









# Evidence-based clinical practice guideline for the management of primary immune thrombocytopenia (ITP) in pediatric population

Guía de práctica clínica basada en la evidencia para el manejo de trombocitopenia inmune primaria en población pediátrica

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## Abstract

**Introduction:** Primary immune thrombocytopenia (ITP) is the most common cause of thrombocytopenia in children, with a reported incidence of 1.1-12.5 cases per 100 000 children. However, currently, there are several definitions of ITP, as well as diagnostic and therapeutic approaches.

**Objective:** To develop an evidence-based clinical practice guideline (CPG) to standardize the definition of ITP and, in this way, reduce the variability of its diagnosis, and to provide indications for the treatment of acute, persistent, and chronic ITP in patients under 18 years of age.

**Materials and methods:** The CPG was prepared by a multidisciplinary group that followed the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines for developing CPGs, formulated PICO clinical questions, and conducted systematic reviews. GRADE evidence profiles were created and recommendations, with their corresponding level of evidence and strength, were made after a panel of experts assessed the benefit-risk balance, the quality of evidence, the patients' values and preferences, and the context in which they should be implemented.

**Results:** A total of 23 recommendations were made to pediatricians, hematologists, and health professionals working in emergency services for treating acute, persistent, and chronic ITP. Overall, the CPG has low quality of evidence, and the recommendations were made in order to improve the success rate of ITP treatment and the prognosis of children with this condition.

**Conclusions:** Although ITP is the main cause of thrombocytopenia in pediatrics, to date there is not enough high-quality evidence that supports the recommendations presented here for its proper classification and treatment in children. Thus, further studies providing high-quality evidence on this issue are required.

**Keywords:** Immune Thrombocytopenia; Clinical Practice Guideline; Pediatrics (MeSH).

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## Resumen

**Introducción.** La púrpura trombocitopénica inmunológica (PTI) es la causa más frecuente de trombocitopenia en población pediátrica, con una incidencia de 1.1 a 12.5 casos por cada 100 000 niños. Sin embargo, en la actualidad hay diferentes definiciones de PTI, así como enfoques diagnósticos y terapéuticos.

**Objetivo.** Desarrollar una guía de práctica clínica (GPC) basada en la evidencia para unificar las definiciones de PTI, y de esta forma reducir la variabilidad de su diagnóstico, y para proporcionar indicaciones para el tratamiento de la PTI aguda, persistente y crónica en pacientes menores de 18 años.

**Materiales y métodos.** La GPC fue desarrollada por un grupo multidisciplinario, el cual siguió las guías GRADE para la realización de GPC, formuló preguntas clínicas PICO y realizó revisiones sistemáticas. Se crearon perfiles de evidencia GRADE y se realizaron las recomendaciones, con su respectivo nivel de evidencia y fortaleza, luego de que un panel de expertos evaluara el equilibrio beneficio-riesgo, la calidad de la evidencia, las preferencias y valoraciones de los pacientes y el contexto en el que debieran implementarse.

**Resultados.** Se formularon 23 recomendaciones para el tratamiento de la PTI aguda, persistente y crónica dirigidas a pediatras, hematólogos y profesionales de la salud que trabajan en servicios de urgencias. En general, la evidencia de la guía es de baja calidad y las recomendaciones fueron formuladas para mejorar la tasa de éxito del tratamiento de la PTI y el pronóstico de estos pacientes.

**Conclusiones.** A pesar de que la PTI es la principal causa de trombocitopenia en población pediátrica, actualmente no hay suficiente evidencia de alta calidad que respalde las recomendaciones aquí presentadas para su adecuada clasificación y tratamiento en niños. Por lo anterior, se requiere realizar nuevos estudios que brinden evidencia de alta calidad en el tema.

**Palabras clave:** Trombocitopenia; Guía de práctica clínica; Pediatría (DeCS).

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## Introduction

Primary immune thrombocytopenia (ITP) is the most common cause of thrombocytopenia in pediatric population. It is an immune disorder characterized by isolated, temporary or persistent thrombocytopenia (platelet count below  $100 \times 10^9/L$ ) without any other underlying cause or disease.<sup>1-3</sup> The incidence reported is between 1.1 to 12.5 cases per 100 000 children and is more frequently observed between 2 and 8 years of age.<sup>4</sup> Clinical manifestations in this population are generally mild, but may be severe in approximately 3% of the cases, ranging from no symptoms or minimal cutaneous manifestations to life-threatening bleeding.<sup>3,5</sup>

The International Working Group (IWG), according to the consensus of Vicenza, Italy, proposed a new terminology with the aim of highlighting the autoimmune pathogenesis of ITP.<sup>6</sup> Their first measure was to keep the acronym ITP but with a different meaning, changing the "P" to "primary" rather than "purpura" (without a completely known cause). Second, the term "immunological" was added due to its physiopathological mechanism. For the purposes of this paper, the name "Primary Immune Thrombocytopenia" (ITP) will be used.<sup>5,7</sup>

Providing treatment to patients with ITP is challenging for clinicians due to the multiple strategies available to control hemorrhagic manifestations and recover platelet count.<sup>8</sup> Such strategies include observation (watch-and-wait), specific pharmacological management with intravenous immunoglobulins, corticosteroids, thrombopoietin receptor agonists (TPO-RAs), and even splenectomy.<sup>1,2,8-10</sup> Although this condition was described more than a hundred years ago,<sup>11</sup> a wide arrange of concepts, definitions, diagnostic and therapeutic approaches are evident in clinical practice.<sup>12</sup> Thus, the objective of this paper is to develop an evidence-based clinical practice guideline (CPG) to standardize the definition of ITP and, thus, reduce the variability of its diagnosis and provide evidence-based indications for the treatment of acute, persistent and chronic ITP in patients under 18 years of age.

