Immune Thrombocytopenia: Updates on Diagnosis, Management and Therapies

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Disclosures

- No financial disclosures related to the content of this talk
- Unrelated financial disclosures
  - BioMarin: honoraria

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Objectives

- Describe the pathophysiology of immune thrombocytopenia (ITP)
- Recognize the presentation of ITP
- Recognize acute or emergent bleeding symptoms in ITP
- Describe the options for treatment of acute bleeding in ITP
- Describe the options for treatment of chronic ITP
- Manage the co-morbidities in patients with ITP

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Classification and Terminology in ITP

- Immune Thrombocytopenia
- Prior terminology:
  - Acute ITP: <6 months duration
  - Chronic ITP: >6 months duration
- Recommended terminology:
  - Newly diagnosed ITP: <3 months
  - Persistent ITP: 3-12 months
  - Chronic ITP: >12 months

Provan D , et al. Blood. 2009; 113: 2386-2392.

What is ITP?

- Immune-mediated platelet destruction leading to low circulating platelet count
- 2-10/100,000 patients
- Gender predominance varies by age

Blanchette V and Bolton-Maggs P. Pediatr Clin N Am. 2008(55): 393-420
Lambert MP and Gernsheimer TB. Blood. 2017;129;2829-2835

Incidence by Age

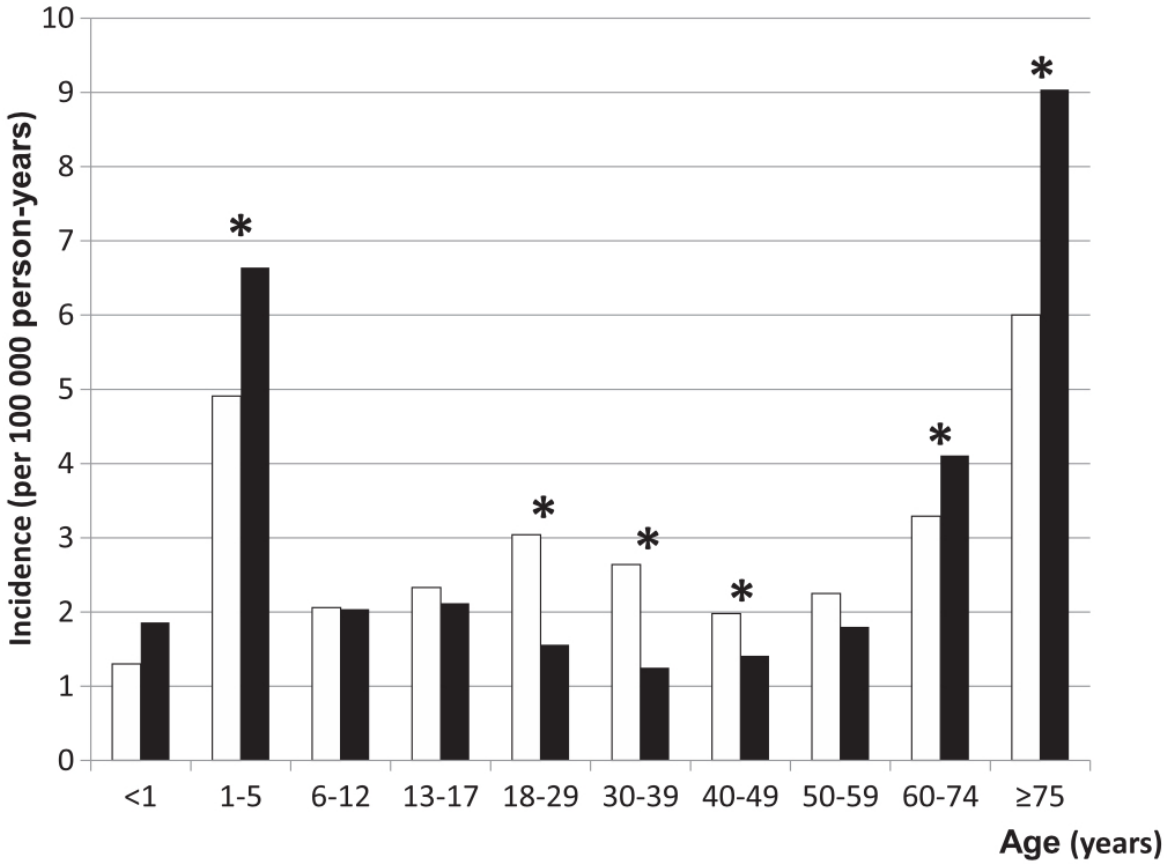

Figure 2. Incidence of ITP in France during the period from mid-2009 to mid-2011 by age and gender. Females, white bars; males, black bars. Stars indicate statistically significant differences among males and females (α = 5%).

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

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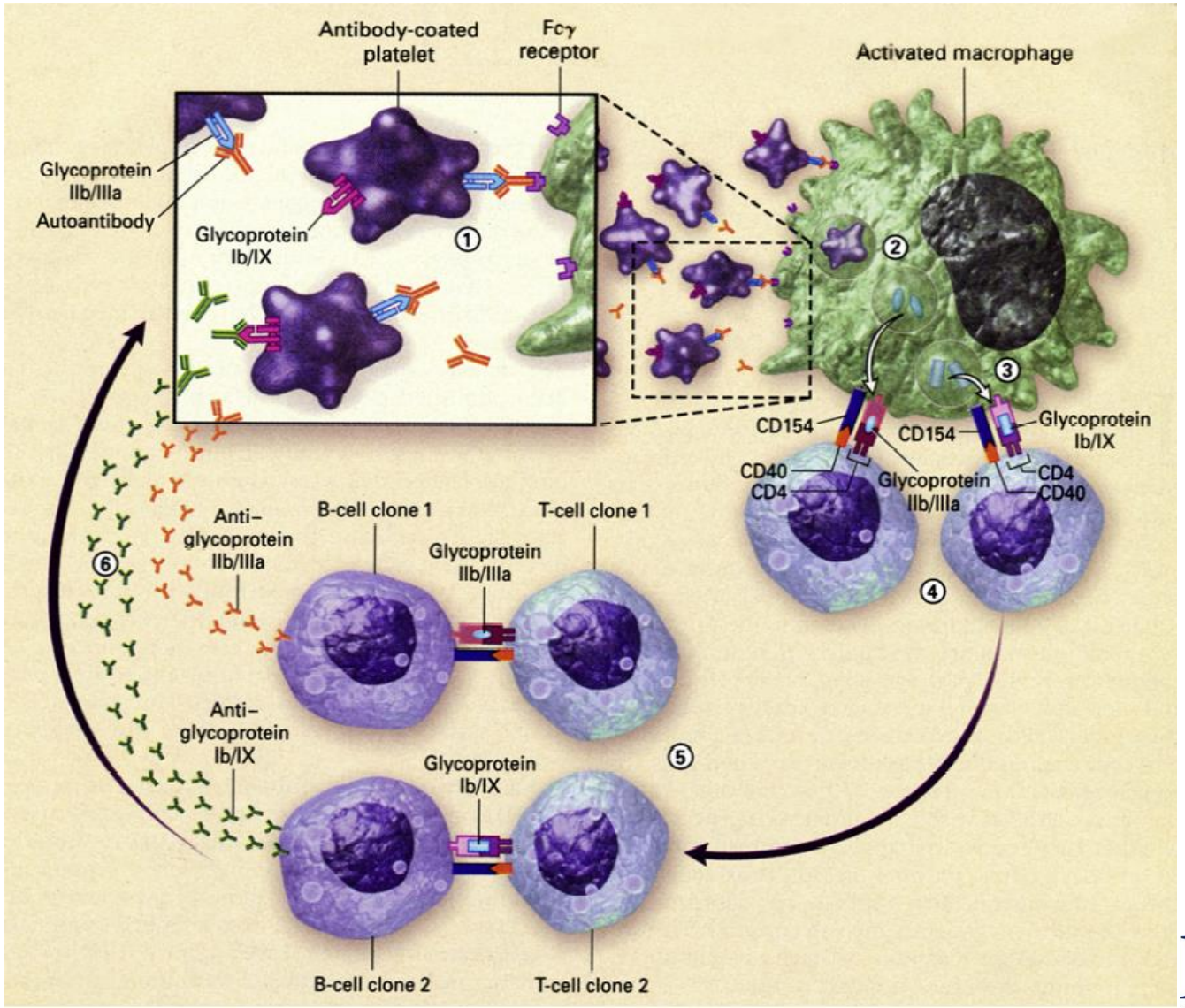
ITP: Pathophysiology

What is ITP?



Cines and Blanchette N Eng J Med 2002. 346 995-1008.

