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Idiopathic thrombocytopenic purpura: a guideline for diagnosis and management of children and adults

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Idiopathic thrombocytopenic purpura (ITP, also known as immune thrombocytopenic purpura) affects both children and adults. In childhood, the peak age is 2–4 years, girls and boys are equally affected, and in most children, the disease is self-limited with spontaneous recovery occurring in several weeks to several months. In adults, ITP is most common among young women, and the disease is more insidious in its onset and chronic in its course. In both children and adults, there are important unresolved issues in diagnosis and management that have major cost implications. For this reason, the American Society of Hematology chose ITP as the disease topic for its initial practice guideline in 1993. In 1996, the practice guideline was published in *Blood*, the Journal of the American Society of Hematology. This review describes the principle features of ITP in children and adults, the process of development of the practice guideline for ITP, and the implications of the guideline for the diagnosis and management of patients with ITP.

Key words: autoimmune thrombocytopenic purpura; idiopathic thrombocytopenic purpura; immune thrombocytopenic purpura; practice guideline; thrombocytopenia.

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Introduction

Idiopathic thrombocytopenic purpura (ITP) is a well recognized disease among children and adults; it is estimated that 10–125 per 1 000 000 persons (children and adults) develop ITP each year (1). No specific criteria establish the diagnosis of ITP; the diagnosis relies on the exclusion of other causes of thrombocytopenia. ITP is defined as isolated thrombocytopenia with no clinically apparent associated conditions or other causes of thrombocytopenia (eg HIV infection, systemic lupus erythematosus, lymphopro-

liferative disorders, myelodysplasia, drug-induced thrombocytopenia, and congenital or hereditary nonimmune thrombocytopenia) (2). Patients with isolated abnormalities on serological tests (eg anti-nuclear or antiphospholipid antibodies), but without clinical evidence of a disorder such as systemic lupus erythematosus, receive the diagnosis of ITP because positive serological tests are frequently encountered in otherwise typical patients (3, 4). The lack of a specific test for ITP presents a diagnostic challenge. In many patients, ITP cannot be distinguished from the acute thrombocytopenia that accompanies viral infection, drug-induced thrombocytopenia, or gestational thrombocytopenia. In addition, there are important controversies regarding management. In children, in whom ITP is generally an acute disease with anticipated spontaneous recovery, there is controversy regarding the relative benefits and risks of specific initial treatment (5). For both children and adults, there is controversy regarding the management of patients with chronic and persistent disease (6). It is not uncommon for patients to experience more difficulty from their treatment than from their disease.

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Underlying all of these uncertainties is the lack of knowledge about the natural history of ITP, its morbidity from bleeding, and its mortality, in both children and adults (2).

Because of these issues, patients with ITP frequently present their physician with important dilemmas in diagnosis and management. To address these problems, the American Society of Hematology sponsored the development of a practice guideline for the diagnosis and management of ITP. This was the first effort of the American Society of Hematology to develop a practice guideline, a decision fuelled by the increasing interest in the role of clinical practice guidelines in improving the effectiveness and efficiency of health care. Medical specialty societies are increasingly aware of their role as sources of guidance for clinical care. Clinical guidelines issued by a specialty society are more readily accepted by their physician members than are guidelines from other sources (7).

This effort comes at a time when clinical practice guidelines are being used increasingly by physicians, professional organizations and health care delivery systems to improve the quality and efficiency of care. A new movement toward 'evidence-based medicine' is placing greater emphasis on critically appraising the scientific support for diagnostic and treatment practices. Systematic reviews of the evidence, which use explicit methods to collect and evaluate relevant studies, are increasingly common and provide the ideal basis for crafting evidence-based practice guidelines (8). It was in this spirit that the American Society of Hematology panel set out to review the evidence for ITP.

Methodology for guideline development

A literature search was performed according to established rules to identify all published reports on the diagnosis and management of ITP. Each article was evaluated independently by two reviewers, and the scientific validity was assessed using published guidelines. The strength of evidence for therapeutic approaches was assessed using the 'levels of evidence' criteria, in which articles are scored from level I, for the strongest evidence from randomized clinical trials with low false-positive and false-negative errors, to level V, the weakest evidence, for case series without a control group (9, 10). During the literature review, it was soon clear that evidence was insufficient to support definitive recommendations based on data. This itself was an important revelation, a disturbing deficiency in decades of clinical publications on ITP, most of which consist of case series without a control group (level V evidence).

