Updated management of immune thrombocytopenia (ITP)

Mohammadreza Bordbar

Pediatrician Hematologist

SUMS-October 2020

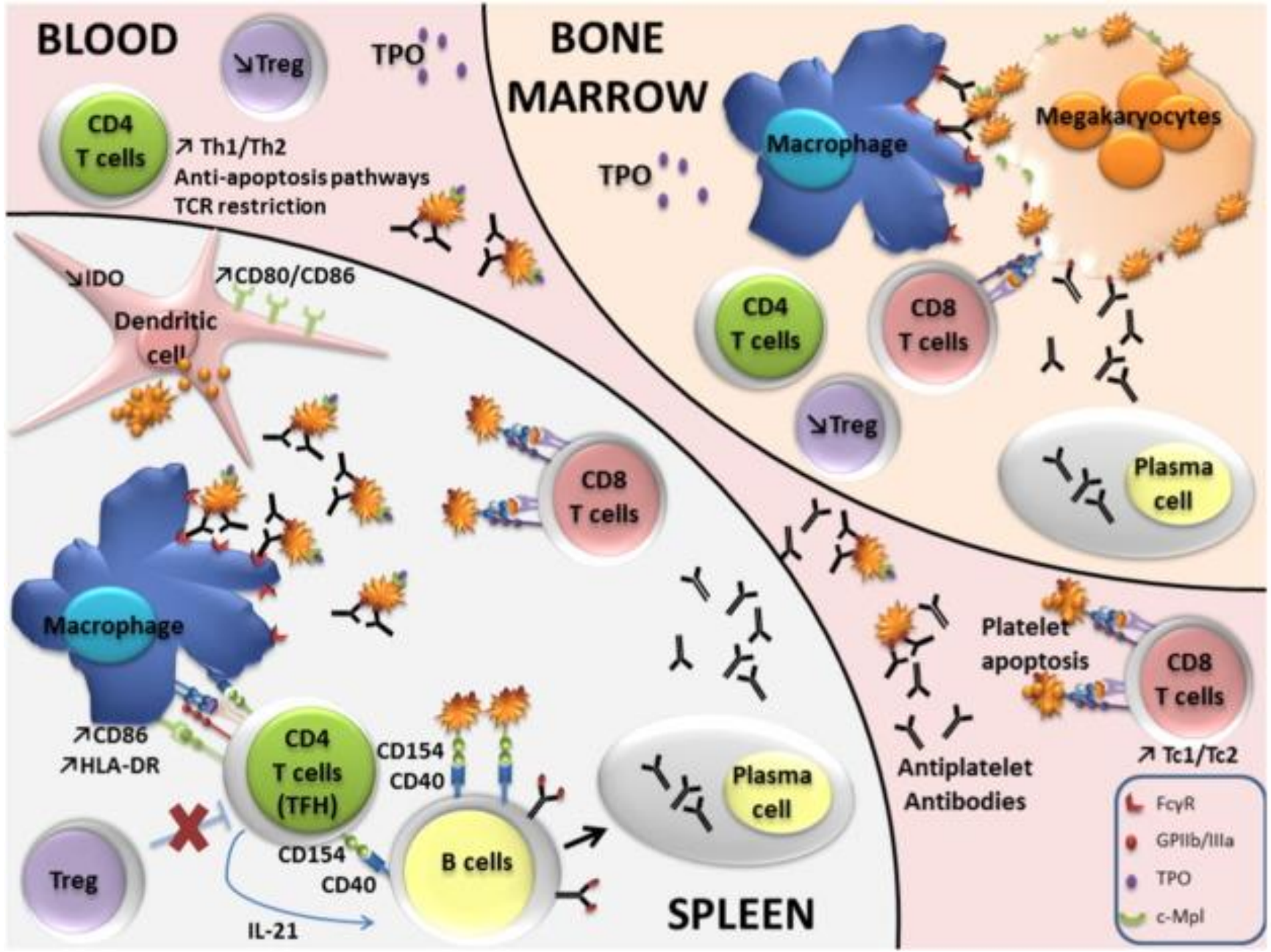
Agenda

- *Introduction*
- *Definitions*
- *Diagnosis*
- *Management (case scenarios)*
- *First-line therapies*
- *Second-line therapies*
- *Family education*

