

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

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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 to standardize decisions in order to help strategies during diagnosis and treatment. The data contained in this manuscript were prepared by and recommended by the *Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular* (ABHH). Even so, all possible decisions on diagnosis and treatment should be evaluated by the physician responsible according to the patient's setting and clinical status.

Aim

To define parameters for the treatment of children and adolescents with ITP based on the best available published evidence. The target audience is the hematologist, pediatrician and medical student.

Description of the evidence collection method

The members of the ABHH Committee responsible for writing the treatment guidelines on primary immune thrombocytopenia (ITP) prepared the main questions on treatment of children and adolescents. Nine questions were structured using the Patient/Problem, Intervention, Comparison and Outcome (PICO) system. The search strategies for specific clinical questions 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 the 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 completely supervised by experts on evidence-based guidelines.

Recommendation degree and evidence level

A: Major experimental or observational studies

B: Minor experimental or observational studies

C: Case reports (uncontrolled studies)

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

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). 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).

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.

What is the correct approach to treat patients with newly diagnosed primary immune thrombocytopenia and active bleeding?

Prospective randomized trials have been performed to evaluate the treatment of children with newly diagnosed ITP with platelet counts $< 20 \times 10^9/L$. More favorable results were obtained with the administration of a single dose of intravenous immunoglobulin (IVIg - 0.8 g/kg) compared to IVIg (1 g/kg/day) for two consecutive days, anti-D immunoglobulin (anti-D - 25 $\mu\text{g/kg/day}$) for two days or oral prednisone (4 mg/kg) for 21 days in 146 pediatric patients aged six months to 18 years old. Anemia was an adverse event related to anti-D administration⁽⁵⁾(A).

Single doses of anti-D (50 $\mu\text{g/kg}$), anti-D (75 $\mu\text{g/kg}$) or IVIg (0.8 g/kg) were compared in 105 children. After 24 hours of treatment, 50%, 72% and 77% of the patients from the anti-D50, anti-D75 and IVIg arms, respectively, achieved platelet counts $> 20 \times 10^9/L$ (p-value = 0.03), suggesting that IVIg and the higher dose of anti-D are effective. However, a significant decrease in the hemoglobin level was observed in the anti-D groups⁽⁶⁾(A).

Another study with 81 children (six months to 14 years old) randomized to receive a single dose of anti-D (75 $\mu\text{g/kg}$) or IVIg (1 g/kg/day) for two consecutive days showed a higher response rate for the IVIg arm (98%) compared to the anti-D arm (76%; p-value = 0.017). After seven days, the platelet count was above $20 \times 10^9/L$ in all patients who had received IVIg, while 12% of the anti-D arm had platelet counts $< 20 \times 10^9/L$. These findings show that the initial treatment of newly diagnosed ITP with IVIg increased the platelet count faster than anti-D⁽⁷⁾(A).

In a study with 25 children aged six months to 14 years old randomized to receive a single dose of anti-D (50 $\mu\text{g/kg}$) or IVIg (0.8 to 1 g/kg), the therapeutic response in 24 hours with both medications was effective to increase the platelet count above $20 \times 10^9/L$. There was a decrease in the hemoglobin level with anti-D. Anti-D can be used only in non-splenectomized Rh-positive patients with a negative direct antiglobulin test (Coombs)⁽⁸⁾(B).

A retrospective analysis of 53 children with newly diagnosed ITP showed that purpura and mucosal bleeding (mean platelet count of $5 \times 10^9/L$) are associated with greater risk of treatment failure with IVIg or anti-D when compared to cases of purpura with bruises and/or petechiae with mean platelet counts of $10 \times 10^9/L$ ⁽⁹⁾(B).

An analysis of different treatments in children with newly diagnosed ITP and moderate bleeding found that IVIg was used in 24% of cases, corticosteroids in 27%, anti-D in 6%, combined therapy in 32% and no therapy in 11%. About 1.7% of these children developed, regardless of the treatment, severe bleeding. Of the children with platelet counts $\leq 20 \times 10^9/L$ and no signs of bleeding or mild bleeding at diagnosis, three (0.6%) developed severe bleeding within 30 days. There was a statistically significant difference (p-value < 0.001) between the platelet count and the treatment chosen (conservative or drug treatment) in patients with no or mild bleeding. The mean platelet counts of patients who received no treatment, anti-D, IVIg, corticosteroids or combined therapy were $28 \times 10^9/L$, $7 \times 10^9/L$, $9 \times 10^9/L$, $12 \times 10^9/L$ and $8 \times 10^9/L$, respectively.⁽¹⁰⁾(B).

Of newly diagnosed ITP patients who had suffered intracranial hemorrhage, 70% were receiving or had received treatment with corticosteroids and 13.6% of these had performed splenectomies⁽¹¹⁾(B).

Splenectomy in the acute phase of ITP is rare. Of 134 under 18-year-old splenectomized patients with ITP, only 21 (15%) had acute ITP (thrombocytopenia < 6 months); the median time between diagnosis and splenectomy was 4.1 months (0.7-5.9 months)⁽¹²⁾(B).

Recommendation: The first line therapy for newly diagnosed ITP patients with platelet counts usually $< 20 \times 10^9/L$ and active bleeding are IVIg, corticosteroids or anti-D. Anti-D can only be used in non-splenectomized Rh-positive patients with a negative direct antiglobulin test (Coombs). Intracranial hemorrhage can occur even during treatment. Splenectomy may be indicated when there is no response to corticosteroids or immunoglobulins and the patient maintains bleeding, including of the central nervous system.

Is there evidence that the parenteral administration of high-dose methylprednisolone is faster and/or more effective than oral corticosteroid therapy?

A trial with 49 children with newly diagnosed ITP (platelet count $< 50 \times 10^9/L$ and < 7 days of disease) comparing oral prednisone (n = 16; 2 mg/kg/day for two weeks), parenteral administration of high-dose methylprednisolone (n = 16; 30 mg/kg/day for three days; 20 mg/kg/day for four days and subsequent reduction with 10, 5, 2 and 1 mg/kg/day for seven days each) and wait and watch (n = 17) showed platelet response in three days in 69% of patients in the high-dose methylprednisolone arm, compared to 2-4 weeks in the oral prednisone arm. In the conservative treatment arm, 29.4% presented spontaneous remission in up to 15 days and 70.6% in up to four weeks. Treatment response in the first and second weeks was significant only for the high-dose methylprednisolone arm (p-value < 0.01) and similar between both oral prednisone and conservative treatment arms⁽¹³⁾(C).

