Improving Outcomes for Pediatric and Adult Patients with IMMUNE THROMBOCYTOPENIA

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Dr. Michele Lambert: Hello, and welcome to today's program. I'm Dr. Michele Lambert, Pediatric Hematologist at the Children's Hospital of Philadelphia. I'm joined today by Dr. Hanny Al-Samkari, Adult Hematologist at Massachusetts General Hospital.

Faculty Disclosures

- **Dr. Michele Lambert** has relevant financial relationships related to consulting from argenx, Dova Pharmaceuticals, Inc. (now Sobi), Janssen Pharmaceuticals, Inc., Novartis AG, Principia Biopharma (now Sanofi), Rigel Pharmaceuticals, Inc., Sanofi, Shionogi Inc., and Sobi, as well as advisory activities from Dova (now Sobi), Octapharma USA, Inc., Principia (now Sanofi), Rigel, and Shionogi. She has received research grants from argenx, Dova (now Sobi), Octapharma, Principia (now Sanofi), Novartis, Rigel, and Sysmex.
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These are our disclosures.

Improving Outcomes for Pediatric and Adult Patients with IMMUNE THROMBOCYTOPENIA

Learning Objectives

- Reviewing the pathophysiology of ITP and the various mechanisms that can be targeted to treat this condition in adult and pediatric patients
- Applying current guideline recommendations for the treatment of pediatric and adult ITP, including the addition of recently approved agents, to practice
- Discussing emerging agents that are currently being developed for ITP and how these agents may be integrated into practice as each is approved
- Selecting ITP therapy that is designed to optimize long-term outcomes, patient preferences, and adherence

Today we're going to discuss *Improving Outcomes for Pediatric and Adult Patients with Immune Thrombocytopenia*. Today our learning objectives are shown and this is what we'll focus on.

Pediatric ITP Diagnosis and Management

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I'm going to start and talk about pediatric ITP diagnosis and management, and then Hanny is going to talk about adult diagnosis and management.

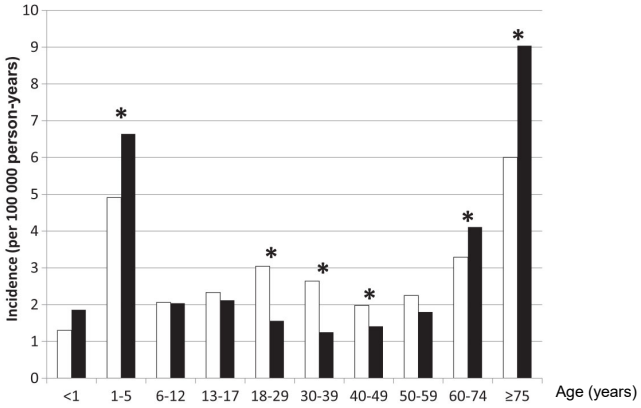
Objectives

Highlight recommendations from 2019 Guidelines

- Pediatric ITP, management of newly diagnosed patient
  - Describe rationale for areas of significant change
  - Discuss limitations and areas of need for future research
  - Emphasize need for shared decision-making in therapy selection

My objectives are to highlight the recommendations from our 2019 guidelines on pediatric ITP management, and describe rationale for areas of significant change, discuss limitations in areas that need future research, and emphasize the need for shared decision-making.

Incidence by Age



Incidence of ITP in France during the period from mid-2009 to mid-2011 by age and gender.
Females, white bars; males, black bars. Stars indicate statistically significant differences among males and females (α = 5%).

Moulis G, et al. *Blood*. 2014;124:3308-3315.

We all know that pediatric ITP peaks at around one to five years and that ITP in general has a bimodal distribution with a peak in early childhood, and then a peak in later adulthood. There is actually a third peak in adolescents and young adults as well and that peak tends to be in female patients, whereas the other two peaks tend to be in male patients.

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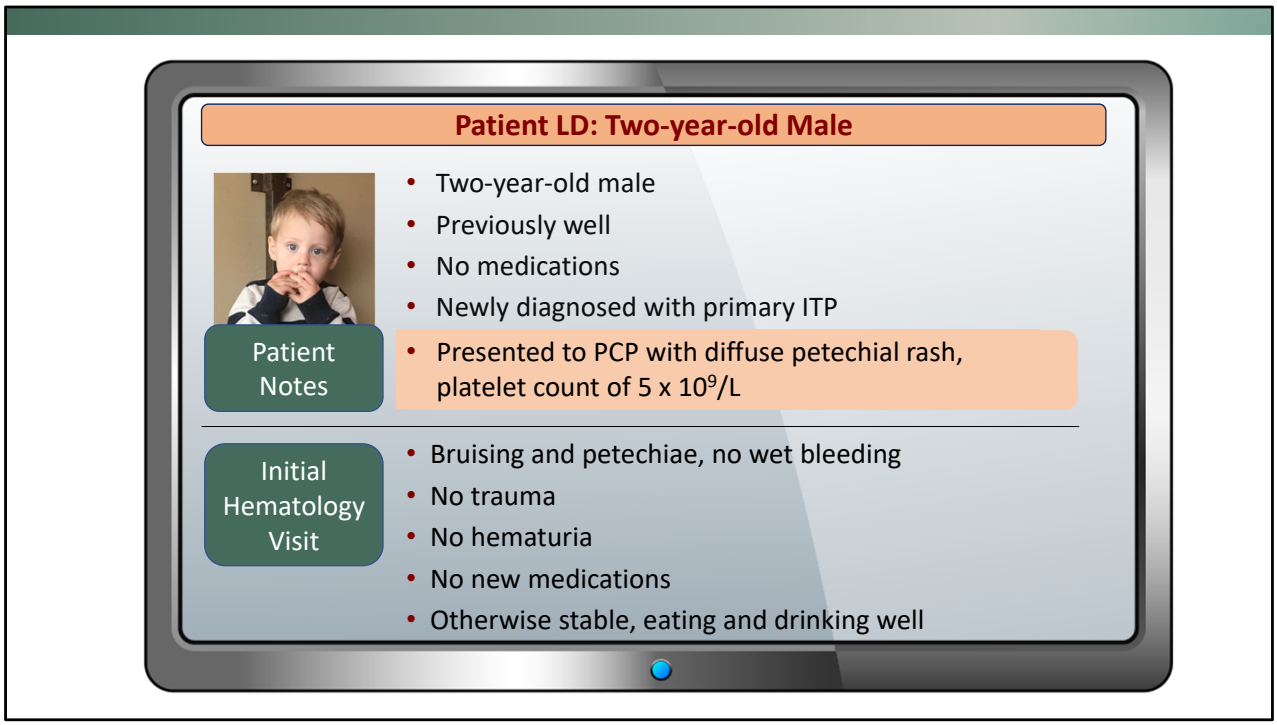

Let's start with a case. Patient LD is a two-year old male, who was previously well on no medications. He presents for his first hematology visit with bruising and petechiae, no wet purpura, he's had no trauma, no hematuria, he has no new medications. He's otherwise stable eating and drinking well, but he did present with a diffuse petechial rash and his platelet count was noted to be 5,000.

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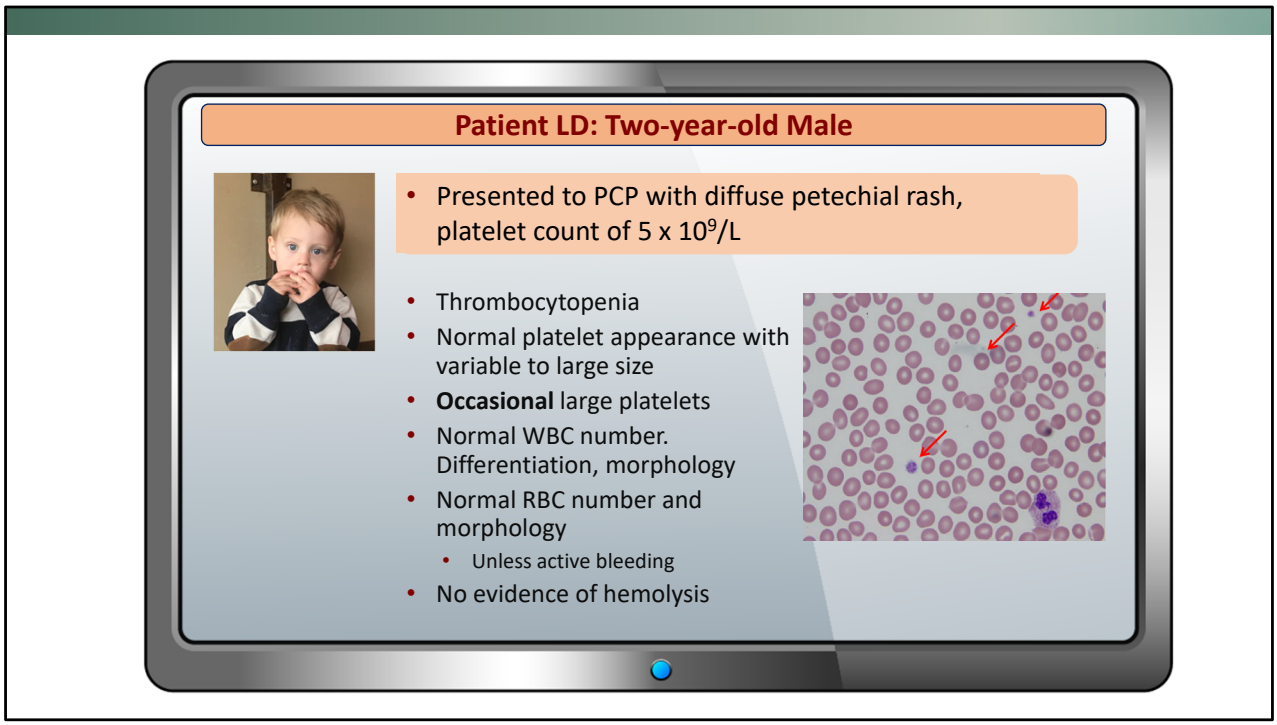

He has thrombocytopenia with normal platelet appearance with variable size, some of them are large. He has normal white cells, normal differentiation and morphology, normal red cell morphology, and he has no evidence of hemolysis. This is what a pediatric patient with ITP should look like, although they may have a mild anemia if they have active bleeding.

2019 ASH Recommendations: Hospitalization

In children with ITP who have no or mild bleeding (skin manifestations), the panel

- ***Suggests* against admission to the hospital in favor of outpatient management**
- Considerations: uncertainty about diagnosis, social/follow-up concerns, distance from hospital

Good Practice Statement
Ensure follow-up with a hematologist within 24-72 hours of diagnosis

What are the 2019 ASH recommendations regarding hospitalization or management of our patients? The question of hospitalization was broken into two parts, patients with a really low platelet count, less than 20, and patients with platelet counts greater than 20. No randomized clinical trials were identified that specifically address this question, but benefits were determined to be trivial, as long as reliable follow up was ensured, and there was significant cost savings.

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. Considerations for hospitalization might be that if you are uncertain about the diagnosis, or if you are not sure about follow up. Or if the patient really lives a long distance from the hospital, and you're going to require them to go home and then come back again, just 24 to 48 hours later, and travel long distances.

2019 Panel Recommendations: Treatment

In children with no or minor bleeding, the panel:

- ***Suggests*** **observation rather than corticosteroids**
- ***Recommends*** **observation rather than IVIG**
- ***Recommends*** **observation rather than anti-D**

Then when thinking about whether or not to treat patients who have no or minor bleeding, just skin bleeding basically, the panel recommends observation over corticosteroids, observation over IVIG, and observation over anti-D globulin. Basically, observation over any first line therapies for pediatric patients with no or minor bleeding, and this recommendation was made with strong to moderate certainty.

Educ Prog 1:405-411.

Epidemiology of Pediatric vs ITP

	Adult ITP	Pediatric ITP
Spontaneous remission	~20%	~75%
Onset	Insidious	Acute
Comorbidities at diagnosis	30%	4%
Medications affecting bleeding risk at diagnosis	More common	Less common

Despotovic JM, Grimes AB. *Hematology Am Soc Hematol Educ Program.* 2018;1:405-411.

We know there are differences in the epidemiology of pediatric and adult ITP. Most of our pediatric patients spontaneously resolve and have very acute onset of their bleeding symptoms. They have very few comorbidities at diagnosis, and they have very few medications that affect their bleeding risk at the time of diagnosis.

These differences really drive the differences in recommendations for management between pediatric and adult ITP, because most of these patients are very healthy. It's a sudden onset of disease, they are very likely to resolve relatively quickly. They are really not on other medications that are going to change the risk calculation for whether or not your patient is going to bleed. That's part of why we have these recommendations that recommend observation over any first-line therapy and pediatric ITP.

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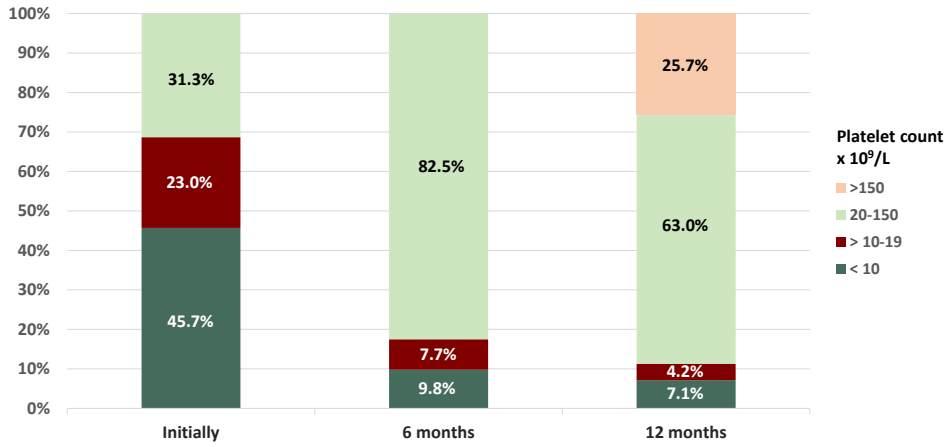
Spontaneous Resolution of ITP Between 6-12 Months is Not Uncommon



Imbach P, et al. *Pediatr Blood Cancer*. 2006;46(3):351-356.

Spontaneous resolution, generally happens between six to 12 months and it's very common in most of our patients. We can look and see in this figure that most patients have platelet counts that are significantly better by six months and almost everybody has resolved by 12 months post their initial diagnosis of ITP.