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Harrington's Classic Experiment

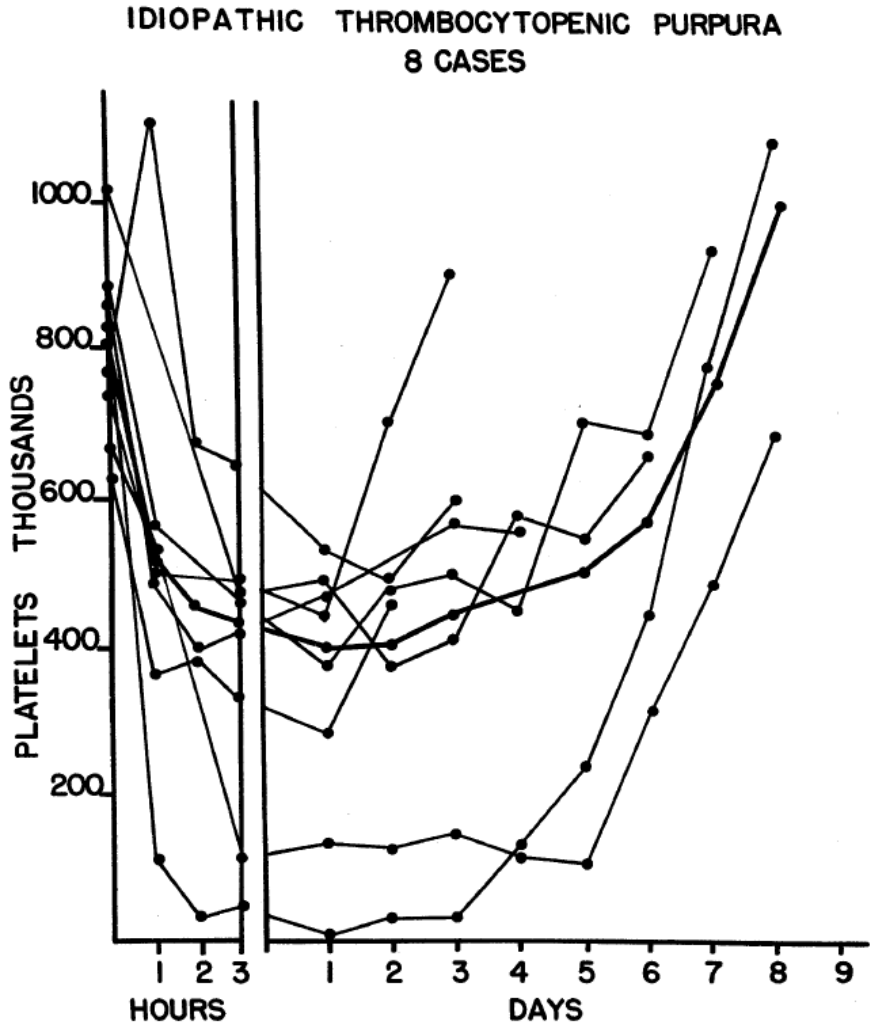

Fig. 1.—Thrombocytopenic effect produced by transfusing 500 c.c. of citrated whole blood or its plasma equivalent from eight patients with thrombocytopenic purpura. Transfusions were given at "0" time. Recipients were healthy laboratory workers or patients with inoperable carcinoma. The mean effect is represented by the heavy line.

Plasma from patients with ITP infused into healthy "volunteers"

- "…prompt and profound decrease in platelets"
- Two had severe GI bleed

Harrington W et al. J Lab Clin Med. 1951; 38:1-10

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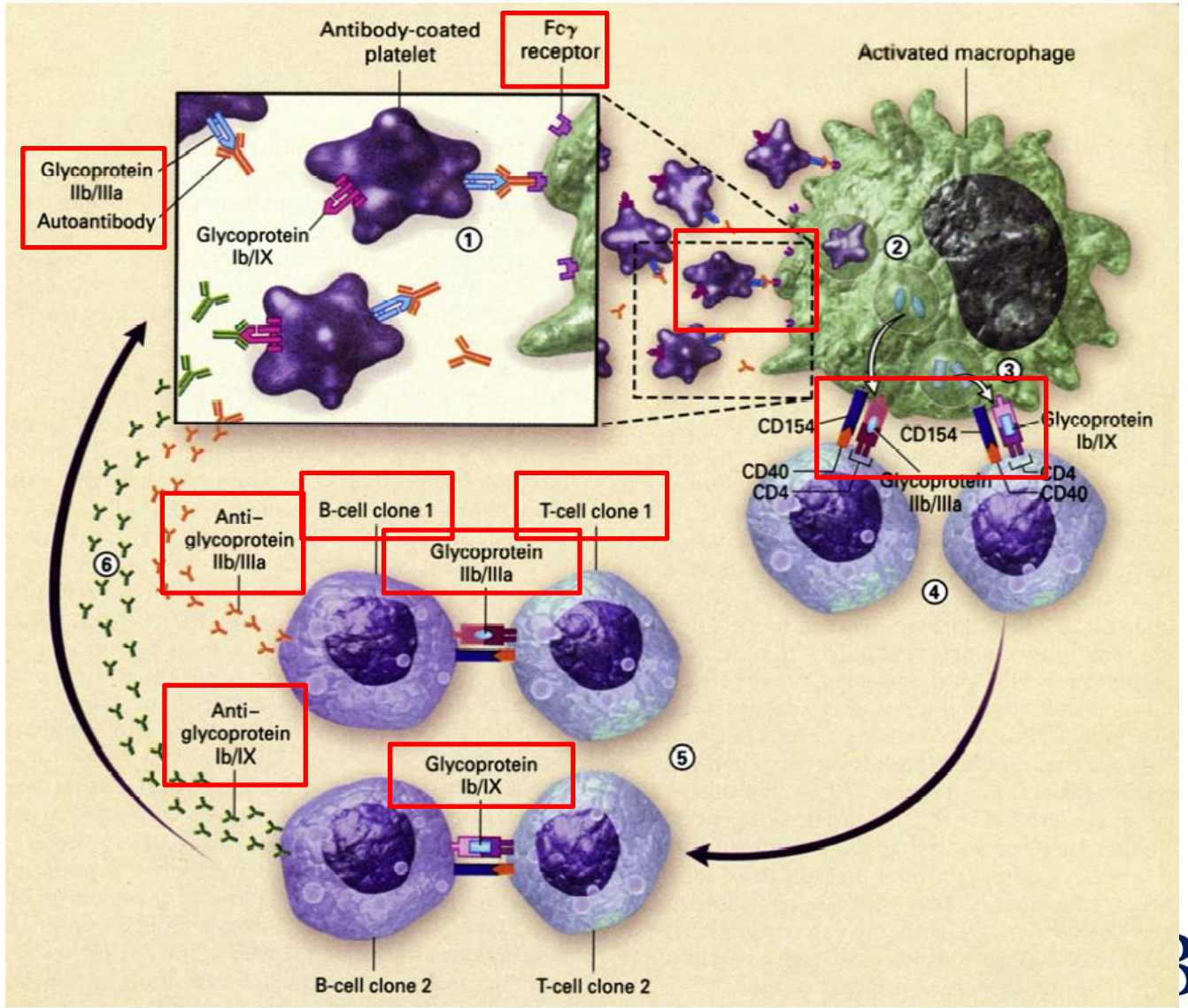
What can go wrong?



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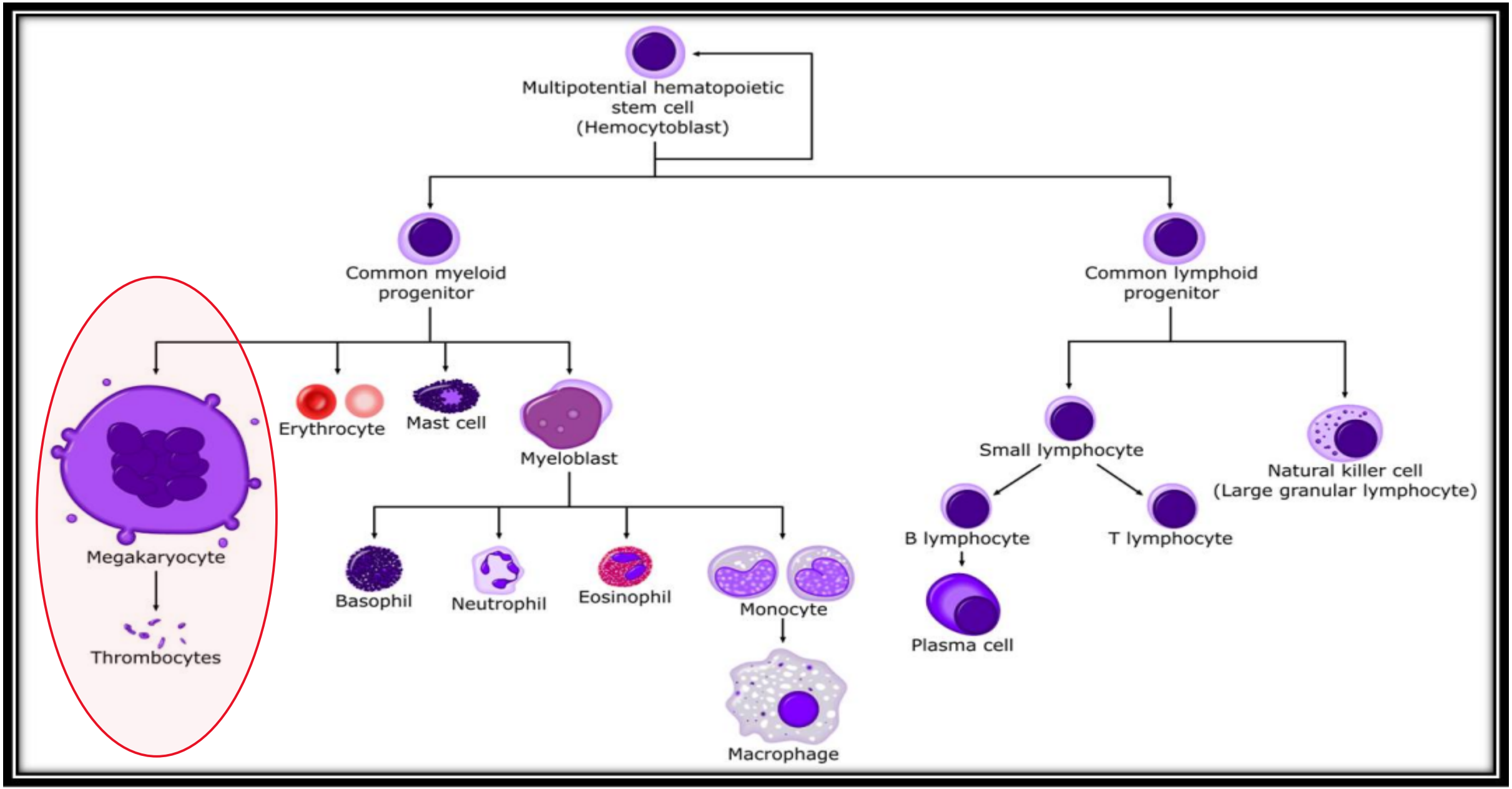
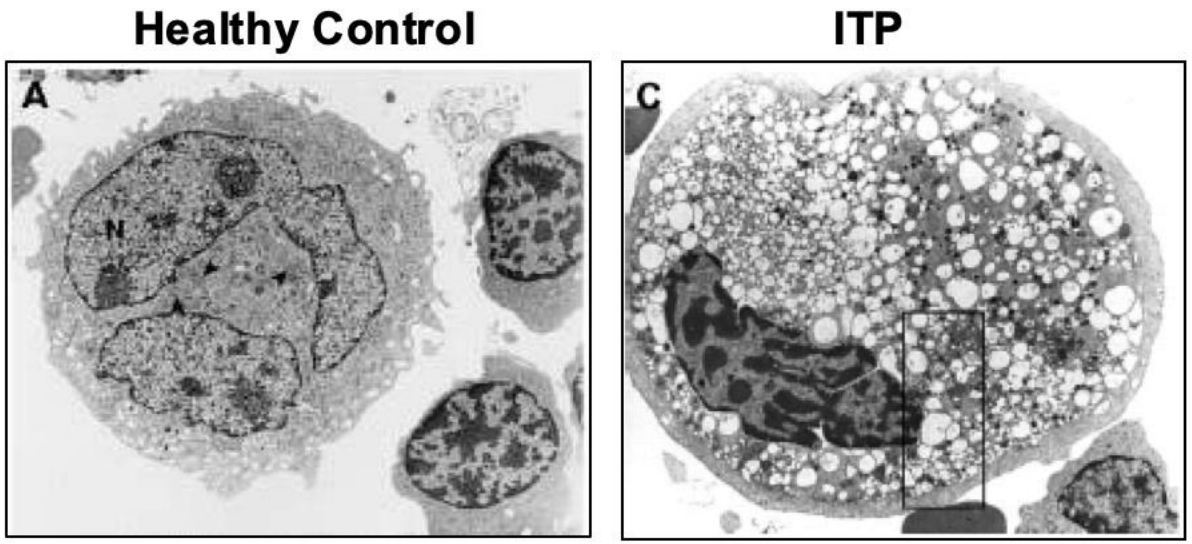


