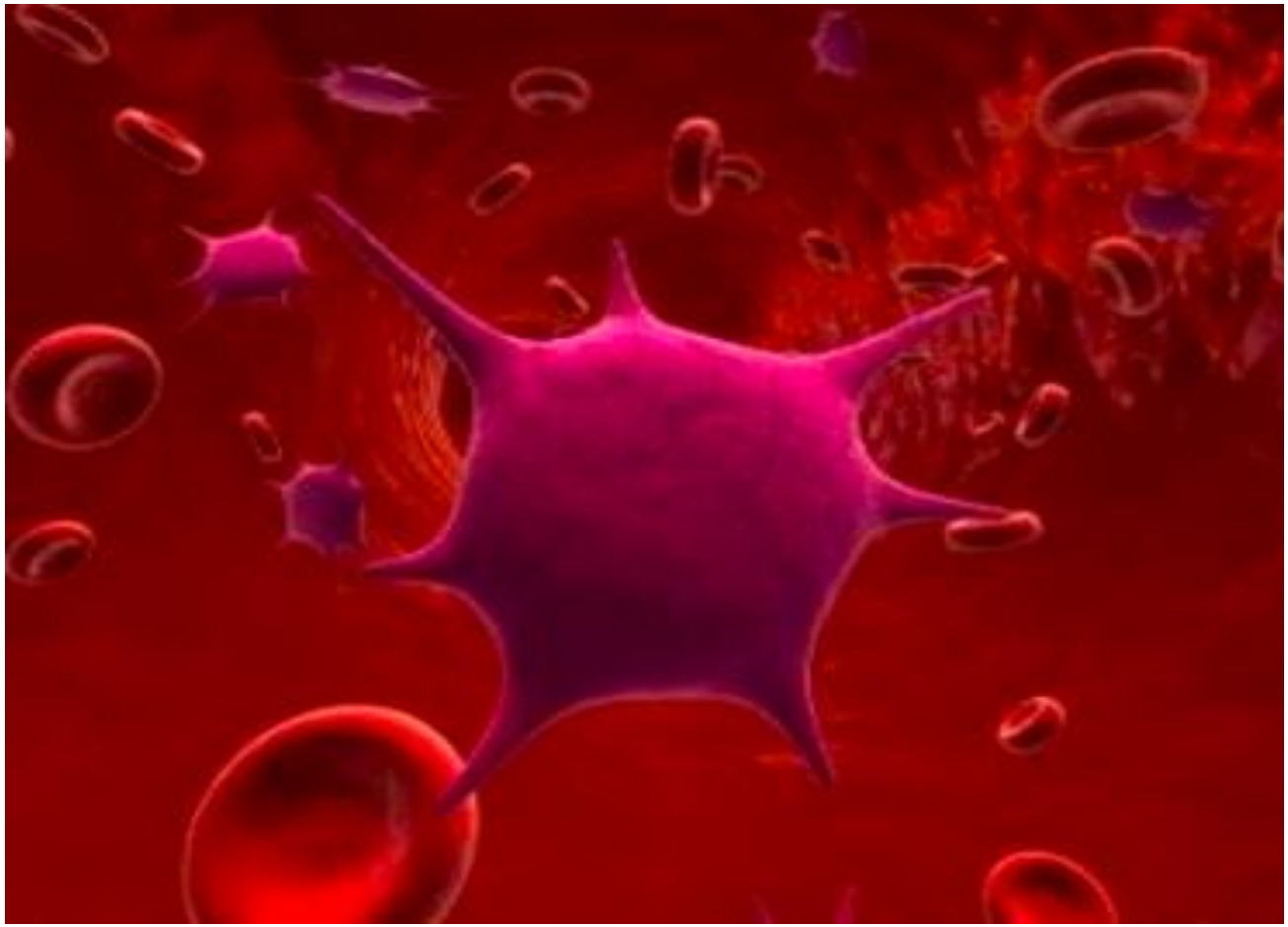
Immune Thombocytopenia Purpura (ITP)



Lise Mozzon MD FRCPC – Summer School 2015

Disclosures

Consultation:

Bayer Healthcare

- *Apixaban*

Bristol-Myers Squibb

- *Rivaroxaban*

Boehringer Ingelheim

- *Dabigatran*

Leo Pharma

- *Tinzaparin*

Pfizer Canada

- *Dalteparin*

Sanofi

- *Enoxaparin*

Objectives

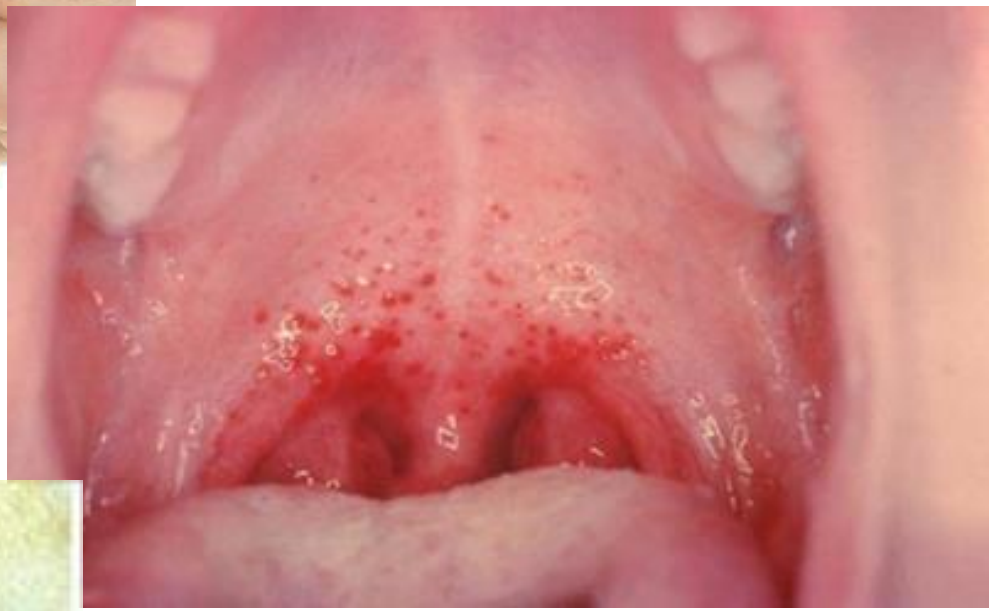
- Review of approach to thrombocytopenia
- Pathophysiology of ITP
- Acute Management
- Chronic management
- Review of Cases

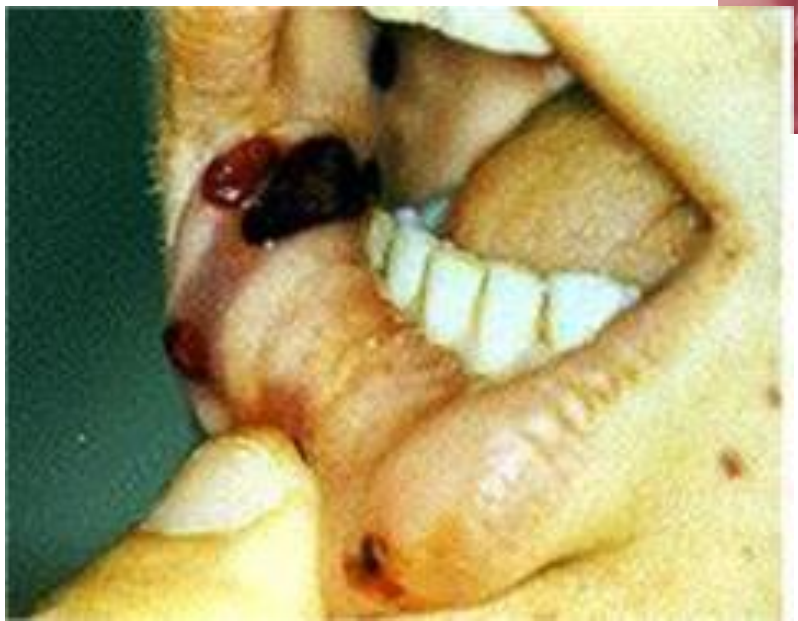
Platelet Facts

- Anucleate – limited capacity to synthesize new proteins
- Primary hemostasis – platelet plug
- Circulate with average life span 7-10 days
- Approximately 1/3 of platelets reside in spleen
  - Splenic sequestration – rarely plt < 40

Epidemiology

- **Adult-onset** ITP is more common in females than males
  - F:M ratio 1.7:1
- 6-7 per 100,000
- increasing prevalence and incidence with age in adults





Definitions

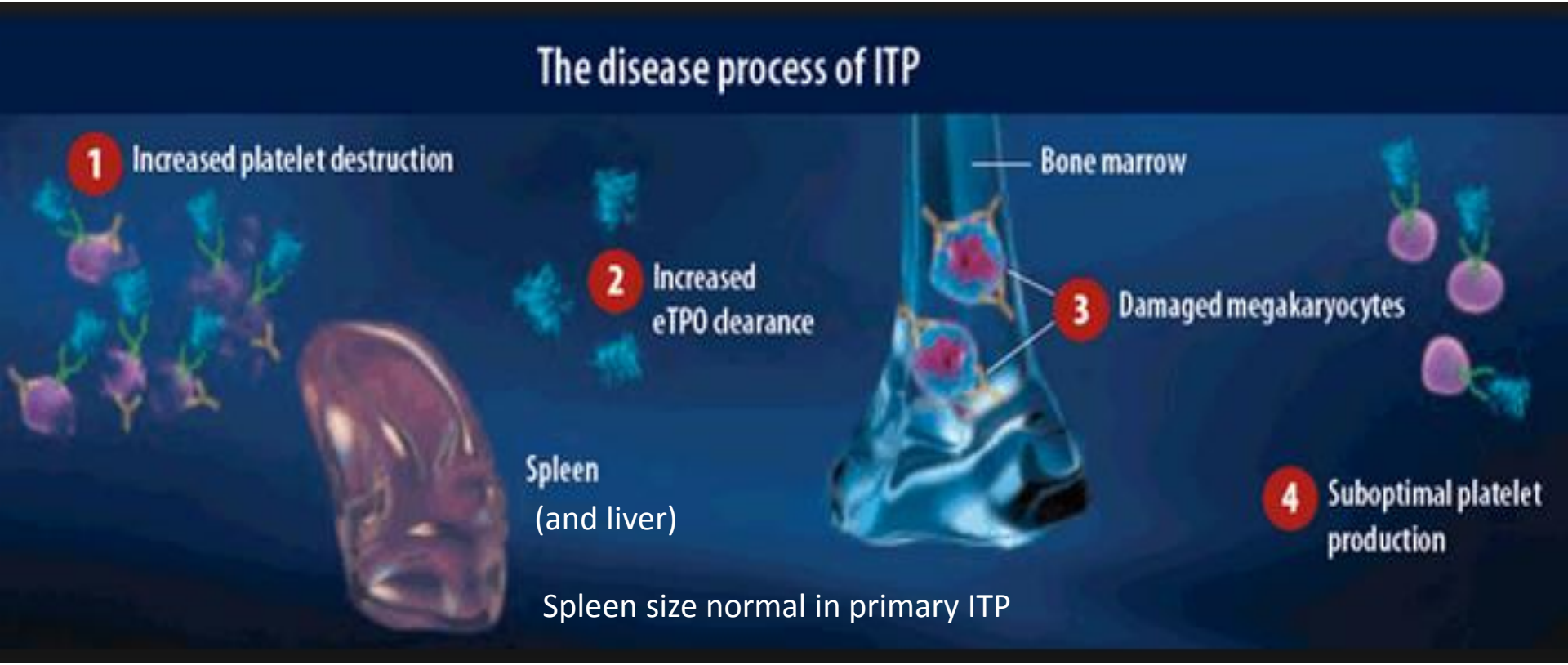
- “Thrombocytopenia” – platelet count < 150,000
- ITP – platelet count <100,000

