

## Idiopathic Thrombocytopenic Purpura: A Practice Guideline Developed by Explicit Methods for The American Society of Hematology

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**I**DIOPATHIC thrombocytopenic purpura (ITP, also known as primary immune thrombocytopenic purpura) is a hematologic disorder for which appropriate diagnostic and treatment strategies are uncertain. In 1994, the American Society of Hematology (ASH) established a panel to produce explicitly developed practice guidelines for the diagnosis and management of ITP. "Explicitly developed," evidence-based practice guidelines, which are being issued increasingly by medical specialty societies, combine a critical appraisal of scientific evidence with practice recommendations that state clearly to what extent the guidelines are based either on published scientific evidence or opinion (eg, clinical experience).<sup>1-4</sup> More details about the clinical practice guideline movement are provided elsewhere.<sup>5-7</sup>

This report begins with a brief summary of the panel's recommendations, followed by a more detailed analysis of its methodology, the findings of the comprehensive literature review, and a full presentation of the recommendations. The report concludes with recommendations for future research. As explained later, the recommendations are based on the panel's opinion, derived from a systematic scoring methodology. (Only recommendations receiving scores of 1.0 to 3.0 or 7.0 to 9.0, as defined later in the text, are cited in this summary.)

### SUMMARY OF RECOMMENDATIONS

#### Children

##### Diagnosis

The diagnosis of ITP is based principally on the history, physical examination, complete blood count, and examination of the peripheral smear, which should exclude other causes of thrombocytopenia. Further diagnostic studies (see Table 7) are generally not indicated in the routine work-up of patients with suspected ITP, assuming that the history, physical examination, and blood counts are compatible with the diagnosis of ITP and do not include atypical findings that are uncommon in ITP or suggest other etiologies. Patients with risk factors for human immunodeficiency virus (HIV) infection should be tested for HIV antibody, and an abdominal computed tomographic (CT) scan or ultrasound examination is appropriate in patients with suspected splenomegaly on initial physical examination. Bone marrow aspiration should be performed to establish the diagnosis in patients with persistent thrombocytopenia (lasting more than 6 to 12 months) and in those unresponsive to intravenous Ig (IVIg), but it should not be performed to establish the diagnosis before initiating IVIg therapy. Additional testing is also generally unnecessary, and sometimes inappropriate, when performed on a routine basis to establish the diagnosis before splenectomy or to evaluate patients who have not

responded to glucocorticoid therapy, IVIg, and splenectomy (see Table 7).

##### Treatment

Children with platelet counts >30,000 should not be hospitalized and do not routinely require treatment if they are asymptomatic or have only minor purpura; they should not be given glucocorticoids, IVIg, or anti-Rh(D) as routine initial treatment. Children with platelet counts <20,000 and significant mucous membrane bleeding and those with counts <10,000 and minor purpura should be treated with specific regimens of IVIg or glucocorticoids (see text). Patients with severe, life-threatening bleeding should be hospitalized and receive conventional critical care measures, along with treatment for ITP: appropriate regimens include high-dose parenteral glucocorticoid therapy, IVIg, and platelet transfusions.

Splenectomy is clearly appropriate or inappropriate in specific clinical situations (see text). If an elective splenectomy is planned, appropriate preoperative therapy includes prophylactic IVIg therapy for patients with platelet counts

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<30,000, and IVIg, parental glucocorticoids, and anti-Rh(D) for patients with platelet counts <10,000. Inappropriate preoperative prophylaxis includes IVIg, oral glucocorticoid therapy, or anti-Rh(D) when platelet counts exceed 50,000, parenteral glucocorticoid therapy when platelet counts exceed 30,000, and platelet transfusions when platelet counts exceed 20,000.

When ITP symptoms persist after primary treatment (glucocorticoid, IVIg) and splenectomy, further treatment is indicated in children with platelet counts <30,000 who have active bleeding. Panel members suggested many treatments as reasonable options but did not reach consensus on any single regimen, reflecting the lack of evidence that any single treatment is more effective than another.

## Adults

### *Diagnosis*

The diagnosis of ITP is based principally on the history, physical examination, complete blood count, and examination of the peripheral smear, which should exclude other causes of thrombocytopenia. Further diagnostic studies (see Table 7) are generally not indicated in the routine work-up of patients with suspected ITP, assuming that the history, physical examination, and blood counts are compatible with the diagnosis of ITP and do not include atypical findings that are uncommon in ITP or suggest other etiologies. Patients with risk factors for HIV infection should be tested for HIV antibody. Bone marrow aspiration is appropriate to establish the diagnosis in patients over age 60 and in patients considering splenectomy. Additional testing is also generally unnecessary, and sometimes inappropriate, when performed on a routine basis to establish the diagnosis before splenectomy or to evaluate patients who have not responded to glucocorticoid therapy and splenectomy (see Table 7). Preoperative thyroid function testing is appropriate to rule out occult hyperthyroidism or hypothyroidism before elective splenectomy.

### *Treatment*

Patients with platelet counts >20,000 should not be hospitalized if they are either asymptomatic or have only minor purpura. Patients with counts >50,000 do not routinely require treatment; they should not be given glucocorticoids or IVIg as routine initial treatment. IVIg is also inappropriate as initial treatment in patients with counts >30,000 who are asymptomatic or have only minor purpura. However, treatment is indicated in patients with platelet counts <20,000 to 30,000, and those with counts <50,000 and significant mucous membrane bleeding (or risk factors for bleeding, such as hypertension, peptic ulcer disease, or a vigorous lifestyle). Initial therapy with glucocorticoids (eg, prednisone) is appropriate in such patients. Hospitalization is appropriate for patients with platelet counts <20,000 who have significant mucous membrane bleeding. Patients with severe, life-threatening bleeding should also be hospitalized and should receive conventional critical care measures, along with treatment for ITP: appropriate regimens include high-dose parenteral glucocorticoid therapy, IVIg, and platelet transfusions.

Splenectomy is clearly appropriate or inappropriate in specific clinical situations (see text). It should not be performed as initial therapy in patients who have no bleeding, minor purpura, or even mucous membrane bleeding. In a patient who has had bleeding symptoms (eg, epistaxis, menorrhagia), splenectomy is often appropriate if platelet counts remain below 30,000 after 4 to 6 weeks of medical treatment. If an elective splenectomy is planned, appropriate preoperative therapy includes prophylactic IVIg or oral glucocorticoid therapy for patients with platelet counts <20,000. Inappropriate preoperative prophylaxis includes IVIg, oral or parenteral glucocorticoid therapy, and anti-Rh(D) when platelet counts exceed 50,000, and platelet transfusions when platelet counts exceed 10,000.

When ITP symptoms persist after primary treatment (glucocorticoid) and splenectomy, further therapy is recommended in patients with platelet counts <30,000 who have active bleeding. The most commonly recommended first-choice treatment options include IVIg, glucocorticoids, accessory splenectomy, and no additional treatment, but other agents may also be appropriate (see text). Women with ITP who are of childbearing age and have counts <10,000 after splenectomy and other treatments should be discouraged from becoming pregnant.

## Pregnant Women

### *Diagnosis*

The diagnosis of ITP during pregnancy generally does not require special laboratory testing (see Table 7). The patient's blood pressure should be measured to rule out preeclampsia as an alternative diagnosis; liver function testing is also appropriate. Patients with risk factors for HIV infection should be tested for HIV antibody.

### *Treatment*

Recommendations for pregnant women are different from other adults in some situations. Pregnant women with ITP and platelet counts >50,000 do not routinely require treatment and should not receive glucocorticoids or IVIg as routine initial therapy. Women with counts of 30,000 to 50,000 in the first- or second trimester also should not receive routine initial treatment. Treatment is required for women with platelet counts <10,000, and for those with platelet counts of 10,000 to 30,000 who are in their second or third trimester or are bleeding. IVIg is appropriate initial treatment for women with platelet counts <10,000 in the third trimester, and for those with counts of 10,000 to 30,000 who are bleeding. In pregnant women who have failed glucocorticoid and IVIg therapy, splenectomy is appropriate in the second trimester in women with platelet counts <10,000 who are bleeding. Splenectomy should not be performed in asymptomatic pregnant women with platelet counts >10,000.

As labor and delivery approach, women with ITP do not require testing for maternal platelet antibodies. Percutaneous umbilical vein blood sampling (PUBS) or fetal scalp vein sampling to measure the fetal platelet count and predict the risk of neonatal bleeding are not necessarily required. PUBS and fetal scalp vein sampling are unnecessary in pregnant

women without known ITP even with platelet counts as low as 40,000 at term. Women with ITP should be delivered by cesarean section in selected circumstances (see text). In general, assuming the fetal platelet count (and the platelet count of previous babies) is unknown, cesarean section is not indicated when the maternal platelet count is  $>50,000$ . If the fetal platelet count is known, cesarean section is appropriate if the fetal count is  $<20,000$ . A maternal platelet count of  $>50,000$  is considered sufficient to prevent complications from excessive maternal bleeding at vaginal delivery or cesarean section. Prophylactic platelet transfusions before delivery are appropriate in women with counts  $<10,000$  who (1) have a planned cesarean section or (2) have epistaxis or other mucous membrane bleeding and are expected to deliver vaginally, but are unnecessary in women with platelet counts  $>30,000$  and no bleeding symptoms.

### Newborns (of Mothers With ITP)

#### Diagnosis

The neonatal platelet count should generally be measured for 3 to 4 days after birth. Brain imaging (eg, ultrasound) should be performed if the platelet count at birth is  $<20,000$ ; brain imaging is also appropriate if the count is 20,000 to 50,000, even in the absence of neurologic abnormalities.

#### Treatment

In newborns without evidence of intracranial hemorrhage (ICH), treatment with IVIg is appropriate if the infant's platelet count is  $<20,000$ . Newborns with platelet counts of 20,000 to 50,000 do not necessarily require IVIg treatment. Newborns with counts  $>50,000$  should not be treated with IVIg or glucocorticoids. Newborns with imaging evidence of ICH should be treated with combined glucocorticoid and IVIg therapy if the platelet count is  $<20,000$ ; they should not be treated with glucocorticoids alone. Women with ITP should not be discouraged from breast feeding.

## METHODOLOGY FOR GUIDELINE DEVELOPMENT

### Topic Selection and Objectives

The ASH selected ITP because of the frequency with which it is encountered by hematologists and because of uncertainty regarding the relative effectiveness and safety of current diagnostic tests and treatments. Although there are no reliable epidemiologic data on the incidence of ITP, estimates are that 10 to 125 per 1,000,000 persons (children and adults) develop ITP each year.<sup>8</sup> The goal of the panel was to issue explicitly developed recommendations, based as much as possible on published, scientific evidence, regarding the diagnosis and treatment of patients with known or suspected ITP.

### Panel Composition

The 15-member panel included 13 hematologists selected to represent the ASH membership. The hematologists included both university-affiliated physicians with research interests in ITP and private practitioners. Panel members represented both pediatric and adult medicine perspectives. The

panel also included two members with expertise in clinical epidemiology and practice guideline methodology.

### Definition of Target Condition

The panel defined ITP as isolated thrombocytopenia with no clinically apparent associated conditions or other causes of thrombocytopenia (eg, HIV infection, systemic lupus erythematosus, lymphoproliferative disorders, myelodysplasia, agammaglobulinemia or hypogammaglobulinemia, drug-induced thrombocytopenia, alloimmune thrombocytopenia, congenital/hereditary nonimmune thrombocytopenia). No specific criteria establish the diagnosis of ITP; the diagnosis relies on the exclusion of other causes of thrombocytopenia. For purposes of this review, the panel excluded from consideration patients with clinically apparent coexisting conditions that can cause immune thrombocytopenia (eg, systemic lupus erythematosus). Patients with isolated abnormalities on serologic tests (eg, antinuclear or antiphospholipid antibodies) but without a clinically evident disorder such as systemic lupus erythematosus were not excluded because positive serologic tests are frequently encountered in patients with typical ITP.<sup>9,10</sup> However, the panel recognized that patients with thrombocytopenia and an associated autoimmune disease may have an illness comparable to ITP.

### Literature Search

A computerized search of the MEDLINE database, performed in April 1994, sought English-language articles published between 1966 and 1994. Search terms (Medical Subject Headings) included: "THROMBOCYTOPENIA," "PLATELET COUNT," "AUTOIMMUNE THROMBOCYTOPENIC PURPURA," "COMPLETE BLOOD COUNT," "BONE MARROW EXAMINATION," "RETICULOCYTE COUNT," "ANTINUCLEAR ANTIBODY TEST," "IGG," "DIAGNOSIS (SH)," and "THERAPY (SH)." The database was also searched on the text word "ITP." The computerized search retrieved 581 articles. This initial reference list underwent substantial expansion after being supplemented with relevant articles from the files of panel members, publications from 1989 through 1995 retrieved with alternate search software ("Reference Update"), and cross-checking against the bibliographies of retrieved articles to identify additional publications (especially those published before 1966). Case reports, case series of less than five patients, review articles, and letters-to-the-editor without primary data were excluded from review. Statements in this report about the number of studies that have examined the efficacy of specific treatments and statements that "no published evidence is available" do not include case reports and other categories of inadmissible evidence.

### Literature Review and Assessment of Evidence

Each article was evaluated independently by two panel members (J.N.G., G.E.R.) to assess scientific validity and verify results. Scientific validity was assessed using published guidelines.<sup>11-15</sup> Literature on the clinical course of ITP was evaluated for the presence of an inception cohort of

**Table 1. Levels of Evidence for Studies Evaluating Effectiveness of Treatment**

| Level of Evidence | Study Design  |
|-------------------|---|
| I Strongest       | Randomized trials with low false-positive and false-negative errors.  |
| II                | Randomized trials with high false-positive and false-negative errors. |
| III               | Nonrandomized studies with concurrent control group.                  |
| IV                | Nonrandomized studies with historical control group.                  |
| V Weakest         | Case series without a control group.                                  |

Data from refs 11, 12, and 14.

consecutive patients, an explicit referral pattern, complete follow-up, and use of objective outcome criteria. The term "inception cohort" refers to a group of patients identified at an early and uniform point in the course of their disease so that patients who die or completely recover are included with patients in whom the disease persists. Most of the ITP literature reviewed in this report pertains to therapy. The strength of the evidence for individual therapeutic approaches was assessed using the "level of evidence" criteria outlined in Table 1.<sup>13,14</sup> Evidence tables in the Results section only present data from level I and level II studies.

### Assessment of Opinion

Most of the literature on the treatment of ITP consists of case series without a control group (level V). For those therapies for which only level V evidence is available, or for which no evidence is available, and for issues on diagnosis that have not been addressed by clinical studies, the opinion of the panel was assessed. Survey instruments were used to assess quantitatively the opinion and strength of consensus of the panel, and these data provide the basis for statements about opinion in the text and tables. The survey instruments were designed at panel meetings in which members were asked to identify the key diagnostic and treatment practices for which opinion would be assessed. The appropriateness of these practices was intentionally not discussed at the meeting to avoid influencing the responses by the opinions of more assertive panel members. A 41-page questionnaire addressing these practices was mailed to panel members in 1994 to be completed independently, without discussion with one another. The questionnaire, which included separate pediatric and adult sections, asked respondents to measure the necessity and appropriateness of diagnosis or treatment in over 1,300 clinical scenarios. In these surveys, "Necessary" was defined as a test or treatment that should be performed; "Appropriate" was defined as a test or treatment that may or may not be necessary, but performing it is not wrong; "Unnecessary" was defined as a test or treatment that need not be performed, but is not necessarily inappropriate; "Inappropriate" was defined as a test or treatment that should not be performed. Questions relating to adult patients were completed by 11 panel members, and questions relating to pediatric patients were completed by six respondents. A second, 25-page questionnaire was circulated in early 1995 to

examine opinions regarding pregnancy and newborn care and to clarify opinions regarding issues identified in the 1994 survey. The 1995 survey examined over 600 issues and was completed by 13 panel members.

Using a modified RAND scoring system,<sup>16,17</sup> the questionnaire asked panelists to quantify the strength of their opinion on a 1 to 9 scale; "9" represented strong agreement with the appropriateness/necessity of the practice and "1" represented strong disagreement. The mean response for each question provided an overall assessment of the panel's opinion regarding the necessity and appropriateness of specific practices. Panel votes are presented in this report only when there was agreement among the panel regarding the necessity or appropriateness of an intervention (mean panel score of 7.0 to 9.0) or agreement that the intervention is unnecessary or inappropriate (mean panel score of 1.0 to 3.0).

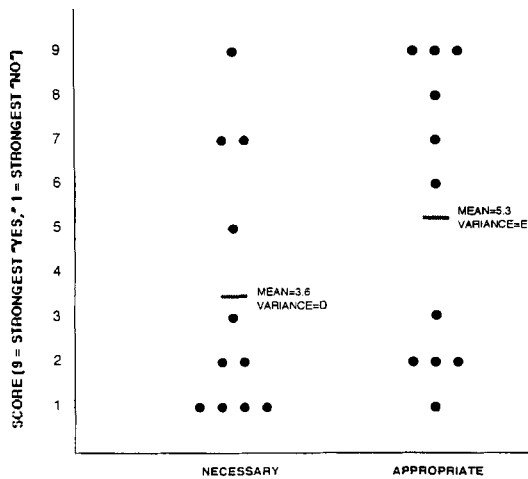
The strength of the panel's inter-observer agreement about the appropriateness/necessity of tests or treatments was graded using the standard deviations (SDs) for responses to each question (Table 2). Panel responses were classified as category A ("Complete or Almost Complete Unanimity"), for example, if the variance in panel member responses to a specific question was more than two SDs below the mean variance. Thus, a score of "1.5, A" signified strong agreement among the panel that the intervention is unne-

**Table 2. Panel Opinion Rating System**

| Score                                       | Definition   |
|---|--|
| <b>Appropriateness of Necessity Scores*</b> |  |
| 1.0-3.0                                     | "Inappropriate" or "unnecessary" (depending on question).  |
| 3.01-6.99                                   | Uncertain appropriateness or necessity.  |
| 7.0-9.0                                     | "Appropriate" or "necessary" (depending on question).  |
| <b>Consensus Codest</b>                     |  |
| A   | "Complete or almost complete unanimity" (panel variance more than 2 SD below the mean variance). |
| B   | "Strong agreement" (panel variance 1 to 2 SD below the mean variance).                           |
| C   | "Moderate agreement" (panel variance less than 1 SD below the mean variance).                    |
| D   | "Moderate disagreement" (panel variance less than 1 SD above the mean variance).                 |
| E   | "Strong disagreement" (panel variance greater than 1 SD above the mean variance).                |

\* Represents mean panel score for response to questions asking for ranking of appropriateness/necessity on a scale of "1" to "9," with "1" representing most "inappropriate/unnecessary" and "9" representing most "appropriate/necessary." Separate scores were obtained for appropriateness and necessity by asking separate, individually worded questions. "Necessary" = test should be performed, "Appropriate" = test may or may not be necessary, but performing it is not wrong, "Unnecessary" = test need not be performed (but is not necessarily inappropriate), "In appropriate" = test should not be performed.

† Strength of agreement among the panel members about appropriateness/necessity, ie, the variance of responses around the mean panel score.



**Fig 1.** Panel responses 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 assumed 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 etiologies. Data points (●) represent the responses of individual panel members (N = 11) on a scale of 1-9, with 1 reflecting complete disagreement and 9 reflecting complete agreement. Horizontal lines (—) represent the mean panel score. Letter codes, which describe the variance, are defined in Table 4.