Shaikh A and Bhartiya D. Pluripotent Stem Cells in Bone Marrow and Cord Blood. Sept 21, 2012. DOI: 10.5772/48133

Mechanisms of ITP: Megakaryocyte Abnormalities

Megakaryocytes may have

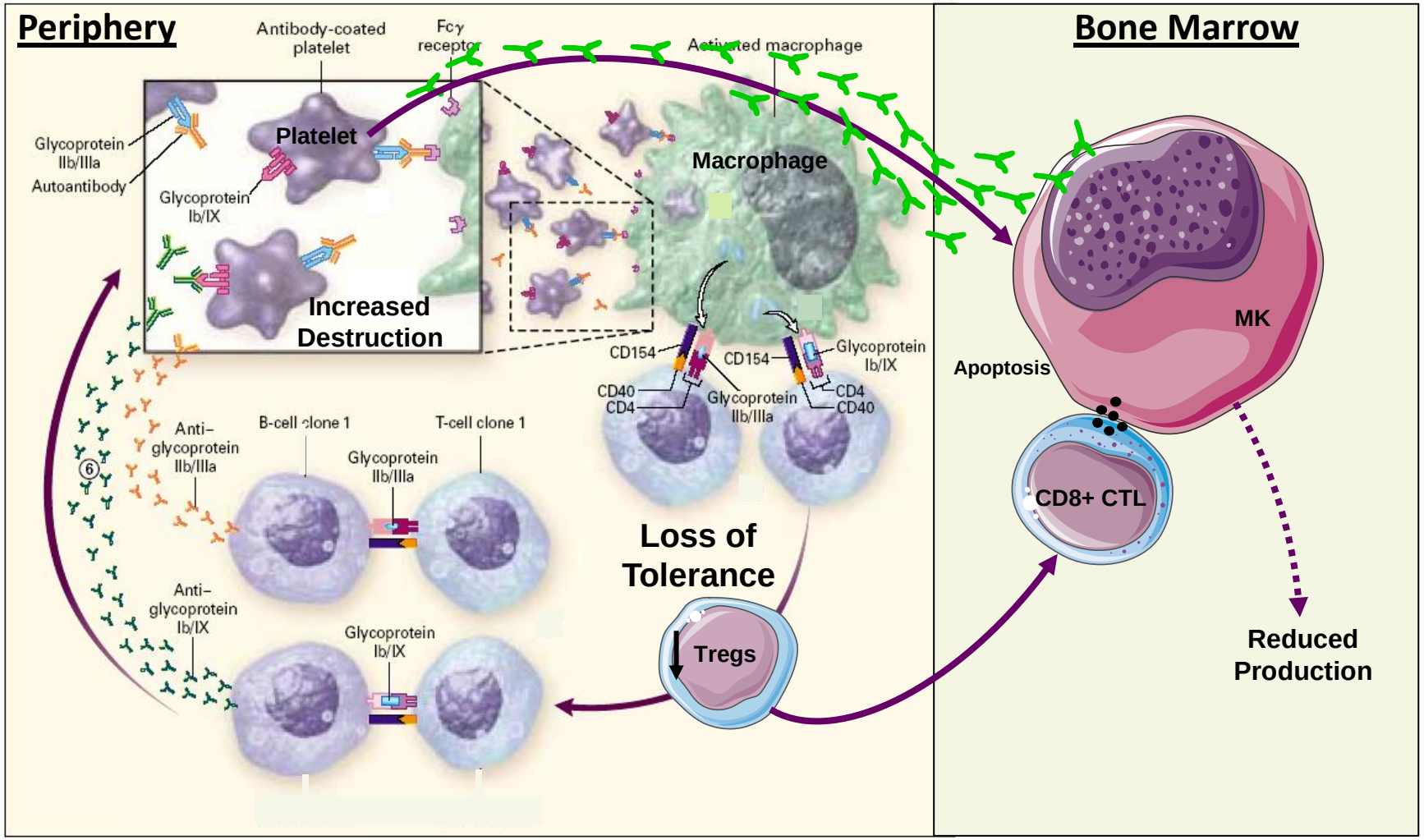
- Impaired development
- Decreased survival
- Abnormal platelet release



Houwerzijl et al. Blood. 2004.

Stahl CP et al. Blood. 1986;67;421-428.
Chang M et al. Blood. 2003;102:887-895.

Mechanisms of ITP: An Update



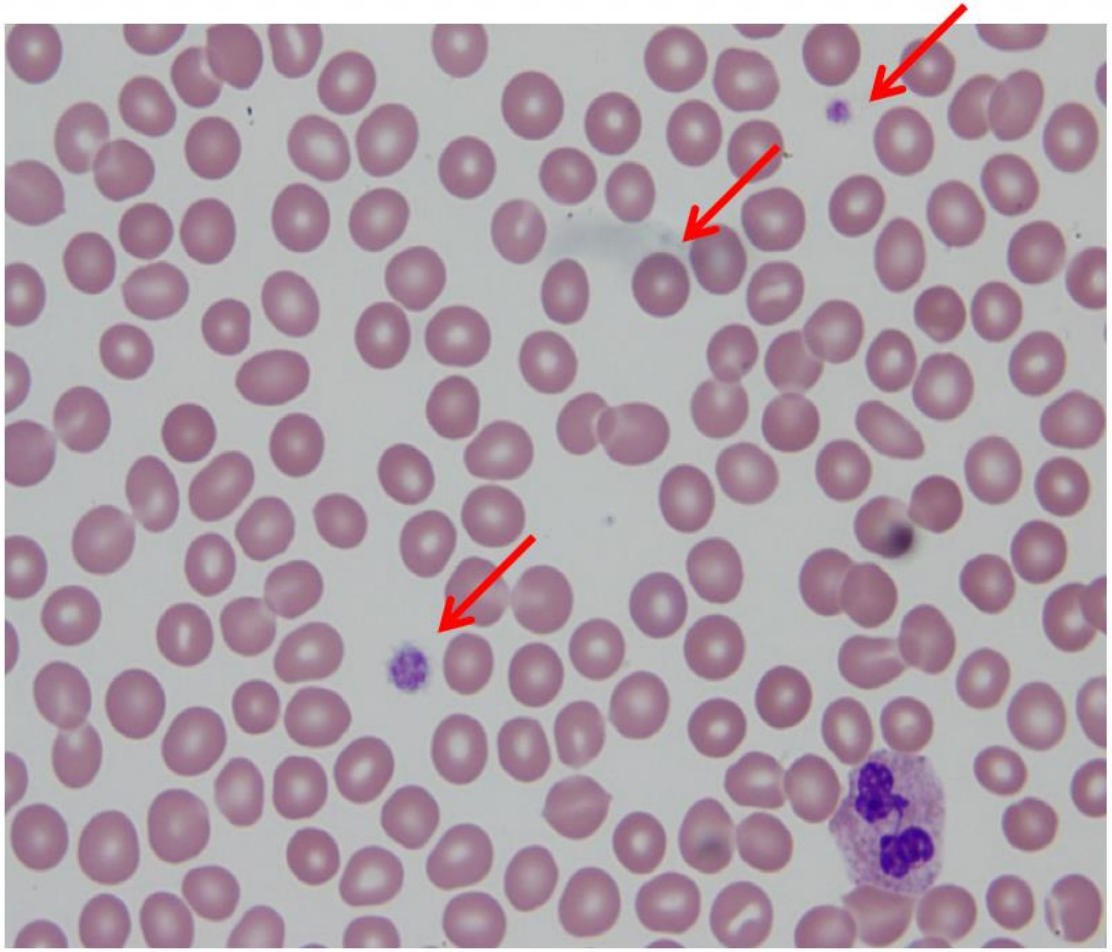
Modified from: Cines and Blanchette N Eng J Med 2002. 346 995-1008. Courtesy of JW Semple PhD