The panel therefore chose to issue opinion-based recommendations, using a novel method for the assessment of opinion that was designed to document

clearly the strength and variance of the individual panelist's opinion. Survey instruments to collect this information were designed at panel meetings. The panel members identified the key diagnostic and treatment practices to be considered but did not discuss their views about the appropriateness of the practices. The questionnaires, which the panel members later completed at home, addressed about 1900 clinical scenarios. The panel members ranked the necessity and appropriateness of diagnostic and treatment interventions for each of these scenarios using a scoring system, modified from the RAND methodology (11, 12), quantified the strength of their opinion on a scale of 1–9, ('9' represented strong agreement with the appropriateness and/or necessity of the practice and '1' represented strong disagreement). The strength of the panel's interobserver agreement about the appropriateness and/or necessity of tests or treatment was graded using standard deviations for each question and assigned consensus codes of A–E ('A' represented complete or almost complete unanimity and 'E' represented strong disagreement) (2).

Because of the lack of valid evidence, essentially all recommendations were based on opinion, but the inherent weakness of opinion-based recommendations was acknowledged. The panel could not reach consensus on many issues other than the 'extremes' of inappropriate and appropriate practice. The guideline was therefore silent on many important and common clinical scenarios.

Results

ITP in Children

Diagnosis. Few clinical studies have evaluated the sensitivity and specificity of diagnostic tests used for children with suspected ITP. There is no 'gold standard' test for ITP; the diagnosis is applied only when there is thrombocytopenia with no other apparent cause. Other aetiologies are uncommon when the history, physical examination, initial blood counts and peripheral smear are compatible with the diagnosis of ITP and do not include atypical findings that are uncommon in ITP or suggest other aetiologies. In one published study of 127 consecutive children with suspected ITP who had bone marrow aspirations, other causes of thrombocytopenia were identified in only 5 (4%) of the children, all of whom had atypical presenting features (13).

A complete blood count and an examination of the peripheral smear are essential in the diagnostic evaluation. The principal features of the examination of the blood smear are the same for children and adults (Table 1). Few other laboratory tests were considered to be necessary or appropriate. Testing for

Table 1. The peripheral blood smear in idiopathic thrombocytopenic purpura (ITP).**Consistent with the diagnosis of ITP**

1. Thrombocytopenia; platelets are normal in size or may appear larger than normal, but consistently giant platelets (approaching the size of red blood cells) should be absent
2. Normal red blood cell morphology
3. Normal white blood cell morphology

Not consistent with the diagnosis of ITP

1. Predominant giant platelets
2. Red blood cell poikilocytosis, schistocytes, polychromatophilia (unless response to bleeding), macrocytes, nucleated red blood cells
3. Leukocytosis or leukopenia, with immature or abnormal cells (although atypical lymphocytes and eosinophilia may occur in children with ITP)

HIV antibody was considered necessary in patients with risk factors for HIV infection. An abdominal computed tomography or ultrasound examination was considered appropriate in patients with suspected splenomegaly on initial physical examination. Bone marrow aspiration was considered both appropriate and necessary to establish the diagnosis in patients with persistent thrombocytopenia (longer than 6–12 months) and in patients unresponsive to intravenous immunoglobulin (IVIg) treatment. However, bone marrow aspiration was considered unnecessary to establish the diagnosis before initiating IVIg therapy and was also considered unnecessary to establish the diagnosis in patients who require more than an initial course of IVIg. There was no consensus on the necessity or appropriateness of bone marrow aspiration before initiating steroid therapy. Platelet antibody tests, both platelet-associated IgG and platelet antigen-specific antibody tests, were considered unnecessary.

Treatment. Essentially all evidence regarding the efficacy of treatment is indirect, inferred by measuring the platelet count rather than by a clinical outcome such as bleeding or mortality. Initial treatment of children has been based on the assumption that increasing the platelet count more rapidly diminishes the risk for serious haemorrhage, though these events are very rare in children with ITP (5). Eleven clinical trials provide level I or level II evidence regarding initial treatment of children with ITP (2). They show that the platelet count increases to levels greater than 20 000–50 000 per μL more rapidly with treatment than without treatment. However, the rise in platelet counts occurs only a few days earlier with treatment, and 30–70% of children recover from severe thrombocytopenia without specific treatment, achieving platelet counts of 50 000–100 000 per μL within 3 weeks (2).