A prospective study in Japan of 184 children aged one month to 14 years (median four years) with acute ITP (< 6 months of thrombocytopenia) without prior treatment, divided the patients into three groups. The group with platelet counts of less than $10 \times 10^9/L$ or with platelet counts between $10 \times 10^9/L$ and $29 \times 10^9/L$ and active bleeding received IVIg (n = 32) or oral prednisolone (2 mg/kg/day - maximum dose 60 mg/day) for two weeks and subsequent dose reduction until day 21 (n = 29), or intravenous methylprednisolone (5 mg/kg/day) for five days (n = 31) or parenteral administration of high-dose methylprednisolone (30 mg/kg/day - maximum dose 1000 mg/day) for three days (n = 27; pulse therapy). The time to achieve platelet counts above $30 \times 10^9/L$ was similar (median three days) between intravenous methylprednisolone, pulse therapy and oral prednisone. The necessity of retreatment in 14 days was lower for those who received intravenous methylprednisolone or pulse therapy when compared to oral prednisone⁽¹⁴⁾(B).

Recommendation: Intravenous methylprednisolone may be effective in children with ITP when it is necessary to increase the platelet count rapidly.

Is dexamethasone pulse therapy better than prednisone?

There are no pediatric studies comparing the response between dexamethasone pulse therapy and oral prednisone in the treatment of newly diagnosed or chronic ITP. Studies have been published comparing different doses of prednisone/prednisolone with a placebo. Most articles published on treatment of acute and chronic ITP patients using dexamethasone had small sample sizes.

High-dose oral dexamethasone (20 mg/m²/day for four days every 28 days for six cycles) was used in 17 children with symptomatic chronic ITP (> 6 months of thrombocytopenia) with platelet counts < 20 x 10⁹/L. All had been treated with prednisone; other treatments included IVIg, anti-D, high-dose methylprednisolone and splenectomy. Thirty days after the last cycle, 35% of patients had normal platelet counts and, after one year, 29% maintained normal platelet counts. No patient diagnosed more than 30 months prior to this treatment had remission. The use of dexamethasone did not provide a uniform response, but it can be considered in the treatment of symptomatic chronic ITP⁽¹⁵⁾(C).

In two trials on chronic ITP refractory to previous treatment (prednisone, IVIg, anti-D or splenectomy) with platelet counts of less than 20 x 10⁹/L, patients received high doses of oral dexamethasone (40 mg/m²/day for four days every 28 days for six cycles). After 72 hours, the platelet count was more than 100 x 10⁹/L in 78% of the cycles (study with 11 children)⁽³⁾(C), and the median platelet count on Day 4 of treatment was 158 x 10⁹/L (study with 13 children)⁽⁴⁾(C). Disease duration did not interfere in the result⁽⁴⁾(C). High-dose dexamethasone was effective in achieving response in chronic ITP and may be an option before splenectomy^(16,17)(C).

High dose oral or intravenous dexamethasone (40 mg/day for over 15-year-old patients and 20 mg/m² in children under 15 years old - maximum dose 40 mg/day for four days every 14 days for four cycles) was administered in 42 children aged two to 17 years old, with newly diagnosed ITP and platelet counts less than 30 x 10⁹/L or more than 30 x 10⁹/L associated with active bleeding and no previous treatment. The median platelet count before treatment was 8 x 10⁹/L. The overall response rate was 85.7%; 67% achieved platelet counts > 50 x 10⁹/L at the end of the first cycle. The relapse-free survival at 15 months was 96% [95% confidence interval (95% CI): 88.8-100.0] and long-term response in a median follow-up of eight months (range: 4-24 months) was 97.2%. The relapse rate after a median of 6.5 months (range: 3-10 months) after response to high-dose dexamethasone was 2.7%⁽¹⁸⁾(B).

High-dose intravenous dexamethasone (20 mg/m²/day - maximum 40 mg/day for four days every 15 days for four cycles) resulted in response in 83.6% of the cases of chronic ITP (more than six months of thrombocytopenia and platelet count < 10 x 10⁹/L with bleeding) in 12 under 18-year-old children. Complete response (platelet count > 150 x 10⁹/L) occurred in 66.6%, partial response (platelet count 50 to 150 x 10⁹/L) in 17% and treatment failure (platelet count < 20 x 10⁹/L) in 17%. Of these patients, 40% responded after the second cycle, 20% after the third cycle and 40% after the fourth cycle. The median response time was five months (range: 3-11 months)⁽¹⁹⁾(B).

High-dose dexamethasone is generally well tolerated and so interruption of treatment is avoided. The adverse events observed were fatigue, moodiness, flushing, headache, irritability, abdominal

pain, striae distensae, hirsutism, acne, weight gain, myalgia, edema, nausea, vomiting, insomnia, anxiety and depression.

Recommendation: In children with chronic ITP, dexamethasone at 20-40 mg/m² per day - maximum 40 mg/day - for four days every 15-28 days for 4-6 cycles is effective and suitable regarding the immediate response and may be a therapeutic option before recommending splenectomy.

What is the role of splenectomy in the treatment of primary immune thrombocytopenia in childhood/adolescence?

Twenty-three splenectomized children with chronic ITP (persistent thrombocytopenia for at least three months) aged between 3 and 17 years old (mean 11.7 ± 1.0 years) had presented clinical signs and symptoms, such as purpura (78%), petechiae (61%), epistaxis (43%), gingival bleeding (30%) and gastrointestinal bleeding (4%) at diagnosis. Prior to splenectomy, patients received a single course (four cases) or multiple courses of IVIg (19 cases); seven patients had poor responses to initial treatment with high doses of IVIg, four patients had good responses and 12 cases had excellent responses. Poor, good or excellent hematological responses were defined as platelet counts < 50 x 10⁹/L, between 50 x 10⁹/L and 150 x 10⁹/L and ≥ 150 x 10⁹/L, respectively. Response to splenectomy was observed in 90% of the children who initially presented responses to IVIg, while if the response to IVIg was poor, response to splenectomy was only 43%. So excellent or good responses to IVIg can predict favorable responses to splenectomy and even children who do not respond to IVIg can be submitted to splenectomy when necessary⁽²⁰⁾(B).