## Materials and methods

The standard methods of the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines for the for the development of CPGs were used.<sup>13</sup> The Guideline Development Group (GDG) included experts in pediatric hematology, pediatricians, epidemiologists, and health professionals. Representatives of the Asociación Colombiana de Hematología y

Oncología Pediátrica (Colombian Association of Pediatric Hematology and Oncology), the Academia Colombiana de Pediatría y Puericultura (Colombian Academy of Pediatrics and Childcare), the Ministry of Health and Social Protection of Colombia, and experts from several Colombian cities made up the expert panel.

The GDG reviewed the relevant clinical aspects to be addressed and the questions were formulated using the PICO format (Population, Intervention, Comparison and Outcomes). Subsequently, the outcomes were prioritized in accordance with the GRADE approach.<sup>13,14</sup>

The information specialist of the Cochrane STI Group performed a systematic search in the PubMed, EconLit, Embase, LILACS, Google Scholar, Cochrane Database of Systematic Reviews (CDSR), and Center for Reviews and Dissemination (CRD) databases. Gray literature sources were also considered, and a manual search was performed. The search included papers published until June 2018, and the strategy can be found in annex 1.

The systematic reviews (SR) conducted for each clinical aspect were evaluated using the AMSTAR checklist.<sup>15</sup> When SRs were not found, primary studies were evaluated using the Cochrane risk of bias tool.<sup>16</sup> If no evidence was found, consensus guidelines were identified. Evidence profiles were built with the help of the website <https://gradepro.org> for the outcomes of the selected studies, and the levels of evidence were scored according to the four GRADE categories for rating quality:<sup>14</sup> high (1), moderate (2), low (3), and very low (4).

The recommendations were discussed and adjusted during a panel of experts, as well the definition of the strength of the recommendations. The GRADE approach offers two grades of recommendation: A or "Strong" and B or "conditional". The strength of each recommendation was determined once benefit-risk balance, quality of evidence, patient's values and preferences, and context in which they should be implemented were analyzed.

Based on the synthesis of evidence, the GDG meetings, and the panel of experts, relevant aspects of the implementation context of the recommendations were identified, which aided in the generation of recommendations considering their applicability. This guideline includes patients' values and preferences extracted from the literature and contributions of the patients' representatives to the panel of experts. The Clinical Practice Guideline (CPG) was reviewed independently by two peer reviewers.

## Results

Table 1 presents all the recommendations made in the CPG.

**Table 1.** Guideline recommendations for the management of ITP in the pediatric population.

Strength of the recommendation	No.	Summary
Strong in favor Very low-quality evidence	1	We recommend performing a complete blood count and a peripheral blood smear in patients under 18 years of age with suspected acute. Results should be reviewed by trained personnel. (A4)
Conditional against Very low-quality evidence	2	We do not suggest to systematically perform bone marrow examination in the pediatric population with typical features of ITP as part of the initial tests for diagnosing this condition. (B4)
Strong against Very low-quality evidence	3	We do not recommend performing bone marrow examination routinely in patients under 18 years of age who received IVIG and have therapeutic failure. (A4)
Conditional in favor Very low-quality evidence	4	We suggest performing a bone marrow examination in patients under 18 years of age with persistent or chronic ITP based on the pediatric hematologist opinion. (B4)