To Treat or Not to Treat…TIKI Trial

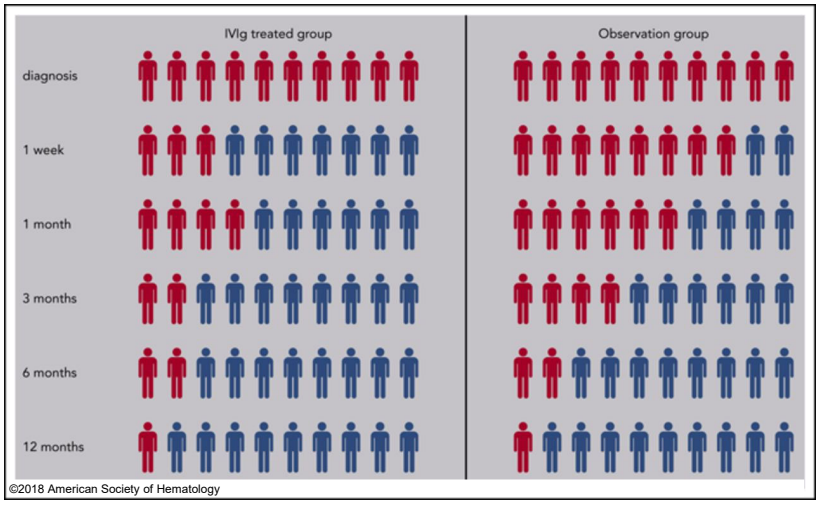
Intravenous immunoglobulin vs observation in childhood immune thrombocytopenia: a randomized controlled trial

Katja M.J. Heitink-Pollé; Cuno S.P.M. Uiterwaal; Leendert Porcelijn; Rienk Y.J.Tamminga; Frans J. Smiers; Nicole L. van Woerden; Judit Wesseling; Gestur Vidarsson; Annemieke G. Laarhoven; Masjade Haas; Marrie C.A. Bruin; for the TIKI Investigators

Heitink-Pollé K, et al. *Blood*. 2018;132(9):883-891.

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. This is a randomized controlled trial that looked at over 200 patients.

To Treat or Not to Treat…TIKI Trial



Heitink-Pollé K, et al. *Blood*. 2018;132(9):883-891.

In this randomized, controlled trial, there was a difference in the time to platelet count recovery early on, and so those patients that got IVIG did have a higher platelet counts at three months. 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.

Epidemiology of Pediatric vs ITP

	Adult ITP	Pediatric ITP
Spontaneous remission	~20%	~75%
Onset	Insidious	Acute
Comorbidities at diagnosis	30%	4%
Medications affecting bleeding risk at diagnosis	More common	Less common (but more bleeding at dx)

Despotovic JM, Grimes AB. *Hematology Am Soc Hematol Educ Program.* 2018;1:405-411.

Then again, less comorbidities and there's fewer medications that are associated with increased bleeding. Although it is interesting to note that bleeding at diagnosis is a little bit more common in pediatric patients. This may be in part due to this very acute and sudden onset of thrombocytopenia.

Severe Bleeding Pediatric vs Adult ITP

- 29 studies included (2225 patients)
  - Reported bleeding as a categorical variable
  - Used a predefined bleeding assessment tool
- 15% of patients met criteria for severe bleeding
  - 9.6% of adults
  - 20.2% of children
- Less likely to have ICH

When we look at severe bleeding in pediatric patients, there was a recent review that looked at 29 studies looking at over 2000 patients reporting bleeding as a categorical variable.

15% of patients met criteria for severe bleeding, and that was 9.6% of adults, but 20% of children. Although the children were much less likely to have intracranial hemorrhage, there was significant bleeding in the pediatric population.

Intracerebral Hemorrhage in Adults and Children with Immune Thrombocytopenia

(Weighted proportions, reported as percentage with 95% confidence intervals)

	Newly-diagnosed, %	Chronic, %	All disease stages, %
Children only (*n* = 1965)	0.4 (0.1–0.9)	1.3 (0.4–2.7)	0.4 (0.2–0.7)
Adults only (*n* = 1896)	0.6 (0–1.8)	1.8 (0.9–2.8)	1.4 (0.9–2.1)
Either children or adults* (*n* = 921)	0.2 (0.2–1.6)	1.6 (0.5–3.1)	1.2 (0.4–2.4)
Overall (*n* = 4782)	0.4 (0.1–0.8)	1.6 (1.0–2.2)	1.0 (0.7–1.3)

*Data for children and adults were not reported separately in these studies
Neunert C, et al. *J Thromb Haemost*. 2015;13:457-464. With permission.

When we look at other studies that specifically looked at things like intracranial hemorrhage in ITP patients. We can see that the incidence of intracranial hemorrhage is higher in adult patients than it is in pediatric patients, but that there is somewhat increased incidence of bleeding.

Why Do Adults Get ICH at Higher Frequency?

- Highest risk in adults >60 years
- 71% had comorbidities
- 29% taking medications which could increase risk of bleeding
- (COMPARED TO 10% OF ALL ADULTS WITH ND ITP)
- Children: 7% with ICH had comorbid conditions, 14% taking meds
- (COMPARED TO 1% OF ALL CHILDREN WITH ND ITP)

Why do adults get intracranial hemorrhage? Well, we think the highest risk for intracranial hemorrhage is in the older adults over 60 years of age. Many of those patients have comorbidities associated with increased risk for intracranial hemorrhage. 29% of those patients are taking medications that increased risk of bleeding compared to overall 10% of adults with newly diagnosed ITP.

In children, 7% of children had comorbid conditions. 14% of those children were taking medications compared to 1% of all children with newly diagnosed ITP. Certainly, taking medications that increase your risk of bleeding or associated with an increased risk of intracranial hemorrhage.

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Case 2: Patient AB

- 14-year-old male, new onset epistaxis
- Platelet count 2 x 10^9/L
- Previously normal counts
- Star hockey player on high school team
- Ongoing intermittent epistaxis, oozing wet purpura
- You decide patient will benefit from treatment

Let's look at another case. This is a 14-year-old male with new onset epistaxis. His platelet count is 2000. He's previously had multiple normal platelet counts. He is a star hockey player on his high school team. He has ongoing intermittent epistaxis and he does have oozing wet purpura. You've decided your patient will benefit from treatment.

Treatment Options Considered in the Guidelines

Initial Treatment Options		
• Observation • Corticosteroids: typically prednis(ol)one • IVIg • IV Anti-RhD immune globulin		
Second-line Treatment Options		
• TPO receptor agonists (romiplostim, eltrombopag) • Rituximab • Splenectomy		
Salvage Treatment Options		
• Azathioprine • Cyclosporin A • Cyclophosphamide	• Danazol • Dapsone • Mycophenolate mofetil	• Vinca alkaloids • HSCT

The question is what treatment are you going to use? Are you going to do corticosteroids, IVIG, anti-D immunoglobulin? Or are you going to go straight to a second line therapy?

Major Challenges

- No uniformly accepted platelet threshold
  - No strong correlation between severe bleeding and platelet count
  - Used as a surrogate for clinical outcomes of interest
  - Heterogeneity above the threshold
- Lack of evidence on hospitalization
- Lack of evidence on observation in certain populations
- Extreme variability in corticosteroid dosing
- Lack of reporting on outcomes of interest

Neunert C, et al. *J Thromb Haemost*. 2015;13(3):457-464.

The major challenges with trying to answer the question of what to do in developing guidelines, is that there were no uniformly accepted platelet thresholds at which really we should be treating all patients. There's not a strong correlation between severe bleeding and platelet count, although platelet count tends to be used as a surrogate for clinical outcomes of interest. There's heterogeneity above which threshold we should be treating, or below which threshold we should be treating patients.

There's lack of evidence for whether hospitalization provides benefit in these patients.

There’s definitely lack of evidence on observation in patients who have mild to moderate bleeding, especially pediatric patients.

There's definitely extreme variability in corticosteroid dosing. When you're looking at all the steroid clinical trials there's dosing that varies from less than one milligram per kilo per day to high dose dexamethasone dosing.

There's a lack of reporting outcomes of interest beyond just bleeding or what the platelet count turns out to be after you treat a patient.

What Treatment?

- Panel considered three separate comparisons
  - Corticosteroids vs anti-D
  - Corticosteroids vs IVIG
  - Anti-D vs IVIG
- Prioritized outcomes included major bleeding, mortality, durable response, remission, HRQoL
- Outcomes specific to individual therapies were also prioritized (hemolysis with anti-D immune globulin)

When the ASH panel considered treatment, they looked at three separate comparisons. They looked at corticosteroids versus anti-D, corticosteroids versus IVIG, and anti-D versus IVIG. That's really the data they were able to pull from the literature. They prioritized outcomes including major bleeding mortality, durable response remission, and health related quality of life. And these outcomes were specific to individual therapies and were also prioritized for example hemolysis with anti-D.

Panel Recommendations: Treatment

In children with newly-diagnosed ITP and non–life-threatening bleeding and/or diminished HRQoL, the panel:

- ***Suggests*** **corticosteroids rather than anti-D immune globulin**
- ***Suggests*** **corticosteroids rather than IVIG**
- ***Suggests either*** **anti-D immune globulin or IVIG**

The recommendations as a result of this analysis, they suggested corticosteroids rather than anti-D, corticosteroids rather than IVIG, and either anti-D or IVIG. This was a strong recommendation with moderate certainty. Corticosteroid recommendation was a conditional recommendation with very low certainty.

Panel Recommendations: Treatment

Major factors influencing panel recommendations:

- Lack of data directly comparing prioritized outcomes
- Other factors considered
  - Cost
  - Patient specific factors (Rh+ for anti-D)

The major factors that influenced the panel recommendations were really lack of data directly comparing the prioritized outcomes. Other factors, including cost and patient specific factors, were also considered and weighing all of that really in general corticosteroids won out.

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Case 2: Patient AB

- After discussing available therapies and guidelines, you plan to start corticosteroid treatment
- What do the guidelines recommend for choice of steroid, dosing and duration of therapy?

After discussing the guidelines, you decide to do corticosteroids, and so then what are you going to do as far as steroid dosing and duration of therapy for this 14-year-old student athlete?

Panel Recommendations: Steroid Preference

In children with newly-diagnosed ITP and non–life-threatening bleeding and/or diminished HRQoL, the panel:

- ***Recommends against*** **courses of corticosteroids longer than 7 days and in favor of courses 7 days or shorter**
- ***Suggests*** **prednisone 2-4 mg/kg/day (120 mg max) x 5-7d rather than dexamethasone 0.6 mg/kg/day (40 mg max) x 4d**

In general, the panel looking at all of the data that was available suggested that in newly diagnosed ITP with non-life threatening bleeding or diminished health related quality of life. Recommended against corticosteroid therapy that lasted longer than seven days in favor of courses that were seven days or shorter, suggesting prednisone over dexamethasone.

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Case 2: Patient AB

- No epistaxis since initial steroids
- Continues to have platelets <10 x 10^9/L with only bruising
- Fatigued and is now also depressed due to activity limitations

You treat your patient with corticosteroids and you notice that there's no epistaxis since he started his steroids, but his platelet count continues to be less than 10. He's only had mild bruising but he's also complaining of fatigue, and he is really getting depressed because he's had his activities significantly limited. He's not allowed to play hockey. His platelet count is so low.

Panel Recommendations

In children with ITP who have non–life-threatening mucosal bleeding and/or diminished health-related quality of life and do not response to first-line treatment:

1) ***Suggests*** **the use of TPO-RAs rather than rituximab**
2) ***Suggests*** **TPO-RAs rather than splenectomy**
3) ***Suggests*** **rituximab rather than splenectomy**

All conditional recommendations based on very low certainty in the evidence of effects

What about children with non-life threatening bleeding or diminished health related quality of life who don't respond to first line treatment? His platelet count is still low even though he's had significant improvement in his platelet count.

The panel looked at different second line therapies and suggested the use of TPOs rather than rituximab, TPOs rather than splenectomy, and rituximab rather than splenectomy in most pediatric patients.

All of these recommendations were conditional based on very low certainty and the level of effects and the evidence of effects and in the level of evidence that was available. In general, we really have very limited data, and especially limited data that compares these different therapies against each other.

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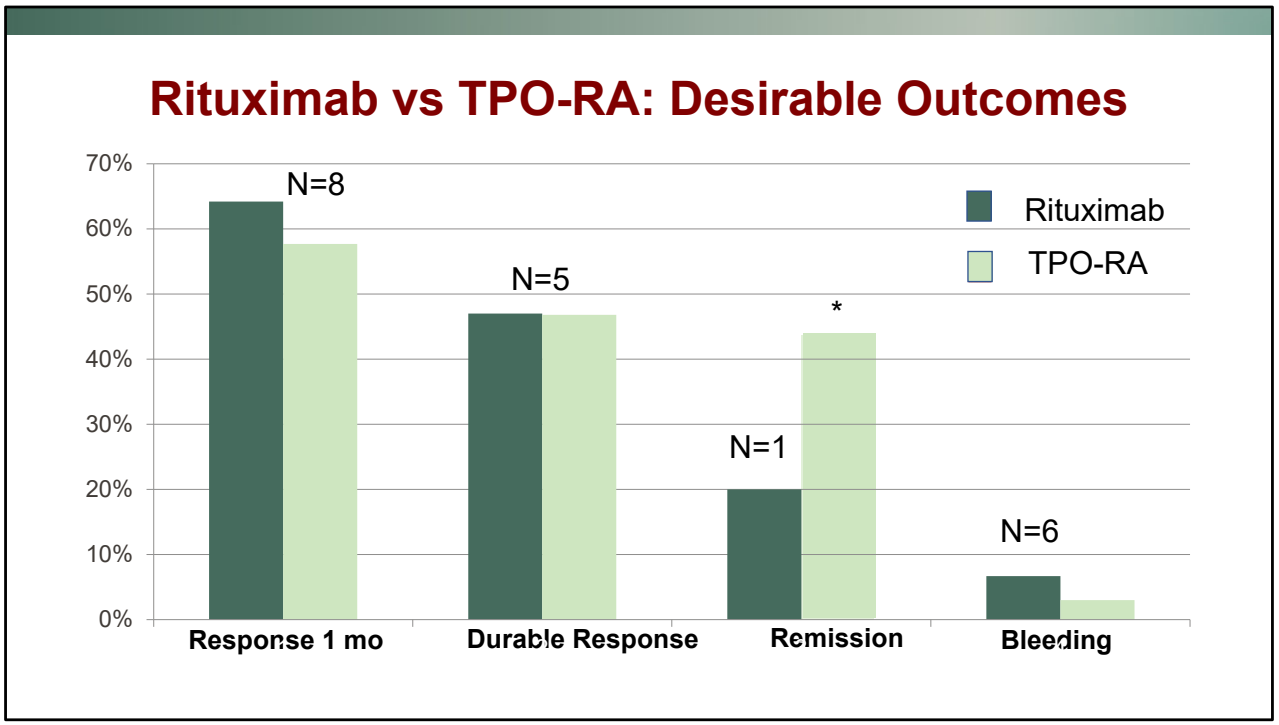

We do have some ability to compare responses over time. When we're looking at durable remissions in rituximab versus the TPO receptor agonist, we can see that TPO receptor agonist in the open label extension randomized clinical trial, did show some durable responses and a significant impact on bleeding.