Under 16-year-old patients with chronic ITP (platelet count < 100 x 10⁹/L, normal or increased megakaryopoiesis in bone marrow and thrombocytopenia > 6 months), who were initially treated with corticosteroids (33%), repeated courses of IVIg (29%), corticosteroid and IVIg (7%) or no drug treatment (31%), may require splenectomies (39%). The indications for splenectomy were resistance to oral prednisone (2 mg/kg/day) after six months of treatment and corticosteroid dependence (prednisone > 0.1 mg/kg/day). Before 1996, the indication for splenectomy was persistent platelet count < 30 x 10⁹/L with recurrent episodes of bleeding or persistent platelet count < 10 x 10⁹/L without bleeding for more than six months. Since 1996 it has been proposed that only cases with recurrent severe bleeding that are not responsive to immunomodulatory during therapy for more than one year are splenectomized. Before splenectomy, all patients had recurrent bleeding episodes. One study followed up splenectomized patients for five to 16 years; 45% remained with complete response (platelet count > 100 x 10⁹/L without treatment for at least two months) and 35% remained with partial response (platelet count > 30 x 10⁹/L without treatment for at least two months). In patients for whom splenectomy failed (platelet count < 30 x 10⁹/L and recurrent bleeding with or without therapy), 85% had been resistant to previous treatment with corticosteroids. Fifty percent of patients with complete response to splenectomy

were corticosteroid dependent. Previous corticosteroid response was predictive of response to splenectomy (p-value = 0.004). Under 10-year-old patients had a lower response to splenectomy than those older than 10 years old (41% versus 59% for complete response and 70% versus 30% for failure, respectively). All patients received pneumococcal vaccination at least two weeks before splenectomy and oral penicillin prophylaxis after splenectomy. Two patients had pneumococcal sepsis. Severe bleeding episodes occurred in 18% of patients⁽²¹⁾(B).

A long term follow up of 402 patients with ITP (median age at diagnosis: 34 years old; range: 1-84 years; 53 ≤ 16 years old at diagnosis; median age at splenectomy: 36 years old; range: 6-85 years; 24 < 16 years old at splenectomy) showed that the surgery was performed at diagnosis in 1% (four cases), during follow-up without prior treatment in 3% (11 cases) and after one or more treatments in 96% (all received corticosteroids and 20% received IVIg). Indication for splenectomy was based on platelet count < 30 x 10⁹/L and/or corticosteroid dependence. Complete response to splenectomy was observed in 66% of cases, partial response in 20% and 14% were refractory to splenectomy. There was no difference in response between patients aged ≤ 16 or > 16 years old. After 48 months of follow up, 23% of the patients who achieved response presented recurrence⁽²²⁾(B).

Splenectomy was performed in 90 children with chronic ITP (platelet count < 50 x 10⁹/L for more than six months) when thrombocytopenia persisted more than six months with bleeding, when transitory response was obtained or the patient had important adverse events (headache and vomiting after IVIg, arterial hypertension and/or Cushing's syndrome after corticosteroids and hemolysis after anti-D). Prior to splenectomy, all patients received IVIg (total dose 2 g/kg/day), 29 patients received anti-D (15 µg/kg/day for three days) and 81 patients received oral prednisone (1-2 mg/kg/day), intravenous methylprednisone (> 5 mg/kg/day) or dexamethasone (24 mg/m²/day for four days). Treatment response was defined as negative if platelet count remained below 50 x 10⁹/L, as positive if the count was above this value and as a good response if it was > 150 x 10⁹/L. Response to splenectomy was considered positive when platelet count remained stable and above 50 x 10⁹/L during follow-up. There was no significant difference between response to splenectomy and the interval between diagnosis and surgery. The platelet count remained > 50 x 10⁹/L in 75% of cases and improved the quality of life in 85%. Treatment responses to pre-splenectomy corticosteroids and IVIg classified as good or positive were correlated with response to splenectomy. There was no difference in the incidence of infections that occurred during follow up (0.028 patient/years) between children submitted or not to antibiotic prophylaxis⁽²³⁾(B).

Of 696 children with ITP, 32.6% (230 patients) had chronic ITP (platelet count < 150 x 10⁹/L for more than six months); 13% (30 cases) underwent splenectomy (mean time 2.5 ± 1.4 years from diagnosis). Normal platelet count was obtained in 73.3% (20 cases) during a mean follow-up of 58.4 ± 46.3 months (range: 12-156). All patients received *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis* vaccines prior to surgery and antibiotic prophylaxis with penicillin or amoxicillin after splenectomy. Spontaneous remission occurred between six months and ten years after diagnosis in 53 (26.5%)

of the 200 non-splenectomized children and of these 56.6% had remission between the 6th and 12th month after diagnosis. Spontaneous remission, when compared to remission induced by splenectomy, was more frequent in younger children (5.0 ± 3.4 years versus 8.0 ± 4.4 years; p-value = 0.008)⁽²⁴⁾(B).

In 134 children with ITP with a median age at diagnosis of 9.5 years old (range: 1.1-17.6), a median age at splenectomy of 11.8 years old (range: 2.7-20.7) and a median duration of disease of 1.8 years (range: 0.1-10.8), splenectomy resulted in complete response in 86.3% of cases, partial response in 9.2% and no response in 4.6%. Splenectomy was performed in 20 children with acute ITP (< 6 months of thrombocytopenia). Complete response was maintained for one year in 80% of cases. Factors associated with complete remission were older age [Odds ratio (OR): 1.3], longer duration of ITP (OR: 2.0) and male gender (OR: 3.1)⁽¹²⁾(B).