**Table 1.** Guideline recommendations for the management of ITP in the pediatric population. (continued)

Strength of the recommendation	No.	Summary
Conditional in favor Very low-quality evidence	5	We suggest performing complete blood group, Rh typing, quantitative immunoglobulin levels and direct antiglobulin (DAT) testing in the initial assessment of pediatric population diagnosed with ITP. (B4)
Conditional in favor Very low-quality evidence	6	We suggest performing HIV testing in patients with risk factors — neonates, adolescents, and young adults— at the time of ITP diagnosis. (B4)
Conditional against Very low-quality evidence	7	We do not suggest routinely measuring antiphospholipid antibodies, anti-DNA, ANA, thrombopoietin levels, and H. pylori testing as part of the initial assessment to diagnose acute ITP in the pediatric population. (B4)
Strong against Low-quality evidence	8	We do not recommend measuring antiplatelet antibodies to diagnose ITP in the pediatric population. (A3)
Strong against Very low-quality evidence	9	We do not recommend using molecular markers as predictors of chronic ITP. (A4)
Strong in favor Very low-quality evidence	10	We recommend treating children diagnosed with ITP without bleeding or with mild bleeding (petechiae, ecchymoses) and platelet count above 20 x10 <sup>9</sup> /L with observation to avoid unnecessary treatments. (A4)
Strong in favor Very low-quality evidence	11	We recommend providing pharmacological treatment to children with moderate bleeding (mucosal bleeding) that is not explained by a cause other than ITP to control the bleeding. (A4)
Strong in favor Very low-quality evidence	12	We recommend administering IVIG (at dosages from 0.8 to 1 g/kg) or a short oral corticosteroid treatment for 4 to 7 days as first-line treatment for pediatric patients with acute ITP to control bleeding. (A4)
Good Practice Point	✓	We suggest administering a dose of prednisone 4 mg/kg/day for 4 days or prednisone 1 to 2 mg/kg/day for up to 14 days to control bleeding.
Conditional in favor Very low-quality evidence	13	We suggest using anti-D as a therapeutic alternative in non-splenectomized patients who are Rh positive and have negative DAT to reduce bleeding and increase platelet counts. Adverse events must be monitored during treatment. (B4)
Good Practice Point	✓	We suggest considering the use of agents that act on primary hemostasis in patients with active mucosal bleeding.
Strong in favor Very low-quality evidence	14	We recommend administering anti-D or conventional doses of corticosteroids and high-dose cycles of dexamethasone (0.6 mg/kg/ day for 4 days) to pediatric patients with persistent or chronic symptomatic ITP, who do not respond to IVIG, to control bleeding. (A4)
Good Practice Point	✓	High-dose dexamethasone may also be considered as an alternative to splenectomy in children and adolescents with persistent or chronic ITP, or in patients who do not respond favorably to splenectomy.
Conditional in favor Moderate quality evidence	15	We suggest using thrombopoietin receptor agonists in pediatric patients with symptomatic persistent and chronic ITP or as an alternative before performing splenectomy to control bleeding. (B2)
Conditional in favor Very low-quality evidence	16	We suggest using rituximab in children with symptomatic, persistent, or chronic ITP who do not respond to treatment with IVIG, anti-D, or corticosteroids to control bleeding. (B4)
Strong in favor Very low-quality evidence	17	We recommend using rituximab in symptomatic children with chronic ITP as a previous alternative to splenectomy. (A4)
Strong in favor Very low-quality evidence	18	We recommend performing emergency splenectomy in patients with ITP and life-threatening bleeding who do not respond to the measures described above. (A4)
Strong in favor Very low-quality evidence	19	We recommend performing a laparoscopic splenectomy due to reduced bleeding and hospital stay. (A4)
Good Practice Point	✓	We suggest considering splenectomy at least 12 months after the diagnosis unless ITP is accompanied by severe bleeding, does not respond to other pharmacological measures, or has a negative impact on quality of life.
Conditional in favor Very low-quality evidence	20	We suggest the combined use of corticosteroid and IVIG to treat patients with ITP presenting with bleeding that may be life-threatening to achieve bleeding control. (B4)
Good Practice Point	✓	Patients with ITP and life-threatening bleeding should be referred immediately to a specialized center.
Strong in favor Very low-quality evidence	21	We recommend performing a platelet transfusion in conjunction with IVIG in patients with ITP and severe hemorrhage that may be life-threatening to control bleeding. (A4)
Conditional in favor Very low-quality evidence	22	We suggest performing an emergency splenectomy in patients with ITP and life-threatening bleeding who do not respond to the measures described above. (B4)
Conditional in favor Very low-quality evidence	23	We suggest administering the scheduled vaccination for mumps, measles, and rubella (MMR) to children with a prior history of ITP. (B4)
Good Practice Point	✓	We suggest administering to children with a history of ITP MMR immunization 8 to 12 weeks after receiving IVIG treatment or 4 weeks after suspending corticosteroids.

Source: Own elaboration.

### Question 1. What are the initial tests that should be performed for diagnosing acute ITP in children?

No SR or primary studies were identified that directly evaluated the operational performance of tests for ITP diagnosis in children. However, the CPG developed by the American Society of Hematology (ASH) in 2011 made recommendations for the diagnosis and treatment of ITP in the pediatric population. The guidelines included blood count and peripheral blood smear as basic diagnostic tests. On the other hand, no sufficient evidence was found to recommend or suggest using routinely antiplatelet antibodies, antiphospholipid antibodies, antinuclear antibodies, thrombopoietin or platelet indexes by means of automated instruments to assess children or adolescents with suspected ITP.

For the initial assessment, immunoglobulin levels should be established as a regular practice to rule out common variable immunodeficiency (CVID), because it may be the initial manifestation of ITP in some patients; however, it is unclear if testing all patients with ITP for CVID is beneficial.<sup>2</sup>

The 1996 CPG recommended performing the HIV test in patients with risk factors, especially neonates,<sup>17</sup> while the 2011 version did not include any statement about this test, except for adolescents and young adults in whom HIV infection or viral hepatitis may present with thrombocytopenia. Neither of the two versions of the guideline made recommendations or statements about direct antiglobulin test (DAT), *H. pylori*, anti-dsDNA, or blood type.

