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Immune Thrombocytopenia: Updated Practice Guidelines in an Evolving Treatment Landscape

Announcer: You're listening to ReachMD. This medical industry feature, titled "Immune Thrombocytopenia: Updated Practice Guidelines in an Evolving Treatment Landscape," is sponsored by Amgen. Your host is Dr. Jennifer Caudle.

Dr. Caudle: The 2019 International Consensus Report, or ICR Recommendations, and the American Society of Hematology, or ASH Guideline updates, reflect the developments made in the management of immune thrombocytopenia or ITP over the last decade.

Today, will be speaking with two experts in their field to discuss these guidelines and their recommendations specifically for adult ITP patients. This is ReachMD and I'm your host, Dr. Jennifer Caudle. Here with me today is Dr. Terry Gernsheimer, board certified hematologist and an author of the 2019 ICR Recommendations. And we're also joined by Keith McCrae, board certified hematologist and an author of the 2019 ASH Guidelines. Dr. Gernsheimer and Dr. McCrae, welcome to you both.

Dr. Gernsheimer: Thank you so much for having me.

Dr. McCrae: Yes, it's great to be here. Thank you.

Dr. Caudle: Before we dive into the ICR Recommendations and ASH Guidelines, Dr. Gernsheimer, can you set the stage for us with some contextual details about ITP? What do we need to know about this disease to start?

Dr. Gernsheimer: Thanks. ITP is an acquired autoimmune disorder characterized by a low platelet count that results from increased platelet destruction and also decreased platelet production. Approximately 2 to 5 persons per 100,000 are newly diagnosed with ITP every year.¹ ITP is classified as newly diagnosed in patients less than 3 months from onset, persistent in patients from 3 to 12 months and chronic in patients who have it for greater than 12 months from onset.² And that's going to be important as we discuss the recommendations in the guidelines.

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- Cindy Neunert, Deirdra R. Terrell, Donald M. Arnold, George Buchanan, Douglas B. Cines, Nichola Cooper, Adam Cuker, Jenny M. Despotovic, James N. George, Rachael F. Grace, Thomas Kühne, David J. Kuter, Wendy Lim, Keith R. McCrae, Barbara Pruitt, Hayley Shimanek, Sara K. Vesely. *American Society of Hematology 2019 Guidelines for Immune Thrombocytopenia*.; 2019.
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Dr. Gernsheimer: Both clinical presentation and disease progression for ITP will vary across patients.¹ Approximately a third of adult ITP patients are totally asymptomatic, but patients can experience unpredictable bleeding events.¹ Luckily, even in the setting of severe thrombocytopenia, usually they do not exhibit bleeding beyond bruising and petechiae (physician input). Patients can also experience fatigue and a limitation in physical activity that's associated with a reduced quality of life in many cases (physician input). Adults are

generally treated if they have bleeding, if their platelet count falls below around 20,000, or if they're in a profession or have a lifestyle that puts them at a significant bleeding risk.¹

<u>Reference</u>

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 Cindy Neunert, Deirdra R. Terrell, Donald M. Arnold, George Buchanan, Douglas B. Cines, Nichola Cooper, Adam Cuker, Jenny M. Despotovic, James N. George, Rachael F. Grace, Thomas Kühne, David J. Kuter, Wendy Lim, Keith R. McCrae, Barbara Pruitt, Hayley Shimanek, Sara K. Vesely. *American Society of Hematology 2019 Guidelines for Immune Thrombocytopenia*.; 2019.

Dr. Caudle: Thanks for that overview now, Dr. McCrae, let me turn to you now on the updated ASH Guidelines. How are the ASH Guidelines developed and what are some top of mind considerations here?

Dr. McCrae: Well, the ASH Guidelines were actually developed by a multidisciplinary panel that included 18 members both adult and pediatric clinical experts, methodologists, and for the first time, the panel also included two patients. This panel was initiated in 2015 and it created a list of prioritized questions. Using the GRADE approach and an evidence to decision framework literature up to May 1st of 2017 was reviewed and resulted in 21 recommendations which focus on the management of ITP in adults and children with newly diagnosed, persistent and chronic ITP refractory to first-line therapy who have non-life threatening bleeding. Now, we won't be talking about the management of children with ITP today, but I'd like to mention that the guidelines also provide specific recommendations for pediatric patients since disease onset, progression, and lack of comorbidities differs in children from that in adults. The diagnosis, emergency management of ITP, pregnancy, and treatments introduced after 2017 were not addressed in the ASH update. The recommended course of action. Most patients would also want the recommended course of action. Conditional recommendation means that different choices may be appropriate for different patients. Most patients throughout this treatment, but many may not. In this case, the physician will need to guide the patient to arrive at a decision consistent with the patient's values and preferences. Now the management approach is discussed in the guideline include therapies such as corticosteroids, I.V. immunoglobulin, anti-D immunoglobulin, rituximab, splenectomy, and the two TPO receptor agonists available up to 2017.¹

