An updated management of ITP

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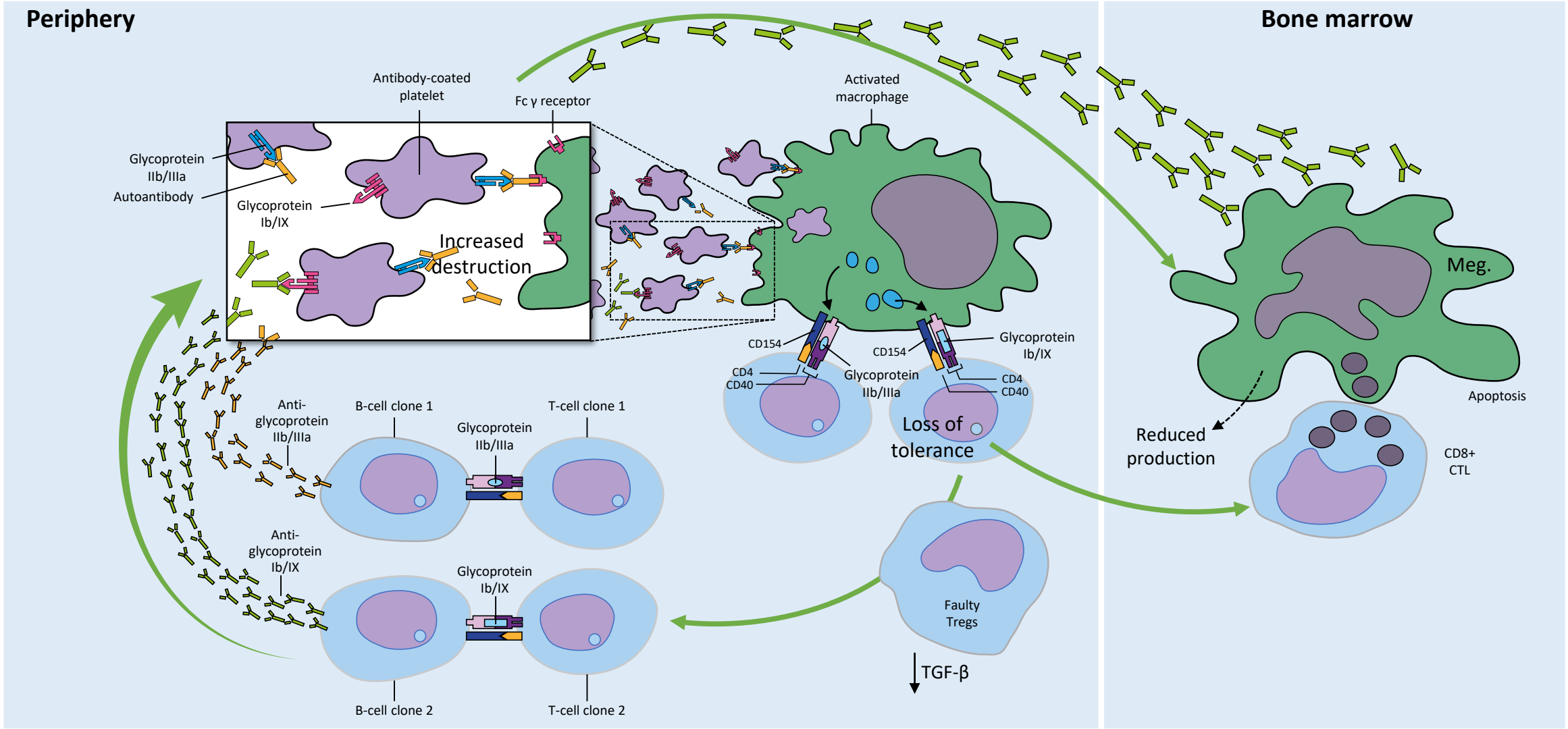
Introduction

- ***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

Modern immunopathogenesis of ITP



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

- *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

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.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 2-year-old boy is brought with complaints of skin petechiae for 2 d. 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) methylprednisolone 30 mg/kg for 3 days

  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

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. 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***

Case 2

- *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

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

ITP in the COVID-19 era

- ITP as a hematologic manifestation of COVID-19
- ITP following COVID-19 vaccination
- Should be differentiated from VITT (vaccine-induced thrombotic thrombocytopenia)
- Normal D-dimer in contrast to VITT
- Approached and treated like ITP of other causes
- Usually responds to steroid and IVIG

J Korean Med Sci. 2021 Nov 8;36(43):e306.
Arch Clin Cases. 2021 Oct 27;8(2):31-36
Respir Med Case Rep. 2021;34:101534

Thrombosis in ITP

- A very rare occurrence
- May occur with treatments with TPO-RA such as eltrombopag
- Secondary causes of ITP such as APLS should be highly considered
- VTE in ITP mainly occurs in the presence of multiple risk factors of TE
- A low platelet count does not protect against VTE
- Risk of VTE recurrence is high, particularly with a history of unprovoked VTE or active cancer
- In this setting, indefinite anticoagulation therapy could be discussed

Cureus. 2021 Aug 27;13(8):e17478
Biomedicines. 2021 Sep 6;9(9):1170
Intern Med J. 2019 Sep;49(9):1154-1162

- A French cohort study on 10039 adult patients with primary ITP
- A higher risk of hospitalisation for **VT** was observed with:

  older age, history of VT, history of cancer,

  splenectomy (HR 3·23, 95% CI 2·26–4·61)

  exposure to corticosteroids (HR 3·55, 95% CI 2·74–4·58)

  TPO-RAs (HR 2·28, 95% CI 1·59–3·26)

  IVIg (HR 2·10, 95% CI 1·43–3·06)

BJH. 2021 Nov;195(3):456-465

- A higher risk of hospitalisation for **AT** was observed with:
  older age, male sex, a history of cardiovascular disease,
  splenectomy (HR 1·50, 95% CI 1·12-2·03)
  exposure to IVIg (HR 1·85, 95% CI 1·36-2·52)
  TPO-RAs (HR 1·64, 95% CI 1·26-2·13)
- Rituximab was not associated with an increased risk.

BJH. 2021 Nov;195(3):456-465

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.

Thank you

for attention