Pediatric Immune Thrombocytopenia (ITP)

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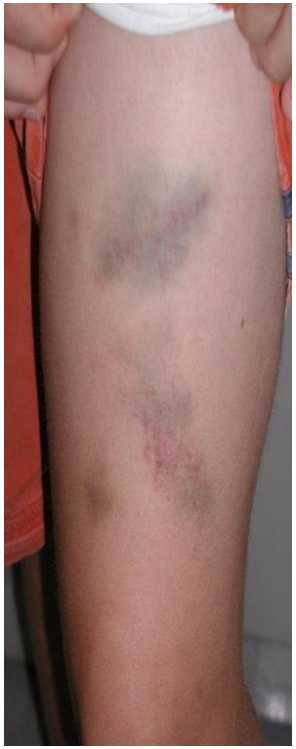
Objectives

- Review the 2011 American Society of Hematology guidelines for the management of ITP
- Discuss the studies that support these recommendations
- Describe the efforts of the ITP Consortium of North America

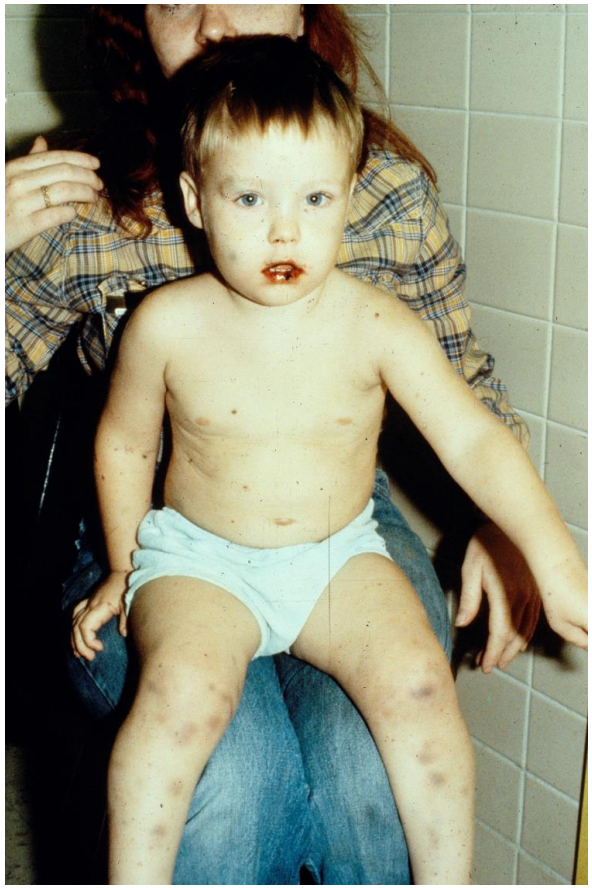
Pediatric ITP

- 6-year-old with a 24-hours of bruising and petechiae with no additional bleeding
- No family history of thrombocytopenia
- Physical examination reveals scattered petechiae and several bruises to the arms and legs
- Complete blood count: platelet count of 8×10^9/l and is otherwise normal
- Peripheral blood smear shows a few large platelets and no other abnormalities



Pediatric of ITP

- Prevalence: 5 in 100,000
- Usually a previously healthy child
- Platelet count increases within 1-3 weeks
- Normalization of platelet count
  - 50% of cases within 6 weeks
  - 65% of cases within 3 months
  - 75 - 80% of cases within 6 months
- Management:
  - Observation
  - Corticosteroids
  - IVIg
  - Anti-D immunoglobulin



2011 ASH Guidelines

blood

2011 117: 4190-4207
Prepublished online February 16, 2011;
doi:10.1182/blood-2010-08-302984

The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia

Cindy Neunert, Wendy Lim, Mark Crowther, Alan Cohen, Lawrence Solberg, Jr and Mark A. Crowther

- Creation of focused clinical questions followed by a systematic review of literature
- Establishment of evidence tables and the development of recommendations based on the GRADE methodology

Neunert and Lim, et al. Blood 2011

Initial Management of ITP

- ***We recommend:***
  - Children with no bleeding or mild bleeding (defined as skin manifestations only, such as bruising and petechiae) be managed with observation alone regardless of platelet count (grade 1B)