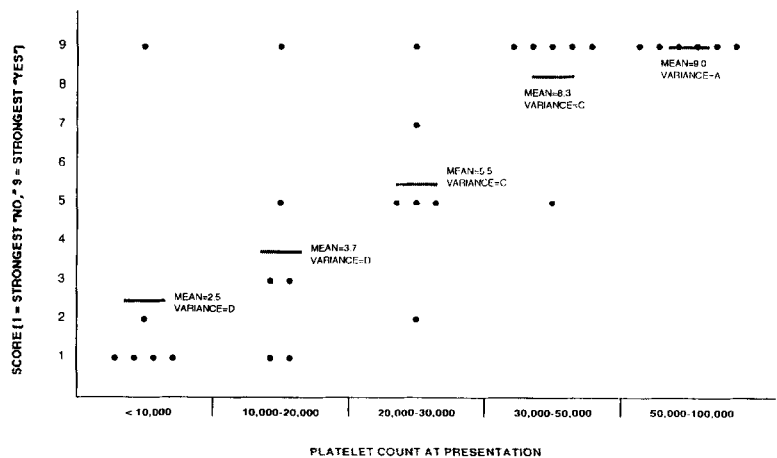
sary/inappropriate, with most panelists assigning scores close to 1.0. A score of 7.5, D meant that, on average, the panel considered the intervention necessary/appropriate, but that wide variation in the responses of individual panel members was noted. These scores were arbitrarily considered as representing a consensus if the mean score was 3 or less or 7 or more.

Figures 1 and 2 display data on two specific questions to illustrate the use of this method to assess opinion and the range of opinions among panel members. For example, when asked to rate the appropriateness of performing a bone marrow aspirate/biopsy in all adult patients at presentation to

establish the diagnosis of ITP, the mean panel score (on a scale of 1 to 9) was 5.3. However, the range of opinion on the panel was wide (category "E"), with one cluster of panel members labeling the practice as inappropriate and another considering it appropriate (Fig 1). Figure 1 also illustrates that scores for necessity are lower than for appropriateness. The results also illustrate trends in opinion across different clinical scenarios. For example, Fig 2 presents mean panel scores in response to a question about the appropriateness of not initiating specific treatment for ITP in children with various platelet counts. A trend of opinion is clear but agreement among the panel is not strong except at the highest platelet counts. At the lowest and higher platelet counts there is a consensus for inappropriateness (mean score <3) and appropriateness (mean score >7), respectively, for withholding initial treatment. Although these views reflect opinion more than science, the panel believes that a structured approach to defining and expressing its opinion is more precise and less subject to bias than arriving at recommendations through open discussion, in which decisions are more likely to be influenced by the opinions of more assertive panel members.

## Recommendations

In almost all aspects of ITP level I evidence is lacking, and there are few level II, III, or IV studies to allow firm, evidence-based recommendations. In general, only level V evidence, or no studies, were available for making recommendations. Therefore, the panel issued recommendations based on opinion, indicating the mean panel score and variance to permit readers to judge the strength of the consensus. Although the sample sizes of voting members were small and some confidence intervals for panel votes were wide, the results can help readers assess the strength of opinion behind specific recommendations. The basis of recommendations is explicitly labeled in the text so that reader can appreciate which recommendations are based on evidence and which are based on opinion. The inherent weakness of opinion-based recommendations is acknowledged; these recommendations should not form the basis for definitive decisions on health care policy. Indications for which the panel could



**Fig 2.** Panel responses 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 and 9 reflecting complete agreement. Horizontal lines (—) represent the mean panel score. Letter codes, which describe the variance, are defined in Table 4.

not reach consensus (scores of 3.1 to 6.9) are generally not listed in the text; thus, recommendations frequently address only the "extremes" of inappropriate and appropriate practice and do not comment on intermediate clinical scenarios that may be common. The fact that the panel did not reach consensus regarding these indications does not necessarily signal the appropriateness or inappropriateness of clinicians' decisions to administer tests or treatments in these settings.

This practice guideline describes a range of approaches to the diagnosis and management of ITP. Its recommendations are not intended to serve as inflexible rules, and they are not inclusive of all proper methods of care or other methods of care that may achieve similar results. Adherence to the guideline will not ensure a successful outcome in every case. The ultimate judgment regarding the care of a particular patient should be made by the physician in light of the clinical data and circumstances presented by the patient and the diagnostic and treatment options available.

### Peer Review

Before the final panel meeting, the report was independently reviewed by eight private practice and university-based hematologists with expertise in adult and/or pediatric ITP (Drs Neil Abramson, Jacksonville, FL; Barbara Alving, Washington, DC; Diana Beardsley, New Haven, CT; Jack Levin, San Francisco, CA; Joan Parkhurst, Oklahoma City, OK; Graham Pineo, Calgary, Alberta, Canada; Gary Ratkin, St Louis, MO; Samuel Silver, Ann Arbor, MI).

## RESULTS

### ITP In Children

#### *Clinical Course*

A critical issue in caring for children with ITP is determining which patients require treatment, either at the time of diagnosis or in the management of chronic disease. To make informed management decisions, prognostic information is needed to predict (1) how platelet counts will respond, with or without therapy, (2) likely health outcomes without treatment, and (3) whether early response to intervention reduces the incidence of adverse outcomes.

*Evidence.* There have been no large prospective studies which assembled an inception cohort of children with ITP and followed the clinical course of untreated patients to document the incidence of clinically important bleeding and mortality. Data on the clinical course of untreated ITP in children come from two types of evidence: (1) case series in which selected children with ITP were not treated and were followed to document the incidence of spontaneous remission, clinically important bleeding, and mortality, and (2) data from untreated control groups in relatively small, brief randomized clinical trials evaluating the effectiveness of alternative treatments. The case-series data are summarized in Table 3.<sup>18-29</sup>

The best data on untreated disease come from two series in which about 75% of patients were not treated initially.<sup>22,25</sup> Most patients had platelet counts <50,000 at presentation, and in one of the reports<sup>22</sup> most had platelet counts <20,000. Of the 221 untreated children, 2 (0.9%) had fatal bleeding

associated with the acute presentation, and 191 (87%) had a complete remission from ITP. The platelet count normalized in 2 to 8 weeks, with one half to two thirds of the patients recovering within 4 weeks.<sup>22,25</sup>

There are limitations to the inferences that can be drawn from these data. First, 25% of the inception cohort in each series were selected for treatment. If clinicians treated patients with the most serious clinical presentations, then the clinical course in the remaining patients may underestimate the frequency of important bleeding and mortality, and may overestimate the rate of spontaneous remission. However, even if it is assumed that patients selected for treatment would not have had a spontaneous remission, then the "least frequency" estimate of the probability of complete spontaneous remission is 191 of 298 (64%). Second, 7% to 14% of patients were lost to follow-up, some of whom may have suffered a relapse of ITP, with bleeding complications or death. In the remaining series in Table 3, the children selected to be followed without treatment represented only 10% to 56% of the inception cohort; patients with more severe clinical presentations were generally treated. Thus, the untreated patients in Table 3 may represent a select population with mild to moderate symptoms who may have a more favorable prognosis than the average child with ITP.

Further information about clinical course in children presenting with severe thrombocytopenia is provided by the control groups of prospective randomized studies.<sup>30-32</sup> In one illustrative study<sup>32</sup> 53 patients, each of whom had platelet counts <20,000 and purpuric symptoms, were randomly assigned to treatment (IVIg or oral prednisone) or no treatment. Among the 16 children who received no treatment, platelet counts increased to >20,000 in a median of 4 days (range, 1 to 132 days) and to >50,000 in a median of 16 days (range, 2 to 132 days). Chronic ITP (defined as a platelet count <150,000 for more than 6 months) occurred in 3 of the 16 patients (19%, 95% confidence interval, 4% to 46%).

Only limited observational data are available regarding the complications of intracranial hemorrhage. In a review of 14 children with intracranial hemorrhage, Woerner et al<sup>33</sup> reported that 4 died and 2 others may have had neurologic sequelae. Of the 30 children with intracranial hemorrhage described in this report<sup>33</sup> and the references in Table 3, 12 (40%) occurred within the first 12 days after diagnosis, including 2 patients with a history of head trauma. The intracranial hemorrhages in the other 18 patients occurred between 1 month and 5 years after diagnosis, typically after glucocorticoids and splenectomy failed to induce a remission. At least 24 of these 30 patients were reported before 1981, when IVIg therapy was initially described.<sup>34</sup>

Unlike ITP in adults, persistent thrombocytopenia is uncommon in children. In the 12 case series in Table 3, 10 defined chronic disease as 6 months of thrombocytopenia and 2 studies defined it as 12 months.<sup>22,24</sup> In the 12 series, ITP resolved in 1,207 (76%) of the 1,597 children who were followed for these time periods. Features of the presenting illness that were associated with an increased risk of chronic persistent thrombocytopenia included a history of purpura for more than 2 to 4 weeks before diagnosis,<sup>23-25,29</sup> female sex,<sup>21-23,28</sup> age over 10 years,<sup>23,28</sup> and a higher platelet count

Table 3. Clinical Course of ITP Children

| Author                             | Location    | Years     | Patients (no.) | Patients Responding With No Therapy* | Patients in Remission at 6 mo† | Hemorrhagic Complications‡ |           |              | Patients in Remission At Last Follow-up† | Patients With Persistent Thrombocytopenia§ |                      |                        |
|------------------------------------|-------------|-----------|----------------|--------------------------------------|--------------------------------|----------------------------|-----------|--------------|--|--|----------------------|------------------------|
|                                    |             |           |                |                                      |                                | ICH                        | Fatal ICH | Other Deaths |  | No.  | Spontaneous Recovery | Deaths From Hemorrhage |
| Komrower and Watson <sup>18</sup>  | UK          | 1948-1953 | 43             | 18/24                                | 25                             | 4                          | 3         | 3¶           | 31                                       | 9  | 2                    | 0                      |
| Choi and McClure <sup>19</sup>     | Canada      | 1950-1964 | 239            | 20/25                                | 105/161                        | 1                          | 1         | 0            | 120/128                                  | 18   | 5                    | 0                      |
| Walker and Walker <sup>20</sup>    | UK          | 1950-1980 | 177            | 51/63                                | 138                            | 1                          | 0         | 1#           | 162                                      | 15   | 5                    | 0                      |
| Ramos et al <sup>21</sup>          | US          | 1952-1977 | 150            | —                                    | 135                            | 0                          | 0         | 0            | 143                                      | 13   | 6                    | 0                      |
| Lusher and Zuelzer <sup>22</sup>   | US          | 1956-1964 | 146            | 101/109                              | 129/142**                      | 1                          | 1         | 0            | 135/142                                  | —  | —                    | —                      |
| Simons et al <sup>23</sup>         | US          | 1956-1973 | 84             | 19/20                                | 50                             | 1                          | 2         | 0            | 58                                       | —  | —                    | —                      |
| Benham and Taft <sup>14</sup>      | Australia   | 1958-1966 | 132            | 13/15                                | 97**                           | 2                          | 0         | 0            | 116                                      | 26   | 10                   | 0                      |
| Lamm and Lovric <sup>25</sup>      | Australia   | —         | 152            | 91/112                               | 116                            | 1                          | 1         | 0            | 147                                      | 29   | 23                   | 1                      |
| den Ottolander et al <sup>26</sup> | Netherlands | —         | 77             | 23/35                                | 38/75                          | 1                          | 1         | 0            | 60                                       | —  | —                    | —                      |
| Hoyle et al <sup>17</sup>          | UK          | 1962-1982 | 136            | 35/41                                | 97/132                         | 1                          | 1         | 0            | 117/132                                  | 16   | 9                    | 0                      |
| Zaki et al <sup>28</sup>           | Kuwait      | 1981-1986 | 60             | 18/23                                | 41                             | 0                          | 0         | 0            | 44                                       | 16   | 2                    | 0                      |
| Robb and Tiedeman <sup>29</sup>    | Australia   | 1968-1987 | 297            | —                                    | 236/289                        | 3                          | 3         | 0            | 163                                      | 37   | 4                    | 2                      |
| Summary                            |             |           | 1,693          | 389/467 (83%)                        | 1,207/1,597 (76%)              | 16 (0.9%)                  | 13 (0.7%) | 4 (0.2%)     | 1,396/1,574 (89%)                        | 179  | 66 (37%)             | 3 (2%)                 |

Abbreviation: ICH, intracranial hemorrhage.

In these series, the upper age limit ranged from 12 to 16 years old.

\* The numerator is the number of patients with a complete response, typically defined as a normal platelet count without relapse; the denominator is the total number of patients managed without specific initial therapy. The response rate for untreated patients is greater than the overall response at 6 mo because of selection of patients with good prognostic features for no treatment.

† A different denominator from the original number of patients indicates that some patients were not followed long enough to be included in the estimate.

‡ Note that 6 of the total 17 deaths occurred in the first (and smallest) study of patients before 1953 Komrower and Watson.<sup>18</sup> Omitting this study, the frequency of fatal intracranial hemorrhage is 9/1,650 (0.5%) and the overall mortality is 10/1,650 (0.6%). Eight of the fatal ICH occurred acutely, within 5 wk of diagnosis; the other 5 occurred between 1 to 2 years after diagnosis. All 4 of the other hemorrhagic deaths occurred acutely within 5 wk.

§ Persistent thrombocytopenia was defined as >6 mo after diagnosis, except for Lusher and Zuelzer<sup>22</sup> and Benham and Taft,<sup>14</sup> who defined persistent thrombocytopenia as >12 mo after diagnosis.

|| Includes 7 patients who had splenectomy <6 mo after diagnosis. No patients were treated with glucocorticoids in this study.

¶ Described only as "uncontrollable bleeding."

# Death due to hemorrhage (not ICH) and presumed sepsis 2 wk after diagnosis.

\*\* The distinction of acute v chronic ITP is determined at 12 mo rather than 6 mo in these two reports, and these are the data for remission at 12 mo.

at presentation.<sup>22</sup> The fate of children with chronic ITP is uncertain, although about one third appear to have spontaneous remissions several months to many years after diagnosis.<sup>35,36</sup>

### Diagnosis

Few clinical studies have evaluated the sensitivity and specificity of the diagnostic tests used for children with suspected ITP, because in the absence of a "gold-standard" test for ITP the diagnosis is based only on the presence of thrombocytopenia with no other apparent cause. Other etiologies are uncommon: in a study of 127 consecutive children with suspected ITP who had bone marrow aspirations, other causes of thrombocytopenia were identified in only 5 (4%) children, all of whom had atypical presenting features.<sup>37</sup> Therefore, in the absence of additional scientific evidence on the accuracy or effectiveness of diagnostic tests for ITP, the panel's recommendations regarding the history, physical examination, laboratory tests, and special procedures are based entirely on opinion.

**Directed history and physical examination.** By definition, the diagnosis of ITP cannot be made without a compatible history and physical examination that excludes other causes of thrombocytopenia. The most likely alternate causes vary with the age of the child. For example, many case series exclude infants less than 4 to 6 months old in part because neonatal alloimmune or autoimmune thrombocytopenia cannot be ruled out at this age. The most important elements of the history and physical examination identified by the panel

are presented in Table 4. The maternal and birth history are especially relevant when evaluating infants. The presence of congenital anomalies in the patient or family members may be a clue for congenital thrombocytopenia, an important consideration in children with persistent thrombocytopenia.<sup>38</sup>

Although the essential elements of the physical examination of children and adults with ITP are generally the same, one difference may be the presence of splenomegaly, which may be slightly more common in children, especially in infants. Data from six case series suggest that the spleen may be palpable in 12% of children with ITP.<sup>18,19,22,24,25,27</sup> However, this may reflect the greater incidence of palpable spleens in children in general, which is estimated to be about 10%.<sup>39</sup>

**Complete blood count with examination of the peripheral blood smear.** A complete blood count and an examination of the peripheral blood smear are essential in ITP. The principal features of the examination of the blood smear that were identified by the panel are the same for children and adults (Table 5). Although most patients with ITP present with platelet-related bleeding, the condition may be first detected by the incidental discovery of thrombocytopenia on routine blood counts. Because ITP is defined by a low platelet count without another apparent cause, the clinician must know the normal values for the laboratory. Aside from thrombocytopenia, the blood counts of patients with ITP should be normal or otherwise readily explained by a coincident disorder (eg, thalassemia minor). The presence of platelet clumps suggests pseudothrombocytopenia (see Adult section, below). Ane-

**Table 4. Principal Elements of the History and Physical Examination in a Child With Suspected ITP**

| <b>History</b>  |  |
|---|--|
| Bleeding symptoms   |  |
| Type of bleeding  |  |
| Severity of bleeding  |  |
| Duration of bleeding  |  |
| Hemostasis with prior invasive procedures   |  |
| Systemic symptoms, especially of recent (within 6 wk) viral illness or exposure to viruses such as varicella, or recurrent infections suggesting immunodeficiency; symptoms of an autoimmune disorder |  |
| Recent live virus immunization  |  |
| Medications, including heparin, quinidine/quinine, and sulfonamides, which may cause thrombocytopenia, and aspirin, which may exacerbate bleeding   |  |
| Risk factors for HIV infection, including maternal HIV status   |  |
| Family history of thrombocytopenia or hematologic disorder  |  |
| In an infant <6 mo old, include perinatal and maternal history  |  |
| Comorbid conditions, which may increase the risk of bleeding  |  |
| Lifestyle, including vigorous and potentially traumatic activities  |  |
| <b>Physical examination</b>   |  |
| Bleeding signs  |  |
| Type of bleeding (including retinal hemorrhages)  |  |
| Severity of bleeding  |  |
| Liver, spleen, and lymph nodes  |  |
| Evidence for infection  |  |
| Presence of dysmorphic features suggestive of congenital disorder, including skeletal anomalies, auditory acuity  |  |
| <b>Specific Congenital Syndromes to Exclude</b>   |  |
| Fanconi syndrome  |  |
| Thrombocytopenia-absent radius  |  |
| Wiskott-Aldrich syndrome  |  |
| Alport syndrome (and its variants)  |  |
| Bernard-Soulier syndrome  |  |
| May-Hegglin anomaly   |  |
| Gray platelet syndrome  |  |

mia, if present, may be caused by bleeding or iron deficiency resulting from chronic thrombocytopenia, but this is uncommon in children. White blood cell morphology should be normal, although some children with ITP may have atypical lymphocytes or eosinophilia.<sup>22,25,40</sup>

**Other laboratory data.** Recommendations regarding other laboratory tests were derived from opinion by a questionnaire completed by six panel members (see text above). The recommendations assume that the history, physical examination, and initial blood counts and smear are compatible with the diagnosis of ITP and do not include atypical findings that are uncommon in ITP or suggest other disease etiologies. For example, a direct antiglobulin test, which the panel did not recommend for patients with a typical presentation of ITP, may be appropriate if the peripheral smear shows red blood cell polychromatophilia with poikilocytosis and spherocytes. Indications for which the panel did not reach consensus (score of 3.1-6.9) are not listed in the text but are summarized in Table 6.