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Rituximab vs TPO-RA: Other EtD criteria

Rituximab	TPO-RA
Attributable Infections: 1.4% Persistent hypogammaglobulinemia Impaired vaccine response Infusion reactions, serum sickness **Patient goals/feasibility**: Short-term treatment No daily medication $ Intravenous 	Infections: 4.8% Thrombosis not seen in ped trials Hepatoxicity (eltrombopag) Iron deficiency (eltrombopag) **Patient goals/feasibility:** Long-term treatment Continuous medication $$$ Oral or subcutaneous 

Rituximab did have attributable infections in about 1.4% of patients, persistent hypogammaglobulinemia, impaired vaccine responses, and infusion reactions, as well as some serum sickness. Rituximab can be expensive although one of the benefits is that there's no daily medication requirement. It's an IV medication. If you're worried about adherence, you know your patient is getting it because your patient comes in and gets it, and it's relatively short term treatment.

The TPO receptor agonists also have some infections associated with them although these are generally minor. There's hepatotoxicity and iron deficiency associated with eltrombopag. There's not significant thrombosis seen in the pediatric trials. Although these are long term treatments, they require continuous medication and they can be quite expensive over the long term, although you can choose between oral or subcutaneous. Choosing the subcutaneous option in bringing your patient into clinic gives you control over whether or not your patient is taking the medication.

Considerations When Using Rituximab for ITP

- Side effects and efficacy should be discussed with families prior to treatment
  - Incidence of severe side effects (anaphylaxis, PML) very rare in ITP
  - Increased risk of infection has been demonstrated
  - Incidence of serum sickness may be higher in children
  - Incidence of sustained response is <30%
  - Very expensive ($3500/100 mg vial, **$85,000** for four doses for patient with BSA 1.3 m^2)
- Recommend monitoring for B-cell recovery and performing needed vaccinations

Zaja F, et al. *Eur J Haematol.* 2010;85:329-334.

Considerations for choosing rituximab, the incidence of the severe side effects anaphylaxis, PML is very rare in ITP, although there is a demonstrated risk of infection. Serum sickness might be a little bit higher in children. The evidence of sustained response really is that it's less than 30% long term responses in pediatric patients. It can be quite expensive to give a course of rituximab for all four doses. It's recommended that we monitor for B-cell recovery, and performing vaccinations again after rituximab in patients who lose their vaccination responses.

Recommendation for TPO-RA > Rituximab

- Risks of TPO-RA thought to be low, potential benefits high
- Value on avoiding immunosuppression given rate of remission

When could rituximab be considered rather than TPO-RA?

- Family/patient preference for avoiding ongoing treatment
- Secondary ITP if underlying immunodeficiency excluded
- Failure of TPO-RA

The risks of TPOs are thought to be low with potential benefits being high and you avoid immunosuppression. This is part of why the panel recommended TPO-RAs over rituximab. However, family preference is really important in this decision making. If a family really wants to avoid ongoing treatment, or if you are thinking that that ITP might be secondary to an underlying immunodeficiency that is already an antibody deficiency rituximab might be a really good choice.

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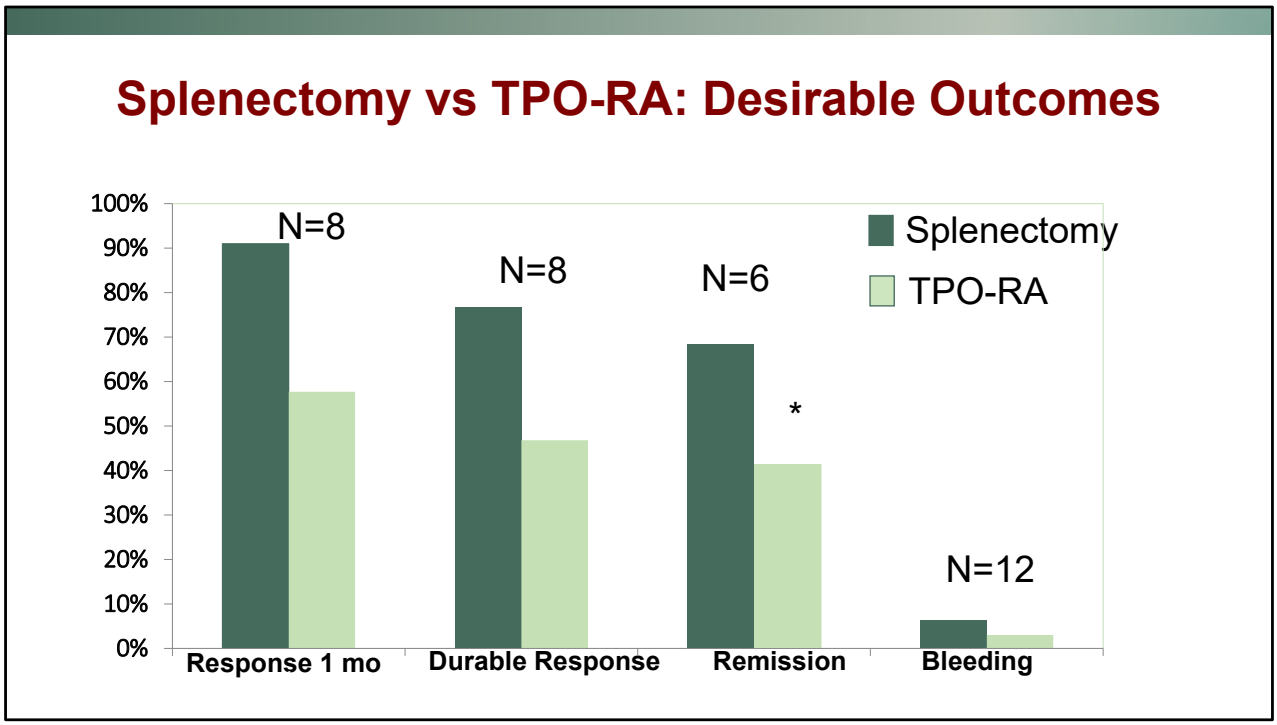

When we're looking at splenectomy, thinking about splenectomy versus a TPO again splenectomy provides the possibility of long-term remission and a durable response. That incidence of durable responses is higher than for the TPO-Ras, that generally is the main reason to choose splenectomy over TPO-RAs. Again, we wouldn't want to choose splenectomy in patients who have newly diagnosed ITP because the rate of spontaneous remission is so high.

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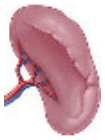
Splenectomy vs TPO-RA: Other EtD Criteria

Splenectomy	TPO-RA
Attributable Infections: 3.8% (sepsis) Operative complications: 5.9% Thrombosis not reported in trials Response not predictable **Patient goals/feasibility**: Short-term single treatment No daily medication $ May not be acceptable to patients 	Infections: 4.8% Thrombosis not seen in pedi trials Hepatoxicity (eltrombopag) Iron deficiency (eltrombopag) **Patient goals/feasibility:** Long-term treatment Continuous medication $$$ Oral or subcutaneous 

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 versus TPO-RA or other treatments in pediatric patients.

Recommendation for TPO-RA > Splenectomy

- Risks of TPO-RA thought to be low, potential benefits high
- Value on avoiding splenectomy given rate of remission

When could splenectomy be considered rather than TPO-RA?

- Chronic ITP (>>12 months) with high value on short-term procedure with chance of long-term remission
- Life-threatening bleeding

There is a value to avoid splenectomy early in pediatric patients who have ITP, but in patients who have chronic ITP, especially the patients who have really long-standing ITP, there's definitely a potential benefit to splenectomy, or in patients who are having life threatening bleeding.

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Patient AB: Shared Decision-making Approach

- **Reason for treatment:** Fatigue, HRQoL
- **Phase of ITP:** Persistent ITP
- **Primary vs Secondary ITP:** Primary
- **AB's preferences:**
  - Reliable increase in platelet count
  - Medication he can take at home
  - Avoid long-term complications since ITP might remit

If we go back to our patient AB and we use the shared decision-making approach and think about our reasons for treatment, which are really fatigue and health-related quality of life. This patient now has persistent ITP, we think it's primary. We ask the patient about his preferences, he really wants a reliable increase in his platelet count. He wants medicine he can take at home. He doesn't want long-term complications because he's hoping his ITP is going to get better. He and his parents are both hoping it's going to get better, but he really wants to be able to get back to playing hockey. He wants something that's going to raise his platelet count and keep it up and keep it steadily up.

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Patient AB: Continued Shared Decision-making

- Four years later, continues on TPO-RA
- Before college, requests splenectomy for possibility of long-term remission
- Undergoes evaluation for underlying immunodeficiency
- Receives recommended vaccines
- Proceeds with splenectomy

You start him on a TPO-RA and 4 years later he's still on the TPO-RA and he's getting ready to go to college. Now he says, "You know what doc? I want a splenectomy because I'm tired of taking this medication every day. I'm going to college. I'll be real, I'm not sure I'm going to remember to take it when I get to school. It's easy when mom reminds me to take it. It's not going to be so easy when I'm living in a dorm." You do your evaluation for immunodeficiency, his receives his recommended vaccines, that includes Pneumovax and making sure he's fully immunized against meningococcus and he proceeds to splenectomy.

Splenectomy Good Practice Statement

The treating physician should ensure that the patient has appropriate **immunizations** prior to splenectomy and that they receive counseling regarding **antibiotic prophylaxis** following splenectomy. The treating physician should educate the patient on prompt recognition and management of **fever** and refer to **current recommendations on pre- and post-splenectomy care**.

This is a really good example of shared decision-making, but it's very important that he receives counseling about antibiotic prophylaxis post splenectomy. That he remembers that he's really trading one medicine for another medicine. He's trading pneumococcal prophylaxis, his penicillin prophylaxis, post splenectomy for his TPO-RA. The difference is that if he forgets his penicillin once in a while, his platelet count is not going to drop. As long as he has the penicillin at home and he knows that he needs to go to the emergency room with fever, it's not as big a deal if he forgets a dose or two with a penicillin. It's very important that he's very well counseled on the importance of his post splenectomy care.

With that, I think that was what I wanted to discuss and I will turn it over to Dr. Al-Samkari to talk about the adult ITP management.

Adult ITP Diagnosis and Management

Hanny Al-Samkari, MD
Assistant Professor of Medicine
Harvard Medical School
Clinical Investigator
Massachusetts General Hospital
Boston, Massachusetts

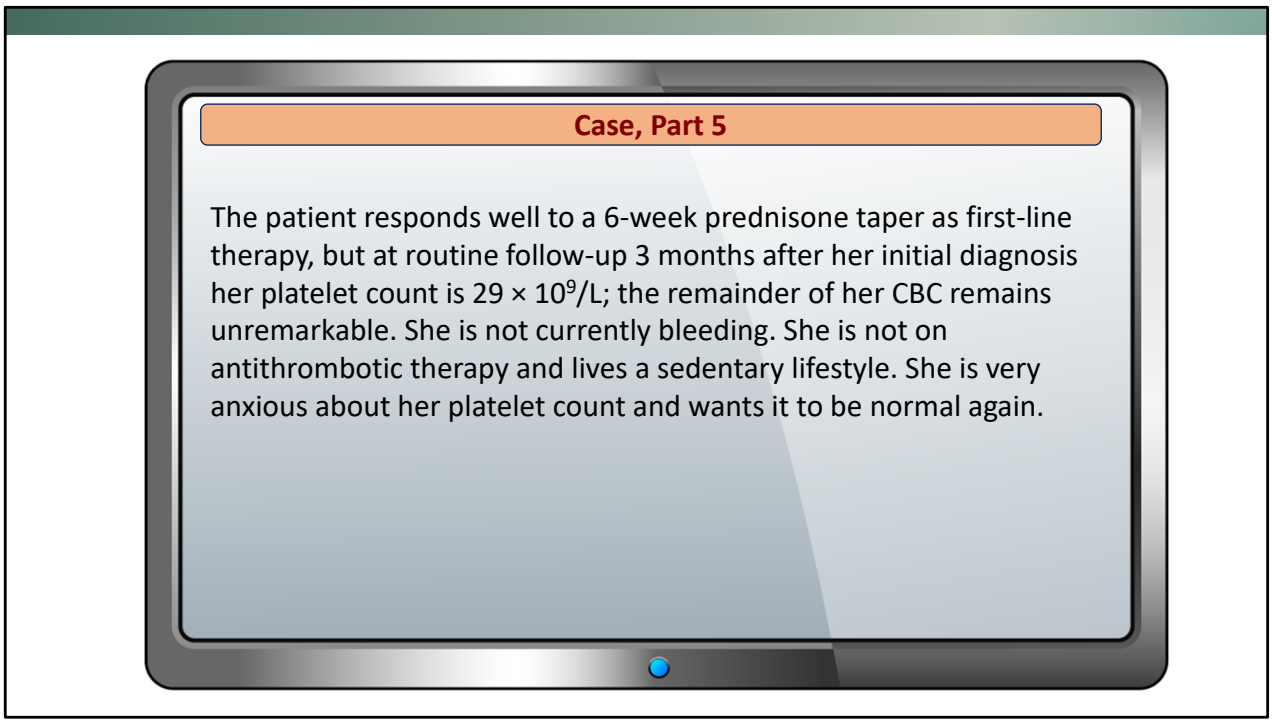
Dr. Hanny Al-Samkari: Absolutely. Thank you very much, Michele. I appreciate that.

ITP in Adults

- Diagnostic Considerations
- Guidelines for First- and Second-line Treatment

I'm going to cover ITP in adults. We're going to talk a bit about diagnostic considerations initially, and then we're going to talk about, excuse me, guidelines for first- and second-line treatment and considerations in first- and second-line treatment. As well as some investigational therapies at the end.

Improving Outcomes for Pediatric and Adult Patients with IMMUNE THROMBOCYTOPENIA



I also have a case that we will use to frame the discussion. A 66-year-old woman with a past medical history of hypertension and Sjogren's syndrome presents to the ED with diffuse petechiae of the upper and lower extremities. She awoke this morning to the taste of iron in her mouth and saw large blood blisters on her oral mucosa. On initial lapse her platelet count is 4,000. The remainder her CBC is unremarkable. She mentions she recovered from a case of bronchitis about three weeks ago.

Etiology: Primary and Secondary ITP

- Primary ITP (80%): Isolated thrombocytopenia, not associated with other disorder
- Secondary ITP (20%): Immunologic thrombocytopenia in association with:
  - Infection (CMV, HCV, HIV, *H. pylori*)
  - Immunodeficiency (CVID, WAS)
  - Autoimmune disorders (SLE, SS, RA, etc.)
  - Lymphoproliferative – (usually CLL)
  - Drugs

Cines DB, et al. *N Engl J Med.* 2002;346(13):995-1008.

This is a classic presentation of newly diagnosed ITP. Again, as in children, we think of ITP and adults as primary versus secondary ITP, and in adults 80% falls into this primary bucket. 20% falls into the secondary bucket of which the ITP is diagnosed in association with a certain infection, immunodeficiency, autoimmune disease, lymphoproliferative disorder, or receipt of a certain medication. If we looked at a pie chart of the breakdown of all the different kinds of secondary ITP, each of these is between 1% and 5% of that 20%, so a very heterogeneous bucket.

