DOI: 10.24287/1726-1708-2023-22-3-68-73

Received 02.05.2023
Accepted 09.08.2023

Helicobacter pylori infection in children with immune thrombocytopenia

Seham M. Ragab[1], Mahmoud A. El-Hawy[1], Samah M. Awad[2], Walaa Alaa Soliman[1], Asmaa A. Mahmoud[1]

[1]*Menoufia University, Menoufia, Egypt*
[2]*National Liver Institute, Menoufia University, Menoufia, Egypt*

Correspondence:
Mahmoud Ahmed El-Hawy,
Department of Pediatrics, Faculty of Medicine, Menoufia University, Shebin El Kom, Egypt
Address: Shebin El Kom, 32511 Menoufia, Egypt
E-mail: mahmodelhawy18@yahoo.com

To detect the association between *Helicobacter pylori* (*H. pylori*) infection and immune thrombocytopenia in children and adolescents. Immune thrombocytopenia (ITP) is a common bleeding disorder in childhood. *H. pylori* is a widespread organism that is present in about 50% of the global population. There is an obvious relation between helicobacter pylori infection and chronic idiopathic thrombocytopenic purpura. A cross-sectional study was conducted in 95 patients with ITP who were recruited from the Hematology Unit, Department of Pediatrics, Menoufia University Hospital in the period from June 2021 to June 2022. The age of the patients ranged between 3.5 and 7.5 years. Fifty-five of them were males and 40 were females. The study was approved by the Ethical Committee of the Faculty of Medicine, Menoufia University. Out of the studied ITP children, 62 (65.3%) were positive for *H. pylori* antigen in stool, and 33 (34.7%) were negative. There was a significant difference between *H. pylori*-positive and *H. pylori*-negative patients regarding the grade of bleeding at presentation; 51 (82.3%) *H. pylori*-positive patients presented with grade 3 bleeding, 35 (56.5%) of them presented with skin and gum bleeding, 16 (25.8%) presented with skin bleeding and epistaxis. There was a statistically significant difference in the rate of recovery between *H. pylori*-negative patients (78.8%) and *H. pylori*-positive patients (22.6%). There was a significant rise in the platelet count in *H. pylori*-positive patients after the treatment of *H. pylori*. The prevalence of *H. pylori* infection in ITP pediatric patients was 65.3%. There was a significant rise in the platelet count in *H. pylori*-positive ITP children after the treatment of *H. pylori*.
Key words: *children, Helicobacter pylori, immune thrombocytopenia*

Seham M. Ragab, et al. Pediatric Hematology/Oncology and Immunopathology. 2023; 22 (3): 68–73.
DOI: 10.24287/1726-1708-2023-22-3-68-73

Immune thrombocytopenia (ITP) in childhood is characterized by isolated thrombocytopenia (platelet count < 100,000/microliter with normal white blood cell count and hemoglobin level) in the absence of other disorders, causing thrombocytopenia [1].

The cause of ITP remains unknown in most cases, but it can be triggered by a viral infection or other immunologic or environmental triggers [2].

ITP was previously known as idiopathic thrombocytopenic purpura or immune thrombocytopenic purpura. The current term Immune Thrombocytopenia preserves the widely-recognized acronym "ITP", while acknowledging the immune-mediated mechanism of the disorder and that patients may have little or no signs of purpura or bleeding [3].

ITP is further categorized into three phases based on the timing and continuation of symptoms. Newly diagnosed ITP is defined as from the time of diagnosis to 3 months from initial diagnosis. Persistent ITP is the continuation of ITP from 3 to 12 months from initial diagnosis and chronic ITP is the continuation of ITP after 12 months from initial diagnosis until resolution [4].

Corticosteroids are usually considered the 1st-line of treatment in ITP; however, during tapering or after discontinuation, the sustained response may be reduced. Patients without sustained response to corticosteroids need other drugs. Intravenous immune globulin (IVIG) and anti-D globulin (anti-Rho) are other 1st-line pharmacological treatments. Rituximab, thrombopoietin agonists (e. g., romiplostim and eltrombopag), and splenectomy are considered the 2nd-line treatment in chronic ITP [5].

H. pylori is a gram-negative bacillus that colonizes the gastric cells. Fecal-oral or oral-oral route is involved in childhood transmission. Moreover, *H. pylori* has a worldwide prevalence and is reported more frequently in developing countries. Besides gastrointestinal diseases, there is evidence suggesting *H. pylori* involvement in ITP [6].