The panel reached consensus that six diagnostic tests were unnecessary in the routine evaluation of children presenting with suspected ITP, and that an additional 12 tests were both

unnecessary and inappropriate (Table 7). Recommendations that diagnostic tests are "inappropriate" refer to performing them on all patients at presentation. Testing for HIV antibody was considered necessary (8.7, B), and appropriate (9.0, A), in patients with risk factors for HIV infection. An abdominal CT scan or ultrasound examination was considered appropriate (8.2, B) 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 (> 6 to 12 months) (7.0, D) and in patients unresponsive to IVIg (8.2, B). However, the panel concluded that it is neither necessary (1.3, B) nor appropriate (2.7, C) to perform a bone marrow aspiration to establish the diagnosis of ITP before initiating IVIg therapy. The test is also unnecessary (3.0, C) to establish the diagnosis in patients who require more than an initial course of IVIg or to allay parental anxiety.

The panel also reached consensus regarding testing in the following specific clinical situations:

(1) *To establish the diagnosis before splenectomy:* Tests that the panel considered unnecessary for this purpose included platelet antigen-specific antibody assay (2.0, C), abdominal CT scan or ultrasound (2.0, C), and serum Ig level (3.0, D). Tests that the panel considered unnecessary and inappropriate included (scores are for appropriateness): serum complement level (1.8, C), chest x-ray (2.5, C), thyroid function studies (2.5, D), platelet survival study (2.5, D), and platelet-associated IgG assay (2.7, C).

(2) *To establish the diagnosis in patients who have failed to respond to glucocorticoid therapy, IVIg, and splenectomy:* Tests that the panel considered unnecessary for this purpose included platelet-associated IgG assay (1.2, A), platelet antigen-specific antibody assay (2.0, C), abdominal CT scan or ultrasound (2.8, C), platelet survival study (2.8, D), lupus anticoagulant or antiphospholipid antibody (3.0, C), and thyroid function testing (3.0, D). Tests that the panel considered unnecessary and inappropriate included chest x-ray (2.2, C) and serum complement level (2.5, D) (scores are for appropriateness).

#### *Treatment*

Essentially all evidence regarding the efficacy of treatment of ITP is indirect, inferred by measuring a surrogate out-

**Table 5. The Peripheral Blood Smear in ITP**

| <b>Consistent with the diagnosis of ITP</b>  |  |
|--|--|
| 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 morphology.  |  |
| <b>Not consistent with the diagnosis of ITP</b>  |  |
| 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).                                  |  |



**Table 6. Indications for Which the Necessity/Appropriateness of Routine Testing Is Uncertain (Based on Opinion of Panel)**

| Indications  | Tests of Uncertain Appropriateness (mean panel scores 3.01-6.99)   |   |
|--|--|---|
|  | Children   | Adults  |
| To establish the diagnosis in all patients at presentation   | ANA (a), direct antiglobulin (a), HIV (a), bone marrow (a), platelet antigen-specific antibody, mean platelet volume, reticulocyte count   | ANA, direct antiglobulin, lupus anticoagulant/APLA (a), chemistry profile, coagulation studies, chest x-ray (a), HIV, bone marrow, mean platelet volume, reticulocyte count (a), thyroid function, urinalysis (a) |
| To establish the diagnosis before splenectomy  | ANA, direct antiglobulin, lupus anticoagulant/APLA, abdominal CT/ultrasound (a), serum immunoglobulins (a), platelet antigen-specific antibody   | ANA, direct antiglobulin, lupus anticoagulant/APLA, serum complement, abdominal CT/ultrasound, bone marrow (n), chest x-ray, platelet antigen-specific antibody, platelet survival, thyroid function              |
| To establish the diagnosis in patients who fail to respond to primary treatment (eg, glucocorticoid) and splenectomy | ANA, direct antiglobulin, lupus anticoagulant/APLA (a), abdominal CT/ultrasound (a), serum immunoglobulins, platelet-associated IgG, platelet antigen-specific antibody, platelet survival, thyroid function | ANA, direct antiglobulin, lupus anticoagulant/APLA, serum complement, abdominal CT/ultrasound, chest x-ray, platelet-associated IgG, platelet antigen-specific antibody, platelet survival, thyroid function      |

*Other tests of uncertain appropriateness:* ANA, to establish the diagnosis in pregnant and nonpregnant women; lupus anticoagulant/APLA, to establish the diagnosis in women at presentation (a) and pregnant women; abdominal CT/ultrasound, for suspected splenomegaly on physical examination in children (n) and adults; HIV, in adult patients with no risk factors for HIV infection; thyroid function, to rule out thyroid disease in all patients at presentation (a) and before elective splenectomy (n).

Tests that the panel considered unnecessary/inappropriate for routine evaluation of all patients (mean scores, 1.0-3.0) are listed in Table 7. Tests which the panel considered appropriate/unnecessary (mean scores, 7.0-9.0) are described in the text. Listed here are the specific clinical scenarios for which the panel assigned a mean panel score of 3.01-6.99, not reaching consensus on whether the test is appropriate/necessary. (a) = appropriateness uncertain, but testing is not necessary, (n) = necessity uncertain, but testing is appropriate.

come, platelet count, rather than a health outcome such as bleeding or mortality. The panel accepted the platelet count as a useful surrogate outcome, because numerous studies of thrombocytopenia show a correlation between platelet counts and clinically important bleeding.<sup>41-44</sup> The limitations of this assumption are highlighted by several factors. First, the association between platelet count and clinically important bleeding has been demonstrated principally in patients with thrombocytopenia with conditions other than ITP. Second, the platelet count may not reflect beneficial or potential harmful effects of treatment that are independent of an effect on platelets.

Even an effect on the platelet count is difficult to validate convincingly based on currently available data, because evidence of treatment efficacy consists largely of reports from uncontrolled case series (level V evidence, the weakest category, Table 1). Without an internal control group for comparison, such studies are unable to clarify whether the favorable results were due to the treatment under study or would have occurred even without treatment (or with another treatment). Although the potential adverse effects of certain treatments for ITP are known, a valid framework for the systematic comparison of benefits and harms is lacking, making it difficult to determine when a treatment results in more harm than good. Given these gaps in the evidence, treatment recommendations in this report rely largely on opinion.

### Hospitalization

*Evidence.* There have been no studies to evaluate the effectiveness of hospitalizing children with ITP.

*Recommendations.* In the absence of evidence, the opinion of the panel was that hospitalization is appropriate for a child with severe, life-threatening bleeding, regardless of the platelet count (9.0, A), and for a child with a platelet count of <20,000 and mucous membrane bleeding that may require clinical intervention (8.2, C). Hospitalization is inappropriate for a child with a platelet count of 20,000 to 30,000 who is asymptomatic (2.8, D) or for a child with a platelet count >30,000 who is either asymptomatic or has only minor purpura (1.0 to 1.5, B) (Table 8). Indications for hospitalization under intermediate conditions are less clear. Hospitalization may also be appropriate for children with platelet counts <20,000 who may be inaccessible or noncompliant (8.2, B) or whose parents request hospitalization (7.0 to 7.4, B).

### Emergency Treatment

*Evidence.* Although there are no published data on the efficacy of different treatments for the management of children with urgent, life-threatening bleeding, evidence regarding the morbidity and mortality associated with severe hemorrhage from thrombocytopenia is extensive.<sup>18,33,45</sup>

*Recommendations.* The opinion of the panel was that the serious consequences of severe, life-threatening bleeding justify the use of several regimens. Assuming that conventional critical care measures are already underway, there was strong agreement (9.0, A) among panel members that appropriate interventions include platelet transfusions, high-dose parenteral glucocorticoid (eg, 30 mg/kg methylprednisolone daily for 3 days), and IVIg, either alone or in combina-

**Table 7. Tests That Are Unnecessary/Inappropriate to Establish the Diagnosis of ITP in All Patients at Presentation (Based on Opinion of Panel)**

| Unnecessary, But May be Appropriate (Mean Panel Score for Necessity, Consensus Code) | Unnecessary and Inappropriate (Mean Panel Score for Appropriateness, Consensus Code) |
|--|--|
| <b>Children</b>  |  |
| Platelet antigen-specific antibody (1.3, B)  | Platelet survival study (1.0, A)   |
| Mean platelet volume (1.8, B)  | Chest x-ray (1.0, A)   |
| Bone marrow (2.0, B)   | Abdominal CT or ultrasound (1.0, A)  |
| HIV test (2.0, B)  | Coagulation studies (1.2, A)   |
| Antinuclear antibody (2.0, C)  | Serum complement level (1.7, C)  |
| Direct antiglobulin test (2.5, C)  | Lupus anticoagulant/APLA (2.0, C)  |
|  | Bleeding time (2.0, C)   |
|  | Platelet-associated IgG (2.2, C)   |
|  | Thyroid function tests (2.3, D)  |
|  | Serum chemistry profile* (2.7, D)  |
|  | Urinalysis (2.8, D)  |
|  | Serum immunoglobulin level (3.0, D)  |
| <b>Adults</b>  |  |
| Lupus anticoagulant/APLA (1.8, B)  | Bleeding time (1.7, C)   |
| Platelet antigen-specific antibody (1.7, C)  | Platelet survival study (2.4, C)   |
| Direct antiglobulin test (2.1, B)  | Serum complement (2.6, D)  |
| Chest x-ray (2.1, C)   | Abdominal CT/ultrasound (2.6, D)   |
| Mean platelet volume (2.4, D)  | Platelet-associated IgG assay (3.0, D)   |
| Reticulocyte count (2.6, D)  |  |
| Urinalysis (2.6, C)  |  |
| Thyroid function tests (2.9, D)  |  |
| <b>Pregnant women</b>  |  |
| Platelet antibody (1.4, B)   | None   |
| Serum fibrin D-dimer (2.4, D)  |  |
| PT/PTT (2.6, C)  |  |
| Lupus anticoagulant/APLA (2.9, D)  |  |
| Uric acid (2.9, D)   |  |

Tests of uncertain appropriateness/necessity are listed in Table 6.

\* Including LDH, BUN, creatinine, and liver function tests.

tion with glucocorticoids. See more detailed discussion of these treatments below.

#### Observation (No Specific Initial Treatment)

**Evidence.** Evidence about the outcomes of not treating ITP is derived from studies of the clinical course of untreated cases (see "Clinical Course"). Two level I studies<sup>31,32</sup> and many level V studies suggest that 30% to 70% of children recover from severe thrombocytopenia, achieving platelet

counts of 50,000 to 100,000 within 3 weeks without specific treatment. Level I evidence indicates that platelet count recovery is more rapid with either IVIg or glucocorticoid therapy than with no specific treatment<sup>30-32,46-48</sup> (see Table 9), but it remains uncertain if this effect on platelet count influences morbidity or mortality. Moreover, the data come from children with severe thrombocytopenia at presentation; no comparable studies have been performed on children with less severe thrombocytopenia. Although it may seem intuitive that less severe thrombocytopenia would provide an even weaker indication for intervention, there is some evidence that children with higher platelet counts may have a greater risk of chronic, persistent thrombocytopenia.<sup>22,49</sup> However, there is no evidence that the risk of developing chronic ITP is lowered by treatment.

**Recommendations.** Current evidence is inadequate to recommend which groups of children with ITP can be safely managed without therapy. The opinion of the panel was that it was appropriate to withhold specific treatment for asymptomatic children with platelet counts of 20,000 to 30,000 (7.0, C), and more strongly for children with platelet counts >30,000 who are asymptomatic or who have only minor purpura (8.3 to 9.0, A-C) (Table 8, Fig 2). The panel acknowledges that some pediatric hematologists who were not represented on the panel do not recommend specific treatment for children presenting with severe thrombocytopenia (platelet counts <20,000); these hematologists believe that careful observation is sufficient and preferable. The panel believed that withholding specific treatment was inappropriate for children with a platelet count <50,000 who present with significant mucous membrane bleeding (1.0, A for platelet count <30,000; 2.0, B for platelet count of 30,000 to 50,000). Not treating children with severe life-threatening bleeding was considered inappropriate (1.0, A) at any platelet count. Although the panel considered it appropriate (7.7 to 8.7, B-C) to withhold treatment at the parents' request for children with platelet counts >30,000, it was considered inappropriate (2.8, D) to do so if the platelet count was <10,000.

#### Glucocorticoid Therapy

**Evidence.** Level I and II studies of the efficacy of glucocorticoids are summarized in Table 9. Randomized clinical trials (level I and II) have shown that glucocorticoids increase the platelet count more quickly than when no specific treatment is administered. For example, the median time to achieve a platelet count of >50,000 was 4 days with prednisone treatment (4 mg/kg/d for 7 days, then tapered) versus 16 days in untreated children.<sup>32</sup> The efficacy of glucocorticoids has only been demonstrated in terms of platelet recovery time and not in terms of morbidity or mortality. All relevant data come from children with acute ITP of recent onset. There have been no randomized controlled studies of glucocorticoid treatment in children with chronic thrombocytopenia.

Three general categories of regimens for glucocorticoids have been evaluated: (1) 1 to 2 mg/kg/d or 60 mg/m<sup>2</sup>/d of oral prednisone for approximately 21 days<sup>27,30,31,46,47,50-52</sup> (level I, II, and V evidence); (2) 4 mg/kg/d of oral prednisone for 7

days then tapered<sup>32,48</sup> (level I evidence); and (3) 10 to 30 mg/kg/d of oral or IV methylprednisolone for several days<sup>52-57</sup> (level II, III, V evidence). Because ITP in children is typically self-limited, the duration of treatment was limited in many studies to 21 days. Initial reports used 2 mg/kg/d, comparable to the adult dose, but more recent studies have used 4 mg/kg/d, which is well-tolerated because the duration of treatment is short. In recent studies,<sup>32,48</sup> the dose of 4 mg/kg/d was continued for only 7 days and the dose was then tapered and discontinued on day 21. Several studies using very high doses (10 to 50 mg/kg/d of methylprednisolone for 3 to 7 days) suggest that platelet count recovery is as rapid as that seen with IVIg,<sup>52,55-57</sup> but similar findings have also been reported with a dose of 4 mg/kg/d for the first 7 days.<sup>32,48</sup>

The potential adverse effects of glucocorticoid therapy include all of the signs and symptoms of hypercortisolism in Cushing syndrome, including facial swelling, weight gain, hyperglycemia, hypertension, cataracts, and behavioral abnormalities.<sup>58</sup> The toxicities of glucocorticoids are dose and duration dependent. Glucocorticoid therapy may increase the risk of growth retardation in children.<sup>59</sup>

**Recommendations.** There is level I evidence that children with acute ITP and severe thrombocytopenia experience more rapid recovery of platelets if given glucocorticoids, but it is unknown if this influences morbidity or mortality. There is also inadequate evidence of the efficacy of glucocorticoids in other patient categories (less severe thrombocytopenia, chronic ITP) to develop definitive recommendations based on the data. The opinion of the panel was that in patients with platelet counts <50,000 it is appropriate (7.0 to 8.4, B-D) to treat severe, life-threatening bleeding initially with high-dose oral (eg, prednisone, 4 to 8 mg/kg/d) or parenteral (eg, methylprednisolone, 30 mg/kg/d) glucocorticoid. High doses of oral glucocorticoid are also appropriate as initial therapy for children with mucous membrane bleeding and platelet counts <20,000 (7.6, C) and for those with minor purpura and platelet counts <10,000 (7.0, D). The panel considered glucocorticoids inappropriate (1.0 to 2.2, A-C) as initial therapy for children with platelet counts >30,000 and no symptoms or only minor purpura (Table 8). Treatment for the sole purpose of determining responsiveness or confirming the diagnosis was considered inappropriate for high-dose parenteral glucocorticoids in patients with platelet counts >10,000, for conventional-dose oral glucocorticoids in patients with platelet counts >20,000, and for high-dose oral glucocorticoids in patients with platelet counts >30,000 (1.0 to 2.8, A-D). When oral glucocorticoids are used, level I studies suggest that the regimens of 1.5 or 2 mg/kg/d for 14 to 21 days,<sup>30,46,47</sup> 60 mg/m<sup>2</sup>/d for 21 days,<sup>31</sup> or 4 mg/kg/d for 7 days, followed by a tapering dose until day 21,<sup>32,48</sup> are more effective than no treatment. These regimens have not been compared with each other, and some may be more effective than others in rapidly reaching a platelet count that may reduce the risk of serious hemorrhage.

### IVIg

**Evidence.** Clinical trials of IVIg therapy for ITP are summarized in Table 9. One level I study has shown that

initial IVIg treatment of children with acute ITP increases the platelet count more rapidly than no specific treatment and than glucocorticoid therapy.<sup>32</sup> Five level V studies<sup>34,60-63</sup> suggest that IVIg will increase the platelet count substantially in a majority of patients, although some do not respond. Less than 10% of patients with chronic ITP have sustained, normal platelet counts without further treatment; in others thrombocytopenia recurs in several weeks to several months. No controlled data clarify whether these occasional prolonged responses without further treatment are different from those that would be observed in untreated children. Repeated treatments with IVIg may sustain platelet counts at a level of >20,000 to 30,000 and be useful to avoid splenectomy. For both acute and chronic ITP, there is no evidence that treatment with IVIg diminishes mortality or morbidity.

The first reported IVIg regimen was 0.4 g/kg daily for 5 consecutive days. Subsequent studies suggested that 1 g/kg for 1 day<sup>64</sup> or 0.4 g/kg/d for 2 days<sup>50</sup> may be sufficient in most responding patients. Recently, a randomized trial showed that a single dose of 0.8 g/kg achieves the same results as the former regimen with less cost and possibly fewer side effects.<sup>48</sup>

Adverse effects of IVIg are common (15% to 75%) but generally mild, including headache, backache, nausea, and fever.<sup>32,65</sup> Aseptic meningitis may occur.<sup>66</sup> Rare reported complications include alloimmune hemolysis<sup>67</sup> and hepatitis C infection.<sup>68-71</sup> No hepatitis C has been reported with viral inactivated products. Other complications have been reported in adults (see below).

**Recommendations.** There is level I evidence that children with acute, previously untreated ITP experience more rapid recovery of platelets with IVIg than with glucocorticoids or no specific therapy, but it is unclear whether this enhancement of platelet recovery influences bleeding or mortality or if there are circumstances in which the disadvantages of IVIg might outweigh its benefits. There is inadequate evidence regarding the efficacy of IVIg in other patient categories to develop definitive recommendations based on data. The opinion of the panel was that, regardless of the platelet count, it is appropriate (7.3 to 8.8, A-D) to treat severe, life-threatening bleeding initially with IVIg. IVIg was also considered appropriate as initial therapy for children with platelet counts <10,000 and minor purpura (1 g/kg for 1 day, 7.2, D) and for children with platelet counts <20,000 and mucous membrane bleeding (7.8 to 8.3, B). In all categories, a dose of 1 g/kg administered on 1 day received higher panel ratings (7.2 to 8.8, A-D) than a total dose of 2.0 g administered over 2 to 5 days (6.4 to 8.2, B-D). IVIg was considered appropriate initial treatment in children with platelet counts below 20,000 in whom inaccessibility or non-compliance is a concern (7.6 to 8.7, B-C). The panel considered IVIg inappropriate (1.0 to 1.2, A) in children with platelet counts >30,000 who are asymptomatic or have only minor purpura (Table 8).