ITP: Diagnostic Criteria

ITP: Diagnostic Criteria

- Exam normal except platelet-type bleeding
  - No significant lymphadenopathy, hepatosplenomegaly
- Platelets <100K, other CBC indices normal
  - 50% of patients present with platelets <20K
- History may be minimal
  - Sudden onset of bruising, petechiae, mucocutaneous bleeding
  - May have history of autoimmune or immune disorder
- Diagnosis of exclusion

Blood Smear Findings

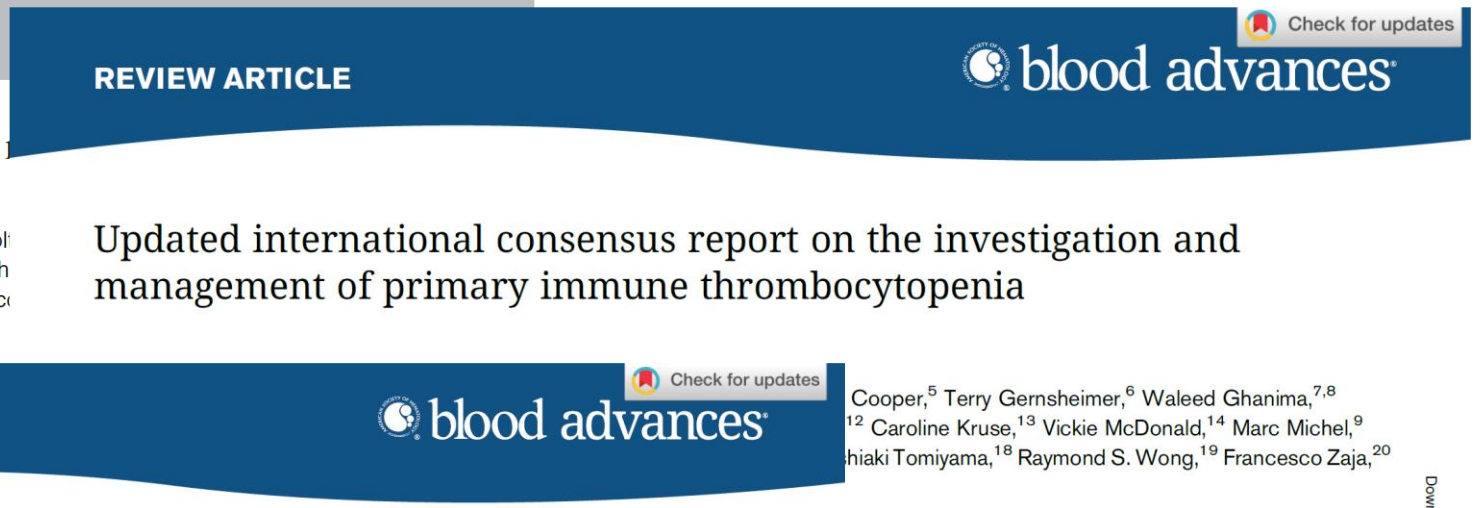


- Thrombocytopenia
- Normal platelet appearance with variable to large size
- **Occasional** large platelets
- Normal WBC number, differentiation, morphology
- Normal RBC number and morphology
  - –Unless active bleeding
- No evidence of hemolysis

Diagnostic Dilemmas in ITP

- Why does ITP develop in some people and not others exposed to same trigger?
  - Hypothesis: Genetic predisposition + trigger
  - How can individual disease biology be identified and targeted?
- Why do patients with similar platelet counts have markedly different clinical phenotypes?
- Why do some patients develop chronic ITP?
  - Can we predict who?

ITP: Guidelines



Neunert C, Terrell DR, et al. Am
Provan D, Arnold DM, et al. Up bocytopenia. Blood Adv. 2019
Provan D, Stasi R, et al. International consensus report on the investigation and management of immune thrombocytopenia. Blood. 2010
Neunert D, Lim W, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011.

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Initial Evaluation: International Working Group Recommendations

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.

ITP: Bleeding Events

Incidence by Age

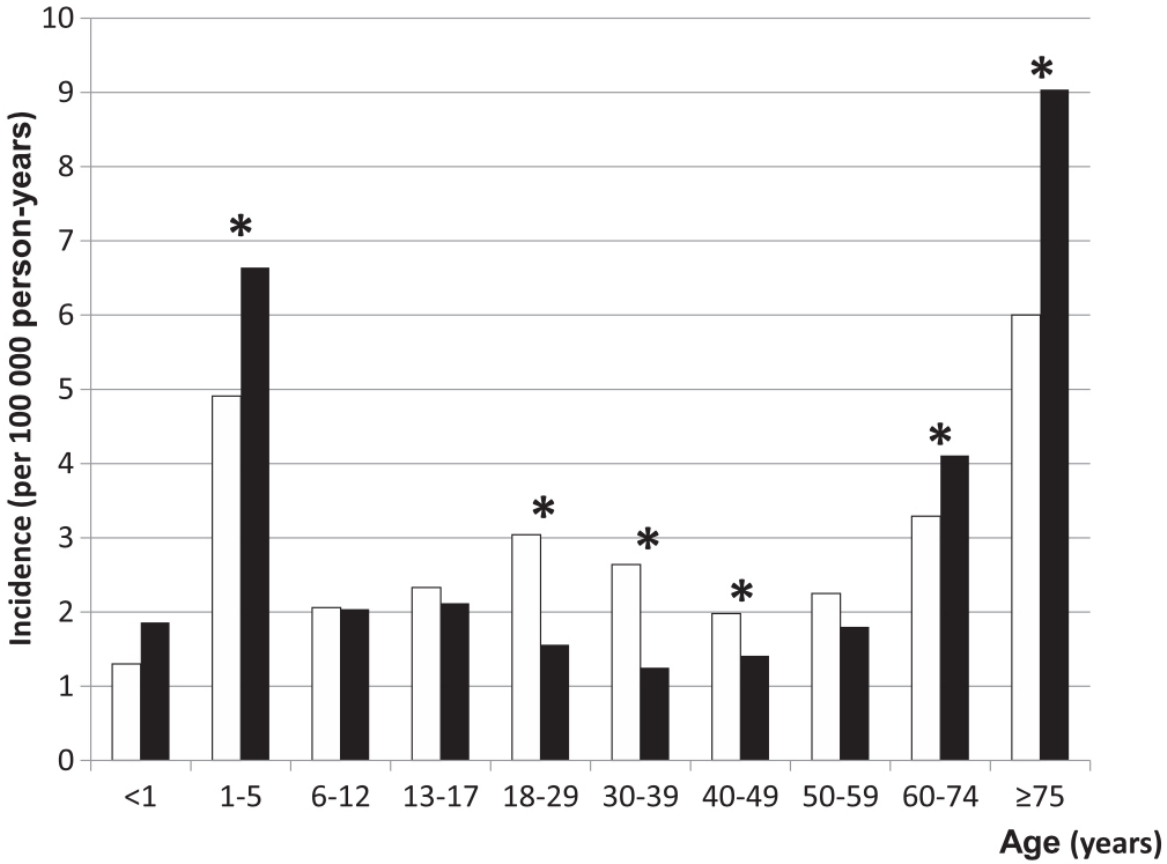

Figure 2. Incidence of ITP in France during the period from mid-2009 to mid-2011 by age and gender. Females, white bars; males, black bars. Stars indicate statistically significant differences among males and females (α = 5%).

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

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Pediatric ITP	Adult ITP
Remission	
>60% by 1 year	20-45% by 6 months
Serious bleeding events	
20% overall <0.5% intracranial hemorrhage	9.5% overall 1.4% intracranial hemorrhage
Comorbidities	
Few	Variable

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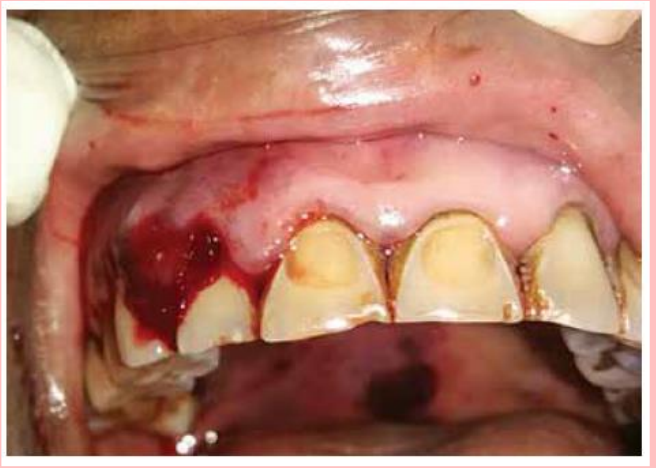
Intracranial Hemorrhage in ITP

- Estimated incidence 0.19-0.78% in children
- Estimated incidence 1.5-1.8% in adults
- In cohort study (adult)/survey report (peds):
  - 90% of patients had platelets <20K, 75% <10K
  - Most present in first 3 months, had prior treatment
- Head trauma (33%) and hematuria (22.5%) most common associated conditions
  - Wet bleeding also frequently identified in ICH cohort
- High mortality and high risk of neurologic sequelae in survivors

Psaila B et al. Blood. 2009; 114:4777-4783.
Melboucy-Belkhir et al. Am J Hematol. 2016;91:E499-501.

Case 1

- 42 year old female presenting to ED with gingival bleeding
  Also complaining of headache 6/10 x 1 day
- PMH significant for ITP diagnosed ~9 months prior, hypertension, hyperlipidemia, arthritis
- Meds: lisinopril, prednisone
- Vitals: Temp 98.8F, HR 91, RR 16, BP 210/87, BMI 35
- Exam: extensive bruising on extremities,
  petechiae over trunk/extremities,
  active gingival oozing, oral purpura



Sivakumar Y, et al. Idiopathic thrombocytopenia purpura – A case report and update of recent treatment modalities. J Sci Dentistry. 2017.

