GUIDELINES

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Adapted guideline for the diagnosis and treatment of primary immune thrombocytopenia for Chinese children (2021)

Working Group of Chinese Guideline for the Diagnosis and Treatment of Childhood Primary Immune Thrombocytopenia | Subspecialty Group of Hematologic Diseases, Society of Pediatrics, Chinese Medical Association | Editorial Board, *Chinese Journal of Pediatrics*

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Funding source
National Science and Technology Major Project, Grant/Award Number: 2017ZX09304029001; Pediatric Special Project, Center for Collaborative Development of Pediatric Discipline, Beijing Hospital Administration, Grant/Award Number: XTZD20180205

Received: 16 November 2021; Accepted: 19 December 2021

INTRODUCTION

Primary immune thrombocytopenia (ITP) of childhood is an acquired, immune-mediated, bleeding disorder characterized by an isolated platelet counts decreased without an identified cause during childhood.[1] The main pathogenesis is loss of immune tolerance, which leads to immune-mediated platelet destruction and/or suppression of platelet production.[2] The annual incidence of ITP in children is 1.6–5.3 per 100 000.[3–5] The diagnosis is exclusive and is clinically heterogeneous.

Two expert consensus reports on ITP in children were published in 2013 and 2019, respectively, in China,[6,7] although no evidence-based clinical practice guidelines are available. In 2019, two high-quality guidelines, that is, *Updated international consensus report (ICR) on the investigation and management of primary immune thrombocytopenia (2019)*[8] and *American Society of Hematology (ASH) guidelines for immune thrombocytopenia*,[9] were published. Based on emerging evidences, these guidelines provided updated recommendations on clinical issues screened by expert working group in the diagnosis and treatment of ITP in children. However, these high-quality evidence-based guidelines cannot be applied to the clinical practice in China directly, considering the difference in culture, social background, resources, ethnicity, and preference of patients or guardians. Therefore, currently available international guidelines warrant appropriate adaptations to facilitate the diagnosis and treatment of ITP in children in China, integrating evidences from China, considering opinions of clinical experts, and following guideline adaptation frameworks. In May 2020, Subspecialty Group of Hematology, Society of Pediatrics, Chinese Medical Association and Editorial Board of *Chinese Journal of Pediatrics* jointly initiated the development of *adapted guideline for the diagnosis and treatment of primary immune thrombocytopenia in children in China (2021)*, where the ADAPTE methodology[10] was applied. This guideline will guide and standardize the clinical decisions for ITP in children in China. This guideline was registered on the website of International Practice Guideline Registry Platform with a registration number IPGRP-2020CN077.

DOI: 10.1002/ped4.12305

This article was originally published in *Chinese Journal of Pediatrics* (DOI: 10.3760/cma.j.cn112140-20210509-00397) in Simplified Chinese and has been translated into English and further adapted. The translation and publication of this article were authorized by Chinese Medical Association.

THE PURPOSES OF THIS GUIDELINE

This adapted guideline is intended to provide evidence-based support, standardize clinical decision, and support the clinical practice for diagnosis and treatment of ITP in children in China.

TARGET POPULATION

This guideline applies to children with primary ITP from 1 month of age to 18 years of age and is not appropriate for children with secondary ITP, neonatal ITP, or non-immune-mediated thrombocytopenia.

USERS

Clinicians, health decision makers, and relevant researchers working on pediatric diseases at all levels of hospitals are the population for whom this guideline is intended.

DEFINITIONS OF RELEVANT TERMS

See supporting File S1.

PROCESS AND METHODOLOGY OF GUIDELINE ADAPTATION

ITP-related guidelines currently available were searched, reviewed, screened, and integrated with the ADAPTE approach.[10–12] During the adaptation of this guideline, the culture and social background, resources, and values specific to China were considered appropriately. Main processes in *WHO Handbook for Guideline Development* (2014) were also taken into account.[12] The ADAPTE framework consists of three phases, nine modules, and 24 steps.

Set-up phase

A team for guideline adaptation was established, including four groups, such as steering committee, guideline development group (GDG), and so on. GDG consisted of 19 pediatric hematologists from children's hospitals and general hospitals, one guideline methodologist, one epidemiologist, and health statistician, one editor from academic journals, one ITP patient, and one guardian, all of whom came from 11 provinces of China. Tens of ITP-related guidelines were identified, allowing the adaptation feasible. At the same time, a management plan for conflicts of interest was developed and all panel members signed a Declaration of Conflict of Interests.

Adaptation phase

After literature research and interviews with different levels of doctors and patients and/or guardians were conducted, clinical questions and outcomes were collected, classified, and integrated. Clinical questions were constructed based on the participant, intervention, comparison, and outcome (PICO) process. Nineteen priority clinical questions and their critical outcomes (initial overall response rate [1 month], sustained overall response rate [6 months], remission rate [12 months], quality of life improvement, and adverse reactions, etc.) were defined through online consensus meeting combined with multiple discussions by the core members of the guideline adaptation workgroup.

