Recommendations for the Diagnosis and Management of Chronic Adult Immune Thrombocytopenia (ITP)

1. **Overview**
   A general summary of immune thrombocytopenia (ITP) and an introduction to the American Society of Hematology (ASH) 2011 clinical guideline update and the International Consensus Report (ICR) recommendations.

2. **Methodology & Grading Systems**
   An overview of the methodologies and definitions for the grades of recommendations.

3. **Pathophysiology & Diagnosis**
   A review of the mechanism by which ITP occurs, disease presentation, diagnostic tests, and the importance of a differential diagnosis.

4. **General Management**
   A summary of overall patient management, including the treatment initiation threshold and the possibility of spontaneous improvement or late remission.

5. **Initial/Emergency Management**
   A synopsis of the key recommendations of the ASH 2011 guideline and the ICR for first-line and emergency treatment of ITP.
6. **Second-line Treatment**
   An overview of second-line treatment recommendations of the ASH 2011 guideline and the ICR, including both medical and surgical options.

7. **Refractory Immune Thrombocytopenia**
   A description of refractory ITP, including the rate of relapse and treatment recommendations made by the ASH 2011 guideline and the ICR.

8. **Diagnosis & Management in Pregnancy**
   A review of ITP diagnosis in pregnancy, treatment recommendations, and management during labor and delivery.

9. **Treatment Considerations**
   General treatment considerations for initial, emergency, second-line, and refractory disease management.

10. **Summary of Recommendations**
    Highlights of the key points for diagnosis of ITP, treatment goals, and recommendations made by the ASH 2011 guideline and the ICR.
This ITP disease education information publication is provided to you as a courtesy of Amgen, Inc. Amgen engaged Haymarket Media Inc. to create the publication and retained complete editorial control over its content.
DEFINITION OF IMMUNE THROMBOCYTOPENIA

- Primary immune thrombocytopenia (ITP) is an immune-mediated disorder characterized by isolated thrombocytopenia
  - ITP is defined by
    - Peripheral blood platelet count <100 x 10^9/L, and
    - Absence of any obvious underlying cause of the thrombocytopenia
- Symptoms of bleeding may not always be present despite the increased risk of bleeding
- The disease was previously termed idiopathic thrombocytopenic purpura but changed to primary immune thrombocytopenia due to a better understanding of the immune-mediated mechanism of the disease, absence of any obvious initiating and/or underlying cause, and the absence of or minimal bleeding symptoms in a large proportion of cases
- Although the definition of ITP has changed over the years, the acronym “ITP” continues to be used in medical practice
- The table below shows ITP classification based on duration

<table>
<thead>
<tr>
<th>Duration</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 months</td>
<td>Newly diagnosed</td>
</tr>
<tr>
<td>3-12 months</td>
<td>Persistent</td>
</tr>
<tr>
<td>≥12 months</td>
<td>Chronic</td>
</tr>
</tbody>
</table>

Source: Rodeghiero 2009.

- ITP was previously classified as being either acute (≤ 6 months) or chronic (> 6 months)
- There is a possibility that patients with persistent or chronic ITP may spontaneously improve or remit from 6 to 12 months, and even years, after diagnosis
- Secondary ITP may also occur in association with another condition, listed below

<table>
<thead>
<tr>
<th>Causes of Secondary Immune Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Antiphospholipid syndrome</td>
</tr>
<tr>
<td>• Autoimmune thrombocytopenia</td>
</tr>
<tr>
<td>• Common variable immune deficiency</td>
</tr>
<tr>
<td>• Drug-induced</td>
</tr>
<tr>
<td>• Lymphoproliferative disorders</td>
</tr>
<tr>
<td>• Post bone marrow transplantation</td>
</tr>
<tr>
<td>• Post vaccination</td>
</tr>
<tr>
<td>• Infection</td>
</tr>
<tr>
<td>- Cytomegalovirus</td>
</tr>
<tr>
<td>- Helicobacter pylori</td>
</tr>
<tr>
<td>- Hepatitis C</td>
</tr>
<tr>
<td>- Human immunodeficiency virus</td>
</tr>
<tr>
<td>- Varicella zoster</td>
</tr>
<tr>
<td>• Systemic lupus erythematosus</td>
</tr>
</tbody>
</table>

Source: Neunert 2011.

INCIDENCE

- Limited information exists about ITP incidence; the current best estimate indicates that ITP is diagnosed at a rate of 3.3 per 100,000 adults per year
GUIDELINES AND RECOMMENDATIONS

Updated recommendations for the management of ITP are now available from 2 distinguished panel reports based on a greater understanding of the disease pathophysiology¹ and availability of additional therapeutic options. The American Society of Hematology (ASH) published an update to its 1996 ITP clinical guideline to provide practicing clinicians with evidence-based guidance for the management of ITP.² An International Consensus Report (ICR) was published with the intent to comment on new data and provide recommendations relating to diagnosis and treatment of ITP.²