Case 1

Laboratory Evaluation:

CBC:

WBC/diff – normal

Hgb: 9.3 gm/dL

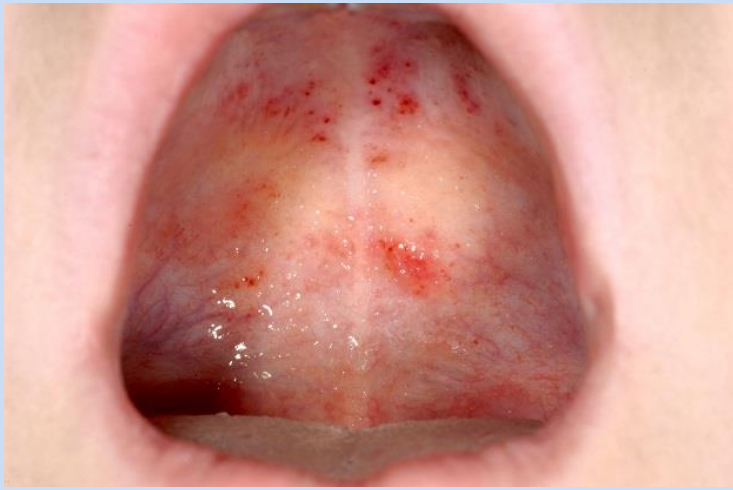
MCV: 71 fL

Plts: $19x10^3/L$

What should you do?

Case 2

- 4 year old male presenting to ED with a 2 week history of progressive bruising, petechiae, and oral petechiae
- No significant PMH
- Meds: none
- Vitals: Temp 98.8F, HR 91, RR 16, BP 90/68, BMI 23
- Exam: extensive bruising on extremities, petechiae over trunk/extremities, few oral petechiae



https://lymphoma-action.org.uk/about-lymphoma-side-effects-treatment/thrombocytopenia-low-platelets

Case 2

Laboratory Evaluation:

CBC:

WBC/diff – normal

Hgb: 11.7 gm/dL

MCV: 78 fL

Plts: $1x10^3/L$

What should you do?

ITP: Management

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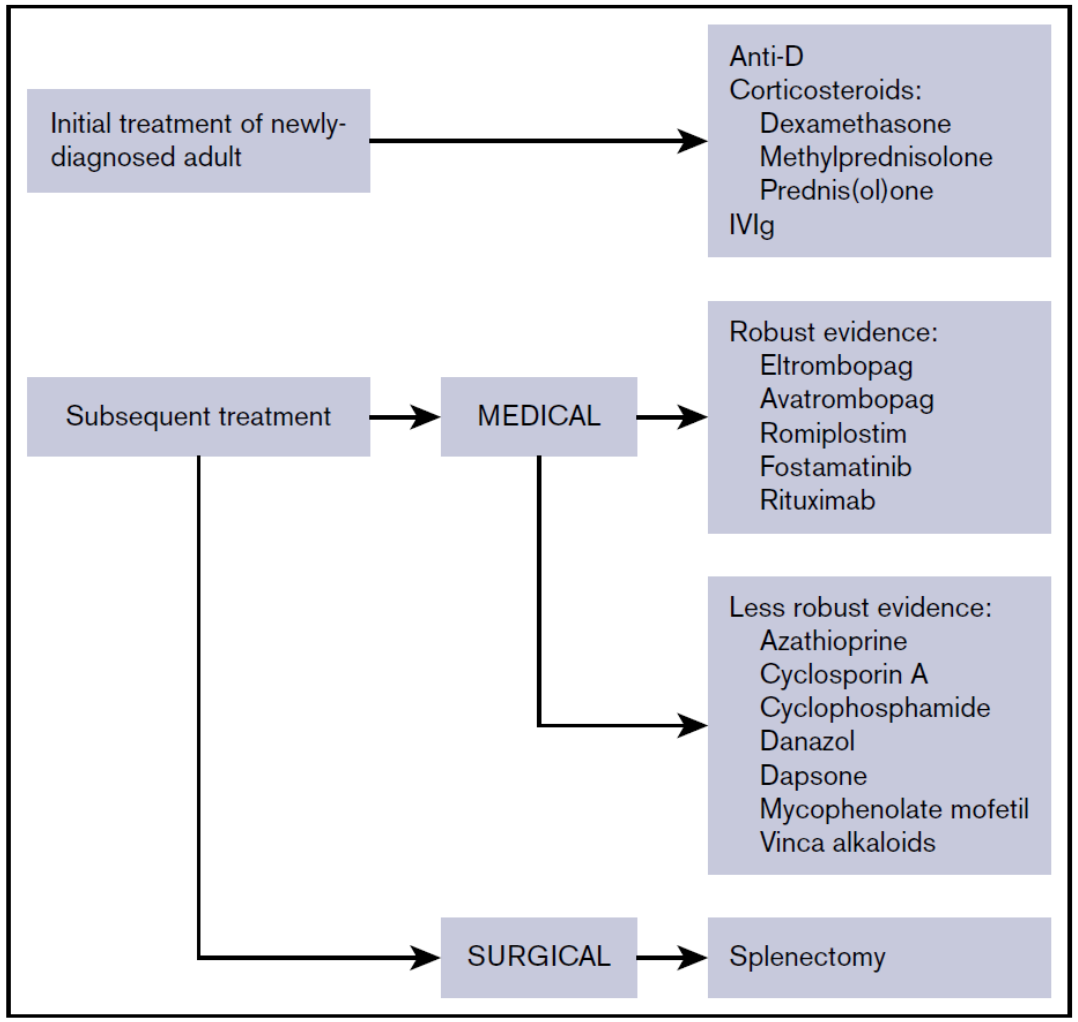
General Guidelines for Thrombocytopenia

- Avoid non-steroidal anti-inflammatory drugs (NSAIDs)
- Avoid activities with high risk of bodily injury
- Cutaneous bleeding: generally not dangerous nor indication for treatment
- Uncontrolled bleeding: generally need for urgent medical attention
- Surgeries and invasive procedures: needs hematologic clearance

Treatment for adult ITP: International Working Group Recommendations



Therapeutic Dilemmas in ITP

- Response to therapy highly variable and unpredictable
- Therapies can have significant side effects
- 15-20% of patients refractory to first line treatments
- Choice of therapy largely guesswork
- Improved understanding of individual patient disease biology could lead to targeted therapy

Tao L et al. J Hematol Oncol.2017;10:46.

To Treat or Not to Treat…
Newly Diagnosed Pediatric ITP

- ASH 2019 Guidelines recommend against basing treatment decisions on platelet count
- Most children with platelet counts <10K without bleeding can safely be managed with appropriate observation
- Individualize therapeutic decisions
  - Patient age, activity, medical conditions, meds
  - Clinical symptoms
  - Parent/practitioner concern
  - Access to medical care
- Goal of treatment is cessation of bleeding/risk/improvement in symptoms

Neunert C et al. Blood. 2011;117:4190-4207

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blood®

Plenary Paper

CLINICAL TRIALS AND OBSERVATIONS

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

Katja M. J. Heitink-Pollé,[1,2] Cuno S. P. M. Uiterwaal,[3] Leendert Porcelijn,[4] Rienk Y. J. Tamminga,[5] Frans J. Smiers,[6] Nicole L. van Woerden,[7] Judit Wesseling,[8] Gestur Vidarsson,[9,10] Annemieke G. Laarhoven,[9,10] Masja de Haas,[4,9-11,*] and Marrie C. A. Bruin,[1,12,*] for the TIKI Investigators

Blood. 2018;132:883-891

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ASH 2019 Guidelines for Adult ITP

- For NEWLY diagnosed ITP:
  - $<20 \times 10^9/L$: suggest admission to hospital for management
    - Suggest treatment with ≤6 weeks of oral steroid
  - $\geq 30 \times 10^9/L$: suggest outpatient management with close follow up
- For established ITP diagnosis:
  - $<20 \times 10^9/L$: with no or minor bleeding, suggest outpatient management
- Individualize therapeutic decisions
  - Patient age, activity, medical conditions, meds
  - Clinical symptoms
  - Patient/practitioner concern
  - Access to medical care

Neunert C et al. Blood. 2019;3:3829-3866

Treatment Options

Front-Line

- Treatment of acute bleeding/bleeding risk
- Goal is rapid improvement
- Effects generally not durable
- Options
  - IVIG
  - WinRho (RhIg)
  - Corticosteroids

Second-Line

- Goal is durable response
- Effects take time to achieve
- Not indicated for emergent bleeding
- Options
  - Rituximab
  - TPO-RA
  - Oral Immunosuppressives
  - Splenectomy

