

Guidelines on the diagnosis of primary immune thrombocytopenia in children and adolescents: Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular Guidelines Project: Associação Médica Brasileira – 2012

Josefina Aparecida Pellegrini Braga¹
 Sandra Regina Loggetto²
 Andrea Thives de Carvalho Hoepers^{3,4}
 Wanderley Marques Bernardo^{5,6}
 Leticia Medeiros⁷
 Mônica Pinheiro de Almeida Veríssimo⁸

¹Universidade Federal de São Paulo – UNIFESP, São Paulo, SP, Brazil

²Centro de Hematologia de São Paulo – CHSP, São Paulo, SP, Brazil

³Centro de Hematologia e Hemoterapia de Santa Catarina – HEMOSC, Florianópolis, SC, Brazil

⁴Universidade Federal de Santa Catarina – UFSC, Florianópolis, SC, Brazil

⁵Universidade de São Paulo – USP, São Paulo, Brazil

⁶Associação Médica Brasileira – AMB, São Paulo, Brazil

⁷Hospital Ana Costa – HAC, Santos, SP, Brazil

⁸Centro Infantil Boldrini, Campinas, SP, Brazil

Introduction

The guidelines project is a joint initiative of the *Associação Médica Brasileira* and the *Conselho Federal de Medicina*. It aims to bring information together in medicine to standardize decisions in order to help strategies during diagnosis and treatment. These data were prepared and recommended by the *Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular* (ABHH). Even though, all possible decisions should be evaluated by the physician responsible for diagnosis and treatment according to the patient's setting and clinical status.

Description of the evidence collection method

The members of the ABHH Committee responsible for writing the diagnostic guidelines on primary immune thrombocytopenia (ITP) prepared the main questions related to the clinical diagnosis of children and adolescents. Seven questions were structured using the Patient/Problem, Intervention, Comparison and Outcome (PICO) system. The search strategies for specific clinical questions (Appendix 1) were applied to the key scientific databases (MEDLINE PubMed, Embase, SciELO, Lilacs and Cochrane Library) for publications up to 2012. The retrieved articles were submitted to a critical appraisal and categorized according to its strength of evidence, giving support to elaborate the answers to the questions. Each selected reference was classified according to the degree of recommendation using the Oxford Classification⁽¹⁾. Each recommendation was discussed by the committee and a consensus was attained. The development of these recommendations was completed supervised by experts on evidence-based guidelines.

Recommendation degree and evidence level

A: Experimental or observational studies of better consistency

B: Experimental or observational studies less consistent

C: Case reports (uncontrolled studies)

D: Opinion without critical evaluation based on consensus, physiological studies or animal models

Aims

To define parameters for the clinical and laboratory diagnoses and evaluate the risk of bleeding in children and adolescents with ITP based on the best available published evidence. The target audience is the hematologist, pediatrician and medical student.

Background

Immune thrombocytopenic purpura (ITP) is an acquired autoimmune disease where the platelet count is $< 100 \times 10^9/L$. Nowadays the immune etiology is well known and not every patient suffers from bleeding and so the terms 'idiopathic' and 'purpura' should be avoided⁽²⁾ (D). In ITP, other causes of thrombocytopenia are not observed and the main problem is the bleeding. Secondary ITP involves immune-mediated forms of thrombocytopenia, such as systemic lupus erythematosus, human immunodeficiency virus (HIV), hepatitis C, drugs, and *Helicobacter pylori*, among others⁽²⁻⁴⁾(D).

Conflict-of-interest disclosure:

The authors declare no competing financial interest

Submitted: 7/1/2013

Accepted: 7/20/2013

Corresponding author:

Josefina Aparecida Pellegrini Braga
 Escola Paulista de Medicina da Universidade
 Federal de São Paulo – EPM/ UNIFESP
 Rua Dr Diogo de Faria, 307 - Vila Clementino
 04037-000 São Paulo, SP, Brazil
 Phone: 55 11 5539-1093
 pellegrini.braga@unifesp.br

www.rbhh.org or www.scielo.br/rbhh

DOI: 10.5581/1516-8484.20130105

When is primary immune thrombocytopenia considered acute, chronic or persistent?

The term acute ITP has recently been replaced by newly diagnosed ITP. It is defined when the platelet count is low for less than three months. Persistent ITP refers to patients who have not achieved remission or not maintained their response to treatment for a period between three and 12 months after diagnosis. When there is no remission of thrombocytopenia 12 months after diagnosis, it is considered chronic^{(2)(D)}.

The terms acute and chronic ITP will be maintained because older publications published before the introduction of the current terminology were used to write these guidelines. Thus, for older studies, acute ITP and chronic ITP are used for cases with up to six months and more than six months of thrombocytopenia, respectively.

Newly diagnosed ITP in children is usually preceded by viral infections and the patient exhibits thrombocytopenia ($< 100 \times 10^9$ platelets/L), petechiae and bruises. About 80% of these patients have spontaneous remission within the first six months after diagnosis; of the remaining 20% of cases, more than 50% have spontaneous remission within the first four years, i.e. platelet count normalizes each year in 10 to 15% of the patients^{(4)(D)}.

Thrombocytopenia persists for more than six months in 33% of children with ITP and for more than 12 months in 10%^{(5)(D)}. Platelet counts normalize (above 150×10^9 platelets/L) by 12 months in about 25.6% of the children who are still thrombocytopenic six months after diagnosis^{(6)(B)}. Ten to 30% of children who have chronic ITP at six months of follow-up achieve remission after this period^{(7)(B)}. Therefore, the follow-up of patients with ITP demonstrates spontaneous remission of thrombocytopenia in 50% of the cases in between six and 12 months, and so it is more appropriate to define chronic ITP as thrombocytopenia that persists for more than 12 months^{(8)(B)}.