### Anti-Rh(D)

**Evidence.** One level I trial<sup>48</sup> (Table 9) compared anti-Rh(D) to IVIg and glucocorticoid as initial therapy in patients with acute ITP and platelet counts <20,000 at presen-

**Table 8. Panel Opinion Regarding Initial Treatment Options in Children**

| Platelet Count  | Treatment Options  |   |   |
|---|--|---|---|
|   | Appropriate<br>(mean panel scores 7-9)   | Appropriateness Uncertain<br>(mean panel scores, 3.1-6.9)   | Inappropriate<br>(mean panel scores, 1-3)                                 |
| <b>Platelet Count &lt;20,000</b>                                |  |   |   |
| Asymptomatic  |  | No treatment*, hospitalization, conventional-dose oral glucocorticoid,† high-dose oral glucocorticoid,‡ high-dose parenteral glucocorticoid,§ IVIg (1 g/kg × 1 d), IVIg (total dose of 2 g/kg given over 2-5 d), anti-D |   |
| Minor purpura   | IVIg (1 g/kg × 1 d), (7.2, D)†<br>High-dose oral glucocorticoid, (7.0, D)¶   | Hospitalization, conventional-dose oral glucocorticoid, high-dose parenteral glucocorticoid, IVIg (total dose of 2 g/kg given over 2-5 d), anti-D   | No treatment (2.5 D)¶   |
| Mucous membrane bleeding that may require clinical intervention | IVIg (1 g/kg × 1 d) (8.3, B)<br>Hospitalization, (8.2, C)<br>IVIg (total dose of 2 g/kg given over 2-5 d), (7.8, B)<br>High-dose oral glucocorticoid, (7.6, C)   | Conventional-dose oral glucocorticoid, high-dose parenteral glucocorticoid, anti-D  | No treatment (1.0 A)  |
| Severe, life threatening bleeding                               | Hospitalization (9.0, A)<br>IVIg (1 g/kg × 1 d) (8.8, A-B)<br>High-dose parenteral glucocorticoid (8.0-8.4, B-C)<br>IVIg (total dose of 2 g/kg given over 2-5 d), (7.8, C)<br>High-dose oral glucocorticoid (7.0-7.4, C-D) | Conventional-dose oral glucocorticoid therapy, anti-D   | No treatment (1.0, A)   |
| <b>Platelet Count 20-30 × 10<sup>3</sup></b>                    |  |   |   |
| Asymptomatic  | No treatment (7.0, C)  | Conventional-dose oral glucocorticoid, high-dose oral glucocorticoid, IVIg (1 g/kg × 1 d), IVIg (total dose of 2 g/kg given over 2-5 d), anti-D   | High-dose parenteral glucocorticoid, (2.6, C)<br>Hospitalization (2.8, D) |
| Minor purpura   |  | No treatment, hospitalization, conventional-dose oral glucocorticoid, high-dose oral glucocorticoid, IVIg (1 g/kg × 1 d), IVIg (total dose of 2 g/kg given over 2-5 d), anti-D  | High-dose parenteral glucocorticoid, (2.6, C)                             |
| Mucous membrane bleeding that may require clinical intervention |  | Hospitalization, conventional-dose oral glucocorticoid, high-dose oral glucocorticoid, high-dose parenteral glucocorticoid, IVIg (1 g/kg × 1 d, IVIg (total dose of 2 g/kg given over 2-5 d), anti-D                    | No treatment (1.0, A)   |
| Severe, life-threatening bleeding                               | Hospitalization (9.0 A)<br>IVIg (1 g/kg × 1 d) (8.5, B)<br>IVIg (total dose of 2 g/kg given over 2-5 d) (8.2, C)<br>High-dose parenteral glucocorticoid (7.6, C)<br>High-dose oral glucocorticoid (7.4, C)                 | Conventional-dose oral glucocorticoid, anti-D   | No treatment (1.0, A)   |

**Table 8 (Cont'd). Panel Opinion Regarding Initial Treatment Options in Children**

| Platelet count $30-50 \times 10^4$                              | Appropriate<br>(mean panel scores 7-9)   | Appropriateness Uncertain<br>(mean panel scores, 3.1-6.9)   | Inappropriate<br>(mean panel scores, 1-3)   |
|---|--|---|---|
| Asymptomatic  | No treatment (9.0, A)  |   | IVIg (total dose of 2 g/kg given over 2-5 d), (1.0, A)<br>IVIg (1 g/kg $\times$ 1 d) (1.2, A)<br>Anti-D (1.2, A)<br>High-dose parenteral glucocorticoid (1.2, B)<br>Hospitalization (1.5, B)<br>High-dose oral glucocorticoid (2.0, C)<br>Conventional-dose oral glucocorticoid (2.0, C)<br><br>IVIg (total dose of 2 g/kg given over 2-5 d) (1.0, A)<br>IVIg (1 g/kg $\times$ d) (1.2, A)<br>Anti-D (1.2, A)<br>High-dose parenteral glucocorticoid (1.2, B)<br>Hospitalization (1.5, B)<br>High-dose oral glucocorticoid (2.2, C)<br>Conventional-dose oral glucocorticoid (2.2, C) |
| Mucous membrane bleeding that may require clinical intervention |  | Hospitalization, conventional-dose oral glucocorticoid, high-dose oral glucocorticoid, IVIg (1 g/kg $\times$ 1 d), IVIg (total dose of 2 g/kg given over 2-5 d) | No treatment (2.0, B)<br>High-dose parenteral glucocorticoid (2.8, D)<br>Anti-D (3.0, D)  |
| Severe, life-threatening bleeding                               | Hospitalization (9.0, A)<br>IVIg (1 g/kg $\times$ 1 d) (8.0, C)<br>High-dose oral glucocorticoid (7.4, C)<br>IVIg (total dose of 2 g/kg given over 2-5 d) (7.3, D)<br>High-dose parenteral glucocorticoid (7.0, D) | Conventional-dose oral glucocorticoid   | No treatment (1.0, A)<br>Anti-D (3.0, D)  |

"Appropriate" and "Not appropriate" = mean panel score of 7.0-9.0 or 1.0-3.0, respectively. "Appropriate" = treatment may or may not be necessary, but performing it is not wrong, "Inappropriate" = treatment should not be performed. Mean panel score is graded on a scale of "1" to "9" with "1" representing low appropriateness and "9" representing high appropriateness. Letter codes following panel scores reflect strength of agreement, the panel consensus (defined by standard deviation) around the mean panel score. "A" = complete or virtual unanimity, "B" = strong agreement, "C" = moderate agreement, "D" = moderate disagreement, "E" = strong disagreement (see Table 4).

\* "No treatment" implies careful observation. In patients with major risk factors for bleeding (eg, elevated blood pressure, ulcer disease, vigorous lifestyle), not treating is considered inappropriate in all patients if the platelet count is  $20-30 \times 10^5$  (2.3 C),  $10-20 \times 10^5$  (1.3, B) or  $<10 \times 10^5$  (1.0, A). Not treating patients less than 3 years of age is also considered inappropriate if the platelet count is  $10-20 \times 10^5$  (1.6, B) or less than  $10 \times 10^5$  (2.4, B).

† Eg, 1-2 mg/kg/d of prednisone.

‡ Eg, 4-8 mg/kg/d of prednisone.

§ Eg, 30 mg/kg/d of methylprednisolone.

|| Anti-D given intravenously.

¶ These recommendations were made only for patients with platelet counts  $<10,000$ .

tation. The time required to increase platelet counts to  $>20,000$  and  $>50,000$  was slightly longer with anti-Rh(D) than with glucocorticoid or IVIg therapy. There are no level I or II data comparing anti-Rh(D) treatment to no treatment, nor is there evidence regarding the effectiveness of anti-Rh(D) in reducing mortality or morbidity from bleeding. Four level V studies<sup>72-75</sup> suggest that anti-Rh(D) may in-

crease the platelet count in about 80% of children with acute and chronic ITP, and that repeated treatments may postpone the need for splenectomy, but the responses are generally transient, lasting a median time of 5 weeks.

The only clinically important adverse effect of anti-Rh(D) appears to be alloimmune hemolysis. All Rh(D)<sup>+</sup> patients develop a positive direct antiglobulin test after treatment,

Table 9. Clinical Trial Evidence: Effectiveness of Glucocorticoids, IVIg, and Anti-D in Initial Treatment of ITP in Children

| Authors                             | N   | Age         | Follow-up | Randomized Treatment Arms  | Outcome   |  |   |                                 |                 | Evidence Level |
|-------------------------------------|-----|-------------|-----------|--|---|--|---|---------------------------------|-----------------|----------------|
|                                     |     |             |           |  | Study Population  | Outcome Measure  | Platelet Count  | Bleeding Symptoms               | Adverse Effects |                |
| McWilliams and Maurer <sup>48</sup> | 27  | 6 yr (mean) | NR        | Prednisone (2 mg/kg/d × 21 d)<br>No treatment<br>Prednisone (60 mg/m <sup>2</sup> /d × 21 d, then tapered)<br>Placebo  | Median time to platelet count of 150K<br>Proportion with platelet count >30K and >100K, and with negative Rumpel-Leede test | 21 d   | NR*<br>NR   | NR*<br>NR                       | 0<br>0          | I              |
| Sartorius <sup>31</sup>             | 93  | 6 mo-16 yr  | >6 mo     | Prednisone (2 mg/kg/d × 14 d, then taper to d 21)<br>Placebo   | Platelet count, bleeding time, clinical bleeding score at d 0-28  | Prednisone > placebo (P < .01)<br>Prednisone > placebo (P < .05) only at d 7 | Prednisone < placebo (by Rumpel-Leede test (P < .01))                         | NR                              | 0<br>0          | I              |
| Buchanan and Holtkamp <sup>30</sup> | 27  | <11 yr      | 28 d      | Prednisone (2 mg/kg/d × 14 d, then taper to d 21)<br>Placebo   | Platelet count, bleeding time, clinical bleeding score at d 0-28  | Prednisone > placebo (P < .05) only at d 7                                   | Prednisone < placebo (P < .05) only at d 7 (bleeding time and clinical score) | Increased appetite, weight gain | 0<br>0          | I              |
| Imbach et al <sup>50</sup>          | 94  | <16 yr      | 1 yr      | Prednisone (60 mg/m <sup>2</sup> /d × 21 d, follow-up protocol for poor response/remissions)<br>IVIg (0.4 g/kg/d × 5 d, follow-up protocol for poor response/remissions) | Proportion with platelet count >100K  | 77%  | NR  | 77% with weight gain or acne    | 0<br>0          | II             |
| Mazzuccconi et al <sup>47</sup>     | 61  | 2-12 yr     | >6 mo     | Prednisone (0.5 mg/kg/d × 1 mo or until platelet normalization)<br>Prednisone (1.5 mg/kg/d × 1 mo or until platelet normalization)                                       | Proportion with platelet count >150K  | 62%  | NR  | NR                              | NR              | I              |
| Belluci et al <sup>51</sup>         | 160 | <15 yr      | >12 mo    | Prednisone (0.25 mg/kg/d × 3 wk)<br>Prednisone (1 mg/kg/d × 3 wk)  | Proportion with platelet count >100K for >3 mo  | 71%  | NR  | NR                              | 0<br>0          | II             |
| Khalifa et al <sup>46</sup>         | 30  | 2 mo-15 yr  | >6 mo     | Methylprednisolone (IV, 10 mg/kg/d × 5 d)<br>Prednisone (2 mg/kg/d × 4 wk)   | Mean platelet count on days 1-14  | Methylprednisolone = IVIg > prednisone (P < .001)                            | NR  | NR                              | 0<br>0          | I              |
| Ozsoyle et al <sup>57</sup>         | 20  | 2 mo-11 yr  | >6 mo     | IVIg (0.4 g/kg/d × 5d)<br>Methylprednisolone (po, 30 mg/kg/d × 3 d, then 20 mg/kg/d × 4 d)<br>IVIg (0.4 g/kg/d × 5 d)  | Proportion with platelet count >150K in 3 d, 6 mo   | 60%, 90% (no difference)   | None  | NR                              | 0<br>0          | II             |
| Blanchette et al <sup>32</sup>      | 53  | 7 mo-14 yr  | 180 d     | Prednisone (4 mg/kg/d × 7 d, then tapered to d 21)   | Median time to platelet count >20K, >50K  | 60%, 75%<br>2 d, 4 d   | NR  | Weight gain, behavioral change  | 0               | I              |

|                                |     |            |         |   |  |  |                   |  |                       |
|--------------------------------|-----|------------|---------|---|--|--|-------------------|--|-----------------------|
| Blanchette et al <sup>46</sup> | 146 | 6 mo-18 yr | 6-32 mo | IVIg (1 g/kg/d × 2 d)<br>No therapy<br>Prednisone (4 mg/kg/d × 7 d then tapered to d 21))<br>IVIg (1 g/kg/d × 2 d)<br>IVIg (0.8 g/kg once)<br>Anti-D (25 µg/kg/d × 2 d) | Median time to platelet count >20k, >50K | 1 d, 2 d (P < .01 v prednisone)<br>4 d, 16 d (P < 0.1 v either treatment)<br>2 d, 3 d  | NR                | 75% with nausea, vomiting, headache, fever   | 0                     |
| Albayrak et al <sup>48</sup>   | 57  | 2 mo-17 yr | 6 mo    | Methylprednisolone (po, 30 mg/kg/d × 7 d)<br>Methylprednisolone (po, 50 mg/kg/d × 7 d)<br>IVIg (0.5 g/kg/d × 5 d)   | Mean platelet count on days 0-30         | 2 d, 2 d<br>1 d, 2 d (P < .05 v prednisone)<br>2 d, 2.5 d (P < .05 v both IVIg regimens)<br>Mean >100K by d 4.<br>No difference among groups | NR<br>1 ICH<br>NR | 16-18% with fever, nausea, vomiting, headache<br>24% with hemoglobin <10 g/dL<br>Increased appetite and Cushingoid appearance<br>Increased appetite and Cushingoid appearance<br>1 pt with aseptic meningitis; 2 with headache, vomiting | 0<br>0<br>0<br>0<br>0 |

\*NR, Not reported.

accompanied by a transient (1 to 2 weeks) decrease in hemoglobin concentration of about 0.5 to 2 g/dL. Although in two studies 4% to 24% of patients had a hemoglobin concentration of <10 g/dL after 7 to 14 days,<sup>48,74</sup> red blood cell transfusion was not required.

**Recommendations.** There is level I evidence indicating that anti-Rh(D) increases the platelet count less rapidly than IVIg or glucocorticoids in children with acute, severe thrombocytopenia (platelet count <20,000). Based on opinion, the panel considered initial treatment with anti-Rh(D) inappropriate (1.0 to 3.0, A-D) for children presenting with platelet counts >30,000 (Table 8). The use of anti-Rh(D) in chronic ITP was not addressed in the panel survey.

### Splenectomy

**Evidence.** Compared to adults, children with ITP are less likely to undergo splenectomy. Sixteen case series (level V evidence)<sup>18-29,76-79</sup> describe outcomes from splenectomy over the past 40 years. In most instances, splenectomy was performed in children in whom thrombocytopenia had persisted for more than 1 year and who had clinically important bleeding. In some case series, children underwent splenectomy earlier in the course of their illness because of uncontrollable hemorrhage that was unresponsive to glucocorticoid therapy. Splenectomy is less frequent in more recent case series.<sup>36</sup> These data consistently show that most children (72% of the 271 children undergoing elective splenectomy in the 16 case series) achieve a complete remission from ITP after splenectomy. An effect of splenectomy on morbidity or mortality has not been shown directly. There are few data on accessory splenectomy in children; it is discussed under Adult Treatment below.

The potential adverse effects of splenectomy include the operative and postoperative complications of bleeding and infection. An important concern for late morbidity and mortality after splenectomy is the long-term risk of fatal bacterial infection, particularly in children less than 5 years old, in whom the risk may be 1 death per 300 to 1,000 patient-years.<sup>80-82</sup> However, most of these observations involved splenectomy for other diseases and predated the current practice of presplenectomy immunization and the administration of postsplenectomy prophylactic penicillin. Prophylactic penicillin has been shown to reduce the risk of infection in children with sickle cell anemia,<sup>83</sup> and this observation may be generalizable to other asplenic children.

**Recommendations.** Although all available evidence is level V, the consistency of observations, the frequency of complete responses to splenectomy, and similar observations in larger samples of adult patients with chronic ITP suggest that splenectomy is an effective therapy. However, there are inadequate data to make evidence-based recommendations on the appropriate indications and timing for splenectomy, on when the harms of splenectomy might outweigh its potential benefits, or on appropriate preoperative management. Many of the case series predated the use of IVIg and anti-Rh(D) therapy, which can provide intermittent support for children with recurrent, symptomatic thrombocytopenia and thereby postpone or avoid the need for splenectomy. The occurrence of spontaneous complete remissions in some chil-

dren with chronic ITP may also lessen the need for this procedure.

The panel reached consensus on only selected indications for splenectomy, such as persistence of disease 12 months after diagnosis with bleeding symptoms and a platelet count of <10,000 (7.5 to 9.0, A-C for ages 3 to 12 years) or of 10,000 to 30,000 with bleeding symptoms (7.6 to 7.9, B for ages 8 and 12), but it considered only certain scenarios. These scenarios assume that primary treatment (glucocorticoid, IVIg, and/or anti-D) was only transiently successful and that there are no medical contraindications to the surgery. The panel had strong disagreement (5.0, E) about the appropriateness of emergency splenectomy in the case of urgent, life-threatening bleeding in which conventional critical care measures are already underway.

If an elective splenectomy is planned, preoperative prophylaxis that the panel considered appropriate to reduce the risk of intraoperative and postoperative bleeding included (1) IVIg (8.8, A), parental glucocorticoid (7.2, D), and anti-D (7.2, D) therapy for platelet counts <10,000 and (2) IVIg therapy for platelet counts of 10,000 to 20,000 (8.5, B) or 20,000 to 30,000 (7.7, B). Indications that were considered inappropriate for preoperative prophylaxis included IVIg for platelet counts >50,000 (2.6, D), platelet transfusion for platelet counts of 20,000 to 30,000 (2.3, D) or >30,000 (1.0, A), anti-D for platelet counts >50,000 (1.0, A), oral glucocorticoid therapy for platelet counts >50,000 (2.6, D), and parenteral glucocorticoid therapy for platelet counts of 30,000 to 50,000 (2.2, C) or >50,000 (1.0, A).

The panel endorsed the recommendations of the Advisory Committee on Immunization Practices that, at least 2 weeks before elective splenectomy, children should be immunized with *Hemophilus influenzae* type b vaccine and, if over 2 years of age, with polyvalent pneumococcal vaccine and quadrivalent meningococcal polysaccharide vaccine.<sup>84</sup>

#### Other Treatments

**Evidence.** Only four level V case series have evaluated other treatment modalities (plasma infusion, azathioprine, danazol, and interferon) for ITP in children.<sup>85-88</sup> The modalities are described in the subsequent section on treatment of adults.

**Recommendations.** There is insufficient evidence to make recommendations about alternative treatment modalities when ITP symptoms persist after primary treatment and splenectomy, or to assess when the benefits of such treatments outweigh their potential harms. Furthermore, the data on the clinical course of ITP in children do not clarify whether further treatment is even necessary under these circumstances. Based on opinion, the panel did not recommend further treatment of children with platelet counts >30,000 who have failed to respond to splenectomy and have no bleeding symptoms (2.0, B for platelet count of 30,000-50,000; 1.0, A for platelet count >50,000). Further treatment was recommended (9.0, A) for children with platelet counts <30,000 who have active bleeding. The panel considered many treatments (and no treatment) to be reasonable options, reflecting the lack of evidence that any single treatment is better than another.