ITP Chronicity

Disease Phase	Duration/Description
Newly diagnosed	<3 months
Persistent	3–12 months Patients lacking spontaneous remission or complete response after treatment
Chronic	>12 months

Provan D, et al. *Blood*. 2010;115(2):168-186.; Neunert CE, et al. *Blood*. 2011;117(16):4190-4207.

We also classify ITP according to its chronicity. We don't say acute ITP, we say newly diagnosed ITP, because acute could be an exacerbation in a patient with chronic ITP and acute on chronic exacerbation. We talk about newly diagnosed ITP, less than three months of duration, persistent ITP, and then chronic ITP. This is relevant because many of the medications we talk about have been approved for certain ITP of a certain chronicity, but not ITP of other chronicities.

Disease Manifestations: Bleeding

- Platelet thresholds for bleeding highly variable
- Typical thresholds for non-elderly, non-anticoagulated patients
- Bleeding risk increases substantially with increased age

Platelet Count (x 10^9/L)	Bleeding Manifestations
>50	None (including with most surgical procedures)
20–50	Potential increased bleeding with significant trauma/surgery
10–20	Higher risk of the above; potential spontaneous petechiae or bruising
<10	Higher risk of spontaneous bleeding, including major bleeding

When we talk about ITP, when we think about ITP, the first thing we think about is, of course, bleeding. As Dr. Lambert pointed out, there is not a specific threshold for adults as well as in children, a platelet count that we say the person is absolutely safe above this threshold or clearly not safe below that threshold. They're really variable and we tend to stick to a threshold of say, above 20,000 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 therapies, anti-platelets and anticoagulation therapies. As well as those who need surgical procedures.

Older adults with ITP in particular tend to not respond, or tend to not have as close of a relationship between their platelet count and their bleeding manifestations, as do younger adults with ITP. We recognize that risk does increase with age. In general, if somebody's platelet count is in the single digits, that's a cause for concern.

Polling Question #1

What symptom is the patient most likely to endorse?

A. Depression
B. Anxiety
C. Headache
D. Fatigue
E. Insomnia

Please select your response to the polling question below the video window.

In our case, a diagnosis of ITP is made. If questioned beyond bleeding symptoms, what symptom is the patient most likely to endorse?

A. Depression
B. Anxiety
C. Headache
D. Fatigue
E. Insomnia

As we think about ITP, we have to remember that this is a bleeding disorder, but it is also a systemic autoimmune problem, which can cause other manifestations, and the consequence of having a very low platelet count can lead to certain psychosocial manifestations and psychiatric manifestations of the disease.

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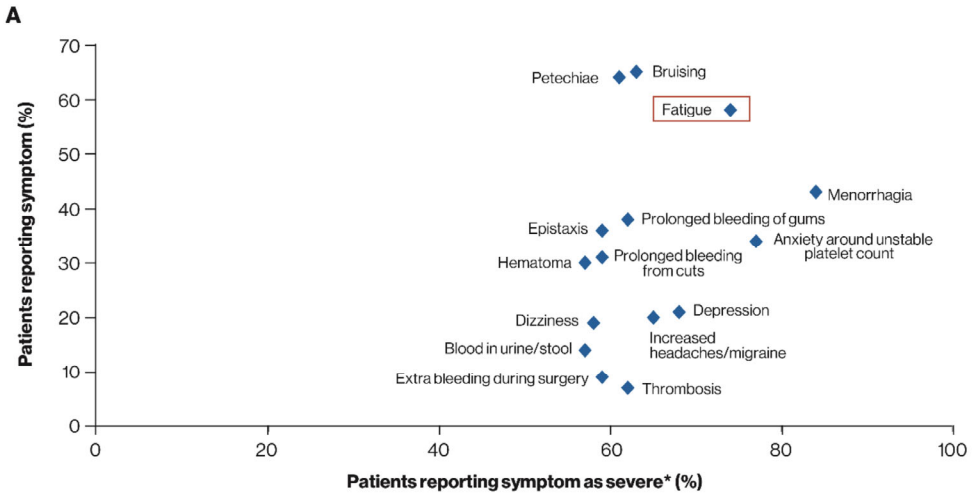
Disease Manifestations: Symptoms at Diagnosis

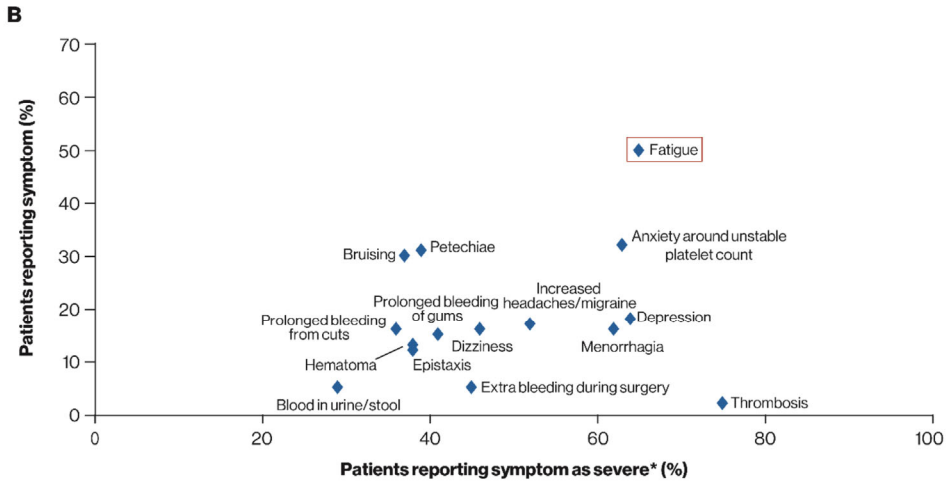


Cooper N, et al. *Am J Hematol*. 2021;96(2):199-207.

If you said fatigue, you were right. Fatigue is very common in adults with ITP being reported by a majority of patients at the time of diagnosis. As you can see, over 70%, this figure was taken from a very large health related quality of life study in ITP called the I-WISh study.

Over 70% of patients with fatigue reported the symptom as severe. But if we look at this, we see petechiae and bleeding are very high in terms of the percentage of patients reporting and that's not surprising. We see a number of other problems on here, right? We see depression on here. We see various bleeding manifestations beyond the typical petechiae and bruising that we see. We see anxiety as a major manifestation and reported as severe in almost 80% of patients. It's something that we have to recognize.

Disease Manifestations: Symptoms Later in Course



Cooper N, et al. *Am J Hematol*. 2021;96(2):199-207.

If we look at the same graph except not at diagnosis, but later in the disease course, there's fatigue again, poking out like a sore thumb with over 50% of patients continuing to describe fatigue and over 60% saying it's severe. We see anxiety still a major issue. More patients reporting severe fatigue and anxiety than reporting severe bleeding.

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.

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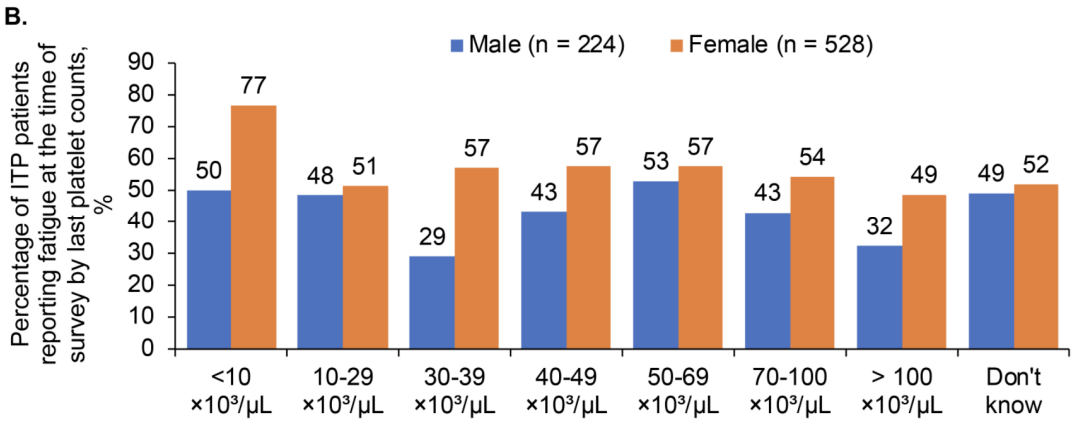
Fatigue May Not Correlate with Platelet Count



Bussel J, et al. *Blood*. 2020 (ASH abstract).

One of the questions that I get all the time is, so fatigue is common, does it correlate with the platelet count? Well from the I-WISh study, it appears that it does not, or at least does not for many patients. Certain patients may swear it does, and they can tell they're having exacerbation because of their fatigue before they even get a platelet count checked. That's absolutely true within certain patient, but on a population level it may not correlate. This is something that we have to recognize and oftentimes have to discuss with our patients. They may not be as forthcoming with fatigue, anxiety and those issues.

Polling Question #2

Which of the following diagnostic tests is indicated at diagnosis in this patient?

A. Bone marrow biopsy
B. Direct glycoprotein specific platelet autoantibodies
C. Hepatitis C serology
D. Antiphospholipid antibodies
E. Direct antiglobulin test

Please select your response to the polling question below the video window.

Going back to the case. Which of the following diagnostic tests is indicated at diagnosis in this patient?

66-year-old patient who presents with newly diagnosed ITP.

A. Bone marrow biopsy
B. Direct glycoprotein specific platelet autoantibodies
C. Hepatitis C serology
D. Antiphospholipid antibodies
E. Direct antiglobulin test

This brings us to what other workup do we need to do in an adult with newly diagnosed ITP. Let's talk about it.

Diagnostic Evaluation of ITP

- Diagnosis of exclusion (really, one of “recognition”)
- Signs and symptoms at diagnosis highly variable
  - Most patients present asymptomatically
  - Diagnosis often occurs via routine blood tests
- Recommended diagnostic evaluation differs slightly between ASH Guidelines and International Consensus Guidelines

ITP is classically thought of as a diagnosis of exclusion, although I like to call it a diagnosis of recognition, sort of know a case when you see it, most of the time. It turns out we're not perfect at this, as you can imagine, but we're pretty good. If you've seen a dozen, two dozen, three dozen cases of ITP, you start to have this recognition that what you're looking at is probably ITP just based on the platelet count, the MPV, the peripheral blood smear, how patients present. Even without doing any workup for other causes of thrombocytopenia.

Most patients do present asymptomatically in adults, and we see the diagnosis via routine blood tests, when somebody is having a blood test checked for another reason. These are not your acute patients that have a platelet count of six. These are patients that have platelet count of 50 or 40, and there's no other explanation for it, so it gets thrown in the ITP bucket. There's this recommended diagnostic evaluation.

Improving Outcomes for Pediatric and Adult Patients with IMMUNE THROMBOCYTOPENIA

Diagnostic Eval: International Consensus 2019

Table 3. 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	Anti-phospholipid 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; refer to text)	
HIV‡	Direct antiglobulin test	
HCV‡	*H pylori*‡	
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.
‡Recommended by the majority of the panel for adult patients in the appropriate geographic setting.

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

The question I presented before, hepatitis C serology would be the correct answer there. Now, there are other tests that may be of use and that at ITP referral centers we often get. Things like platelet auto antibody testing, things like a thrombopoietin level, things like antiphospholipid testing. These are things that can be relevant. Certainly, if you talk to your patient, and a patient has a history of significant autoimmune disease, you may want to get antiphospholipid testing, for example. The rest of these are really patient and situation dependent.

We Are Not Perfect at Clinical Diagnosis

- McMaster ITP registry: 12.2% adults diagnosed with ITP ultimately did not have it; 3.1% of patients diagnosed with other causes of thrombocytopenia had ITP
- 14% of children diagnosed with ITP ultimately did not have it[1]
- Many “ambiguous” cases in clinical practice

[1]Bryant N, et al. *Clin Pediatr (Phila).* 2011;50(3):225-230.; Arnold M, et al. *Blood Adv*. 2017;1(25):2414-2420.

Now, we are not perfect at diagnosing ITP. The McMaster ITP registry looked at this, and we're right about 85% of the time, but about 12% of the time, people who were diagnosed with ITP ultimately didn't have it, and 3% of patients that were diagnosed with something else ultimately did have it. This is a major ITP referral center. This was in adults, there was a similar study done in children with similar findings. We do have these ambiguous cases in practice.

Improving Outcomes for Pediatric and Adult Patients with IMMUNE THROMBOCYTOPENIA

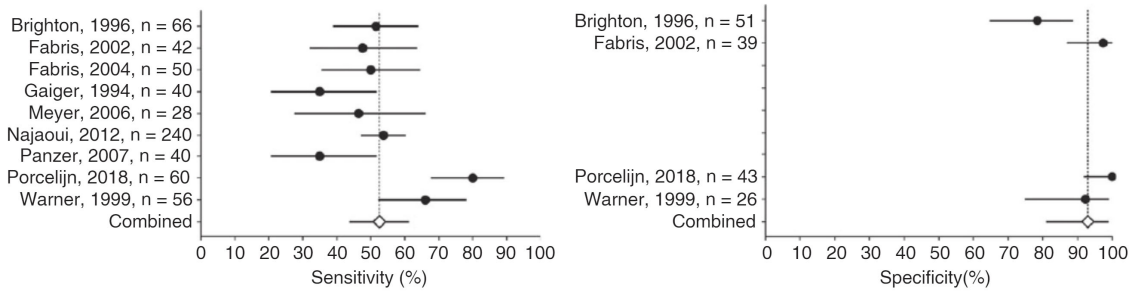
Platelet Autoantibody Testing

		Clinical Considerations		Laboratory Criteria (ISTH Recommendations)					
Study	No. assays in ITP patients	ASH 2011 guidelines	Adults or children only	ACD-A anticoagulant	Recommended blood volume	Direct test	Anti-GPIIb/IIIa and GPIb/IX	Central lab	Sensitivity
Brighton 1996	81	×	?	×	?	✓	✓	✓	**49%**
Warner 1999	56	×	?	✓	?	✓	✓	✓	**66%**
Fabris 2002	65	×	?	?	?	✓	✓	✓	**60%**
McMillan 2003	282	✓	✓	×	?	✓	✓	✓	**55%**
Chan 2003	59	×	×	✓	?	✓	×	✓	**73%**
Fabris 2004	50	×	✓	?	?	✓	✓	✓	**50%**
Davoren 2005	216	×	×	×	✓	✓	✓	✓	**53%**
Chen 2012	64	×	?	×	?	✓	×	✓	**39%**
Najaoui 2012	240	×	?	×	?	✓	✓	✓	**54%**
He 2013	50	✓	×	×	×	✓	✓	✓	**44%**
Zhao 2015	71	✓	×	×	×	✓	✓	✓	**39%**
Porcelijn 2018	149	✓	?	×	?	✓	✓	✓	**81%**
Al-Samkari 2020	360	✓	✓	✓	✓	✓	✓	✓	**90%**

Al-Samkari H, et al. *Blood Adv.* 2020;4(1):9-18.