The characteristics of chronic ITP patients are age older than 10 years, insidious onset of symptoms more than two weeks prior to diagnosis, skin and oral mucosa bleeding and platelet count $> 20 \times 10^9/L$ ^{(9)(B)}.

Insidious onset of bleeding more than 14 days before diagnosis is a predictive factor associated with chronic compared to acute ITP^{(10)(B)}. Symptoms lasting for more than 14 days before diagnosis suggest the chronic form of the disease^{(11)(B)}. The proportion of cases of chronic ITP increases with age at diagnosis. The mean age of patients with chronic ITP at the time of diagnosis (ten years) was greater than that of patients with acute ITP (5.1 years). Mucosal bleeding was more common in patients with acute disease (50%) than those with chronic disease (23%; p -value = 0.002)^{(12)(B)}.

In patients diagnosed with ITP, some factors are significantly associated with the probability that the thrombocytopenia is acute or chronic. ITP is more likely to be chronic when the child's age is greater than ten years (41%) or the platelet count is greater than $50 \times 10^9/L$ (45%); if these two conditions are combined, the chance of chronic disease is 50%. ITP is acute in 84% of under ten-year-old patients with a platelet count of less than $50 \times 10^9/L$. The chance that the ITP is acute is 93% in patients younger than 12 months^{(13)(B)}.

Recommendation: Acute ITP or newly-diagnosed ITP is characterized by a platelet count of less than $100 \times 10^9/L$ and often by petechiae and bruises; bleeding is usually more intense within the three months following diagnosis. When remission is not attained or response to treatment is not sustained in three to 12 months, it is considered persistent ITP. When the thrombocytopenia persists for more than 12 months, ITP is considered chronic. Some diagnostic factors that suggest the chronic form are age older than ten years, platelet count greater than $50 \times 10^9/L$, mild bleeding and insidious onset of symptoms for more than 14 days prior to diagnosis.

What are the criteria that must be present for the definition of refractory primary immune thrombocytopenia and for complete and partial remission?

The definition of complete remission or complete response to treatment is a platelet count $\geq 100 \times 10^9/L$ with no clinically relevant bleeding. The definition of remission or partial response is a platelet count between 30 and $100 \times 10^9/L$ or double the baseline platelet count with no clinically relevant bleeding. Refractory ITP occurs when there is splenectomy failure associated to severe ITP. Severe ITP is considered when bleeding is occurring at diagnosis and requires treatment, or when new sites of bleeding requiring increased doses of or changes in medication appear. Treatment failure occurs when platelet count remains $< 30 \times 10^9/L$ in two different measurements or when the increase in platelet count is less than twice the baseline value^{(14-16)(D)}. So that the concept of response is not exclusively based on the platelet count, as bleeding resolution should also be considered. There are recommendations to avoid the terms 'partial' or 'minimal' response due to the criterion heterogeneity. The idea of refractoriness is based on the expectancy that a response to splenectomy occurs in 60% of cases^{(2)(D)}.

In another ITP study, the definition used for complete response was platelet count $\geq 100 \times 10^9/L$ for more than three months without treatment, partial remission was platelet count between 50 and $90 \times 10^9/L$ for more than three months without treatment, active disease when platelet was $< 50 \times 10^9/L$ with or without treatment and spontaneous remission when it occurs without splenectomy^{(17)(C)}.

Recommendation: The definition of complete spontaneous remission or complete response to treatment is a platelet count $\geq 100 \times 10^9/L$ without clinically significant bleeding. Partial spontaneous remission or partial response to treatment is a platelet count between 30 and $100 \times 10^9/L$ or twice the baseline platelet count and again without clinically significant bleeding. Refractory ITP is related to splenectomy failure with maintenance of severe ITP. This last definition does not apply to patients with accessory spleen. Response failure occurs when the platelet count is $< 30 \times 10^9/L$ in two different measurements or the increase in platelets is less than twice the baseline value.

When should the diagnosis of primary immune thrombocytopenia in a patient with thrombocytopenia be considered? At what platelet count should primary immune thrombocytopenia be investigated?

The mean platelet count in healthy children aged six months to 18 years old was observed to be 279×10^9 platelets/L $\pm 51 \times 10^9$ platelets/L⁽¹⁸⁾(C).

A platelet count less than 100×10^9 /L suggests the diagnosis of ITP. In certain populations, a platelet count between 100 and 150×10^9 /L can be considered normal^(2,15)(D).

Besides a platelet count less than 100×10^9 /L, it is recommended that the patient should be followed up for a period of two to six months or to have two low platelet counts for the diagnosis of ITP^(19,20)(D).

Recommendation: For the diagnosis of ITP, the platelet count must be less than 100×10^9 /L. If the patient is asymptomatic, thrombocytopenia should be confirmed with two further measurements and clinical follow-up of two to six months.

Is there evidence to support bone marrow examination to confirm diagnosis of primary immune thrombocytopenia? When is a bone marrow examination indicated?

In thrombocytopenic patients, a bone marrow examination allows a differential diagnosis between bone marrow diseases and unrelated diseases⁽²¹⁾(B). A bone marrow aspirate is recommended for patients who have clinical findings (splenomegaly) with an atypical blood count (anemia, neutropenia)⁽³⁾(D). Bone marrow aspirate in children with suspected ITP should be made when corticosteroid use is considered vital^(3,22)(D)⁽²³⁾(C).

Differential diagnosis between ITP and inherited thrombocytopenia in children can be attained through an investigation of the family history and an analysis of peripheral blood cells. In this case, a bone marrow examination plays a small role⁽²⁴⁾(C).

In children older than six months with ITP there is no difference in quality of life whether a bone marrow aspirate is performed at diagnosis or only in high risk patients (pancytopenia) or whether it is not collected⁽²⁵⁾(C).

In 332 children between six months and 18 years old with initial diagnosis of ITP (50×10^9 platelets/L without further changes in the blood smear), bone marrow aspirates identified only one case of bone marrow failure and none of acute leukemia⁽²⁶⁾(C).

