Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

# Thrombocytopenia: Updated Review

Terry Gernsheimer, MD

Seattle Cancer Care Alliance

University of Washington School of Medicine

Fall, 2020

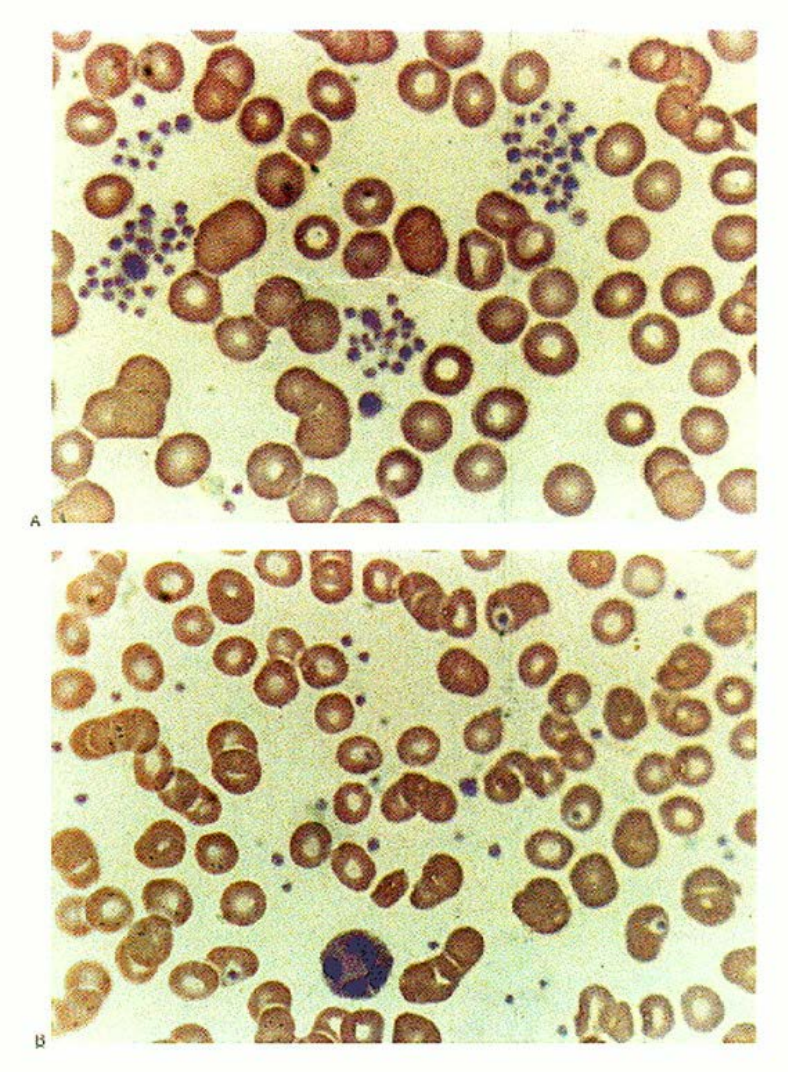
**Discussion of off-label drug use**:

Rituximab, mycophenolate, vincristine, azathioprine, cyclosporine, cyclophosphamide, danazol, dapsone, sirolimus, pentasacharides, antifibrinolytic agents, anti-RhD, prostacycline, tirofiban, aspirin