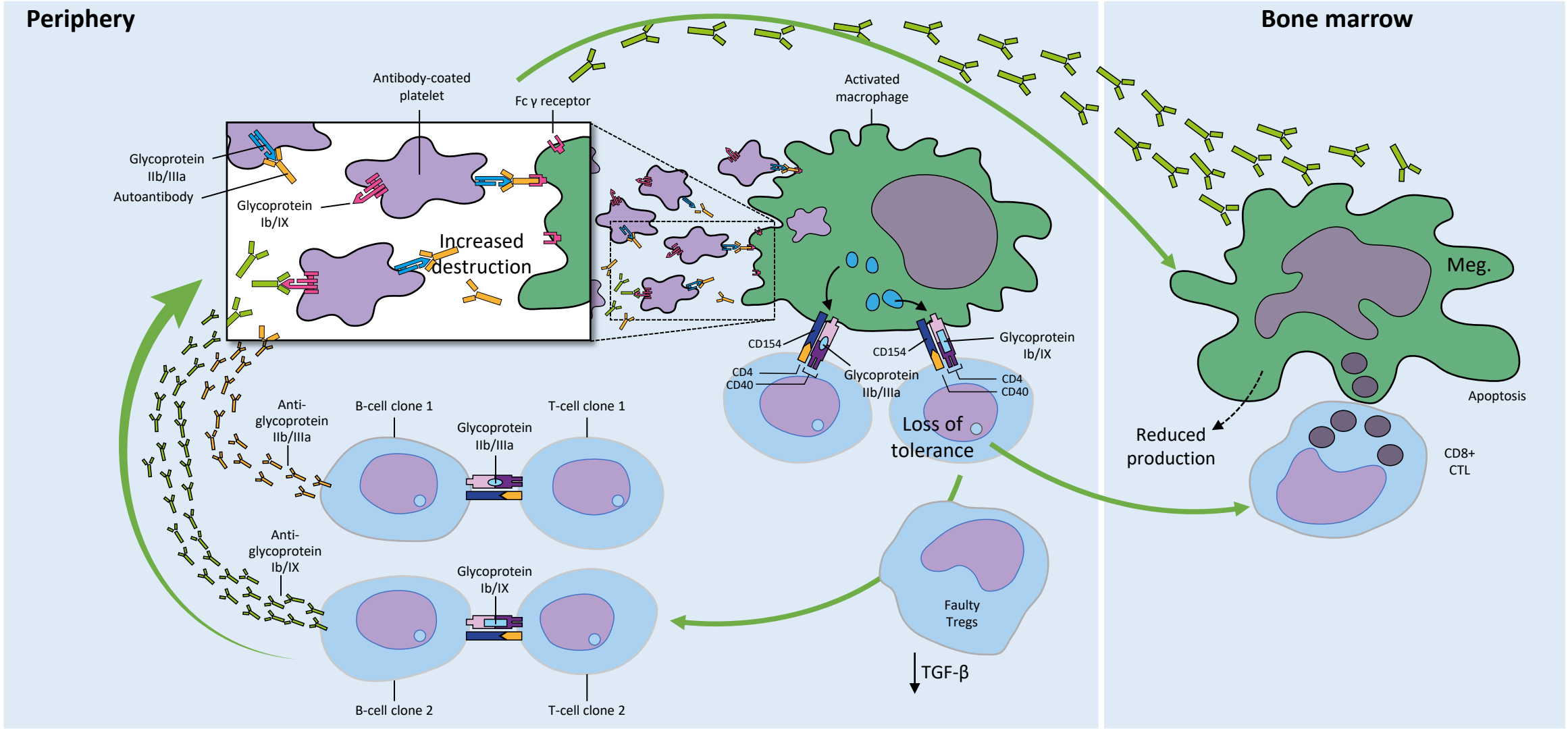
Introduction

- ***Immune thrombocytopenia*** *not "idiopathic thrombocytopenic purpura"*
- *Acquired autoimmune disorder*
- *Platelet destruction and impaired production*
- *Incidence of 2-5/100,000*
- *Primary or secondary*
- *A diagnosis of exclusion of other causes of thrombocytopenia*
- *A platelet count less than* 100×10^9 */L*

1. Yong M, et al. Br J Haematol.2010;149(6):855-864.
2. Terrell DR,et.al. Am J Hematol. 2010;85(3):174-180.
3. Michel M. Seminars in Hematology. January 2013;50(1):, S50–S54


BLOOD
↘Treg
TPO
CD4
T cells
↗ Th1/Th2
Anti-apoptosis pathways
TCR restriction
↘IDO
↗CD80/CD86
Dendritic
cell
CD8
T cells
Macrophage
↗CD86
↗HLA-DR
CD4
T cells
(TFH)
CD154
CD40
CD154
CD40
Treg
B cells
IL-21
Plasma
cell
SPLEEN
BONE
MARROW
TPO
Macrophage
Megakaryocytes
CD4
T cells
CD8
T cells
↘Treg
Plasma
cell
Platelet
apoptosis
CD8
T cells
↗ Tc1/Tc2
Antiplatelet
Antibodies
FcγR
GPIIb/IIIa
TPO
c-Mpl

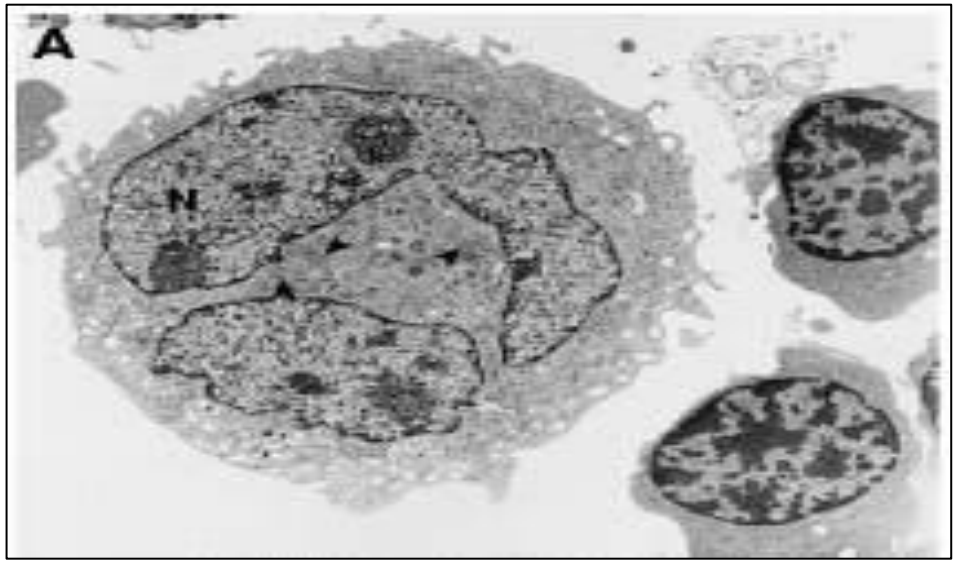
Modern immunopathogenesis of ITP



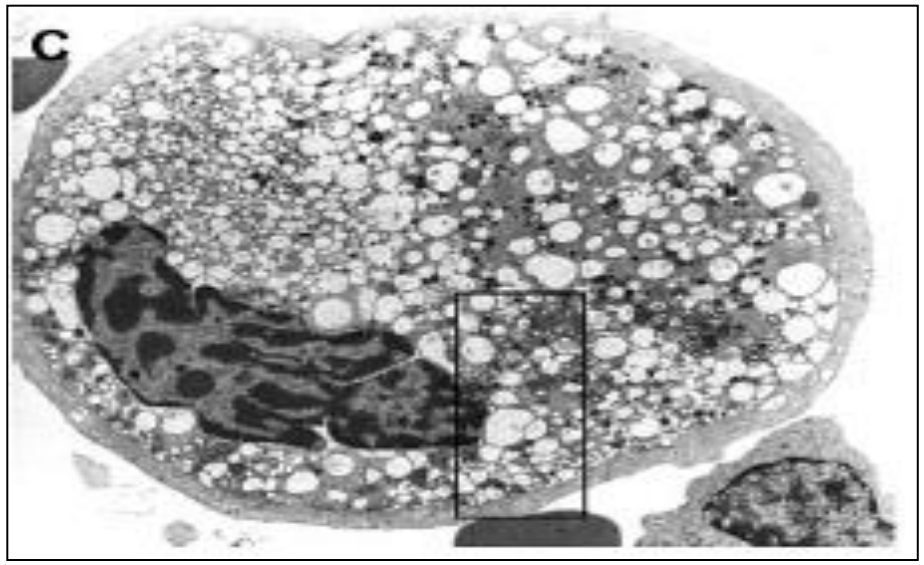
Modified from: Cines DB & Blanchette VS. *N Eng J Med* 2002;346:995–1008