One of the initial therapeutic alternatives is the administration of anti-D immunoglobulin to some patients, but it is essential to confirm that they are Rh-positive, are not splenectomized and have a negative DAT test before proceeding.<sup>2,8</sup> Case series studies were used to support this recommendation, therefore the quality of the evidence was very low.

#### What is the utility of bone marrow (BM) examination for diagnosing ITP in the pediatric population?

No SR directly evaluated the operational performance of this test for the diagnosis of ITP.

The CPG developed by the ASH stated that BM examination is not necessary in children and adolescents with ITP who present with typical clinical manifestations, or in patients who fail to respond to intravenous immunoglobulin (IVIG) therapy, nor do they suggest conducting a BM examination in patients who are going to start treatment with corticosteroids or who will undergo splenectomy.<sup>2</sup> For recommendation purposes, the authors declare absence of evidence.

The Spanish Society of Hematology and Hemotherapy made recommendations for the diagnosis and treatment of ITP in children and adults. For the pediatric population, the guidelines recommended performing the BM examination to patients whose clinical manifestations are atypical, have abnormal blood count, and when cell morphology of the peripheral blood smear has not been evaluated by an expert, especially if corticosteroids will be initiated.<sup>18</sup> The evidence that supported this recommendation was obtained from a clinical protocol.

A retrospective cohort study evaluated BM examination in pediatric patients with acute ITP to rule out

leukemia as a differential diagnosis. In patients with typical and atypical ITP, 484 BM examinations were performed. No leukemia cases were detected in a sample of 332 children with typical ITP, while 3 of the 152 patients who were classified as atypical ITP were diagnosed with leukemia. The study considered that the risk of leukemia was less than 1%, which does not exceed the risk of leukemia in the general population.<sup>19</sup>

#### What is the utility of antiplatelet antibody test to diagnose ITP in the pediatric population?

A study with diagnostic tests evaluated the operative performance of antiplatelet antibodies to detect ITP in children and adults. The clinical diagnoses of 59 patients with ITP and 59 patients with diagnoses other than ITP were studied and the types of antibodies detected were IgG, IgM, and IgA. As a result, acceptable test performance was found for IgG alone (sensitivity: 66.1%, specificity: 84.7%, PPV: 81.3%, NPV: 71.4%), IgG and IgM (sensitivity: 74.6%, specificity: 79.7%, PPV: 78.6%, NPV: 75.8%) and IgG, IgM and IgA (sensitivity: 74.6%, specificity: 78%, PPV: 77.2%, NPV: 75.4%).<sup>20</sup> The quality of evidence was low due to limitations in the risk of bias and indirect evidence.

#### What is the utility of molecular studies to diagnose ITP in the pediatric population?

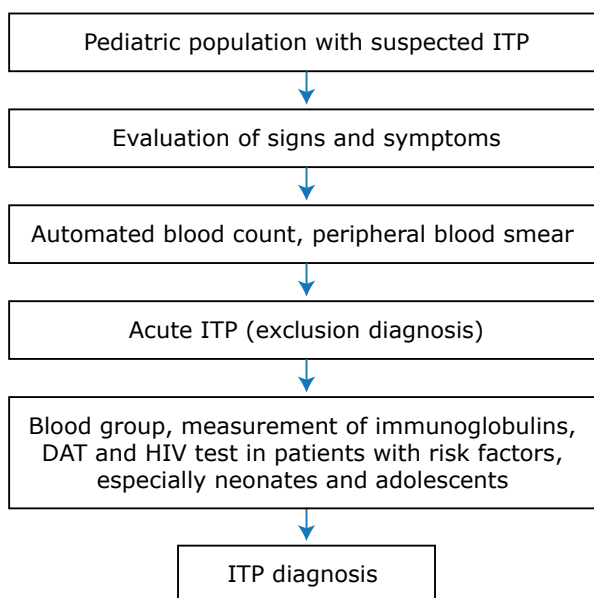
A SR of observational studies was carried out to evaluate the presence of molecular markers as predictors of chronic ITP in patients with a recent diagnosis. The review compared the frequency of molecular markers in patients with chronic ITP and in recovery, without finding differences in the markers DNMT3B 579 T/G, FCyRIIa-131 H/R, and FCyRIIIa-158 F/V.<sup>21</sup> The quality of the evidence was very low due to limitations in the risk of bias and imprecision.

#### Evidence from patients

A qualitative study evaluated decision-making in the context of treatment of children recently diagnosed with ITP. The experiences and perceptions of the parties involved were identified through focus groups with children, parents, and health professionals. Children manifested anxiety, fear, confusion, and the need to understand the disease and treatment options. Also, it was found that the way how the disease is perceived depends on the age of the patients, being more difficult for adolescents. The parents or caregivers express that they feel anxiety, fear, and confusion in relation to the disease. They also state that they do not feel part of the decision-making process. Health professionals assume that they do their best and do not consider the parents for discussing management options. Providing information to parents and children is recommended, as well as maintaining a high level of communication.<sup>22</sup>

#### Recommendations

See recommendations 1-9 and good practice points described in Table 1. The diagnostic algorithm can be found in Figure 1.