A recent consensus suggests that the bone marrow aspirate is not necessary in children with clinical signs and symptoms of ITP, including those under treatment with corticosteroids or before splenectomy⁽¹⁵⁾(D).

Bone marrow aspirate was performed in 72% of 400 children with ITP followed up for 10 years and the initial diagnosis was not changed in any of the cases⁽¹³⁾(B).

Recommendation: There is no consistent evidence justifying the need of a bone marrow examination for ITP diagnosis. However, bone marrow aspirate should be performed whenever there are changes such as anemia or neutropenia, when there are signs/symptoms different from bleeding and prior to prescribing corticosteroids.

Which etiological factors are involved in secondary immune thrombocytopenia? Which exams should be done to investigate primary immune thrombocytopenia?

In adult patients with ITP, there is a need for laboratory exams as 14% of cases have a secondary etiology. The main causes of secondary ITP are infectious diseases (HIV, hepatitis C, cytomegalovirus and *H. pylori*), immune disorders (rheumatoid arthritis and anti-phospholipid syndrome), lymphoproliferative diseases (non-Hodgkin lymphoma) and post transplantation (bone marrow and liver)⁽²⁷⁾(C).

In Canada, 198 patients aged between one and 18 years with chronic ITP (more than six months) were evaluated regarding primary (no identifiable cause except previous viral infection) and secondary causes (pre-existing disease such as systemic lupus erythematosus or HIV infection); 7.1% of the patients had secondary ITP⁽²⁸⁾(C).

Comorbidities were observed in 3.9% of 1784 children with ITP enrolled in the Pediatric and Adult Registry on Chronic ITP. They were aged between three months and 16 years and the comorbidities were splenomegaly (1%), gastrointestinal disease (0.7%), cardiovascular disease (0.5%), thyroid disease (0.3%), cancer (0.2%), diabetes (0.2%), and hypertension (0.06%). Exams such as bone marrow aspirate, anti-nuclear antibodies (ANA), HIV and hepatitis C are more frequently performed in adults than in children (p-value < 0.0001). However, positive results for children vs. adults are similar for HIV (1% vs. 1%) and anti-phospholipid antibodies (10% vs. 6%) but different for hepatitis C (0% vs. 3%), *H. pylori* (17% vs. 31%), anti-nuclear antibodies (18% vs. 10%) and anti-platelet antibodies (67% vs. 47%). Hepatitis C and *H. pylori* are more common in adults, and anti-nuclear and anti-platelet antibodies are more often positive in children⁽²⁹⁾(B).

There is a 20% increase in risk of *H. pylori* infection in adults with ITP (number needed to harm - NNH: 5)⁽³⁰⁾(B). An eight-year follow-up of adults with ITP associated with *H. pylori* infection demonstrates maintenance of platelet response after eradication therapy⁽³¹⁾(C). In children, the importance of *H. pylori* is still conflicting as most trials were carried out with few patients and were not randomized. In the Netherlands, three (6.4%) of 47 patients under 16 years with $< 100 \times 10^9$ platelets/L for more than 1 year were infected with *H. pylori* and, after treatment, two achieved partial response ($> 50 \times 10^9$ platelets/L and increases in platelets to twice the baseline level) and one achieved a complete response ($> 150 \times 10^9$ platelets/L). Of the 44 children that were negative for *H. pylori*, no complete or partial response was obtained in six months of follow-up. The prevalence of *H. pylori* infection found in this study (6.4%) is not statistically different from the prevalence in Dutch

children without ITP (10.8%) suggesting that there is no causal relation between chronic ITP and *H. pylori* infection. Improvement in platelet count of infected children after *H. pylori* treatment may have occurred due to the natural evolution of ITP⁽³²⁾(B).

An Italian study of 244 under 18-year-old patients with chronic ITP (platelet count < 100 x 10⁹/L for more than 12 months) found an incidence of children infected by *H. pylori* of 20.5% (n = 50); 37 received *H. pylori* treatment. The agent was eradicated in 33 (89.2%) patients and platelet counts improved in 39.4% (13/33) within one year, while in the *H. pylori* negative group, only 17/166 (10.2%) of the patients had spontaneous remission (p-value < 0.005). Of the patients treated for *H. pylori* infection, seven achieved complete response ($\geq 150 \times 10^9$ platelets/L) and six had partial response ($\geq 50 \times 10^9$ platelets/L). So, patients whose *H. pylori* was successfully eradicated showed increases in platelet counts suggesting a need to further investigate the relationship between ITP and *H. pylori* in pediatric patients⁽³³⁾(B).

There are two prospective randomized trials assessing the relationship of platelet recovery in children with chronic ITP following *H. pylori* eradication. In Thailand, of 55 four- to 18-year-old patients with chronic ITP (platelet count < 100 x 10⁹/L for more than six months) associated with *H. pylori*, eradication did not increase the response in six months of follow-up compared to patients who were not submitted to eradication. The prevalence of *H. pylori* infection was 29.1%⁽³⁴⁾(A). In Brazil, the prevalence of *H. pylori* infection in 85 children aged between 2 and 18 years with chronic ITP (< 150 x 10⁹ platelets/L for over six months) was 25.9% (n = 22) and the eradication rate with treatment was 92.3%. The results showed high platelet counts in patients with chronic ITP after being cured for *H. pylori* infection (57.1%) compared to infected patients that remained untreated (0%). The rate of spontaneous recovery of platelet count in non-infected patients was 33.3%⁽³⁵⁾(A).