ITP autoantibodies stimulate apoptosis in megakaryocytes

Ultrastructure of normal and ITP megakaryocytes



Normal megakaryocyte

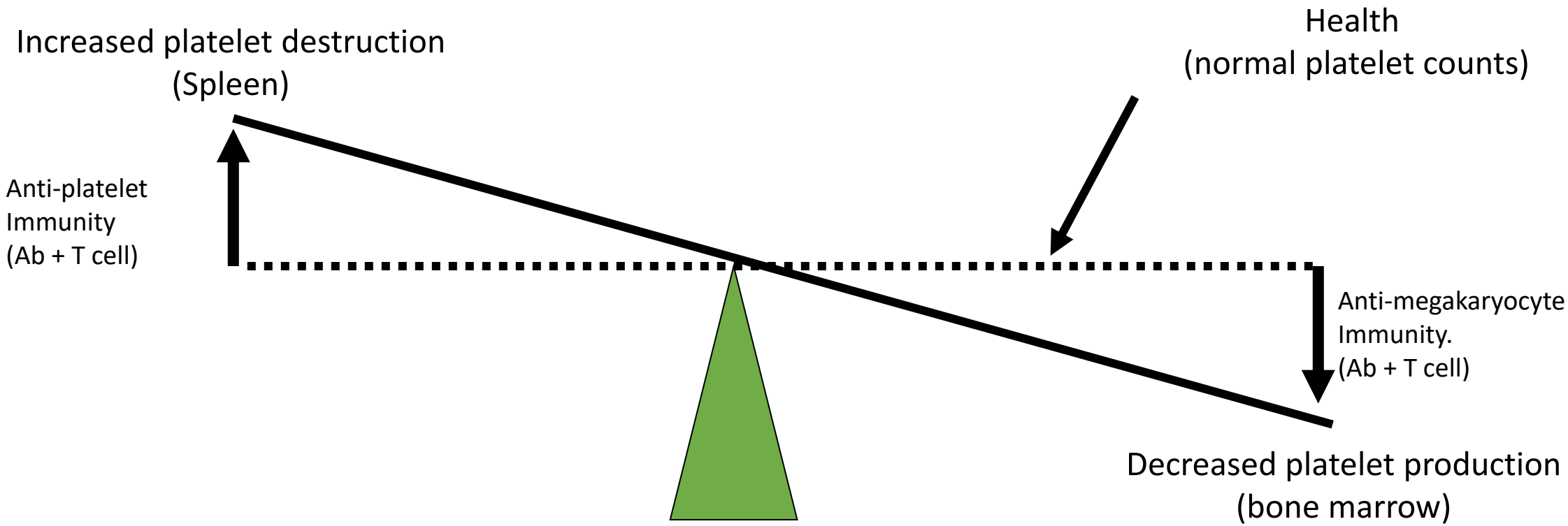


ITP megakaryocyte

Autoantibodies inhibit megakaryocyte growth *in vitro* and promote apoptosis resulting in impaired thrombopoiesis

Houwerzijl EJ *et al. Blood* 2004;103:500–506

Today: ITP is due to two reasons



ITP effector immunity is comprised of antibodies and T cells

Semple JW & Provan D. *Curr Opin Hematol* 2012;19:357–362

- *Sudden-onset thrombocytopenia/bleeding in an otherwise well child*
- *Typically affects children 2-6 years*
- *Age-related spontaneous remission*
- *74% in children<1 yr; 67% in 1-6 yr; 62% in 10-20 yr*
- *Unpredictable bleeding*
- *ICH in 0.1-0.4% of children (higher in adults, 1.4%)*
- *Significant impact on health-related quality of life (HRQoL)*

1. Bennett CM, et al. Pediatr Blood Cancer. 2018;65(1).
2. Neunert C, et al. J Thromb Haemost. 2015;13(3):457-464

Causes of secondary ITP in children

**Antiphospholipid syndrome*

**IgA deficiency*

**Wiskott-Aldrich syndrome*

**Lymphoproliferative disorder*

**Vaccination side effect*

**Rheumatoid arthritis*

**Autoimmune thrombocytopenia (e.g. Evans syndrome)*

**Common variable immune*

**Drug side effect*

**Bone marrow transplantation side effect*

**Systemic lupus erythematosus*

**Hypersplenism*

**Infection (eg. CMV, H. pylori, HBV, HCV, HIV, VZV, parvovirus, etc.)*

Neunert C, et al. Blood 2011;117:4190-207

Table 3. Definition of terms in 2019 ASH guideline on ITP

Terms and definitions
Corticosteroid-dependent: Ongoing need for continuous prednisone >5 mg/d (or corticosteroid equivalent) or frequent courses of corticosteroids to maintain a platelet count ≥30 × 10^9/L and/or to avoid bleeding
Durable response: Platelet count ≥30 × 10^9/L and at least doubling of the baseline count at 6 mo
Early response: Platelet count ≥30 × 10^9/L and at least doubling baseline at 1 wk
Initial response: Platelet count ≥30 × 10^9/L and at least doubling baseline at 1 mo
Major bleeding: (1) WHO grade 3 or 4 bleeding, (2) Buchanan severe grade, (3) Bolton-Maggs and Moon "major bleeding," (4) IBLS grade 2 or higher, or (5) life-threatening or intracerebral hemorrhage bleeding
Minor bleeding: Any bleeding not meeting the criteria for "major bleeding"
Newly diagnosed ITP: ITP duration of <3 mo
Persistent ITP: ITP duration of 3-12 mo
Chronic ITP: ITP duration of >12 mo
Remission: Platelet count >100 × 10^9/L at 12 mo

IBLS, ITP Bleeding Scale; WHO, World Health Organization.

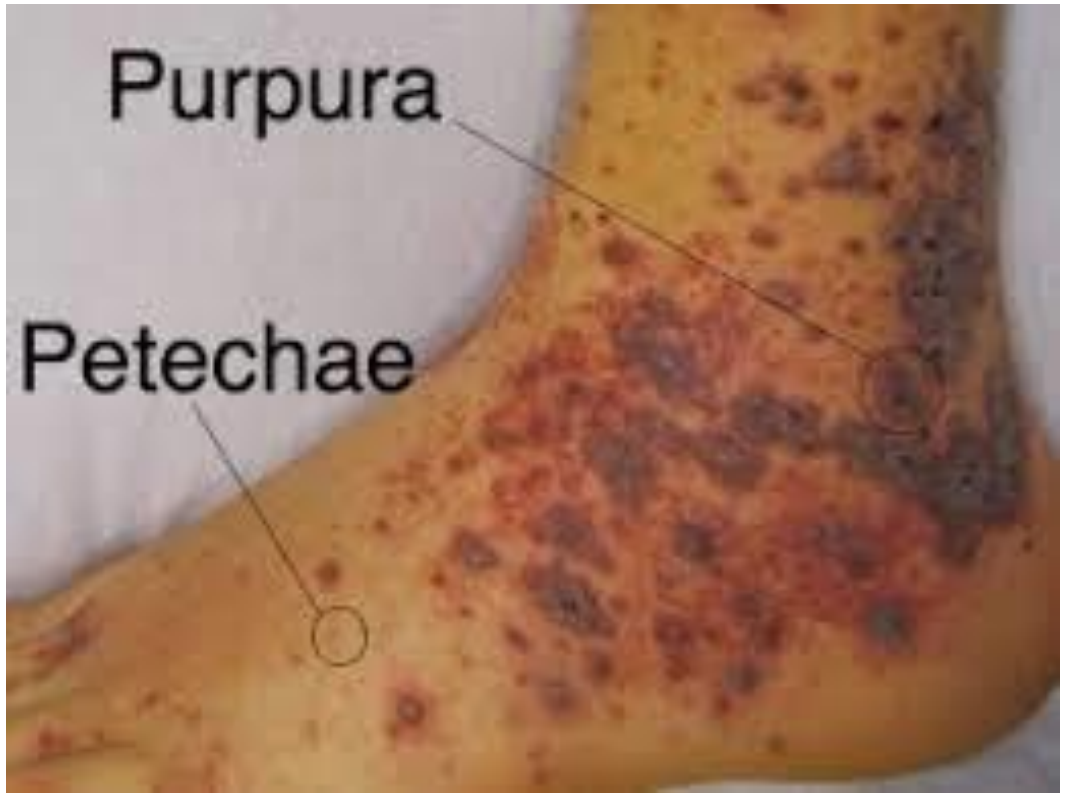
Neunert C, et.al. ASH 2019 guidelines for ITP. Blood advances 2019;3(23):3829-66