**Figure 1.** Diagnostic algorithm.  
Source: Own elaboration.

### Question 2. What is the efficacy and safety of the treatment for acute ITP?

No SR that directly evaluated observation as an alternative treatment was identified.

However, in 2012, during the meeting of experts at the Intercontinental Cooperative ITP Study Group in Switzerland on personalized care for patients with ITP, the consensus took into consideration the differences in the presentation and clinical evolution of ITP between adults and children. Younger patients have a higher rate of spontaneous recovery between 7 and 12 months after the initial diagnosis, when no specific treatment has been administered.

The consensus also established that observation can be considered before initiating pharmacological treatment, taking into account the risk-benefit ratio in the pediatric population.<sup>23</sup> Nevertheless, the overall quality of the evidence was very low because the source was expert opinion.

### What is the efficacy and safety of intravenous immunoglobulin (IVIg) for the treatment of acute ITP in the pediatric population?

Two randomized controlled trials (RCT) evaluated the efficacy and side effects of IVIg compared to anti-D immunoglobulin (anti-D Ig) for the treatment of acute ITP. The first RCT evaluated children with platelet count below  $20 \times 10^9/L$  who were randomized to receive a single intravenous dose of anti-D Ig  $75 \mu g/kg$  or IVIg  $1 g/kg$  for two consecutive days (total dose  $2 g/kg$ ),<sup>24</sup> while the other evaluated the administration of anti-D Ig at doses of  $50 \mu g/kg$  intravenously and repeated IVIg doses of  $250 mg/kg$  for 2 consecutive days. No differences were observed in the increase in platelet count 72 hours after initiating treatment or in response 7 days after initiating treatment.<sup>25</sup> In this regard, the overall quality of the evidence was very low due to a high risk of bias, heterogeneity, and imprecision.

One SR compared the effects of high doses (total dose of  $2 g/kg$ ) with low doses (less than  $2 g/kg$ ) of IVIg for

the treatment of acute ITP in children and adults in 13 RCTs. No differences were observed in the complete response rate, frequency of bleeding, time to achieve the increase in platelet count, platelet count after 2 weeks of treatment, and the risk of developing chronic ITP ( $p > 0.05$ ). Less adverse events were found at lower IVIg doses.<sup>26</sup> In this case, the overall quality of the evidence was very low due to high risk of bias, indirect evidence, and imprecision.

### What is the efficacy and safety of corticosteroids for the treatment of acute ITP in the pediatric population?

One SR evaluated the efficacy and safety of corticosteroids compared to IVIg treatment for acute ITP in children. Ten RCTs were included. The primary outcome evaluated was the number of patients with platelet count  $> 20 \times 10^9/L$  48 hours after initiating treatment. Secondary outcomes included the number of patients with platelet count  $> 20 \times 10^9/L$  at 24 and 72 hours, the number of patients who developed chronic ITP or and intracranial hemorrhage, and mortality.

It was found that the probability of achieving a platelet count  $> 20 \times 10^9/L$  at 48 hours after starting treatment significantly favored IVIg (RR: 0.74, 95%CI: 0.65-0.85) regardless of the dose of corticosteroids or IVIg. It was evident that children treated with corticosteroids for acute ITP were 26% less likely to achieve a platelet count  $> 20 \times 10^9/L$  at 48 hours and an increase in platelet count was observed at 24 and 72 hours in the group that received IVIg.<sup>27</sup> No RCTs were found in the update and the overall quality of the evidence was low due to a high risk of bias and heterogeneity.

### What is the utility of dexamethasone compared with prednisone for the treatment of acute ITP in the pediatric population?

One SR evaluated 8 studies on the efficacy of dexamethasone for the treatment of acute ITP compared with prednisone. The studies included patients aged