Neunert, C, Lim, W., et al. Blood 2011

Who and When to Treat

Intercontinental Cooperative ITP Study Group (ICIS)

Founded in 1997

500 physicians from over 60 countries

Over 4000 patients registered on ICIS studies

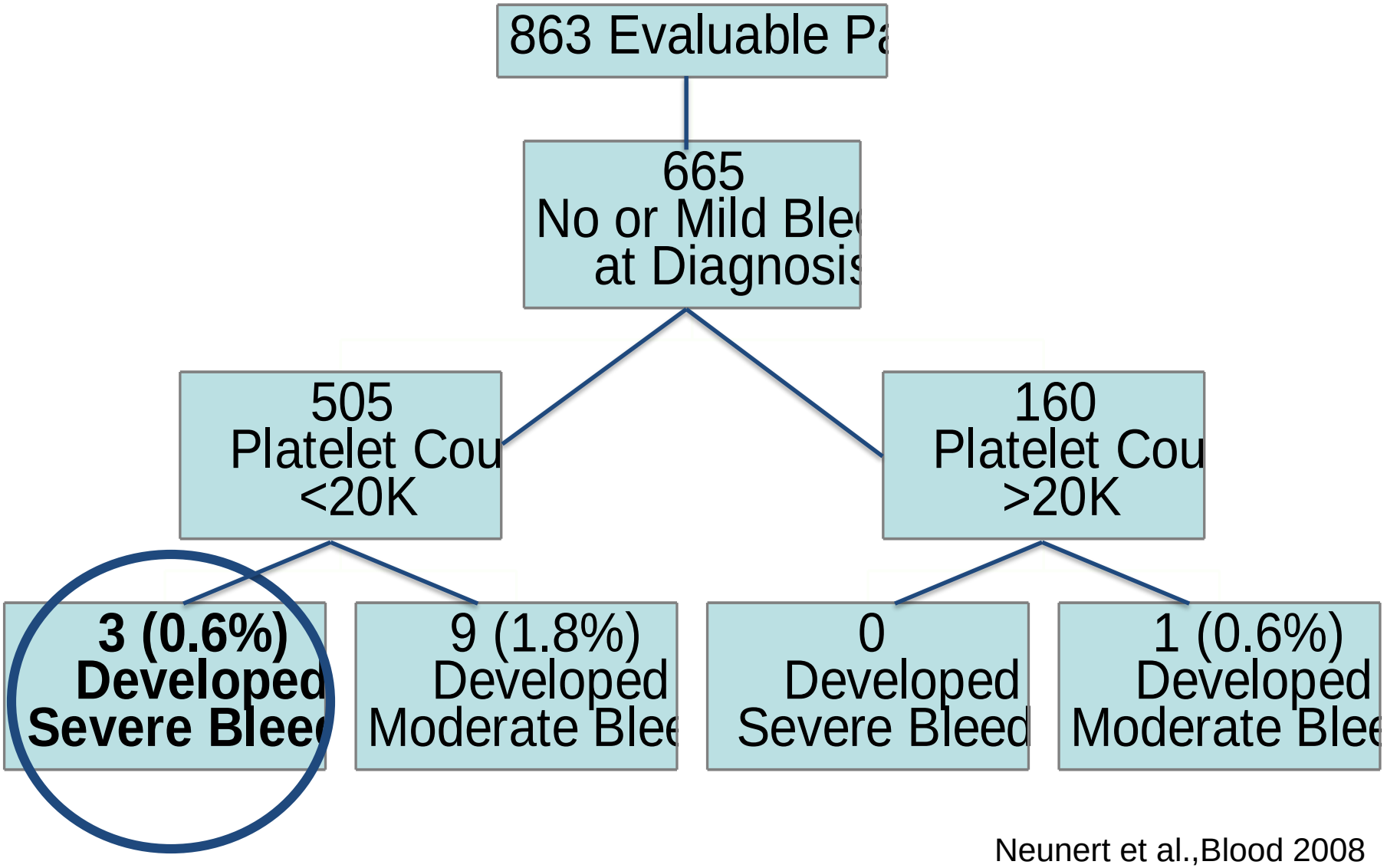
http://pages.unibas.ch/itpbasel/

ICIS Registry II: Aims

- To determine the frequency, timing, site, and severity of hemorrhage in children with ITP
  - At diagnosis and during the following 28 days
- 863 patients had bleeding severity assessments available at diagnosis and day 28