The association of ITP with cytomegalovirus infection is statistically significant (p-value < 0.01); the prevalence of the positive antigen in bone marrow is 61.7% with 20.9% being serum IgM positive and 86.4% being serum IgG positive. Antigen bone marrow positivity is higher in chronic rather than in acute cases (92.3% vs. 55.8%), while serum IgM positivity is higher in acute (23.5%) rather than in chronic cases (7.7%), but not statistically significant. In serum IgG, the positivity is statistically similar in acute (86.7%) and chronic cases (84.6%). The patient's response to the treatment of ITP, however, is significantly better in cases that are negative for bone marrow antigens compared to those that are positive, while it is similar between patients that are positive or negative for serum IgG or IgM⁽³⁶⁾(B). The presence of cytomegalovirus associated with ITP may be related to refractoriness to treatment, but the use of antiviral drugs favors a response⁽³⁷⁾(C).

An analysis of 31 children (median age eight years) with acute and chronic ITP showed that those over 12-years old have a greater chance of having positive ANA and antithyroid antibodies (ATA) than those under the age of 12 years (p-value < 0.03). In chronic ITP, children tend to have more positive ANA and ATA than the general pediatric population, but these figures are not statistically significant (ANA: p-value = 0.14; ATA: p-value = 0.19). Patients with acute ITP who had these autoantibodies at diagnosis are more likely to develop chronic ITP. During a two year follow-up, no

patient developed an autoimmune disease⁽³⁸⁾(B).

Data on the relationship between ITP and human erythrovirus (parvovirus) B19 infection are scarce. The prevalence in 47 newly-diagnosed children was 13%⁽³⁹⁾(B), while another study including 15 patients did not identify the human erythrovirus (parvovirus) B19⁽⁴⁰⁾(C).

There is an association between ITP and exposure to certain antibiotics, non-steroidal anti-inflammatory drugs, acetaminophen, mucolytics and measles, mumps and rubella (MMR) vaccine⁽⁴¹⁾(A).

Recommendation: On considering the risk of association between immune thrombocytopenia and adult infectious diseases (hepatitis C, HIV, cytomegalovirus and *H. pylori*) and immunological diseases (antiphospholipid syndrome), as well as the benefit of response to treatment in children, it is necessary to investigate these diseases with specific tests to establish the correct treatment.

Is there evidence of significant bleeding risk related to different platelet counts in patients with primary immune thrombocytopenia?

The severity of bleeding in children with ITP is inversely correlated with the platelet count, irrespective of treatment^(42,43)(B). For example, 97% of all degree 3 bleeding episodes (moderate mucosa without the necessity of treatment) and degree 4 bleeding (severe mucosa or internal bleeding) occur with platelet counts less than 20 x 10⁹/L. In a study of 80 children, when epistaxis was degree 2 or higher (mild to severe bleeding), the platelet count was less than 10 x 10⁹/L⁽⁴³⁾(B).

Patients with < 10 x 10⁹ platelets/L tend to have more moderate to severe bleeding compared to those with more than 10 x 10⁹ platelets/L. For example, when platelet count is < 10 x 10⁹/L, about 60% of the cases have mild skin bleeding, while when the platelet count is between 10 and 20 x 10⁹/L, no bleeding or skin bleeding are observed in 76% of the cases (p-value < 0.01). This observation suggests that, in cases of severe thrombocytopenia (< 20 x 10⁹ platelets/L), an observational approach may not be suitable⁽⁴⁴⁾(B). Clinically significant bleeding occurs in 47% of children with ITP when the platelet count is < 5 x 10⁹/L, in 26% when the platelet count is between 5 and 9 x 10⁹/L, in 13% when it is between 10 and 19 x 10⁹/L, in 7% between 20 and 50 x 10⁹/L, and when the platelet count is over 50 x 10⁹/L, the risk falls to 5%⁽⁴⁵⁾(B).

There is a relationship between the severity of bleeding and platelet count in patients between four months and 20 year olds in the acute phase of ITP, and there is an increased risk of moderate bleeding when the platelet count is below 20 x 10⁹/L⁽⁴⁶⁾(B).

Recommendation: In children with ITP, the intensity of bleeding is inversely proportional to the platelet count with the suggested critical level for major bleeding complications being 20 x 10⁹ platelets/L.

Is there any correlation between the characteristics of primary immune thrombocytopenia and thrombocytopenia in newborns?

The prevalence of thrombocytopenia in the newborn of mothers with ITP ranges between 15 and 50% for platelet counts between $50 \times 10^9/L$ and $100 \times 10^9/L$ and between 4.9 and 44% for severe thrombocytopenia ($< 50 \times 10^9$ platelets/L)^{(47-52)(C)}^{(53)(A)}.

Evaluations before (67.7%) and during (32.3%) pregnancy of 88 women (127 pregnancies) diagnosed with ITP and their 130 newborns was performed. Mean platelet count of the newborns was $216 \times 10^9/L \pm 78 \times 10^9/L$ at birth. However, 15.4% of them had platelet counts below $100 \times 10^9/L$, 8.5% were below $50 \times 10^9/L$ and 2.3% below $20 \times 10^9/L$. Only one fetus had severe complications with an intrauterine intracranial hemorrhage. The influence of several maternal parameters was assessed and there was no positive correlation between the thrombocytopenia of the newborns and the duration of maternal ITP, splenectomy before pregnancy, duration of the mother's ITP, treatment during pregnancy or before the delivery, the progressive decline of the platelet count during pregnancy and type of delivery. A maternal platelet count $< 100 \times 10^9/L$ at birth shows a trend for thrombocytopenia ($< 100 \times 10^9$ platelets/L) in the newborn (p-value = 0.043). The study observed two patterns of thrombocytopenia, one at birth and the second a few days after birth. Six newborns with normal platelet counts at birth developed thrombocytopenia by their 6th day of life^{(47)(C)}.