PubMed, Embase, Wanfang Database, China Academic Journals Full-text Database, VIP Database for Chinese Technical Periodicals, and Chinese Biomedical Literature Database were searched. Websites of Medlive, WHO, UpToDate, NICE, and International Practice Guideline Registry Platform were also researched for retrieval and screening of guidelines. The main search terms include: "idiopathic thrombocytopeni*," "immune thrombocytop*," "werlhof* disease," "autoimmune thrombocytopeni*," "primary thrombocytopeni*," "ITP," "practice guidelines as topic," "guidelines," "guideline," "guidance," "recommendation," and "consensus," and the corresponding Chinese translation of "idiopathic," "primary," "immune," "platelet decrease," "guideline," "guidance," "consensus," "specification," and "draft" (Table S1). Inclusion criteria include: (a) participants were children with ITP aged from 1 month to 18 years[7]; (b) intervention and comparison were not limited; and (c) study types were clinical guideline, consensus, guidance, draft, and specification. Exclusion criteria include: (a) guidelines specific to secondary, infection-related, congenial, or hereditary thrombocytopenia, and so forth; (b) translation or interpretation version of guidelines from non-Chinese languages; and (c) full-text failed to be found. The screening criteria for source guidelines are as follows: (a) being published after 2010; (b) score for the rigor development domain of Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument II (AGREE II)[13] is greater than 70%; and (c) overall quality being taken into account. A recommendation matrix was used to compare diagnoses and treatments corresponding to the clinical questions of the adapted guideline. Clinical experts and methodologists jointly assessed the consistencies between search strategy and retrieval results, selection of evidences, summary and interpretation of evidences with the supported recommendations, appraised the recommendations, and determined the acceptability and feasibility of implementation in China. Three source guidelines were selected[8,9,14] (Figure S1).

Based on the defined clinical questions and the evidence search interval in source guidelines, we supplemented evidences of diagnosis in English from January 2010 to May 2020, evidences of treatment in English from January 2018 to May 2020, local evidences of children with ITP in China as of May 2020 (Table S1). In addition, literature screening, data extraction, and quality evaluation were performed.

Cochrane risk-of-bias tool and quality assessment tool for case series studies were used to evaluate the methodological quality of randomized controlled trials and case series studies, respectively, with appropriate adjustment of the actual quality for the specific clinical questions. The key items were to be considered comprehensively in order to compare and integrate evidences from source guidelines and supplementary evidences. Evidence level and grade of recommendation in this guideline were consistent with ICR.[8] These processes included at least verification of results by a trained rater and discussion with a third party.

Based on the recommendations from the source guidelines for each clinical question and the integration of supplementary evidences and the evidence from source guidelines, considering the medical environments, medical resources, cost-effectiveness, feasibility, preferences, and values of Chinese parents and/or guardians (13 representatives of children with ITP or their guardians participated in the survey), we developed the adapted recommendations and the corresponding rationale to create the draft guideline. After discussion and assessment, during the adaptation, the recommendations from the source guidelines were dealt with in the following different ways and were rephrased: (a) if the content and main idea of proposed recommendations were consistent with the source guidelines, the recommendations from the source guidelines were adopted; (b) if the content and main idea of proposed recommendations were partly consistent with the source guidelines, the proposed recommendations were adapted; and (c) if the content and main idea of the proposed recommendations were not consistent with the source guidelines, the recommendations from the source guidelines would not be adopted, and new recommendations were developed after reconsideration. After two rounds of Delphi survey and an online consensus meeting, the adapted recommendations and the rationale were revised, improved, and finalized. In addition, the evidence level and grade of recommendation for all recommendations were discussed and established.

Finalization phase

A questionnaire was designed to investigate the suitability from three aspects: the degree of agreement with the recommendations, the clarity of the statements, and the clinical feasibility. A total of 57 clinicians and three guardians of patients completed the survey. Furthermore, five famous hematologists and one authoritative methodologist in guideline development were invited for external written review of this guideline. Ninety-nine and 27 feedback opinions were obtained, respectively. The full-text guideline was furthermore revised and refined, and 19 clinical questions were combined into 12 final questions. This guideline was submitted to the Society of Pediatrics, Chinese Medical Association for consultation. It was also sent to guideline issuing bodies and developers for consultation and permission for copyright. This guideline was finally submitted to the steering committee for review and release.

CLINICAL QUESTIONS AND RECOMMENDATIONS IN THIS ADAPTED GUIDELINE

This guideline includes 12 clinical questions (four for diagnosis and eight for treatment), resulting in 24 recommendations (Table S2). Evidence level and grade of recommendation adopted by ICR were used to classify evidences and recommendations (Tables 1 and 2).[8] There are four dimensions for each clinical question: recommendations from this guideline, supplementary evidences, rationale of adaptation, and instructions for implementation.

TABLE 1 Evidence levels[8]

Evidence level	Definition
Ia	Evidence obtained from meta-analysis of RCTs
Ib	Evidence obtained from ≥1 RCT
IIa	Evidence obtained from ≥1 well-designed controlled study without randomization
IIb	Evidence obtained from ≥1 other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlated studies, and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Note: Reprinted with permission from Provan et al. (2019).[8]
Abbreviation: RCT, randomized controlled trial.

