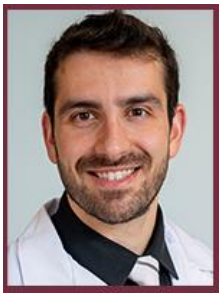
Practical Hematologist

Diagnosis and Management of Pediatric and Adult Patients with Immune Thrombocytopenia



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Introduction

As part of the *Improving Outcomes for Pediatric and Adult Patients with Immune Thrombocytopenia* program, Dr. Michele P. Lambert, Attending Physician in the Division of Hematology at Children's Hospital of Philadelphia, and Dr. Hanny Al-Samkari, Assistant Professor of Medicine at Harvard Medical School, share their expertise regarding the evidence-based diagnosis and management of pediatric and adult patients with ITP.

Pediatric ITP: Management and Treatment Selection

What are the 2019 American Society of Hematology (ASH) recommendations regarding hospitalization or management of pediatric patients with no or minor bleeding?

In general, the guidelines recommend against admission to the hospital in favor of outpatient management regardless of platelet count, ensuring that a pediatric hematologist sees the patient within 24 to 72 hours of diagnosis.[1] Considerations for hospitalization might be if you are uncertain about the diagnosis, if you are not sure about follow up, or if the patient lives a long distance from the hospital.[1]

When thinking about whether or not to treat patients who have no or minor bleeding, the panel recommends observation over corticosteroids, intravenous immunoglobulin (IVIG), and anti-D globulin.[1] Most of our pediatric patients (~75%) spontaneously resolve and have very acute onset of their bleeding symptoms.[2] They have very few comorbidities at diagnosis, and they have very few medications that affect their bleeding risk at the time of diagnosis.[2] These differences really drive the variability in recommendations for management between pediatric and adult ITP, because most of these patients are very healthy.

TIKI Trial: Treatment with or without IVIG for children with ITP

When we're looking at whether or not to treat our patients, we have very nice data that recently came out in the form of the TIKI trial that actually randomized pediatric patients to get IVIG versus observation.[3] In this trial, there was a difference in the time to platelet count recovery early on, and so those patients that got IVIG did have higher platelet counts at three months.[3] By six months that difference in platelet count recovery was really negligible, and by a year there was no difference in platelet counts between the two groups.[3]

Once you've decided your patient will benefit from treatment, what treatment should you use?

When the ASH panel considered treatment, they prioritized outcomes including major bleeding mortality, durable response remission, and health-related quality of life.[1] The major factor that influenced the panel recommendations was lack of data directly comparing the prioritized outcomes. Other factors, including cost and patient-specific factors, were also considered, and weighing all of that, corticosteroids won out.[1]

In general, the panel recommended against corticosteroid therapy that lasted longer than seven days in favor of courses that were seven days or shorter, suggesting prednisone over dexamethasone.[1]

What about children with non-life-threatening bleeding or diminished health-related quality of life who don't respond to first-line treatment?

The panel looked at different second-line therapies and suggested the use of thrombopoietin receptor agonists (TPO-RAs) rather than rituximab or splenectomy, and rituximab rather than splenectomy in most pediatric patients.[1]

The risks of TPO-RAs are thought to be low with potential benefits being high, and you avoid immunosuppression.[1] However, family preference is really important in this decision making. If a family wants to avoid ongoing treatment, or if you are thinking that ITP might be secondary to an underlying immunodeficiency, rituximab might be a good choice.[1]

There is value to avoiding splenectomy early in pediatric patients who have ITP, but in patients who have chronic ITP, especially those who have long-standing ITP, there's definitely a potential benefit to splenectomy.[1] There is an attributable infection risk in the form of sepsis, and there are operative complications associated with pediatric splenectomy. It's important to keep that in mind when discussing the risk benefit of splenectomy vs TPO-RAs or other treatments in pediatric patients.

Adult ITP: Diagnosis and Treatment Selection

How is ITP classified in adults?

As in children, we think of ITP in adults as primary vs secondary; in adults, 80% fall into the primary bucket.[5] We also classify ITP according to its chronicity. We don't say “acute” ITP, we say “newly diagnosed”, because acute could be an exacerbation in a patient with chronic ITP. We talk about newly diagnosed ITP (<3 months in duration), persistent ITP (3-12 months), and then chronic ITP (>12 months).[6] This is relevant because many of the medications we talk about have been approved for ITP of a certain chronicity, but not ITP of other chronicities.

What is the platelet threshold for bleeding risk?

There is not a specific platelet threshold for adults as well as in children, where we say the person is absolutely safe above this threshold or clearly not safe below that threshold. We tend to stick to a threshold of say, above 20,000, which puts most adults with ITP out of the danger zone in terms of spontaneous bleeding risk. We often require a higher number in those patients who are receiving antithrombotic, anti-platelet, and anticoagulation therapies, as well as those who need surgical procedures. We also recognize that risk increases with age. In general, if somebody's platelet count is in the single digits, that's a cause for concern.

What symptom(s) are most commonly reported by patients?

Fatigue is very common in adults with ITP, being reported by a majority (70%) of patients at the time of diagnosis. Over 70% of patients with fatigue reported the symptom as severe.[8] We also see petechiae and bleeding are very high in terms of the percentage of patients reporting, as well as depression and various bleeding manifestations beyond the typical petechiae and bruising that we see. We see anxiety as a major manifestation, which is reported as severe in almost 80% of affected patients.[7]

Later in the disease course, over 50% of patients continue to describe fatigue and over 60% say it's severe.[7] We see anxiety is still a major issue. More patients report severe fatigue and anxiety than report severe bleeding.[7]

I think it's really important that we recognize that there are multiple pillars of symptoms in ITP that we have to think about. Bleeding is of course the first, and physicians are very good about being concerned about their patient's bleeding and bleeding risk. We have to recognize the other symptoms of ITP like fatigue, as well as the psychological consequences of having this disease, and the toxicity of our therapies. We have to consider those really almost as equally important in many cases.