- ***Recurrent ITP:*** *return of thrombocytopenia/symptoms after at least 3 months of remission, sustained without treatment.*
- ***Severe ITP:*** *Patients who have 'clinically relevant bleeding', i.e., bleeding symptoms that warrant treatment, not necessarily a low plt count*
- ***Refractory ITP:*** *Child with ITP who has failed first line therapy as well as splenectomy, and continues to experience clinically significant bleeding*

Bansal D, et al. Indian J Pediatr (October 2014) 81(10):1033–1041

Diagnosis:

- *Abrupt onset of skin bleeds in a previously well child*
- *Pallor proportionate to bleeds- observed in 15 % of children, particularly in those with epistaxis, hematuria or GI bleed*
- *Absence of fever, lymphadenopathy, hepatosplenomegaly or bone pains*
- *No diagnostic tests to confirm ITP*


Purpura
Petechae

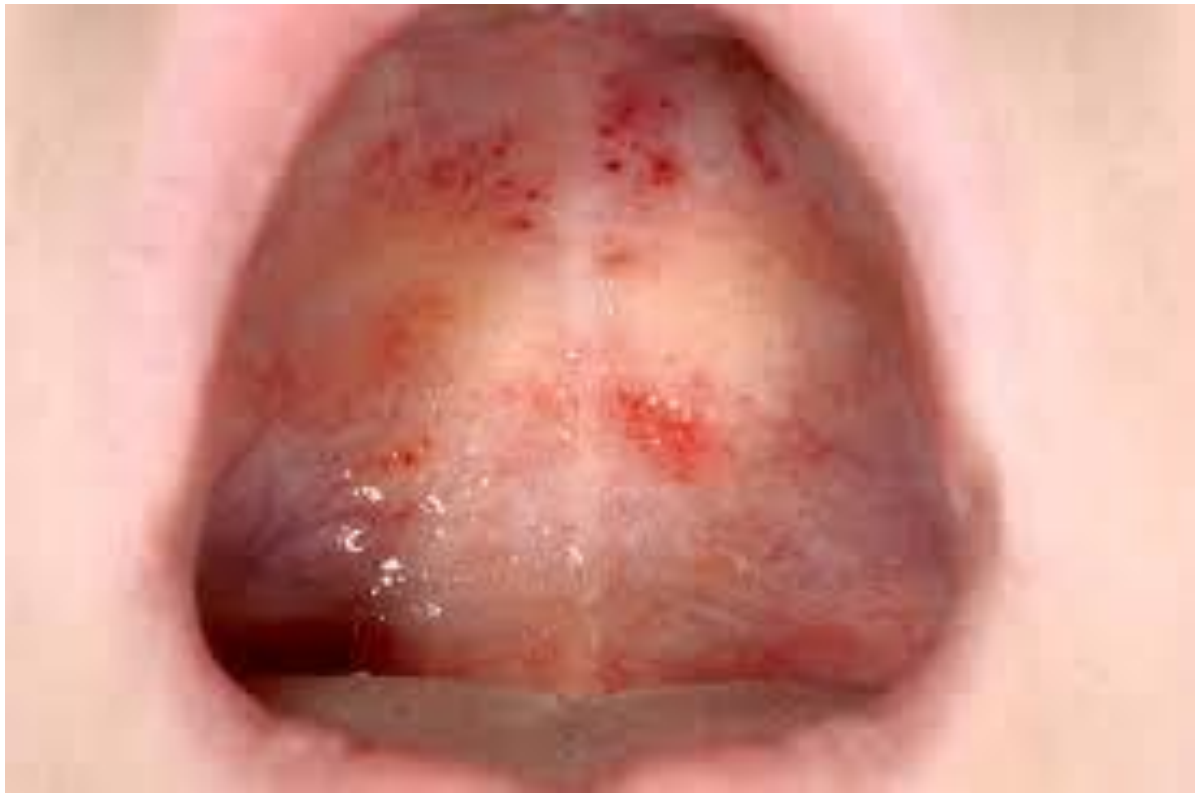


Table 1 Differential diagnosis: ITP, acute leukemia and aplastic anemia

Clinical features	Acute ITP	Acute leukemia	Aplastic anemia
Lymphadenopathy	No[a]	±	No
Hepatosplenomegaly	Spleen tip: 5–10 %	±	No
Bone pains	No	±	No
Anemia	Proportionate to bleeds	Disproportionate to bleeds	Disproportionate to bleeds
Hemogram	Isolated thrombocytopenia, large platelets	High or low TLC, lymphocytosis, atypical cells or blasts	Pancytopenia, lymphocytosis, macrocytosis

[a] Small cervical lymph nodes is a common finding in young children. *TLC* Total leucocyte count

Investigations not necessary in newly-diagnosed ITP

- *BM examination (if the diagnosis is certain with HX, PE, and PBS)*
- *Viral markers (HIV, Hepatitis B or C, TORCH study)*
- *ANA*
- *Immunoglobulin levels*
- *H.pylori test*

Bansal D, et al. Indian J Pediatr (October 2014) 81(10):1033–1041
Neunert C, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia.Blood 2011;117:4190-207

Management of newly-diagnosed ITP

- *Majority of patients will not have life-threatening bleeds*
- *Disease has a self-limiting nature*
- *Therapy does not modify the disease course*
- *No evidence that medical therapy reduces the incidence of ICH*

Case 1:

- *A 15-mo-old boy is brought with complaints of skin petechiae for 2 d. He had received MMR vaccine 2 wk earlier. He is active and playful. There is no pallor, lymphadenopathy or organomegaly. Platelet count: 8×10^{9}/L, normal Hb, white and differential cell count. Peripheral smear is normal except for occasional large platelets. He is diagnosed as 'newly diagnosed ITP' by the pediatrician.*