The clinical and laboratory features of 29 newborns were evaluated. Of 29 mothers with ITP with a mean age of 28 ± 5.3 years, 16 (55%) had been diagnosed before the start of pregnancy and 13 (45%) during pregnancy. The platelet counts at birth of 14 (48%) of the newborns were 9 to $148 \times 10^9/L$ with 17% (n = 5) showing mucosal or gastrointestinal bleeding. There was no case of intracranial hemorrhage. The main risk factors associated to ITP in the newborn were advanced maternal age (30 ± 5.3 versus 25.3 ± 3.8 years) and male gender (both p-values < 0.05). Maternal thrombocytopenia ($< 50 \times 10^9$ platelets/L) at childbirth, recurrence of ITP during pregnancy and the need for platelet transfusion during pregnancy were associated with severe newborn thrombocytopenia (p-value < 0.05). Splenectomy and drugs prescribed to the mother were not correlated to newborn thrombocytopenia, but the sample size of this study was small. There was no significant difference between newborns with and without thrombocytopenia (p-value > 0.05) in respect to whether the mother had positive antiplatelet antibodies or not. However, the duration of thrombocytopenia in the newborn was higher when the mother had platelet autoantibodies^{(48)(C)}.

In another study, the mean age of 284 pregnant women diagnosed with ITP was 24.8 ± 6.5 years; 38 were diagnosed during pregnancy and 62 before pregnancy. Of 286 newborns, the platelet count was evaluated in only 212, with 48 (22.6%) having $< 100 \times 10^9$ platelets/L. No case of intracranial hemorrhage was observed. Some babies were born with normal platelet counts and developed thrombocytopenia within the first five days of life. No correlations were found between the incidence of newborn thrombocytopenia and the mother's

diagnosis (before or during pregnancy), the ITP clinical condition (remission does not guarantee that the newborn will have a normal platelet count) and the type of treatment during pregnancy or at childbirth. Thrombocytopenia prevalence was significantly higher in newborns of mothers who maintained a complete ($> 100 \times 10^9$ platelets/L without concomitant treatment) or good response ($> 100 \times 10^9$ platelets/L with concomitant treatment) after splenectomy compared to those treated with corticosteroids (p-value < 0.01)^{(49)(C)}.

In a review of 15 children born to mothers with ITP over a ten-year follow-up, the incidence of severe thrombocytopenia ($< 50 \times 10^9$ platelets/L) was 20%; there were no statistically significant differences between the mothers who received intravenous immunoglobulin before delivery and those who did not. No intracranial hemorrhages, seizures or other complications were reported in the newborns. Risk factors for thrombocytopenia in the newborn were low maternal platelet count at childbirth, minimum maternal platelet count during pregnancy, history of maternal ITP, IgG level associated with low platelet count, and the mother having antiplatelet autoantibodies^{(50)(C)}.

In the evaluation of 29 pregnant women with ITP and their 32 newborns, the mothers' platelet count at childbirth ranged from 9 to $133 \times 10^9/L$ (mean 81×10^9 platelets/L with 21% having $\leq 50 \times 10^9$ platelets/L). Fourteen newborns (44%) presented with thrombocytopenia ($< 50 \times 10^9$ platelets/L) and four (12.5%) with platelet counts between 50 and $150 \times 10^9/L$. A platelet count below $50 \times 10^9/L$ in mothers was a predictor for thrombocytopenia in the newborn (p-value < 0.027) compared to platelet counts above $50 \times 10^9/L$. The treatment of maternal ITP with prednisone did not show significant effects on the newborn's platelet count^{(51)(C)}.

None of 61 babies born to 50 mothers with ITP diagnosed before or during pregnancy suffered from thrombocytopenia-related death or disease; 4.9% had platelet counts lower than $50 \times 10^9/L$. There was a drop in the platelet count after birth in 66% of the newborns. Moreover, there was no association between thrombocytopenia in the newborn and the maternal platelet count, maternal treatment with corticosteroids, IgG levels associated with platelets and splenectomy^{(52)(C)}.

A comparison of 28 newborns of mothers with ITP treated with low doses of betamethasone from the 37th week of gestation until birth and untreated mothers showed that the mean platelet counts of the mothers at childbirth were $99 \times 10^9/L$ and $95 \times 10^9/L$, respectively (p-value > 0.05). Between the two groups of newborns, there was no significant difference in the platelet count, with 14.2% of each group having severe thrombocytopenia ($< 50 \times 10^9$ platelets/L). Thrombocytopenia between 50×10^9 platelets/L and 150×10^9 platelets/L was observed in 50% of the newborns in the group of treated mothers and 42.8% of the untreated mothers. Some patients developed thrombocytopenia on the 4th day of life. The prevalences of neonatal thrombocytopenia were 64% and 57% in the treated and untreated groups, respectively. The number of bleeding complications was similar in both groups. Therefore maternal treatment with low-dose corticosteroid does not prevent thrombocytopenia or bleeding in newborns^{(53)(A)}.

Recommendation: There is no correlation between the incidence of thrombocytopenia in the newborn and the duration of maternal ITP, the mothers' clinical conditions, splenectomy before pregnancy, treatment during pregnancy or before delivery, and delivery type. The risk factors found for thrombocytopenia in the newborn were the severity of mother's thrombocytopenia at delivery ($< 50 \times 10^9$ platelets/L), maternal age, male gender and the presence of antiplatelet autoantibodies. It is essential to monitor the newborn in the early days of life due to the possibility of transient thrombocytopenia which may become severe.