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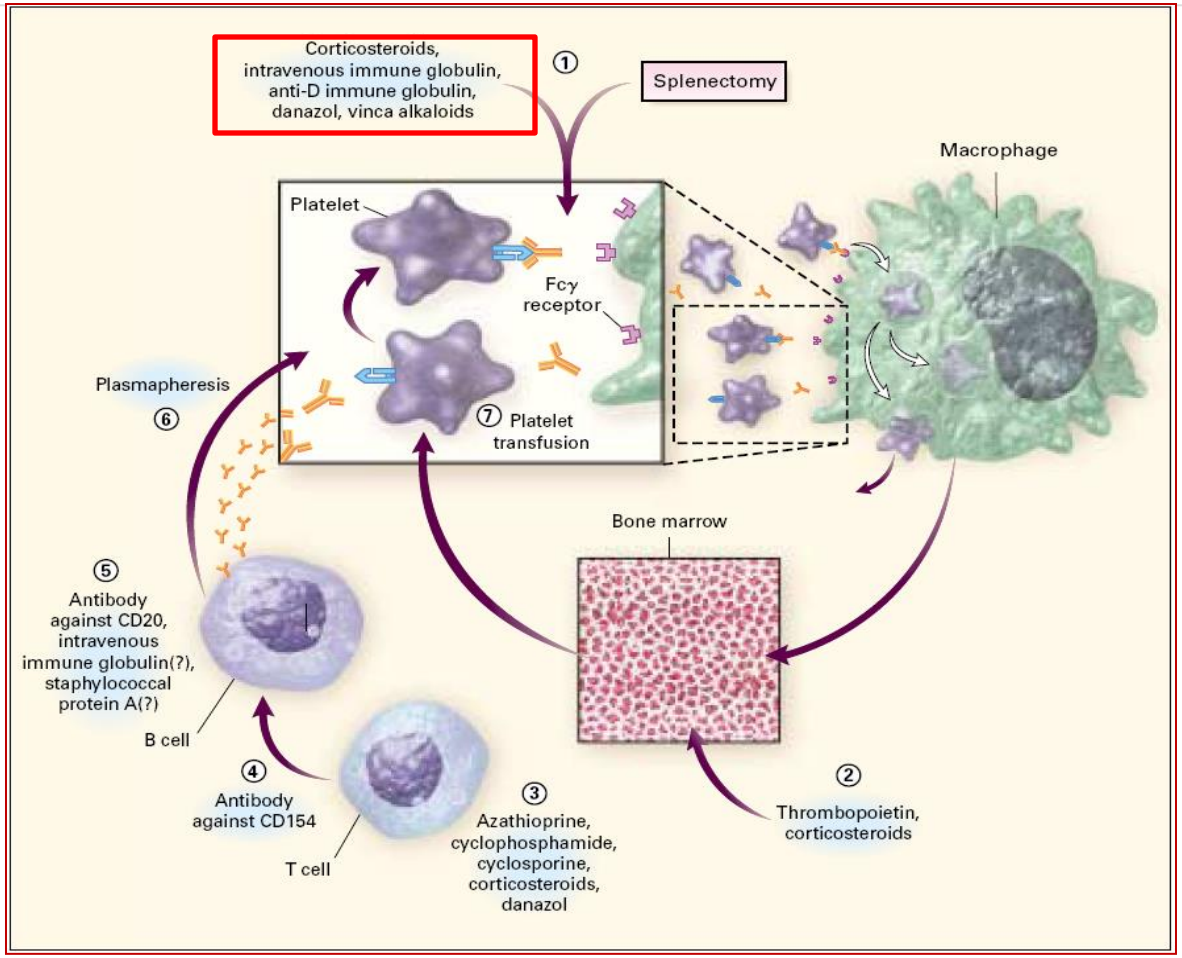
What Treatment?



Cines DB, Blanchette VS. NEJM 2002;346:995-1008.

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Front-Line Therapies

IVIG: pooled human plasma (~20,000 donors/dose)

- IV administration over several hours, effects up to 4 weeks
- Adverse effects include **headache**, nausea, vomiting, fever, chills
- $35,000 per dose for 70 kg person
- **Black box warnings: thrombosis, renal failure**

Anti-D made from pooled plasma (~500 donors/dose)

- IV administration over <1 hour, effects up to 5 weeks
- **Black box warning: intravascular hemolysis, renal failure**

Steroids: too numerous to list, short duration of effect

- Cheap

What About Platelet Transfusion?

- Generally contraindicated in patients with ITP
- “Adding fuel to the fire”
- 10-60 minutes post transfusion, platelet count is likely unchanged
- Transfusion has a role in the management of life-threatening bleeding
- May have some benefit in certain types of ITP

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- Not indicated for emergent bleeding
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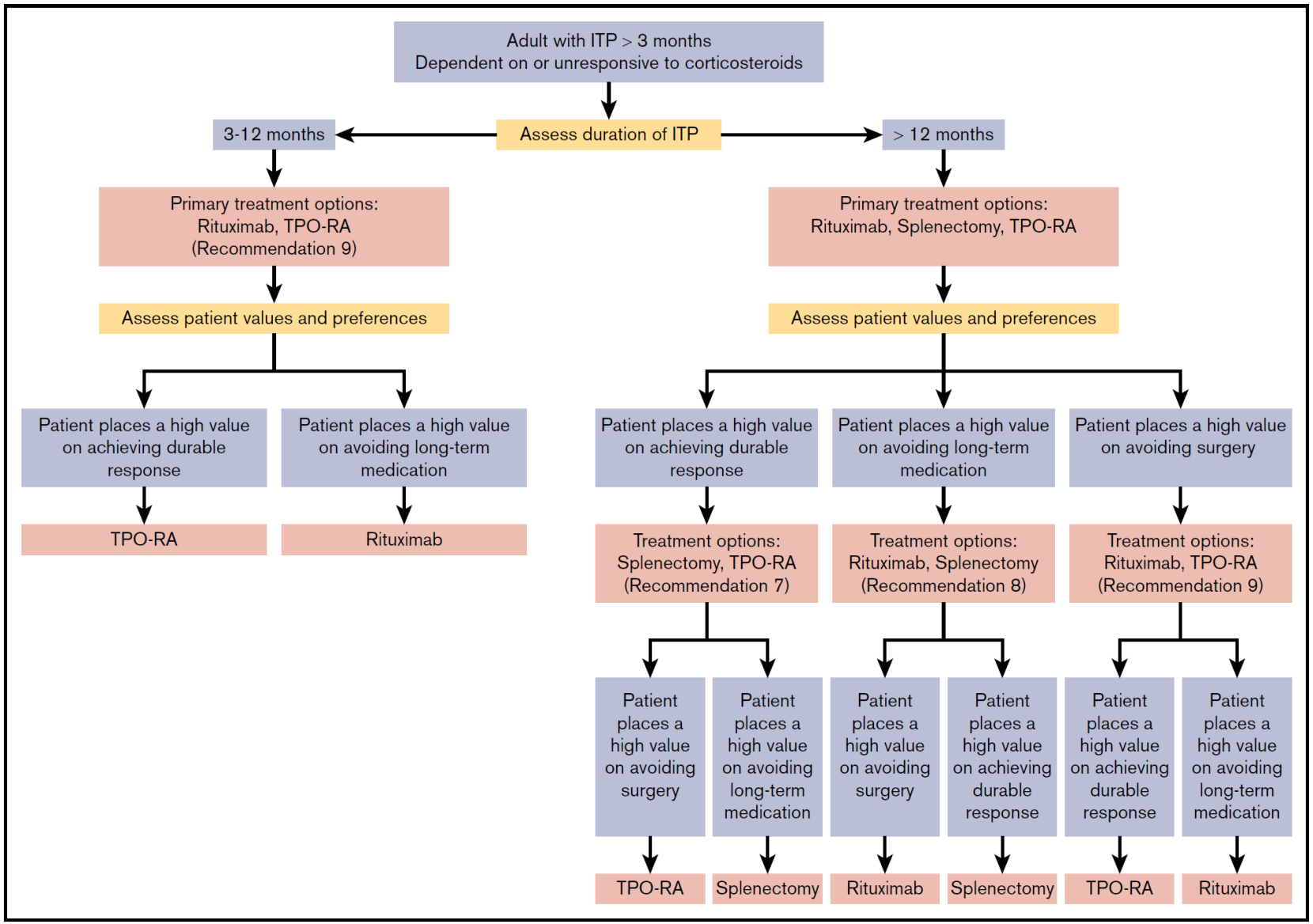
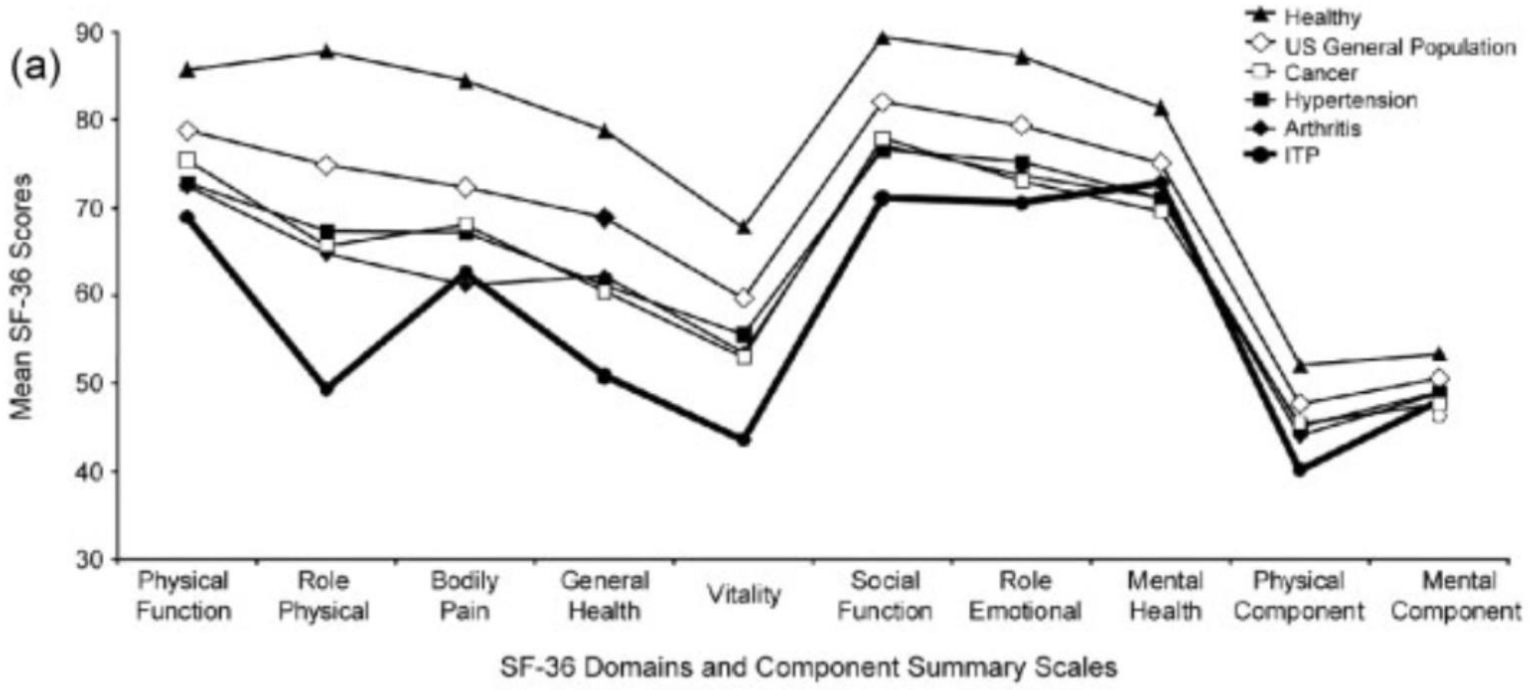
  - Splenectomy
  - Rituximab
  - Oral Immunosuppressives
  - TPO-RA