- ***Q1: Should the patient be admitted to the hospital?***

- *The ASH guideline panel suggests **against admission** to the hospital rather than outpatient treatment*
- *The referring physician should ensure that the patient has follow-up with a hematologist within 24 to 72 hours of diagnosis*
- ***Admission to the hospital may be preferable if:***

  - patients with uncertainty about the diagnosis

  - those with social concerns

  - those who live far from the hospital

  -those for whom follow-up cannot be guaranteed

Neunert C, et.al. ASH 2019 guidelines for ITP. Blood advances 2019;3(23):3829-66

- ***Q2: How to treat the child?***

  a) Corticosteroid 4mg/kg/d for 1 wk

  b) IVIG 1g/kg single dose

  c) Anti-D 75 mcg/kg IV infusion

  d) Observe the child

- *In children with newly diagnosed ITP who have **no or minor bleeding**, the ASH guideline panel suggests **observation** rather than corticosteroids, IVIG or Anti-D immunoglobulin*
- ***Treatment may be appropriate if:***
- *a) Follow up cannot be assured*
- *b) Child stays at a remote place*
- *c) Concerns regarding high activity level*
- *d)Upcoming invasive procedure with risk of bleeding.*

Neunert C, et.al. ASH 2019 guidelines for ITP. Blood advances 2019;3(23):3829-66
Bansal D, et al. Indian J Pediatr (October 2014) 81(10):1033–1041

First-line therapies

- ***IVIg and anti-D:***
- *blocks FC receptors of macrophages in RES*
- *Slow the clearance of antibody-coated platelets*
- ***Corticosteroid:***
- *a) inhibition of phagocytosis and antibody synthesis*
- *b) improved platelet production*
- *c) increased microvascular stability*

Treatment of children with non–life-threatening bleeding and/or diminished health-related quality of life (HRQoL)

- *In children with newly diagnosed ITP who have **non–life-threatening mucosal bleeding and/or diminished HRQoL**, the ASH guideline panel suggests **corticosteroids** rather than anti-D immunoglobulin or IVIG*
- *the ASH guideline panel suggests either anti-D immunoglobulin or IVIG*
- ***Anti-D** should be reserved for patients who are[1]:*
  - *-Rh-positive*
  - *-DCT negative*
  - *-not splenectomized*

1. Jang JH, et al. Management of immune thrombocytopenia: Korean experts recommendation in 2017. Blood Res 2017;52:254-63

Corticosteroid duration and type

- *the ASH guideline panel suggests **prednisone (2-4 mg/kg per day; maximum, 120 mg daily, for 5-7 days)** rather than dexamethasone (0.6 mg/kg per day; maximum, 40 mg per day for 4 days)*
- *The ASH guideline panel recommends against courses of corticosteroids longer than 7 days rather than **courses 7 days or shorter***

Table 2 First-line drugs for treatment of ITP [4, 9]

	Intravenous immunoglobulin	Anti-D	Corticosteroids[a]
Dose	1. Traditional dose: 2 g/kg divided over 2–5 d 2. Low dose: 0.8–1.0 g/kg single dose	50–75 μg/kg short i.v infusion	**Oral prednisolone** 1. Traditional regimen: 2 mg/kg/d in 3 divided doses (max: 60–80 mg/d) for~21 d 2. 4 mg/kg/d×7 d; tapered and stopped by day 21 3. 2 mg/kg/d×14 d; tapered and stopped by day 21 4. 4 mg/kg/d in 3–4 divided doses for 4 d with no tapering (max: 180 mg/d) **Methyl prednisolone** • 30 mg/kg/d (max : 1 g/d) IV or PO for 3 d
Common adverse effects	Fever, flu-like symptoms, headache[$], mild hemolytic anemia and neutropenia	Fever, chills[b], nausea and vomiting, fall in hemoglobin[c]	Hyperglycemia, gastritis, hypertension, behavioral changes, fluid retention, weight gain
Rare adverse events	Aseptic meningitis (10 %), anaphylaxis, renal failure, risk of viral transmission	Massive IV hemolysis, secondary renal failure	
Advantages	Rapid increase in platelet counts	Less expensive than IVIg, shorter infusion	Not a blood product, low cost
Disadvantages	Long duration of infusion, cost, hospitalization, a blood product	Cannot be used in Rh negative or splenectomized individuals	Bone marrow examination suggested prior to steroids (not mandatory)
Efficacy (%)	70–80	70–80	60–70
Approximate cost of therapy for a 15 kg child	0.8 g/kg: Rs. 17,250 to 62,500 (5 g vial: Rs. 5750 to 25,000)	Rs. 15,000 (300 μg vial: Rs. 4990)	Oral prednisolone: Rs. 200 Methyl prednisolone: Rs. 2000

[a] Irrespective of platelet count, oral steroids should not be continued for >2–3 wk, even at low doses—to avoid toxic effects. [$] May result in suspicion of intracranial bleed and need for CT head to rule it out

[b] Infusion related side effects can be ameliorated with acetaminophen/ steroid premedication

[c] Obligatory hemolysis is inevitable with an average decline in Hb of 0.5–1 g/dL; most cases of hemolysis do not require medical intervention

Bansal D, et al. Indian J Pediatr (October 2014) 81(10):1033–1041

Q3. Can live vaccines can be administered in the context of ITP?

- *In a child who has developed ITP following measles or MMR vaccination, ASH guidelines advise for measuring antibody titers and withholding further dose if titers are achieved.*
- *If titers are low, further dose of MMR vaccine should be administered at appropriate time.*
- *live virus vaccination (including MMR) is not contraindicated in children with non-vaccine related ITP.*

Neunert C, et al. Blood 2011;117:4190-207

Q4. How to administer vaccines (e.g. DPT) to a thrombocytopenic child?

- *Vaccines can be safely administered with needles less than 23G, followed by application of sustained and firm pressure to the injection site for at least 5 min*

Case 2

- *A 5-y-old girl is brought with complaint of epistaxis for 1 h. Parents have noticed skin bleeds for last 2 d. She has been otherwise well. No lymphadenopathy or organomegaly. Platelet count: 12×109/L. Other cell lines and peripheral smear are unremarkable.*

- ***Q1- What are the treatment steps to control bleeding?***

Management of epistaxis

- *Sitting position with neck flexed (chin touching the chest)*
- *Apply sustained pressure by pinching the soft part of the nose between the thumb and index finger for 20 min continuously*
- *Don’t interrupt the maneuver for checking for any bleed*
- *Nasal pack if bleeding persists*
- *Tranexamic acid*
- *First-line therapies*

Bansal D, et al. Indian J Pediatr (October 2014) 81(10):1033–1041

Case2 (continue)

- *Nose-pinching maneuver for controlling epistaxis was initiated. Despite this, bleeding continued. IVIg (800 mg/kg, single dose) was administered. Bleeding became passive on Day 2. The platelet count was 10×109/L on Day3. On Day7, the platelet count was 8×109/L.*

Q2- How to proceed in a situation of non-responsiveness to IVIg?