# Approach to thrombocytopenia

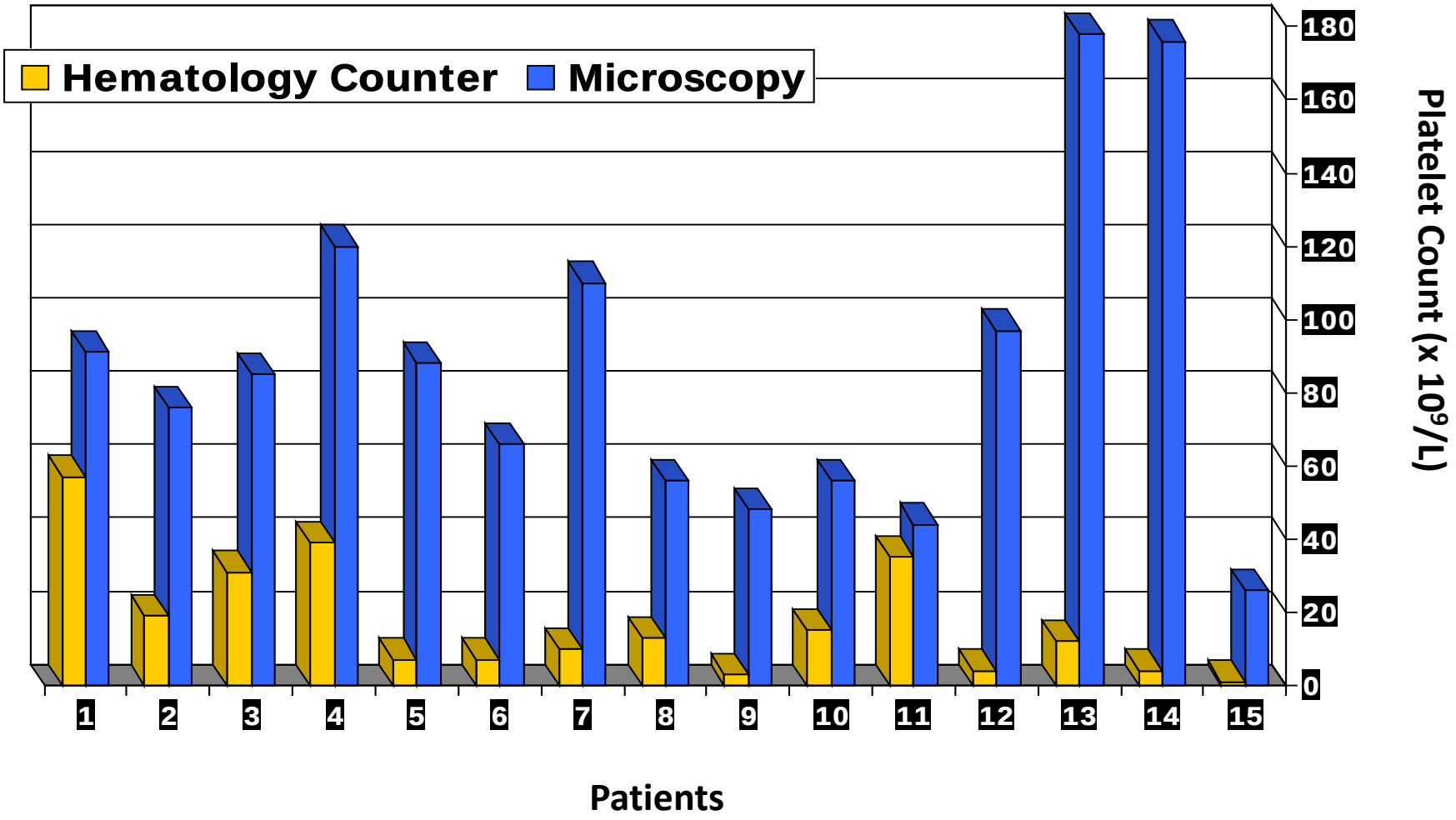
- History
- Physical examination
- Complete blood count
- Peripheral blood smear

# Pseudo-thrombocytopenia




**Shalev, O. et. al. N Engl J Med 1993;329:1467**

# Platelet count errors in macrothrombocytopenia




Noris, P. et al., Am. J. Medicine, 1998; 104: 355-360

# Mechanisms of thrombocytopenia

- Decreased production
- Increased destruction
- Increased splenic sequestration
- Dilutional

# Disorders of production: MYH9-related platelet disorders

| Clinical features | May-Hegglin | Sebastian | Fechner | Epstein |
|---|---|---|---|---|
| Macrothrombocytopenia | Yes | Yes | Yes | Yes |
| Leukocyte inclusions | Yes | Yes | Yes | No |
| Hearing impairment | No | No | Yes | Yes |
| Cataracts | No | No | Yes | No |
| Nephritis | No | No | Yes | Yes |

From Seri, M., et al., *Medicine*, 2003, 82(3):203-215

# Hereditary thrombocytopenia

- Autosomal dominant
  - MYH9 Gene mutations e.g. May Hegglin
    - Tpenia, large platelets, neutrophil inclusions
  - Gray Platelet Syndrome – large, ↓ α granules, pmn granules
- Autosomal recessive
  - Congenital amegakaryocytic thrombocytopenia
  - Thrombocytopenia with Absent Radii
  - Bernard Soulier syndrome large plts w/ ↓ GPIb
- Sex-linked recessive
  - Wiskott-Aldrich syndrome –
    - small plts, immunodefic, eczema

# Congenital thrombocytopenias

- Macrothrombocytopoenia
  - MyH9
  - GP1B
  - GATA1-X-linked
- Microthrombocytopenias
  - WAS
- Normal platelet size
  - ANDRD26
    - Predisposition to MDS and AML (30 X increase)
  - RUNX1
  - MPL
  - ADAMTS13

# Acquired thrombocytopenia: ↓ Production

## Are other Cell Lines Affected?

- Intrinsic marrow abnormalities
- Vitamin deficiencies
- Toxins
- Drugs
- Infection
- Marrow infiltration
- Liver disease