One just quick point about platelet autoantibody testing, highly variable studies on this. One major reason why all of the guidelines don't recommend it as standard despite the fact that we recognize that patients with ITP often have these platelet autoantibodies, is that it's so difficult to do it right. There's 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.

Platelet Autoantibody Testing



- Pediatric ITP systematic review with similar findings:
  - Sensitivity 36-80%
  - Specificity 80-100%

The specificity seems to be better. In a ITP systematic review in adults here, the specificity seem to be above 90%, that's one useful aspect of this testing. With sensitivity mired in the overall 50% to 70% range, it's much more challenging to recommend this, and use it as a diagnostic test. Similar findings in a pediatric ITP systematic review.

Differential Diagnosis

- Pseudothrombocytopenia
- Clonal hematopoiesis
- Liver disease
- Hereditary thrombocytopenias
- Acute viral infection
- Hematologic malignancy
- Drug-induced thrombocytopenia
- Gestational thrombocytopenia
- Micronutrient deficiencies

We have to remember in adults our differential diagnosis of ITP, so very common for patients that have this mild thrombocytopenia, that perhaps they have some undiagnosed liver disease. Perhaps they have undiagnosed clonal hematopoiesis, things to consider.

Polling Question #3

Which of the following is the next best step in the management of this patient?

A. Prednisone 1 mg/kg daily over a 6-week taper
B. Dexamethasone 40 mg daily x 4 days for 2-3 every-other-week cycles
C. IVIG 1 g/kg x 2 days
D. Prednisone plus IVIG
E. Dexamethasone plus IVIG

Please select your response to the polling question below the video window.

We're going back to our case. A patient is admitted for treatment of newly diagnosed ITP. When told she is to receive treatment, including corticosteroids, she becomes anxious. As she states a prior three-day methylprednisolone pulse given for a complication of her Sjogren's gave her severe anxiety and insomnia while she was getting the pulse.

Which of the following is the next best step in the management of this patient?

A. Prednisone 1 mg/kg daily over a 6-week taper
B. Dexamethasone 40 mg daily x 4 days for 2-3 every-other-week cycles
C. IVIG 1 g/kg x 2 days
D. Prednisone plus IVIG
E. Dexamethasone plus IVIG

We could give her a modest dose, moderate dose of prednisone over a six-week taper which is a typical treatment course in adult ITP. We could say, "Well, let's give the dex pulse." We could give her IVIG, or we could give her a combination of those things.
In this case, it's very reasonable to give either IVIG or a moderate dose prednisone taper. She probably won't have the same symptoms she did with the very high methylprednisolone pulse of one gram per day with a smaller dose of prednisone, but if she did, one could then switch, for example, to IVIG. Those are the options. Now, she's not actively having severe bleeding, so we really don't need to reach for combination therapy at this point.

Treatment Approach

- Maintain safe platelet count with minimal toxicity
- Toxicity of therapies (esp. steroids) can be worse than disease
- Manage constitutional symptoms and anxiety
- Consider many factors when determining if treatment is warranted:
  - Bleeding or not; patient-specific thresholds for spontaneous bleeding
  - Comorbidities predisposing to bleeding (including antithrombotic medication, SSRIs, etc)
  - Toxicities of therapies
  - Activity and lifestyle; anxiety
  - Need for surgery or myelosuppressive therapies

When we talk about treatment of ITP, we talk about treat the disease while trying to minimize the toxicity as best as possible. One of the things we recognize nowadays is that we use too much steroids in this disease. Michele, pediatric colleagues, you have this way better than we do. In the adult setting, corticosteroids are the most common treatment selected in any course of therapy, first line, second line, third line. There's recent data on this. We've got to do better. We need to follow your lead in the pediatric world.

In addition to managing the platelet count and the bleeding, we have to make sure that we're not causing toxicity. We need to make sure that we're engaging in shared decision-making. I'm about to get to that in a second line therapy. Which is the same in adults as in pediatrics in terms of the shared decision-making being a very important aspect, talk to patients about what their values are, and find the right therapy that works for them and their comorbidities.

Dr. Michele Lambert: I'll just point out that seven days of steroids versus taper over six weeks. We're talking about a monumental difference even in the lower dose of steroids that you're proposing.

Treatment Approach

- Maintain safe platelet count with minimal toxicity
- Toxicity of therapies (esp. steroids) can be worse than disease
- Manage constitutional symptoms and anxiety
- Consider many factors when determining if treatment is warranted:
  - Bleeding or not; patient-specific thresholds for spontaneous bleeding
  - Comorbidities predisposing to bleeding (including antithrombotic medication, SSRIs, etc)
  - Toxicities of therapies
  - Activity and lifestyle; anxiety
  - Need for surgery or myelosuppressive therapies

Dr. Hanny Al-Samkari: That's exactly right. In adults, if we were to stop after seven days, we probably wouldn't have much benefit at all, but at the same time people go way longer than six weeks. People are on it for 12 weeks or 16 weeks sometimes before they get on another therapy. That's something you really want to avoid. It's just so easy to restart the steroids when the platelet count drops. It's harder to start a second line therapy in terms of the activation energy to do that. It shouldn't be, right?

Dr. Michele Lambert: We do seven days and we're like, "Oh, you failed. Okay. Time to move to the next line of therapy."

Dr. Hanny Al-Samkari: That's something that we should be doing much more in the adult world.

Tx of Newly-Diagnosed ITP in Adults: ASH 2019

Question	Situation	Recommendation
Corticosteroids vs observation	Platelet count of <30 x 10^9/L who are asymptomatic or have minor mucocutaneous bleeding	Corticosteroids rather than management with observation
	Platelet count of ≥30 x 10^9/L who are asymptomatic or have minor mucocutaneous bleeding	Against corticosteroids and in favor of management with observation
Inpatient vs outpatient management	Platelet count of <20 x 10^9/L who are asymptomatic or have minor mucocutaneous bleeding	Admission to hospital rather than management as an outpatient
	Platelet count of ≥20 x 10^9/L who are asymptomatic or have minor mucocutaneous bleeding	Management as an outpatient rather than hospital admission
Duration/ Type of corticosteroids	In adults with newly diagnosed ITP	Against a prolonged course (>6 weeks including treatment and taper) of prednisone and in favor of a short course (≤ 6 weeks)
	In adults with newly diagnosed ITP	Either prednisone (0.5-2.0 mg/kg per day) or dexamethasone (40 mg per day for 4 days) as the type of corticosteroid for initial therapy

Neunert CE, et al. *Blood Adv.* 2019;3(23):3829-3866.

Here are some additional differences between adults in pediatrics just in terms of what the American Society of Hematology guidelines recommend. First one, platelet count less than 30,000 who are asymptomatic in terms of the corticosteroids versus observation in newly diagnosed patients, the recommendation is for corticosteroids rather than management with observation in those patients the first time around. If patients have a count of greater than 30, then observation is recommended.

It's also recommended that patients who have a platelet count of less than 20 at the time of their first presentation with ITP, newly diagnosed ITP, or if they have even just minor bleeding. That they are, in fact, admitted to the hospital rather than management as an outpatient, which is very different in adults than in the pediatric world. Michele, I saw you shaking your head. Thoughts on that?

Dr. Michele Lambert: We try so hard not to admit anyone with ITP, unless they're having lots of bleeding. If you're having a lot of bleeding, significant menorrhagia, your hemoglobin is seven, GI bleeding, something like that and intracranial hemorrhage, heaven forbid, then we'll admit you. If you have epistaxis and it stops, then we're going to send you home with prednisone. Bye, see you tomorrow.

Tx of Newly-Diagnosed ITP in Adults: ASH 2019

Question	Situation	Recommendation
Corticosteroids vs observation	Platelet count of <30 x 10^9/L who are asymptomatic or have minor mucocutaneous bleeding	Corticosteroids rather than management with observation
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Neunert CE, et al. *Blood Adv.* 2019;3(23):3829-3866.

Dr. Hanny Al-Samkari: We have these ITP hostages in the hospital waiting for their platelet count to get above 20,000 or 30,000, so they can go home. Sometimes that takes several days. It's very rare for somebody to have a significant bleeding event, but based on the difference in adult patients versus pediatric patients, these were the recommendations. There can be more going on in an adult patient where they can have comorbidities, potentially higher risk for a major bleeding event and recommendation admission to the hospital.

Then as I've really already harped on, really want to limit the duration of steroids in these patients. You don't need to use massive doses of prednisone, 1 mg per k or something close to that is fine. Then the dexamethasone pulse is just 40 times 4 days, often will need to be repeated once or twice in that initial six-week period.

Tx of Newly-Diagnosed ITP in Adults: ASH 2019

- IVIG with steroids when more rapid increase in platelets required
- IVIG or anti-D if steroids contraindicated
- Pregnant patients receive either steroids or IVIG

Neunert CE, et al. *Blood Adv.* 2019;3(23):3829-3866.

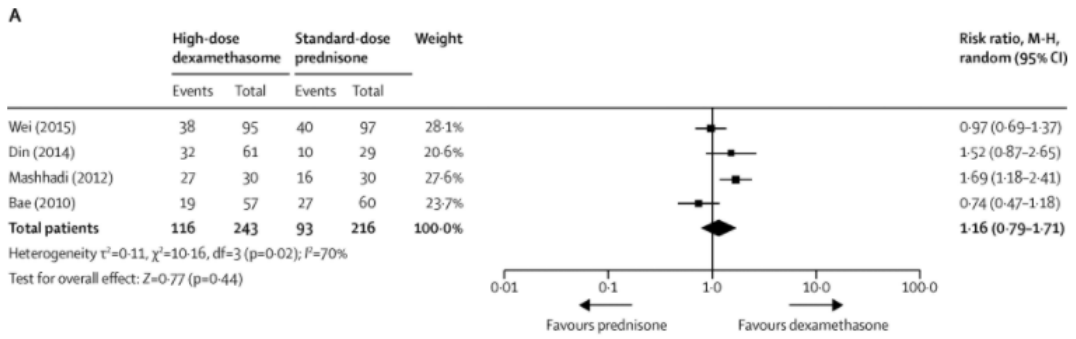
In terms of other recommendations, IVIG is recommended when a more rapid increase in platelet counter is required. Patients presenting with more substantial bleeding or at high risk for having sub-severe bleeding based on their comorbidities or other issues that that patient has. If corticosteroids are truly contraindicated, you can go directly to IVIG or anti-RhD immunoglobulin. Then pregnant patients receive either steroids or IVI G in the newly diagnosed setting.

Corticosteroids in ITP

	Dexamethasone	Prednisone
Dose/Regimen	40 mg daily for 4 days every 2-4 wk for 1-4 cycles	Generally, 1 mg/kg/day for ~2 weeks followed by taper; no more than 6 weeks total
Initial Response Rate	80-90%	~80%
Overall Response Rate @ 6 mo	**No difference**	
Time to Response	2-7 days	
Toxicities	Typical steroid toxicities – increased appetite, weight gain, insomnia, fluid retention, anxiety, etc.	
Toxicities in Elderly	Increased risk for psychosis	

I don't want to spend too much time on steroids, but just to remind everybody that in meta-analyses of large randomized controlled trials in adults, there really is not a significant difference between doing a prednisone taper and doing dexamethasone pulsing in an adult patient with ITP. You may get a slightly quicker response with the dexamethasone pulse at the cost of perhaps a higher risk of having acute steroid-related side effects, things like insomnia, anxiety, and potentially psychosis. That is especially true for older adults, so we have to keep that in mind.

Prednisone vs Dexamethasone: ORR at 6 Months



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	High-dose dexamethasone		Standard-dose prednisone		Weight	Risk ratio, M-H, random (95% CI)
	Events	Total	Events	Total		
Wei (2015)	38	95	40	97	28·1%	0·97 (0·69–1·37)
Din (2014)	32	61	10	29	20·6%	1·52 (0·87–2·65)
Mashhadi (2012)	27	30	16	30	27·6%	1·69 (1·18–2·41)
Bae (2010)	19	57	27	60	23·7%	0·74 (0·47–1·18)
Total patients	**116**	**243**	**93**	**216**	**100·0%**	**1·16 (0·79–1·71)**

Heterogeneity τ^2=0·11, χ^2=10·16, df=3 (p=0·02); I^2=70%

Test for overall effect: Z=0·77 (p=0·44)

Mithoowani S, et al. *Lancet Haematol.* 2016;3(10):e489-e496.

This is just an example of that graphically. Overall response rate at six months, no significant difference between prednisone, and dexamethasone.

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IVIG

Dosing	0.4 g/kg/d for 5 d or infusions of 1 g/kg/d for 1-2 d
Response Rate	80%
Time to Response	Often within 24-48 hours, up to 4-5 days
Toxicities	• Headache • Aseptic meningitis • Venous thromboembolism • Infusion-related symptoms (eg, flushing, fever, chills, nausea, etc.) • Potential anaphylactoid reactions in patients with IgA deficiency; in these cases use IgA-depleted IVIG
Duration of Response	Typically 3-4 weeks

IVIG, we want to use this in our patients who have steroid contraindications or who are actively acutely bleeding. Those patients also are 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. 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.

IV Anti-Rh(D) Immune Globulin

- Response rate similar to IVIG
- Response within 4-5 days
- Toxicity:
  - Hemolytic anemia, fevers/chills
  - Rare DIC, renal failure
- Duration of response typically 3-4 weeks

Anti-RSG immunoglobulin really is not reached for as much anymore, but in those patients who cannot receive IVIG, patients who are RH positive, this is a treatment option. It has a response rate similar to IVIG. You just have to look out for the hemolytic anemia that you're going to give the patient, mild hemolytic anemia, very rare cases of DIC.

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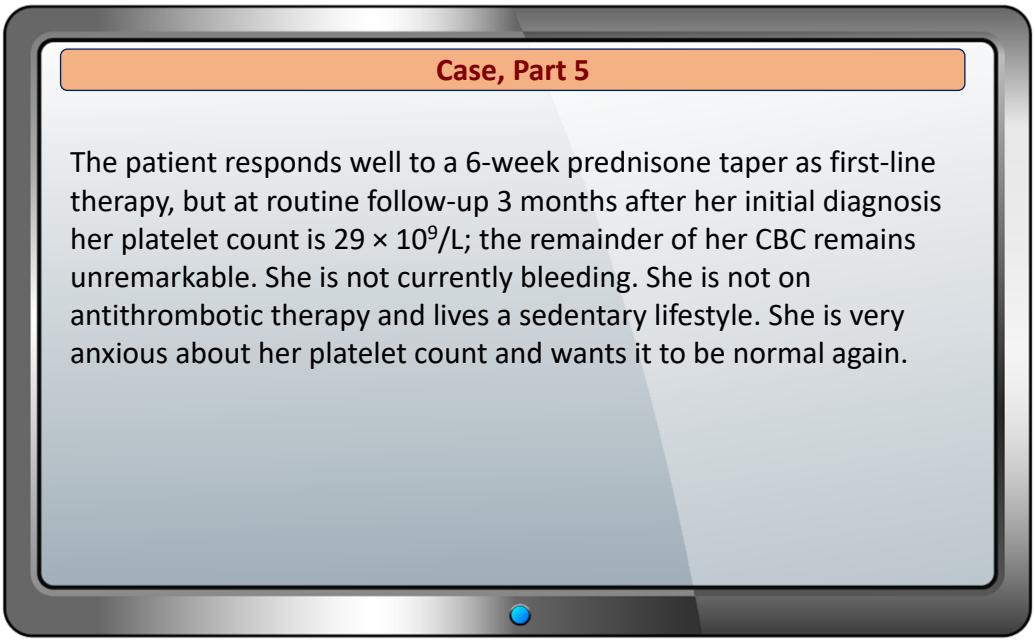

Back to our case, the patient responds well, the six-week prednisone taper for his first-line therapy, but at routine follow-up three months after initial diagnosis, the platelet count is 29,000. The remainder of her CBC remains unremarkable, not currently bleeding, not on antithrombotic therapy, lives a sedentary lifestyle. Very anxious about her platelet count, wants it to be normal again.