Host antibodies against cytotoxin-associated gene A (Cag A), which is a virulence factor of *H. pylori* can increase the rate of platelet clearance due to mimicry between Cag A and platelet associated IgG. In addition to specific antibodies, down regulation of monocyte FcR receptors may shift the balance toward the increased phagocytic activity of monocytes, which may ultimately lead to thrombocytopenia [7].

Various antibiotics and proton pump inhibitors are widely used for the treatment of *H. pylori*. Several

recent reviews of previously published studies have shown that the eradication of *H. pylori* infection in patients with chronic ITP improved thrombocytopenia in about half of the cases [8].

We aimed to detect the association between *H. pylori* infection and ITP in children and adolescents.

MATERIALS AND METHODS

Study design

This cross-sectional study was conducted in ninety-five patients who were recruited from the Hematology Unit, Department of Pediatrics, Menoufia University Hospital. The study was carried out in the period from June 2021 to June 2022, to explore the prevalence of *H. pylori* among ITP children. There were 55 male and 40 female patients aged from 3.5 to 7.5 years. Full history taking was carried out, the results of physical and clinical examination were recorded. The study was approved by the Ethical Committee of the Faculty of Medicine, Menoufia University. An informed consent was obtained from caregivers of the patients prior to the recruitment.

Inclusion criteria:

1) children who were diagnosed with ITP based on the criteria of the American Society of Hematology (ASH) (the initial platelet count < 100 000/mm^3, normal Hb% and total leukocyte count) [9];

2) children who were reported positive for *H. pylori*;

3) Signed informed consent.

Children with other causes of thrombocytopenia such as; HCV, HBV, or HIV, drugs, lymphoproliferative disorders, other auto-immune disorders, and children with active life-threatening bleeding at the time of recruitment were excluded.

Sample collection and assay

Complete blood count (blood film, cell morphology and reticulocyte count) was performed at the time of presentation. Complete blood count was carried out using Sysmex KX21 automated hematology analyzer, Japan. During follow up, manual platelet count was performed: after 48 hours, one week, one month, three months, six months, 1 year (in patients who completed 1 year of follow up), before and after treatment of *H. pylori* (in patients positive for *H. pylori* antigen in stool).

H. pylori stool antigen test was performed in all cases, then the test was repeated for *H. pylori*-positive children 6 weeks after receiving treatment of *H. pylori*. Patients were asked to collect a specimen from their stool. Stool samples were stored at –20°C until use. The stool specimens were analyzed for *H. pylori* antigen. A commercial kit, DRG® *H. pylori* Ag (stool) ELISA (EIA-4354) was used as described by its manufacturer. Two procedures are available: a quantitative method able to provide a quantification of *H. pylori* Ag in the specimen and a qualitative method.

Statistical analysis

The data were analyzed by SPSS (Statistical Package for the Social Sciences) version 20 (SPSS Inc. IBM SPSS statistics for windows, version 20.0, Armnok, NY: IBM Corp). Descriptive statistics were calculated as percentage (%), mean and standard deviation (SD) for each variable. The Chi-squared test (χ^2) was used to study the association between two qualitative variables, and Fisher's exact test – to study the association between two qualitative variables. The Student's t-test was used for the comparison of two groups having normally distributed quantitative variables, and the Mann–Whitney test (non-parametric test) – for the comparison of two groups having not normally distributed quantitative variables. A *p*-value of < 0.05 was considered statistically significant.

RESULTS

The age of the children with ITP ranged from 3.5 to 7.5 years. Fifty-five of them were males and 40 were females. The majority of them recovered from ITP within three to six months from the initial presentation, regardless of treatment. The most common grade of bleeding at presentation was grade III. Most of the studied patients had skin bleeding either alone or associated with epistaxis or gum bleeding. Out of the studied ITP children, 62 (65.3%) were positive for *H. pylori* antigen in stool, and 33 of them (34.7%) were negative for *H. pylori* antigen in stool (*table 1*).

There is a statistically significant difference in the rate of recovery from ITP between *H. pylori*-negative patients (78.8%) in comparison to *H. pylori*-positive patients (22.6%). Also, as regards the rate of persistent ITP or chronic ITP; 35% of *H. pylori*-positive patients were diagnosed with chronic ITP, but only 6% of *H. pylori*-negative patients were diagnosed with chronic ITP. Thirteen percent of *H. pylori*-positive patients were diagnosed with persistent ITP, but only 1% of *H. pylori*-negative patients was diagnosed with persistent ITP (*table 2*).