# Thrombocytopenia in liver disease

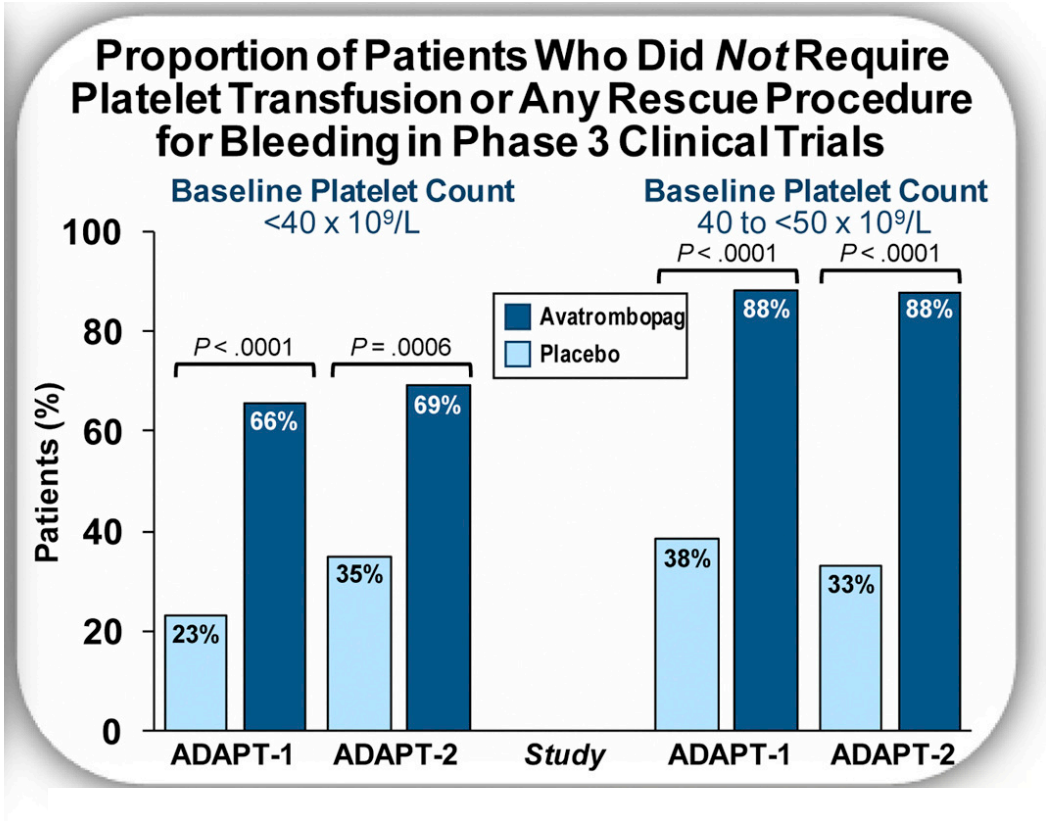
- Multifactorial
  - Splenomegaly
  - Decreased TPO
  - Increased turnover
  - Immune
    - Hepatitis C
    - Autoimmune hepatitis
- Therapy
  - Transfusion
  - Eltrombopag (HCV)
  - Avatrombopag for procedures

# Increasing platelet production for procedures in cirrhosis

N= placebo 158, Avatrombopag 277

**Procedure**

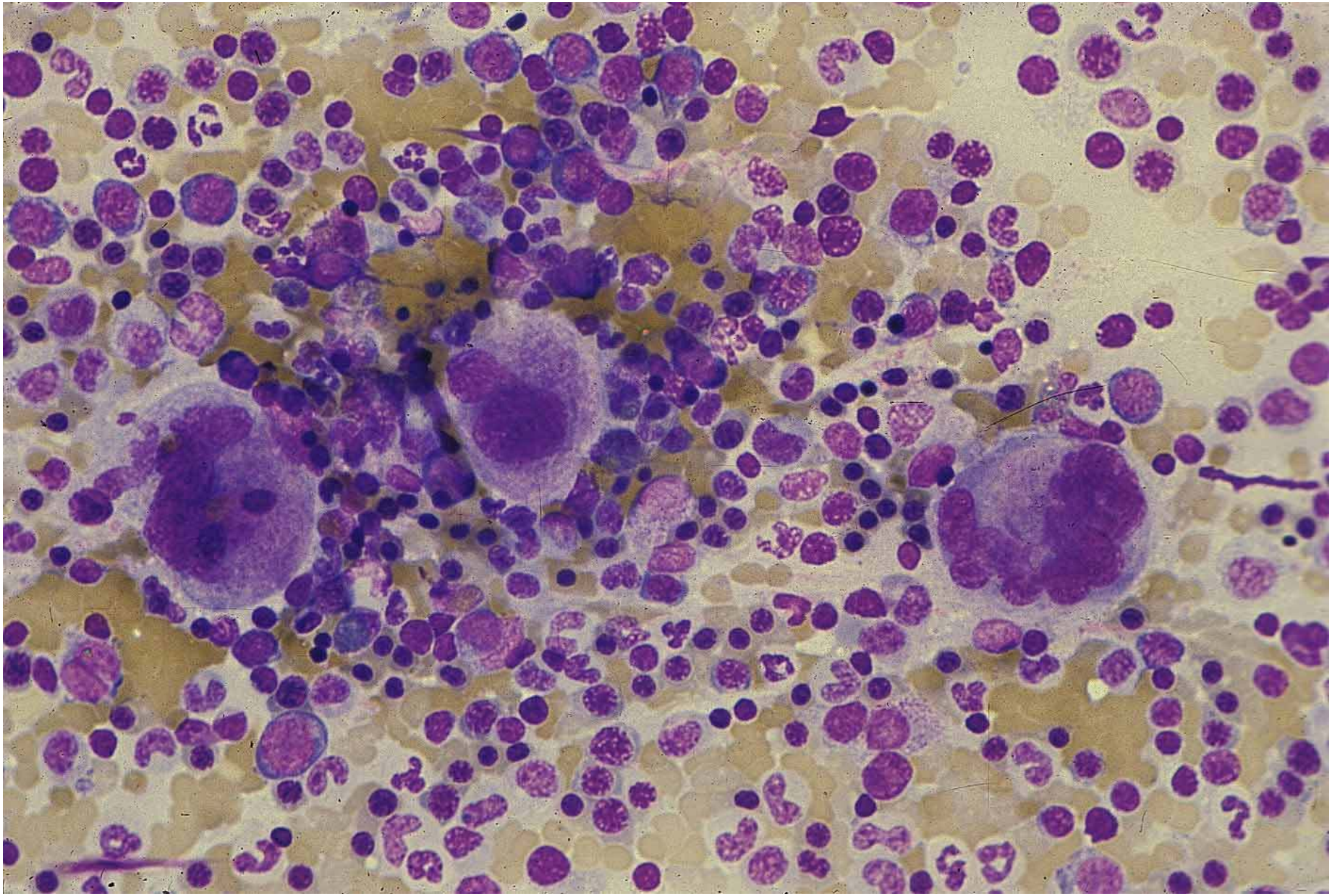
- Paracentesis
- Endoscopy
- Colonoscopy
- Liver biopsy
- Ablation
- Chemoembolization
- Dental procedures
- TIPS
- Laparoscopic
- Vascular catheterizaton