Polling Question #4

What should we do now?

A. Dexamethasone 40 mg daily x 4 days for 2-3 every-other-week cycles
B. IVIG 1 g/kg x 2 days
C. Initiate romiplostim 3 mcg/kg/week
D. Refer for splenectomy
E. Observation and reassurance

Please select your response to the polling question below the video window.

All right, so what would we do now?

It's 29,000. She's sedentary, not on any blood thinners. Give her more steroids, give her more IVIG, no need to do those things. We talk about using romiplostim, referral for splenectomy. Patient hasn't had ITP for at least a year, so we would avoid splenectomy generally, observation and reassurance.

A. Dexamethasone 40 mg daily x 4 days for 2-3 every-other-week cycles
B. IVIG 1 g/kg x 2 days
C. Initiate romiplostim 3 mcg/kg/week
D. Refer for splenectomy
E. Observation and reassurance

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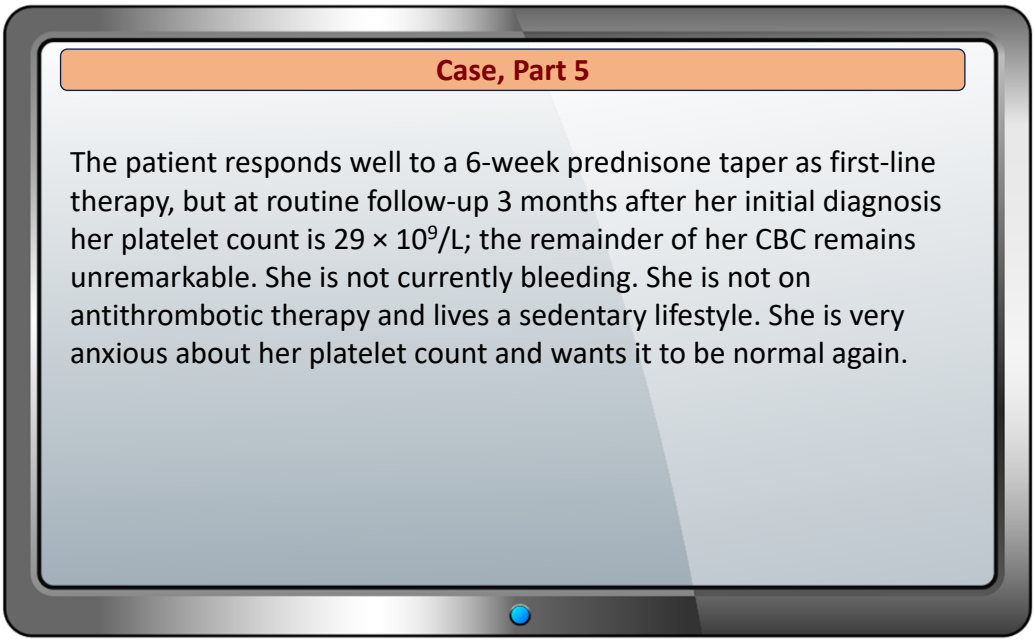

There are multiple potential right answers here. We have to talk about the patient's needs. She's very anxious. She may prefer to be on something to know her platelet count is going to be normal. Perhaps a long-term treatment is in the cards here.

Treatment Approach

- Maintain **safe platelet count with minimal toxicity**
- **Toxicity of therapies** (esp. steroids) can be **worse than disease**
- **Manage** constitutional symptoms and **anxiety**
- Consider many factors when determining if treatment is warranted:
  - **Bleeding or not**; patient-specific thresholds for spontaneous bleeding
  - **Comorbidities predisposing to bleeding** (including antithrombotic medication, SSRIs, etc.)
  - **Toxicities** of therapies
  - **Activity and lifestyle**; anxiety
  - Need for surgery or myelosuppressive therapies

Again, our goals here are to maintain a safe platelet count, minimal toxicity. We want to make sure our treatment is not worse than the disease. We want to obviously prevent bleeding, but at the same time, we have to consider all of the aspects and issues related with chronic therapies or potentially a surgery.

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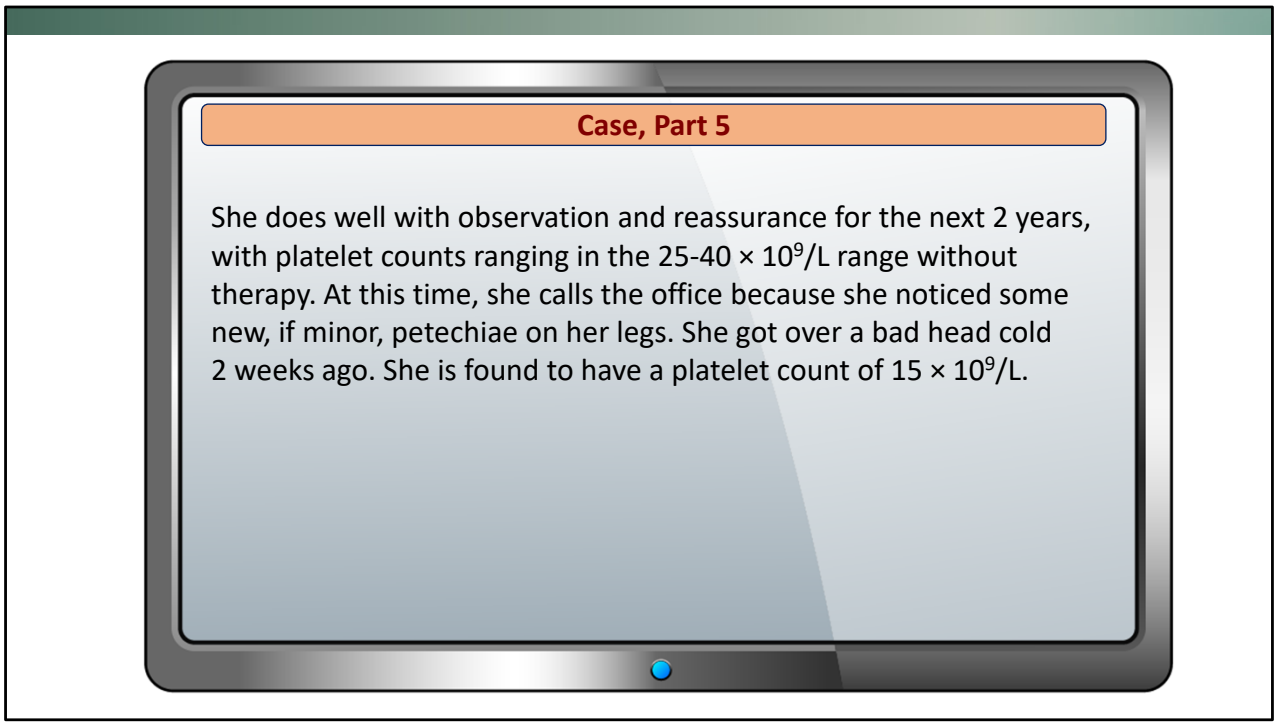

She does well with observation and reassurance, at which time her platelet accounts are 25,000 to 40,000. At this time, she calls the office because she noticed some new if minor petechiae in her legs. She got over a bad cold two weeks ago. She's found to have a platelet count of 15,000, so what do we do now?

Polling Question #5

What should we do now?

A. Admit and begin 6-week prednisone taper
B. IVIG 1 g/kg x 2 days
C. Initiate romiplostim 3 mcg/kg/week
D. Refer for splenectomy
E. Initiate rituximab 375 mg/m^2 x 4 infusions

Please select your response to the polling question below the video window.

Do we admit her? We probably don't need to admit her, she doesn't have newly diagnosed disease, and she's only had very minor petechiae. We could think about giving her some IVIG and start romiplostim or rituximab or refer for splenectomy.

A. Admit and begin 6-week prednisone taper
B. IVIG 1 g/kg x 2 days
C. Initiate romiplostim 3 mcg/kg/week
D. Refer for splenectomy
E. Initiate rituximab 375 mg/m2 x 4 infusions

Treatment Approach

- Maintain safe platelet count with minimal toxicity
- **Toxicity of therapies (esp. steroids) can be worse than disease**
- Manage constitutional symptoms and anxiety
- Consider many factors when determining if treatment is warranted:
  - **Bleeding or not**; patient-specific thresholds for spontaneous bleeding
  - Comorbidities predisposing to bleeding (including antithrombotic medication, SSRIs, etc.)
  - Toxicities of therapies
  - Activity and lifestyle; anxiety
  - Need for surgery or myelosuppressive therapies

Let's use this to talk about the treatment approach in second line. I have the same slide here because we have to remember the same things about avoiding excessive toxicity and doing a shared decision-making approach with regards to these different options with the patient

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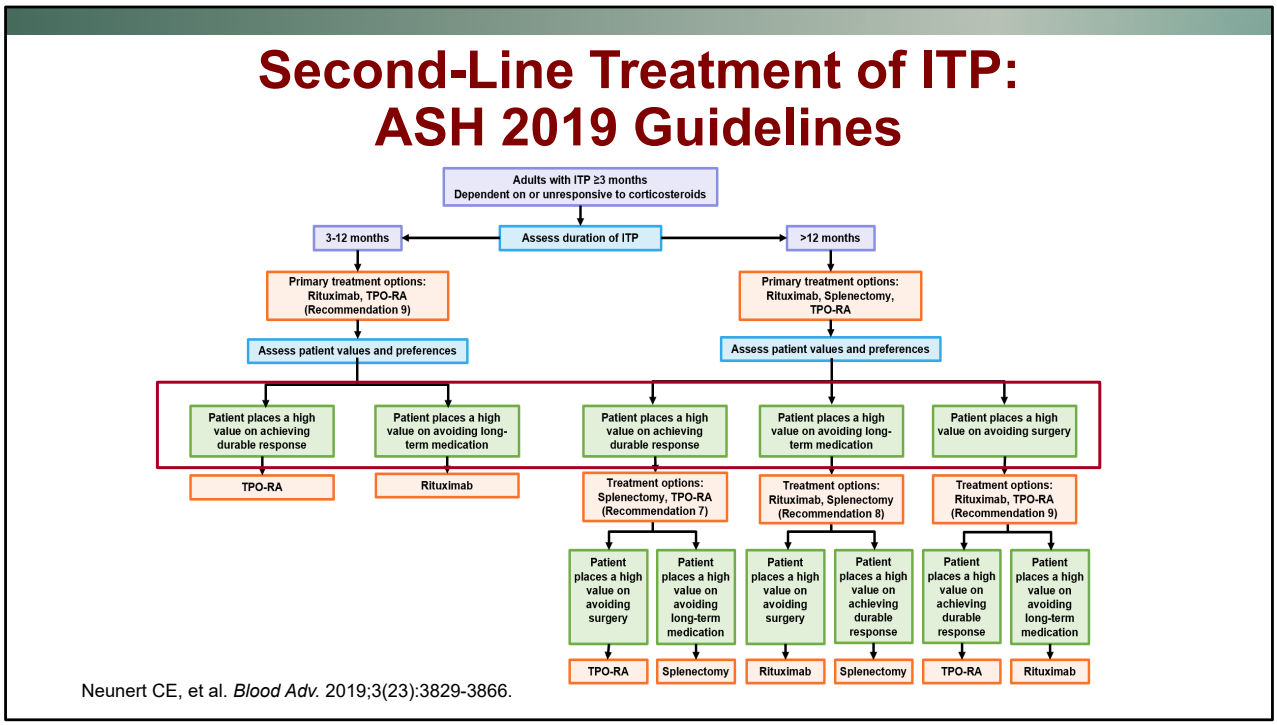

This figure is from the American Society of Hematology updated guidelines, and I really want to direct your focus to the patient places a high value on row.

Which is right here, this first row of green boxes here. That's true for every single treatment option. We want to talk to our patients about what they value, talk to them about what they would like to avoid, and 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.

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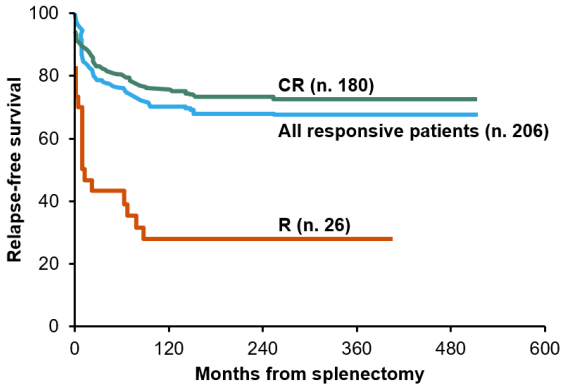
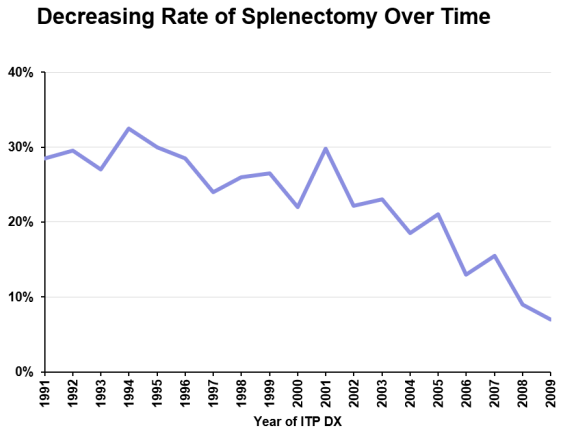
Splenectomy for ITP in the Past: The "Two-thirds Cure"



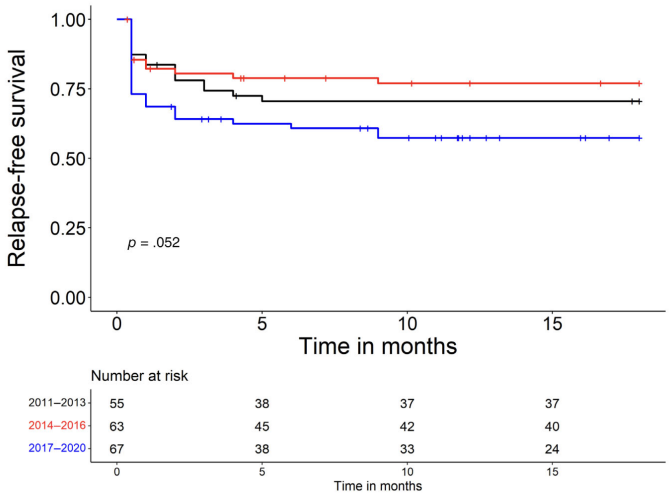


Boyle S, et al. *Blood.* 2013;121(23):4782-4790.; Vianelli N, et al. *Haematologica.* 2013;98(6):875-880.