Second Line Therapy in Adult ITP



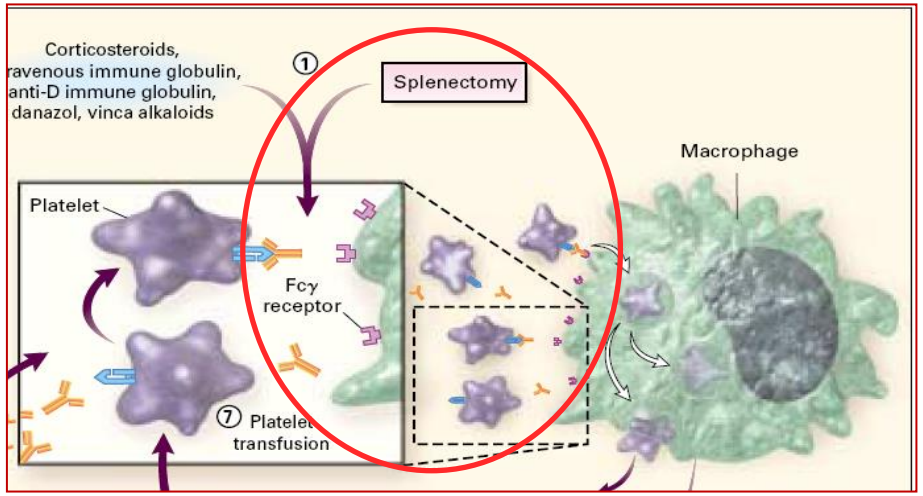
Quality of Life in Adult ITP



McMillan R et al. Am J Hematol. 2008; 83:150-154.

Splenectomy

- Splenectomy (70-80% response rate)
  - Decreased platelet clearance
  - Major concern is post-splenectomy sepsis
    - Delay in very young children
    - Vaccinate for encapsulated organisms if possible
    - PCN prophylaxis
- Increased thrombosis risk
- Those who fail may become more responsive to therapy



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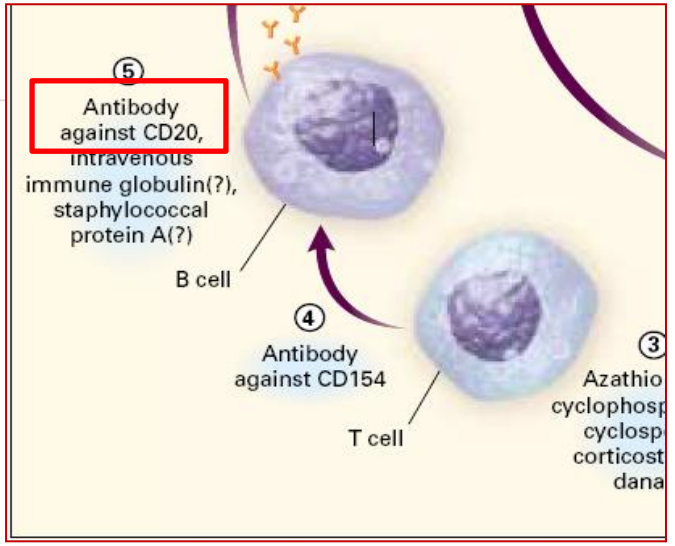
Rituximab



- Anti-CD20 monoclonal antibody
  - Decreased antiplatelet antibody production
  - Decreased antigen presentation to T cells
  - Elimination of autoreactive memory B cells
- Variable dosing regimen
- Very expensive ($3500/100 mg vial, $85,000 for four doses for patient with BSA 1.3 m^2)
- Approximately 60% short term response rate in children (<30% hold response >1 year)

Zaja F, et al. Eur J Haematol. 2010; 85: 329-334.
Kalpatthi R, Bussel J. Curr Opin Pediatr. 2008;20:8-16
Cooper N, Bussel JB. Current Rhem Rep. 2010;12:94-100.

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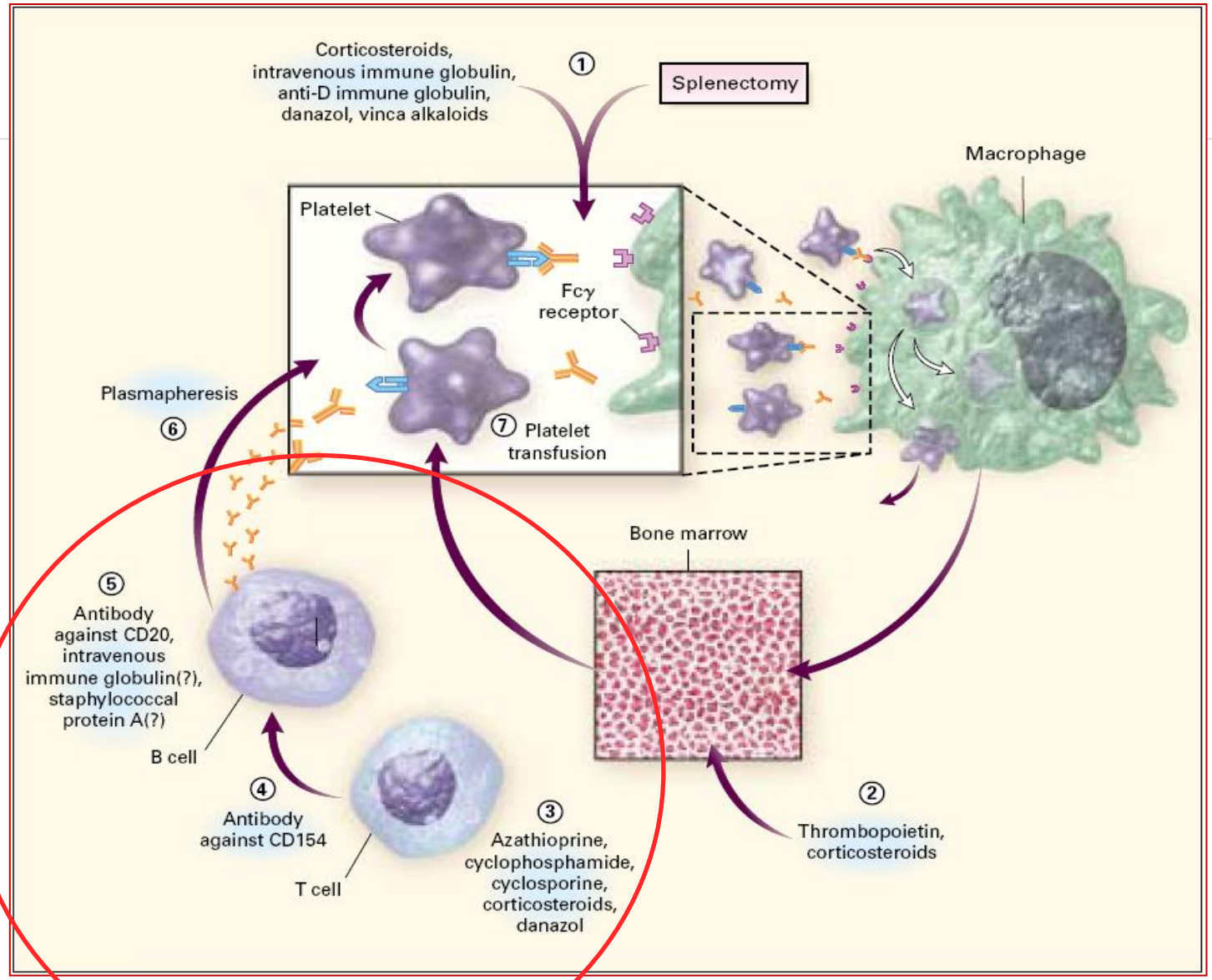
Other Immunosuppresants



Cines DB, Blanchette VS. NEJM 2002;346:995-1008.

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Thrombopoietin (TPO)

- Last major hematopoietic growth factor identified (1994)
- Major physiological regulator of platelet production
- No platelet count “sensor”
  - Produced in liver at constant rate
  - Circulating levels regulated by receptor-mediated clearance by platelets and megakaryocytes
- TPO levels should be inversely proportional to rate of platelet production (not platelet count)

Carver-Moore K et al. Blood. 1996;88:883-888
Bunting S et al. Blood. 1997; 90:3423-3429
Nugent D, et al. BJH. 2009; 146:585-596.