Gastroenterology 2018; 155:705-718

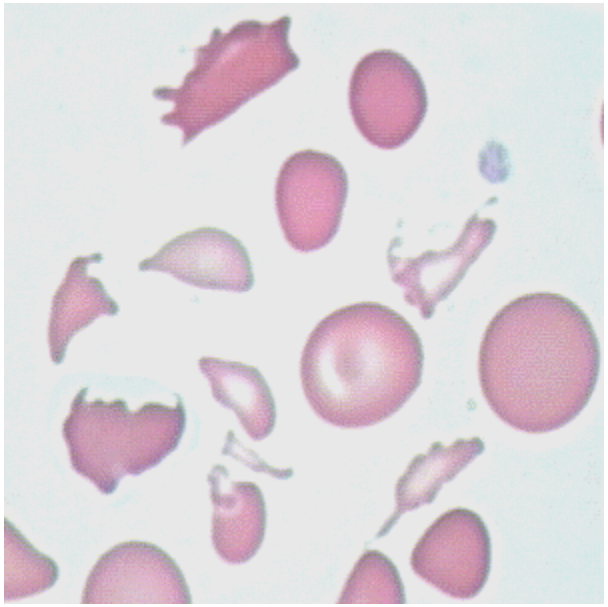
# Thrombocytopenia due to increased platelet destruction and consumption

- Platelet lifespan < 10 Days
  - Increased platelet turnover
- Normal or increased megakaryocytes
- Immune or non-immune



# Isolated platelet consumption: MAHA

- Disruption of laminar flow
- Vasculitis
- Malignancy
- Malignant hypertension
- Cryoglobulinemia
- Infection
  - Septic emboli, rickettsia



- Thrombotic Thrombocytopenic Purpura & Hemolytic Uremic Syndrome

Is platelet transfusion contraindicated?

Goel et al. Blood. 2015; 125(9):1470-1476

# Isolated platelet consumption

- Thrombotic Thrombocytopenic Purpura
  - Adults
  - Classic pentad
  - Rx - plasma exchange
- Secondary TTP
  - Drugs, HIV, pregnancy, malignancy
- Congenital TTP
- Thrombotic microangiopathies with acute kidney injury
  - Complement mediated –C-TMA (HUS)
  - Shigatoxin (Stx HUS) 0157:H7 Ecoli

# TTP & atypical HUS

| | TTP | C-TMA |
|---|---|---|
| Pathophysiology | ADAMTS13 Deficiency | Aberrant activation of alternative C' pathway<br>Factor H gene mutations (25%), others |
| Clinical | Tpenia/anemia more severe | Renal insufficiency more prominent |
| Therapy<br><br><br><br>High risk disease | Plasma<br>Plasma exchange + corticosteroids, rituximab<br>Caplacizumab | Chronic<br>C5 inhibition<br>Eculizumab, ravulizumab |
| | | |

# Immune platelet destruction

- Auto-Immune
  - Primary – "ITP"
  - Secondary
    - Collagen-Vascular Disease
    - Malignancy
    - Infection
    - HIV
- Drug induced
  - vanc, pcns, quinine
- Allo-immune
  - Post-Transfusion Purpura
  - Neonatal Alloimmune Thrombocytopenia

# Recommendations for diagnosis of primary ITP

- Diagnosis principally one of exclusion
- History & PE
- Full blood count, retic & peripheral blood examination
- Helicobacter pylori infection detection by breath test or stool antigen (regional)
- HBV, HIV, HCV
- Quantitative Immunoglobulins
- DAT
- Other testing in selected individuals (ab, imaging)
- Bone marrow in selected individuals only

Provan D et al. *BloodAdvances* 2019;3: 3780-3817.