It is important for clinicians to consult both the ASH 2011 guideline and the ICR recommendations for a comprehensive understanding of ITP treatment, because the ASH 2011 guideline refers readers to the ICR recommendations for a more in-depth review of some clinical areas.⁴

■ In April 2011, ASH published an update of its original 1996 ITP practice guide- line that
  – Focuses on changes in the definition and management that have occurred since the 1996 guideline was published⁴
  – Offers a summary of literature describing diagnosis and management of ITP, focusing on changes that have occurred since 1996⁴
■ The ICR recommendations on the investigation and management of ITP was published in January 2010 providing
  – Information on pertinent new data², and
  – Consensus-based recommendations for the management and diagnosis of ITP²

REFERENCES

**Methodology**

**Expert Panels**

**American Society of Hematology**
- The panel was comprised of a total of 6 members; 5 members having prior publications on immune thrombocytopenia (ITP) and its treatment, 4 members with expertise in systematic reviews and guideline development, and 3 members with clinical expertise in management of ITP
- None had conflicts of interest regarding products recommended in the guideline

**International Consensus Report**
- Comprised of 22 members with clinical and research expertise in ITP from 8 countries (Australia, Canada, France, Italy, Spain, Switzerland, United Kingdom, and United States)

**Methods**

**American Society of Hematology**
- Conducted a literature review to update the 1996 American Society of Hematology (ASH) guideline
- Systematic reviews, meta-analyses, and randomized controlled trials were given preference during the review
- An external panel, which included ASH’s Committee on Practice, Subcommittee on Quality of Care, and content experts, reviewed the guideline. The document was subsequently approved by the authors, the external panel, and the ASH Executive Committee

**International Consensus Report**
- The International Consensus Report (ICR) conducted a literature review using the National Library of Medicine PubMed database
- Recommendation grades were based on level of evidence

**Literature Review Process**

<table>
<thead>
<tr>
<th>ASH 2011 Guideline</th>
<th>ICR Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Used MEDLINE and EMBASE databases</td>
<td>• Used search terms relevant to ITP within the National Library of Medicine PubMed database</td>
</tr>
<tr>
<td>• Included literature from 1996 to December 2009</td>
<td>• Included abstracts from various annual meetings from 2003 to 2007*</td>
</tr>
<tr>
<td>• Literature review was used to answer a series of focused clinical questions</td>
<td></td>
</tr>
</tbody>
</table>

*Meetings included ASH, the European Hematology Association, and the International Society on Thrombosis and Haemostasis
ASH = American Society of Hematology; ICR = International Consensus Report; ITP = Immune thrombocytopenia
Sources: Neunert 2011; Provan 2010
GRADING SYSTEMS

The ASH 2011 guideline grading was based on a determination of the level of evidence but also incorporated the panel’s assessment of clinical benefit versus risk. The ICR grading was based purely on the panel’s determination of the level of evidence.

GRADINGS OF RECOMMENDATION

ASH 2011 Guideline Grading for Recommendations (1A, 1B, 1C, 2A, 2B, 2C)

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>Evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 High degree of confidence that desirable outcome of an intervention exceeds undesirable effects in most patients</td>
<td>A Supported by consistent evidence from RCTs or exceptionally strong observational studies</td>
</tr>
<tr>
<td>2 Lower degree of confidence that desirable outcome of an intervention exceeds undesirable effects in most patients</td>
<td>B Supported by RCTs with important limitations or strong evidence from observational studies</td>
</tr>
</tbody>
</table>

ICR Recommendations Based on Grade (A, B, or C) and Level of Evidence (Ia, Ib, Ila, Iib, III, IV)

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia Obtained from meta-analysis of RCTs</td>
<td>A Requires at least one RCT as part of a body of evidence of overall good quality and consistency (evidence levels Ia and Ib)</td>
</tr>
<tr>
<td>Ib Obtained from at least one RCT</td>
<td></td>
</tr>
<tr>
<td>Ila Obtained from at least one well-designed, controlled non-randomized study</td>
<td>B Requires well-conducted clinical trials but no RCTs (evidence levels Ila, Ilb, and III)</td>
</tr>
<tr>
<td>Iib Obtained from at least one other type of well-designed quasi-experimental study</td>
<td></td>
</tr>
<tr>
<td>III Obtained from well-designed non-experimental descriptive studies (eg, comparative studies, correlated studies, case reports)</td>
<td></td>
</tr>
<tr>
<td>IV Obtained from expert committee reports or opinions and/or clinical experience of respected authorities</td>
<td>C Requires evidence from expert opinion and/or clinical experience (evidence level IV)</td>
</tr>
</tbody>
</table>

In some settings, a strong recommendation may be derived from lesser quality evidence if intervention results in important clinical benefit and either toxicity is uncommon or is strongly outweighed by the potential benefit.

RCT = Randomized controlled trial.
Sources: Neunert 2011; Provan 2010.