## ITP in Adults

### Clinical Course

An understanding of the clinical course of ITP in adults is essential to make informed management decisions, to know which patients require treatment either at the time of diagnosis or in the management of chronic disease, and to estimate morbidity and mortality, with and without treatment.

**Evidence.** ITP in adults is typically a chronic disease. However, the clinical course of untreated disease is uncertain, because, in contrast to children, patients with symptomatic thrombocytopenia are generally treated initially with glucocorticoids. Despite this bias, which would tend to underestimate the severity of untreated disease, the data suggest that the course of ITP is more serious in adults than in children, with an estimated rate of fatal hemorrhage of 5%, due mainly to intracranial hemorrhage (Table 10). Most data on fatal hemorrhages were collected in previous decades, when platelet transfusions and IVIg were unavailable and supportive care for critical complications was less effective. Thus, current mortality rates may be less than 5%. At equivalent platelet counts, hemorrhagic complications may be more common in older patients.<sup>89,90</sup> There are no long-term follow-up data on outcomes in adults with incidentally discovered asymptomatic thrombocytopenia. In addition, the relative incidence of symptomatic versus incidentally discovered thrombocytopenia is unknown.

Table 10 presents 12 case series from 12 countries with patient observations spanning 61 years.<sup>26,90-100</sup> The data show that spontaneous remission of chronic ITP occurs infrequently; approximately 5% of patients had an apparent spontaneous recovery after failing to respond completely to glucocorticoid, splenectomy, and any subsequent therapy. In the earliest series,<sup>91</sup> which occurred before the introduction of glucocorticoid therapy when splenectomy was considered the only effective treatment, 26 of the 78 patients had no therapy: 10 of the 26 had an insidious onset of symptoms, and only 1 patient had a remission, after 3 years of persistent thrombocytopenia; the other 16 patients had an acute onset of symptoms, and 11 had a complete recovery within 3 months. In contrast, a subsequent series involving 46 patients reported no complete remissions in the 12 untreated patients.<sup>92</sup> In another series,<sup>96</sup> spontaneous remission occurred in 8 of 16 patients with persistent ITP. Other series in Table 10 reported rare patients who recovered spontaneously. These data are difficult to interpret because of small sample sizes, distant past observations, and uncertain diagnoses of ITP. Unlike children, essentially all adult patients received glucocorticoid therapy and half underwent splenectomy. Despite treatment, 36% of patients had persistent thrombocytopenia at the time of last follow-up.

### Diagnosis

**History and physical examination.** The history and physical examination are aimed at detecting alternative causes of thrombocytopenia. The most important elements of the history and physical examination identified by the panel are presented in Table 11. The primary objective of the history is to assess the type of bleeding and to distinguish platelet-



**Table 10. Clinical Course of ITP: Adults**

| Author                              | Location                   | Years     | Patients (no.) | Patients With Complete Remission on No Therapy* | Hemorrhagic Complications† |       |              |                   | Patients in Complete Remission* at Last Follow-up‡ | Patients With Persistent Thrombocytopenias§ |                        |
|-------------------------------------|----------------------------|-----------|----------------|---|----------------------------|-------|--------------|-------------------|--|---|------------------------|
|                                     |                            |           |                |   | Acute Deaths               |       | Other Deaths | No.               |  | Spontaneous Recovery                        | Deaths From Hemorrhage |
|                                     |                            |           |                |   | ICH                        | Other |              |                   |  |   |                        |
| Watson-Williams et al <sup>81</sup> | Scotland                   | 1928-1957 | 78             | 12/26   | 4                          | 1     | 0            | 46/62 (74)        | —  | —   |                        |
| Carpenter et al <sup>92</sup>       | US                         | 1945-1959 | 46#            | 0/12  | 2                          | 0     | 0            | 20/35 (57)        | —  | —   |                        |
| Thompson et al <sup>83</sup>        | US                         | 1945-1970 | 66             | 3   | —                          | —     | 4            | 37/62 (60)        | —  | —   |                        |
| Meyers <sup>84</sup>                | US                         | 1950-1961 | 71             | 0   | 2                          | 0     | 2            | 56/57 (84)        | 0  | 2   |                        |
| Jiji et al <sup>85</sup>            | US                         | 1951-1972 | 91             | 0   | —                          | —     | 5            | 53/86 (64)        | —  | —   |                        |
| Picozzi et al <sup>86</sup>         | US                         | 1959-1969 | 38             | 0   | 0                          | 0     | 0            | 25/36 (69)        | 8  | 0   |                        |
| Ikkala et al <sup>87</sup>          | Finland                    | 1966-1973 | 41             | 1   | —                          | 2     | 1            | 27/38 (71)        | 0  | 0   |                        |
| Difino et al <sup>88</sup>          | US                         | 1971-1979 | 62             | 0   | 0                          | 3     | 3            | 34/51 (67)        | 18   | 3   |                        |
| Jacobs et al <sup>89</sup>          | South Africa               | 1971-1981 | 148            | 1   | 1                          | 1     | 0            | 78/146 (53)       | 18   | 0   |                        |
| den Ottolander et al <sup>26</sup>  | Netherlands                | —         | 69             | 1   | —                          | —     | —            | 39/69 (57)        | —  | —   |                        |
| Pizzuto and Ambriz <sup>100</sup>   | Central and South America# | —         | 934            | 9   | 27**                       | —     | 19**         | 577/887 (65)      | 384  | 14  |                        |
| Cortelazzo et al <sup>90</sup>      | Italy                      | 1982-1989 | 117            | —††   | —                          | —     | 1            | 33/67 (49)        | —  | —   |                        |
| Summary                             |                            |           | 1,761          | 27  | 36                         | 7     | 35           | 1,027/1,606 (64%) | 465  | 22 (5%)                                     |                        |

Abbreviation: ICH, intracranial hemorrhage.

\* Complete remission is defined as a normal platelet count on no therapy continuing to the time of the last observation. In almost all patients there was no opportunity to observe a spontaneous remission because steroids were begun at the time of diagnosis. In the first two series, a substantial number of patients were untreated when, before 1950, splenectomy was the only effective modality.

† Acute hemorrhagic deaths are arbitrarily defined as occurring within 6 mo of diagnosis. Other hemorrhagic deaths occurred after 6 mo, or the time was not specified—and it was unclear even if all of these were due to hemorrhage from ITP.

‡ The number of patients is less than the original series by deaths and patients lost to follow-up. This estimate is largely dependent on the duration of follow-up, which was variable.

§ Patients who failed to achieve a complete response to glucocorticoid, splenectomy, and subsequent therapy. In contrast to children, persistence is defined as lack of response to treatment rather than by an arbitrary time.

|| This group contained 3 children less than 12 years old, and it was not stated if they were among the patients whose ITP resolved.

¶ Numbers in parentheses are percentages.

# This study was a collaborative effort of 10 institutions.

\*\* This report stated that 27 of the total of 46 hemorrhagic deaths were due to ICH, 9 due to gastrointestinal or pulmonary bleeding, and 10 due to "massive" purpura, but these etiologies were not distinguished according to time from diagnosis.

†† 49 patients with platelet counts over 30,000/ $\mu$ l and no bleeding symptoms were not treated and apparently had no major hemorrhagic complications. Whether any complete remissions occurred is not stated. These patients are not included in the estimate of patients in complete remission at last follow-up.

**Table 11. Principal Elements of the History and Physical Examination in an Adult Suspected of Having ITP**

| <b>History</b>  |  |
|---|--|
| Bleeding symptoms   |  |
| Type of bleeding  |  |
| Severity of bleeding  |  |
| Duration of bleeding  |  |
| Hemostasis with prior surgeries, pregnancies  |  |
| Systemic symptoms, including weight loss, fever, headache, and symptoms of autoimmune disorders such as arthralgias, skin rash, alopecia, and venous thrombosis |  |
| Risk factors for HIV infection  |  |
| Pregnancy status  |  |
| Medications, including heparin, alcohol, quinidine/quinine, and sulfonamides, which may cause thrombocytopenia, and aspirin, which may exacerbate bleeding      |  |
| Transfusion history   |  |
| Family history of thrombocytopenia, including bleeding symptoms and symptoms of autoimmune disorders  |  |
| Comorbid conditions which may increase the risk of bleeding, such as gastrointestinal disease, central nervous system disease, urologic disease                 |  |
| Lifestyle, including vigorous and potentially traumatic activities  |  |
| <b>Physical Examination</b>   |  |
| Bleeding signs  |  |
| Type of bleeding (including retinal hemorrhages)  |  |
| Severity of bleeding  |  |
| Liver, spleen, and lymph nodes; jaundice and other stigmata of liver disease  |  |
| Evidence for infection, particularly bacteremia or HIV infection  |  |
| Evidence for autoimmune disease, such as arthritis, goiter, nephritis, or cutaneous vasculitis  |  |
| Evidence for thrombosis   |  |
| Neurologic function   |  |
| Skeletal anomalies  |  |

related mucocutaneous bleeding from delayed visceral hematomas, which are characteristic of coagulation disorders.

Drug-induced thrombocytopenia must always be considered and may be difficult to exclude. Drugs most commonly associated with thrombocytopenia include quinidine and quinine-containing medications among nonhospitalized patients, and heparin among hospitalized patients. A case-control study<sup>101</sup> also reported an association with sulfonamides, sulfonyleureas, dipyridamole, and salicylates. Alcohol also causes thrombocytopenia, as well as chronic liver disease that can lead to congestive splenomegaly and increased platelet pooling. Finally, the history should consider the patient's lifestyle, which may influence the goals of treatment. A sedentary individual, for example, may tolerate a lower platelet count than a patient whose profession or hobbies involve a high level of exertion or potential trauma.

Physical examination is principally directed at assessing the type and severity of bleeding and at excluding other causes of thrombocytopenia. Splenomegaly, for example, provides evidence against ITP. A large study<sup>102</sup> reported that less than 3% of ITP patients had splenomegaly. This corresponds with the observation that about 3% of healthy young adults have palpable spleens.<sup>103</sup> Signs of liver disease or lymphadenopathy may suggest lymphoproliferative, autoim-

mune, or infectious diseases. Acute and severe thrombocytopenia may be a manifestation of bacteremia or viral infection; HIV infection is commonly associated with thrombocytopenia.<sup>104</sup> Acute anemia, neurologic, or renal abnormalities may suggest thrombotic thrombocytopenic purpura. Neurologic function and fundoscopic examination also provide a baseline in the event of subsequent central nervous system bleeding. Additionally, hearing impairment and skeletal anomalies may suggest disorders associated with congenital thrombocytopenia.<sup>38</sup>

*Complete blood count with examination of a peripheral blood smear.* A complete blood count and examination of a peripheral blood smear are essential in diagnosing ITP. Incidentally detected thrombocytopenia on a routine blood count is often the first clue to the diagnosis. The evaluation of a low platelet count should distinguish between true thrombocytopenia and pseudothrombocytopenia, which occurs in about 0.1% of adults,<sup>105-108</sup> most commonly due to innocent platelet agglutinins that cause platelet clumping in the presence of the anticoagulant EDTA. In each patient, thrombocytopenia must be confirmed by direct examination of the peripheral blood smear. The principal elements of the blood smear examination for ITP are described above for children and in Table 5. Particularly in older patients, evidence for myelodysplasia should be carefully evaluated, including the presence of the Pelger-Huet anomaly, nucleated red blood cells, schistocytes, and immature granulocytes.<sup>109</sup> Other peripheral blood smear abnormalities may suggest the presence of a viral infection, megaloblastic hematopoiesis, or microangiopathic disorders.

*Other laboratory data.* Recommendations regarding other laboratory tests were derived from opinion by a questionnaire completed by 11 panel members. The recommendations assume that the history, physical examination, and initial blood counts and smear were compatible with the diagnosis of ITP and do not include atypical findings that are uncommon in ITP or suggest other disease etiologies. If atypical findings are present, then additional diagnostic evaluation may be necessary. Indications for which the panel could not reach consensus are not listed here but are summarized in Table 6.

The panel reached consensus that 8 tests were unnecessary as part of the routine evaluation of adults presenting with suspected ITP, and that an additional 5 tests were both unnecessary and inappropriate (Table 7). Testing for HIV antibody was considered necessary (8.6, B), as well as appropriate (8.8, B), in patients with risk factors for HIV infection. There was no consensus on the appropriateness or necessity of a bone marrow aspirate/biopsy to establish the diagnosis in all adult patients at presentation (Fig 1). Bone marrow examination was considered appropriate to establish the diagnosis in patients over age 60 (7.8, C) and in patients considering splenectomy (7.5, D). The test was considered unnecessary (2.7, C) to establish the diagnosis for medicolegal protection. Thyroid function testing was considered appropriate (7.0, C) to rule out occult hyperthyroidism or hypothyroidism only before an elective splenectomy. The panel also reached consensus regarding testing in the following situations:

(1) *To establish the diagnosis before splenectomy:* Tests that the panel considered unnecessary for this purpose included platelet antigen specific antibody assay (1.7, C), serum complement level (1.8, C), platelet survival study (1.9, C), and direct antiglobulin test (2.6, C). The panel considered platelet associated IgG assay both unnecessary and inappropriate (3.0, D).

(2) *To establish the diagnosis in patients who have failed to respond to glucocorticoid therapy and splenectomy:* Tests that the panel considered unnecessary for this purpose included platelet-associated IgG assay (1.7, B), platelet-antigen specific antibody assay (1.8, C), serum complement level (2.0, C), platelet survival study (2.4, D), and direct antiglobulin test (2.9, D).

### Treatment

As with children, inferences regarding the effectiveness of treating ITP in adults were based on the surrogate outcome measure of the platelet count (see above).

### Hospitalization

*Evidence.* There have been no studies to evaluate the effectiveness of hospitalizing adults with ITP.

*Recommendations.* The opinion of the panel was that hospitalization is appropriate for patients with severe, life-threatening bleeding, regardless of the platelet count (8.8, B), as well as for patients with platelet counts <20,000 who have significant mucous membrane bleeding (8.1, C) or who are inaccessible or noncompliant (8.2-8.6, B-C). Hospitalization was considered inappropriate (1.1 to 2.2, A-C) for patients with platelet counts >20,000 who are either asymptomatic or have only minor purpura. Indications for hospitalization under intermediate conditions are less clear (Table 12).

### Emergency Treatment

*Evidence.* There have been no studies to evaluate the effectiveness of different regimens for the emergency treatment of severe bleeding.

*Recommendations.* Although evidence for the effectiveness of treatment regimens is lacking, the opinion of the panel is that the serious consequences of severe, life-threatening bleeding justify the use several regimens. Assuming that conventional critical care measures are already underway, the opinion of the panel was that appropriate interventions include high-dose parenteral glucocorticoid therapy (1 g of methylprednisolone daily for 3 days) and IVIg, either alone or in combination (9.0, A), and platelet transfusions (7.5, D). See further discussion of individual treatments below.

### Observation (No Specific Initial Treatment)

*Evidence.* The only evidence regarding the outcomes of not treating adults with ITP is a level V, prospective study of selected patients with platelet counts >30,000 and no symptomatic bleeding (49 of 117 total patients with ITP).<sup>90</sup> No adverse events were reported among these 49 patients during a mean follow-up period of 30 months. Other data

suggest that spontaneous, serious bleeding is rare (<5% of patients) with platelet counts >10,000, and is reported in about 40% of patients with platelet counts <10,000.<sup>41</sup> Clinically important bleeding with trauma rarely occurs at platelet counts >50,000.<sup>41</sup>

*Recommendations.* Current evidence is inadequate to state with certainty which groups of patients with ITP can be safely managed without therapy. The opinion of the panel was that not providing specific initial treatment was appropriate (7.0 to 7.8, C-D) in patients who have platelet counts >50,000 and are either asymptomatic or have only minor purpura. The panel believed that withholding treatment was inappropriate for patients with a platelet count <20,000, regardless of their symptoms (1.2 to 1.8, B), and for patients with a platelet count <50,000 who present with significant mucous membrane bleeding (1.0, A for platelet count <20,000; 1.2 to 2.0, B for platelet count of 20,000 to 50,000) or who have risk factors for bleeding, such as hypertension, peptic ulcer disease, or vigorous lifestyle (1.0 to 1.1, A for platelet count <20,000; 1.6, B for platelet count of 20,000 to 30,000; 2.9, C for platelet count of 30,000 to 50,000). Not treating severe life-threatening bleeding was considered inappropriate (1.0, A for platelet count <50,000). The panel considered it inappropriate (1.6 to 1.9, B-C) to withhold treatment at the patient's request if the platelet count was <20,000. Patient inaccessibility or noncompliance was considered an inappropriate reason not to treat patients with platelet counts of 20,000 to 30,000 (2.3, C) or <20,000 (1.2 to 1.3, B).

### Glucocorticoid Therapy

*Evidence.* Glucocorticoids have been the standard initial treatment for adults with moderate to severe thrombocytopenia and symptomatic purpura since their introduction in 1950. Uncontrolled data regarding the efficacy of glucocorticoid treatment are summarized in the 12 case series in Table 10. Of these patients, 82% were treated initially with glucocorticoid preparations. The experience of these patients, which are all reported in level V studies, suggests that most increase their platelet count initially. Although it has been suggested that very high doses of glucocorticoid may result in a more rapid increase of the platelet count,<sup>110,111</sup> two level II studies suggested equal efficacy in adults of different regimens of low-dose prednisone (0.5 mg/kg v 1.5 mg/kg<sup>47</sup> and 0.25 mg/kg v 1.0 mg/kg.<sup>51</sup> Fewer (3% to 50%) patients maintain normal platelet counts once therapy is discontinued, although there is an unexplained, extreme variation in reported remission rates among the level V studies. No randomized controlled studies have compared glucocorticoid with no treatment, and there is no evidence of an effect of glucocorticoid treatment on morbidity or mortality. A randomized trial involving 40 patients (level II) compared glucocorticoid therapy to IVIg and both in combination as initial treatment and demonstrated no difference in response, although this study is too small to make definitive conclusions.<sup>112</sup>

The potential adverse effects of glucocorticoids include all of the signs and symptoms of hypercortisolism in Cushing syndrome, including facial swelling, weight gain, hypergly-

cemia, hypertension, weight gain, cataracts, and behavioral abnormalities.<sup>58</sup> Perhaps the greatest risk is the development of osteoporosis; although there are no data in patients with ITP, an objective decrease in bone density has been documented in patients with rheumatoid arthritis after the equivalent of only 10 mg of prednisone daily for 20 weeks.<sup>113</sup> The toxicities of glucocorticoids are dose and duration dependent.

**Recommendations.** There is consistent level V evidence that glucocorticoids can achieve early responses, most of which are transient. Although this suggests a role for initial glucocorticoid therapy in symptomatic patients, there are otherwise few data from which to develop evidence-based recommendations on specific indications. Based on opinion, the panel concluded that glucocorticoid therapy (prednisone, 1 to 2 mg/kg/d) was appropriate initial treatment in patients with platelet counts <30,000, including asymptomatic patients (6.8 to 8.6, C), patients with minor purpura (7.7 to 8.6, C), and those with significant mucous membrane or vaginal bleeding (8.5 to 8.6, B-C) (Table 12). Glucocorticoid therapy was also considered appropriate for patients with platelet counts of 30,000 to 50,000 if clinically important bleeding was present (7.3, C) and for patients with severe, life-threatening bleeding, regardless of the platelet count (7.1 to 7.8, C-D). The recommended duration of glucocorticoid treatment is addressed below. Glucocorticoid therapy was considered inappropriate initial treatment when the platelet count is >50,000 and the patient is either asymptomatic (2.2, C) or has only minor purpura (3.0, D).