There was no statistically significant difference in demographic characteristics (age at diagnosis and sex) among the studied ITP children regarding the presence of *H. pylori* antigen in stool. But there is a significant difference between *H. pylori*-positive and negative ITP children regarding the grade of bleeding at presentation; 51 (82.3%) *H. pylori*-positive ITP children presented with grade 3 bleeding, 35 (56.5%) of them presented with skin and gum bleeding, 16 (25.8%) – with skin bleeding and epistaxis (*table 3*).

During follow-up, platelet count was performed at different times after 1st-line of treatment and we found that there was no significant difference regarding the initial platelet count between *H. pylori* antigen positive or negative studied ITP children, however, a platelet count was significantly higher in *H. pylori*-negative ITP children in comparison to *H. pylori*-positive ones at 48 hours, one week, one month, 3 months, 6 months, and 1 year after 1st-line of treatment (*table 4*).

Regarding 1st-line treatment of ITP in the studied ITP children, 28 patients received high-dose dexamethasone only, 31 received oral prednisolone only, 29 received IVIG either followed by steroid therapy or not, and 7 patients did not require any treatment, with a spontaneous improvement during follow-up. In the studied group, 47 patients required 2nd-line treatment in the form of eltrombopag; either after treatment with oral prednisone or after treatment with high-dose dexamethasone (*table 5*).

There was a significant difference in the platelet count among *H. pylori*-positive ITP children after treatment of *H. pylori*; the median platelet count before treatment of H. pylori was 70 × 10^3/mm^3, after treatment – 109 × 10^3/mm^3 (*table 6, figure*).

After the eradication of *H. pylori* in *H. pylori*-positive ITP children, there was a significant rise of platelet count in all patients who received high-dose dexamethasone, oral prednisone and IVIG as 1st-line treatment, and eltrombobag as 2nd-line treatment respectively as shown in *table 6*.

DISCUSSION

In the present study, the age of children with ITP ranged from 3.5 to 7.5 years. Fifty-five of them were males and 40 were females. This age range and male predominance were similar to Abdollahi et al. [10] study. The majority of them recovered from ITP within three to six months from the initial presentation, regardless of treatment. This agreed with Akbayram et al. [11] who reported that 73.5% of patients completely resolved within 6 months after the onset of the disease and 26.5% of patients had progressed into chronic ITP.

The most common grade of bleeding at presentation was grade III. Most of the studied patients had skin bleeding either alone or associated with epistaxis or gum bleeding. This is in agreement with Zafar et al. [12] who reported that the vast majority of their patients presented had a clinically significant bleed that required medical treatment. This is in contrast to Bennett et al. [13] who reported that more than half of the patients had no or only mild bleeding. A reason might be that acute ITP is also treated by general pediatricians and only complicated cases are referred to pediatric hematologists/oncologists.

Table 1
Demographic and clinical characteristics of the studied ITP children

Characteristics	Studied ITP children (*n* = 95)
Age at diagnosis, years:	
mean ± SD	5.4 ± 2.3
median (IQR)	5 (3.5–7.5)
Sex, *n* (%):	
male	55 (57.9)
female	40 (42.1)
Types of ITP, *n* (%):	
recovered	41 (43.2)
persistent	14 (14.7)
chronic	40 (42.1)
Grade of bleeding, *n* (%):	
grade I	7 (7.4)
grade II	33 (34.7)
grade III	55 (57.9)
Type of bleeding, *n* (%):	
skin bleeding only	40 (42.1)
skin and gum bleeding	39 (41.1)
skin bleeding and epistaxis	16 (16.8)
H. pylori antigen in stool, *n* (%):	
positive	62 (65.3)
negative	33 (34.7)

Note. Here and in tables 3, 4, 6: IQR – interquartile range.