REFERENCES

**PATHOPHYSIOLOGY**

- Historically, immune thrombocytopenia (ITP) was thought to be due to increased platelet destruction caused by autoantibodies\(^1,2\).
  - About 50% to 60% of platelets in patients with ITP are coated with immunoglobulin G antibodies\(^3\).
  - These antibody-covered platelets are recognized by tissue macrophage receptors, resulting in their phagocytosis\(^3\).
  - The pathogenesis resulting in autoantibody production remains unknown\(^3\).
- It is now recognized that ITP is also a result of suboptimal platelet production\(^2\).
  - The autoimmune process not only enhances platelet clearance, it also inhibits platelet production in the bone marrow and increases megakaryocyte destruction\(^4,5\).
  - Plasma levels of endogenous thrombopoietin (eTPO) are suboptimal because of accelerated clearance by accelerated removal of eTPO bound to antibody-coated platelets, binding to megakaryocytes in the marrow, and absence of increased synthesis in response to thrombocytopenia\(^4-7\).

**DISEASE PRESENTATION**

- The signs and symptoms of ITP vary widely at presentation, ranging from no symptoms or minimal bruising to serious bleeding\(^2\).
- Serious bleeding may include gastrointestinal, intracranial hemorrhage, mucosal, or ecchymosis\(^2\).
- Bleeding risk is correlated, to some extent, with the severity of the thrombocytopenia\(^2\).

**DIAGNOSIS IN ADULTS**

- There is no “gold standard” diagnostic test to reliably confirm an ITP diagnosis\(^1,2\).
- Typically, there are multiple diagnostic tests, shown below, used as part of the basic patient evaluation\(^1,2\).

<table>
<thead>
<tr>
<th>RECOMMENDED DIAGNOSTIC TESTS FOR IMMUNE THROMBOCYTOPENIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tests</strong></td>
</tr>
<tr>
<td>CBC</td>
</tr>
<tr>
<td>Peripheral blood film</td>
</tr>
<tr>
<td>Bone marrow examination</td>
</tr>
<tr>
<td>HIV and HCV</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em></td>
</tr>
</tbody>
</table>

ASH = American Society of Hematology; CBC = Complete blood count; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; ICR = International Consensus Report.
Sources: Neunert 2011\(^1\); Provan 2010.\(^2\)
The approach to diagnosis starts with a thorough patient/family history and physical examination to identify evidence of bleeding. Alternative causes of thrombocytopenia should also be considered before making a diagnosis of ITP.

### ALTERNATIVE CAUSES OF THROMBOCYTOPENIA IN DIFFERENTIAL DIAGNOSIS

- Infection with
  - Cytomegalovirus
  - *Helicobacter pylori*
  - Hepatitis C
  - Human immunodeficiency virus
  - Varicella zoster
- Lymphoproliferative disorders
- Autoimmune/immunodeficiency disorders (eg, systemic lupus erythematosus)
- Liver disease (eg, alcoholic liver cirrhosis)
- Medication use or exposure to toxins
- Bone marrow diseases (eg, myelodysplastic syndromes, leukemia)
- Recent transfusions or immunizations
- Inherited thrombocytopenic disorders
- Antiphospholipid syndrome

Sources: Neunert 2011; Provan 2010.

The American Society of Hematology (ASH) 2011 guideline does not recommend routine measurement of antiplatelet, antiphospholipid, or antinuclear antibodies in patients with suspected ITP and considers measurement of thrombopoietin (TPO) levels of unproven or uncertain benefit.

The International Consensus Report (ICR) did not find sufficient evidence to recommend or suggest the routine use of antiplatelet, antiphospholipid, antinuclear antibodies, and TPO levels in evaluation of patients with suspected ITP.

### REFERENCES

The primary goals of treatment for immune thrombocytopenia (ITP) are to achieve a platelet count that will prevent major bleeding and to attain a sustained increase of the platelet count that is considered hemostatic for the individual patient\(^1\)\(^-\)\(^3\).

It is not the goal to normalize platelet count\(^1\)\(^,\)\(^3\).

**OVERALL PATIENT MANAGEMENT**

- Patient management should be modified to each individual patient\(^1\)\(^,\)\(^2\).
- Treatment should be chosen based on
  - Presence and severity of bleeding\(^1\)\(^,\)\(^2\)
  - How rapidly platelet counts need to rise\(^1\)
  - Other considerations specific to each patient as described below\(^1\)\(^,\)\(^2\).

**FACTORS TO CONSIDER WHEN ASSESSING IF TREATMENT IS NECESSARY**

<table>
<thead>
<tr>
<th>ASH 2011 Guideline</th>
<th>ICR Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of bleeding</td>
<td>Extent of bleeding</td>
</tr>
<tr>
<td>Bleeding risk based on previous bleeding episodes and coincident risk factors for bleeding (eg, age, hypertension, etc.)</td>
<td>Comorbidities predisposed to bleeding and patient need for non-ITP medications that may cause bleeding</td>
</tr>
<tr>
<td>Activity level</td>
<td>Complications of specific therapies and tolerance of side effects</td>
</tr>
<tr>
<td>Potential side effects of treatment</td>
<td>Activity and lifestyle</td>
</tr>
<tr>
<td>Patient preference</td>
<td>Accessibility of care</td>
</tr>
<tr>
<td></td>
<td>Patient expectations and patient worry about disease burden</td>
</tr>
</tbody>
</table>

ASH = American Society of Hematology; ICR = International Consensus Report; ITP = Immune thrombocytopenia.