- **Newly diagnosed** - diagnosis to 3 months
- **Persistent** - 3 to 12 months from diagnosis
- **Chronic** - lasting for more than 12 months

- **Refractory** = chronic ITP post splenectomy
  - plt <30 more than 3 months post-splenectomy = failed splenectomy

- Regardless of the definitions – very heterogenous population
  - Presentation and response to therapy quite variable
  - ? True primary ITP vs late presentation of systemic disorder and secondary ITP

Pathophysiology



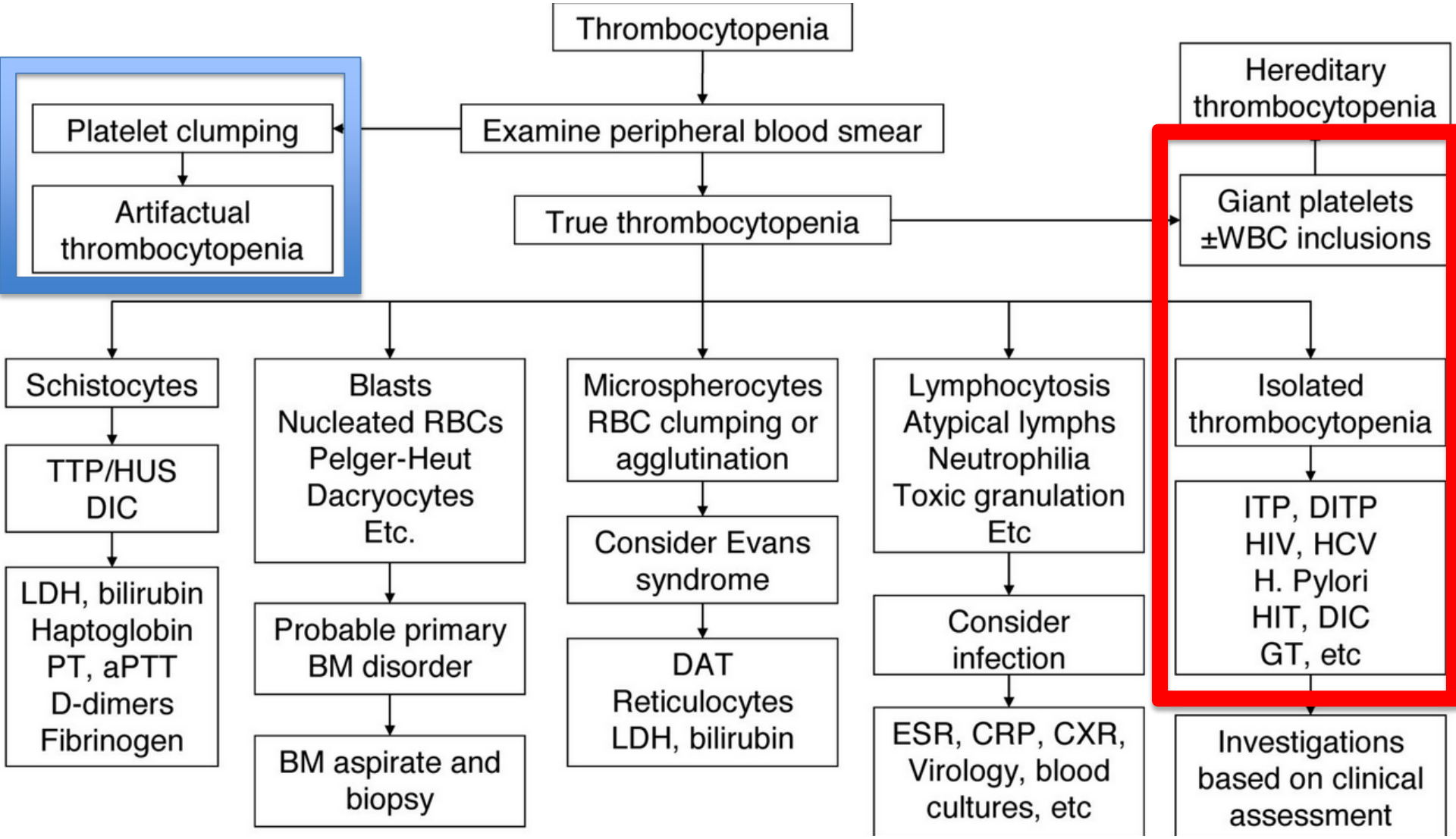
- formation of antiplatelet antibodies directed at platelet surface antigen s (GP)
  - Only detectable in 60% of patients
- B-cell tolerance is perturbed in ITP - immune tolerance defects
  - IVIg response in 80%
- Cytotoxic T cell involvement