Neunert et al.,Blood 2008

ICIS: Subsequent Bleeding

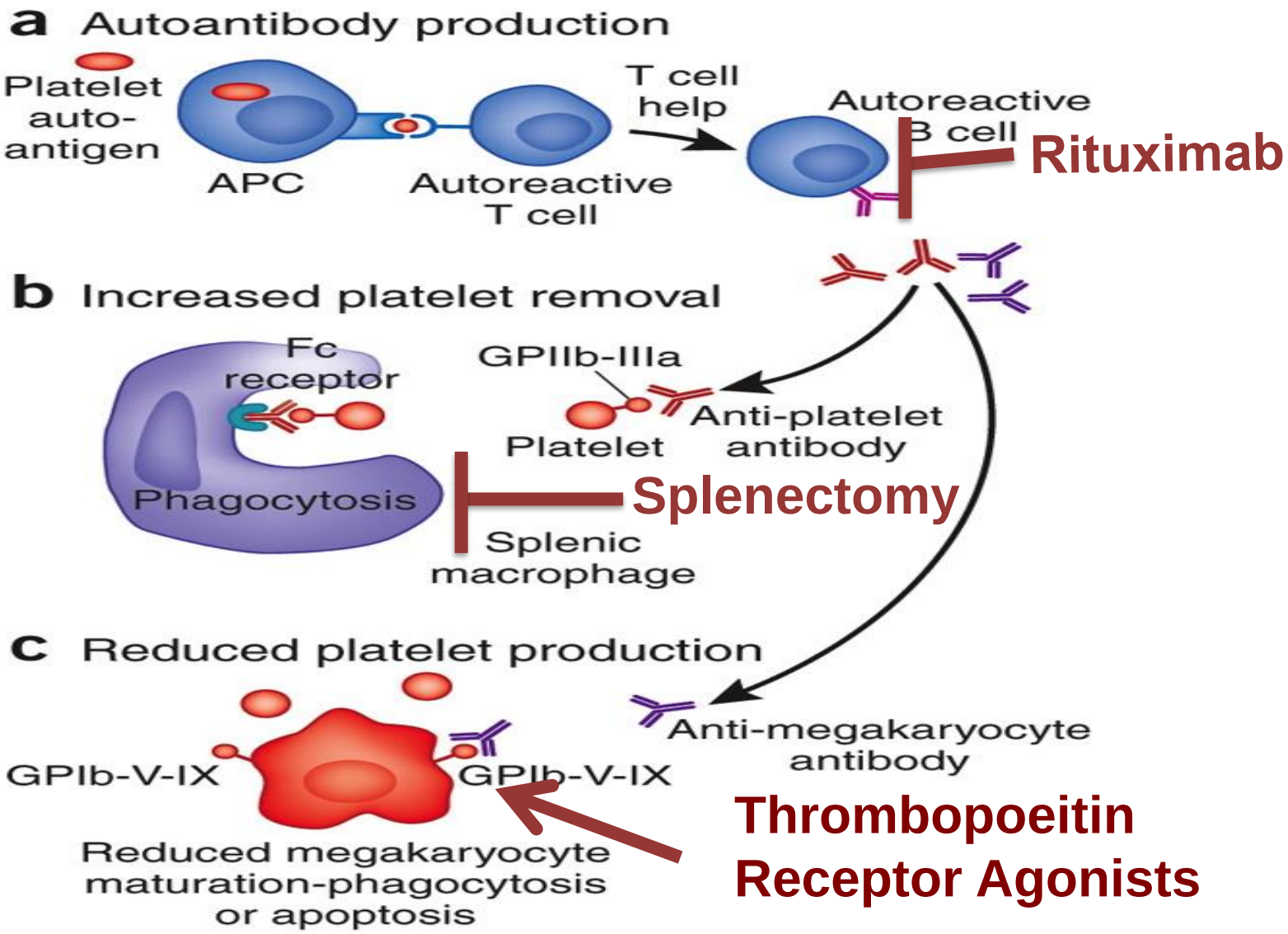


Neunert et al.,Blood 2008

Persistent and Chronic ITP

- 6 months later the child continues to have a platelet count of 20 $x10^9$/l
- No response to IVIg and anti-D
- Decline in response to periodic corticosteroids
- Suffers from recurrent epistaxis and as a result is being sent home from school
- Parents are wondering whether the child can return to soccer practice