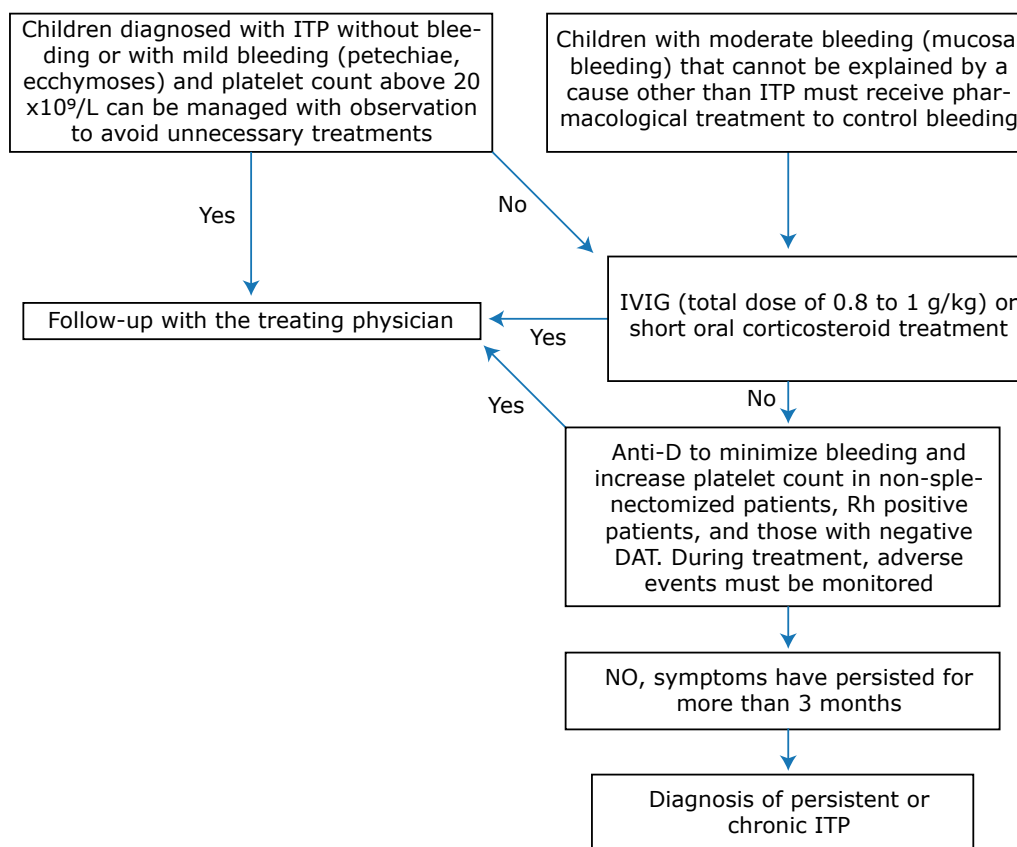
16 and older with a new diagnosis of ITP. No differences were found in sustained response ( $p > 0.05$ ). A subgroup analysis showed that 2 or more cycles of dexamethasone or administered as consolidation therapy had a better sustained response compared with prednisone. The same benefit was evidenced in the overall response and the complete response to treatment. Patients who received dexamethasone had fewer adverse events.<sup>28</sup> The overall quality of the evidence was very low due to high risk of bias, indirect evidence, and imprecision.

Furthermore, one SR evaluated the efficacy and safety of high doses of dexamethasone compared to prednisone

to increase long-term platelet count. Nine studies with 329 pediatric patients were included. Between 1 and 3 dexamethasone cycles of 40 mg per day were administered for 4 days. No differences were reported in the initial and long-term response ( $p > 0.05$ ).<sup>29</sup> The overall quality of the evidence was very low due to high risk of bias, indirect evidence, and imprecision.

### Recommendations

See recommendations 10-13 and the good practice points listed in Table 1. Figure 2 shows the algorithm for the treatment of acute ITP.



**Figure 2.** Treatment algorithm of acute ITP. Source: Own elaboration.

### Question 3. What is the efficacy and safety of the treatment for persistent and chronic ITP?

Between 13 and 36% of patients with ITP may not respond or have a partial response to first-line treatment and will develop persistent or chronic ITP. This group of patients will require a second-line treatment.<sup>11,30,31</sup>

One RCT evaluated 6 cycles of dexamethasone at high doses (0.6 mg/kg/day) for 4 days, compared to IVIG in 20 children with chronic ITP. Partial or complete remission was achieved in 25% of patients treated with corticosteroids.<sup>32</sup> The overall quality of the evidence was very low due to a high risk of bias, inconsistency, and imprecision.

Moreover, 2 SR were identified. The first presented a network meta-analysis that lacked evidence of direct comparisons to evaluate the efficacy and safety of

TPO-RAs for the treatment of persistent or chronic ITP (eltrombopag and romiplostim) in children. The second included 5 RCTs that compared TPO-RAs with placebo. The overall response (RR: 0.57, 95%CI: 0.21-1.56), the incidence of adverse events (RR: 0.96, 95%CI: 0.66-1.39), the duration of the response (RR: 2.48, 95%CI: 0.2-2.73) and the number of patients who received rescue treatment (RR: 0.73, 95%CI: 0.2-2.73) were similar for eltrombopag and romiplostim. However, eltrombopag may have a lower risk of general bleeding (RR: 0.43, 95%CI: 0.23-0.80) and clinically significant bleeding (RR: 0.33, 95%CI: 0.12-0.89) compared to romiplostim. The most common adverse events (AE) with TPO-RAs were headache, upper respiratory tract infection, nasopharyngitis, rhinitis, cough, and diarrhea. No thromboembolic events, malignant lesions or deaths were observed, and no patient withdrew from

the study as a consequence of an AE.<sup>33,34</sup> The overall quality of the evidence was low due to heterogeneity, indirect evidence, and imprecision.

A SR evaluated the efficacy and safety of rituximab in children with ITP and secondary immune thrombocytopenia who did not respond to the most used first-line treatments. 18 studies were included, mainly case series. A complete response to rituximab was found in patients with ITP (defined as platelet count  $>100 \times 10^9/L$ ), as well as a response rate (defined as platelet count  $>30 \times 10^9/L$ ) of 39% and 68%, respectively, with a response duration of approximately 12.8 months. AE occurred in 41.1% of the patients, of whom 84.3% presented with mild to moderate events. Severe reactions included type 3-4 serum sickness (0.8%) and type 3-4 hypersensitivity reaction (0.5%), which forced treatment withdrawal. Four patients developed infections after using rituximab. No deaths associated with rituximab were reported.<sup>35</sup> The overall quality of the evidence was very low due to a high risk of bias, heterogeneity, and imprecision.