TABLE 2 Grading of recommendation[8]

Grade of recommendation	Definition	Level of evidence
A	Requires ≥1 RCT as part of a body of literature of overall good quality and consistency addressing specific recommendation	Evidence levels Ia and Ib
B	Requires the availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation	Evidence levels IIa, IIb and III
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality	Evidence level IV

Note: Reprinted with permission from Provan et al. (2019).[8]
Abbreviation: RCT, randomized controlled trial.

Guideline questions related to diagnosis

Clinical question 1: Should children with the typical features of ITP have bone marrow aspirate smear performed at initial diagnosis?

Recommendations:

1. In children with the typical features of ITP, if glucocorticoid is not indicated, we suggest against a routine bone marrow aspiration being performed at initial diagnosis (Level III evidence, Grade B recommendation).
2. In children with the typical features of ITP, we suggest that a bone marrow aspiration be completed at initial diagnosis before implementing glucocorticoid therapy (Level III evidence, Grade B recommendation).
3. In children without the typical features of ITP, we recommend that a bone marrow aspiration be performed at initial diagnosis (Level III evidence, Grade B recommendation).

Supplementary evidence:

None.

Rationale for adaptation:

This guideline adapted the recommendations in source guidelines. The evidences from source guidelines: Three studies included in the 2011 ASH guideline showed that only one case of aplastic anemia (AA) was detected by bone marrow aspiration among 827 children with the typical features of ITP.[5,15,16] Therefore, the source guideline recommends that bone marrow aspiration is unnecessary in children and adolescents with the typical features of ITP. The abilities to judge the "typical features of ITP" vary in China, which means possibility of missed diagnosis and difficulties in subsequent diagnosis and treatment. Meanwhile, bone marrow aspiration is cost-effective and simple and a questionnaire survey showed a high acceptability (11/13) of bone marrow aspiration among guardians of children with ITP in China. Therefore, the above adapted recommendation was developed.

Instructions for implementation:

In determining whether a child has "the typical features of ITP," a peripheral blood smear should be performed to find morphological platelet abnormalities.

Clinical question 2: Should children who have no response to first-line treatment have bone marrow aspiration smear completed?

Recommendation:

In children who have no response to first-line treatment, we recommend that a bone marrow aspiration be completed (Level III evidence, Grade B recommendation).

Supplementary evidence:

None.

Rationale for adaptation:

This guideline did not adopt recommendation from the source 2011 ASH Guideline, but adapted that from the source 2019 ICR guideline. ASH Guideline 2011 does not recommend that children who have no response to first-line treatment have bone marrow aspirate smear performed. Similarly, ICR 2019 recommends that only those children who relapse after response, have no response to initial treatment, are candidates of splenectomy, or demonstrate other abnormalities in blood cell count or morphology have bone marrow aspirate performed. Nonetheless, it is more likely that platelet count decrease is caused by other factors among those children with prior diagnosis of ITP who have no response to first-line treatment, which means bone marrow aspirate will present more benefits. Therefore, the above recommendation is provided.

Instructions for implementation:

The wording "have bone marrow aspirate completed" means that those children who do not have bone marrow aspirate performed need to complete this procedure before further treatments. And also, among those children who have already performed this procedure, it is not necessary to repeat it.

Clinical question 3: Should bone marrow examination include bone marrow aspiration and bone marrow biopsy for children with persistent or chronic ITP?

Recommendation:

We recommend that bone marrow examination should include both bone marrow aspiration and bone marrow biopsy for the purpose of re-assessment of children with persistent or chronic ITP (Level IIa evidence, Grade B recommendation).

Supplementary evidence:

Three publications are supplemented, including two case reports[17,18] and one case series report.[19] There are a total of 84 children with history of chronic ITP, among whom 20 children were finally diagnosed with other diseases.

Rationale for adaptation:

This guideline adopted recommendations from source guidelines. When ITP has lasted for a long period, especially during the chronic phase, the possibility of spontaneous remission is low, while the risk of other underlying diseases is high, making it necessary to perform bone marrow examination to rule out other diagnoses.

TABLE 3 Timing, indications, evidence level, and recommendation grade of bone marrow aspiration among children with ITP

Patient group	Clinical feature	Diagnosis and treatment plan	Bone marrow aspiration	Evidence	Recommendation
Newly diagnosed	Typical ITP	Glucocorticoids are unnecessary	Not suggested	III	B
Newly diagnosed	Typical ITP	Glucocorticoids are planned to be dosed	Suggested	III	B
Newly diagnosed	Atypical ITP	To confirm diagnosis and differential diagnosis	Recommended	III	B
Repeated treatment	No response to first-line treatment	Re-assessment	Recommended	III	B
Repeated treatment	Persistent or chronic	Re-assessment	Recommended	IIa	B

Abbreviation: ITP, immune thrombocytopenia.

Instructions for implementation:

The risk of adverse reactions arising from bone marrow biopsy is high among young children, especially among infants under 1-year old. Caution should be exercised when performing such examinations. The timing and indications of bone marrow aspiration are shown in Table 3.