- *a) Second dose of IVIg*
- *b) high-dose methylprednisolone*
- *c) Bone marrow aspiration*
- *d) no further therapy is required*

- *Response to first-line drugs supports the diagnosis of ITP*
- *non-responsiveness is expected in 20-30 % patients*
- ***If there is no active bleeding, no further therapy is required, regardless of persistent thrombocytopenia.***
- *BM examination is not recommended in this setting according to the ASH guideline.*

Indian J Pediatr (October 2014) 81(10):1033–1041
Neunert C, et al. Blood 2011;117:4190-207

Case 3

- *A 10-y-old girl presented with multiple episodes of epistaxis and skin bleeds for 3 d. Platelet count: 4× 10^{9}/L. Clinical and hematological picture was suggestive of ITP. She was advised to take oral prednisolone 4mg/kg for 5 days. Next day, she complained of headache and vomiting. Non contrast CT-head revealed ICH with midline shift.*

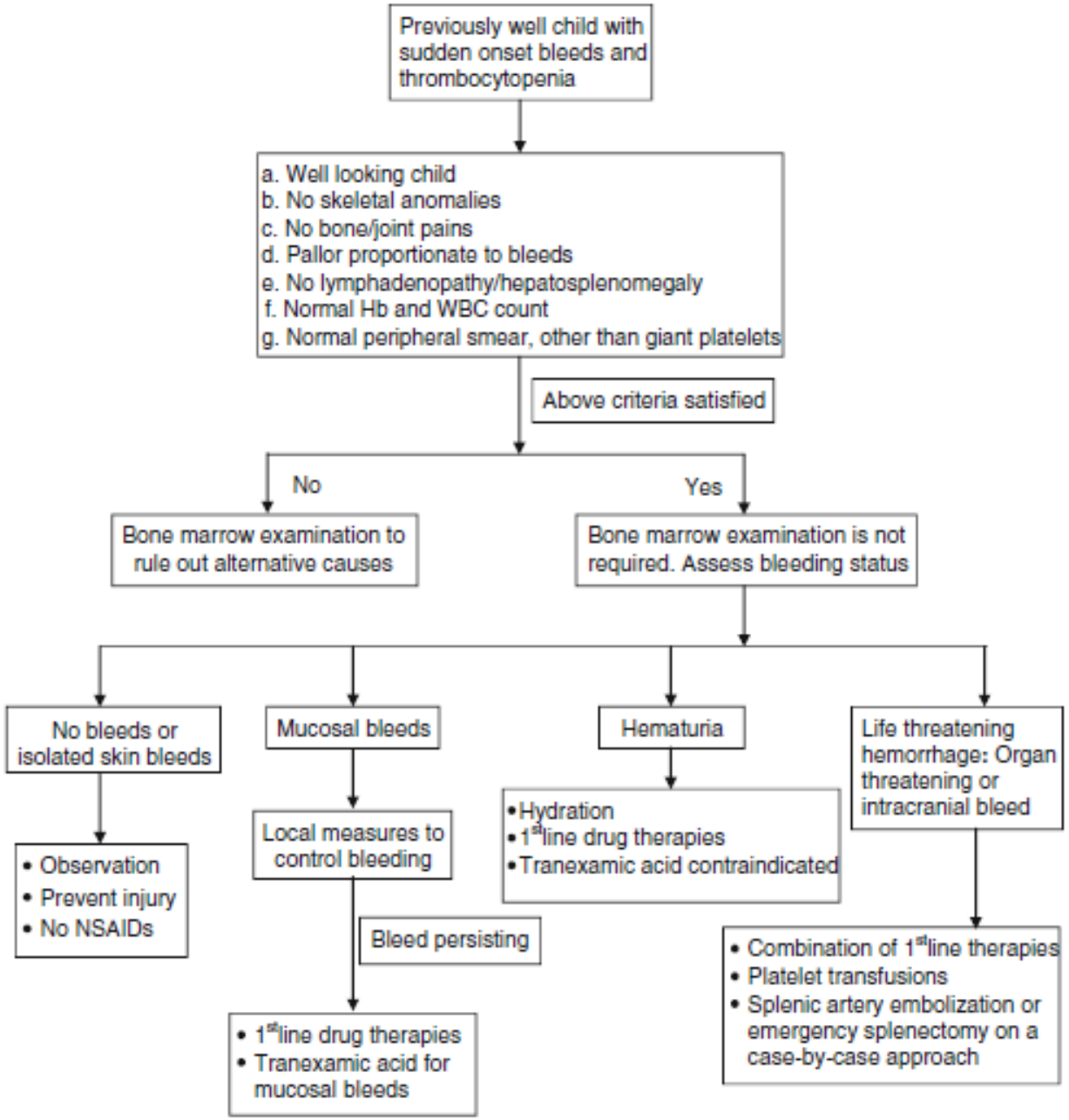
- ***Q1- How to treat?***

Management of life-threatening hemorrhage

- *Maintenance of airway, breathing and circulation (ABC)*
- *Neuroprotection*
  - *head elevation*
  - *mannitol or hypertonic saline if features of raised ICP*
- *First-line therapies in combination*
  - ***methylprednisolone+ IVIG/Anti-D** (may be repeated for 1-2 days)*
- ***Platelet transfusion (2-3 fold higher dose)**; continuous infusion may be beneficial*
- ***Splenectomy/**Splenic artery embolization*
- *rFVII 90-120 mcg/kg q2-3 h in refractory cases (off-label)*

Bansal D, et al. Indian J Pediatr (October 2014) 81(10):1033–1041

Approach to a child with suspedted ITP



Bansal D, et al. Indian J Pediatr (October 2014) 81(10):1033–1041

Second-line treatments

- *No response to first-line therapies*
- *The primary goal is to maintain a safe platelet count to prevent bleeding, not to achieve complete remission of disease*
- *Observation is preferred if no significant bleeding*
- *Long-term steroid should be minimized*
- *Cytotoxic drugs should be used very carefully*

Jang JH, et al. Management of immune thrombocytopenia: Korean experts recommendation in 2017. Blood Res 2017;52:254-63

Management of children with ITP who do not have a response to first-line treatment

- *In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment, the ASH guideline panel suggests the use of **TPO-RAs** rather than rituximab or splenectomy*
- *The ASH guideline panel suggests **rituximab** rather than splenectomy*

Neunert C, et.al. ASH 2019 guidelines for ITP. Blood advances 2019;3(23):3829-66

Rituximab

- *A chimeric monoclonal antibody that depletes B lymphocytes by binding to the CD20 antigen surface marker*
- ***375 mg/m ^{2} per week for 4 times.***
- *39% complete response (platelet count ≥100×10 ^{9}/L)*
- *68% partial response (platelet count ≥30×10 ^{9}/L)*
- *median response duration of 12.8 months*
- *Testing for hepatitis B status is recommended (risk of viral reactivation)*
- *Vaccination either before therapy or after full recovery of B cell function*