Consideration of Secondary Causes
- Multiple approaches

Table 2. Selected differential diagnoses according to the clinical scenario

Thrombocytopenia in. . .				
Ambulatory patient	Acutely ill patient	Pregnant patient	Cardiac patient	Patient with thrombosis
• ITP	• DIC	• Gestational	• HIT	• HIT
• Drug-induced	• Infection/sepsis	• ITP	• Cardiac bypass	• Antiphospholipid antibody syndrome
◦ Chemotherapy	• Drug-induced	• HELLP	• GPIIb/IIIa inhibitor related	• Paroxysmal nocturnal hemoglobinuria
◦ Misc Drugs	◦ HIT		• TTP-related to clopidogrel or ticlopidine	
• Infections	◦ Miscellaneous		• Dilutional	
◦ EBV	◦ Drugs			
◦ HIV	• TTP-HUS			
◦ Others	• Post transfusion purpura			
• Connective tissue disorders				
◦ SLE				
◦ Rheumatoid arthritis				
◦ Antiphospholipid antibody syndrome				
• Hypersplenism				
• Primary marrow disorder				

Diff Dx by Peripheral blood findings:



THROMBOCYTOPENIA

↓ Production

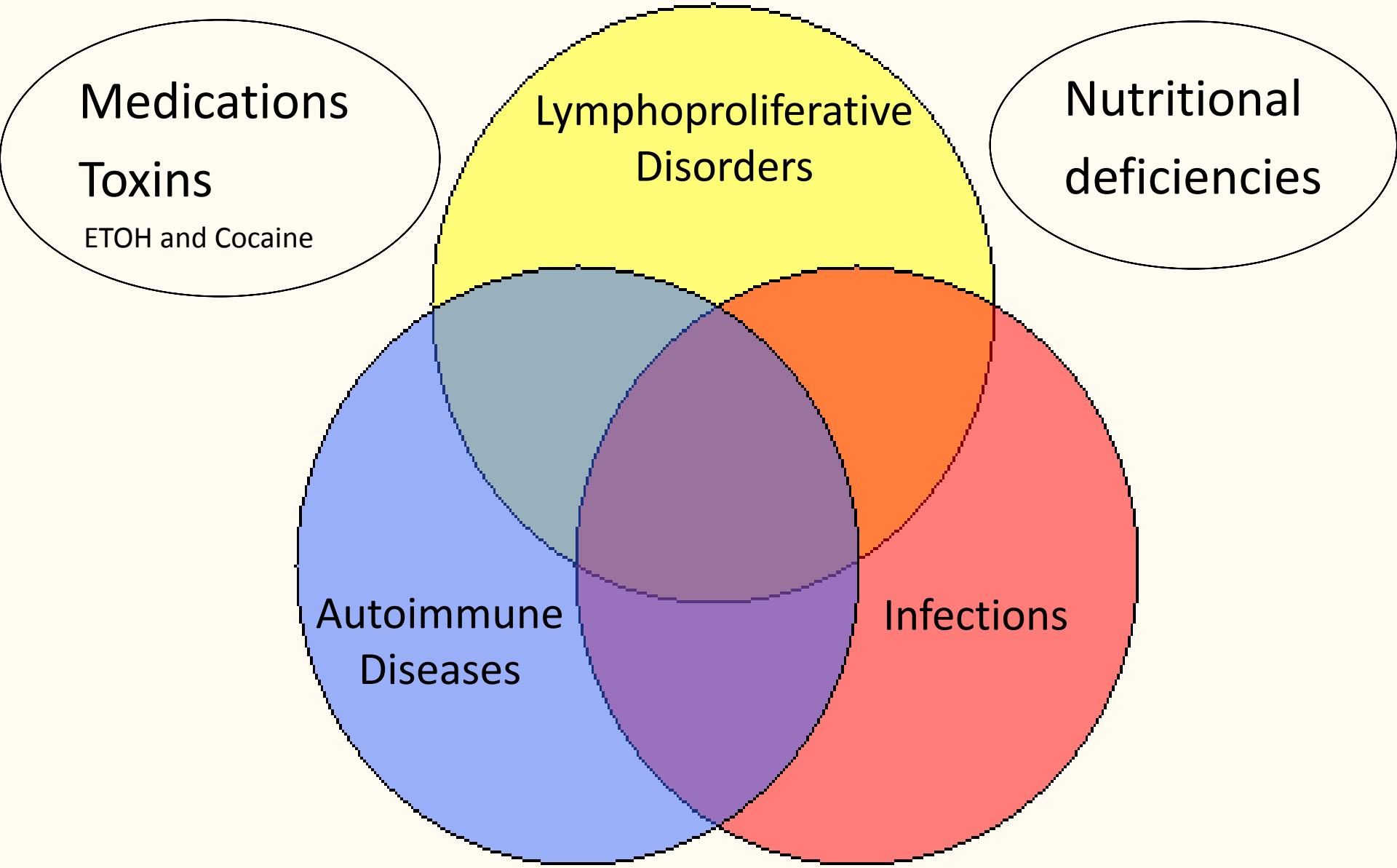
- **Marrow damage**
  - Aplasia
  - Drugs/toxins
  - Hepatitis
  - Malignancy
- **Congenital defects**
  - Fanconi anemia
  - TAR syndrome
  - Rubella
  - May-Hegglin anomaly
  - Wiskott-Aldrich syndrome
  - Autosomal dominant
- **Ineffective production**
  - B_{12}/Folate deficiency