Clinical question 4: Should autoimmune panel be retested and genetic tests be performed when children with persistent or chronic ITP are re-assessed?

Recommendation:

When children with persistent or chronic ITP are re-assessed, we suggest that autoimmune panel be retested and genetic test be performed as appropriate (Level IIa evidence, Grade B recommendation).

Supplementary evidence:

Seven studies are supplemented, providing consistent evidences with source guidelines. Two case reports showed that three children with previous diagnosis of chronic ITP were diagnosed with hereditary thrombocytopenia.[20,21] Five retrospective case series studies include 120 children with chronic ITP in total, among whom 11 children were finally diagnosed with systemic lupus erythematosus (SLE) by means of autoimmune panel, and two were diagnosed with immune deficiency.[22–26] Among 309 children with previous diagnosis of chronic thrombocytopenia, 141 children were diagnosed with hereditary thrombocytopenia by means of genetic test.[20,21,23–25]

Rationale for adaptation:

This guideline adopted recommendations from source guidelines. When ITP evolves into chronic phase, there is a significant increase in the risk of developing autoimmune disease or the presence of an underlying hereditary disease, and thus above-mentioned tests are required.

Instructions for implementation:

Genetic test is carried out once and does not require retest.

Guideline questions related to treatment

Clinical question 5: Should platelet count be a consideration in treatment decisions for children with ITP?

Recommendation:

Platelet counts in children with ITP shall be considered secondary factors for treatment decision, whereas bleeding and whether life is interfered with by the disease are considered primary factors (Level IV evidence, Grade C recommendation).

Supplementary evidences:

A retrospective study included 264 patients with ITP to assess platelet count threshold for bleeding, treatment-related infection, and the effectiveness of second-line treatment. This study showed that platelet counts threshold correlated with the occurrence of bleeding, with 15×10^9 L^{-1} being the optimal cutoff for predicting any bleeding, while 20×10^9 L^{-1} had the highest negative predictive value for severe bleeding.[27]

Rationale for adaptation:

This guideline adapted the recommendations in source guidelines. Although all three source guidelines tend to consider bleeding and "interference with life by disease" as the primary factors for treatment decisions,[8,9,14] supplementary evidences showed that platelet counts still correlate with bleeding severity. Accordingly, this guideline includes platelet count $<20 \times 10^9$ L^{-1} as a consideration for treatment decisions.

Instructions for implementation:

In China, treatment decisions are commonly made on basis of platelet counts. But platelet counts in children with ITP

do not correlate well with clinical risk of bleeding; that is, when platelet counts are $<20 \times 10^9$ L^{-1}, most children do not present with bleeding, and vice versa.[28] Furthermore, platelet counts are influenced by a variety of factors, and reference ranges vary widely depending on age, sex, and sampling methods (refer to *Reference intervals of blood cell analysis for children*[29]). This guideline weakens the position of platelet count in treatment decision and uses the severity of bleeding as a key measure for clinical judgment to avoid overtreatment.

Clinical question 6: Should newly diagnosed children with ITP who have grades 0–2 bleeding and whose lives are not interfered with by the disease be observed and followed up or treated?

Recommendations:

1. We suggest close observation and follow-up for newly diagnosed children with ITP who have grades 0–2 bleeding and whose lives are not interfered with by the disease (Level Ib evidence, Grade A recommendation).
2. If the platelet count is $<20 \times 10^9$ L^{-1}, which is an indicator of increased risk of bleeding, we suggest that treatment be initiated (level III evidence, Grade B recommendation).

Supplementary evidences:

The same as the supplementary evidence of clinical question 5.[27]

Rationale for adaptation:

This guideline adapted the recommendations in source guidelines. The ASH Guideline 2019 and ICR 2019 recommend and suggest clinical observation and follow-up rather than treatment, respectively. Evidences of source guidelines showed that the risk of severe bleeding in newly diagnosed children with ITP and a platelet count of $<20 \times 10^9$ L^{-1} is 0.17%–0.24%[28,30–32]; supplementary evidences suggested that a platelet count of $<20 \times 10^9$ L^{-1} is more likely to be associated with severe bleeding.[27] On the other hand, because of the uneven distribution of medical resources in China and the various distance of families to medical institutions, we recommend that treatment be initiated while more intensive observation and follow-up are in place (increasing the frequency of platelet count tests and clinical bleeding monitoring).

Instructions for implementation:

For children who need close observation and follow-up, protections from trauma and infection are needed to reduce the risk of bleeding. The platelet count and change trend of the children should be reviewed regularly to assess the risk of bleeding in a timely manner.

Clinical question 7: Should newly diagnosed children with ITP who have grades 0–2 bleeding but whose lives are interfered with by the disease be treated as an outpatient or admitted to the hospital? Should IVIG or glucocorticoids be initiated as conventional first-line treatment? Should short course or prolonged course of glucocorticoids be initiated as conventional first-line treatment? Should conventional dose or high dose of glucocorticoid therapy be initiated?