Splenectomy was indicated for 19 children with chronic ITP (mean age: 12 years; range: 7-17 years) with a mean time between diagnosis and surgery of 32 months (range: 3.5-120) because of bleeding refractory to therapy (corticosteroids, anti-D, IVIg or rituximab) and contraindication to medication. After splenectomy, 68% of children achieved complete response, 16% partial response and 16% did not respond to surgery. There was no correlation between initial response to treatment before splenectomy (anti-D, IVIg or rituximab) and response to splenectomy. However there may be a correlation between the absence or presence of response to preoperative corticosteroids and complete postoperative response (100% and 50%, respectively)⁽²⁵⁾(B).

In 37 splenectomized children with chronic ITP, 20 had had complete response to corticosteroids. Of these, 80% achieved complete response to splenectomy. The surgery was successful in 75% of the eight patients who did not have any response to corticosteroid therapy. These findings suggest that there is no correlation between previous response to corticosteroids and response to splenectomy⁽²⁶⁾(B).

Recommendation: Splenectomy in children may be indicated in cases of chronic ITP refractory to drug treatment with recurrent bleeding. This may determine the hematologic response (complete or partial) in up to 80% of cases.

Is there evidence of predictive clinical or laboratory criteria of response to splenectomy in primary immune thrombocytopenia?

In 32 patients aged six months to 17 years diagnosed with ITP (platelet count < 20 x 10⁹/L) treatment response to IVIg and splenectomy was defined as excellent (platelet count > 150 x 10⁹/L in one week), good (platelet count between 50 x 10⁹/L and 149 x 10⁹/L) or poor (platelet count < 50 x 10⁹/L). Patients with good or excellent responses to IVIg (95%) had an excellent response to splenectomy. IVIg response had sensitivity, specificity, positive and negative predictive values of 91%, 66%, 87% and 75%, respectively in predicting response to splenectomy. Corticosteroid treatment and time between diagnosis and splenectomy did not correlate with response to splenectomy⁽²⁷⁾(B).

In an Italian study with 90 children, splenectomy was performed in patients with ITP when thrombocytopenia persisted for more than six months after diagnosis and when there was bleeding, transitory therapeutic success or adverse events. Response to splenectomy occurred in 75% patients. Response to IVIg and corticosteroids before surgery was predictive of response to splenectomy, but the interval between diagnosis and surgery was not⁽²⁴⁾(B).

An analysis of 19 patients showed that indications for splenectomy in children with ITP included bleeding symptoms refractory to treatment and drug contraindication. After splenectomy, 70% of patients had complete response (mean platelet count: $399 \times 10^9/L \pm 173 \times 10^9/L$), 20% partial response (mean platelet count: $64 \times 10^9/L \pm 19 \times 10^9/L$) and 10% no response (mean platelet count: $20 \times 10^9/L \pm 20 \times 10^9/L$). There was no correlation between response to splenectomy and anti-D, IVIg or rituximab response. Using a platelet count of $100 \times 10^9/L$ as a cut-off point, the preoperative hematological response to corticosteroids was predictive of response to splenectomy. In this population there was an inverse relationship between the platelet count with corticosteroids and the platelet count after splenectomy⁽²⁵⁾(B).

In a study published in 2011 on 37 patients with ITP followed up for ten years, there was no significant difference between the response to splenectomy and age (the age at diagnosis was 10 ± 5 years old and the age at splenectomy was 12 ± 4 years old). In this group, complete response to splenectomy (mean platelet count $324 \times 10^9/L \pm 147 \times 10^9/L$) was found in 84% and partial response (mean platelet count $104 \times 10^9/L \pm 29 \times 10^9/L$) in 16%. There was no association between the patients' response to IVIg, anti-D or rituximab and response to splenectomy (p-value = 0.24). There was a correlation between corticosteroid response and the response to splenectomy⁽²⁶⁾(B).

Recommendation: The immediate preoperative and postoperative platelet counts and the preoperative response to corticosteroids and IVIg are predictors of response to splenectomy.

Is there indication for vaccination in patients who will be submitted to splenectomy? Which vaccines are indicated?

In a study of 264 patients splenectomized due to different underlying diseases, the mean age was 8.5 ± 4.5 years old. Comparing the ages between children with infection (positive blood culture for encapsulated bacteria) and without infection, those with no infection (96%) were older than those with infection (mean age at surgery 8.7 ± 4.4 years versus 3.0 ± 2.6 years; p-value < 0.0001). Infections occurred four days to 9.7 years after splenectomy, with patient age ranging from eight months to 14.4 years. The infection and mortality rates were 3.8% and 0.4%, respectively. Higher rates of infection (13.8% versus 0.5%) and mortality (1.5% versus 0%) were found in patients of up to five years old at the time of splenectomy compared to over five-year-old children. All children received antibiotic prophylaxis and 70% were immunized (54% against pneumococcus and 16% against

pneumococcus associated with *H. influenzae* type b). None were immunized against *N. meningitidis*. Patients with infections were vaccinated in, on average, two weeks before the splenectomy, while those who did not have infections received the vaccine on average 4.5 months before, suggesting that the time between vaccination and surgery is important. Thus, early pneumococcal immunization is associated to lower risk of infection and the preoperative immunization is associated to lower risk of severe infections compared to postoperative immunization (2.6% versus 7.1%). Infections in immunized patients occurred on average 2.1 years (median 5.5 months) after splenectomy, while the non-immunized patients had infections on average two weeks (median two weeks) after the surgery. About 77% of infections occurred before five years after splenectomy (recommended period for revaccination). None of the revaccinated patients presented infections. The incidence of infection and mortality reduced by 47% and 88%, respectively with prophylaxis⁽²⁸⁾(B).

Of the asplenic children (12 with congenital asplenia and ten with surgical splenectomy, including three with ITP), 75% received the 23-valent pneumococcal polysaccharide vaccine and 82% received antibiotic prophylaxis. In this group, the incidence of invasive infection caused by *S. pneumoniae* was 1.5%. Clinical manifestations included bacteremia, meningitis, bacteremia with acute otitis media or sinusitis or pneumonia and meningitis with osteomyelitis, with a mortality of 27% (six patients, all with meningitis)⁽²⁹⁾(C).

