter pylori is a recognized cause of gastroduodenal disorders including gastritis, peptic ulcer, gastric cancer, and mucosa-associated lymphoid tissue lymphoma (MALToma). Eradication of this bacterium may contribute to histological improvement of gastritis (19) , reduction in peptic ulcer recurrence (20) , and remission of MALToma (21) .

In recent years, several studies have investigated the relationship between *H.pylori* and extra-gastroduodenal disorders, including autoimmune-associated diseases. With regard to idiopathic thrombocytopenic purpura (ITP), which is induced by autoantibodies against platelets, studies to determine the effect of *H. pylori* eradication on platelet recovery have provided conflicting results.

The aim of this work was to assess the prevalence of *H. pylori* infection in Egyptian patients with ITP and the efficacy of *H. pylori* eradication on the platelets count.

The possible role of *H. pylori* infection in the development of ITP is a subject of extensive investigation. Systematic reviews of past literature showed an overall platelet response in more than 50% of the patients successfully treated for the infection and increased response rates in countries with a high prevalence of *H. pylori* infection in background populations (22). In the meta-analysis performed by Arnold et al , the cumulative sample size of cases was 282 patients with ITP (pooling 11 studies, eight from Japan), 205 of whom were *H. pylori* positive and 77 patients were *H. pylori* negative. All patients underwent eradication treatment. The odds of achieving a platelet count response following eradication therapy were increased by 14.5 times in patients with *H. pylori* infection (51.2% vs 8.8%) (23).

In our study there is a strong association between *H.pylori* infection and ITP ,41 out of 50 ITP patients were *H. pylori* positive (82%) , eradication therapy for *H.pylori* was given for 39 ITP patients, the other 2 patients lost follow up . Six months after *H.pylori* eradication, complete recovery occurred in 15 patients (38.46%) , partial recovery in 11 patients(28.20%), with total responders 26 patients(66,66%) ,13 patients (33.33%) showed no response. That goes with an agreement with Gasbariini et al who reported that 11of 18 patients(61%) with ITP (mean age, 45 years) were infected with *H pylori*, and in 8patients(73%) in whom successful eradication was achieved there was a significant increase in platelet count 4 months after therapy (16) . Emilia et al more recently demonstrated that 13of 30 patients(43%) with ITP (mean age, 50 years) were infected with *H pylori*, and platelet recovery occurred in 12 of 13(92%) treated patients (24).

Veneri *et al.,* showed that 34 of 52 ITP adult patients(65.4%) were infected by *H. pylori* and bacterium eradication was accompanied by a long-term platelet response in 32 (94%) of them, the effect of *H. pylori* eradication on platelet count did not depend on the severity of ITP (25). In Japan, Kohda *et al.,* reported that *H.pylori* infection was found in 25of 40 ITP patients(62%) (mean age, 53 years), and 12(63%) of the 19 treated patients showed a significant increase in platelet count (26). Results of 2 studies supported platelet recovery in ITP patients following *H.pylori* eradication. Hino *et al.,* and Hashino *et al.,* demonstrated that *H pylori* was detected in 21 of 30 (70%) (mean age, 54 years) and 14 of 22 (64%) (mean age, 49 years) of the patients, respectively, and platelet recovery was obtained in 44% (8 of 18) and 69% (9 of 13) of successfully treated patients, respectively (27,28).

In contrast to our study, Ahn and Suvajdzić *et al.,* described a poor response to *H. pylori* eradication therapy in patients with ITP in the United States and the United Kingdom,6 of 23(26%) patients , 1of 15 ITP (7%) patients respectively (29,30).This difference may be due to small number studied cases.

In our study there was statistical significant difference between *H.pylori* positive and *H.pylori* negative among ITP patients regarding age and sex.

In this study concurrent steroid (prednisone) given in patients with a count between 20,000 and 50,000 per µl or if significant internal or mucocutaneous bleeding has developed, hospitalization may be needed with or without platelet transfusion. Gasbariini *et al.,* also allow concurrent steroid therapy for platelet counts less than 100x 10^9/L, a factor that may have exaggerated the response (16). The initial platelet counts were above 75 x 10^9/L in all patients, suggesting milder disease, and it was not clear whether patients were continued on previous ITP therapy or had a wash outperiod prior to *H. pylori* eradication.

An effect of concurrent ITP therapy on post-eradication platelet counts is a potential confounder in some studies. As mentioned previously, the high response rate reported by Gasbarrini *et al.,* may have been affected by concurrent use of steroids if platelet counts dropped below 100x10^9/L (16). It was evident that some studies allowed concurrent ITP therapy but did not stipulate whether changes to this therapy were made in the post-eradication phase (31). Some authors required a 1–3 months washout period of no therapy prior to eradication (32), while others allowed concurrent ITP therapy that had been stable for 1–6 months prior to eradication . In some cases, the authors did not allow changes to concurrent ITP therapy after the eradication therapy had begun (33). In our study 26(52.0%) of 50 ITP patients, 19(48.7%) of 39 *H.pylori* infected ITP patients were receiving prednisone at time of inclusion , 14(73.6%) of 19 patients achieved platelet response (CR+PR), 5(26.31%) of 19 were non responders (NR), 20(51.28%) of 39 *H.pylori* infected patients were not receiving any treatment at time of study 12 (60.0%) of

20 achieved platelet response (CR+PR) , 8(40.0%) were non-responders (NR) (p value= 0.364) so there is no significant difference between platelet response in patients who received prednisone and those who received nothing at time of study .

In this study the effect of prior treatments before time of inclusion on platelet count after *H.pylori* eradication was estimated, 17 of 26 recovered (CR+PR) patients (65.38%) were splenctomized prior to study , 3 of 26 recovered patients (11.53%) received IVIg prior to study 23of 26 recovered patients(88.46%) received prednisone prior to study , these results go with an agreement with Veneri *et al.,* stratified patients based on prior therapy and median platelet counts ,a higher than expected response rate to *H. pylori* eradication was found in the group where free from immunosuppressive therapy (34). By contrast, no difference in response rates between previously untreated and treated cases was found in a larger cohort (31). Other authors have shown better platelet responses to *H. pylori* eradication therapy in steroid-naive patients than in patients previously treated with steroids (26).

The majority of studies have treated only *H. pylori* positive patients with the assumption that *H.pylori* plays a predominant role in the pathogenesis of ITP.

Our study showed no statistic significant difference between responders and non- responders as regard age, sex and duration of illness. This in agreement with Hee Sang *et al.* (35).

To determine if the *H pylori* eradication regimen could have nonspecific effects on the platelet count, in our study the nine ITP patients who are *H pylori* negative were also treated with the same eradication regimen. No response regarding platelets count was reported , similar results were obtained in two studies in which eradication therapy was administered to *H. pylori*-negative patients and failed to show any platelet response in 14 patients, suggesting that, in *H. pylori*-associated ITP, eradication of H. pylori is the operative mechanism rather than other effects of the eradication protocol (36).

The reported efficacy of Omeprazole to increase platelet counts in patients with ITP has been attributed to a variable and sometimes transient anti-*H.pylori* effect (37).

5. Conclusion

Patients with ITP should be initially tested for *H. pylori* status, and if present, infection should be eradicated before initiating a hazards conventional ITP treatment .Larger controlled clinical trials are recommended to determine the predictor of response , response rate and durability and optimal time of therapy .

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