### IVIg

**Evidence.** IVIg has been studied more in children than in adults, in whom it is used primarily for patients who are unresponsive to glucocorticoids and other therapies. Relevant data come largely from case series,<sup>64,114-126</sup> level V evidence, most of which describe patients with severe, chronic thrombocytopenia who were observed for a short duration after IVIg treatment. Most, but not all, patients in these series experienced an increased platelet count with IVIg. Among patients with chronic ITP (usually defined in these series as >3 to 4 months), platelet counts increased in about 75% of patients and reached normal levels in about half of patients. In more than 75% of patients who initially responded, the platelet count returned to pretreatment levels, usually within 3 to 4 weeks. In one study,<sup>125</sup> patients were given subsequent infusions of IVIg to maintain platelet counts above 20,000; about one third of the patients who required repeated infusions ultimately became refractory to IVIg but an equal number appeared to have long-term responses. No studies have compared IVIg to no treatment or measured the effects of IVIg on morbidity or mortality. As noted earlier, one randomized study<sup>112</sup> did not detect a difference in outcomes among patients treated initially with IVIg, prednisone, or the combination of IVIg and prednisone.

The dose of IVIg has been the subject of several studies. As in children, the original dose of IVIg was 0.4 g/kg/d administered on 5 consecutive days. Subsequently, the same total dose was administered as 1 g/kg/d on 2 consecutive days.<sup>64</sup> One randomized study<sup>127</sup> showed no difference in the

response of patients with chronic ITP to 1 g/kg given once or on 2 consecutive days (level II trial). For "maintenance therapy," a higher dose (1 g/kg v 0.5 g/kg as a single infusion) was found to yield a greater platelet count response, but the same frequency of treatments was necessary to maintain a platelet count >20,000.<sup>64</sup>

The adverse effects of IVIg are common (15% to 75%) but generally mild, including headache, backache, nausea, and fever.<sup>32,65</sup> Aseptic meningitis may occur.<sup>66</sup> Rare reported complications include alloimmune hemolysis<sup>67</sup> and hepatitis C infection.<sup>68-71</sup> No hepatitis C has been reported with viral inactivated products. Cases of renal failure,<sup>128,129</sup> pulmonary insufficiency,<sup>130</sup> and thrombosis, including stroke and myocardial infarction,<sup>131,132</sup> have been reported as complications of IVIg treatment.

**Recommendations.** There is no evidence regarding the efficacy of IVIg as initial treatment and only level V evidence that it can achieve temporary improvements of platelet counts in patients who are refractory to initial treatment. Further, a benefit of IVIg in terms of morbidity or mortality remains uncertain. Therefore, evidence-based recommendations regarding appropriate indications are not possible at this time. Based on opinion, the panel concluded that IVIg was appropriate initial treatment only for patients with platelet counts <50,000 who have severe, life-threatening bleeding (7.0 to 8.5, C-D). The panel believed that IVIg was inappropriate initial treatment for patients with platelet counts of 30,000 to 100,000 who were asymptomatic (1.1 to 1.6, A-B) or who had only minor purpura, (1.3 to 2.2, B-C). There was strong disagreement (category E) among the panel about the appropriateness of IVIg as initial therapy for patients with platelet counts <20,000 who are asymptomatic or have only minor purpura, or for patients with risk factors for bleeding, such as hypertension, peptic ulcer disease, or a vigorous lifestyle.

### Anti-(Rh) D

**Evidence.** Five level V studies of anti Rh(D) in adults, suggest that it can transiently increase platelet counts, usually lasting for 2 to 3 weeks, in about half of unsplenectomized patients; response rates in splenectomized patients were less.<sup>126,133-136</sup> Evidence regarding its effect on morbidity or mortality is lacking.

The only clinically important adverse effect of anti-Rh(D) appears to be alloimmune hemolysis. All Rh(D)<sup>+</sup> patients develop a positive direct antiglobulin test after treatment, accompanied by a transient (1 to 2 weeks) decrease in hemoglobin concentration of about 0.5 to 2 g/dL. Although in two studies 4% to 24% of patients had a hemoglobin concentration of <10 g/dL after 7 to 14 days,<sup>48,74</sup> red blood cell transfusion was not required.

**Recommendations.** There is insufficient evidence to make recommendations regarding anti-Rh(D) treatment in adults. The opinion of the panel on anti-Rh(D) treatment of adults was not assessed.

### Splenectomy

**Evidence.** Splenectomy was the first effective treatment for ITP<sup>137</sup> and was an established therapeutic modality long

Table 12. Panel Opinion Regarding Initial Treatment Options in Adults

| Platelet Count   | Treatment Options  |   |   |
|--|--|---|---|
|  | Appropriate<br>(mean panel scores, 7-9)  | Appropriateness Uncertain<br>(mean panel scores, 3.1-6.9) | Inappropriate<br>(mean panel scores, 1-3)   |
| Platelet Count <20,000   |  |   |   |
| Asymptomatic   | Prednisone* (8.6, C)   | Hospitalization, IVIg†                                    | No treatment‡ (1.4-1.8, B)<br>Splenectomy (2-5, D)                                  |
| Minor purpura  | Prednisone (8.6, C)  | Hospitalization, IVIg                                     | No treatment (1.2-1.5, B)<br>Splenectomy (2.5, D)                                   |
| Mucous membrane or vaginal bleeding that may require clinical intervention | Prednisone (8.5-8.6, B-C)<br>Hospitalization (8.1, C)                          | IVIg  | No treatment (1.0, A)<br>Splenectomy (2.9, D)                                       |
| Severe, life threatening bleeding  | Hospitalization (8.8, B)<br>IVIg (8.5, C)<br>Prednisone (7.6, D)               | Splenectomy   | No treatment (1.0, A)   |
| Platelet Count 20-30 × 10 <sup>3</sup>                                     |  |   |   |
| Asymptomatic   |  | Prednisone, IVIg  | No treatment§<br>Hospitalization (1.8, B)<br>Splenectomy (2.5, D)                   |
| Minor purpura  | Prednisone (7.7, C)  | IVIg  | No treatment§<br>Hospitalization (2.2, C)<br>Splenectomy (2.5, D)                   |
| Mucous membrane or vaginal bleeding that may require clinical intervention | Prednisone (8.5, B)  | Hospitalization, IVIg                                     | No treatment (1.2, B)<br>Splenectomy (2.5, D)                                       |
| Severe, life-threatening bleeding  | Hospitalization (8.8, B)<br>IVIg (8.0, D)<br>Prednisone (1-2 mg/kg/d) (7.8, D) | Splenectomy   | No treatment (1.0, A)   |
| Platelet Count 30-50 × 10 <sup>3</sup>                                     |  |   |   |
| Asymptomatic   |  | Prednisone  | No treatment  <br>Hospitalization (1.2, B)<br>IVIg (1.6, B)<br>Splenectomy (2.1, D) |
| Minor purpura  |  | Prednisone  | No treatment  <br>Hospitalization (1.3, B)<br>IVIg (2.2, C)<br>Splenectomy (2.4, D) |
| Mucous membrane or vaginal bleeding that may require clinical intervention | Prednisone (7.3, C)  | Hospitalization, IVIg                                     | No treatment (2.0, B)<br>Splenectomy (2.4, D)                                       |
| Severe, life-threatening bleeding  | Hospitalization (8.8, B)<br>Prednisone (7.8, C)<br>IVIg (7.0, D)               |   | No treatment (1.0, A)<br>Splenectomy (2.7, D)                                       |

“Appropriate” and “Not appropriate” = mean panel score of 7.0-9.0 or 1.0-3.0, respectively, “Appropriate” = treatment may or may not be necessary, but performing is not wrong. “Inappropriate” = treatment should not be performed. Mean panel score is graded on a scale of “1” to “9”, with “1” representing low appropriateness and “9” representing high appropriateness. Letter codes following panel scores reflects strength of agreement, the panel consensus (defined by standard deviation) around the mean panel score. “A” = complete or virtual unanimity, “B” = strong agreement, “C” = moderate agreement, “D” = moderate disagreement, “E” strong disagreement (see Table 4).

\* Prednisone dose, 1-2 mg/kg/d.

† IVIg regimen, 1-2 g/kg given over 1-5 days.

‡ “No treatment” implies careful observation.

§ Not treating patients with a platelet count of 20-30 × 10<sup>5</sup> is inappropriate for patients age 60 or older (2.7, D) or for patients who have major risk factors for bleeding (eg, elevated blood pressure, ulcer disease, vigorous lifestyle) (1.6, B). For all other patients, appropriateness is uncertain.

|| Not treating patients with a platelet count of 30-50 × 10<sup>5</sup> is inappropriate for patients who have major risk factors for bleeding (eg, elevated blood pressure, ulcer disease, vigorous lifestyle) (2.9, C). For all other patients, appropriateness is uncertain.

before glucocorticoid therapy was introduced in 1950. Thirty-six case series describe the results of splenectomy, but all provide only level V evidence.<sup>26,76,90-100,102,138-161</sup> Moreover, the relevance of early studies to current clinical practice may be limited, because splenectomy was often performed as initial therapy and because early series often combined the results of children and adults. Not surprisingly, therefore, early studies reported better long-term results. In most recent case series restricted to adults, splenectomy was performed in patients who were either unresponsive to initial glucocorticoid therapy or in those for whom continued glucocorticoid therapy was required to maintain a safe platelet count. Most studies suggest that approximately two thirds of patients achieve and sustain a normal platelet count after splenectomy and require no additional therapy. Most other patients experience a lesser increase or only transient normalization of platelet counts, with approximately half of the relapses occurring within 6 months of splenectomy.<sup>158</sup> Over 80% of platelet responses occur within several days; responses may occur after 10 days but are uncommon.<sup>102,158</sup> There is some evidence that the rate and magnitude of platelet recovery may have prognostic value. Durable platelet responses has been correlated with platelet counts >150,000 on the first<sup>155</sup> or third postoperative day<sup>158</sup> or >500,000 on the 10th postoperative day.<sup>157</sup> No preoperative clinical parameters appear to have similar prognostic value; studies of the predictive value of an initial response to glucocorticoid therapy have yielded conflicting results. As in other aspects of ITP, younger patients appear to respond better to splenectomy than older patients.<sup>155,157,158</sup> No studies have specifically reported on morbidity or mortality after splenectomy.

Some evidence is available regarding the adverse effects of splenectomy in adults. Even in the face of severe thrombocytopenia, the immediate risks of clinically important intraoperative and postoperative hemorrhage appear small, approximately 1% in the 36 cited case series. Operative mortality rates were less than 1%, an impressive figure because these data include reports before the advent of platelet transfusions, IVIg, and effective antibiotics to manage postoperative infections. Most operative deaths occur in older patients with coexisting illnesses.<sup>45</sup> Postoperative morbidity may be related to the extent of previous glucocorticoid therapy.<sup>102</sup> Splenic or portal vein thrombosis may occur after splenectomy.<sup>162,163</sup> Postsplenectomy patients have a small but significantly increased susceptibility to fatal bacterial infection, although this appears to be less important in adults than in children. The estimated risk of fatal bacterial infection in splenectomized adults is about 1 per 1,500 patient-years,<sup>80,82</sup> but these estimates are from the era before immunization for *Strep pneumoniae* and were determined in patients splenectomized for other diseases.

**Recommendations.** Although all available evidence is level V, the efficacy of splenectomy is supported by the consistent incidence of sustained normalization of platelet counts in patients who had previously been refractory to glucocorticoid therapy for several weeks or years. However, there are inadequate data to make evidence-based recommendations on the appropriate indications and timing for splenectomy, on when the benefits of splenectomy outweigh

**Table 13. Panel Opinion Regarding Preoperative Prophylaxis Against Bleeding Before Elective Splenectomy in Adults**

| Appropriate               |                |         |
|---------------------------|----------------|---------|
| Preoperative Prophylaxis  | Platelet Count | Score   |
| IVIg                      | <10,000        | 7.9 (D) |
|                           | 10,000-20,000  | 7.5 (D) |
| Oral glucocorticoid       | <10,000        | 7.7 (C) |
|                           | 10,000-20,000  | 7.3 (C) |
| Appropriateness Uncertain |                |         |
| Preoperative Prophylaxis  | Platelet Count |         |
| IVIg                      | 20,000-50,000  |         |
| Platelet transfusion      | <10,000        |         |
| Anti-D                    | <50,000        |         |
| Oral glucocorticoid       | 20,000-50,000  |         |
| Parenteral glucocorticoid | <50,000        |         |
| Inappropriate             |                |         |
| Preoperative Prophylaxis  | Platelet Count | Score   |
| IVIg                      | 50,000-100,000 | 2.1 (C) |
|                           | 10,000-20,000  | 2.3 (D) |
|                           | 20,000-30,000  | 1.9 (C) |
|                           | 30,000-50,000  | 1.4 (B) |
| Anti-D                    | 50,000-100,000 | 1.1 (A) |
|                           | 50,000-100,000 | 1.8 (C) |
| Oral glucocorticoid       | 50,000-100,000 | 2.7 (D) |
| Parenteral glucocorticoid | 50,000-100,000 | 2.1 (C) |

"Appropriateness" and scores are defined in text and Table 2. Doses and regimens were not specified in the questions to the panel.

its potential harms, and on appropriate preoperative management.

Based on opinion, the panel reached consensus on only selected indications for splenectomy. Assuming that primary treatment (glucocorticoid) has been unsuccessful and that there are no medical contraindications to the procedure, the panel considered splenectomy appropriate in the following hypothetical situations: (1) patients who have had the diagnosis for 6 weeks, have a platelet count <10,000, and have no bleeding symptoms, (7.5, C), and (2) patients who have had the diagnosis for 3 months, have experienced a transient or incomplete response to primary treatment, have a platelet count of <30,000, and are either bleeding (8.5, B) or not bleeding (7.4, C). The panel reached consensus that splenectomy is inappropriate in nonbleeding patients who have had the diagnosis for 6 months and have a platelet count >50,000 and low hemostatic risk (eg, not engaged in potentially traumatic activities) (1.9, C). The panel also considered splenectomy inappropriate (1.6 to 2.9, C-D) as initial therapy in patients who have no bleeding, minor purpura, or even significant mucous membrane bleeding. Further recommendations regarding the appropriate timing of splenectomy in patients who do not respond completely to initial glucocorticoid treatment are presented below.

If an elective splenectomy is planned, the panel considered it appropriate to provide preoperative prophylaxis with IVIg

(7.5 to 7.9, D) or oral glucocorticoid therapy (7.3 to 7.7, C) in patients with platelet counts <20,000 to reduce the risk of intraoperative and postoperative bleeding (Table 13). Preoperative prophylaxis that the panel considered inappropriate included treatment for platelet counts >50,000, using IVIg (2.1, C), oral or parental glucocorticoid therapy (2.1 to 2.7, C-D), or anti-D (1.8, C). Platelet transfusions were considered inappropriate as preoperative prophylaxis for platelet counts >10,000 (1.1 to 2.3, A-D).

The panel endorsed the recommendations of the Advisory Committee on Immunization Practices that, at least 2 weeks before elective splenectomy, patients should be immunized with polyvalent pneumococcal vaccine, *Hemophilus influenzae* b vaccine, and quadrivalent meningococcal polysaccharide vaccine.<sup>84</sup>

#### Other Treatments

**Evidence.** The treatment options discussed in this section have not been compared with other treatments (or to no treatment) in controlled trials and have not been shown to reduce clinically important bleeding or mortality. The order of discussion does not reflect their relative effectiveness or appropriateness.

**Splenic radiation.** Two level V studies of 18 patients who had not responded to at least 1 month of glucocorticoid therapy and in whom splenectomy was contraindicated reported that four patients achieved sustained (>3 to 12 months) platelet counts >100,000.<sup>164,165</sup> A potential adverse effect of splenic radiation is the production of adhesions surrounding the spleen, which may complicate subsequent splenectomy.

**Partial splenic embolization.** One level V study described 26 patients who had not completely responded to glucocorticoid therapy who then underwent angiographically directed gelfoam embolization; seven maintained platelet counts >100,000 for 9 to 67 months with no additional therapy.<sup>166</sup> In this report the adverse effects of partial splenic embolization included fever, pain, and nausea in 81% to 100% of patients and perisplenic fluid or pleural effusion in 10% to 19% of patients. Another potential adverse effect is splenic abscess or rupture.

**Accessory splenectomy.** Eight case series (level V evidence)<sup>152,167-173</sup> suggest that platelet counts are increased in about half of patients, and 10% to 30% of patients may have sustained, normal platelet counts. During primary splenectomy, the abdomen is generally inspected for accessory spleens; in the 11 case series of splenectomy in which the observation and removal of accessory spleens was mentioned<sup>76,138,140,142,146,150,152,155,156,161,174</sup> accessory spleens were observed in 15% of patients. In a study<sup>173</sup> of 65 patients who either failed splenectomy or relapsed after splenectomy, 12% of patients were found to have an accessory spleen by radio-nuclide imaging. No studies have shown that accessory splenectomy reduces morbidity or mortality. The potential adverse effects of accessory splenectomy are similar to those of splenectomy.

**Azathioprine.** Four case series (level V evidence)<sup>100,175-178</sup> suggest that about 20% of patients may achieve a normal platelet count, sustained for several months to years without

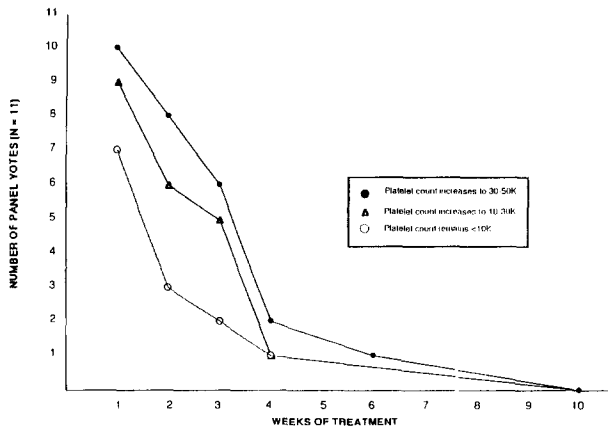
treatment. An additional one half of patients may improve their platelet counts but require continuous azathioprine treatment. Continuous treatment for at least four months appears to be necessary before a patient is considered unresponsive.<sup>178</sup> The potential adverse effects of azathioprine include reversible leukopenia and a small, but possibly significant, increase of developing a malignancy<sup>179</sup> and in the risk of developing fetal malformations during pregnancy.<sup>180</sup> One study<sup>178</sup> of 53 patients with persistent thrombocytopenia reported that five died from hemorrhage with severe thrombocytopenia. It is uncertain if the high mortality was caused by preferential selection of severely affected patients, lack of efficacy, or worsened thrombocytopenia caused by azathioprine-induced marrow suppression.