The panel responses to the question regarding the appropriateness of offering no specific initial treatment for children with ITP and symptoms of only minor purpura are presented in Figure 1. There was no consensus among the panel except at the highest platelet counts, for which the option of offering no treatment received the strongest support. However, at the lowest platelet count (< 10 000/ μL), although the panel as a whole did not support offering no specific initial treatment, six individual panel members had votes that ranged from the strongest negative to the strongest positive opinion (2). Four panel members felt it was absolutely wrong to offer no specific initial treatment, while one voted that it was absolutely correct.

The panel concluded that oral glucocorticoid or IVIg is appropriate as initial therapy for children with platelet counts of less than 10 000 per μL and minor purpura. This conclusion created the strongest critical reaction to the practice guideline. Two letters to the editor were published in response to this recommendation, representing the concerns of both American and British paediatricians that the recommendation would adversely affect the practice of paediatric haematologists who routinely do not recommend specific initial treatment for children with severe thrombocytopenia and only minor purpura (14–16).

There are no published data on the efficacy of treatments for the management of children with

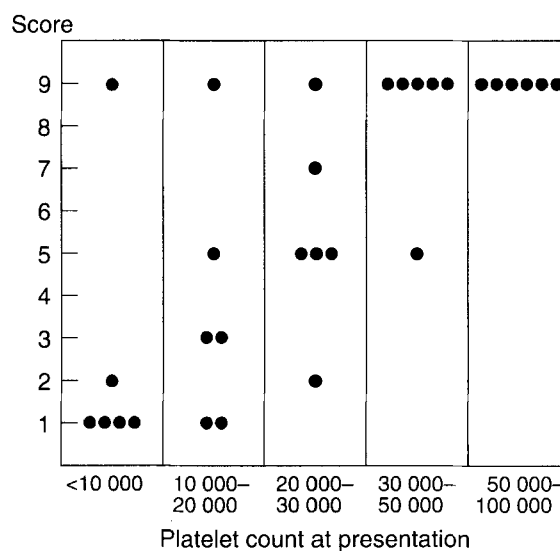


Figure 1. Response of the American Society of Hematology ITP Practice Guideline Panel to a question regarding the appropriateness of offering no specific initial treatment for children presenting with ITP and symptoms of only minor purpura. Data points (•) represent the responses of individual panel members ($n = 6$) on a scale of 1–9, with 1 reflecting complete disagreement (treatment is appropriate) and 9 reflecting complete agreement (treatment is not appropriate). (Reproduced from (2) with permission.)

urgent, life-threatening bleeding. Assuming that conventional critical care measures are already ongoing, there was strong agreement on the panel that treatment with platelet transfusions, high-dose intravenous glucocorticoid (eg 30 mg/kg methylprednisolone) and IVIg, alone or in combination, was appropriate (2).

ITP in adults

Diagnosis. As with children, a complete blood count and examination of the peripheral blood smear were considered essential for the diagnosis (Table 1). Figure 2 presents the panel responses to a question regarding the necessity and/or appropriateness of performing a bone marrow aspiration or biopsy to establish the diagnosis of ITP in all adult patients at presentation. The panel votes reflect the complete spectrum of opinion about necessity and appropriateness. Laboratory tests that were considered appropriate were testing for HIV antibody in patients with risk factors for HIV infection, bone marrow examination in patients over 60 years of age and in those considering splenectomy, and thyroid function testing to rule out occult hyperthyroidism or hypothyroidism before an elective splenectomy. Tests that were considered unnecessary or inappropriate included

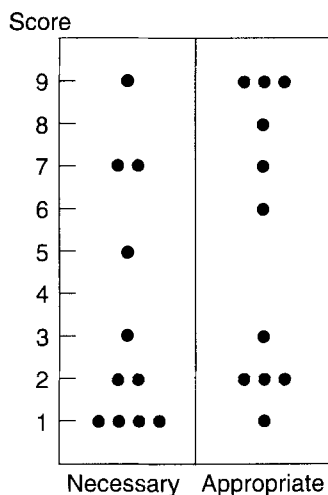


Figure 2. Responses of the American Society of Hematology ITP Practice Guideline Panel to the question, 'Is it necessary/appropriate to order a bone marrow aspiration/biopsy to establish the diagnosis of ITP in all adult patients at presentation? This question assumes that the history, physical examination, and initial blood counts with examination of the blood smear are compatible with the diagnosis of ITP and do not include atypical findings that are uncommon in ITP or suggest other aetiologies.' Data points (•) represent the responses of individual panel members ($n = 11$) on a scale of 1–9, with 1 reflecting the strongest no (complete disagreement) and 9 reflecting the strongest yes (complete agreement). (Reproduced from (2) with permission.)