# Summary of recommendations for initial treatment of ITP

| | **ASH 2020[1]** | **ICR Recommendations[2]** |
|---|---|---|
| Platelet count threshold for treatment | ≤30 × $10^9$/L | <20-30× $10^9$/L<br>Individualize to patient & phase |
| First-line treatment | Corticosteroids (prednisone, methyprednisolone or dexamethasone)<br>taper off by 6 weeks | same |
| First-line treatment if corticosteroids are contraindicated | IVIg or anti-D | same |
| Emergency treatment | IVIg plus corticosteroids | High-dose IV corticosteroids plus IVIg<br>platelet transfusions<br>antifibrinolytic drugs |

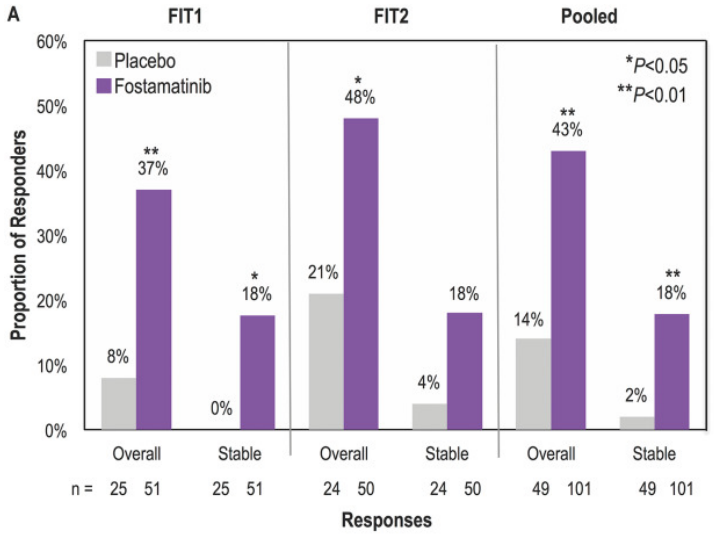
Neunert C et al. *BloodAdvances* 2019;3:3829–66; Provan D et al. *BloodAdvances* 2019;3: 3780-3817

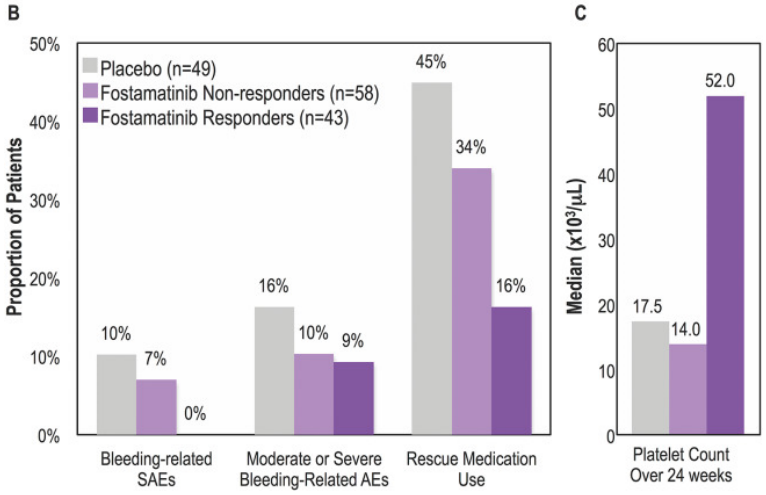
# Summary of recommendations for treatment of persistent (>3 months) ITP

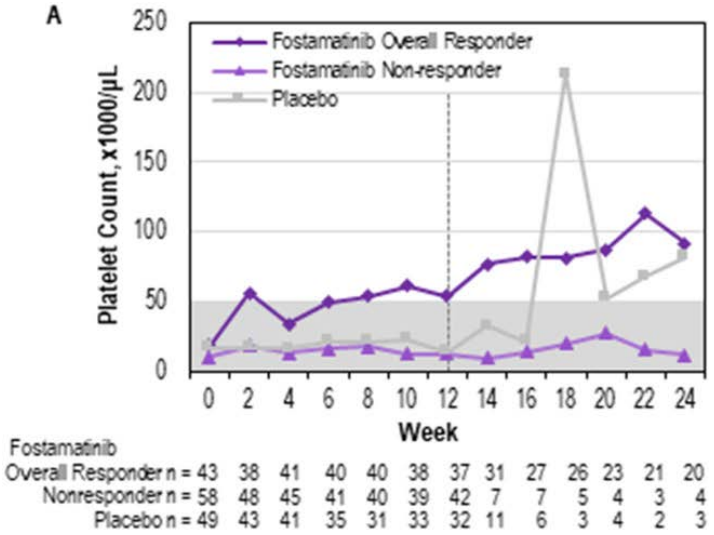
| Treatment type/parameter | ASH 2020[1] | ICR Recommendations[2] |
|---|---|---|
| Platelet count threshold for treatment | ≤30 × $10^9$/L | Treat to maintain platelet count >20-30× $10^9$/L<br>Individualize to patient & phase<br>Minimize toxicity |
| Subsequent Therapy | TPO receptor agonists<br>Rituximab<br>Splenectomy | TPO receptor agonists<br>Rituximab<br>Fostamatinib<br>Splenectomy |
| Agents with less robust evidence /subsequent treatment | Azathioprine<br>Cyclosporin A<br>Cyclophosphamide<br>Danazol | Dapsone<br>Mycophenolate mofetil<br>Vinca alkaloids<br>TPO RA switch |