Reference

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Dr. Caudle: If we turn to the 2019 ICR Recommendations, Dr. Gernsheimer, can you give us an overview of those recommendations?

Dr. Gernsheimer: Sure. The updated ICR builds on an earlier 2010 report, an expert panel of 22 and again, this included patients, was formed to include global perspectives and additional focus on the patient's viewpoint. The panel critically reviewed and graded all relevant articles between 2009 and 2018. And based on the data that was formulated, updated consensus includes recommendations on diagnosis and management of ITP in adults, also during pregnancy and in children, and as well as quality of life considerations. We graded the evidence A, B, or C; Grade A, requiring at least one randomized controlled trial as part of a body of literature of overall good quality and consistency. Grade B requiring availability of well-conducted clinical studies, and Grade C requiring evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities. The panel didn't agree on every recommendation, but 85 percent of recommendations did achieve 85 percent agreement. Management approaches discussed in the report include those that were just mentioned by Dr. McCrae, except that the ICR Guidelines includes the three available TPO-RAs that became available in 2018. But treatment introduced after 2019 were not addressed in this update.¹

Reference

- Drew Provan, Donald M. Arnold, James B. Bussel, Beng H. Chong, Nichola Cooper, Terry Gernsheimer, Waleed Ghanima, Bertrand Godeau, Tom'as Jos 'e Gonz alez-L'opez, John Grainger, Ming Hou, Caroline Kruse, Vickie McDonald, Marc Michel, Adrian C. Newland, Sue Pavord, Francesco Rodeghiero, Marie Scully, Yoshiaki Tomiyama, Raymond S. Wong, Francesco Zaja, and David J. Kuter. Updated International Consensus Report on the Inestigation and Management of Primary Immune Thrombocytopenia.; 2019.
- Dr. Caudle: So, with those overviews of the ASH Guidelines and ICR Recommendations, let's focus on the major updates and key

themes from each, starting with recommendations around steroid use. Dr. McCrae, what do the ASH Guidelines recommend here?

Dr. McCrae: Well, corticosteroids are frequently used as the first-line therapy in newly-diagnosed adult patients with a platelet count of less than approximately 30,000.¹ Now in the ASH Guidelines, it's pointed out that steroids should not be used for periods longer than six weeks, and that includes both treatment and taper in newly diagnosed ITP patients.¹ Chronic steroid use puts patients at risk for significant therapy-associated side effects such as weight gain, hyperglycemia, gastric irritation, infection, and steroid myopathy, as well as mood disturbances.^{1,2} In fact, mental health should be monitored during a patient's course of corticosteroid therapy due to the potential impacts this course of treatment can have on this measurement.¹

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- Cindy Neunert, Deirdra R. Terrell, Donald M. Arnold, George Buchanan, Douglas B. Cines, Nichola Cooper, Adam Cuker, Jenny M. Despotovic, James N. George, Rachael F. Grace, Thomas Kühne, David J. Kuter, Wendy Lim, Keith R. McCrae, Barbara Pruitt, Hayley Shimanek, Sara K. Vesely. *American Society of Hematology 2019 Guidelines for Immune Thrombocytopenia*.; 2019.
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Dr. Caudle: And Dr. Gernsheimer, I'll pose the same question to you with respect to the ICR Recommendations, what was the consensus regarding first line steroid use in adult patients?