Table 2
Types of ITP among the studied patients regarding *H. pylori* antigen in stool

Parameter	*H. pylori* antigen in stool among the studied ITP children, *n* (%)		χ^2 test	*p*-value
	Positive (*n* = 62)	Negative (*n* = 33)		
Types of ITP:				
recovered	14 (22.6)	26 (78.8)	28.17	< 0.001*
persistent	13 (21.0)	1 (3.0)		
chronic	35 (56.5)	6 (18.2)		

*Note. Here and in tables 3, 4, 6: * – highly significant difference.*

Table 3
Comparison of the demographic and clinical characteristics among the studied ITP children regarding *H. pylori* antigen

Characteristics	*H. pylori* antigen in stool among the studied ITP children		Test of significance	*p*-value
	Positive (*n* = 62)	Negative (*n* = 33)		
Age at diagnosis (median (IQR))	5 (3.5–8) years	4 (3.25–6.5) years	Mann–Whitney test = 1.61	0.11
Sex:				
male	37 (59.7%)	18 (54.5%)	χ^2 test = 0.23	0.63
female	25 (40.3%)	15 (45.5%)		
Grade of bleeding:				
grade I	0 (0%)	7 (21.2%)	χ^2 test = 46.29	< 0.001*
grade II	11 (17.7%)	22 (66.7%)		
grade III	51 (82.3%)	4(12.1%)		
Type of bleeding:				
skin bleeding only	11 (17.7%)	29 (87.9%)	χ^2 test = 43.99	< 0.001*
skin and gum bleeding	35 (56.5%)	4 (12.1%)		
skin bleeding and epistaxis	16 (25.8%)	0 (0 %)		

The prevalence of *H. pylori* infection among the patients in these studies were 20%, 90.47%, 66.2% respectively while in our study it was 62 cases (65.3%). In this study we found that out of the studied ITP

Table 4
Follow-up of platelet count among the studied ITP children regarding *H. pylori* antigen

Parameter	*H. pylori* antigen in stool among the studied ITP children		Test of significance	*p*-value
	Positive (*n* = 62)	Negative (*n* = 33)		
Platelet count at presentation (mean ± SD), × 10^3/mm^3	10.4 ± 2.5	9 ± 3.0	t-test = 0.67	0.39
Platelet count after 48 hours from treatment (median (IQR)), × 10^3/mm^3	45 (39–50)	99 (90–105)	Mann–Whitney test = 6.82	< 0.001*
Platelet count after the 1st week of treatment (mean ± SD), × 10^3/mm^3	132.3 ± 26.0	233.4 ± 46.7	t-test = 11.52	< 0.001*
Platelet count after the 1st month of treatment (median (IQR)), × 10^3/mm^3	107.5 (79.7–135)	250 (205–260)	Mann–Whitney test = 6.26	< 0.001*
Platelet count after the 3rd month of treatment (median (IQR)), × 10^3/mm^3	35 (25–91.2)	250 (225–285)	Mann–Whitney test = 6.30	< 0.001*
Platelet count after the 6th month of treatment (median (IQR)), × 10^3/mm^3	62.5 (45–96.2)	270 (230–300)	Mann–Whitney test = 6.45	< 0.001*
Platelet count after the 1st year of treatment (median (IQR)), × 10^3/mm^3	70 (55.5–97.5)	290 (250–300)	Mann–Whitney test = 6.27	< 0.001*

Table 5
Lines of treatment among ITP children regarding *H. pylori* antigen

Parameter	*H. pylori* antigen in stool among the studied ITP children, *n* (%)		Test of significance	*p*-value
	Positive (*n* = 62)	Negative (*n* = 33)		
Treatment: high dose of dexamethasone only (24 mg/m^2/day/4 days) (1–4 courses) high dose of dexamethasone and IVIG oral prednisone only (2–4 mg/kg/day/1 week) followed by withdrawal over 1 week oral prednisone and IVIG IVIG only (1–2 gm/kg/dose) observation only	19 (30.6) 13 (21.0) 21 (33.9) 8 (12.9) 0 (0.0) 1 (1.6)	9 (27.3) 3 (9.1) 10 (30.3) 4 (12.1) 1 (3.0) 6 (18.2)	χ^2 test = 11.88	0.03*
Second-line treatment (Eltrombopag): high dose of dexamethasone and Eltrombopag (25–75 mg per day) oral prednisone and Eltrombopag (25–75 mg per day)	21 (50.0%) 21 (50.0%)	1 (20.0%) 4 (80.0%)	Fisher's exact test = 1.61	0.35