**Cyclophosphamide.** Five case series (level V evidence)<sup>100,181-185</sup> suggest that cyclophosphamide increases platelet counts in 60% to 80% of patients, and 20% to 40% of patients maintain normal platelet counts for 2 to 3 years after discontinuing treatment. The primary toxicity of cyclophosphamide is reversible leukopenia. More serious adverse effects have been reported, including alopecia, teratogenicity, infertility, and urinary bladder hemorrhage and fibrosis.<sup>179</sup> Carcinogenicity, including increased risk of myelodysplasia and acute leukemia, has been suggested in case reports.<sup>186,187</sup>

**Vinca alkaloids.** Twelve case series (level V evidence)<sup>100,188-198</sup> and a level II study that compared two methods of vinblastine administration<sup>199</sup> suggest that vinca alkaloids may produce a transient increase in platelet counts lasting 1 to 3 weeks in two-thirds of patients, but a sustained normal platelet count (requiring no further treatment for at least 3 months) occurs in less than 10% of patients. The populations in these studies were heterogeneous, including untreated patients and patients with ITP of short duration, chronic refractory ITP, and with mild to severe thrombocytopenia. Potential adverse effects of vinca alkaloids include neutropenia (vinblastine), fever, and inflammation/thrombophlebitis at the infusion site; neuropathy was reported in 10 of the 13 reports. One death from sepsis during a leukopenic episode was reported after vinblastine infusion.<sup>199</sup> In one study of the infusion of "vinblastine-loaded" platelets (platelets incubated with vinblastine), 3 of 16 patients had a 30% to 80% decrease in their platelet count within 24 hours of treatment.<sup>192</sup>

**Danazol.** Fourteen case series (level V evidence),<sup>200-213</sup> in which about half of the patients were from a single institution, reported variable rates of response to danazol, ranging from 10% to 80%. The potential adverse effects of danazol include weight gain, headaches, hair loss, myalgia, amenorrhea, and liver dysfunction. Danazol has been a suspected cause of acute thrombocytopenia in seven patients.<sup>213-216</sup> Danazol may be contraindicated in patients with preexisting liver disease; one case series reported abnormal liver function tests in 41% of patients.<sup>211</sup>

**Ascorbic acid (vitamin C).** Eight case series (level V evidence)<sup>217-224</sup> reported that 15% of patients had increased platelet counts, but other medications were being taken concurrently. The potential adverse effects of ascorbic acid include occasional epigastric pain or dyspepsia.



**Fig 3.** Length of time panel members would continue initial prednisone treatment (1 mg/kg) before adding to or changing the regimen in a hypothetical 30-year-old woman who presented initially with a platelet count <10,000. Votes were stratified to reflect different platelet count responses to treatment. The figure illustrates that, if the platelet count remains below 10,000, 4 panel members would add to or change treatment after 1 week, whereas 1 panel member would not change treatment until 10 weeks.

**Colchicine.** Two case series<sup>225,226</sup> report conflicting level V evidence regarding the effectiveness of colchicine. The principal adverse effect of colchicine is dose-dependent diarrhea.

**Protein A-immunoabsorption.** One case series (level V evidence)<sup>227</sup> reported that 18 of 72 patients achieved a platelet count >100,000, which was sustained in 16 patients. Earlier publications<sup>228,229</sup> included segments of this same patient population (Guthrie TH, personal communication, August 1995). The potential adverse effects include fever, chills, nausea, vomiting, and urticaria, which occur in most patients. Hypotension, serum sickness, and leukocytoclastic vasculitis with thrombosis have also been reported.<sup>227,230,231</sup>

**Plasma exchange.** Three case series (level V evidence)<sup>232-234</sup> reported that platelet counts increased to normal for 1 to 4 weeks in 5 of 18 patients with chronic ITP; no sustained responses were described. Potential adverse effects include allergic reactions to plasma proteins and a risk for transmissible viral infections.

**2-Chlorodeoxyadenosine.** One case series (level V evidence) of seven patients reported no favorable responses.<sup>235</sup>

**Combination chemotherapy.** One case series (level V evidence) of 10 patients<sup>236</sup> reported that five patients achieved normal platelet counts that were sustained for 11 to 126 months. Four patients died, 3 from intracerebral hemorrhage and 1 from a stroke when the platelet count was normal. The potential adverse effects of combination chemotherapy include marrow suppression with leukopenia and worsening of thrombocytopenia, and the risks cited above for individual agents, cyclophosphamide and vinca alkaloids.

**Interferon- $\alpha$  (IFN- $\alpha$ ).** Four case series (level V evidence)<sup>237-241</sup> reported that 25% of patients achieved platelet counts greater than 100,000 for 1 week to 7 months. The major adverse effects include fever, fatigue, and myalgias.

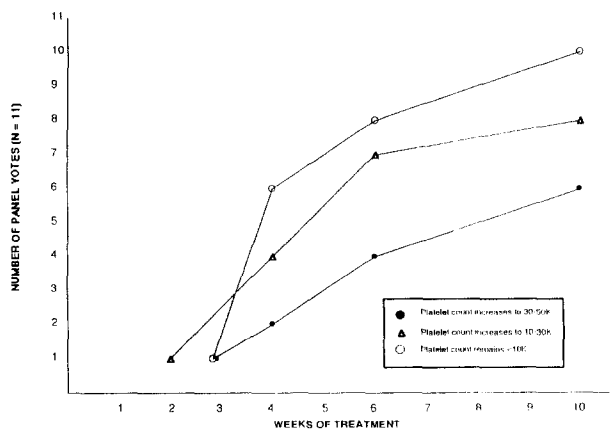
Some reports<sup>241-243</sup> suggest that IFN- $\alpha$  may worsen thrombocytopenia.

**Cyclosporine A.** No published evidence that met panel criteria is available.

**Aminocaproic acid.** In contrast to other modalities discussed in this section, aminocaproic acid has not been used to increase the platelet count but rather to diminish bleeding symptoms. One case series (level V evidence)<sup>244</sup> of seven patients suggested that it helped control bleeding. Its potential adverse effects include an increased risk of thromboembolism.

### Recommendations

To assess opinion on the management of patients who do not respond, or respond incompletely, to initial treatment with prednisone, the panel ranked selected treatment options for a hypothetical 30-year-old woman who presents with a platelet count <10,000 and bleeding symptoms consisting of purpura, menorrhagia, and epistaxis and who is treated initially with prednisone (1 mg/kg/d). Depending on the platelet count, most panel members would alter the treatment plan after 2 to 4 weeks if the patient did not respond (or responded incompletely) to this dose of prednisone (Fig 3). Most panel members would recommend elective splenectomy after 4 to 6 weeks of unsuccessful medical therapy (Fig 4). However, the range of opinions on the panel included one panel member who recommended splenectomy as early as 2 weeks and another who did not recommend splenectomy after 10 weeks with no response. Most panel members would use IVIg at some time during the course of treatment for persistent platelet counts <30,000. Other preferred options were increased doses of prednisone, dexamethasone, anti-D,



**Fig 4.** Length of time after which panel members would recommend splenectomy after treating a hypothetical 30-year-old woman who presented initially with a platelet count <10,000. 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 to 6 weeks of unsuccessful medical therapy. Panel member opinions were varied, with one panelist recommending splenectomy as early as 2 weeks and another not recommending splenectomy even after 10 weeks of unsuccessful treatment.



and danazol. If this hypothetical patient responded with a normal platelet count at 3 weeks, but then relapsed to a platelet count of 10,000 when prednisone was tapered over the following 5 weeks, most panel members recommended prompt splenectomy, though the range of time was 1 to 10 weeks after the occurrence of the relapse. Three of 11 panel members did not recommend splenectomy in this situation, but favored a repeat trial of prednisone or the use of danazol.

The indications for further treatment in patients who are refractory to primary treatment with glucocorticoids and splenectomy are unclear. There are insufficient data to develop evidence-based recommendations for when different treatments should be used, for comparing one treatment with another, or for assessing which treatments result in more good than harm. Based on opinion, the panel recommended against further treatment of patients with platelet counts >30,000 who have failed to respond to splenectomy and have no bleeding symptoms (2.7, C for platelet count of 30,000 to 50,000; 1.3, B for platelet count >50,000). Further treatment was recommended (8.9, A) for patients with platelet counts <30,000 who have active bleeding. In patients who have responded incompletely to treatment with both prednisone and splenectomy, the preferred treatment options recommended by the panel are listed in Table 14. Reflecting the lack of evidence that any single treatment is more effective than another, there was little panel consensus regarding preferred regimens.

## ITP in Pregnant Women and Newborns

### Diagnosis

**Evidence.** The diagnosis of ITP is more difficult during pregnancy because the presentation may closely resemble that of gestational thrombocytopenia (also termed incidental thrombocytopenia of pregnancy). Gestational thrombocytopenia is the most common cause of thrombocytopenia during pregnancy, occurring in as many as 5% of pregnant women at term<sup>245,246</sup> and accounting for about 75% of cases of thrombocytopenia at term.<sup>245</sup> Thrombocytopenia associated with pregnancy-induced hypertension and the HELLP syndrome (an acronym used to describe hemolysis, elevated liver function tests, and a low platelet count) accounted for most of the remaining 25% of cases.<sup>245</sup> Pregnancy-induced hypertension, or preeclampsia, occurs in about 10% of pregnancies, principally after 20 weeks of gestation, and thrombocytopenia may occur in up to 25% of these patients.<sup>245-248</sup> ITP is therefore a relatively uncommon cause of thrombocytopenia in pregnancy. 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 during late gestation, (4) that is not associated with fetal thrombocytopenia, and (5) that resolves spontaneously after delivery. Platelet counts are typically greater than 70,000, with about two thirds being between 130,000 and 150,000. ITP cannot be distinguished from gestational thrombocytopenia with certainty because the diagnosis of both conditions is based on the observation of thrombocytopenia with no other apparent cause. Although ITP may compose a higher percentage of cases when the

platelet count is <70,000, or when thrombocytopenia is discovered earlier in pregnancy, gestational thrombocytopenia may still be the appropriate diagnosis if the thrombocytopenia resolves spontaneously after delivery. However severe, refractory thrombocytopenia presumably due to ITP may also promptly remit after delivery.<sup>249</sup>

The differential diagnosis between ITP and gestational thrombocytopenia is generally of little clinical importance with regard to the mother, because most cases in which the diagnosis is unclear involve mild thrombocytopenia that does not threaten maternal health. However, the presence of mild thrombocytopenia may influence the decision for regional anesthesia at vaginal delivery, though spinal or epidural hematomas have not been reported in thrombocytopenic women at delivery.<sup>250</sup> The differential diagnosis between ITP and gestational thrombocytopenia is clinically important with regard to the fetus, because ITP with even mild thrombocytopenia may harm the fetus, whereas gestational thrombocytopenia does not.<sup>245</sup>

### Recommendations

Current evidence does not provide a scientific basis for distinguishing ITP from gestational thrombocytopenia. A thorough history is important because evidence of previous thrombocytopenia at a time when the patient was not pregnant suggests the diagnosis of ITP. When no prior platelet counts are available and other causes of thrombocytopenia are excluded, the diagnosis rests largely on the severity of thrombocytopenia and the time during gestation when thrombocytopenia is first discovered.

For example, the panel was given the hypothetical case of a healthy primiparous woman with no history of thrombocytopenia, no bleeding symptoms or pregnancy complications and whose history, physical examination, and initial blood counts and smear are compatible with the diagnosis of ITP. In such a case, the panel would consider ITP the likely diagnosis if the platelet count was below 50,000 (7.3 to 8.5, B-C for platelet count of 30,000 to 50,000; 8.8 to 9.0, A-B, for <30,000) at any time during pregnancy. ITP would be considered an unlikely diagnosis if the platelet count was more than 70,000 in the third trimester or at term (1.3 to 2.1, B).

The diagnosis of ITP during pregnancy does not require special laboratory testing. Blood pressure measurement was considered necessary (7.6, D), and appropriate (8.9, A), to rule out preeclampsia in the evaluation for ITP. Liver function tests were also considered appropriate (7.5, C). In patients with risk factors for HIV infection, testing for HIV antibody was considered necessary (7.5, D) and appropriate (8.9, A). The panel reached consensus that five tests in particular were unnecessary as part of the routine evaluation of pregnant women presenting with suspected ITP (Table 7).

### Treatment During Pregnancy

**Evidence.** There are few data to distinguish management of ITP in pregnant women from that of nonpregnant patients. However, management in the antepartum period is distinctive because of concerns about the teratogenicity of certain

**Table 14. Panel Opinion Regarding Preference for Various Treatment Modalities in an Adult Patient Who Has Responded Incompletely to Prednisone and Splenectomy**

| Platelet Count | Bleeding Symptoms* | Treatment Options†       |                          |                          |
|----------------|--------------------|--------------------------|--------------------------|--------------------------|
|                |                    | Higher Preference‡       | Intermediate Preference‡ | Lower Preference‡        |
| <10,000        | Yes                | IVIg                     | Low-dose glucocorticoid  | Anti-D                   |
|                |                    | Accessory splenectomy    | Vinca alkaloids          | Ascorbic acid            |
|                |                    | High-dose glucocorticoid | Cyclophosphamide         | Cyclosporine             |
|                |                    | Danazol                  | Combination chemotherapy | Colchicine               |
|                |                    | Azathioprine             | Protein A column         | Interferon               |
| 15-25,000      | Yes                | IVIg                     | Low-dose glucocorticoid  | Anti-D                   |
|                |                    | Accessory splenectomy    | Danazol                  | Ascorbic acid            |
|                |                    | High-dose glucocorticoid | Vinca alkaloids          | Cyclosporine             |
|                |                    | Azathioprine             | Cyclophosphamide         | Colchicine               |
|                |                    | Combination chemotherapy | Interferon               |                          |
|                |                    | Protein A column         |                          |                          |
| <10,000        | No                 | IVIg                     | Low-dose glucocorticoid  | Anti-D                   |
|                |                    | Accessory splenectomy    | High-dose glucocorticoid | Ascorbic acid            |
|                |                    | Danazol                  | Vinca alkaloids          | Colchicine               |
|                |                    | Azathioprine             | Cyclophosphamide         | Cyclosporine             |
|                |                    | Combination chemotherapy | Interferon               |                          |
|                |                    | Protein A column         |                          |                          |
| 15-25,000      | No                 | (None)                   | High-dose glucocorticoid | Ascorbic acid            |
|                |                    |                          | Accessory splenectomy    | Vinca alkaloids          |
|                |                    |                          |                          | Colchicine               |
|                |                    |                          |                          | Protein A column         |
|                |                    |                          |                          | Anti-D                   |
|                |                    |                          |                          | Cyclophosphamide         |
|                |                    |                          |                          | Combination chemotherapy |
| 30-50,000      | No                 | (None)                   | (None)                   | High-dose glucocorticoid |
|                |                    |                          |                          | Accessory splenectomy    |
|                |                    |                          |                          | Danazol                  |
|                |                    |                          |                          | Ascorbic acid            |
|                |                    |                          |                          | Low-dose glucocorticoid  |
|                |                    |                          |                          | Anti-D                   |

It is assumed that the patient is a 30-year-old otherwise healthy woman who has responded incompletely to initial therapy consisting of prednisone, 1 mg/kg/d, and splenectomy. For each clinical situation, the panel was asked to rank in order their preference among the treatment options listed below. If it was believed that more than one treatment option should be used concurrently, they were ranked with the same number. If any treatment options were believed to be not indicated or inappropriate, they were not selected. This question was completed by 11 panel members.

\* Bleeding symptoms, when indicated, consist only of purpura, intermittent spontaneous epistaxis, and gingival bleeding.

† Treatment options are defined as follows: "Low-dose glucocorticoid" would begin with 1 mg/kg/d of prednisone and would taper to the lowest dose supporting an acceptable platelet count, with the goal of establishing an effective dose at which side effects would be tolerable. "High-dose glucocorticoid" would be dexamethasone, 40 mg/d for 4 days, repeated every 4 weeks for 6 cycles. "IVIg" would be given as needed at a dose of 1 g/kg, or repeated intermittently at a lower dose, to maintain an acceptable platelet count. "Anti-D" would be given as needed. "Accessory splenectomy" assumes radioisotope scanning studies demonstrate a probable accessory spleen. "Vinca alkaloids" includes vincristine and vinblastine. "Cyclophosphamide" would be given daily orally or as intermittent intravenous doses. "Combination chemotherapy" would include cyclophosphamide-vincristine-prednisone (CVP), CVP-procarbazine, or cyclophosphamide-etoposide-prednisone. Modalities not selected by any panel members included dapson, plasma exchange, 6-mercaptopurine, methotrexate, and 2-chlorodeoxyadenosine.

‡ Options ranked as higher preferences received votes from 8-11 panel members, intermediate preference 4-7 panel members, and lower preference 0-3 panel members. Within each preference list, the order was determined using a score derived by the mean ranking of the treatment option divided by the number of votes that option received.

drugs, the timing of delivery and the requirement for good hemostasis at delivery, and the risk of neonatal hemorrhage. Some neonates born to mothers with ITP develop thrombocytopenia, because of placental transfer of anti-platelet antibodies, and may be at increased risk of intracranial hemorrhage (ICH). Clinically important intrauterine hemorrhage

has not been reported in ITP, in contrast to neonatal alloimmune thrombocytopenia.<sup>245,248</sup> In 30 series published since 1980 that reported on thrombocytopenia in 656 neonates born to mothers with ITP, the risk of a newborn having a platelet count <50,000 ranged from 0% to 60%, with a weighted mean of 13%.<sup>245,251-279</sup> One third (28) of the throm-

**Table 15. Fetal Samples To Assess Neonatal Thrombocytopenia and Intracranial Hemorrhage in Infants Born to Mothers With ITP**

| Case Series*    | No. of Pregnancies/Births | Fetal Platelet Count†       |                        | No. of Infants With ICH‡ or Death |
|-----------------|---------------------------|-----------------------------|------------------------|-----------------------------------|
|                 |                           | <50,000<br>(no. of infants) | <20,000                |                                   |
| A. ≥10 patients | 286/288                   | 29<br>10.1% (6.6-13.5%)§    | 12<br>4.2% (1.9-6.5%)  | 0                                 |
| B. <10 patients | 34/34                     | 8<br>23.5% (9.2-37.8%)      | 4<br>11.8% (1.0-22.6%) | 0                                 |

| 29 Infants With Platelet Counts <50,000 From Case Series Reporting 10 or More Patients |   |
|--|---|
| Mode of Delivery   | Bleeding Symptoms in the Infant¶                        |
| Cesarean section   | 17  |
| Vaginal delivery   | 5   |
| Not stated   | 7   |
|  | 9/29 (31%; 7/17 cesarean section, 2/5 vaginal delivery) |

\* All case series published from January 1980-December 1990 in which a fetal platelet count was reported were reviewed. Case series were divided between those reporting 10 or more patients and those reporting <10 patients.

† Data were examined to determine the timing of the neonatal platelet count; fetal platelet counts, or platelet counts "at birth," were distinguished from later counts which may be lower. Platelet counts were accepted as fetal or "at birth" if they were obtained from cord blood either by prenatal percutaneous cordocentesis (PUBS) or umbilical vein blood at delivery, or from a fetal scalp vein confirmed by a neonatal platelet count.

‡ ICH, intracranial hemorrhage.

§ 95% confidence interval.

|| Data insufficient for analysis from reports with <10 patients.

¶ Bleeding symptoms included petechiae, purpura, melena, or hematuria.