Abnormal distribution

- **Splenomegaly**
  - Liver disease
  - Myelofibrosis

↑ Destruction

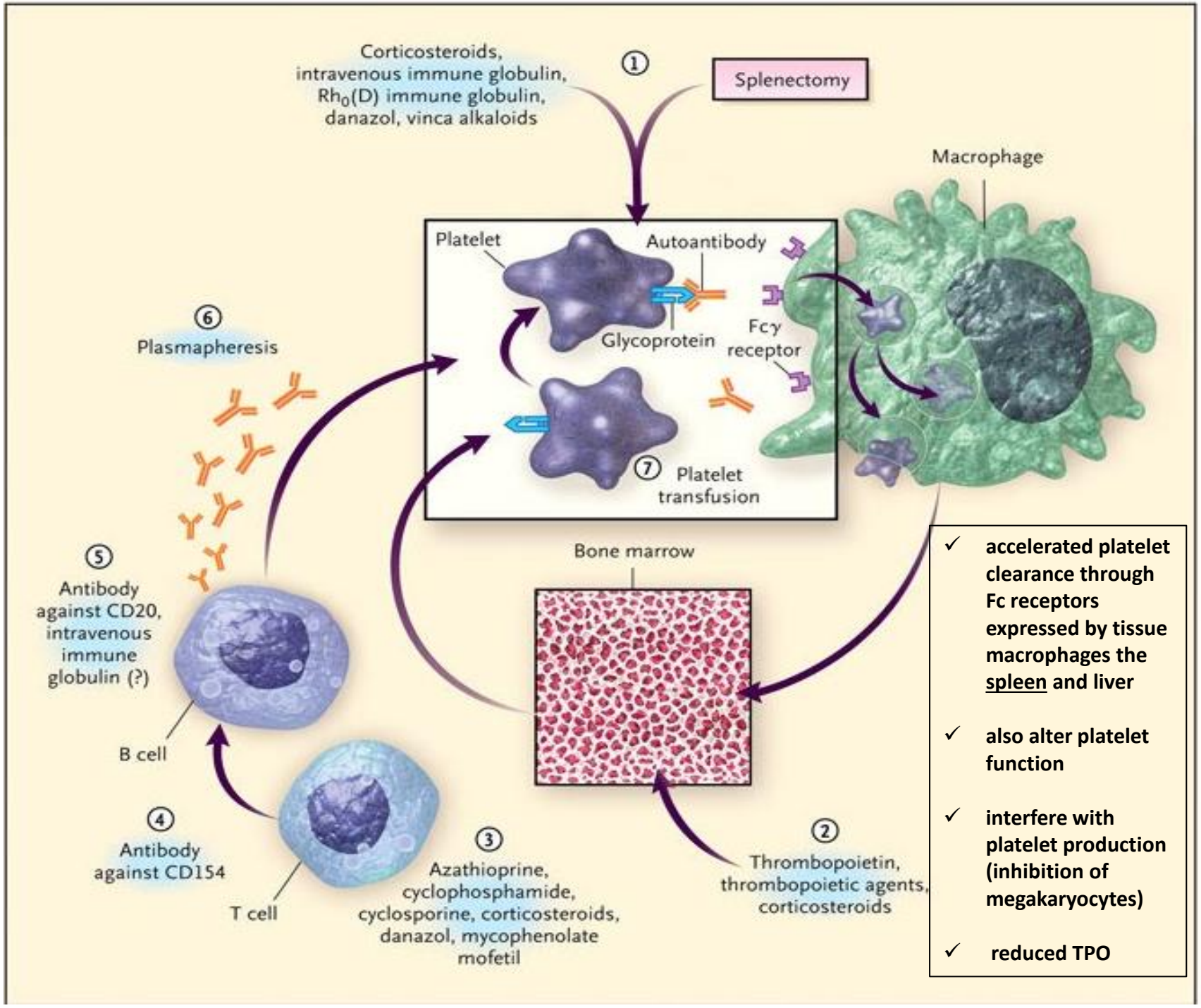
- **Nonimmune**
  - DIC
  - Hemolytic-uremic syndrome
  - TTP
  - HELLP syndrome
- **Immune**
  - Drug induced
  - Secondary to
    - SLE
    - Alloimmunization
    - Lymphoproliferative disease
    - AIDS
  - ITP