Sources: Neunert 2011\(^1\); Provan 2010.\(^2\)

Treatment decisions in women with chronic ITP may be influenced by heavy menstrual periods that interfere with their daily activities or result in iron deficiency anemia\(^1\).

It is important to keep in mind that these recommendations are intended as guides only and should not supersede the physician’s judgment based on the patient’s specific needs and preferences\(^1\)\(^,\)\(^2\).
TREATMENT INITIATION THRESHOLD

- The American Society of Hematology (ASH) 2011 guideline suggests that treatment should be administered to newly diagnosed patients with a platelet count <30 x 10^9/L, consistent with the current practice of most clinicians (Grade 2C)\(^1\)
  - However, the ASH 2011 guideline recognizes that no evidence was found to identify a minimum platelet count threshold at which the average ITP patient should be treated\(^1\)

- The International Consensus Report (ICR) recognizes that patients with platelet counts >50 x 10^9/L rarely need treatment in the absence of the following specific situations\(^2\):
  - Bleeding due to platelet dysfunction or another hemostatic defect
  - Clearly identified comorbidity for bleeding
  - Trauma
  - Surgery
  - Mandated anticoagulation therapy
  - Lifestyle/profession predisposing the patient to trauma

SPONTANEOUS IMPROVEMENT OR LATE REMISSION

- Spontaneous improvement or late remissions may occur but are less common in adults\(^1\)

- Patients may experience remission 6 to 12 months after diagnosis or even years later\(^1,2\)

- Spontaneous improvement or late remissions have been observed in patients without treatment and some may remit off treatment\(^1\)
  - A spontaneous remission rate of approximately 9% (8/87 patients) was observed in patients with no treatment and platelet count >50 x 10^9/L in one study\(^1\)
  - Approximately 29% (17/59 patients) of non-splenectomized patients with persistent ITP achieved remission 6 months to 3 years later in another study\(^1\)

REFERENCES

FIRST-LINE TREATMENT
Corticosteroids are recommended by both the American Society of Hematology (ASH) 2011 guideline and the International Consensus Report (ICR) as first-line therapy for patients with newly diagnosed immune thrombocytopenia (ITP).  

<table>
<thead>
<tr>
<th>RECOMMENDATIONS FOR FIRST-LINE TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASH 2011 Guideline</strong></td>
</tr>
<tr>
<td>• Long courses of corticosteroids (eg, prednisone 1 mg/kg/day for 3 weeks) recommended (Grade 2B)</td>
</tr>
<tr>
<td>• IVIg may be used with corticosteroids when a more rapid increase in platelet count is required (Grade 2B)</td>
</tr>
<tr>
<td>• When corticosteroids are contraindicated, either IVIg or anti-D (in appropriate patients) may be used (Grade 2C)</td>
</tr>
<tr>
<td>• With IVIg, a single dose of 1 g/kg should be used initially (Grade 2B)</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>

* The ASH 2011 guideline grading scale was based on a determination of the level of evidence (letter grade of A [highest], B, or C), as well as the panel’s opinion of clinical benefit vs risk (numerical grade of 1 [highest], 2, or 3). See card 2 for the complete definition of the grading scale.
† The ICR grading scale was based purely on the panel’s determination of the level of evidence and is not meant to imply comparison of safety or efficacy of the treatments. See card 2 for the complete definition of the grading scale.

Anti-D = Intravenous anti-D immunoglobulin; ASH = American Society of Hematology; ICR = International Consensus Report; IVIg = Intravenous immunoglobulin.

Sources: Neunert 2011; Provan 2010.

EMERGENCY TREATMENT
Candidates for emergency treatment have an urgent need to raise platelet counts in order to rapidly achieve adequate hemostasis.  

Characteristics of patients requiring emergency treatment include  
− Active hemorrhage that is limb- or sight-threatening, in the central nervous system, in the gastrointestinal tract, or in the genitourinary tract  
− High risk of significant bleeding  
− Need for surgical procedure
General treatment measures include the cessation of drugs reducing platelet function, blood pressure control, menses inhibition, and minimizing trauma.

**TREATMENT RECOMMENDATIONS**

The ASH 2011 guideline and the ICR recommend corticosteroids and intravenous immunoglobulin as initial emergency treatment. Evidence supporting other interventions (see below) is limited, but they may be considered.