Second-Line Therapy



Wei and Jackson Nat Med 2008;14:720-721

Splenectomy

- Splenectomy is successful therapy
  - Complete remissions across studies: 75%
- No consistent predictors of response
- Loss of immune protection
- Long term concerns for blood clots

Mantadakis et al. J Ped Hem Onc 2000, Kuhne et al. Ped Blood Cancer 2007, Ramenghi et al. Ped Blood Cancer 2006, Donato et al. Ped Blood Cancer 2006, Crary and Buchanan Blood 2009

ASH Guidelines

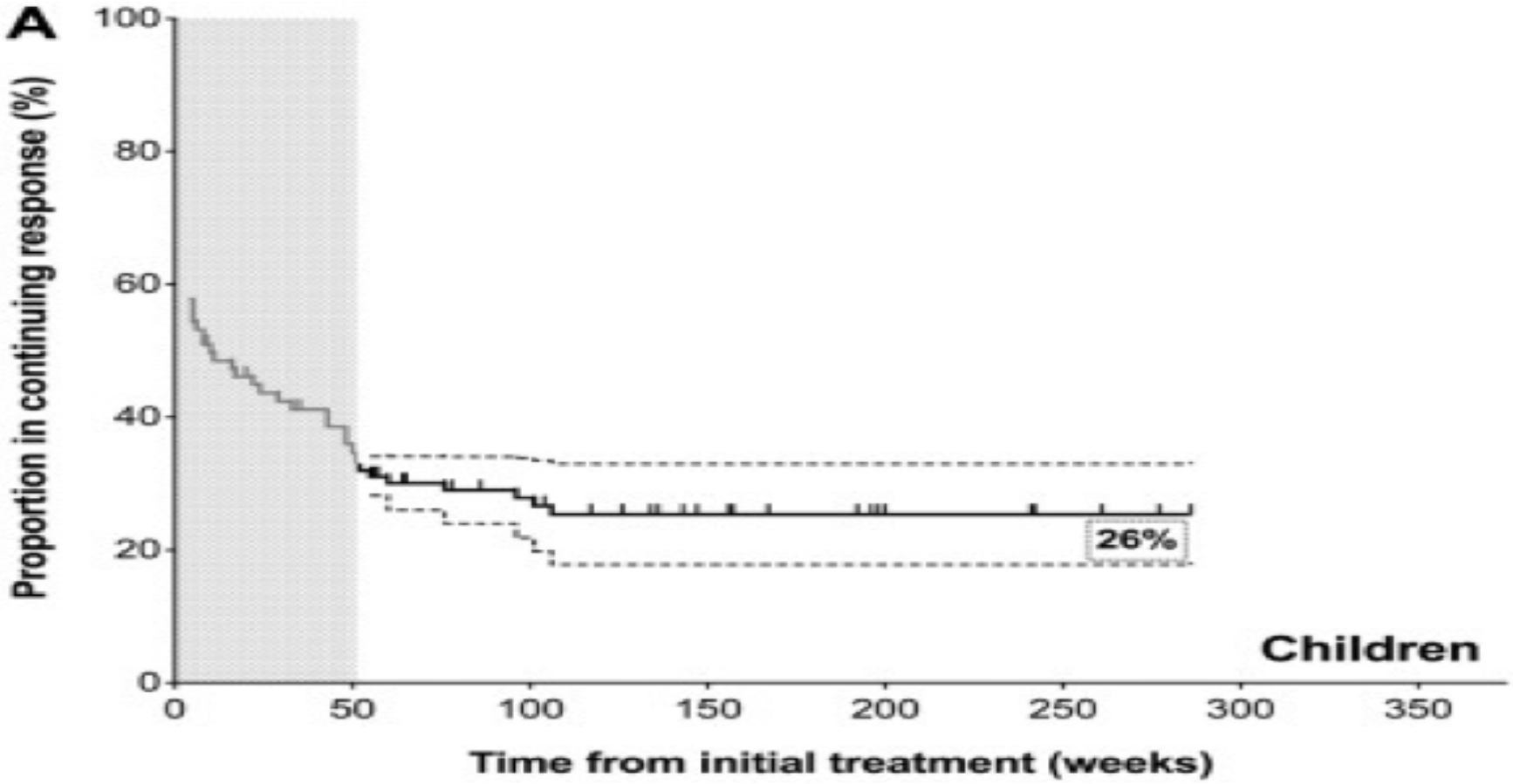
- ***We recommend:***
  - Splenectomy for children and adolescents with chronic and persistent ITP who have:
    - Significant or persistent bleeding
    - Lack of responsiveness or intolerance to first line therapies
    - Need for improved quality of life (grade 1B)