### What is the efficacy and safety of splenectomy in the treatment of persistent and chronic ITP in the pediatric population?

Splenic macrophages have an increased expression of receptors for the immunoglobulin crystallizable region (FcγR), which mediates the uptake of antibodies that coat platelets.<sup>36</sup> Spleen serves as a niche for immune cells promoting formation of platelet antibodies.<sup>37,38</sup>

Splenectomy is an option to manage patients who do not respond to first-line treatment. The high rates of spontaneous remission within the first 12 months following diagnosis, associated comorbidities, and new drugs have led to consider this therapeutic option as a last resort in chronic ITP or in case of emergency due to severe life-threatening bleeding.<sup>2,39</sup>

The cohort of the French National Reference Center for Auto-Immune Cytopenia in Children (CEREVANCE) was evaluated to describe the outcomes of children with persistent or chronic ITP treated with splenectomy. 79 children were identified, of whom 78% underwent surgery due to one or more episodes of visceral or mucosal bleeding considered significantly severe in chronic ITP. The mean duration of ITP before splenectomy was 24 months, with an average of 2 months of pharmacological treatment before the procedure. Complete response was achieved in 77% of the cases and the 5-year relapse-free survival was 51%. No deaths or sepsis were reported. 37% of the children needed pharmacological treatment after splenectomy.<sup>40</sup>

Another study evaluated laparoscopic splenectomy (LS) for ITP in 18 pediatric patients; 98% of them responded initially to laparoscopic splenectomy and 76.5% showed complete response at one year, 61.8% at 5 years, and 33% at 10 years.<sup>41</sup>

A retrospective study analyzed patients diagnosed with persistent or chronic ITP or who underwent splenectomy between 1995 and 2009 in India. 93.1% of the children presented an initial response to splenectomy, and of these, 74% achieved complete

remission; 88.5% of the children maintained the response 2 months after the splenectomy. Overall survival at 5 and 10 years was 98% (range 96.4-99.6%) and 5-year event-free survival was 79.1% (range 74.5-83.7%) and 70% at 10 years (range 62.5-77.5%). The most frequent complications were associated with nonspecific infections with negative cultures in 8% of patients.<sup>42</sup>

In this regard, the overall quality of the evidence was very low due to a high risk of bias and imprecision.

### What is the efficacy and safety of laparoscopic splenectomy compared to open surgery in the treatment of ITP in pediatric population?

A SR was conducted to compare clinical outcomes between laparoscopic splenectomy (LS) and traditional open splenectomy (OS) in children. Of the 922 participants included in the 10 studies, 508 LSs and 414 OSs were performed. Shorter hospital stays and less blood loss were reported after LS, but there was a longer operating time compared to OS. No significant difference was observed between LS and OS in terms of the elimination of accessory spleens or postoperative complications ( $p > 0.05$ ).<sup>43</sup> The overall quality of the evidence was very low due to high risk of bias, indirect evidence, and imprecision.

### Recommendations

See recommendations 14-19 and the good practice points described in Table 1. The algorithm for the treatment of chronic and persistent ITP can be found in Figure 3.

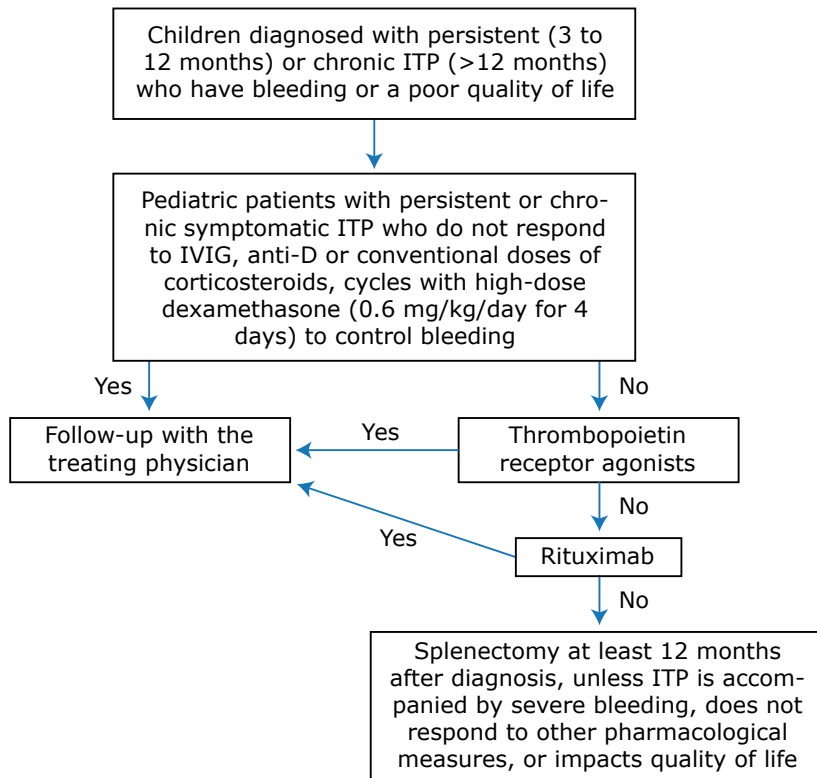
### Question 4. What is the emergency treatment for a patient with ITP who is experiencing life-threatening bleeding?