### EMERGENCY TREATMENT OPTIONS

<table>
<thead>
<tr>
<th>Treatment Stage</th>
<th>ASH 2011 Guideline</th>
<th>ICR Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Treatment</strong></td>
<td>• IVIg in combination with corticosteroids when a rapid increase in platelet count is needed (Grade 2B)</td>
<td>• High-dose IV corticosteroids and IVIg should be used initially in emergency situations (Grade C) • Platelet transfusions with or without IVIg</td>
</tr>
<tr>
<td><strong>Alternative Emergency Treatment Options</strong></td>
<td>• Platelet transfusions in combination with continuous IVIg • Recombinant factor VIIa (care needed due to risk of thrombosis) • Antifibrinolytics (aminocaproic acid and tranexamic acid) • Emergency splenectomy with or without IVIg and/or corticosteroids (for truly life-threatening bleeding)</td>
<td>• Anti-D • Vinca alkaloids • Antifibrinolytics (oral or IV aminocaproic acid and tranexamic acid) in combination with first-line therapy (Grade C) • Emergency splenectomy</td>
</tr>
</tbody>
</table>

† The ASH 2011 guideline grading scale was based on a determination of the level of evidence (letter grade of A [highest], B, or C), as well as the panel’s opinion of clinical benefit vs risk (numerical grade of 1 [highest], 2, or 3). *See card 2 for the complete definition of the grading scale.*

§ The ICR grading scale was based purely on the panel’s determination of the level of evidence and is not meant to imply comparison of safety or efficacy of the treatments. *See card 2 for the complete definition of the grading scale.*

Anti-D = Intravenous anti-D immunoglobulin; ASH = American Society of Hematology; ICR = International Consensus Report; IVIg = Intravenous immunoglobulin.

Sources: Neunert 2011; Provan 2010.

### REFERENCES

**MEDICAL TREATMENT**

The American Society of Hematology (ASH) 2011 guideline and the International Consensus Report (ICR) discuss various medical options for patients failing first-line treatment. Neither expert publication provides a sequence for how second-line treatment should be approached.\(^1^,2\)

### SECOND-LINE MEDICAL TREATMENT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ASH 2011 Guideline*</th>
<th>ICR Recommendations†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombopoietin receptor agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Recommended for patients who relapse after splenectomy or have contraindications to splenectomy and failed at least one other therapy (Grade 1B)</td>
<td>• Recommended for patients failing at least one line of therapy such as corticosteroids or IVIg (Grade A)</td>
<td></td>
</tr>
<tr>
<td>• May be considered for patients who have failed one line of therapy such as corticosteroids or IVIg (Grade 2C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-CD20 antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• May be considered for patients at risk of bleeding who have failed one line of therapy, such as corticosteroids, IVIg, or splenectomy (Grade 2C)</td>
<td>• May be considered in patients with refractory or relapsed ITP (Grade B)</td>
<td></td>
</tr>
<tr>
<td>• Contraindicated in patients with active hepatitis B infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppressives and corticosteroid-sparing drugs</td>
<td>• Each agent has unique potential toxicities that must be considered by the patient and clinician</td>
<td>• Immunosuppressive agents may be used in patients failing other therapies (Grade B)</td>
</tr>
<tr>
<td>• Evidence-based recommendations on appropriate indications or timing of use are not made due to inadequate research</td>
<td>• Corticosteroid-sparing drugs may be useful in elderly patients and when splenectomy is contraindicated (Grade B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Immunosuppressives may be used as a single agent or in combination with corticosteroids (Grade B)</td>
</tr>
</tbody>
</table>

* The ASH 2011 guideline grading scale was based on a determination of the level of evidence (letter grade of A [highest], B, or C), as well as the panel's opinion of clinical benefit vs risk (numerical grade of 1 [highest], 2, or 3). See card 2 for the complete definition of the grading scale.

† The ICR grading scale was based purely on the panel’s determination of the level of evidence and is not meant to imply comparison of safety or efficacy of the treatments. See card 2 for the complete definition of the grading scale.

ASH = American Society of Hematology; ICR = International Consensus Report; ITP = Immune thrombocytopenia; IVIg = Intravenous immunoglobulin.

Sources: Neunert 2011\(^1\); Provan 2010.\(^2\)

While both publications provide recommendations for treatment of immune thrombocytopenia (ITP) based on assessment of evidence, the ASH 2011 guideline refers readers to the ICR recommendations for a more in-depth review of some clinical areas.\(^1\)

### SURGICAL TREATMENT: SPLENECTOMY

Splenectomy is recognized by both the ASH 2011 guideline and the ICR recommendations as the only treatment to provide sustained off-treatment remissions lasting ≥1 year in approximately two-thirds of patients.\(^1^,2\) *(Please see recommendations on the next page.)*
Experts agree that spontaneous improvement or late remission of ITP may occur 6 to 12 months, or even years, after diagnosis.1,2

COMPLICATIONS OF SPLENECTOMY

There are various complications associated with splenectomy that must be considered, such as

- Bleeding and the need for transfusions1,2
- Infection2
- Intra-abdominal adhesions leading to obstruction and thrombosis1
- Hernia formation1
- Nerve palsies1
- Prolonged hospitalization or hospital readmission2
- Requirement for additional intervention2

PROPHYLACTIC VACCINATION

Splenectomized patients have a risk of infection from *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*.2

RECOMMENDATIONS FOR PROPHYLACTIC VACCINATION

ASH 2011 Guideline

- Advise clinicians to consult regularly-updated vaccination recommendations made by national health-related entities (eg, Centers for Disease Control and Prevention)