Medications
Toxins
ETOH and Cocaine
Lymphoproliferative Disorders
Nutritional deficiencies
Autoimmune Diseases
Infections

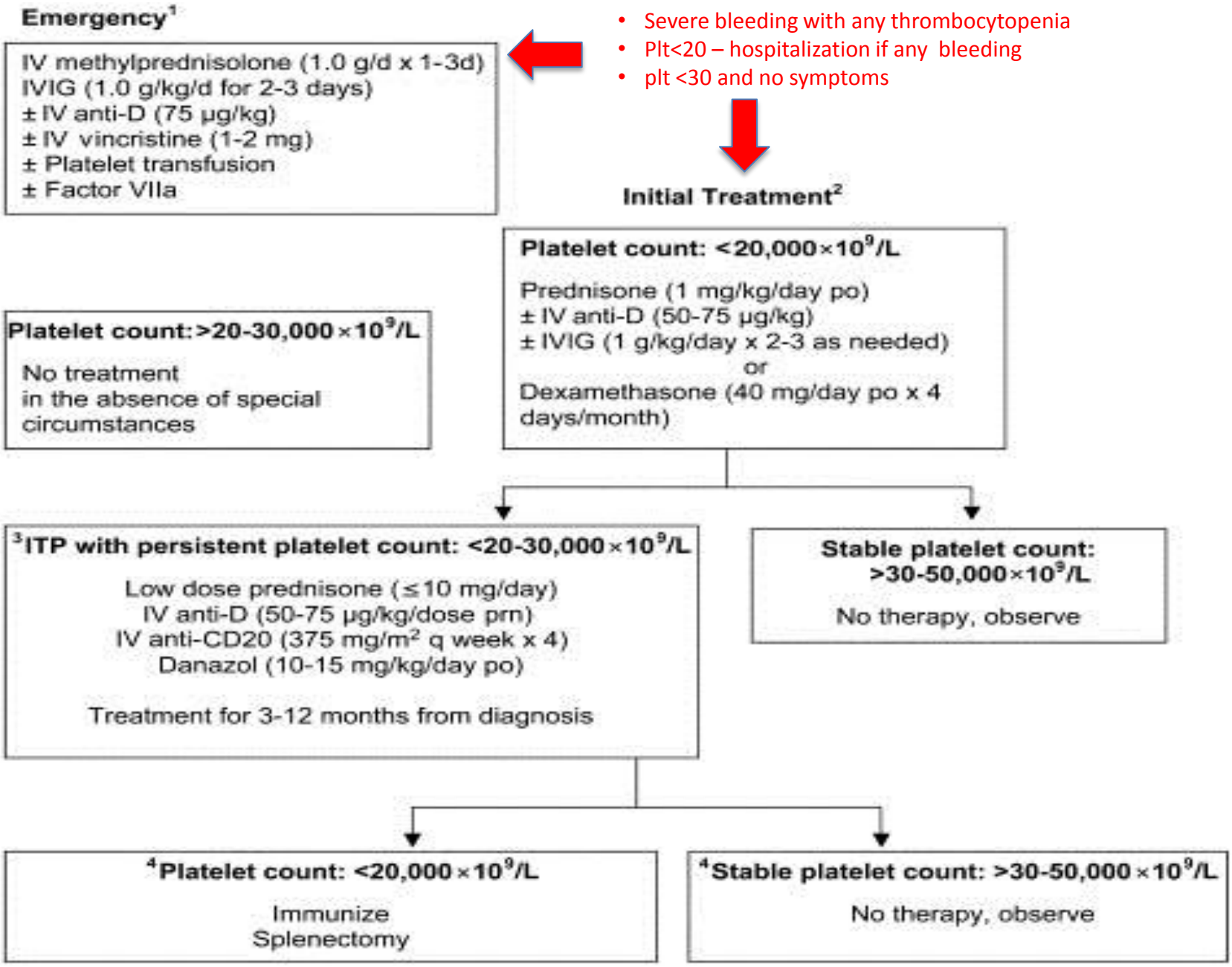
Diagnosis Primary ITP

- Diagnosis of exclusion
- Platelet <100
- No other cell lines are typically down – Evans syndrome (hemolytic anemia)
- No reliable Ab testing
  - IgG autoantibodies to platelet GPs
  - may be multiple targets (ex. GPIIb/IIIa, GPIb/IX, etc.)
  - Autoantibodies only detectable in 60%

- Bone marrow biopsy
  - increased megakaryocyte, no other abnormalities
  - Recommended for >60 yo R/O hematologic malignancy
  - Preformed before splenectomy – R/O hypoplasia or fibrosis



- ✓ **accelerated platelet clearance through Fc receptors expressed by tissue macrophages the <u>spleen</u> and liver**
- ✓ **also alter platelet function**
- ✓ **interfere with platelet production (inhibition of megakaryocytes)**
- ✓ **reduced TPO**