Liang Y, Zhang L, Gao J, Hu D, Ai Y. Rituximab for children with immune thrombocytopenia: a systematic review. PLoS One 012;7:e36698

Splenectomy

- The main location of both platelet destruction and antiplatelet-antibody production
- Laparoscopic splenectomy is preferred
- complete vaccinations for encapsulated organisms at least 2 weeks prior to splenectomy
- Prophylactic antibiotics are required for 2 years after splenectomy
- Complete response rates of 70–80%

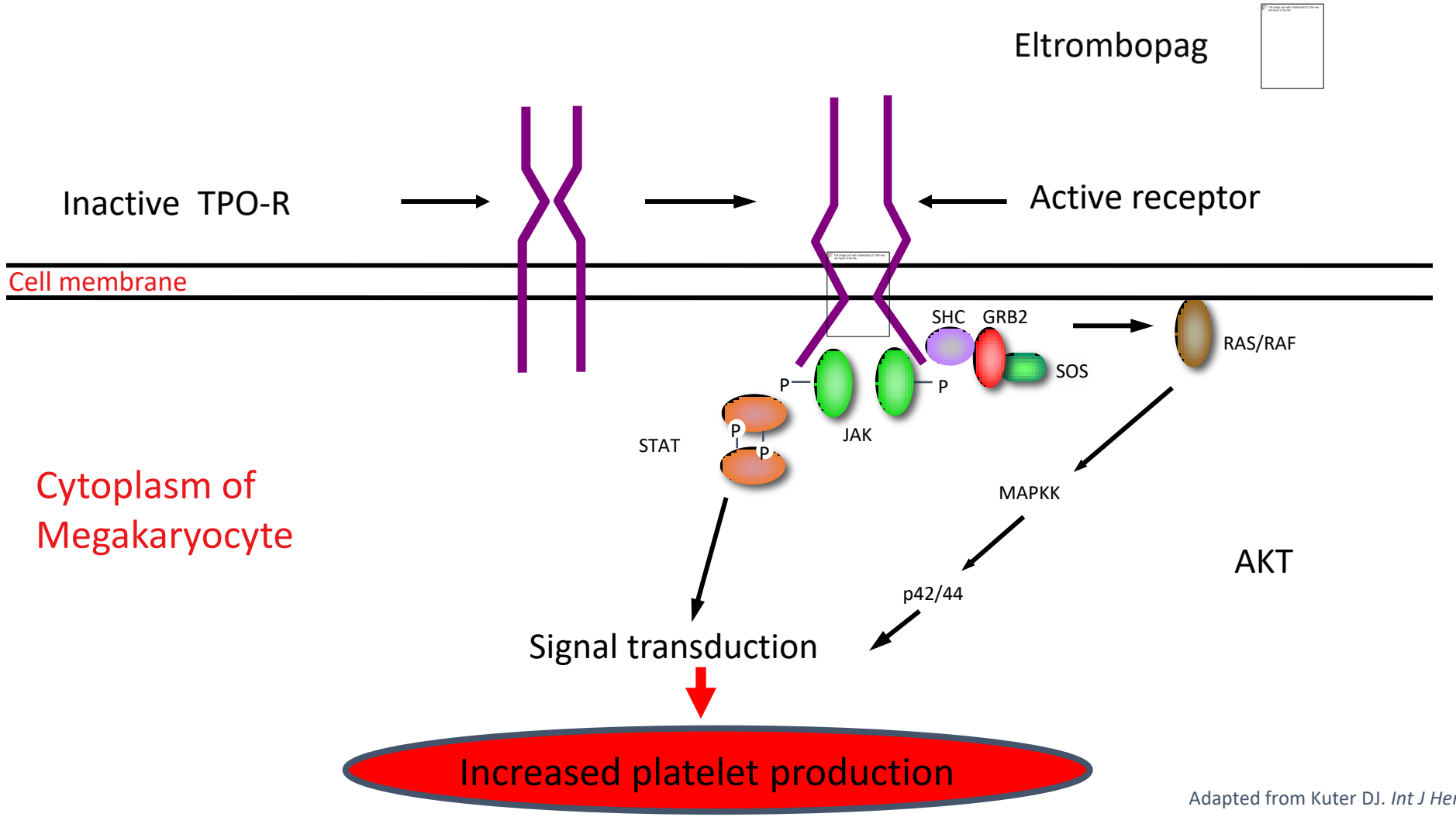
Mantadakis E, et al. J Pediatr Hematol Oncol 2000;22:148-53
Aronis S, et al. Acta Paediatr 2004;93:638-42

TPO-RAs:

- **Eltrombopag:**
- an oral, non-peptide TPO-RA administered daily, which activates the thrombopoietic receptor through the transmembrane domain
- Approved for children ≥1 year of age with chronic ITP who have not achieved an appropriate response with other drugs or splenectomy
- starting dose between 12.5 and 50 mg daily depending on age and ancestry.
- 62% of the eltrombopag-treated group achieved a response with platelets ≥50×10 ^{9}/L at least once without rescue
- 40% of the eltrombopag-treated group maintained a platelet count of ≥50×109/L for 6 weeks or more
- headache, upper respiratory tract infection, diarrhea, nausea, and vomiting
- Elevated liver enzymes

Bussel JB, et al. Lancet Haematol 2015;2:e315-25.
Grainger JD, et al. Lancet 2015;386:1649-58