ICR Recommendations

- Recommend prophylactic vaccination preferably 4 weeks before or 2 weeks after splenectomy
- Revaccination is based on country-specific recommendations

ASH = American Society of Hematology; ICR = International Consensus Report.
Sources: Neunert 20111; Provan 2010.2

REFERENCES

DEFINITION OF REFRACTORY IMMUNE THROMBOCYTOPENIA

Patients are considered to have refractory immune thrombocytopenia (ITP) if they
- Do not attain hemostatic platelet count either after splenectomy; after first- and second-line medical treatment; or after initially responding to splenectomy and relapsing thereafter; and
- Either exhibit severe ITP or have a risk of bleeding that requires therapy based on the clinical judgment of the treating physician.

RATE OF RELAPSE

- Approximately 20% of patients who have had splenectomy or been treated with first- and second-line pharmacologic agents do not attain a stable hemostatic platelet count.
- Approximately 10% to 20% of patients who initially respond to splenectomy will experience relapse.
- It is possible for some patients to tolerate severe thrombocytopenia with platelet counts as low as 10 x 10^9/L.

TREATMENT OF REFRACTORY IMMUNE THROMBOCYTOPENIA

THERAPEUTIC GOALS

- Main goal of therapy in patients with refractory ITP is to achieve a platelet count sufficient to prevent clinically significant bleeding with the least toxicity.
- Considerations for treatment selection should include the agent’s potential to induce an acute response and a long-lasting response with minimal adverse reactions.

TREATMENT RECOMMENDATIONS

- The ASH 2011 guideline strongly recommends against further treatment in asymptomatic patients postsplenectomy who have platelet counts >30 x 10^9/L (Grade 1C).
- Both the ASH 2011 guideline and the ICR recommend the administration of thrombopoietin (TPO) receptor agonists for refractory ITP patients. In addition, both reports identify other options as listed on the table located on the next page.
### TREATMENT RECOMMENDATIONS FOR REFRACTORY IMMUNE THROMBOCYTOPENIA

<table>
<thead>
<tr>
<th>ASH 2011 Guideline*</th>
<th>ICR Recommendations†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommends:</strong> TPO-receptor agonists (Grade 1B)</td>
<td>• TPO-receptor agonists (Grade A)</td>
</tr>
<tr>
<td><strong>Suggests:</strong> Anti-CD20 antibodies (Grade 2C)</td>
<td>• Anti-CD52 antibodies (Grade B)</td>
</tr>
<tr>
<td></td>
<td>• Combination chemotherapy (Grade B)</td>
</tr>
<tr>
<td></td>
<td>• Hematopoietic stem-cell transplantation (HSCT) (Grade B)</td>
</tr>
</tbody>
</table>

* The ASH 2011 guideline grading scale was based on a determination of the level of evidence (letter grade of A [highest], B, or C), as well as the panel’s opinion of clinical benefit vs risk (numerical grade of 1 [highest], 2, or 3). See card 2 for the complete definition of the grading scale.

† The ICR grading scale was based purely on the panel’s determination of the level of evidence and is not meant to imply comparison of safety or efficacy of the treatments. See card 2 for the complete definition of the grading scale.

ASH = American Society of Hematology; ICR = International Consensus Report; TPO = Thrombopoietin.

Sources: Provan 2010²; Neunert 2011.³

ICR recommendations include other alternative options for refractory patients but use is limited due to adverse effects. Alternative treatment options listed below are not FDA-approved for the treatment of ITP²

- Combination chemotherapy (Grade B)²
  - Anti-CD52 antibodies (Grade B)²
    - May cause severe immunosuppression
    - Prolonged prophylaxis with antifungal, antibacterial, and antiviral agents is usually necessary
  - Hematopoietic stem-cell transplantation (Grade B)²
    - Warranted only in patients with severe refractory ITP who have bleeding complications unresponsive to other treatment
    - May cause fatal toxicities, including neutropenic fever, cerebral hemorrhage, and septicemia

### REFERENCES

IMMUNE THROMBOCYTOPENIA IN PREGNANCY

- Immune thrombocytopenia (ITP) is estimated to occur in 1 in 1000 to 1 in 10,000 pregnant women.¹
- Pregnant individuals may have lower platelet counts than normal, which is also known as gestational thrombocytopenia.¹
  - May be due to a combination of hemodilution and increased platelet activation and clearance.¹

DIAGNOSIS

The diagnosis of ITP during pregnancy remains one of exclusion based on medical history, physical examination, blood count, and blood smear examination.¹

- The American Society of Hematology (ASH) 2011 guideline and the International Consensus Report (ICR) recommendations note that there is no difference between the work-up for pregnant and non-pregnant individuals.¹,²
- Additional medical conditions should be taken into consideration before making a diagnosis of ITP.¹