References

1. Centre for Evidence Based Medicine [Internet]. Oxford: University of Oxford; 2011. [cited 2012 Nov 21]. Available from: <http://www.cebm.net>.
2. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, Bussel JB, Cines DB, Chong BH, Cooper N, Godeau B, Lechner K, Mazzucconi MG, McMillan R, Sanz MA, Imbach P, Blanchette V, Kühne T, Ruggeri M, George JN. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113(11):2386-93. Comment in: *Blood*. 2009;114(9):2003-4; author reply 2004.
3. Segel GB, Feig SA. Controversies in the diagnosis and management of childhood acute immune thrombocytopenic purpura. *Pediatr Blood Cancer*. 2009;53(3):318-24.
4. De Mattia D, Del Vecchio GC, Russo G, De Santis A, Ramenghi U, Notarangelo L, Jankovic M, Molinari AC, Zecca M, Nobili B, Giordano P, Acquaviva A, Amendola G, Baronci C, Binda S, Bisogno G, Bussetti C, Ciliberti A, Citterio M, Del Principe D, Farruggia P, Ladogana S, Magro S, Maserà G, Menichelli A, Nardi M, Parodi E, Pession A, Tucci F, Vimercati C; AIEOP-ITP Study Group. Management of chronic childhood immune thrombocytopenic purpura: AIEOP consensus guidelines. *Acta Haematol*. 2010;123(2):96-109.
5. Bennett CM, Tarantino M. Chronic immune thrombocytopenia in children: epidemiology and clinical presentation. *Hematol Oncol Clin North Am*. 2009;23(6):1223-38.
6. Imbach P, Kühne T, Müller D, Berchtold W, Zimmerman S, El-Alfy M, et al. Childhood ITP: 12 months follow-up data from the prospective registry I of the Intercontinental Childhood ITP Study Group (ICIS). *Pediatr Blood Cancer*. 2006;46(3):351-6.
7. Imbach P, Zimmerman S. Local and cultural aspects of childhood idiopathic thrombocytopenic purpura: a summary of statements from the 12 countries worldwide. *J Pediatr Hematol Oncol*. 2003;25(Suppl 1):S68-73.
8. Donato H, Picón A, Martínez M, Rapetti MC, Rosso A, Gomez S, et al. Demographic data, natural history, and prognostic factors of idiopathic thrombocytopenic purpura in children: a multicentered study from Argentina. *Pediatr Blood Cancer*. 2009;52(4):491-6.
9. El-Alfy M, Farid S, Maksoud AA. Predictors of chronic idiopathic thrombocytopenic purpura. *Pediatr Blood Cancer*. 2010;54(7):959-62.
10. Zeller B, Rajantie J, Hedlund-Treutiger I, Tedgård U, Wesenberg F, Jonsson OG, et al. Childhood idiopathic thrombocytopenic purpura in the Nordic countries: epidemiology and predictors of chronic disease. *Acta Paediatr*. 2005;94(2):178-84.
11. Robb LG, Tiedeman K. Idiopathic thrombocytopenic purpura: predictors of chronic disease. *Arch Dis Child*. 1990;65(5):502-6.
12. Glanz J, France E, Xu S, Hayes T, Hambidge S. A population based, multisite cohort study of the predictors of chronic idiopathic thrombocytopenic purpura in children. *Pediatrics*. 2008;121(3):e506-12.
13. Watts RG. Idiopathic thrombocytopenic purpura: a 10-year natural history study at the Children's Hospital of Alabama. *Clin Pediatr (Phila)*. 2004;43(8):691-702.
14. Grace RF, Long M, Kalish LA, Neufeld EJ. Applicability of 2009 international consensus terminology and criteria for immune thrombocytopenia to a clinical pediatric population. *Pediatr Blood Cancer*. 2012;58(2):216-20.
15. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117(16):4190-207.
16. Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood*. 2010;115(2):168-86.
17. Jayabose S, Levendoglu-Tugal O, Ozkaynak MF, Visintainer P, Sandoval C. Long-term outcome of chronic idiopathic thrombocytopenic purpura in children. *J Pediatr Hematol Oncol*. 2004;26(11):724-6.
18. Strauß G, Vollert C, von Stackelberg A, Weimann A, Gaedicke G, Schulze H. Immature platelet count: A simple parameter for distinguishing thrombocytopenia in pediatric acute lymphocytic leukemia from immune thrombocytopenia. *Pediatr Blood Cancer*. 2010;57(4):641-7.
19. Ruggeri M, Fortuna S, Rodeghiero F. Heterogeneity of terminology and clinical definitions in adult idiopathic thrombocytopenic purpura: a critical appraisal from a systematic review of the literature. *Haematologica*. 2008;93(1):98-103.
20. Ruggeri M, Fortuna S, Rodeghiero F. Heterogeneity of terminology and clinical definitions in adult idiopathic thrombocytopenic purpura: a critical appraisal from literature analysis. *Pediatr Blood Cancer*. 2006;47(5 Suppl):653-6.
21. Chandra H, Chandra S, Rawat A, Verma SK. Role of mean platelet volume as discriminating guide for bone marrow disease in patients with thrombocytopenia. *Int J Lab Hematol*. 2010;32(5):498-505.
22. Anoop P. Decision to perform bone marrow aspiration in immune thrombocytopenic purpura must be based on evidence. *Pediatr Hematol Oncol*. 2008;25(1):91-2. Comment in: *Pediatr Hematol Oncol*. 2007;24(3):205-7.
23. Naithani R, Kumar R, Mahapatra M, Agrawal N, Pati HP, Choudhry VP. Is it safe to avoid bone marrow examination in suspected ITP? *Pediatr Hematol Oncol*. 2007;24(3):205-7.
24. Bader-Meunier B, Proulle V, Trichet C, Debray D, Gabolde M, Yvart J, et al. Misdiagnosis of chronic thrombocytopenia in childhood. *J Pediatr Hematol Oncol*. 2003;25(7):548-52.
25. Klaassen RJ, Doyle JJ, Krahn MD, Blanchette VS, Naglie G. Initial bone marrow aspiration in childhood idiopathic thrombocytopenia: decision analysis. *J Pediatr Hematol Oncol*. 2001;23(8):511-8.
26. Calpin C, Dick P, Poon A, Feldman W. Is bone marrow aspiration needed in acute childhood idiopathic thrombocytopenic purpura to rule out leukemia? *Arch Pediatr Adolesc Med*. 1998;152(4):345-7.
27. Cirasino L, Robino AM, Cattaneo M, Pioltelli PE, Pogliani EM, Morra E, et al. Reviewed diagnosis of primary and secondary immune thrombocytopenic purpura in 79 adult patients hospitalized in 2000-2002. *Blood Coagul Fibrinolysis*. 2011;22(1):1-6.
28. Belletrutti M, Ali K, Barnard D, Blanchette V, Chan A, David M, Luke B, Price V, Ritchie B, Wu J; Canadian Pediatric Chronic ITP Working Group; Canadian Pediatric Thrombosis and Hemostasis Network. Chronic immune thrombocytopenic purpura in children: a survey of the Canadian experience. *J Pediatr Hematol Oncol*. 2007;29(2):95-100.
29. Kühne T, Berchtold W, Michaels LA, Wu R, Donato H, Espina B, Tamary H, Rodeghiero F, Chitlur M, Rischewski J, Imbach P; Intercontinental Cooperative Immune Thrombocytopenia Study Group.