Just to briefly mention each of these second-line therapies that we think about in adult patients, splenectomy, in the past we thought of it as the two-thirds cure. Because a lot of the old data showed durable response rates when given in the second-line setting before other therapies, after steroids and/or IVIG. Durable response rates of about 60 to 70%, but we're doing less and less splenectomy as we have more and more medical therapies. The patients getting splenectomy are a little bit more selected out.

Splenectomy for ITP in the Modern Era: Not as Great

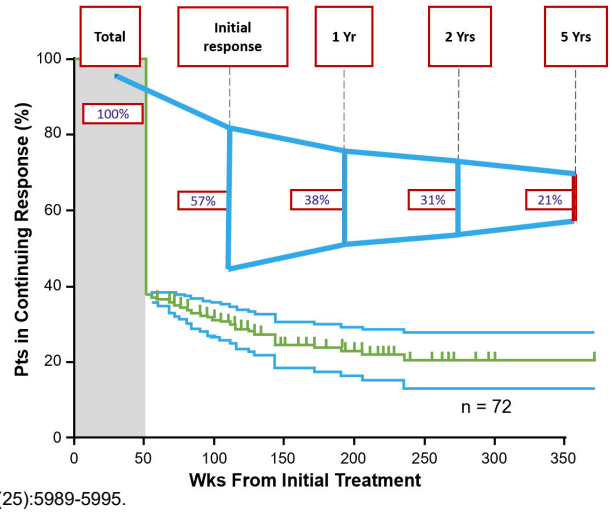
- Patients failing both rituximab and a TPO-RA undergoing splenectomy had 46% response (6 of 13 patients)
- For most patients in 2022, success rate is worse than 50/50
- Predictors of nonresponse: Age>75, >4 prior lines of treatment



Mageau A, et al., *Am J Hematol.* 2022;97(1):10-17.

In the modern era, it's not two-thirds secure anymore, it's really more of a coin flip. In one recent study in adults with ITP receiving prior therapy with TPO-RA and rituximab and failing those, the response rate to splenectomy was actually less than 50% in that group. It's really important to consider these predictors of non-response. Older adults, more than four prior lines of therapy. We have to consider that nowadays.

Rituximab: Decent Initial But Poor Long-term Response Rates



Patel V, et al. *Blood.* 2012;119(25):5989-5995.

Rituximab, I like to think of rituximab and adults as really being kind of a longer-term band aid. We're probably not curing too many people with rituximab. The long-term response rate has dropped pretty low, even if the initial response rates are closer to the 50 to 60% range. You have to think about that. It's not free lunch. It's not as difficult as some of the more long-term therapies, but we're probably not going to put the patient in a long-term durable remission.

Dr. Michele Lambert: I usually say you want to break from medication for a couple of months.

Dr. Hanny Al-Samkari: Exactly. That's right. Because it's like a longer-term IVIG in some ways.

Thrombopoietin Receptor Agonists

Agent	Romiplostim	Eltrombopag	Avatrombopag	Lusutrombopag
MOA	• Peptibody • Binds to extracellular domain of TPO receptor	• Small molecule • Binds to transmembrane portion of TPO receptor		
Initial dose	SC injection: 1 mcg/kg given weekly	PO: 50 mg once daily	PO: 20 mg once daily	PO: 3 mg once daily
Food interactions	N/A	Yes	No	No
Hepatotoxicity	No	Yes – monitor hepatic function	No	No
FDA approved	Aug 2008	Nov 2008	June 2019	July 2018
Indications	• Immune thrombocytopenia (adults and children)	• Immune thrombocytopenia (adults and children) • Hepatitis C-associated thrombocytopenia • Severe aplastic anemia	• Periprocedural thrombocytopenia in CLD patients • Immune thrombocytopenia (adults)	• Periprocedural thrombocytopenia in CLD patients

Cheloff A, et al. *J Blood Med.* 2019;10:313-321.

With thrombopoietin receptor agonists, we have multiple different options. These are the four drugs that are approved in the United States for various things, only three of them are approved for ITP. Romiplostim, eltrombopag, and avatrombopag are the ones available for ITP.

Patients often prefer an oral treatment in terms of eltrombopag or avatrombopag, but romiplostim is certainly an effective agent and is good for those patients that are not so good at taking their medication at home, because you're going to come into the clinic to get the medicine.

Avatrombopag is newer, doesn't quite have the safety record as the other two TPO-RAs in terms of the duration of experience, but doesn't have the dietary restrictions that eltrombopag has. Eltrombopag not going to absorb very well if patients have a meal that has significant calcium, magnesium, or dietary fat, that's most meals. It can be challenging for some patients to take eltrombopag and again 10% hepatotoxicity rate with eltrombopag that we don't see with our other TPO-RAs.

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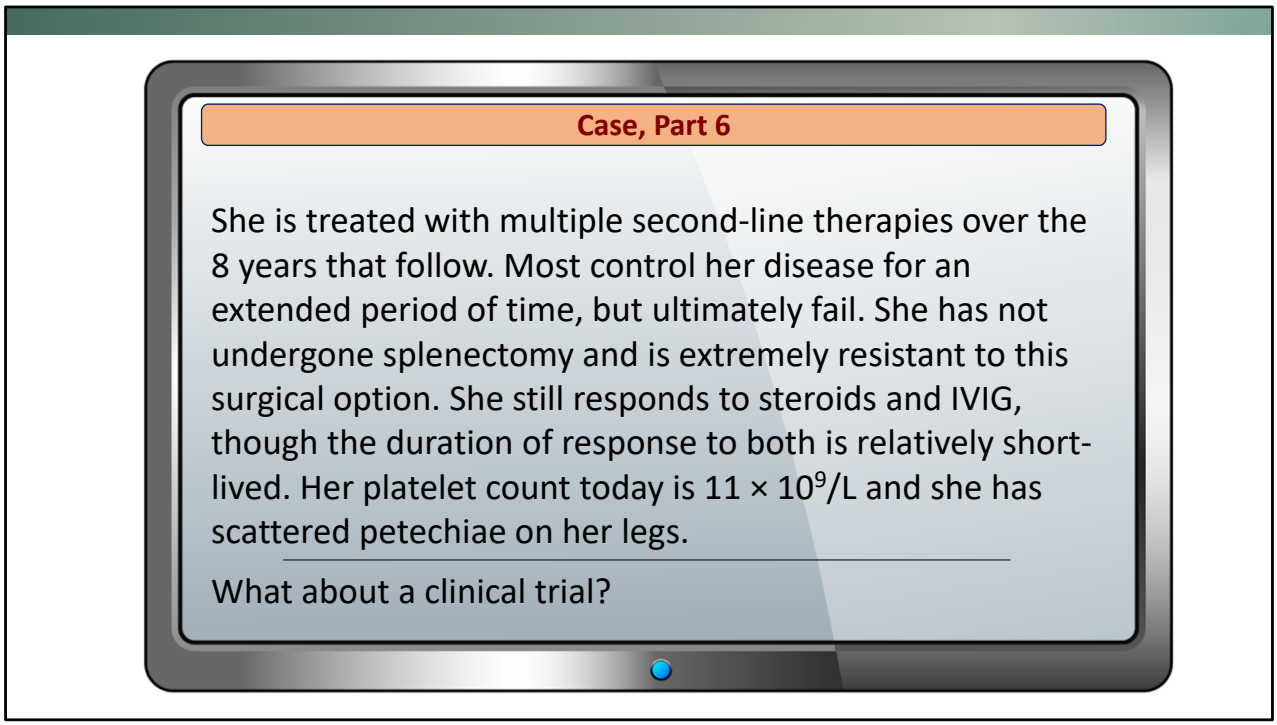


The patient is treated with multiple second-line therapies over eight years, the eight years that follow most control disease for an extended period of time, but ultimately fail. She's not undergone splenectomy, is extremely resistant to the surgical option. She still responds to both steroids and IVIG, though the duration of response is both relatively short-lived, for both is relatively short-lived. Platelet count today is 11,000. She has scattered petechia in her legs.

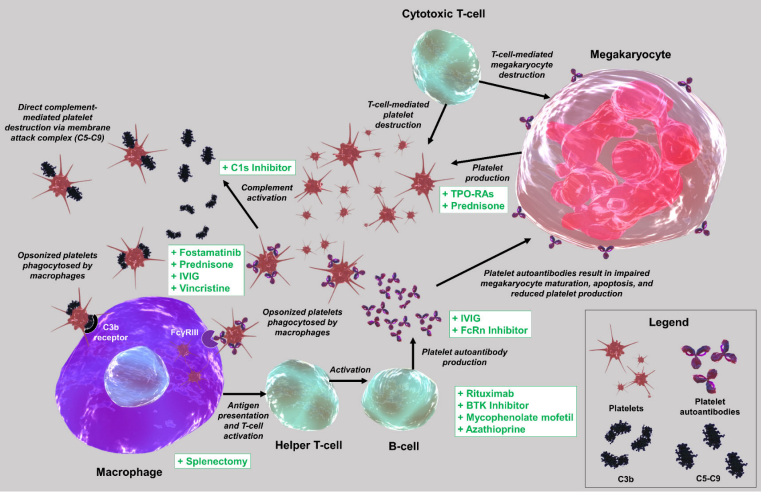
What do we do now? Do we give her chronic steroids? I hope not. Do we give her more IVIG, just every two weeks? It's a lot of IVIG.

In patients like this, she doesn't want a splenectomy. We should really think about a clinical trial of an investigational drug, because we don't want to observe a patient and reassure her, her platelet count as 11,000.

Investigational Therapies for ITP

I'm going to finish things off by just talking briefly about some investigational therapies for ITP.

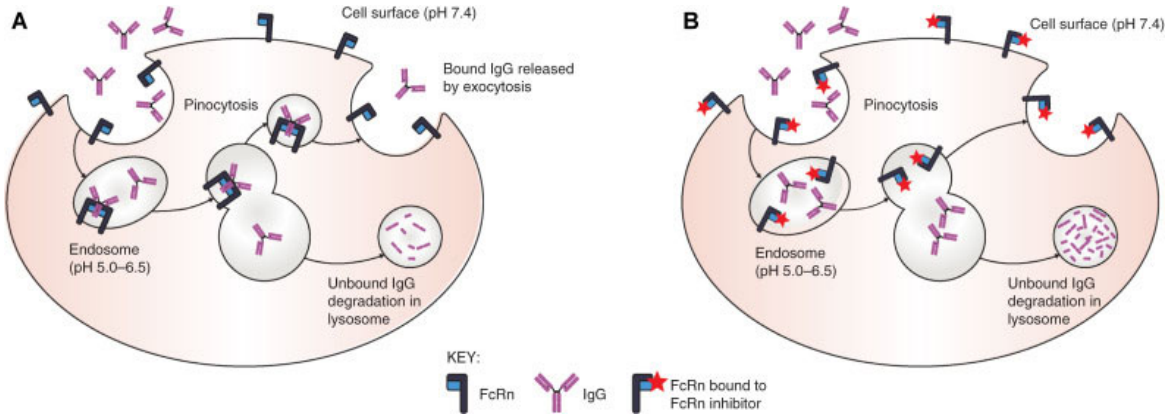
ITP Has Complex Pathophysiology—Including Many Potential Therapeutic Targets



Al-Samkari H, et al. *Semin Thromb Hemost*. 2020;46(3):275-288.

I have this here, just a remind us that ITP is a complicated disease. It's more than a disease of just platelet autoantibodies destroying platelets. There's involvement of cytotoxic T-cells, there's involvement of complement. There's inadequate production of platelets. Not decreased production, but inadequate production of platelets in the bone marrow to meet the really high rates of destruction.

Neonatal Fc Receptor Antagonists



Patel D, et al. *Clin J Allergy Clin Immunol.* 2020;146(3):467-478.

One class that's being evaluated right now in clinical trials is the neonatal Fc receptor antagonists. Neonatal Fc receptor antagonists, they block this neonatal Fc receptor.

What is that? 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. When you take it out, block the receptor, that half-life goes down to about seven days. You're circulating IgG levels dropped by about 66%. That includes both normal IgG that you have in there, and as well as pathologic, platelet autoantibodies. We can reduce our platelet autoantibodies by blocking the neonatal Fc receptor. That is exactly the strategy that is being used with a couple of drugs.

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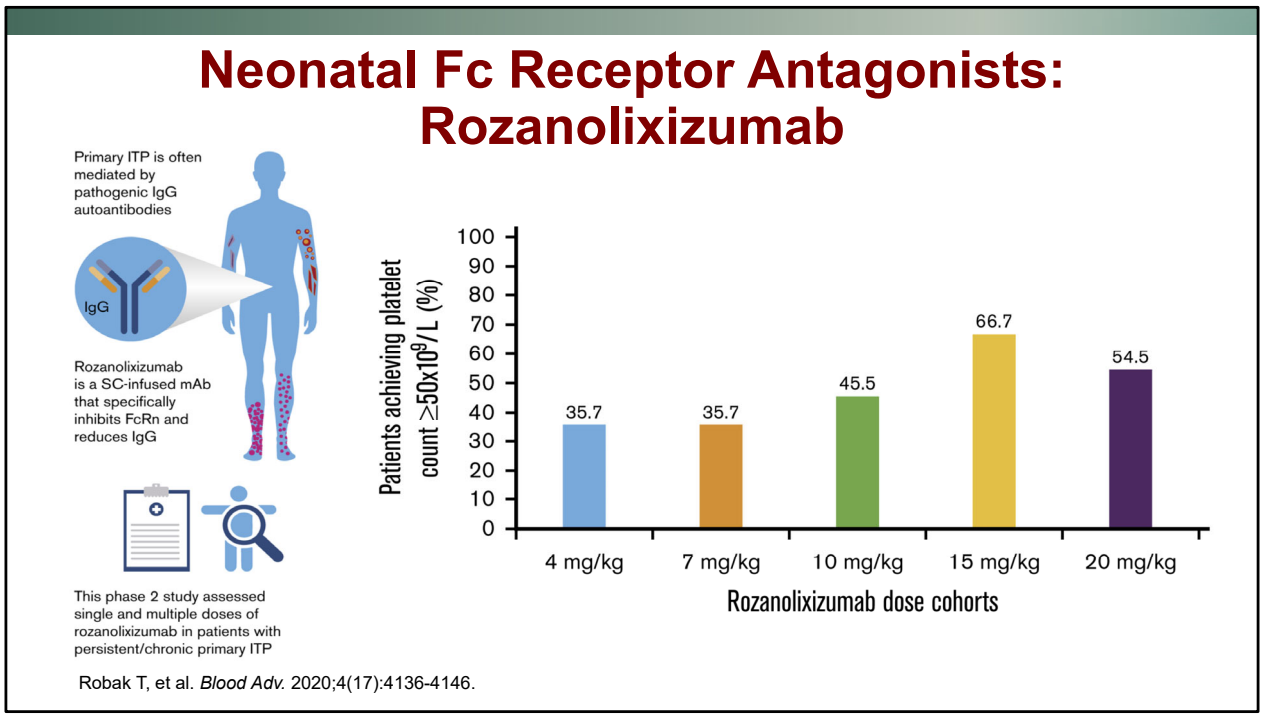

One of them is called rozanolixizumab. Rozanolixizumab is a humanized monoclonal antibody that's been evaluated in phase 2 study, to treat ITP, and really does provoke a response and improve platelet counts in relatively dose-dependent fashion, with the most common side effect being headache.