### DIAGNOSIS OF IMMUNE THROMBOCYTOPENIA IN PREGNANCY

<table>
<thead>
<tr>
<th>Considerations</th>
<th>ASH 2011 Guideline*</th>
<th>ICR Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate diagnostic tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Complete blood count²</td>
<td>• Antiphospholipid antibodies (eg, anticardiolipin antibodies)¹</td>
</tr>
<tr>
<td></td>
<td>• Peripheral blood smear²</td>
<td>• Coagulation screening¹</td>
</tr>
<tr>
<td></td>
<td>• Testing for HIV and HCV (in high-risk populations)²</td>
<td>• SLE serology¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Liver function tests¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Peripheral blood smear¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reticulocyte count¹</td>
</tr>
<tr>
<td>Differential diagnosis</td>
<td>• Pregnancy-induced hypertension (Preeclampsia)³</td>
<td>• Gestational thrombocytopenia¹</td>
</tr>
<tr>
<td></td>
<td>• Gestational thrombocytopenia (Incidental thrombocytopenia of pregnancy)³</td>
<td>• Preeclampsia¹</td>
</tr>
<tr>
<td></td>
<td>• HELLP syndrome³</td>
<td>• HELLP syndrome¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Disseminated intravascular coagulation¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Massive obstetrical hemorrhage¹</td>
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<tr>
<td></td>
<td></td>
<td>• Acute fatty liver¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Antiphospholipid antibody syndrome¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Folate deficiency¹</td>
</tr>
</tbody>
</table>

* The ASH 2011 guideline did not update its diagnostic criteria for pregnant patients from the previous 1996 guideline due to lack of new evidence; information provided is from the ASH 1996 guideline.

ASH = American Society of Hematology; ICR = International Consensus Report; HELLP = Hemolysis, elevated liver enzyme levels, and low platelet count; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; SLE = Systemic lupus erythematosus.

Sources: Provan 2010¹, Neunert 2011², George 1996.³
TREATMENT DURING PREGNANCY

Management of pregnant patients who develop ITP is the same as patients who have chronic ITP and are not pregnant.\(^1,2\)

- The ASH 2011 guideline does not identify a platelet count threshold for treatment\(^2\)
- ICR recommendations indicate pregnant women in the first two trimesters who are symptomatic, have platelet counts ranging from 20 to 30 \(\times\) 10\(^9\)/L, and require an increase in platelet count to a level considered safe should receive treatment\(^1\)

<table>
<thead>
<tr>
<th>ASH 2011 Guideline†</th>
<th>ICR Recommendations‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicates either corticosteroids or IVIg as first-line therapy (Grade 1C)</td>
<td>Recommends corticosteroids as first-line therapy (Grade C)</td>
</tr>
<tr>
<td></td>
<td>IVIg is recommended if corticosteroids are ineffective, produce significant side effects, or if rapid platelet increase is needed</td>
</tr>
<tr>
<td></td>
<td>Limited evidence may support use of anti-D in Rh+, non-splenectomized women (Grade B)</td>
</tr>
</tbody>
</table>

\(^†\) The ASH guideline grading scale was based on a determination of the level of evidence (letter grade of A [highest], B, or C), as well as the panel’s opinion of clinical benefit vs risk (numerical grade of 1 [highest], 2, or 3). See card 2 for the complete definition of the grading scale.

\(^‡\) The ICR grading scale was based purely on the panel’s determination of the level of evidence and is not meant to imply comparison of safety or efficacy of the treatments. See card 2 for the complete definition of the grading scale.

Corticosteroids and IVIg are considered to be safe to the fetus, but may have maternal side effects including exacerbation of gestational diabetes and post-partum psychiatric disorders\(^2\)

MANAGEMENT DURING LABOR AND DELIVERY

- The ASH 2011 guideline and ICR recommendations indicate that the mode of delivery should be based on obstetric indications (ASH Grade 2C; ICR Grade B)\(^1,2\)

REFERENCES
GENERAL PRINCIPLES

- The American Society of Hematology (ASH) 2011 guideline and the International Consensus Report (ICR) provide recommendations for the management and treatment of immune thrombocytopenia (ITP)\(^1,2\).
- Both reports provide clinicians with clear principles and strategies for patient care but do not establish a sequence of treatment options for the management of ITP patients\(^1,2\).

INDIVIDUALIZING TREATMENT

Both publications maintain that their recommendations are intended as guides only and should not supersede the physician’s judgment when making treatment decisions based on the patient’s specific needs, characteristics, or preferences\(^1,2\).

INITIAL TREATMENT

- It is important to first consider the extent or the severity of bleeding and the risk of bleeding based on
  - Bleeding history, or
  - The presence of comorbidities predisposing the patient to bleeding\(^1,2\).