A rapid increase in platelet count is necessary in patients with ITP and severe bleeding with hemodynamic instability or risk of death.<sup>1</sup> Emergency treatment includes platelet transfusions, combination of IVIG and corticosteroids, or emergency splenectomy.<sup>2</sup> Other procedures, such as plasmapheresis, have not proven to be useful.<sup>44</sup>

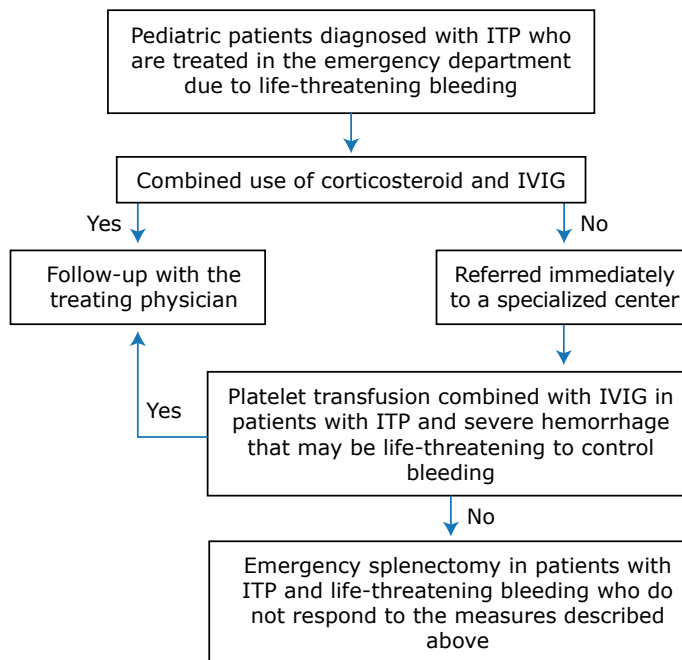
No evidence was found in SR or clinical trials that directly evaluated interventions for emergency treatment. The guidelines developed by consensus by the Spanish Society of Hematology and Hemotherapy in 2011 recommended a combined treatment of corticosteroids and IVIG to achieve rapid platelet increase. In cases of severe bleeding, they recommended platelet transfusions and emergency splenectomy when a surgical emergency is considered.<sup>18</sup> The recommendations were based on two case series.

### Recommendations

See recommendations 20-22 and the good practice points described in Table 1. The algorithm for the emergency treatment of ITP can be found in Figure 4.



**Figure 3.** Treatment algorithm of persistent or chronic ITP. Source: Own elaboration.



**Figure 4.** Algorithm of emergency treatment of ITP. Source: Own elaboration.

**Question 5. What is the vaccination recommendation for pediatric patients with ITP?**

Vaccines may trigger immune thrombocytopenia, with an incidence of 1 to 3 cases per 100 000 children vac-

inated,<sup>45,46</sup> and 1 case of ITP in 32 300 doses within 6 weeks after immunization.<sup>47</sup> Its pathophysiological mechanism is related to the elevation of IgG antibody levels.<sup>48</sup> Clinical manifestations in these patients appear to be less severe than those caused by natural infection.<sup>47,49</sup>



There are other ITP triggering vaccines, such as the recombinant hepatitis B vaccine,<sup>50</sup> influenza,<sup>51</sup> oral polio, among others.<sup>52</sup>

One SR that included 12 observational studies evaluated the risk of ITP in children vaccinated against measles, mumps, and rubella (MMR), as well as the risk of recurrence of thrombocytopenia after vaccination. The incidence of ITP associated with MMR vaccine was between 0.087 and 4 ( $\bar{x}$ :2.6) cases per 1 000 000 doses of vaccines. The symptoms in 93% of the children with ITP associated with vaccination resolved spontaneously within 6 months after diagnosis. The incidence of ITP after natural infection with rubella or measles virus is higher, ranging from 6 to 1 200 cases per 100 000 infected. Vaccination with MMR in non-vaccinated patients with ITP and revaccination of patients with a history of ITP did not lead to recurrence of thrombocytopenia.<sup>53</sup> The overall quality of the evidence was very low due to high risk of bias and publication bias.

## Recommendations

See recommendation 23 and the good practice points described in Table 1.

## Conclusions

The GDG assessed the published CPGs and concluded that none of them could be adapted, so a new guideline was elaborated, taking into account the context of the implementation and the preferences of the patients. Moreover, ITP definitions were standardized since the intention of this document is to achieve a timely diagnosis and provide treatment options to minimize adverse events, complications, and sequelae.

Although ITP is the first cause of thrombocytopenia in pediatrics, there are no high-quality studies that support the formulation of recommendations. Therefore, it is necessary to develop studies with high methodological rigor on this condition. The guideline was developed based on high standards and can be adopted, adapted, and implemented at the national, regional, and global level.

## Conflicts of interest

None stated by the authors.

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