- Newly diagnosed immune thrombocytopenia in children and adults: a comparative prospective observational registry of the Intercontinental Cooperative Immune Thrombocytopenia Study Group. *Haematologica*. 2011;96(12):1831-7.
30. Shaikh KH, Ahmed S, Ayyub M, Anwar J. Association of Helicobacter pylori infection with idiopathic thrombocytopenic purpura. *J Pak Med Assoc*. 2009;59(10):660-3.
 31. Kikuchi T, Kobayashi T, Yamashita T, Ohashi K, Sakamaki H, Akiyama H. Eight-year follow-up of patients with immune thrombocytopenic purpura related to H. pylori infection. *Platelets*. 2011;22(1):61-4.
 32. Neefjes VM, Heijboer H, Tamminga RY. H. pylori infection in childhood chronic immune thrombocytopenic purpura. *Haematologica*. 2007;92(4):576.
 33. Russo G, Miraglia V, Branciforte F, Matarese SM, Zecca M, Bisogno G, Parodi E, Amendola G, Giordano P, Jankovic M, Corti A, Nardi M, Farruggia P, Battisti L, Baronci C, Palazzi G, Tucci F, Ceppi S, Nobili B, Ramenghi U, De Mattia D, Notarangelo L; AIEOP-ITP Study Group. Effect of eradication of Helicobacter pylori in children with chronic immune thrombocytopenia: a prospective, controlled, multicenter study. *Pediatr Blood Cancer*. 2011;56(2):273-8.
 34. Treepongkaruna S, Sirachainan N, Kanjanapongkul S, Winaichatsak A, Sirithorn S, Sumritsopak R, et al. Absence of platelet recovery following Helicobacter pylori eradication in childhood chronic idiopathic thrombocytopenic purpura: a multi-center randomized controlled trial. *Pediatr Blood Cancer*. 2009;53(1):72-7.
 35. Kawakami E, Brito HS, Braga JP, Machado RS, Loggetto SR, Granato C. Helicobacter pylori infection and chronic thrombocytopenic purpura in children and adolescents - a randomized controlled trial. *Gastroenterology*. 2012;142(5 Sup 1):S-184
 36. Ding Y, Zhao L, Mei H, Zhang SL, Huang ZH. Role of myeloid human cytomegalovirus infection in children's idiopathic thrombocytopenic purpura. *Pediatr Hematol Oncol*. 2007;24(3):179-88.
 37. DiMaggio D, Anderson A, Busse JB. Cytomegalovirus can make immune thrombocytopenic purpura refractory. *Br J Haematol*. 2009;146(1):104-12. Comment in: *Br J Haematol*. 2010;149(3):454-5.
 38. Pratt EL, Tarantino MD, Wagner D, Hirsch Pescovitz O, Bowyer S, Shapiro AD. Prevalence of elevated antithyroid antibodies and antinuclear antibodies in children with immune thrombocytopenic purpura. *Am J Hematol*. 2005;79(3):175-9.
 39. Heegaard ED, Rosthøj S, Petersen BL, Nielsen S, Karup Pedersen F, Hornsleth A. Role of parvovirus B19 infection in childhood idiopathic thrombocytopenic purpura. *Acta Paediatr*. 1999;88(6):614-7.
 40. Miron D, Luder A, Horovitz Y, Izkovitz A, Shizgreen I, Ben David E, et al. Acute human parvovirus B-19 infection in hospitalized children: A serologic and molecular survey. *Pediatr Infect Dis J*. 2006;25(10):898-901.
 41. Bertuola F, Morando C, Menniti-Ippolito F, Da Cas R, Capuano A, Perilongo G, et al. Association between drug and vaccine use and acute immune thrombocytopenia in childhood: a case-control study in Italy. *Drug Saf*. 2010;33(1):65-72.
 42. Pansy J, Minkov M, Dengg R, Quehenberger F, Lackner H, Nebl A, et al. Evaluating bleeding severity in children with newly diagnosed immune thrombocytopenia: a pilot study. *Klin Padiatr* 2010;222(6):374-7.
 43. Buchanan GR, Adix L. Grading of hemorrhage in children with idiopathic thrombocytopenic purpura. *J Pediatr*. 2002;141(5):683-8.
 44. Chandra J, Ravi R, Singh V, Narayan S, Sharma S, Dutta AK. Bleeding manifestations in severely thrombocytopenic children with immune thrombocytopenic purpura. *Hematology*. 2006;11(2):131-3.
 45. Medeiros D, Buchanan GR. Major hemorrhage in children with idiopathic thrombocytopenic purpura: immediate response to therapy and long-term outcome. *J Pediatr*. 1998;133(3):334-9. Comment in: *J Pediatr*. 1998;133(3):313-4.
 46. Neunert CE, Buchanan GR, Imbach P, Bolton-Maggs PH, Bennett CM, Neufeld EJ, Vesely SK, Adix L, Blanchette VS, Kühne T; Intercontinental Childhood ITP Study Group Registry II Participants. Severe hemorrhage in children with newly diagnosed immune thrombocytopenic purpura. *Blood* 2008; 112(10):4003-8. Comment in: *Blood*. 2008;112(10):3918-9.
 47. Koyama S, Tomimatsu T, Kanagawa T, Kumasawa K, Tsutsui T, Kimura T. Reliable predictors of neonatal immune thrombocytopenia in pregnant women with idiopathic thrombocytopenic purpura. *Am J Hematol* 2012;87(1):15-21.
 48. Ozkan H, Cetinkaya M, Köksal N, Ali R, Güneş AM, Baytan B, et al. Neonatal outcomes of pregnancy complicated by idiopathic thrombocytopenic purpura. *J Perinatol*. 2010;30(1):38-44.
 49. Fujimura K, Harada Y, Fujimoto T, Kuramoto A, Ikeda Y, Akatsuka J, et al. Nationwide study of idiopathic thrombocytopenic purpura in pregnant women and the clinical influence on neonates. *Int J Hematol*. 2002;75(4):426-33.
 50. Asano T, Sawa R, Araki T, Yamamoto M. Incidence of thrombocytopenia in infants born to mothers with idiopathic thrombocytopenic purpura. *Acta Paediatr Jpn*. 1998;40(2):112-5.
 51. al-Mofada SM, Osman ME, Kides E, al-Momen AK, al-Herbish AS, al-Mobaireek K. Risk of thrombocytopenia in the infants of mothers with idiopathic thrombocytopenia. *Am J Perinatol*. 1994;11(6):423-6.
 52. Burrows RF, Kelton JG. Low fetal risks in pregnancies associated with idiopathic thrombocytopenic purpura. *Am J Obstet Gynecol*. 1990;163(4Pt 1):1147-50. Comment in: *Am J Obstet Gynecol*. 1991;164(5 Pt 1):1362-3.
 53. Christiaens GC, Nieuwenhuis HK, von dem Borne AE, Ouwehand WH, Helmerhorst FM, van Dalen CM, et al. Idiopathic thrombocytopenic purpura in pregnancy: a randomized trial on the effect of antenatal low dose corticosteroids on neonatal platelet count. *Br J Obstet Gynaecol*. 1990;97(10):893-8. Comment in: *Br J Obstet Gynaecol*. 1991;98(3):334-6.