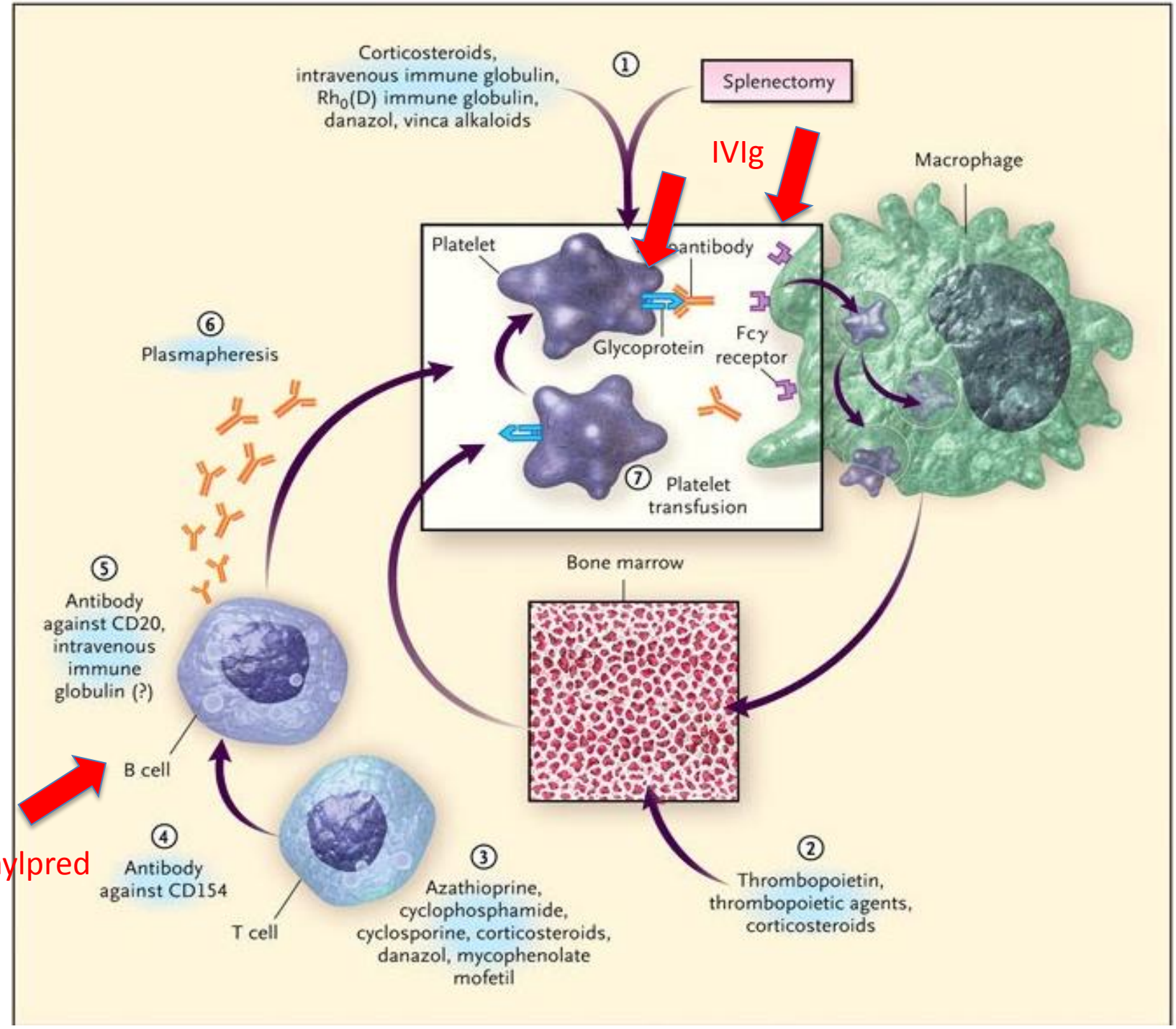


Cines and Bussell, "How I treat ITP". Blood. October 2005, vol. 106, no 7

Emergent Management of ITP

- Need rapid (although temporary) improvement of platelet count
- considered if Platelet< 10,000 or bleeding

1. **IVIg**
2. **Methylpred**
3. **Platelet transfusion**
4. **Consider Transexamic acid, desmopressin**


Corticosteroids, intravenous immune globulin, $Rh_0(D)$ immune globulin, danazol, vinca alkaloids
1
Splenectomy
IVIg
Macrophage
Platelet
antibody
Glycoprotein
Fcγ receptor
6
Plasmapheresis
7
Platelet transfusion
5
Antibody against CD20, intravenous immune globulin (?)
Bone marrow
B cell
Methylpred
4
Antibody against CD154
T cell
3
Azathioprine, cyclophosphamide, cyclosporine, corticosteroids, danazol, mycophenolate mofetil
2
Thrombopoietin, thrombopoietic agents, corticosteroids

Prednisone First-line Therapy

Prednisone 1 mg/kg po OD (if platelets < 30) – continue for 2-4 weeks

- Response rate 2/3 - plts > 50 but only 20% of these pts will have sustained response
- Most responders do so by 2 weeks

  - At platelet > 50
  - Start taper 10 mg qweek until 20 mg then 5 mg qweek until 10 mg then 2.5mg per week thereafter
  - Counsel patients re: side effects of steroids (hypertension, diabetes, cataracts, skin changes, muscle weakness, mood changes, weight gain, osteoporosis, AVN, infections, etc.)
  - Patients who are on prednisone for >1 month - calcium (1000 mg/d), Vit D (800 IU/d) and PPI
  - Consider Bisphosphonate at 3months if still on Pred or repeated courses
  - yearly monitoring of bone mineral density
  - Relapse >50%