Eltrombopag: mechanism of action



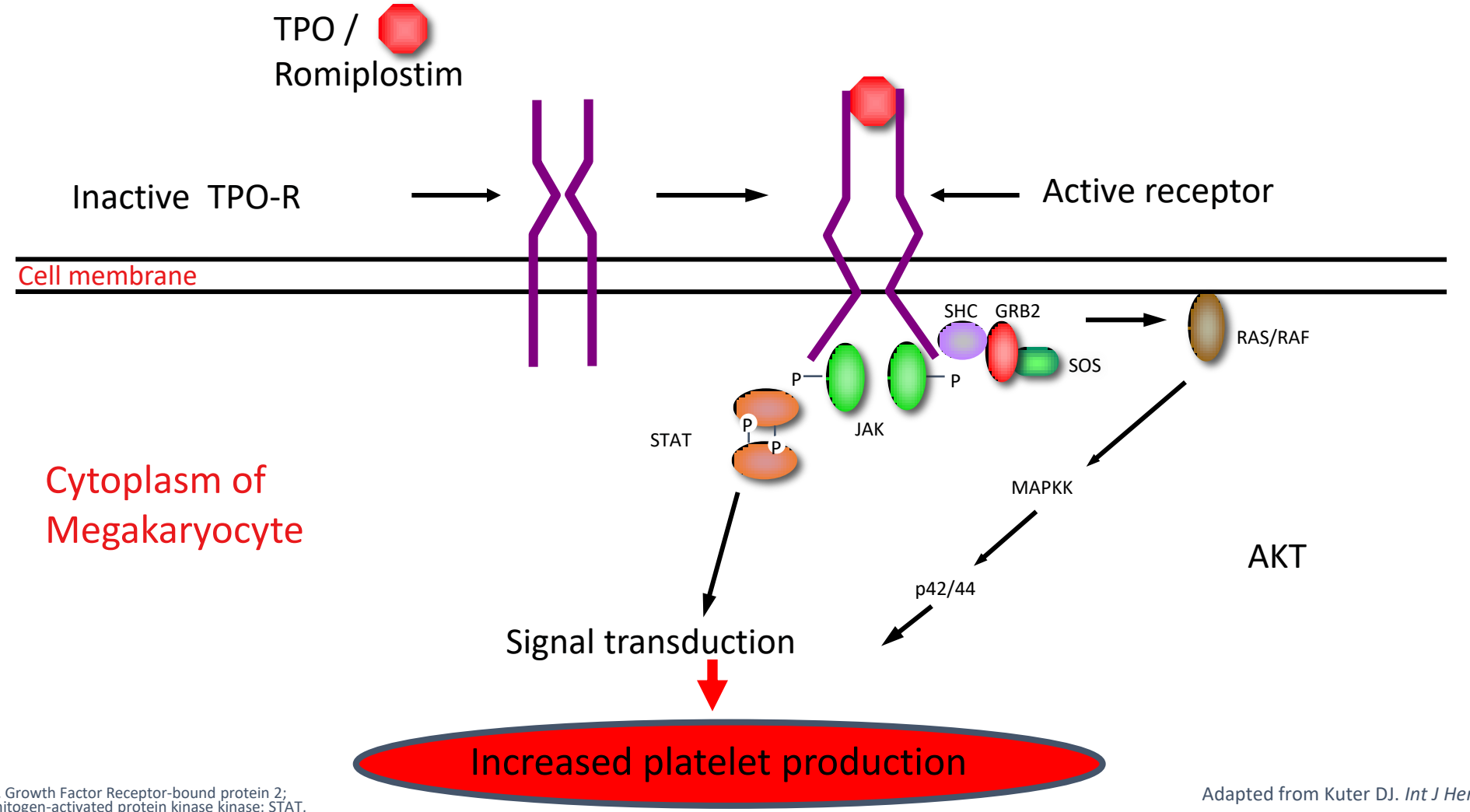
Adapted from Kuter DJ. *Int J Hematol* 2013;98:10–23

Romiplostim:

- Subcutaneous injection once a week.
- 1-10 mcg/kg weekly
- Platelet response in 52% of treated group
- BM reticulin fibrosis
- Adverse effects:
  1. allergic reactions: pruritus, urticaria, chills and fever
  2. serum sickness
  3. progressive multifocal leukoencephalopathy (PML)

Cines DB, et al. Int J Hematol 2015;102:259-70.

TPO/romiplostim: mechanism of action



AKT, protein kinase B; GRB2, Growth Factor Receptor-bound protein 2; JAK, Janus kinase; MAPKK, mitogen-activated protein kinase kinase; STAT, signal transducer and activator of transcription

Adapted from Kuter DJ. *Int J Hematol* 2013;98:10–23

Other treatments

- **Azathioprine 1-2 mg/kg/day**

  -takes several months for full effect

  - durable response in 51-64%

  - safe in pregnancy

  - Adverse effects: nausea, infection, liver function abnormalities, neutropenia, and anemia

- **Cyclophosphamide: 1.5-3 mg/kg/day**
  - slow onset of effect
  -durable response 60% in 2 studies
  - Adverse effects: bone marrow suppression, infection, infertility, secondary malignancies, and hemorrhagic cystitis

- **Cyclosporine A: starting dose 3-6 mg/kg (Max 200 mg/d)**
  - durable response 20-44%
  - adverse effects: gingival hyperplasia, hypertension,nephrotoxicity, and nausea

➢ **Danazol:**

- 15 mg/ kg (Max 400-600 mg/day)
- durable response (9-96%)
- Adverse effects: androgenic effects, elevated liver function tests , weight gain, acne, rash, mood changes, amenorrhea, and virilization
- LFT should be monitored monthly

➢ **Dapsone:**

- 50-100 mg daily
- durable response 0-55%
- Adverse effects: nausea, hemolysis, methemoglobinemia
- Contraindicated in G6PD deficiency

- **Mycophenolate mofetil (Cell Cept):**

  - 1300 mg/m^2 (Max 2 gr)

  -slow effect

  - durable response 56-62%

  - Adverse effects: diarrhea, neutropenia, anemia, viral infections, a small increased risk of malignancy (prolonged use), progressive multifocal leukoencephalopathy, pure red aplasia.

➢ Vinca alkaloids:

- Vincristine 1.5 mg/m^2, Vinblastin 6 mg/m^2 weekly
- rapid response in 7 days
- durable response 0-42%
- Adverse effects: vincristine neuropathy, vinblastine-associated bone marrow suppression, constipation, hyponatremia, infusion site vesication

Common errors in the management of ITP

- Administering platelet enhancing drugs for a low platelet count rather than symptoms.
- Prolonged (several weeks to months) administration of steroids.
- Platelet transfusions for a very low platelet count, with minor mucosal and skin bleeds.
- Suboptimal management of epistaxis: Inadequate local pressure.
- Underutilization of tranexamic acid and hormonal therapy for control of mucosal bleeds.

Counselling the family

- Points to emphasize during a parent-physician communication:
- 1. ITP is a **self-limiting disorder** and most children (70–80 %) undergo spontaneous remission over a period of 6 months
- 2. A significant percentage (40–50 %) of children with chronic ITP undergo remission over 4–5 y as well
- 3. There is a small but definite risk of **ICH (<1 %)** which persists till the resolution of thrombocytopenia
- 4. **Treatment has not been proven to reduce the incidence of ICH**, nor does it reduce the chances of progression to chronic ITP

Counselling the family

- 5. **Avoid trauma**, particularly head injury. Use helmets during outdoor play, cycling, etc.
- 6. **Avoid NSAIDS** (aspirin, ibuprofen, etc.) and **intramuscular injections**. Paracetamol can be administered for fever/pain.
- 7. Skin bleeds may be widespread and appear worrisome. They are not considered ‘serious bleeds’; specific therapy is typically not indicated.
- 8. Epistaxis can often be managed with local pressure. Tranexamic acid mouth washes are useful for gum bleeding. If mucosal bleeds are persistent, systemic therapy is warranted.
- 9. Patient should be brought to physician’s notice in case of headache, hematuria or GI bleeding.

Thanks for your attention