*Note. * – significant difference.*

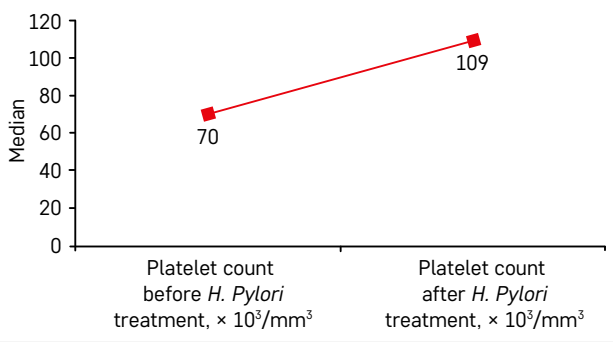
Table 6
Comparison of platelet count before and after *H. pylori* treatment among *H. pylori*-positive ITP children

Parameter	*H. pylori*-positive ITP children (*n* = 62)	Test of significance	*p*-value
Platelet count before *H. pylori* treatment (median (IQR)), × 10^3/mm^3	70 (60–95)	–	–
Platelet count after *H. pylori* treatment (median (IQR)), × 10^3/mm^3	109 (95–151.2)	Wilcoxon signed- rank test = 6.79	< 0.001*
Parameter	**ITP children who received high-dose dexamethasone**	**Test of significance**	***p*-value**
Platelet count before *H. pylori* treatment (median (IQR)), × 10^3/mm^3	70 (56.2–108.7)	–	–
Platelet count after *H. pylori* treatment (median (IQR)), × 10^3/mm^3	105 (90–180)	Wilcoxon signed- rank test = 4.86	< 0.001*
Parameter	**ITP children who received oral prednisone**	**Test of significance**	***p*-value**
Platelet count before *H. pylori* treatment (median (IQR)), × 10^3/mm^3	70 (60–95)	–	–
Platelet count after *H. pylori* treatment (median (IQR)), × 10^3/mm^3	120 (95–150)	Wilcoxon signed- rank test = 4.68	< 0.001*
Parameter	**ITP children who received Eltrombopag**	**Test of significance**	***p*-value**
Platelet count before *H. pylori* treatment (mean ± SD), × 10^3/mm^3	64.3 ± 19.9	–	–
Platelet count after *H. pylori* treatment (mean ± SD), × 10^3/mm^3	100.7 ± 27.6	Paired t-test = 15.78	< 0.001*

children, 62 patients (65.3%) were positive for *H. pylori* antigen in stool, 33 patients (34.7%) were negative for *H. pylori* antigen in stool.

These differences likely reflect the variation in the prevalence of *H. pylori* infection in the general populations of different countries, which is higher in developing countries and lower in developed countries. Previous reports in children with chronic idiopathic thrombocytopenia showed a different prevalence rate of *H. pylori* infection among countries, ranging from 0%

Figure
A comparison of platelet count before and after *H. pylori* treatment among *H. pylori*-positive ITP children



in Finland to 6.4% in the Netherlands, 12.9% in Iran, 20% in Japan, 20.5 % in Italy, 29.1% in Thailand, 31.4% in Turkey, and 40.9% in Taiwan [14].

Abdollahi et al. [10] showed that the percentage of *H. pylori*-Ag positive children in the case group was 90.47% while in the control group, it was 28.12% and Ahmed et al. [15]; illustrated that the percentage of ITP children with *H. pylori* infection in the patient group was 66.2% while in the control group, it was 29.8%. These results supported the association between *H. pylori* infection and ITP.

There is a statistically significant difference in the rate of recovery of ITP between *H. pylori*-negative patients (78.8%) in comparison with *H. pylori*-positive patients (22.6%). According to the rate of persistent ITP or chronic ITP; 35% of *H. pylori*-positive patients were diagnosed with chronic ITP, but only 6% of *H. pylori*-negative patients were diagnosed with chronic ITP. Thirteen percent of *H. pylori*-positive patients were diagnosed with persistent ITP, but only 1% of *H. pylori*-negative patients was diagnosed with persistent ITP.

This is in contrast to Jaing et al. [16] who reported that neither the response to corticosteroids, nor the final outcome was influenced by the *H. pylori* status in 63 patients with newly diagnosed ITP but stated that there was a positive association between *H. pylori* infection and chronic ITP. Also, Cheng et al. [17] reported that there was no significant difference in the remission rate between the ITP children with *H. pylori* infection and those without *H. pylori* infection in the same age group [16, 17].