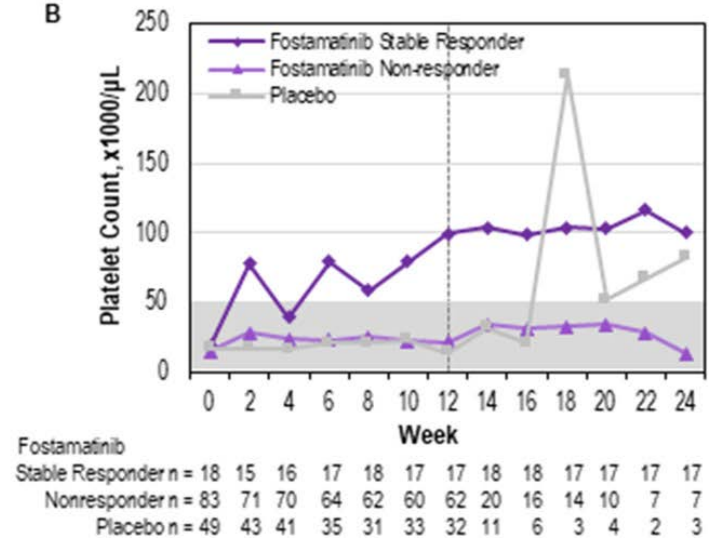
Neunert C et al. *BloodAdvances* 2019;3:3829–66; Provan D et al. *BloodAdvances* 2019;3: 3780-3817

# Syk kinase inhibition:
# Fostamatinib for refractory persistent/chronic ITP




Bussel J, et al. Hematology. 2018; 93: 921-930

# Treatment of drug induced thrombocytopenia

- Stop offending agent(s)
- Severe: IVIg
- Severe refractory: Plasma exchange
  Dialysis
- Severe adjunctive therapy
  - Platelet transfusions
  - Antifibrinolytic agents

- Testing for drug dependent antibody

# Clinical diagnosis of HIT

- History of heparin exposure
- Thrombocytopenia during and after heparin exposure (<150,000)
  - Drop in platelet count (>50%) rather than absolute thrombocytopenia
  - Thrombocytopenia recovers after heparin withdrawal
- With or without thrombotic complications
- Unusual presentations
  - Absence of expected increase, skin necrosis, delayed onset

# Laboratory tests for HIT

## Functional (activation)

- **Serotonin release**
- **ATP release**

- **Platelet aggregation**
- **Flow cytometry**

## Antigen

- **Heparin-PF4 ELISA**
- **Other IA**

# Clinical scoring system for HIT pretest probability:

# "The 4Ts"

| 4T's | 2 points | 1 point | 0 point |
|---|---|---|---|
| Thrombocytopenia | Platelet count fall >50% and platelet nadir ≥20* | Platelet count fall 30–50% or platelet nadir 10–19 | Platelet count fall <30% or platelet nadir <10 |
| Timing of platelet count fall | Clear onset between days 5–10 or platelet fall ≤1 day (prior heparin exposure within 30 days)† | Consistent with days 5–10 fall, but not clear (e.g. missing platelet counts); onset after day 10‡; or fall ≤1 day (prior heparin exposure 30–100 days ago) | Platelet count fall <4 days without recent exposure |
| Thrombosis or other sequelae | New thrombosis (confirmed); skin necrosis§; acute systemic reaction postintravenous unfractionated heparin (UFH) bolus | Progressive or recurrent thrombosis¶; Non-necrotizing (erythematous) skin lesions§; Suspected thrombosis (not proven)** | None |
| Other causes for thrombocytopenia | None apparent | Possible†† | Definite†† |

**0-3 Points: Low pretest probability of HIT; lab testing not indicated**

**4-5 Points: Intermediate pretest probability of HIT**

**6-8 Points: High pretest probability of HIT**

Lo et al (2006) *Journal of Thrombosis and Hemostasis.*

# Alternate thrombotic therapy

Low Molecular Wt Heparin

<u>Anti-platelet agents</u>

Prostacycline, tirofiban, aspirin

<u>Direct Thrombin Inhibitors</u>

Argatroban

Bivalirudin

DOACs?