After splenectomy in 538 patients (15 patients under 15 years old; 96 with hematological diseases), the incidence of bacteremia was 2.3 per 100 person-years at risk, 45% of cases within 30 days after surgery and only one case of *S. pneumoniae* (in an adult). No case of bacteremia or cases of *N. meningitidis* or *H. influenzae* type b were observed in under 15-year-old children. All children had received pneumococcal vaccines, while only 59% of adults had been vaccinated. There is evidence that pneumococcal vaccine reduces the risk of postoperative bacteremia⁽³⁰⁾(B).

In a retrospective study of 33 pediatric patients with chronic ITP (> 6 months of thrombocytopenia), splenectomy was indicated in persistent severe thrombocytopenia (platelet count < $10 \times 10^9/L$) with purpura and epistaxis, menorrhagia or recurrent bleeding (hematuria, melena, etc.). Pneumococcal vaccine had been administered in 75% of cases, most preoperatively, and 40% had also been immunized for *N. meningitidis*. Some patients were not on penicillin prophylaxis. After 25 years of follow up, there was only one death by infection (mortality rate of 3.1%), while the other patients showed no bacterial infections⁽³¹⁾(C).

In a study of 134 splenectomized children with ITP, 84.3% were vaccinated about 30 days before splenectomy while 15.7% did not receive vaccinations. Considering the vaccinated group, 82.8% of vaccinations were against *S. pneumoniae*, 50.8% against *H. influenzae* type b and 48.5% against *N. meningitidis*. Fever without sepsis occurred postoperatively in 9.7% of patients and less than 1% had postoperative sepsis. Antibiotic prophylaxis (mostly with penicillin) was given to 94% of patients. During a period of 225.2 patient-years, the risk of sepsis was 0.031 per patient-year, without deaths. Of the patients who developed sepsis, only one patient had not received a vaccination⁽¹²⁾(C). In splenectomized patients ($48.3\% \leq 16$ years old and 51.7% adults) for different indications, invasive infections occurred in

3.2% of cases with an overall mortality rate of 1.4%. The mean time of follow up was 6.9 years. The incidence of infection among children and adults was similar, but mortality was higher in children (1.7%) versus adults (1.3%; p-value < 0.001). The incidences of infection were higher among patients with thalassemia major (8.2%) and sickle cell anemia (7.3%; p-value < 0.01), while the lowest incidences were found in patients with ITP (2.1%) and trauma (2.3%). The highest mortality rates were observed for patients with thalassemia major (5.1%) and sickle cell anemia (4.8%; p-value < 0.01) and the lowest were observed in patients splenectomized for trauma (1.1%), ITP (1.2%) and spherocytosis (1.3%; p-value < 0.00001). Considering only the 194 children with ITP, the incidence of infection was 2.6% and the mortality rate was 1.5%. Among the 358 cases with identified etiologic agents, streptococcal pneumonia was the most common infection (66%) with 55.3% of mortality. The highest mortality rate however was attributed to gram-negative bacteria (62%) and *N. meningitidis* (58.8%; p-value = 0.017)⁽³²⁾(B).

Patients splenectomized due to ITP (n = 196), hypersplenism (n = 78), non-Hodgkin lymphoma (n = 89), hemolytic anemia (n = 55), Hodgkin's disease (n = 9) and without pre-existing hematological disease (n = 452) were evaluated for response to the 23-valent pneumococcal polysaccharide vaccine and trivalent inactivated influenza vaccine. Initially the heptavalent pneumococcal conjugate vaccine was used and then the 23-valent pneumococcal vaccine. Of all of the patients, 72% were adults and 28% were children (< 18 years old). At the time of splenectomy, 92.6% were over 18 years old and 7.4% were children. Sixty-one percent of the ITP cases were under 18 years old. The main indication for splenectomy in adults and children was ITP (4.04 splenectomies/1000 person-years). Immunization against *S. pneumoniae* was performed in 16.5% of the splenectomized patients (21.4% for ITP cases) and immunization against influenza in 53.1% of the patients (62.8% for ITP cases). Infection episodes are more common in splenectomized rather than in non-splenectomized patients (151 visits/100 person-years versus 120 visits/100 person-years; p-value < 0.0001). The risk of death to splenectomized patients due to hematological diseases is significantly higher when compared to non-splenectomized patients [individual analysis of ITP patients shows Hazard Ratio (HR): 1.57; 95% CI: 1.08-2.29]. For splenectomized patients, pneumococcal immunization was associated with decreased risk of death when the effect of the influenza vaccine was not considered (HR: 0.68; 95% CI: 0.47-1.00). However, no benefit was observed with the pneumococcal vaccine after adjusting for the effect of the influenza vaccine (HR: 7.1; 95% CI: 0.70-1.65). The risk of death decreased by 54% for all asplenic patients who received the influenza vaccine, including the subgroup of patients with ITP⁽³³⁾(B).

The immune response of 20 asplenic patients (16 splenectomized and four with congenital asplenic - none with ITP) aged between five and 25 years old (mean: 14.7 years) to a dose of *H. influenzae* type b conjugate vaccine demonstrated that the geometric mean antibody concentration prior to vaccination (3.21 µg/mL) rose significantly after vaccination to 6.78 µg/mL. At 4.5 years after vaccination the geometric mean antibody concentration was similar to that of unvaccinated children. The *H. influenzae* type b conjugate vaccine provides extended protection in asplenic patients⁽³⁴⁾(B).

One study compared splenectomized patients who received pneumococcal vaccines and developed severe pneumococcal infections with non-splenectomized patients who were also vaccinated with pneumococcal vaccines and developed severe pneumococcal infections. Splenectomy was performed in patients with Hodgkin's disease, ITP, hemolytic anemia and trauma. Of the 33 splenectomized patients, 48.4% had pneumococcal sepsis, 21.2% pneumococcal meningitis and 30.3% had both infections. All patients received 12- or 14-valent pneumococcal vaccines. Considering the pneumococcal serotypes isolated in the infections, 63.3% were included in the vaccine, in particular the 6A, 14, 19F and 23F serotypes. The most common serotype not included in the vaccine was 22F. The mean interval between pneumococcal vaccine and pneumococcal infection was ten months for serotypes included in the vaccine and 6.7 months for serotypes not included. Comparatively, of the 22 non-splenectomized patients who had received pneumococcal vaccinations (sickle cell anemia, hematological malignancies and diseases that impaired the immunological system), 59% had pneumonia due to *S. pneumoniae*, 27.2% had sepsis and 13.6% meningitis. A pneumococcal serotype was a vaccine type in 63.6% of cases and non-vaccine serotypes in 36.3% of cases. The most common serotypes isolated related to the vaccine were 6A, 19F and 23F, and those isolated unrelated to vaccine were 6B and 19A. The mean interval between vaccination and pneumococcal infection was 7.4 months⁽³⁵⁾(B).