Recommendations:

1. We suggest that those children be treated as outpatients, and we also suggest hospital admission for the children under special circumstances, such as excessive anxieties, residence far from the hospital, and inability to ensure follow-up (Level IV evidence, Grade C recommendation).
2. We suggest that glucocorticoids be chosen as conventional first-line treatment rather than intravenous immunoglobulin (IVIG) (Level Ia evidence, Grade A recommendation).
3. We recommend that short course of glucocorticoids be chosen as conventional first-line treatment rather than prolonged course of glucocorticoids (Level IV evidence, Grade C recommendation).
4. We suggest that conventional dose of glucocorticoids be chosen rather than high dose of glucocorticoids as hormone therapy (Level IV evidence, Grade C recommendation).

Note: Short course of treatment refers to the administration of glucocorticoids with medium potency such as prednisone or methylprednisolone, 3–4 mg·kg^{-1}·day^{-1}, maximum 120 mg·day^{-1}, with abrupt discontinuation after 4–7 days of administration; or 1–2 mg·kg^{-1}·day^{-1}, maximum 60 mg·day^{-1}, with tapering doses after 7–14 days of administration as appropriate, for a total course of <6 weeks.

Supplementary evidence:

None.

Rationale for adaptation:

This guideline adopted the recommendations in source guidelines and adapted the specific doses and administrations of glucocorticoids in notes. ASH Guidelines 2019 proposed that children with ITP who have grades 0–2 bleeding be treated with prednisone 2–4 mg·kg^{-1}·day^{-1}; maximum 120 mg·day^{-1} for 5–7 days. Conventional administrations in China are to start treatment with full dose of prednisone, 2 mg·kg^{-1}·day^{-1} for 4 weeks followed by tapering doses over several months. However, this prolonged course of glucocorticoids does more harm than good, because (a) it does not improve the long-term

remission rate, (b) it significantly affects the growth and development of children with ITP, and (c) it significantly reduces the quality of life among children with ITP.[8] Therefore, this guideline combines both expert opinions and clinical experience to propose a full dose with abrupt discontinuation after 4–7 days of administration, or followed by tapering doses after 7–14 days of administration, and the maximum dose of prednisone are reduced to 120 and 60 $mg \cdot day^{-1}$, respectively. In addition, with reference to *Chinese guideline on the diagnosis and management of adult primary immune thrombocytopenia (2020 edition)*,[1] for the tapering doses after 7–14 days of administration, two regimens both with a total course of <6 weeks are provided for clinical choice.

Instructions for implementation:

Even if a child with ITP chooses to be followed up in the outpatient setting, complete blood count and constant observation of bleeding are required in order to adjust treatment in a timely manner. Therefore, children or guardians under observation in outpatient setting are required to have good compliance and the ability to recognize early changes in their conditions and to seek timely medical attention. If they cannot meet the outpatient follow-up requirements, hospitalization will be considered. For children who choose to use IVIG, the potential adverse effects and costs need to be explained to the family in advance. Before administration of glucocorticoids, bone marrow aspiration needs to be completed.

Clinical question 8: Should children with ITP who have grade 3 bleeding be treated as outpatient or be admitted to the hospital? Should IVIG or glucocorticoids be chosen as emergency treatment? When choosing glucocorticoids as emergency treatment, should conversional dose or high dose of glucocorticoids be administered?

Recommendations:

1. We suggest hospitalization (Level IV evidence, Grade C recommendation).
2. We suggest IVIG over glucocorticoids for emergency treatment (Level IV evidence, Grade C recommendation) (Note: The starting dose of IVIG is 0.8–1.0 $g \cdot kg^{-1}$. If the retest on the next day shows that the platelet count is $<50 \times 10^9\ L^{-1}$, then use one more dose as before; if it is $\geq 50 \times 10^9\ L^{-1}$, then discontinue).
3. If glucocorticoids are chosen as emergency treatment, we suggest high-dose glucocorticoids therapy over routine doses (Level IV evidence, Grade C recommendation).

Note: High-dose glucocorticoid therapy refers to dexamethasone 0.6 $mg \cdot kg^{-1} \cdot day^{-1}$, maximum 40 $mg \cdot day^{-1}$ for 4 days with abrupt discontinuation; pulse therapy with methylprednisolone (maximum 30 $mg \cdot kg^{-1} \cdot day^{-1}$, total dose not exceeding 1 $g \cdot day^{-1}$) can be chosen in case of severe disease (tending to grade 4 bleeding) for 3–7 days, followed by tapering dose as appropriate with a total course of <6 weeks. If the bleeding is severe (tending to grade 4 bleeding), we suggest that high-dose glucocorticoids are administered in combination with IVIG to rapidly raise the platelet count and control the bleeding more quickly.

Supplementary evidence:

None.