<u>Pentasacharides</u>

Fondaparinux

# Cardiac surgery with history of HIT

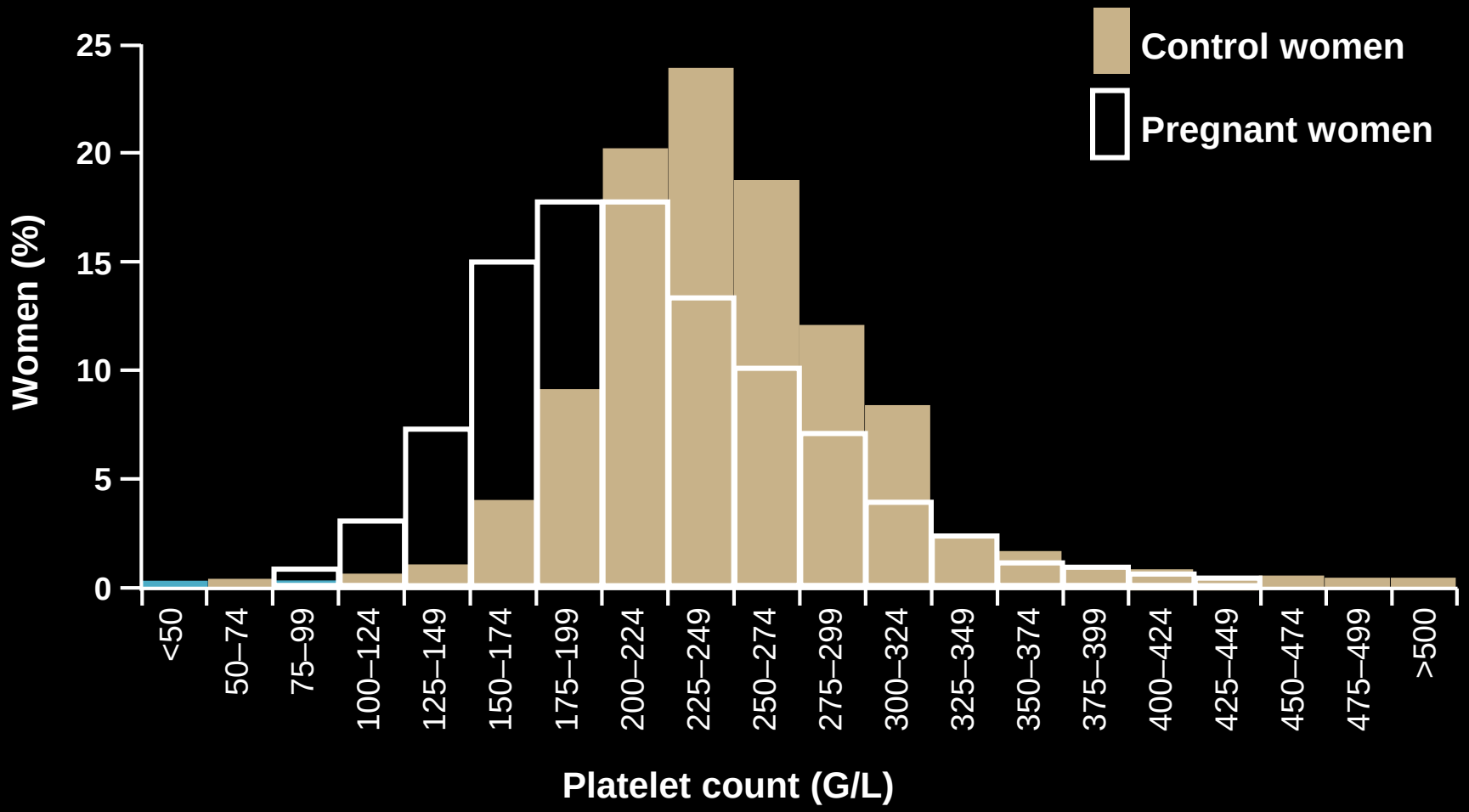
- Delay 3-6 months
- Antibody (ELISA) Neg
- Expose during CPB only
- Use alternate anticoagulation post-op

- Experimental:
  - Plasma Exchange
  - IVIg

# Warfarin in HIT

- Contraindicated until platelet count recovery (or >100,000) due to decreased Protein C
- Use with a thrombin inhibitor
  - Associated with progression of DVT to venous limb gangrene
  - Caution if INR >4
- Do not use loading dose

# Platelet count at term in healthy pregnancy




Boehlen F et al. *Obstet Gynecol* 2000;95:29–33

# Pregnancy-associated thrombocytopenia

- Isolated Thrombocytopenia
  - Incidental (Gestational)
  - Immune (ITP)
  - Drug-induced
    - HIT
  - Congenital
  - Type IIb vWD

- Systemic Disorders
  - Preeclampsia
  - HELLP syndrome
  - Acute fatty liver
  - Thrombotic microangiopathies
  - SLE / Antiphospholipid antibodies
  - DIC
  - Viral infection
  - Nutritional deficiencies
  - Hypersplenism
  - Bone marrow dysfunction

# Evaluation of thrombocytopenia in pregnancy

| | |
|---|---|
| Clinical History & Physical Exam | History of thrombocytopenia<br>Bleeding history<br>Hypertension |
| Review blood smear | Pseudothrombocytopenia<br>Large platelets<br>Fragments |
| Laboratory evaluation | Coagulation testing, vWF<br>Thyroid testing<br>LFTs<br>Virus – HIV, HCV, H Pylori<br>ANA, Lupus anticoagulant, ACLA |

Gernsheimer T , James A, Stasi R. *Blood* 2013 ;121:38-47

# Immune thrombocytopenia (ITP) in pregnancy

- Incidence: 1 in 1,000  to 1 in 10,000 pregnancies
- Most common cause of thrombocytopenia in 1st trimester
- Pathogenesis--autoantibodies targeting platelet gp's or T cell dysregulation and direct toxicity
- 31% require intervention
- Incidence of neonatal thrombocytopenia ~20%
  - 4% severe