platelet antibody tests (both platelet-associated IgG assays and platelet antigen-specific antibodies) (2).

Treatment. There are no well-controlled clinical studies on which to base recommendations for treatments of adults with ITP. The panel opinion was that it is appropriate to offer oral prednisone (1–2 mg/kg/day) to asymptomatic patients with platelet counts of less than 20 000 per μL , to patients with platelet counts of 20 000–30 000 per μL who have minor purpura, or to those with platelet counts of 30 000–50 000 per μL who have mucous membrane or vaginal bleeding that may require clinical intervention. IVIg is recommended for patients with severe, life-threatening bleeding (2).

There is no evidence and very little consensus about how to treat patients who do not respond, or respond only incompletely or transiently, to initial prednisone treatment. Figure 3 presents the responses of the panel to a question regarding the proper management of a hypothetical patient who presented initially with a platelet count of 10 000 per μL and bleeding symptoms consisting of purpura, menorrhagia and epistaxis, and who is treated initially with prednisone (1 mg/kg/day). Depending on the platelet count, most panel members would alter the treatment after 2–4 weeks if the patient did not respond, or responded incompletely, to this dose of prednisone. Figure 3 also illustrates the varied opinions about when to recommend elective splenectomy in such patients. One haematologist recommended splenectomy as early as after 2 weeks, while another would not recommend splenectomy even after 10 weeks with no response.

Perhaps the most difficult management problem in ITP is the patient who is refractory to primary treatment with glucocorticoids and splenectomy. There are insufficient data to develop evidence-based recommendations for when treatments are indicated, for comparing one treatment with another, or for assessing which treatments result in more good than harm. The lack of evidence was reflected in the absence of consensus among the panel members regarding whether any treatment is more effective than another treatment or no treatment. The absence of clear recommendations for these difficult patients was another cause for disappointment with the guideline. However, the guideline documented that the only evidence in this area consists of case series without controls, which is the weakest class of clinical evidence.

For management of critical, life-threatening bleeding, there was strong agreement among the panel that, in addition to conventional critical care measures, appropriate treatment includes platelet transfusions, high-dose intravenous glucocorticoid, and IVIg, either alone or in combination (2).