Rationale for adaptation:

This guideline adopted recommendations in source guidelines, but adapted the specific administration of glucocorticoids in the notes and proposed IVIG in combination with glucocorticoid therapy in cases of severe bleeding. The ICR 2019 proposes that if moderate to severe bleeding occurs, IVIG therapy is preferred or high-dose glucocorticoids administered prior to IVIG therapy. The recommended dose of prednisone shall be 4 $mg \cdot kg^{-1} \cdot day^{-1}$ for 4 days with a maximum dose of 200 $mg \cdot day^{-1}$, or 1–2 $mg \cdot kg^{-1} \cdot day^{-1}$ with a maximum dose of 80 $mg \cdot day^{-1}$ for 1–2 weeks; if response is observed, the dose should be tapered gradually and the duration should not exceed 3 weeks; if there is no response to the initial dose within 2 weeks, the dose should be tapered rapidly and discontinued within 1 week. Although supplementary data comparing prednisone and dexamethasone for the treatment of ITP in children who have grade 3 or higher bleeding are lacking, studies in adults[33–35] have shown that pulse therapy with high-dose dexamethasone have a higher early (1 week) response rate if platelet counts are used as primary outcome measures. Therefore, we suggest dexamethasone in this setting. Taking into account national situation in China and expert opinions and considering the high risk of serious and life-threatening bleeding in children with grade 3 bleeding, we suggest that emergency treatment with high-dose glucocorticoids be administered after initial IVIG emergency treatment, or be combined with IVIG if the condition is severe (tending to grade 4 bleeding).

Instructions for implementation:

In special cases, such as hospital bed limitation, treatment in outpatient setting or emergency room with close observation is also an option. IVIG combined with glucocorticoids will increase platelet counts faster and more effectively. Here high-dose glucocorticoid therapy includes high-dose dexamethasone regimen. Dexamethasone 0.6 $mg \cdot kg^{-1} \cdot day^{-1}$, prednisone 4 $mg \cdot kg^{-1} \cdot day^{-1}$, and methylprednisolone 3–4 $mg \cdot kg^{-1} \cdot day^{-1}$ have the same anti-inflammatory effect, although dexamethasone is a long-acting hormone, and even 4 days of administration produce a longer period of exposure to glucocorticoid than that of the medium-acting hormones, which makes

dexamethasone dose regimen equal to a pulse regimen with high-dose glucocorticoid.

Clinical question 9: Should children with persistent or chronic ITP be observed and followed up or treated?

Recommendations:

1. We suggest observation and follow-up if grades 0–2 bleeding occurs without interference with life by disease (Level IV evidence, Grade C recommendation).
2. We suggest conventional treatment if there are grades 0–2 bleeding and interference with life by disease, and the specific treatment plan needs to be determined in the context of the child's previous condition (Level IV evidence, Grade C recommendation).
3. We suggest emergency treatment for grade 3 bleeding and rescue treatment for grade 4 bleeding to reduce bleeding symptoms to grades 0–2 (Level IV evidence, Grade C recommendation).

Supplementary evidence:

None.

Rationale for adaptation:

This guideline adapted recommendations in source guidelines and supplemented recommendation (3). The ICR 2019 recommends close observation and follow-up for children with persistent or chronic ITP, and treatment is suggested when life is interfered with by the disease. The choice of treatment needs to be determined by the response of the child with ITP to previous treatments, but the source guidelines do not give sufficient description of emergency and rescue treatment for grades 3–4 critical bleeding. Therefore, this guideline, based on China's national conditions and clinical practice needs, combined with expert opinions, proposed different treatment strategies according to the severity of bleeding (grades 0–2, grade 3, and grade 4 bleeding) on basis of source guidelines.

Instructions for implementation:

Treatment decisions need to be made according to the bleeding situation. Children with grades 0–2 bleeding whose lives are not interfered with by disease can still be observed and followed up. But children with platelet counts $<20 \times 10^9$ L^{-1} need to be followed up with increased frequency and closely observed for changes in bleeding. Treatment should be started when their lives are interfered with by disease. Children with grades 3–4 bleeding need to be treated immediately with emergency or resuscitation therapy, and conventional treatment should be started after the bleeding is recovered to grades 0–2. Treatment strategy for children with ITP needs to be determined by previous treatment and the response to treatments. First-line conventional treatment is indicated in those who have not received treatment yet; second- or third-line conventional treatments are indicated in those who have not responded to first-line treatments.

Clinical question 10: Should children with ITP who have no response to first-line treatment and still need treatment be treated with a thrombopoietic agent, rituximab, or splenectomy as second-line treatment?

Recommendations:

1. We suggest conventional second-line treatment with thrombopoietic agents rather than rituximab (Level Ib evidence, Grade A recommendation).
2. We suggest choosing conventional second-line treatment with thrombopoietic agents rather than splenectomy (Level Ib evidence, Grade A recommendation).
3. We suggest choosing conventional second-line treatment with rituximab rather than splenectomy (Level III evidence, Grade B recommendation).

Supplementary evidences:

One observational study (91 cases) was added.[36] For recommendation (1), after combination with the source guideline evidences (including nine observational studies), the results were as follows: seven observational studies (n = 566) suggested a lower initial overall response rate in the rituximab group compared with the thrombopoietin receptor agonists (TRAs) group (RR = 0.9, 95% CI: 0.78–1.05); in six observational studies (n = 298), the sustained overall response rate was higher in the TRAs group compared with rituximab (RR = 0.99, 95% CI: 0.81–1.21); one observational study reported 30 children treated with rituximab, with six children achieving remission; in seven observational studies (n = 320), the incidence of major bleeding was higher in the rituximab group compared with TRAs group (RR = 0.81, 95% CI: 0.37–1.79); four observational studies included 187 children treated with TRAs and no thrombosis occurred. The rate of improvement in quality of life was not reported in the above studies. There is no supplementary evidence for recommendations (2) and (3).