- ***We suggest:***
  - Splenectomy or other interventions with potentially serious complications be delayed for at least 12 months, unless accompanied by severe disease, unresponsive to other measures or other quality of life considerations (grade 2C)

Neunert, C, Lim, W., et al. Blood 201

Rituximab

- Early response rates
  - Pediatric: 31% -68%
- Long term remission rates are lower



Patel et al Blood 2012

Rituximab

- No dosing data available
  - Possible that we are overdosing
- Associated with adverse events (n= 190)
  - 41.1% patients experienced adverse events
  - Possible injury to the immune system in young children
- Response may be delayed

Liang et al. PloS one 2012

ASH Guidelines

- ***We suggest:***
  - Rituximab
    - Be considered for children or adolescents with ITP who have significant ongoing bleeding despite treatment with IVIg, anti-D, or conventional doses of corticosteroids (grade 2C)

    - Be considered as an alternative to splenectomy in children and adolescents with chronic ITP or in patients who do not respond favorably to splenectomy (grade 2C)

Neunert, C, Lim, W., et al. Blood 2011

TPO - RAs

- Two agents available
  - Romiplostim: Weekly subcutaneous injection
  - Eltrombopag: Daily oral mediation
- Monitored with weekly CBC and titrated based on platelet count
- Increase platelet count, decrease bleeding, reduce additional medications, and improve health-related quality of life (HRQoL)
- Discontinuation results in thrombocytopenia
- If one does not work you can consider using the other

Polverelli et al. Brit J of Haematol 2013, D'Arena et al. Blood 2013, Ghadaki et al. Transfusion

ASH Guidelines

“……..Studies are ongoing, but there are no published data to guide the use of these agents in children…….”

Romiplostim

- ITP for ≥ 6 months with a baseline platelet count ≤ 30 $\times 10^9$/L (n=62)

	Romiplostim	Placebo	P-value
Weekly platelet count ≥ 50×10^9/L in 6 of the final 8 weeks	52%	10%	0.002
Overall response: ≥ 4 platelet responses between weeks 2-25	71%	20%	0.0002

- Reduced the need for rescue medications
- Half the patients on concurrent medications discontinued

Bussel et al. Lancet 2016

Eltrombopag: PETIT and PETIT 2

- 7 week response

	Eltrombpag	Placebo	P-value
Platelet count ≥ 50×10^9/L at least once during the first 6 weeks	62%	32%	0.011
Platelet count ≥ 50×10^9/L for ≥ 60% of the visits from weeks 2-6	36%	0%	0.002

- 13 week response

	Eltrombpag	Placebo	P-value
Platelet count ≥ 50×10^9/L at least once during the first 6 weeks	62%	17%	0.00018
Platelet count ≥ 50×10^9/L for ≥ 75% of the visits from weeks 5-12	40%	3%	< 0.001

Bussel et al. Lancet Hematology 2015

TPO-RAs: Safety Data

- No grade serious bleeding events
- No fatal events
- Increased platelet count >400 $x10^9/l$
- Eltrombopag:
  - Increased liver enzymes
  - Two cataracts: both on corticosteroids
- No thrombosis
- No bone marrow change

Grainger et al. Lancet 2015


How do we make things better?

ITP Consortium of North America

ICON IS A COLLABORATIVE RESEARCH EFFORT

We are dedicated to improving the understanding, treatment, and quality of life of pediatric patients with ITP.