In an epidemiological study published in 1997 of 149 patients (14 patients under 15 years old), the indications for splenectomy were hematological diseases (27%), trauma (33%), incidental (12%), accidental (20%) and others (8%). Of the children who received pneumococcal vaccinations, 35.7% had received it within the five years preceding splenectomy. Based on the anti-pneumococcal antibody titers, revaccination was required in one case (20%) in the immunized group less than five years before surgery and in 63% (five patients) in the group that had been immunized more than five years before surgery. A presumed protective level of antibodies was found in 52% of the immunized patients. The mean interval between splenectomy and the pneumococcal vaccination was 23 ± 8 days when given before splenectomy and 78 ± 3 days when given after splenectomy. In relation to *H. influenzae* type b vaccine, two children (1%) and 59 adults (40%) required revaccination. Thus, it was observed that 37% of the 149 splenectomized patients after ten years of follow up were still protected both for *S. pneumoniae* and for *H. influenzae* type b⁽³⁶⁾(B).

Recommendation: Due to increased risk of infections by *S. pneumoniae* in splenectomized patients, both children and adults, the pneumococcal vaccine is indicated and should be performed before splenectomy. Immunization against other encapsulated agents such as *H. influenzae* type b and *N. meningitidis* should also be performed at least 14 days before splenectomy. An annual vaccination against the influenza virus is also recommended.

Is there indication of penicillin prophylaxis after splenectomy?

Functional or anatomical asplenia is associated with a higher risk of severe bacterial infection or sepsis after splenectomy by encapsulated germs. There are no specific studies for ITP in relation to the need for prevention of these infections. Thus, recommendations for the use of penicillin prophylaxis in splenectomized patients with ITP are based on experience in children with sickle cell disease. As pneumococcal vaccines do not protect completely against infections, antibiotic prophylaxis has been recommended regardless of the vaccination status⁽³⁷⁾(B)⁽³⁸⁻⁴²⁾(D).

The need for antibiotic prophylaxis using oral or intramuscular penicillin in patients with sickle cell disease and functional asplenia is already well established due to the risk of invasive infections by *S. pneumoniae*⁽⁴³⁻⁴⁵⁾(A). A multicenter, randomized, double-blind, placebo-controlled trial showed that oral penicillin V prophylaxis daily (125 mg twice a day) reduces the incidence of sepsis by *S. pneumoniae* in children with sickle cell disease who begin treatment before the age of three years. The trial was terminated eight months early, after a mean of 15 months of follow-up, because there was an 84% reduction in the incidence of severe bacterial infection in the group treated with penicillin compared with the placebo group (p-value = 0.0025)⁽⁴⁴⁾(A).

Little evidence exists in cases of splenectomized patients, but it has already been observed that the incidence of infections and mortality in splenectomized children decreased by 47% and 88%, respectively with antibiotic prophylaxis and with immunization⁽²⁸⁾(B).

A retrospective study in Denmark between 1969 and 1978 evaluated 456 under 15-year-old splenectomized children, 52 of whom had ITP followed up on average for 6.2 years. In ITP, 11.5% of post-splenectomy infections (meningitis or pneumococcal bacteremia) were observed with 50% mortality. Under 4-year-old patients had a higher probability to develop infection after splenectomy. These data suggest the need for pneumococcal vaccines and antibiotic prophylaxis with penicillin for splenectomized children⁽²⁹⁾(B).

In a group of 318 splenectomized patients aged ten and 26 years old, 118 of whom had chronic ITP (> 6 months of thrombocytopenia), overwhelming infections were observed in 5.7% of the cases, 56% of which occurred within six months of the splenectomy. About 60% of the patients were on oral penicillin prophylaxis. The prevalence of overwhelming infections after splenectomy in patients who had more knowledge about the risk of sepsis was lower than in those who understood less (1.4% versus 16.5%, respectively; p-value < 0.001). Comparing the prevalence among patients on regular and irregular oral penicillin prophylaxis, overwhelming infections after splenectomy occurred in 2.7 and 10%, respectively (p-value < 0.01). The incidence of overwhelming infections after splenectomy in patients who received pneumococcal vaccines decreased from 7.3% to 3.2% (p-value < 0.05). These data reinforce the importance of proper guidance about oral penicillin prophylaxis and pneumococcal vaccines for splenectomized patients, regardless of the underlying disease⁽⁴⁶⁾(B).

In a study of 40 patients with overwhelming infections after splenectomy aged 18 months and 85 years old, the interval between splenectomy and infection ranged from 24 days to 59 years (60% of cases between ten and 30 years). Overwhelming infections were more frequent in patients aged 30-49 years old.

The main reason for splenectomy was trauma (13 cases), followed by Hodgkin's lymphoma (eight cases), ITP (six cases), hemolytic anemia (five cases), injury in abdominal surgery (four cases), chronic lymphocytic leukemia, chronic granulomatous disease and myelofibrosis with thrombocytopenia associated with systemic lupus erythematosus (one case each). The mortality rate due to infection was 45% (19 patients). Thirty-one cases of pneumococcal pneumonia and six cases of pneumococcal meningitis without sepsis were diagnosed, totaling 37 infection episodes (88%) due to *S. pneumoniae*. Another five cases of sepsis were by *Klebsiella pneumoniae*, *Escherichia coli* and *Salmonella typhimurium*. Only 12 patients had received pneumococcal vaccinations and ten of these suffered pneumococcal infections; at least four had possible vaccine failures. The pneumococcal vaccine used was the 23-valent which contains 85% of the strains found in the infections. Only 22% were on antibiotic prophylaxis. This study confirmed that the higher risk of overwhelming infections after splenectomy does not only occur in the first years after surgery, but that this risk remains for years⁽³⁷⁾(B). Thus, it is important always to be alert for febrile episodes in splenectomized patients.