Rationale for adaptation:

This guideline adopted recommendations in source guidelines. The supplementary evidences are consistent with the findings of the source guideline evidences. In China, children and their guardians prefer not to have splenectomy when first-line treatment fails.

Instructions for implementation:

There are two classes of thrombopoietic drugs in China, recombinant human thrombopoietin (rhTPO) and TRAs. The former is administered by subcutaneous injection, which can take effect faster and avoid the impact of gastrointestinal absorption on drug efficacy and is suitable for

children with heavy bleeding. But it should be noted that continued or repeated use is not suggested for children who have no response after more than 14 days of administration. The use of eltrombopag requires attention to liver injury. The administration of thrombopoietic agents also requires attention to risks such as thrombosis and myelofibrosis after platelet counts increase.[37] Although TRAs are recommended as the first choice for second-line treatment in several national and international guidelines, this class of drugs requires long-term administration and is a heavy burden for the children's families. Other second-line treatments or drug combinations can be chosen first in clinical practice to reduce the cost of treatment.[38] Adverse reactions such as acquired hypogammaglobulinemia and complication of serious infections need to be monitored during rituximab treatment.

Clinical question 11: When should splenectomy be considered in children with ITP?

Recommendations:

Splenectomy should be considered in children with ITP who meet all the follow criteria and re-assessed by experienced hematologists: (a) failure to respond to existing first- and second-line medical therapy; (b) recurrent severe bleeding (grades 3–4) and/or interference with life by disease; (c) an age of >5 years old, and (d) disease duration longer than 1 year (Level IV evidence, Grade C recommendation). Prior to splenectomy, relevant vaccinations need to be done according to our national situation and the latest immunization schedule.

Supplementary evidence:

None.

Rationale for adaptation:

This guideline adopted recommendations in ICR 2019.

Instructions for implementation:

Indications and contraindications of splenectomy should be strictly followed. It is necessary to ensure that the child has been vaccinated according to the latest national immunization schedule before splenectomy. Prophylactic antibacterial drugs, hematological test and imaging monitoring, and antiplatelet therapy should also be considered for children with reactive increased platelet count to prevent thrombosis.

Clinical question 12: What should be the rescue treatment for children with ITP who have grade 4 bleedings?

Recommendation:

When grade 4 bleeding occurs in children with ITP, we suggest rescue therapy with combined platelet transfusion, pulse therapy of high-dose methylprednisolone, and pulse therapy of high-dose IVIG to ensure the most effective and rapid platelet counts elevation for effective hemostasis. At the same time, the addition of a thrombopoietic agent may be considered (Level 4 evidence, Grade C recommendation).

Note: Pulse therapy with high-dose methylprednisolone refers to the administration of a maximum dose of 30 $mg \cdot kg^{-1} \cdot day^{-1}$ with a total dose not exceeding 1 $g \cdot day^{-1}$ followed by tapering doses as appropriate after 3 days. The total duration of treatment is <6 weeks. Pulse therapy with high-dose IVIG refers to 1.0 $g \cdot kg^{-1} \cdot day^{-1}$ for 2 days.

Supplementary evidence:

None.

Rationale for adaptation:

This guide adopted the recommendations in source guidelines and made some slight adaptations. The ICR 2019 recommends combination therapy for children with ITP who have grade 4 bleeding, which includes platelet administered as a bolus followed by continuous transfusion, and suggests the administration of antifibrinolytics as appropriate if bleeding persists. In addition, TRAs are also suggested for grade 4 bleeding because they may help the child respond quickly and prevent a drop in platelet count in case that initial emergency treatment fails. Considering our national situation, (a) the clinical experience with platelet bolus mentioned in the source guideline is insufficient, so it is changed to "platelet transfusion"; (b) for thrombopoietic agents, while there is no direct evidence of rhTPO for grade 4 bleeding in children with ITP, based on the clinical experience in China, rhTPO has the following advantages when administered in critical illness: (i) faster onset of action than oral TRAs; (ii) subcutaneous administration ensures drug absorption in critical illness; and (iii) no hepatic metabolism.

Instructions for implementation:

The critical condition of grade 4 bleeding can occur at any stage of unremitting disease; it is necessary to rapidly elevate platelet counts and stabilize vital signs to gain time for subsequent treatment. It should be noted that platelet transfusion is not recommended for children with ITP who have non-grade 4 bleeding. In such case, antifibrinolytics can be dosed (especially in case of gastrointestinal bleeding), or emergency splenectomy can be performed as appropriate.

Flowchart of diagnosis and treatment for children with ITP in China

Flowchart of diagnosis and treatment for children with ITP in China is shown in Figure 1.