TPO Levels in Thrombocytopenic States

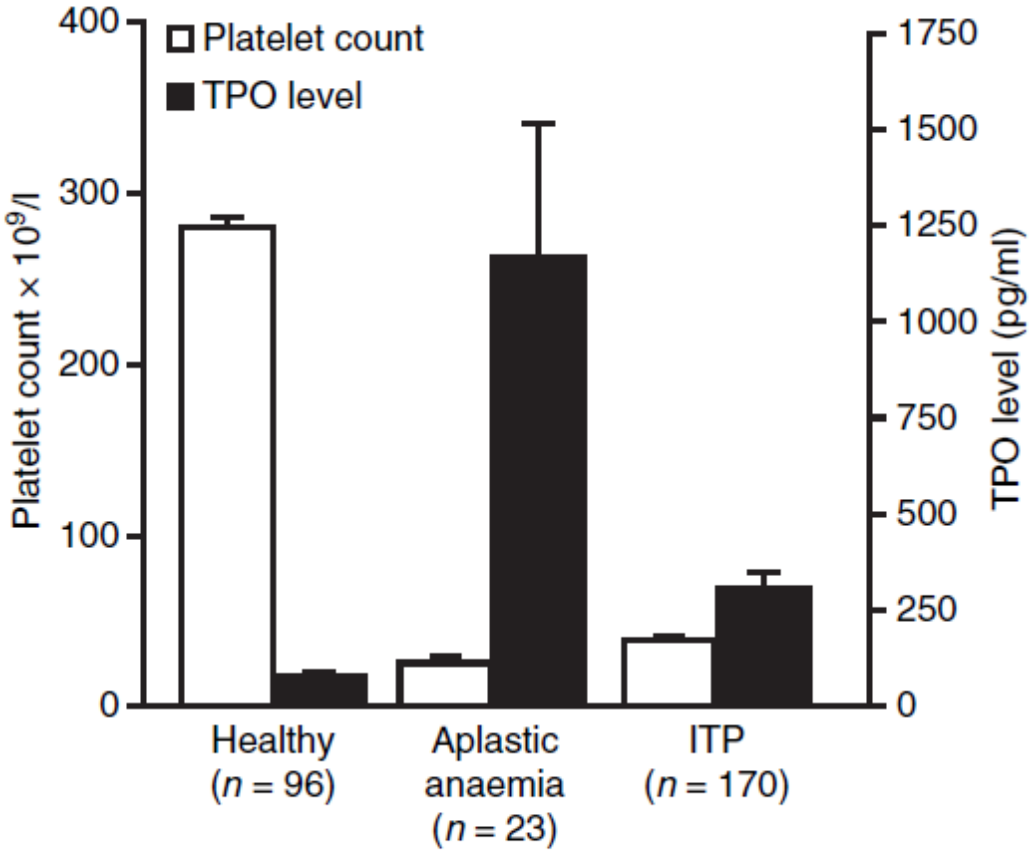

Fig 2. Platelet counts and TPO levels in subjects with ITP, aplastic anaemia, and healthy controls. TPO levels are normal in 75% of ITP patients despite lower than normal circulating platelet numbers. Data are from Nichol (1998).

Nugent D, et al. BJH. 2009; 146:585-596.

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Thrombopoietin receptor (TPO-R) Agonists

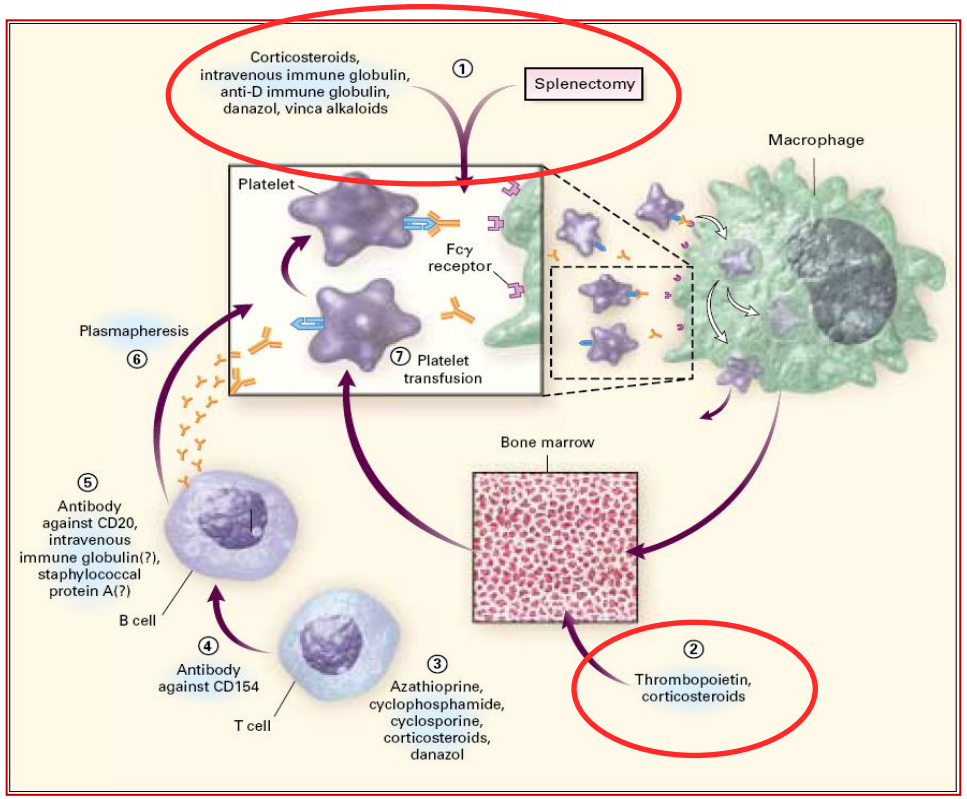
- Romiplostim (Nplate®)
  - Subcutaneous injection weekly
  - FDA approved in adults in 2008, peds 2018
- Eltrombopag (Promacta®)
  - Oral once daily dosing
  - FDA approved in adults in 2008, peds in 2015
- Avatrombopag (Doptelet®)
  - Oral once daily (or less) dosing
  - FDA approved in adults in 2018, currently in pediatric trials

Imbach P, Crowther M. NEJM. 2011.365: 734-741.

Increased Production:
TPO Agonist

Steady State

Decreased Destruction:
Steroids, IVIG, WinRho, Rituximab, Splenectomy, Immunomodulators



Taylor Kim MD

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Other Agents

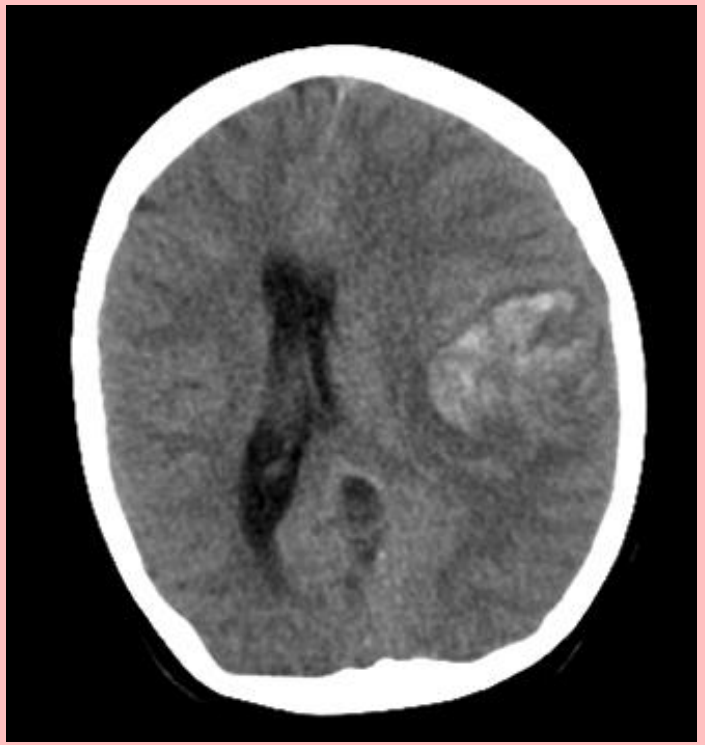
- Fostamatinib (Tavalisse®)
  - Oral dose 1-2 times daily
  - Tyrosine kinase (SYK) inhibitor
  - FDA approved in adults in 2018, limited pediatric investigations
- Pipeline drugs

Podolanczuk A, et al. *Blood.* 2009;113:3154-3160.

Roback T, et al. *Blood Adv*. 2020; 4(17):4136-4146

Case 1

- 42 year old female, HTN, oral bleeding, headache
- Hemoglobin 9.3 gm/dL, platelets 19 x 10^9/L
- Mentions she has been taking ibuprofen for arthritis
- Course: emesis x 2 in ED, lethargic on repeat exam
  - Stat CT head
- Patient with ITP and ICH
  - IV corticosteroids, platelet drip, IVIG
  - Anti-hypertensives
  - Surgery consult for emergent splenectomy
  - Neurosurgery consult
- Iron deficiency anemia diagnosed secondary to heavy menstrual bleeding
- Will need hematology follow up for aggressive management of thrombocytopenia



Case 2

- 4 year old male, new onset isolated thrombocytopenia, no active bleeding, no other complaints
- Plts 1K, mentions just received 4 year old vaccinations

Should you admit?

Recommendation 10a

In children with newly diagnosed ITP and a platelet count of $<20 \times 10^9$/L who have no or mild bleeding (skin manifestations) only, the ASH guideline panel *suggests against* admission to the hospital rather than outpatient treatment (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remark**: For patients with uncertainty about the diagnosis, those with social concerns, those who live far from the hospital, and those for whom follow-up cannot be guaranteed, admission to the hospital may be preferable.

Should you treat?

Recommendation 11

Recommendation 12

Recommendation 13

In children with newly diagnosed ITP who have no or minor bleeding, the ASH guideline panel *recommends* observation rather than anti-D immunoglobulin (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯).

Mantadakis E. J Pediatr. 2010:623-8.

ITP: Take home points

- ITP = Immune Thrombocytopenia
- Important to fully evaluate patients presenting with presumed ITP
- Individual patient factors affect bleeding risk
- Treatment is not based solely on platelet count
- Multiple options for treatment of ITP are available
- Quality of life and patient input is important to consider when choosing treatments

Questions?

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