There was no statistically significant difference in demographic characteristics (age at diagnosis and sex) among the studied ITP children regarding the presence of *H. pylori* antigen in stool. Ahmed et al. [15] reported no difference in gender, age between *H. pylori*-positive and negative ITP patients.

But in our study, there was a statistically significant difference between *H. pylori*-positive and negative ITP children regarding the grade of bleeding at presentation; 51 (82.3%) *H. pylori*-positive ITP children presented with grade III bleeding, 35 (56.5%) of them – with skin and gum bleeding, 16 (25.8%) – with skin bleeding and epistaxis. Regarding all tested parameters other than the platelet count, there was no significant statistical difference between children at presentation.

Ikuse et al. [1] defined ITP as an immune-mediated acquired disease characterized by thrombocytopenia (peripheral blood platelet count < 100,000/μL with normal white blood cell count and hemoglobin level), in the absence of other causes or disorders that may be associated with thrombocytopenia.

During follow-up, platelet count platelet count was performed at different times after 1st-line of treatment and we found that there was no significant difference regarding the initial platelet count between *H. pylori*-Ag positive or negative studied ITP children, however, a platelet count was significantly higher in *H. pylori*-negative ITP children in comparison to *H. pylori*-positive ones at 48 hours, one week, one month, 3 months, 6 months, 1 year after 1st-line of treatment.

This is in agreement with Hodeib et al. [9] who reported that the platelet count was statistically significant higher among *H. pylori* stool antigen (HpSA)-negative children than HpSA-positive children.

In spite of different lines of treatment used in our study for the treatment of ITP, there was a significant difference in the platelet count among *H. pylori*-positive ITP children after treatment of *H. pylori*; the median platelet count before treatment of *H. pylori* was 70 × 10^3/mm^3, after treatment, it was 109 × 10^3/mm^3.

Hodeib et al. [9] reported that there was a significant rise in the mean platelet count in *H. pylori*-positive children from 70.6 ± 4.8 × 10^3/mm^3 to 110.8 ± 15.1 × 10^3/mm^3 after *H. pylori* eradication therapy.

After the eradication of *H. pylori* in *H. pylori*-positive ITP children, there was a significant rise of platelet count in all patients who received high-dose dexamethasone, oral prednisone and IVIG as 1st-line of treatment, and eltrombopag as 2nd-line of treatment, respectively. This is in agreement with Pezeshki et al. [20], who reported that several meta-analyses and random clinical trials have already reported a positive outcome of *H. pylori* eradication on the platelet count of patients with ITP. For instance, the systemic reviews and meta-analyses of seventeen studies involving 788 ITP patients showed statistically significant increases in platelet counts in successfully eradicated patients compared to controls, and untreated and non-eradicated patients [21].

CONCLUSION

The prevalence of *H. pylori* infection among ITP pediatric patients was 65.3%. There was a significant

response in the platelet count among *H. pylori*-positive ITP children after treatment of *H. pylori*.

ACKNOWLEDGMENTS
The authors would like to express their gratitude to the participants of this study.