Dr. Gernsheimer: Recommendations are very similar to those in the ASH Guideline. ICR Recommendations prioritized corticosteroids for initial treatment of newly diagnosed patients. But we also said that the corticosteroids should be tapered by six to eight weeks maximum, even if the platelet count drops during the tapering period.¹

Reference

 Drew Provan, Donald M. Arnold, James B. Bussel, Beng H. Chong, Nichola Cooper, Terry Gernsheimer, Waleed Ghanima, Bertrand Godeau, Tom'as Jos 'e Gonz alez-L'opez, John Grainger, Ming Hou, Caroline Kruse, Vickie McDonald, Marc Michel, Adrian C. Newland, Sue Pavord, Francesco Rodeghiero, Marie Scully, Yoshiaki Tomiyama, Raymond S. Wong, Francesco Zaja, and David J. Kuter. Updated International Consensus Report on the Inestigation and Management of Primary Immune Thrombocytopenia.; 2019.

Dr. Caudle: For those of you who are just tuning in, you're listening to ReachMD. I'm your host, Dr. Jennifer Caudle. And here to give us a breakdown of the updated International Consensus Report, or ICR Recommendations, and the American Society of Hematology or ASH Guidelines, are doctors Terry Gernsheimer and Keith McCrae.

So now that we know what these two guidelines recommend regarding first-line steroid use, let's consider recommendations for secondline therapies in patients who haven't responded to corticosteroids.

Dr. McCrae, given that historically, splenectomies often followed corticosteroids, what have the updated ASH Guidelines said about splenectomy?

Dr. McCrae: Well, historically splenectomy has been used after corticosteroids based on the high percentage of patients that achieve remission following surgical intervention. In fact, long-term studies suggest that remission is obtained in about two-thirds of patients who undergo splenectomy.^{1,2} Because a significant number of patients will not respond, other agents, however, are preferred for management prior to splenectomy because of the long-term increased risk of infection and thrombosis in patients who are splenectomized. That, coupled with the risk of surgical morbidity and mortality, has led to the updated ASH Recommendations to wait at least one year after diagnosis, if possible, before performing splenectomy.^{1,2}

References

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Dr. Caudle: And Dr. Gernsheimer, is there anything to add from the ICR standpoint?

Dr. Gernsheimer: The ICR also recommends to wait at least 12 months and actually as long as 24 months from diagnosis for the safety reasons that Dr. McCrae just outlined, as well as the potential for spontaneous remission with trials of other agents first.¹

Reference

 Drew Provan, Donald M. Arnold, James B. Bussel, Beng H. Chong, Nichola Cooper, Terry Gernsheimer, Waleed Ghanima, Bertrand Godeau, Tom'as Jos 'e Gonz alez-L'opez, John Grainger, Ming Hou, Caroline Kruse, Vickie McDonald, Marc Michel, Adrian C. Newland, Sue Pavord, Francesco Rodeghiero, Marie Scully, Yoshiaki Tomiyama, Raymond S. Wong, Francesco Zaja, and David J. Kuter. *Updated International Consensus Report on the Inestigation and Management of Primary Immune Thrombocytopenia.*; 2019.

Dr. Caudle: Now, staying with you, Dr. Gernsheimer, can you speak more about the concept of spontaneous remission and give us ICR's perspective on this topic?

Dr. Gernsheimer: Yes, remission refers to the resolution of disease with normal or near-normal platelet counts. Remission can be induced by therapy or sometimes occurs spontaneously.¹⁻³ In some studies, as many as 30 percent of adult patients have achieved remission in the first year of diagnosis.⁴ Many of these patients may not require any further therapy. There is some scientific literature that suggests a correlation between early treatment and/or intensification of therapy to achieve remission.^{3,5,4}, But really, there has been little controlled data to support this hypothesis. Currently, there's no universal or consensus definition for remission.³ Both ASH and the ICR refer to remission, albeit differently. In the ICR, remission is referred to as the platelet count of at least 30,000 in the absence of ITP treatment and doesn't specify a duration. The ICR mentions that this can be achieved with some of the newer agents, such as the TPO receptor agonists.³

<u>References</u>

- Cindy Neunert, Deirdra R. Terrell, Donald M. Arnold, George Buchanan, Douglas B. Cines, Nichola Cooper, Adam Cuker, Jenny M. Despotovic, James N. George, Rachael F. Grace, Thomas Kühne, David J. Kuter, Wendy Lim, Keith R. McCrae, Barbara Pruitt, Hayley Shimanek, Sara K. Vesely. *American Society of Hematology 2019 Guidelines for Immune Thrombocytopenia*.; 2019.
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Dr. Caudle: And Dr. McCrae, turning back to you do you have any additional information to add on this topic?