Learn more

Our Mission

The Pediatric ITP Consortium of North America is a collaborative research effort that includes investigators from centers

For ICON Investigators

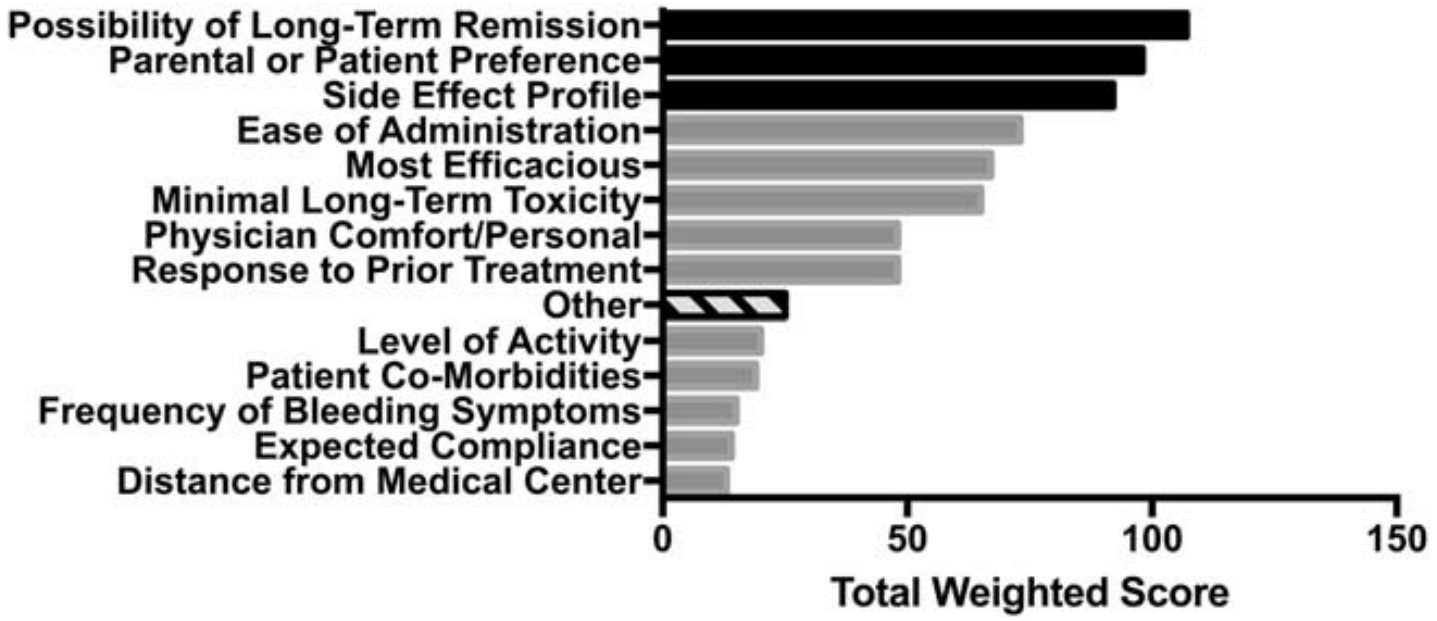
Consortium Investigators can find information about ITP studies run through the consortium and at consortium sites,

ICON 1

- Dr. Rachael Grace, Boston Children's
- Pediatric ITP patients started on second-line ITP treatment
- Investigating decision making factors and outcomes
  - Physician decision making
  - Treatment plans
  - Patient reported outcomes
  - Bleeding assessment
  - Platelet counts
- Data: Baseline, 1mth, 6mth,and 12mth

ICON 1

- Rituximab (36%)
- Romiplostim (26%)
- Eltrombopag (17%)
- Oral Immunosuppressants (16%)
- Splenectomy (3%)
- Dapsone (3%)



Grace et al., AJH 2018

ICON 1: Results

- **Physician Decision Making in Selection of Second-Line Treatments in Immune Thrombocytopenia in Children. Am J Hematol 2018 Apr 16.**
  - Patient preference and physician perception of treatment characteristics ranked high
  - Guidelines, clinical characteristics and health system factors were ranked low