Adapted with permission from Burrows RF, Kelton JG: Pregnancy in patients with idiopathic thrombocytopenic purpura: Assessing the risks for the infant at delivery. *Obstetrical & Gynecological Survey*, volume 48, number 12, pp 781-788, 1993.<sup>280</sup>

bocytopenic infants had bleeding complications; however, these data are difficult to evaluate because of inconsistencies in the reported severity of bleeding. Of the 28 infants with bleeding complications, 4 had intracranial hemorrhage and 2 of these infants died; 2 were premature.<sup>252,278,279</sup> Whether any infants had permanent sequelae is unknown. A review of studies from 1980 to 1990<sup>280</sup> concluded that 10% of infants born to women with ITP have a fetal platelet count <50,000 and 4% have a fetal platelet count <20,000 (Table 15). In this analysis, studies describing fetal platelet counts obtained before or at birth were distinguished from studies describing only neonatal platelet counts (see Table 15), which may have been obtained some time after delivery and may therefore have been lower than the platelet count at birth. Further review of studies of an additional 552 pregnancies (557 live births) for which only neonatal platelet counts were reported documented seven infants (1.3%) with intracranial hemorrhage or death.<sup>280</sup>

Maternal or fetal platelet counts have limited utility in predicting the risk of hemorrhage or in informing decisions about whether cesarean section is indicated. Cesarean section is often recommended over vaginal delivery on the assumption that it is less traumatic to the newborn, but there is no direct evidence of this benefit<sup>281,282</sup> (Table 15). The maternal platelet count does not correlate with the fetal platelet count.<sup>245,253,255,258,260-262,265,269,270,274</sup> Fetal platelet count specimens can only be obtained through percutaneous umbilical blood sampling (PUBS) or fetal scalp vein sampling after cervical dilation; newborn samples can be obtained at birth by umbilical cord sampling or capillary blood specimens obtained by heel prick. Each test has its limitations. Although

platelet counts obtained by PUBS within 5 days before delivery appear to correlate with platelet counts at birth,<sup>269,276,283</sup> the procedure should be performed only by experienced physicians at referral centers, with patients prepared for immediate cesarean section in the event of fetal complications. PUBS can induce fetal distress, bleeding, and death; bradycardia is noted in 2% to 14% of fetuses.<sup>269,270,283-286</sup> Fetal scalp vein specimens can only be obtained after cervical dilation, and accurate platelet counts are obtained in only one half to two thirds of attempts because of inadequate samples and platelet clumping.<sup>271,287,288</sup> Fetal scalp vein sampling may cause a cephalohematoma. Platelet levels in fetal scalp vein samples may be more accurately assessed by examining a stained blood smear.<sup>272,289</sup>

An important difference between the treatment of ITP in pregnant women and nonpregnant adults is the potential adverse effects of treatment on the course of pregnancy and fetal development. Glucocorticoids, for example, are considered safe in terms of potential teratogenicity but may have other fetal toxicities.<sup>290</sup> In the mother they may exacerbate gestational diabetes mellitus and postpartum psychiatric disorders.<sup>246</sup> IVIg is considered to be safe for the fetus, having only adverse effects for the mother as described above. Cytotoxic agents such as cyclophosphamide, vinca alkaloids, and azathioprine are avoided during pregnancy because of an assumed risk of teratogenicity, although there are few data regarding the magnitude of the risk.<sup>180,291-293</sup> Splenectomy may increase the risk of preterm labor during the first trimester and can be technically difficult because of the size of the uterus in the third trimester, but data regarding the magnitude of risk are lacking.

### Recommendations

The special issues in caring for pregnant women with ITP cannot be addressed through evidence-based recommendations, because there is no evidence that current testing and treatment options produce a better outcome for the mother or newborn. Recommendations based on opinion were derived from a questionnaire completed by nine panel members with expertise in obstetrical and neonatal care of ITP. In the panel's opinion, women with ITP should not be discouraged from becoming pregnant if they have platelet counts >50,000 (1.7 to 2.4, B-D), but they should be discouraged if they have a platelet count <10,000 after splenectomy and other treatments (8.0, B).

**Prenatal care.** The panel's opinion was that it is appropriate (but not necessary) for prenatal care of women with ITP to be managed by an obstetrician who specializes in high-risk pregnancies (7.4, D) or for such a specialist to act as a consultant (8.3, C). The panel reached consensus about the following treatment options during the prenatal period (options for which the panel could not reach consensus are listed in Table 6).

(1) *No treatment.* Observation (no specific treatment) was considered appropriate for women with platelet counts >50,000 (8.3-9.0, A-C) and those with platelet counts of 30,000 to 50,000 in the first and second trimesters (7.5 B) but inappropriate in women with platelet counts <10,000 (1.0 to 1.3, A-B) or in women with platelet counts of 10,000 to 30,000 who are in their second or third trimester (1.8 to 2.9, B-C) or are bleeding (1.0 to 1.3, A-B).

(2) *Glucocorticoids.* There was strong disagreement about the appropriateness of treating pregnant women initially with glucocorticoids (eg, prednisone) when platelet counts are <10,000. However, the panel agreed that glucocorticoid therapy is inappropriate when platelet counts exceed 50,000 (1.0, A for first-second trimester, 2.0, C for third trimester) or when platelet counts of 30,000 to 50,000 occur in the first-second trimester (2.3 to 2.6, D).

(3) *IVIg.* The panel considered IVIg appropriate initial treatment in the third trimester for pregnant women with platelet counts <10,000 (7.0 to 7.4, D) or for women with platelet counts of 10,000 to 30,000 who are bleeding (7.4, D). After failure of initial glucocorticoid treatment, IVIg was considered appropriate in any trimester in women with platelet counts <10,000 (8.8 to 9.0, A-B), in women with platelet counts of 10,000 to 30,000 who are bleeding (8.5 to 8.8, B), and in asymptomatic women with counts of 10,000 to 30,000 in the third trimester (8.5, B). However, like glucocorticoids, IVIg was considered inappropriate when platelet counts exceed 50,000 (1.0 to 1.3, A-B) or when counts of 30,000 to 50,000 occur in the first-second trimester (1.6 to 1.8, B-C).

(4) *Splenectomy.* Splenectomy was considered appropriate in women in the second trimester who have failed glucocorticoid and IVIg therapy, have platelet counts <10,000, and are bleeding (7.3, C), but it was considered inappropriate in asymptomatic patients with counts >10,000 (1.3 to 2.9, B-D for counts of 10,000 to 50,000; 1.0, A for counts >50,000).

**Table 16. Panel Opinion Regarding the Role of Percutaneous Umbilical Blood Sampling and Fetal Scalp Vein Platelet Count**

| Maternal Clinical Features  |                      |                   |   |
|---|----------------------|-------------------|---|
| Platelet Count History  | Prior History of ITP | Prior Splenectomy | Recommendations   |
| 75,000 at term, normal in 1st trimester   | No                   | No                | Not recommended<br>PUBS (1.3, B)<br>FPC (1.7, C)        |
| 75,000 in 1st trimester, which remains unchanged on no treatment throughout pregnancy | No                   | No                | Not recommended<br>PUBS (2.1, C)<br>FPC (2.4, D)        |
| 40,000 in 3rd trimester, normal in 1st trimester                                      | No                   | No                | Not recommended<br>PUBS (2.9, C)<br>FPC (3.0 D)         |
| Normal  | Yes                  | No                | Not recommended<br>PUBS (2.0, B)<br>(FPC, no consensus) |
| Normal  | Yes                  | Yes               | Not recommended<br>FPC (2.7, D)<br>(PUBS, no consensus) |
| Normal, but previous infant with count of 20,000 at birth                             | Yes                  | Yes               | (No consensus)  |

Assumes pregnancy is otherwise uncomplicated and that PUBS procedures are commonly performed at the hospital. "Recommended" and "Not recommended" = mean panel score of 7.0-9.0 or 1.0-3.0, respectively, for necessity/appropriateness. Scores are defined in text and Table 2.

Abbreviations: PUBS, percutaneous umbilical blood sampling; FPC, fetal scalp vein platelet count.

In summary, there was a difference in the panel's approach to treating ITP in pregnant women and nonpregnant adults (Table 12). The panel agreed that glucocorticoids were appropriate initial therapy in nonpregnant adults but could not reach consensus about whether they were more or less appropriate than IVIg in pregnant women. The wide variation of opinion regarding prednisone and IVIg as initial treatment reflected a difference in the panel's choice for one agent or the other. In nonpregnant adults, IVIg was considered appropriate initial treatment only for severe, life-threatening bleeding, whereas in pregnant women it was also recommended as initial treatment for women with platelet counts <10,000 or counts of 10 to 30,000 accompanied by bleeding. The panel also set a higher threshold for the indications for splenectomy in pregnant women than in nonpregnant adults, reflecting its concern about the risks to the mother and fetus.

**Antepartum care.** Current data provide an inadequate basis for making evidence-based recommendations on whether and how to predict the risk of neonatal thrombocytopenia and on the preferred route of delivery as term approaches. The panel's opinion was that a history of a previous infant with a platelet count <50,000 at birth (and no evidence of alloimmune thrombocytopenia) was important information in estimating the risk of fetal thrombocytopenia (8.1, B). Beyond the history, however, the panel had little enthusiasm for laboratory testing to predict risks. It considered testing for maternal platelet antibodies unnecessary (2.3, B). The panel also lacked enthusiasm for performing PUBS (2.0, B) in women with known ITP and normal platelet counts (and no prior history of splenectomy), or fetal scalp vein sampling when such women have had prior splenectomy (2.7, D) (Table 16). In pregnant women without known

**Table 17. Panel Opinion Regarding the Management of Delivery in a Primiparous Woman With Known ITP**

| Maternal Platelet Count | Prior Splenectomy | Fetal Platelet Count | Cesarean Section          | Vaginal Delivery          |
|-------------------------|-------------------|----------------------|---------------------------|---------------------------|
| Normal                  | No                | NA                   | Not recommended<br>1.0, A | Recommended<br>9.0, A     |
| Normal                  | Yes               | NA                   | Not recommended<br>2.1, B | Recommended<br>8.0, B     |
| 100-150,000             | No                | NA                   | Not recommended<br>1.3, B | Recommended<br>8.6, B     |
| 50-100,000              | No                | NA                   | Not recommended<br>1.8, B | Recommended<br>8.4, B     |
| <50,000                 | Yes               | NA                   | No consensus              | No consensus              |
| <50,000                 | No                | NA                   | Not recommended<br>2.6, B | Recommended<br>7.6, B     |
| 50-100,000              | Yes               | NA                   | Not recommended<br>2.9, B | Recommended<br>7.3, B     |
| 50-100,000              | Yes               | 50,000 (scalp vein)  | No consensus              | Recommended<br>7.0, D     |
| 50-100,000              | No                | 50,000 (scalp vein)  | Not recommended<br>2.9, D | Recommended<br>7.4, D     |
| Normal                  | Yes               | <50,000 (PUBS)       | No consensus              | No consensus              |
| Normal                  | Yes               | <20,000 (PUBS)       | Recommended<br>7.9, B     | Not recommended<br>2.4, B |

Assumes no current treatment and an otherwise uncomplicated pregnancy. "Recommended" and "Not recommended" = mean panel score of 7.0-9.0 or 1.0-3.0, respectively. Scores are defined in text and Table 2.

Abbreviation: NA, not applicable or not known.

ITP, the panel also did not support performing PUBS (1.3 to 2.9, B-C) or fetal scalp vein sampling (1.7 to 3.0, C-D), even with maternal platelet counts of 40,000 to 75,000 at term. Nonetheless, the panel acknowledged that information obtained from these tests would influence the preferred route of delivery (see below). The panel reached consensus about the following potential interventions to reduce newborn complications (options for which consensus was not reached are listed in Table 6).

(1) *Maternal treatment.* Given the hypothetical case of a pregnant woman who had ITP and a previous infant with a platelet count of 20,000 at birth, glucocorticoid therapy to increase the fetal platelet count before delivery was considered unnecessary (2.1, B) and inappropriate (3.0, C). In this case, IVIg was also considered unnecessary (2.9, C).

(2) *Prophylactic platelet transfusions.* Platelet transfusions to prevent maternal bleeding during labor and delivery were considered unnecessary for women with platelet counts >30,000 and no bleeding symptoms for either vaginal delivery (1.0, A) or cesarean section (1.0, A for >50,000; 2.9, D for 30 to 50,000). Platelet transfusions were considered to be indicated in women with platelet counts <10,000 who have minor purpura and who require cesarean section (7.9, D) and in women with platelet counts <10,000 who have epistaxis or other mucous membrane bleeding (7.1, D for vaginal delivery; 8.4, B for cesarean section).

(3) *Route of delivery.* When asked to define the minimum platelet count required for vaginal delivery with no anticipated maternal bleeding complications, the panel's voting range was 10,000 to 50,000, with a mean of 27,000. When asked to define the minimum platelet count required for cesarean section with no anticipated maternal bleeding complications, the panel's voting range of 30,000 to 50,000 with

a mean of 44,000. Tables 17 and 18 present panel opinions about the probability of neonatal thrombocytopenia and the appropriateness of vaginal delivery/cesarean section in a hypothetical primiparous woman and in a multiparous woman in her second pregnancy, respectively, both with known ITP. In both instances, cesarean section was considered appropriate (7.9 to 8.1, B) if the fetal platelet count, as determined by PUBS, is <20,000, but inappropriate in other circumstances. For example, assuming the fetal platelet count (and the platelet count of previous babies) is unknown, cesarean section is not indicated when the maternal platelet count is: (1) >100,000 (1.0 to 2.1, A-B), (2) 50,000 to 100,000 (1.6 to 2.9, B), and (3) <50,000 (in primiparous women, only if splenectomy has not been performed) (2.6, B).

(4) *Neonatology consultation.* The panel also addressed the necessity and appropriateness of having a neonatologist in the labor or delivery room. The consultation was considered appropriate (7.0, C-D) if there is a history of a previous infant with a platelet count <20,000 at birth, as well as in a hypothetical case in which a PUBS platelet count of 40,000 was obtained at 37 weeks. The panel agreed that the consultation was unnecessary (2.5, C) in the case of a multiparous woman with known ITP, no prior splenectomy, and a normal platelet count throughout pregnancy (assuming that unfavorable PUBS data or history on previous infants were unavailable).

#### *Treatment of Newborns*

*Evidence.* There is evidence that neonates born to mothers with ITP can, during the first week of life, either develop thrombocytopenia or experience further deterioration of thrombocytopenia noted at birth. A study of 61 neonates born to 50

**Table 18. Panel Opinion Regarding the Management of Delivery in a Woman in Her Second Pregnancy With Known ITP**

| Maternal Platelet Count | Prior Splenectomy | Platelet Count of Prior Baby | Fetal Platelet Count | Cesarean Section          | Vaginal Delivery          |
|-------------------------|-------------------|------------------------------|----------------------|---------------------------|---------------------------|
| Normal                  | No                | NA                           | NA                   | Not recommended<br>1.0, A | Recommended<br>9.0, A     |
| Normal                  | Yes               | NA                           | NA                   | Not recommended<br>2.1, B | Recommended<br>8.0, B     |
| 100-150,000             | No                | NA                           | NA                   | Not recommended<br>1.3, B | Recommended<br>8.6, B     |
| 50-100,000              | No                | NA                           | NA                   | Not recommended<br>1.6, B | Recommended<br>8.4, B     |
| <50,000                 | Yes               | Normal                       | NA                   | Not recommended<br>2.0, B | Recommended<br>7.9, C     |
| <50,000                 | No                | Normal                       | NA                   | Not recommended<br>1.6, B | Recommended<br>8.3, B     |
| 50-100,000              | Yes               | <50,000                      | NA                   | No consensus              | No consensus              |
| 50-100,000              | No                | <50,000                      | NA                   | No consensus              | No consensus              |
| Normal                  | Yes               | NA                           | 50,000 (PUBS)        | No consensus              | No consensus              |
| Normal                  | Yes               | NA                           | 20,000 (PUBS)        | Recommended<br>8.1, B     | Not recommended<br>2.4, C |

Assumes no current treatment, an otherwise uncomplicated pregnancy, and that the prior baby was delivered by an uncomplicated vaginal delivery. "Recommended" and "Not recommended" = mean panel scores of 7.0-9.0 or 1.0-3.0, respectively. Scores are defined in text and Table 2.

Abbreviation: NA, not applicable or not known.

women with ITP reported that platelet counts decreased in two-thirds of infants, with most (83%) infants reaching their nadir by day 1 or 2 and 100% reaching their nadir by day 6.<sup>288</sup> Platelet counts stabilized or began to rise by day 7 in all infants.<sup>288</sup> There is little direct evidence of an association between these transient decreases in platelet counts and the risk of adverse health outcomes (eg, ICH), nor is there evidence that treating such infants reduces neonatal morbidity or mortality. However, neonatal thrombocytopenia can contribute to mortality and neurologic morbidity.<sup>294</sup> IVIg has been shown to increase the platelet count in thrombocytopenic infants born to mothers with ITP (level V evidence).<sup>295</sup> The potential adverse effects of treatment modalities are reviewed above.

**Recommendations.** 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 both necessary (7.7, C) and appropriate (8.8, B) to obtain repeat platelet counts on the newborn if the neonatal platelet count at birth was low (eg, 50,000). Even when newborns have normal platelet counts, the panel's opinion was that repeat testing should be performed, on average, for 3 to 4 days (range = 0 to 7 days; two panel members voted against any repeat testing). The panel considered brain imaging (eg, ultrasound) appropriate, even in the absence of neurologic abnormalities, if the platelet count at birth was <50,000 (7.3 to 8.1, C); imaging was considered necessary (7.6, D) if the count was <20,000. If the infant has imaging evidence of ICH, combined treatment with glucocorticoids and IVIg was considered necessary (7.9, D) and appropriate (8.0, D) if the platelet count is <20,000. Treating such children with glucocorticoids alone was considered inappropriate (1.1, A). In newborns without evidence of ICH, treatment with IVIg alone was considered appropriate (8.0, C) if the infant's platelet count is <20,000, unnecessary for platelet

counts of 20,000 to 50,000 (2.7, D), and unnecessary and inappropriate for counts of 50,000 to 100,000 (2.9, D). Treating the newborn with glucocorticoids alone was considered unnecessary at any platelet count (1.3 to 3.0, B-D) and inappropriate (2.6, D) if the platelet count exceeds 50,000. Combined treatment with glucocorticoids and IVIg was, considered unnecessary (2.0, C) and inappropriate (2.9, D) in infants with platelet counts exceeding 50,000.

The panel's opinion was that women with ITP should not be discouraged from breast feeding (1.4, B).

#### PRIORITIES FOR FUTURE RESEARCH

The evidence-based literature review of ITP provided the opportunity to identify priorities for research. An important finding of our literature review was the lack of rigorous clinical trial data on which to base recommendations for the care of patients with ITP, affecting virtually every decision a clinician commonly encounters. The panel identified the following research priorities.

(1) There is a need for rigorous prospective studies of the clinical course of untreated ITP in patients 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 need to define clinical features of children presenting with ITP that may predict which children can be followed without treatment and what features can reliably predict the risk of intracranial hemorrhage and the occurrence of chronic ITP.

(3) There is a need to obtain more methodologically rigorous data on the clinical course of chronic refractory ITP, 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 of chronic refractory ITP. As noted above, current evidence consists largely of level V evidence (uncontrolled case series), making it 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 the clinical outcomes of bleeding and mortality. In practice, the platelet count plays an important role in decision making despite the lack of definitive data on its prognostic importance in patients with ITP.

(5) There is a need for randomized clinical trials to evaluate many of the therapies currently used in 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 treatment.

(6) There is a need for data on the costs of treatment regimens.

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