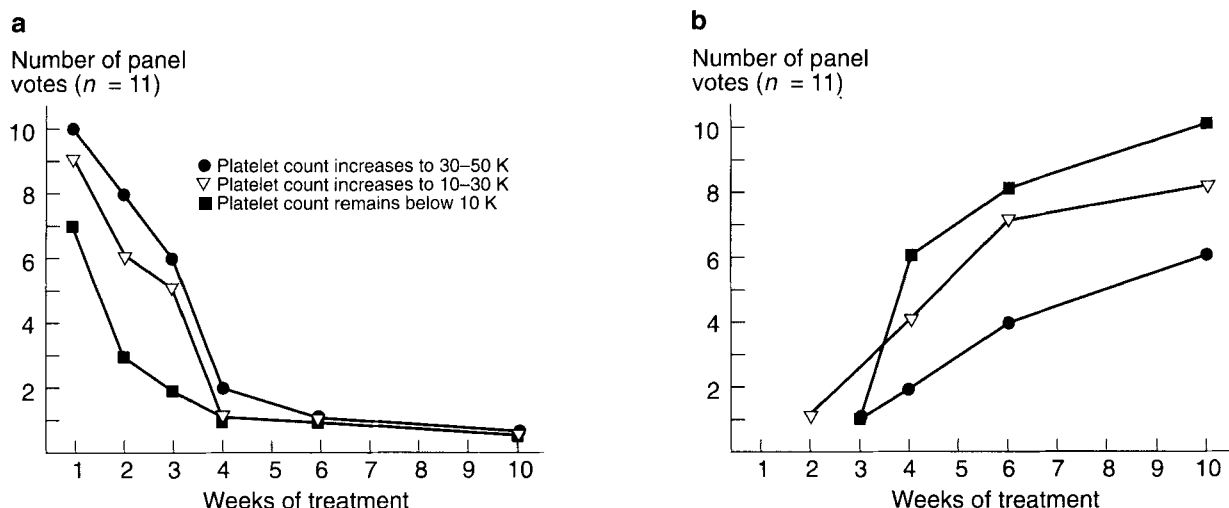


Figure 3. (a) Length of time the American Society of Hematology ITP Practice Guideline Panel members would continue initial prednisone treatment (1 mg/kg/day) before adding to or changing the regimen in a hypothetical 30-year-old female who presented initially with a platelet count of less than 10 000. The votes were stratified to reflect different platelet count responses to treatment. The Figure illustrates that, if the platelet count remains below 10 000, four panel members would add to or change treatment after 1 week, whereas one panel member would not change treatment until 10 weeks.

(b) Length of time after which the panel members would recommend splenectomy after treating a hypothetical 30-year-old female who presented initially with a platelet count of less than 10 000. The votes were stratified to reflect different platelet count responses to treatment. The Figure illustrates that, in a patient with persistent severe thrombocytopenia (platelet count that remains < 10 000), most panel members would recommend splenectomy after 4–6 weeks of unsuccessful medical therapy. The opinions of the panel members were varied, with one panelist recommending splenectomy as early as after 2 weeks and another not recommending splenectomy even after 10 weeks of unsuccessful treatment. (Reproduced from (2) with permission.)

ITP in pregnant women and newborns

Diagnosis. The diagnosis of ITP is more difficult during pregnancy because the presentation may be indistinguishable from gestational thrombocytopenia (also termed incidental thrombocytopenia of pregnancy). Gestational thrombocytopenia is the most common cause of thrombocytopenia during pregnancy, occurring in approximately 5% of pregnant women at term and accounting for 75% of cases of thrombocytopenia at term (17). Thrombocytopenia associated with pre-eclampsia accounts for most of the remaining cases. Gestational thrombocytopenia is characterized by 1) asymptomatic, mild thrombocytopenia; 2) with no past history of thrombocytopenia except possibly during a previous pregnancy; 3) that occurs late during gestation; 4) that is not associated with fetal thrombocytopenia; and 5) that resolves spontaneously after delivery. Platelet counts are typically greater than 70 000 per μL , with about two-thirds being above 130 000 per μL . In patients with mild thrombocytopenia and no past history of thrombocytopenia, the distinction between ITP and gestational thrombocytopenia is impossible but this is of little clinical importance to the mother, because mild thrombocytopenia will not threaten maternal health or the management of delivery. However, the differential diagnosis is clinically

important with regard to the fetus, because ITP with even mild thrombocytopenia may be associated with neonatal thrombocytopenia whereas gestational thrombocytopenia is not (17).

The diagnosis of ITP during pregnancy does not require special laboratory testing. Platelet antibody tests were considered unnecessary.

Treatment. Management of maternal thrombocytopenia does not differ from management of non-pregnant patients, except for concerns about the teratogenicity of certain drugs, the timing of delivery and the requirement for good haemostasis at delivery, and the risk of neonatal haemorrhage. A review of published data from 1980 to 1990 found that 10% of infants born to women with ITP have a platelet count at birth of less than 50 000 per μL and 4% have a platelet count at birth of less than 20 000 per μL (18). The frequency of neonatal intracranial haemorrhage is unknown, but it is probably less than 1%. Data on neonatal intracranial haemorrhage came from individual case reports or small series; no incident of intracranial haemorrhage at birth was reported in case series including 10 or more patients (18). Bleeding symptoms in infants did not differ among those delivered by caesarean section or vaginal delivery (18).

The panel's opinion was that it is important to know from the history whether a pregnant woman

has had a previous infant with a platelet count of less than 50 000 per μL at birth with no evidence for alloimmune thrombocytopenia. Siblings appear to face a similar risk for thrombocytopenia. Beyond the history, however, there were no consensus recommendations for special procedures. There were, for example, no circumstances in which percutaneous umbilical blood sampling (PUBS) or fetal scalp vein sampling at delivery were recommended. The panel members acknowledged that, if information obtained from PUBS was available, it would influence the preferred route of delivery. A fetal platelet count of less than 20 000 per μL by PUBS was regarded as an appropriate consideration for delivery by caesarean section.