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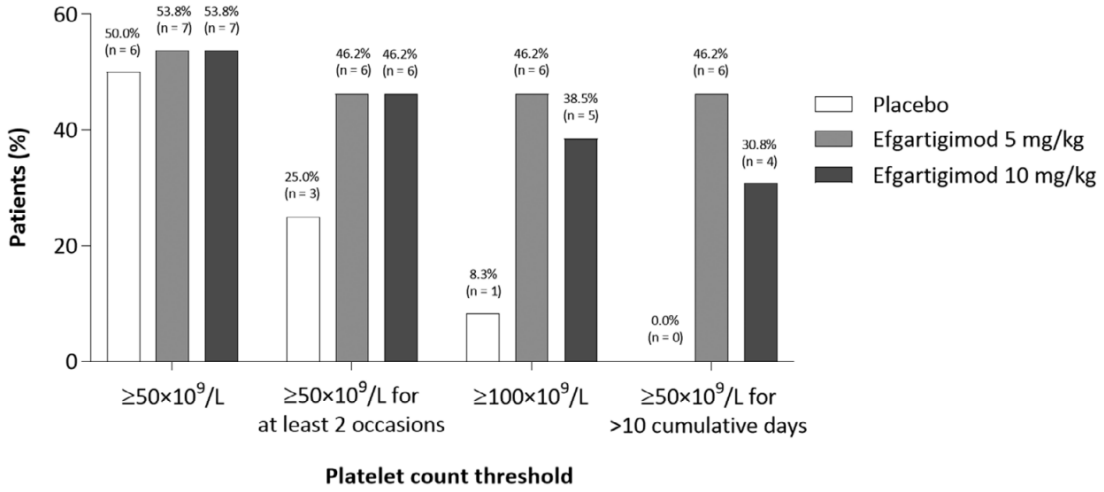
Neonatal Fc Receptor Antagonists: Efgartigimod



Newland A, et al. *Am J Hematol.* 2020;95(2):178-187.

Another drug is called efgartigimod, and efgartigimod is an antibody Fc fragment that is being evaluated in ITP, in a phase 2 study also shown to be effective in raising the platelet counts in patients.

As we raise the threshold for what we consider our response here, we see the placebo arm start to fail as we have greater than 50,000 once. Placebo arm does pretty well, but then when we say twice greater than a 100,000 or greater than 50,000 for at least 10 consecutive days, we have the placebo arm failing the efgartigimod arms having a 30 to 50% response rate.

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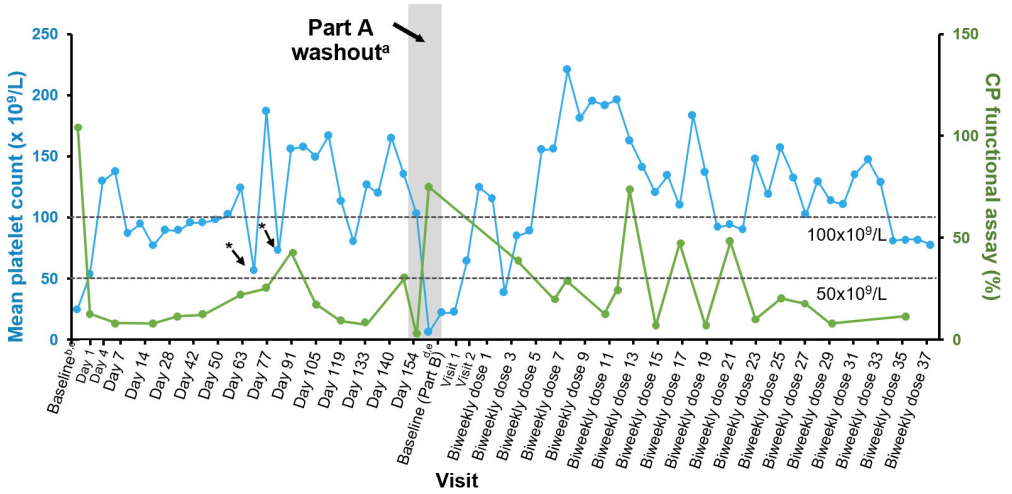
Complement Inhibition in ITP: Sutimlimab



Broome C, et al. *Blood.* 2022;140(Supplement 1):5306-5308.

When we look at complement inhibition in ITP, there are actually a couple drugs being evaluated in this regard. This figure is from a phase 1 study of 12 patients treated with sutimlimab. Sutimlimab is an anti-C1s monoclonal antibody, blocks the classical complement pathway, while leaving the other two complement pathways intact, important for infection risk as we think about that. This drug is FDA proved already for the treatment of cold agglutinin disease, and recently published phase one study demonstrates the efficacy in ITP.

About 6 out of 12 patients or half of patients responded nicely. This is every two-week infusions of sutimlimab, complement activity. The green line drops like a rock, platelet count recovers nicely. Then when you wash out those reverts, and then when you restart the drug, you get the benefit back once again.

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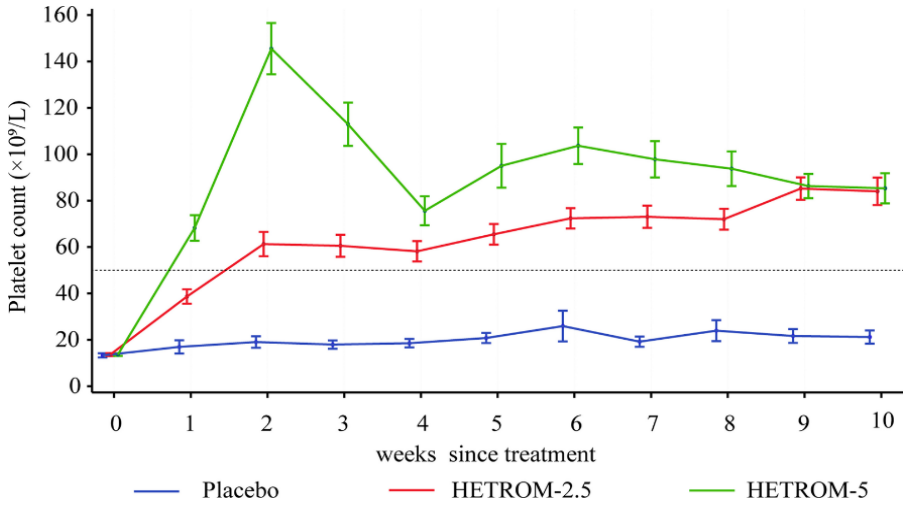
New TPO-RA: Hetrombopag



Mei H, et al. *J Hematol Oncol.* 2021;14(1):161.

There is a new thrombopoietin receptor agonist that has been developed in China called hetrombopag, in a very large trial in China was shown to be effective in ITP. Right now use is restricted to China but who knows what will happen with this drug.

Effects of BTK Inhibition

Pathophysiologic Mechanisms in ITP

B-cells, plasma cells	Monocyte, macrophage	Mast cells, basophils	Neutrophils	T cells
Blocks B-cell receptor Inhibits plasma cell differentiation and antibody production	Blocks IgG-mediated FcgR activation, phagocytosis, inflammatory mediators	Blocks IgE-mediated FceR activation and degranulation	Inhibits activation, adhesion, recruitment, oxidative burst	No effect
BTK inhibition				

Kuter D, et al. *N Engl J Med.* 2022;386(15):1421-1431.

Then lastly, BTK inhibitors which have been available now for lymphoid malignancies for quite some time. There's recognition that these drugs may have value in ITP given their very potent effects on the B-cell compartment.

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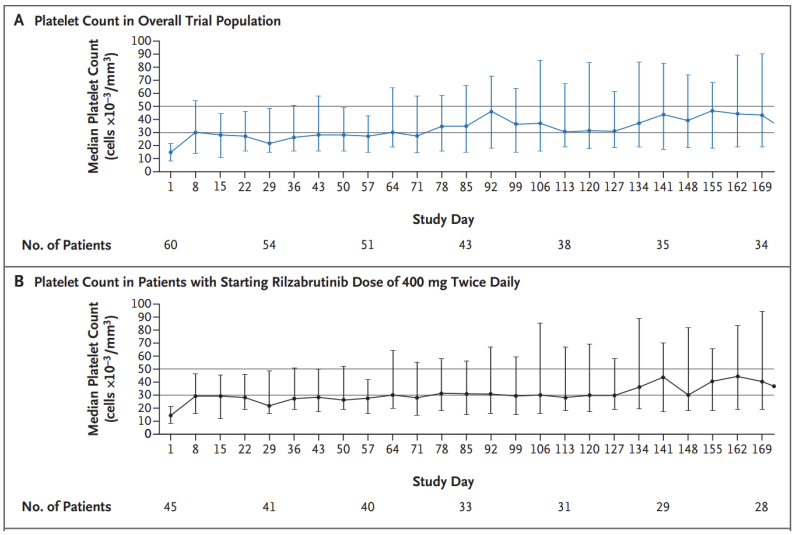
BTK Inhibitor for ITP: Rilzabrutinib



Kuter D, et al. *N Engl J Med.* 2022;386(15):1421-1431.

There is a BTK inhibitor currently under investigation at ITP called rilzabrutinib. Rilzabrutinib is a BTK inhibitor that in a clinical trial, phase 1, 2 clinical trial of patients with very relapsed/refractory ITP, that have received a median of five prior therapies, had disease for longer than six years median. Very heavily pretreated group, had about a 40% response rate in raising the platelet count. Those patients who responded, they typically had a durable response. This is a certainly potentially promising drug.

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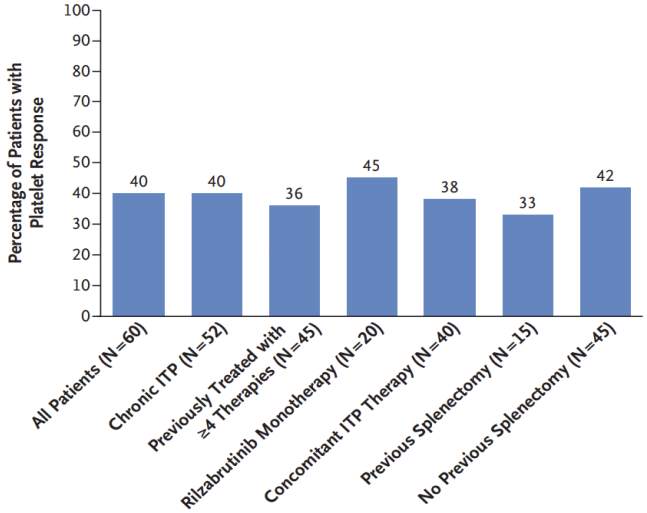
BTK Inhibitor for ITP: Rilzabrutinib

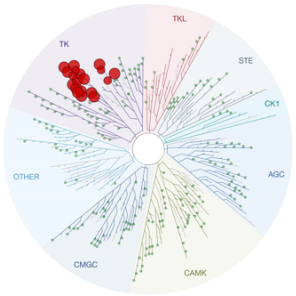


Kuter D, et al. *N Engl J Med.* 2022;386(15):1421-1431.

Now, when we break it down by the different subgroups, we have essentially 40% response rate, irrespective of if they had a prior splenectomy or not, they had four or more therapies or not. This is obviously promising for these very relapsed refractory patients.

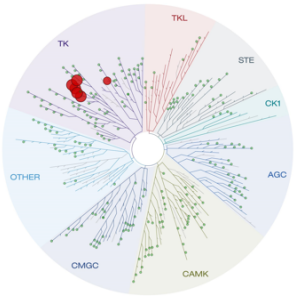
BTK Inhibitor for ITP: Rilzabrutinib

Ibrutinib Kinase Selectivity



21 kinases inhibited >90%

PRN1008 Kinase Selectivity



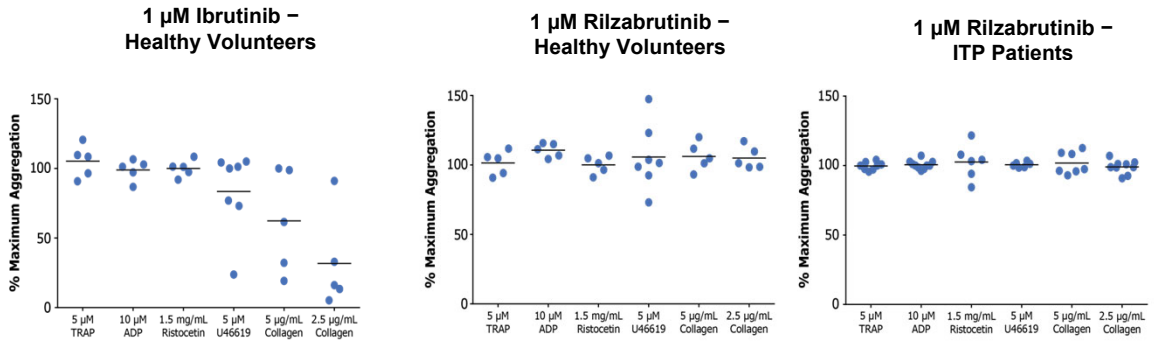
6 kinases inhibited >90%

Kuter D, et al. *N Engl J Med.* 2022;386(15):1421-1431.

You might say, "Well, wait a minute, Hanny. These drugs cause a platelet aggregation defect and reduction in platelet function, right? Ibrutinib certainly increases the bleeding risk, we wouldn't want to do this in ITP patients."

I would certainly agree with you that the BTK inhibitors we use to treat lymphoma do seem to have this impact, but rilzabrutinib or PRN1008 has more selectivity for specific kinases and it does appear to avoid this.

BTK Inhibitor for ITP: Rilzabrutinib



Kuter D, et al. *N Engl J Med.* 2022;386(15):1421-1431.

In a small study done looking at healthy volunteers, and ITP patients receiving these drugs, and having platelet aggregation measured. While platelet aggregation was impaired with certain agonists, with ibrutinib, it was not impaired with rilzabrutinib. This is borne out in the early phase studies done with rilzabrutinib, does not appear as though this drug is causing patients to bleed.

With that, we've gone through a whirlwind through the treatment of both pediatric and adult ITP in the modern day, and thank you very much.