Despite its potential advantage of saving lives, there are some issues in relation to oral antibiotic prophylaxis, including patient compliance, the optimal duration of treatment and the effect of prophylaxis on the development of pneumococcal resistance to penicillin. Compliance to antibiotic treatment is highly variable and often sub-optimal, even with educational reinforcement about the importance of antibiotic prophylaxis in the population⁽⁴⁶⁻⁴⁹⁾(B). The age at which antibiotic prophylaxis is stopped is often an empirical decision. Children with sickle cell disease without previous severe pneumococcal infections or surgical splenectomy and with appropriate clinical follow-up may stop penicillin prophylaxis at five years old⁽⁴⁵⁾(A). However, there is no consensus on the appropriate age to discontinue antibiotic prophylaxis. The Canadian Pediatric Society recommends that the discontinuation of antimicrobial prophylaxis in asplenic or hyposplenic patients is five years old or one year after splenectomy or depending on patients' clinical characteristics⁽³⁸⁾(D). The American Academy of Pediatrics indicates discontinuation at five years old as long as the patient has not presented with any invasive pneumococcal infection and has completed the vaccination scheme⁽³⁹⁾(D). The British Committee for Standards in Hematology suggests prophylaxis mainly during the first two years after splenectomy for all patients up to 16 years old and when there is involvement of the immune function⁽⁴⁰⁾(D). Continuous prophylaxis may increase the risk of strains resistant to antibiotics. Penicillin resistance was observed in children with repeated cycles of acute otitis media treatment⁽⁵⁰⁾(D). In patients with sickle cell disease on penicillin prophylaxis, penicillin-resistant pneumococcal strains were found in the oropharynx, associated with penicillin use⁽⁵¹⁾(A) or not⁽⁵²⁾(B)⁽⁵³⁾(A). A Brazilian study showed that, in children with sickle cell anemia on penicillin prophylaxis who had received the 7-valent pneumococcal vaccine, the prevalence of nasopharyngeal colonization by pneumococcal bacteria was 17% versus 11% in a control group of healthy children. The prevalence of penicillin-resistant strains was 57.5% in the patients with sickle cell disease and 25% in the control group⁽⁵⁴⁾(A).

Apart from pneumococcus, invasive infections by *H. influenzae* or by *N. meningitidis* are also considered important in splenectomized patients. Therefore, these patients should be vaccinated before surgery. If the splenectomized patient has direct or indirect contact with patients with invasive infections by these agents, the same prophylaxis proposed for non-splenectomized individuals should be provided using rifampicin (10 mg/kg twice/day for four doses - maximum 600 mg each dose) or, if the patient is less than one month old, 5 mg/kg twice/day for four doses. Alternative prophylaxis can be made with ceftriaxone (125 mg) single dose for under 12-year-old children, ceftriaxone (250 mg) single dose for over 12-year-old children or ciprofloxacin (500 mg) single dose for adults. As prophylaxis reduces the risk of infection but not of invasive disease, splenectomized patients should be carefully evaluated in the event of fever⁽⁴¹⁾(D).

Although the effectiveness of prophylactic antibiotics has been proven only in children with sickle cell disease, it is recommended that all children with asplenia or splenectomy receive prophylactic antibiotics. Several consensus guidelines recommend that patients and family members should be advised about the risks of infection in splenectomized patients, on vaccinations against pneumococcus, meningococcus, *H. influenzae* type b and influenza virus (annual) and on prophylactic antibiotics in under 5-year-old children and for at least one year after surgery. The maintenance of prophylaxis will depend on the individual characteristics of each patient⁽³⁷⁾(B)⁽³⁸⁻⁴²⁾(D). However, the pneumococcal polyvalent vaccine, the *H. influenzae* type b conjugate vaccine and the antibiotic prophylaxis reduce, but do not eliminate the risk of sepsis in children with sickle cell disease⁽⁵⁵⁾(B). Therefore, despite the use of prophylaxis and vaccines, patients should be monitored for febrile episodes and receive antibiotics for suspected bacterial infections⁽³⁷⁾(B)⁽³⁸⁻⁴²⁾(D).

The most widely used antibiotic for prophylaxis against infections by pneumococcus is penicillin. The daily dose of oral penicillin V is 125 mg twice per day in under 3-year-old children, 250 mg twice per day in over 3-year-old children and 500 mg twice per day in adults. Children who have not suffered any invasive pneumococcal infection and have completed the vaccine schedule for pneumococcus can stop prophylaxis at five years old^(38,39,41)(D)⁽⁴⁴⁻⁴⁵⁾(A). If the option is penicillin G benzathine, the dose in children under 27 kg is 600,000 IU every three weeks and for weight > 27 kg, the dose is 1,200,000 IU every three weeks⁽⁴¹⁾(D). As an alternative to penicillin, in cases of hypersensitivity, erythromycin is used at a dose of 250-500 mg per day in adults and over 8-year-old children, 250 mg/day in patients aged 2-8 years old and 125 mg/day in under 2-year-old children⁽⁴¹⁾(D). There are no randomized studies to evaluate the effectiveness of amoxicillin as a prophylactic antibiotic in patients with sickle cell disease or in splenectomized patients, but it may be an option in cases of pneumococcal resistance to penicillin⁽³⁸⁾(D).

Recommendation: The use of penicillin prophylaxis in splenectomized patients with ITP is indicated based on experience with children with asplenia or sickle cell disease who are at increased lifelong risk for sepsis and severe infections, especially in the first years after splenectomy. The vaccination scheme against encapsulated germs (pneumococcus, meningococcus and *H. influenzae* type b) and the administration of oral penicillin V daily or penicillin G benzathine every three weeks for at least two years after

splenectomy are recommended to significantly reduce the risk of infections in this population. It should be noted that the patient may present infections after discontinuation of antibiotic prophylaxis. Regarding the dose of oral penicillin V, 125 mg = 200,000 IU, 250 mg = 400,000 IU, and 500 mg = 800,000 IU⁽⁵⁶⁾(D).

Is there evidence that rituximab benefits patients with immune thrombocytopenia? In which situations is rituximab recommended?