1. Gill KK & Kelton JG. *Semin Hematol* 2000;37:275–289; 2. Won YW et al. *Korean J Intern Med* 2005;20:129–134;  3. Fujimura K et al. *Int Hematol* 2002;75:426–433

# Management of ITP in pregnancy

- Indications for therapy
  - First and second trimesters
    - Symptomatic
    - Platelet count 20–30,000x$10^9$/L
    - Procedures
- Monitor more frequently in third trimester
- Therapy based on risk of maternal haemorrhage
  - Therapy of mother does not affect fetal platelet count
- First-line therapy
  - Corticosteroids
  - IVIg
- Combine first-line therapies in refractory patients

Gernsheimer T , James A, Stasi R. *Blood* 2013 ;121:38-47

# Management of refractory ITP in pregnancy

## Second-line therapies

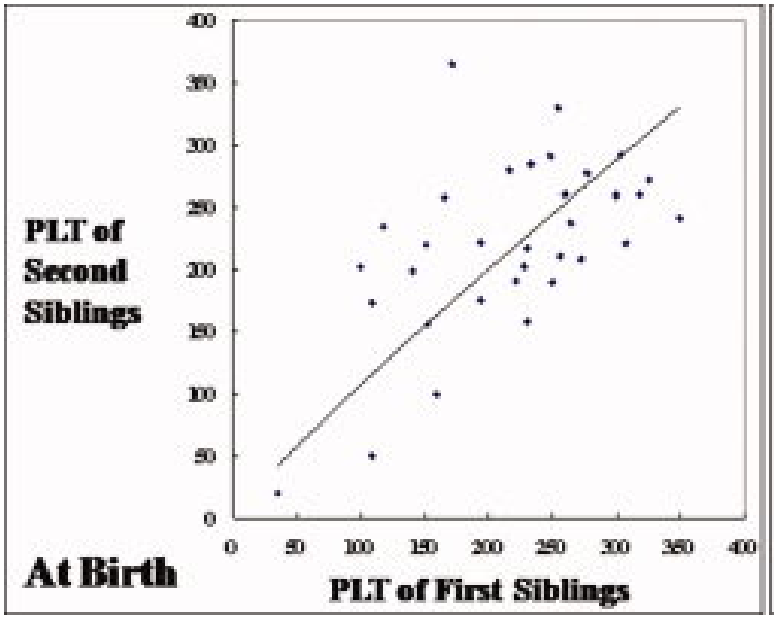
- IV anti RhD
- Splenectomy
  - Rarely performed, best performed in the second trimester
- Azathioprine
- Cyclosporine
- HDMP with IVIg or azathioprine if refractory to oral corticosteroids or IVIg

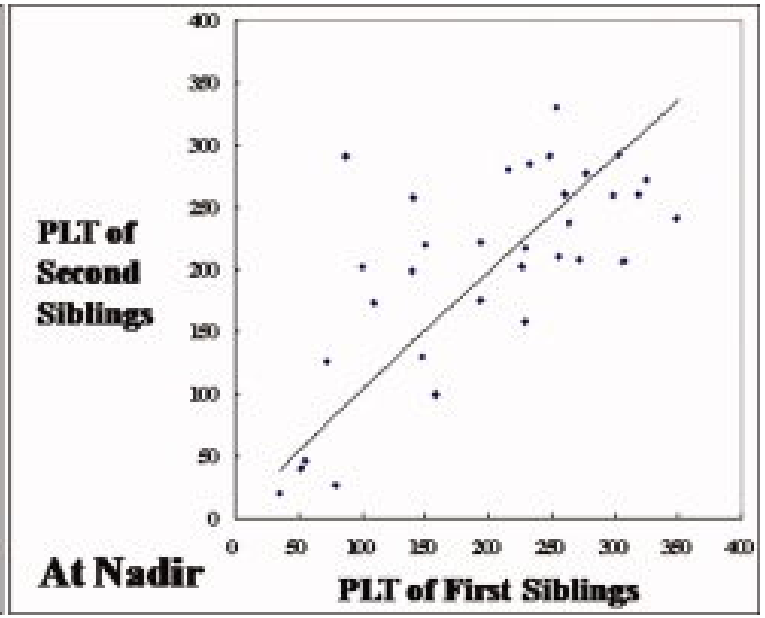
## Should not be used

- Other immunosuppressive drugs
- +/- rituximab
- Vinca alkaloids, danazol
- TPO receptor agonists, TPO

Gernsheimer T , James A, Stasi R. *Blood* 2013 ;121:38-47

# Correlation of sibling platelet counts at birth and at nadir




$P = 0.001$ $P < 0.0001$

Koyama S, et al. Am J Hematol. 87:15-21, 2012

# Management of delivery

- Mode of delivery determined by obstetric indications
  - Most neonatal haemorrhage occurs at 24–48 hrs
  - Fetal platelet count measurement not recommended
  - Avoid procedures with increased fetal bleeding risk

- Epidural anaesthesia
  - Risk of spinal hematoma unknown
  - Platelets of 70,000/μL
  - Consider other hemostatic parameters and history
  - Usefulness of thromboelastography unclear

Gernsheimer T , James A, Stasi R. *Blood* 2013 ;121:38-47

*Thanks for your attention!*