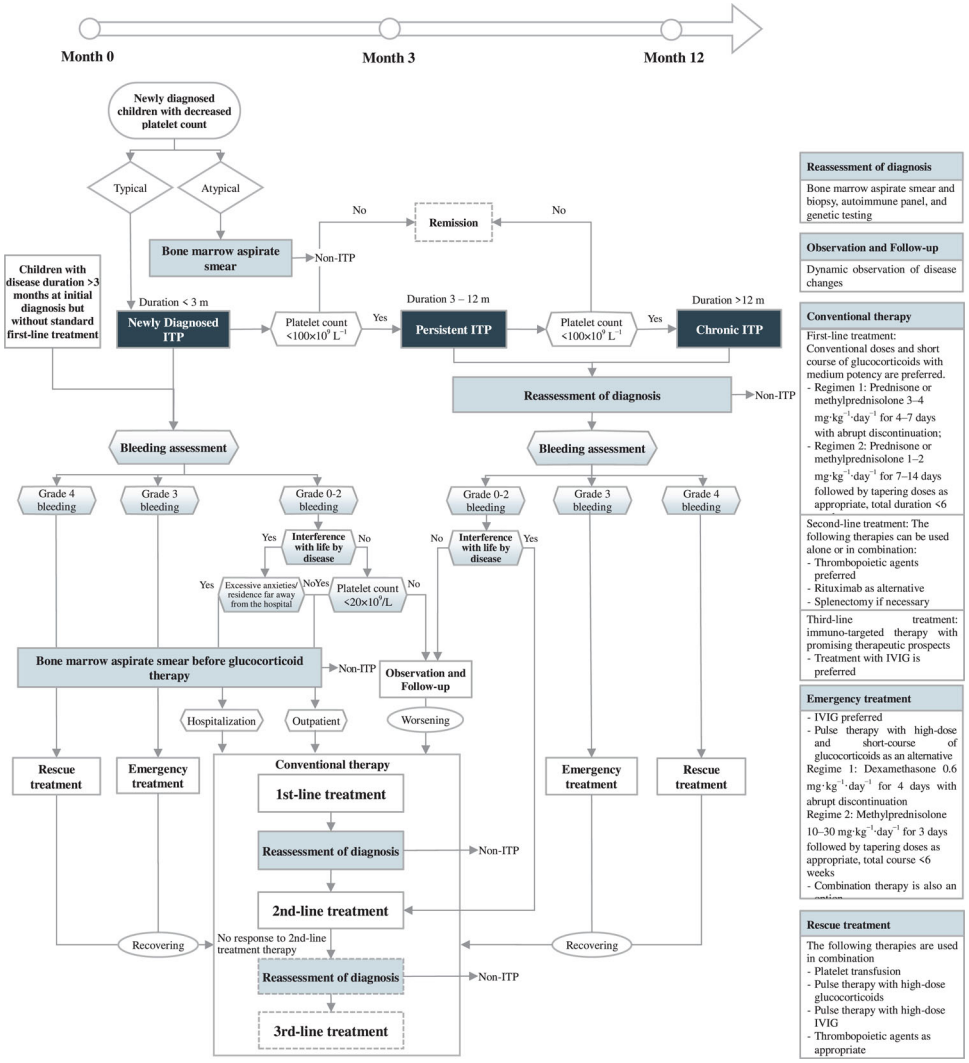

FIGURE 1 Flowchart of diagnosis and treatment of Chinese children with primary immune thrombocytopenia. ITP, primary immune thrombocytopenia; IVIG, intravenous immunoglobulin

Favorable and unfavorable factors in the implementation of this guide and prospects

Favorable factors in the implementation of this guideline include: supplementary of evidences in English and local evidence from China, the consideration of factors such as the specificity of the medical environment in China and the preferences and values of Chinese parents/guardians during the development of the adapted recommendation. Unfavorable factors include: (a) lack of a "gold standard" for ITP as an exclusionary condition; and (b) evidences from some interventional studies were not included for evaluation as a result of factors like bleeding severity and/or quality of life were not considered in these studies. Limitations of this guideline include: no coverage of third-line drugs and low number of children/guardians involved; and the evidence level and strength of recommendation grade from ICR was used in this guideline, taking into account implementability, readability, and affordability.

We hope that future interventional clinical studies of ITP can provide high-quality clinical evidence of the efficacy and safety of different interventions under different bleeding conditions and/or quality of life. With the in-depth understanding of the pathogenesis and related therapeutic advances, precise diagnosis and targeted treatment of ITP are expected in the future.[39–42]

Experts who draft the guideline

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Listing of experts

See supporting File S2.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Working Group of Chinese Guideline for the Diagnosis and Treatment of Childhood Primary Immune Thrombocytopenia; Subspecialty Group of Hematologic Diseases, Society of Pediatrics, Chinese Medical Association; Editorial Board, *Chinese Journal of Pediatrics*. Adapted guideline for the diagnosis and treatment of primary immune thrombocytopenia for Chinese children (2021). *Pediatr Investig.* 2022;6:63–74. https://doi.org/10.1002/ped4.12305