Appendix

Search strategies by question for the clinical guidelines for primary immune thrombocytopenia in children and adolescents - diagnosis

When is primary immune thrombocytopenia considered acute, chronic or persistent?

(Purpura, Thrombocytopenic, Idiopathic OR Werlhof Disease OR Autoimmune Thrombocytopenic Purpura OR Purpura, Thrombocytopenic) AND ((CLASSIFICATION) OR (time factors) OR (International Classification of Diseases) OR (phases) OR (chronic AND acute))

What are the criteria that must be present for the definition of refractory primary immune thrombocytopenia and for complete and partial remission?

(Purpura, Thrombocytopenic, Idiopathic OR Werlhof Disease OR Autoimmune Thrombocytopenic Purpura OR Purpura, Thrombocytopenic OR Immune Thrombocytopenia) AND (long-term OR treatment outcome OR response OR refractory OR remission OR relapsed OR relapsing OR criteria OR definition) AND (platelet OR title OR etiology/broad [filter] OR prognosis/broad [filter] OR therapy/broad [filter] OR epidemiologic methods OR comparative study)

When should the primary immune thrombocytopenia diagnosis in a patient with thrombocytopenia be considered? At what platelet count should primary immune thrombocytopenia be investigated?

(Purpura, Thrombocytopenic, Idiopathic OR Werlhof Disease OR Autoimmune Thrombocytopenic Purpura OR Purpura, Thrombocytopenic OR Immune Thrombocytopenia) AND platelet AND diagnosis/broad [filter]

Is there evidence to support bone marrow examination to confirm diagnosis of primary immune thrombocytopenia?

When is bone marrow examination indicated?

(Purpura, Thrombocytopenic, Idiopathic OR Werlhof Disease OR Autoimmune Thrombocytopenic Purpura OR Purpura, Thrombocytopenic OR Immune Thrombocytopenia OR Thrombocytopenia) AND (Bone Marrow OR Bone Marrow Cells OR Bone Marrow Examination OR bone marrow biopsy OR bone marrow aspiration OR bone marrow aspirate) AND (Diagnosis/broad [filter] OR Diagnosis [filter])

Which etiological factors are involved in secondary immune thrombocytopenia (or secondary immune thrombocytopenic purpura)? Which exams should be done to investigate primary immune thrombocytopenia?

(Purpura, Thrombocytopenic, Idiopathic OR Werlhof Disease OR Autoimmune Thrombocytopenic Purpura OR Purpura, Thrombocytopenic OR Immune Thrombocytopenia) AND (HIV OR Hepatitis OR Cytomegalovirus OR Helicobacter pylori OR rheumatic disease OR Antiphospholipid Syndrome OR Thyrotropin OR Neoplasms OR Blood cell count) AND (etiology/broad[filter] OR diagnosis/broad[filter])

Is there evidence of significant bleeding risk related to different platelet counts in patients with primary immune thrombocytopenia?

(Purpura, Thrombocytopenic, Idiopathic OR Werlhof Disease OR Autoimmune Thrombocytopenic Purpura OR Purpura, Thrombocytopenic OR Immune Thrombocytopenia) AND (Hospitalization OR admission OR hospital OR hospitalized)

Is there any correlation between the characteristics of primary immune thrombocytopenia and thrombocytopenia in newborns?

(Postnatal Care OR Infant, Newborn) AND (Purpura, Thrombocytopenic, Idiopathic OR Werlhof Disease OR Autoimmune Thrombocytopenic Purpura OR Purpura, Thrombocytopenic)