Dr. McCrae: Well, yes, I would agree with Dr. Gernsheimer that the issue of remission can be somewhat confusing. I would also add that sometimes different clinical trials may use different definitions of remission.^{1,2} Now, the most clear definitions in ITP were developed in 2009 by an International Working Group, or IWG, which focused more on responses to therapy rather than remissions per se. The IWG to find a complete response as achieving a platelet count greater than 100,000 in the absence of bleeding. Now, any response or a response was defined as a platelet count of at least 30,000 and at least a two -fold increase from the baseline platelet

count. Remission is basically a response that is maintained off of therapy.³ The 2019 ASH Guideline refers to remission as achieving a platelet count of at least 100,000 off therapy by 12 months after diagnosis. Hopefully, as we develop additional therapies that are able to induce a more long-standing and treatment-free remission, the definition of remission and the duration of response required to achieve it will become more standardized.¹

<u>References</u>

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Dr. Caudle: And Dr. McCrae, are there any other key themes in the updated ASH Guidelines that are significant to take note of?

Dr. McCrae: Well, yes. One very important point is that incorporation of the patient voice or values into decision-making, especially with respect to second-line treatment of ITP lasting for three months or more, has been incorporated throughout the guidelines. The updated 2019 ASH Guidelines have also now provided a treatment algorithm for distinguishing between second-line therapies with patient value and preferences as its focal point. Different options are available and based on the patient's preference. Now, any of these options may potentially provide a long-term response. For example, if patients place a high value on avoiding surgery, opting for medical therapy with TPO-RAs or rituximab is posed as an ideal option. Rituximab or splenectomy may also be recommended if the patient wishes to avoid long term medication use. But due to the paucity of head-to-head prospective comparisons of the many ITP therapies, particularly those used as second-line agents, the ASH Guidelines panel sought to prioritize treatment strategies that avoided significant medication-related side effects.

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Dr. McCrae: Now there's many medication-related side effects. In addition to patient preferences, these are considered when making these second-line treatment choices. TPO-RAs carry risks such as arthralgia, headache, and a slight increased risk of thrombosis.¹ Rituximab carries a risk of infusion-related reactions. In addition, administration of rituximab results in B cell depletion, and this can impair vaccine response for up to six to nine months after treatment.^{2,3,4,5,6} So it's critical to reassess decision-making and patient preference regularly. However, there's no real single second-line treatment that's optimal for all adult patients with ITP.

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Dr. Caudle: And Dr. Gernsheimer back to you, you know, any key themes in the updated ICR Guidelines that you would like to address?

Dr. Gernsheimer: Yes, the ICR report includes recommendations for additional therapies that may be effective in patients with refractory disease. These recommendations for therapies that are not approved for ITP are based on expert opinion. The ICR Guidelines also include recommendations for adjunctive therapies that may be effective in the event of serious bleeding.¹

Deference

- <u>Reference</u>
 - 1. Drew Provan, Donald M. Arnold, James B. Bussel, Beng H. Chong, Nichola Cooper, Terry Gernsheimer, Waleed Ghanima, Bertrand Godeau, Tom'as Jos 'e Gonz alez-L'opez, John

Dr. Caudle: Well, this has been a great overview on the respective ITP guideline updates, but before we close Dr. Gernsheimer, let me return to you for the final word. Are there any additional highlights or takeaways you think point us towards the future of ITP management?

Dr. Gernsheimer: As we discussed, the ASH and the ICR 2019 Guidelines provide recommendations from experts and from panels of patients for the management of adult ITP with non-life threatening bleeding. But these guidelines also provide recommendations for the pediatric population, both of them. And the ICR recommendation includes discussion on disease management for patients who are pregnant as well. The major update to the guidelines include incorporating patient values and treatment selection.^{1,2} And I think that this is really very important because the patients view of how they need to be treated and what their own goals are, really need to be taken into account. And that helps us to focus on reducing corticosteroid use and also deferring splenectomies for at least a year in adult patients with ITP.

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Dr. Caudle: Well, that's a great way to wrap up our panel discussion today. So on that note, I'd like to thank my guests, doctors Keith McRae and Terry Gernsheimer for joining me. Doctors, it was wonderful having you on the program.

Dr. Gernsheimer: Thank you was a pleasure.

Dr. McCrae: Yes, I enjoyed it. Thank you so much.

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