A systematic literature review of refractory ITP (newly diagnosed or chronic) in under 18-year-old patients included 14 studies (including several case reports and one longitudinal observational study) with 312 patients, all with platelet counts of less than $50 \times 10^9/L$. The treatment of choice was intravenous rituximab and efficacy analysis was performed on studies with more than five patients. About 10% of patients had been splenectomized. Pooled data showed that response rate (platelet count $\geq 30 \times 10^9/L$) and complete response rate (platelet count $\geq 100 \times 10^9/L$) to rituximab were, respectively, 68% and 39%. Pooled analyses of data from 14 studies with 243 patients showed that the median times to obtain response and of response duration were three weeks and 12.8 months, respectively. At the time of analysis of the median duration of response, 56.5% of the patients maintained the response to treatment with rituximab. It is important to note that there was significant heterogeneity between the studies⁽⁵⁷⁾(C).

Of the 190 patients reported in 11 studies with more than five patients, 41.1% had adverse events. Most of the adverse events (84.7%) observed in 23 studies were mild to moderate with the most frequent being allergic reactions (pruritus, urticaria, chills and fever). Serum sickness (fever, rash, arthralgia and fatigue) after one or two doses of rituximab, infections (varicella, pneumonia, enteroviral meningoencephalitis), prolonged hypogammaglobulinemia leading to increased susceptibility to infections were also described. No death has been reported⁽⁵⁷⁾(C).

Recommendation: Treatment with rituximab in patients with ITP unresponsive to conventional treatment can produce a response (complete or partial) but adverse events may occur. However, randomized studies with rituximab are required to evaluate its efficacy and safety in children and adolescents with refractory ITP.

What is the platelet level to indicate treatment and which is the therapeutic option in newborns of mothers with primary immune thrombocytopenia?

Evaluation of 32 newborns of 29 pregnant women with ITP showed that seven neonates (21.8%) were born with platelet counts $\leq 50 \times 10^9/L$. Three newborns with clinical manifestations had platelet counts of less than $15 \times 10^9/L$ and skin bleeding, umbilical cord bleeding or gastric bleeding; all received IVIg and prednisone, as well as platelet transfusions in cases of more important hemorrhages. All children with platelet counts $\leq 50 \times 10^9/L$ received IVIg and prednisone⁽⁵⁸⁾(C).

In 39 pregnant women with ITP, thrombocytopenia $\leq 53 \times 10^9/L$ was observed in 16% of the newborns but there were no cases of death or intracranial hemorrhage. All these neonates received IVIg, combined or not with corticosteroids and/or platelet transfusions⁽⁵⁹⁾(C).

On reviewing 15 children born to mothers with ITP during a follow up period of ten years, the incidence of severe thrombocytopenia ($< 50 \times 10^9/L$) was 20%, with no intracranial hemorrhage, seizures or other complications in the newborns. No child required treatment with corticosteroids, IVIg or platelet transfusions⁽⁶⁰⁾(C).

Evaluating 46 neonates of mothers with ITP diagnosed before or during pregnancy, eleven (23.9%) infants were born thrombocytopenic. Of these, three had platelet counts of less than $30 \times 10^9/L$, five had platelet counts between $30 \times 10^9/L$ and $99 \times 10^9/L$ and three had platelet counts between $100 \times 10^9/L$ and $149 \times 10^9/L$. No severe bleeding was reported. Five newborns (10.8%) presented hemorrhage symptoms at birth: two (4.3%) had thrombocytopenia ($53 \times 10^9/L$ and $50 \times 10^9/L$) and hematuria ($n = 1$) or petechiae and cephalohematoma ($n = 1$); three (6.5%), despite normal platelet counts at birth, had petechiae and one also had cephalohematoma. Due the potential risk of bleeding, three patients with platelet counts $\leq 30 \times 10^9/L$ received IVIg (1 g/kg/day) for two days, with adequate responses in eight, eight and 42 days after treatment⁽⁶¹⁾(C).

Another investigation studied 13 pregnant women (one twin) with ITP, and only one newborn (7.1%) presented thrombocytopenia ($50 \times 10^9/L$) at delivery, without the need for treatment. There were two (14.2%) fetal deaths without signs of bleeding and morphologically normal. None of the children showed clinical signs of hemorrhage or other neonatal complications⁽⁶²⁾(C).

Clinical and laboratory characteristics of 29 newborns of 29 pregnant women diagnosed with ITP were evaluated. Fourteen neonates (48%) had platelet counts of less than $150 \times 10^9/L$ and of these, 50% had less than $50 \times 10^9/L$, 28.5% between $50 \times 10^9/L$ and $99 \times 10^9/L$ and 21.5% between $100 \times 10^9/L$ and $149 \times 10^9/L$. Mucosal and/or gastrointestinal bleeding was reported in 17% ($n = 5$) of the newborns. Transfusion was necessary in two neonates (6.9%) with gastrointestinal bleeding with platelet counts of $9 \times 10^9/L$ and $19 \times 10^9/L$, respectively who received IVIg (1 g/kg/day) for two days and prednisolone (2 mg/kg/day). All newborns with platelet counts less than $100 \times 10^9/L$ (78.5%, $n = 11$) received IVIg, even when there was no associated bleeding⁽⁶³⁾(C).

In a retrospective analysis of 130 newborns of 127 pregnancies of 88 women diagnosed with ITP, 15.4% showed platelet counts below $100 \times 10^9/L$, 8.5% below $50 \times 10^9/L$ and 2.3% below $20 \times 10^9/L$. Treatment at birth with prednisolone, IVIg and/or platelet transfusions was performed in 3.8% of these newborns. Only one fetus had an intracranial hemorrhage, but it was intrauterine⁽⁶⁴⁾(C). In this article there is no report of platelet levels in which treatment was indicated.

Recommendations: In the absence of bleeding, there is no defined value in relation to the ideal platelet count to indicate treatment in newborns of mothers with ITP. It is recommended to treat newborns with platelet count $\leq 50 \times 10^9/L$ and, in

cases of platelet counts between $\leq 50 \times 10^9/L$ and $100 \times 10^9/L$, start treatment only in the presence of bleeding. Intravenous immunoglobulin is the treatment most commonly used.

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