Treatment of newborns. There are no data from which to develop evidence-based recommendations on newborn care when the mother has ITP. Based on opinion, the panel considered it necessary to obtain repeat platelet counts on the newborn if the neonatal platelet count at birth was low. This was because platelet counts may decrease further after birth, with a nadir up to 7 days after birth (19). Brain imaging was considered appropriate, even in the absence of neurologic abnormalities, if the platelet count at birth was less than 50 000 per μL . If the infant had imaging evidence of intracranial haemorrhage, combined treatment with glucocorticoids and IVIg was considered necessary. Even in newborns without evidence of intracranial haemorrhage, treatment with IVIg was considered appropriate if an infant's platelet count was less than 20 000 per μL .

Conclusions

The major finding of the American Society of Hematology's ITP practice guideline effort was that evidence was insufficient to support strong or definitive recommendations. Although this conclusion may seem disheartening, clinicians should appreciate that the diagnosis and management of ITP, as presented in current textbooks and reviews, are not based on firm data but rather on observations from case series that lacked controls, which is the weakest class of clinical evidence. There are no firm data on the incidence of ITP, its natural history, the mortality rate and frequency of major bleeding episodes, and the relative risks and benefits of different treatments. This absence of data may come as a revelation to many clinicians who have assumed that recommendations in standard medical texts are based on firm evidence. One reason for the absence of evidence on the diagnosis and management of ITP may be the relatively benign nature of the disease. This may have decreased the sense of urgency to perform rigorous

clinical studies. Despite the occurrence of often frighteningly low platelet counts, mortality from ITP is thought to be low and many treatments appear to have some efficacy, at least as measured by transient increases in the platelet count. Physicians who worry about the appropriateness of their approaches to the diagnosis and treatment of ITP can take comfort in the lack of data and the fact that, at this time, the evidence does not dictate a right or a wrong approach. For the future, these controversies will not be resolved by debate but only by well-designed clinical trials that assess the most important clinical outcomes: bleeding and death.

The ITP panel also broke new ground in the methodology of practice guideline development (20). Beyond its use of grading systems to rate the quality of the supporting evidence, which is well-described elsewhere (10), the panel introduced a new approach for quantifying the strength and variation of expert opinion. The scoring system proved useful in defining issues for which there was consensus and, perhaps more importantly, in displaying the dramatic range of opinions that can exist when experts disagree. This clearly demonstrated how the absence of data bears no relation to the strength of opinion. Notwithstanding the limitations of opinion as a basis for health policy, our methods make explicit for clinicians and policy makers when guidelines are based on opinion as well as the strength of the consensus behind them.

Priorities for future research

Perhaps the most important outcome of our literature review of ITP was to identify priorities for future clinical research. The current absence of evidence from well-designed clinical trials affects virtually every decision a clinician commonly encounters in the care of patients with ITP. Priorities for future clinical research were outlined by the panel:

1. There is a need for rigorous prospective studies of the clinical course of untreated ITP in adults presenting with mild or moderate thrombocytopenia and no clinically important bleeding. These studies should include long-term follow-up and should emphasize the clinical outcomes of bleeding and mortality.
2. There is a similar need for rigorous prospective studies to define the need for specific initial treatment in children including the clinical features of children that predict the risk of intracranial haemorrhage and chronic thrombocytopenia.
3. There is a need for firm data on the clinical course of chronic refractory ITP in both adults and children, especially the course of untreated disease

in patients without clinically important bleeding. These natural history data are especially important for evaluating the efficacy of treatment. From current evidence, it is difficult to prove that treatment is beneficial or to exclude the possibility that some treatments are more harmful than no treatment.

4. There is a need for studies to assess the prognostic relation of the platelet count, at initial presentation and subsequently, to clinical outcomes of bleeding and mortality. Currently, the platelet count serves

as the key to decision-making despite the lack of definitive data on its prognostic importance.

5. There is a need for randomized clinical trials to evaluate the therapies currently used for patients with ITP. These trials should focus on measuring the benefits of therapy in terms of the clinical outcomes of bleeding and mortality, as well as the adverse effects of treatments.
6. There is a need for data on the costs of treatment regimens.

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