PATIENT-SPECIFIC FACTORS FOR INITIAL TREATMENT

<table>
<thead>
<tr>
<th>Patient-Specific Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of activity and lifestyle</td>
</tr>
<tr>
<td>Tolerance to side effects</td>
</tr>
<tr>
<td>Comorbidities and the need for non-ITP medications</td>
</tr>
<tr>
<td>Patient expectations and patient worry about disease burden</td>
</tr>
<tr>
<td>Patient preference</td>
</tr>
<tr>
<td>Accessibility of care</td>
</tr>
</tbody>
</table>

ITP = Immune thrombocytopenia.
Source: Provan 2010.\(^2\)

EMERGENCY TREATMENT

- The aim of emergency treatment is to rapidly increase platelet count\(^1\).
- Emergency treatment should be considered if an ITP patient is experiencing any of the following:
  - Active hemorrhage that is limb- or sight-threatening, in the central nervous system, in the gastrointestinal tract, or in the genitourinary tract\(^1,2\).
  - High risk of significant bleeding\(^2\)
  - Need for surgical procedure\(^2\).
SECOND-LINE TREATMENT

■ The ASH 2011 guideline and the ICR recommendations provide clinicians with both medical and surgical options for patients failing initial treatment with corticosteroids, IV immunoglobulin, or IV anti-D immunoglobulin1,2

■ Clinicians should note that a specific sequence of treatment options for second-line management is not provided1,2

– Various options are presented to assist the clinician with tailoring the treatment strategy for each individual ITP patient1,2

PATIENT-SPECIFIC FACTORS FOR SECOND-LINE TREATMENT

| • Severity of bleeding | • Patient activity level |
| • Risk factors for bleeding | • Patient expectations |
| • Tolerance to side effects | • Patient preferences |

Sources: Neunert 20111; Provan 2010.2

■ The ICR recommendations state that depending on the clinical setting, splenectomy is deferred in most patients for at least 6 months2

– This may be due to patient preferences2, active comorbidities2, and spontaneous improvement or late remission that may occur from 6 to 12 months, or even years, after diagnosis1,2

REFRACTORY DISEASE

■ Clinicians should discuss the risks and benefits of further therapy in those patients who may still require treatment after failing first- and second-line therapy2

■ Although the ICR recommendations discuss treatment options for patients failing first- and second-line therapy, there is no sequence on how treatment should be approached2

REFERENCES

DIAGNOSIS

- The diagnosis of immune thrombocytopenia (ITP) is made after other causes of thrombocytopenia are excluded\(^1,2\)
- There is no “gold standard” diagnostic test to confirm an ITP diagnosis\(^1,2\)

TREATMENT GOAL

- The primary goal of treatment is to sustain a platelet count associated with adequate hemostasis to prevent serious or major bleeding\(^1,2\)
- Normalizing platelet counts is **NOT** a goal of treatment\(^1,2\)

COMPARISON OF RECOMMENDATIONS

A summary of recommendations from the American Society of Hematology (ASH) 2011 guideline and the International Consensus Report (ICR) is provided below.

<table>
<thead>
<tr>
<th>SUMMARY OF RECOMMENDATIONS FOR IMMUNE THROMBOCYTOPENIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Type/Parameter</strong></td>
</tr>
<tr>
<td>Platelet count threshold for treatment</td>
</tr>
<tr>
<td>First-line treatment</td>
</tr>
<tr>
<td>First-line treatment if corticosteroids are contraindicated</td>
</tr>
<tr>
<td>- Anti-D is not advised in patients with bleeding caused by a decline in hemoglobin or in those with evidence of hemolysis</td>
</tr>
<tr>
<td>Emergency treatment</td>
</tr>
</tbody>
</table>

*(table continued on next page)*
### SUMMARY OF RECOMMENDATIONS FOR IMMUNE THROMBOCYTOPENIA (continued)

<table>
<thead>
<tr>
<th>Treatment Type/ Parameter</th>
<th>ASH 2011 Guideline*</th>
<th>ICR Recommendations†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-line treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>Splenectomy; patients who fail corticosteroids (Grade 1B)</td>
<td>Splenectomy; recommended waiting period &gt;6 months after diagnosis (Grade C)</td>
</tr>
<tr>
<td>Medical</td>
<td>TPO receptor agonists (Grade 2C) or those contraindicated to splenectomy (Grade 1B), or anti-CD20 antibodies (Grade 2C)</td>
<td>Chemotherapy agents (Grade B), immunosuppressive agents (Grade B), corticosteroid-sparing agents (Grade B), anti-CD20 antibodies (Grade B), or TPO receptor agonists (Grade A)</td>
</tr>
<tr>
<td>Treatment of refractory ITP</td>
<td>TPO receptor agonists (Grade 1B) or anti-CD20 antibodies (Grade 2C)</td>
<td>TPO receptor agonists (Grade A) Anti-CD52 antibodies (Grade B) Combination chemotherapy (Grade B) Hematopoietic stem-cell transplantation (Grade B)</td>
</tr>
<tr>
<td>Treatment in pregnancy</td>
<td>Corticosteroids or IVIg (Grade 1C)</td>
<td>Corticosteroids or IVIg (Grade 1C)</td>
</tr>
</tbody>
</table>

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Anti-D = Intravenous anti-D immunoglobulin; ASH = American Society of Hematology; ICR = International Consensus Report; ITP = Immune thrombocytopenia; IVIg = Intravenous immunoglobulin; TPO = Thrombopoietin.

Sources: Neunert 2011; Provan 2010.

### REFERENCES