FUNDING
Not specified.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

References

1. Ikuse T., Toda M., Kashiwagi K., Maruyama K., Nagata M., Tokushima K., et al. Efficacy of *Helicobacter pylori* Eradication Therapy on Platelet Recovery in Pediatric Immune Thrombocytopenic Purpura-Case Series and a Systematic Review. Microorganisms 2020; 8 (10): 1457.
2. Kim B.J., Kim H.S., Jang H.J., Kim J.H. *Helicobacter pylori* eradication in idiopathic thrombocytopenic purpura: a meta-analysis of randomized trials. Gastroenterol Res Pract 2018; 2018: 6090878, 1–8.
3. D'Orazio J.A., Neely J., Farhoudi N. ITP in Children. J Pediatr Hematol Oncol 2013; 35: 1–13.
4. Consolini R., Renee Forbes L., Wahlstrom J., Pignata C., Giardino G., Gallo V. Unbalanced immune system: immunodeficiencies and autoimmunity. Front Paediatr 2016; 4: 1–9.
5. Ghanima W., Godeau B., Cines D.B., Bussel J.B. How I treat immune thrombocytopenia: the choice between splenectomy or a medical therapy as a second-line treatment. Blood 2012; 120 (5): 960–9.
6. Mentis A., Lehours P., Mégraud F. Epidemiology and Diagnosis of *Helicobacter pylori* infection. Helicobacter 2015; 20: 1–7.
7. Eghbali A., Siavashan V.R., Bagheri B., Afzal R.R. Impact of *Helicobacter pylori* Eradication in Children with Acute Immune Thrombocytopenia: A Randomized Controlled Study. Arch Pediatr Infect Dis 2019; (7): 98–102.
8. Frydman G.H., Davis N., Beck P.L., Fox J.G. *Helicobacter pylori* eradication in patients with immune thrombocytopenic purpura: a review and the role of biogeography. Helicobacter 2015; 20 (4): 239–51.
9. Hodeib M.M., Ali A.G., Kamel N.M., Senosy S.A., Fahmy E.M., Abdelsadik A., et al. Impact of eradication therapy of *Helicobacter pylori* in children with chronic immune thrombocytopenic purpura. Egyptian Pediatric Association Gazette 2021; 69 (1): 1–4.
10. Abdollahi A., Shoar S., Ghasemi S., Zohreh O.Y. Is *Helicobacter pylori* infection a risk factor for idiopathic thrombocytopenic purpura in children? Ann Afr Med 2015; 14 (4): 177–81.
11. Akbayram S., Dogan M., Ustyol L., Akgun C., Peker E., Bilici S., et al. The clinical outcome of 260 pediatric ITP patients in one center. Clin Appl Thromb Hemost 2011; 17 (6): E30–5.
12. Zafar H., Anwar S., Faizan M., Riaz S. Clinical features and outcome in paediatric newly diagnosed immune thrombocytopenic purpura in a tertiary care centre. Pak J Med Sci 2018; 34 (5): 1195–9.
13. Bennett C.M., Neunert C., Grace R.F., Buchanan G., Imbach P., Vesely S.K., et al. Predictors of remission in children with newly diagnosed immune thrombocytopenia: Data from the Intercontinental Cooperative ITP Study Group Registry II participants. Pediatr Blood Cancer 2018; 65 (1): e26736.
14. Hooi J.K.Y., Lai W.Y., Ng W.K., Suen M.M.Y., Underwood F.E., Tanyingoh D., et al. Global Prevalence of *Helicobacter pylori* Infection: Systematic Review and Meta-Analysis. Gastroenterology 2017; 153 (2): 420–9. DOI: 10.1053/j.gastro.2017.04.022
15. Ahmed A.Z., Radwan A.M., Rizk H.L. The Role of *Helicobacter Pylori* Infection in Idiopathic Thrombocytopenic Purpura in Children. Egyptian Journal of Hospital Medicine 2021; 82 (2): 193–8.
16. Jaing T.H., Tsay P.K., Hung I.J., Chiu C.H., Yang C.P., Huang I.A. The role of *Helicobacter pylori* infection in children with acute immune thrombocytopenic purpura. Pediatr Blood Cancer 2006; 47 (2): 215–7.
17. Cheng Y.Y., Xiong H., Xu Z.L., Li J.X., Li H., Cai W., et al. Association between *Helicobacter pylori* infection and newly diagnosed childhood immune thrombocytopenia. Zhongguo Dang Dai Er Ke Za Zhi 2015; 17 (1): 22–5.
18. Stasi R., Sarpatwari A., Segal J.B., Osborn J., Evangelista M.L., Cooper N., et al. Effects of eradication of *Helicobacter pylori* infection in patients with immune thrombocytopenic purpura: a systematic review. Blood 2009; 113 (6): 1231–40.
19. Noonavath R.N., Lakshmi C.P., Dutta T.K., Kate V. *Helicobacter pylori* eradication in patients with chronic immune thrombocytopenic purpura. World J Gastroenterol 2014; 20 (22): 6918–23.
20. Pezeshki S.M.S., Saki N., Ghandali M.V., Ekrami A., Avarvand A.Y. Effect of *Helicobacter Pylori* eradication on patients with ITP: a meta-analysis of studies conducted in the Middle East. Blood Res 2021; 56 (1): 38–43.
21. Franchini M., Cruciani M., Mengoli C., Pizzolo G., Veneri D. Effect of *Helicobacter pylori* eradication on platelet count in idiopathic thrombocytopenic purpura: a systematic review and metaanalysis. J Antimicrob Chemother 2007; 60: 237–46.