- **Comparison of Bleeding Tools in a Cohort of Pediatric Patients with ITP: Data from the Pediatric ITP Consortium of North America ICON1 Study, ASH 2016**
  - Neither bleeding tool matched the platelet count

ICON 1

- **Clinical Characteristics and Quality of Life of Children with ITP Starting Second Line Treatments: Data from the ITP Consortium of North America ICON1 Study, ASH 2016**
  - Physician assessment of patient HRQoL was similar to the child and parent proxy report of HRQoL
  - Longer duration of ITP was associated with a better HRQoL

- **Health Related Quality of Life and Fatigue Improve on Second Line Treatments in Pediatric Immune Thrombocytopenia (ITP), ASH 2017**
  - All second line treatments appear to significantly improve HRQoL in ITP
  - Fatigue scores were less affected by second line treatment

ICON 2

- Retrospective Review Of Off-label Thrombopoietin Receptor Agonists Use In Pediatric Patients

  - Report patterns of use
  - Evaluate the efficacy
  - Report the safety
  - Determine dosing practices

Neunert et al., Pediatr Blood Cancer 2016

ICON 2: Response

	Overall (n=87)	Romiplostim (n=51)	Eltrombopag (n=36)
Consecutive	62 (71%)	37 (73%)	26 (72%)
Single	70 (80%)	43 (84%)	27 (75%)
Subjective			
Stable	35 (40%)	24 (47%)	11 (31%)
Intermittent	12 (14%)	9 (17%)	3 (8%)
Waned	11 (13%)	6 (12%)	5 (14%)
No response	11 (13%)	6 (12%)	5 (14%)
Other	18 (33%)	6 (12%)	12 (33%)

Neunert et al., Pediatr Blood Cancer 2016

ICON 2: Conclusions

- Wide range of use
  - Need to establish data on ideal population
  - Possible indication for newly diagnosed patients or prior to surgery
- Clinical response
  - 40% with stable ideal dose
  - 26% had no response or a waning response
  - 40% discontinued for lack efficacy, inconvenience, or side effect concerns
- New safety signals not previously detected
  - Thrombosis and neutralizing antibody
- Not curative therapy

Neunert et al., Pediatr Blood Cancer 2016

Move towards individualized treatment…..

Patient-Related Outcomes

What we really need to know:

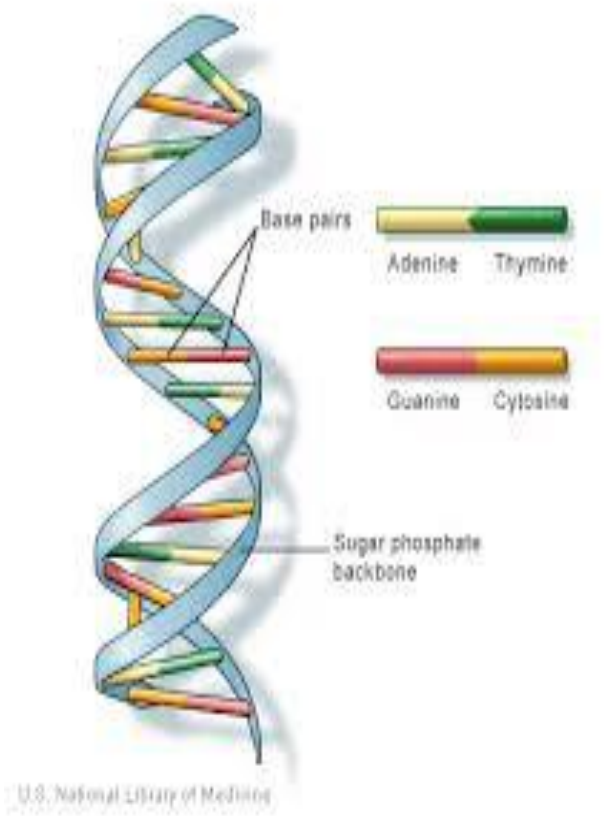
- True severity of disease or risk of bleeding
- Negative impact of drug side effects
- Cost of medications
- Priorities of the patients and families

- **Impact of the disease and treatment on the patient**

Individual Biology

What we really want to predict:

- Response to treatment
- Development of chronic disease
- Risk for bleeding



Not all patients are the same

New Research Strategies

- Health- related quality of life assessment
- Cost analysis
- Comparative effectiveness
  - Direct comparison of strategies
  - Balances benefits and harms
- Qualitative methods
- Biology correlates

Current ICON Studies

- ITP Biobank Study
  - Jenny Despotovich, Baylor College of Medicine
- Upfront therapy with TPO-RAs
  - Kristin Shimano, UCSF
- Biomarkers of Fatigue in ITP
  - Michele Lambert, CHOP
- Platelet parameters and bleeding risk in ITP
  - Rachael Grace, Boston Children's Hospital
- Pathway to Care
  - Michelle Neier, Morristown Medical Center
- Shared-Decision Making in ITP

Evidence AND Experience

- Currently revising the 2011 Guidelines
- Including patient representatives
- Prioritizing outcomes of interest for assessing clinical trials
- Piloting strategies to address areas of no or low level evidence

Management Strategy

BENEFITS

- Rise in platelet count
- Reduced symptoms and additional medications
- Improved HRQoL
- Remission

RISKS

- Adverse effects
- Costs
- Inconvenience

PATIENT FACTORS

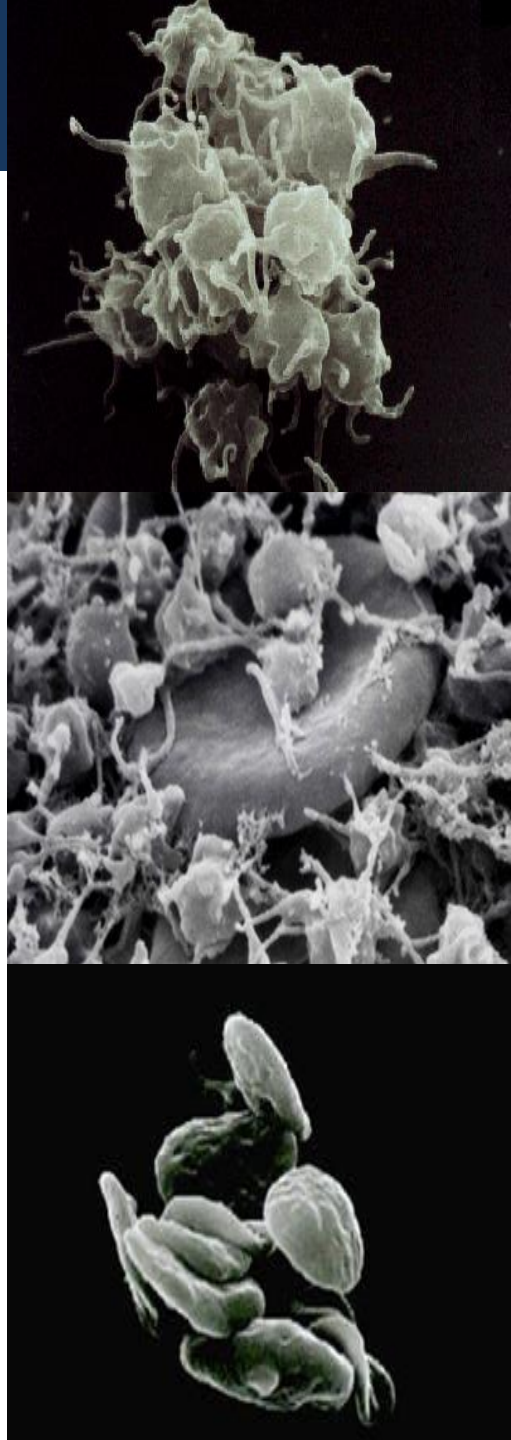
- Duration of ITP
- Contraindications
- Previous treatments
- Biologic markers

Conclusions

- Evidence is lacking to guide management of pediatric ITP
- Physicians often rely on experience to determine treatment approaches
- Application of patient-related outcomes and understanding physician decision-making can help to merge evidence with experience
- Ultimately patients may require an individualized treatment approach and understanding biology may assist with this

Acknowledgements

- Intercontinental ITP Study Group
- American Society of Hematology
- ITP Consortium of North America
- Platelet Disorder Support Association
- Drs. George Buchanan and Jim George



Questions