"ITP is classically thought of as a diagnosis of exclusion, although I like to call it a diagnosis of recognition."

According to the International Consensus Guidelines (**Table 1**), we have a series of very simple things that are recommended for all adults with ITP, which includes your typical history, physical, CBC, peripheral blood film examination, and quantitative immunoglobulin level measurements, which are relevant to understand if there are any immunodeficiency correlates, as well as understanding what that looks like before giving certain therapies like rituximab.[6] Then we have hepatitis serologies and HIV.[6]

Table 1. Recommendations for the diagnosis of ITP in children and adults

Basic evaluation in all patients	Tests of potential utility in the management of an ITP patient	Tests of unproven or uncertain benefit*
Patient history	Glycoprotein-specific antibody (can be used in difficult cases, has poor sensitivity, and is not a primary diagnostic test)	TPO level
Family history	Antiphospholipid antibodies (including anti-cardiolipin and lupus anticoagulant) if there are clinical features of antiphospholipid syndrome	Reticulated platelets/immature platelet fraction
Physical examination	Anti-thyroid antibodies and thyroid function	
CBC and reticulocyte count	Pregnancy test in women of childbearing potential	Bleeding time
Peripheral blood film	Antinuclear antibodies	Serum complement
Quantitative Ig level measurement∇	Viral PCR for EBV, CMV, and parvovirus	
Blood group (Rh)	Bone marrow examination (in selected patients)	
HIV	Direct antiglobulin test	
HCV ǂ	*H pylori* ǂ	
HBV		

CMV, cytomegalovirus; EBV, Epstein-Barr virus; PCR, polymerase chain reaction; PTT, partial thromboplastin time; RH, rhesus; TPO, thrombopoietin.
*These tests have no proven role in the differential diagnosis of ITP from other thrombocytopenias and do not guide patient management.
∇Quantitative Ig level measurement should be considered in children with ITP and is recommended in children with persistent or chronic ITP as part of the reassessment evaluation.
ǂRecommended by the majority of the panel for adult patients in the appropriate geographic setting.

One major reason why all of the guidelines don't recommend anti-platelet autoantibody testing as standard, despite the fact that we recognize that patients with ITP often have these platelet autoantibodies, is that it is so difficult to do it right. There are so many things that can impact the results, and there is a lot of variability in the sensitivity found in a whole host of studies in the literature.[8]

"When we talk about treatment of ITP, we talk about treating the disease while trying to minimize the toxicity as best as possible."

One of the things we recognize nowadays is that we use too many steroids in the treatment of this disease. In the adult setting, corticosteroids are the most common treatment selected in any course of therapy; first-line, second-line, or third-line. We've got to do better.

There are some differences between adults and pediatrics in terms of what the ASH guidelines recommend. For newly diagnosed patients with a platelet count less than 30,000 who are asymptomatic, the recommendation is for corticosteroids rather than management with observation.[1] If patients have a count of greater than 30,000, then observation is recommended.[1] It's also recommended that patients who have a platelet count of less than 20,000 at the time of their first presentation with ITP, or if they have even just minor bleeding, that they are admitted to the hospital rather than management as an outpatient, which is very different in adults than in the pediatric world.[1]

When should we consider IVIG?

We want to use this in our patients who have steroid contraindications or who are actively, acutely bleeding. Those patients who are also at significantly increased risk of having bleeding relative to the general population, especially in patients who've had a prior substantial bleed during an ITP exacerbation, we want to think about IVIG.[1]

We have to remember that IVIG is not a completely benign treatment. There are potential side effects, things like headache, aseptic meningitis, venous thromboembolism, so we have to consider that.

How do we select among second-line therapies?

We want to talk to our patients about what they value.[1] Talk to them about what they would like to avoid, as that can really help guide us. Because we don't have randomized controlled trials comparing avatrombopag to rituximab, or comparing splenectomy to romiplostim, we don't have high-quality data comparing these second-line therapies.

What investigational therapies for ITP are currently being studied?

One class that's being evaluated right now in clinical trials is the neonatal Fc receptor antagonists. That is a receptor that is responsible for the half-life of circulating IgG. With this receptor intact, circulating IgG has a half-life of about 21 days.[9] When you take it out, block the receptor, that half-life goes down to about seven days. Your circulating IgG levels dropped by about 66%, that includes both normal IgG that you have in there, and as well as pathologic, platelet autoantibodies.[9] We can reduce our platelet autoantibodies by blocking the neonatal Fc receptor. This strategy is being used for a couple of investigational drugs (ie, rozanolixizumab and efgartigimod).[10,11]

When we look at complement inhibition in ITP, there are a couple drugs being evaluated in this regard. Sutimlimab is an anti-C1s monoclonal antibody, which blocks the classical complement pathway while leaving the other two complement pathways intact; this is important for infection risk as we think about that.[12] This drug is FDA-approved already for the treatment of cold agglutinin disease, and a recently published phase one study demonstrates the efficacy in ITP.[12]

There's also recognition that BTK inhibitors (ie, rilzabrutinib), which have been available for lymphoid malignancies for quite some time, may have value in ITP given their very potent effects on the B-cell compartment.[13]

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