- Longer course prednisone - preferred over pulse dexamethasone 40mg x 4 days

- If steroids contraindicated, use IVIG or anti-D

Chronic Management

- **Anti- D – WinRho SDF**
  - For Rh+ patients
- **Danazol**
  - Unclear mechanism – attenuated androgen
- **Rituximab – Anti CD-20**
- **Thrombopoetin (TPO) mimetics**
  - Romiplostim (S/C monthly)
  - Eltrombopag (oral daily) – dietary restrictions

Acute on Chronic presentations
- Prednisone
- Intermittent IVIg

Check for and treat H Pylori infection – molecular mimicry

- Eradication improved counts 50% patients with no additional immunosuppressive therapy

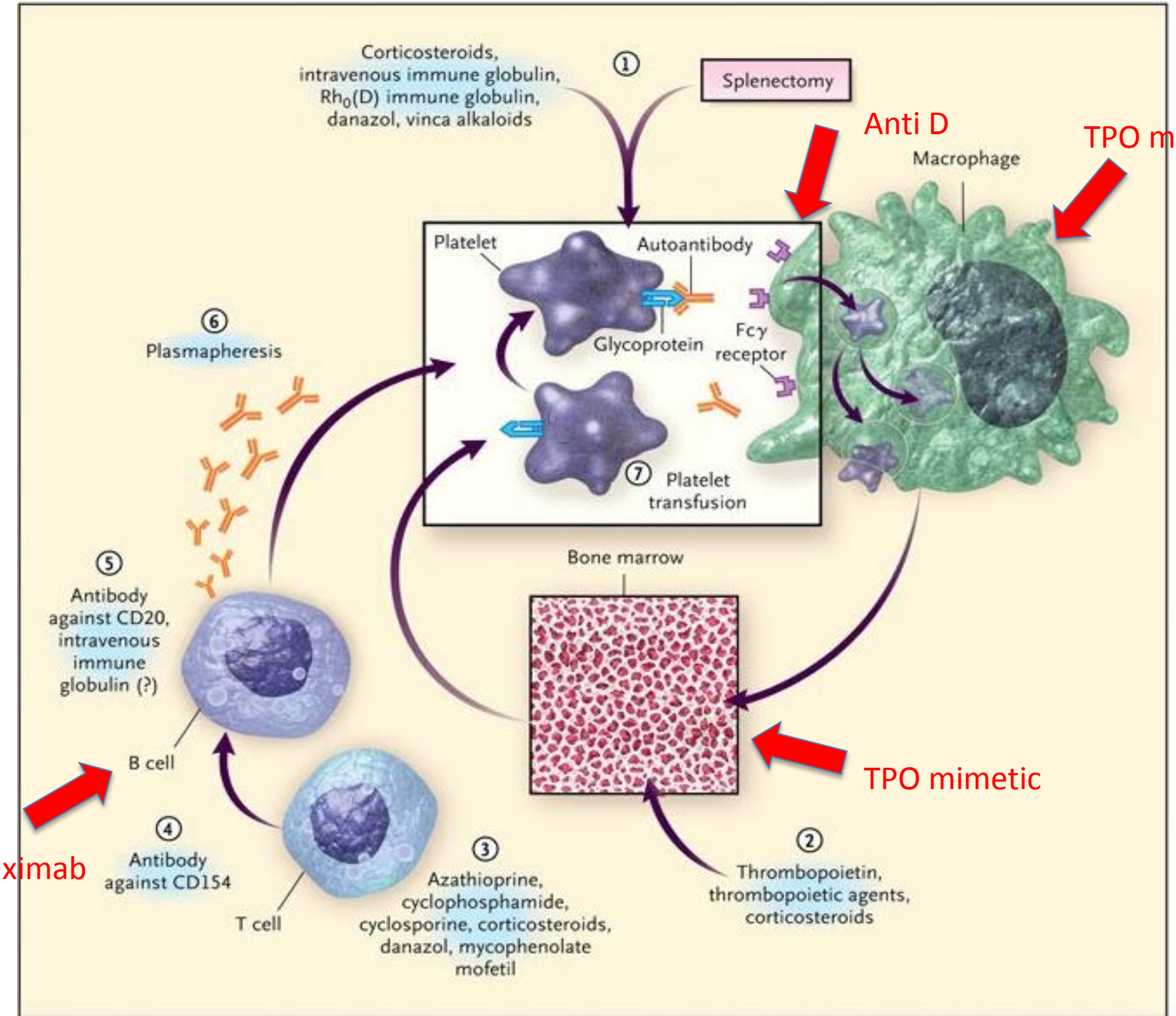

Corticosteroids, intravenous immune globulin, $Rh_0(D)$ immune globulin, danazol, vinca alkaloids
1
Splenectomy
Anti D
TPO mimetic
Macrophage
Platelet
Autoantibody
Glycoprotein
Fcγ receptor
6
Plasmapheresis
7
Platelet transfusion
Bone marrow
5
Antibody against CD20, intravenous immune globulin (?)
B cell
Rituximab
4
Antibody against CD154
T cell
3
Azathioprine, cyclophosphamide, cyclosporine, corticosteroids, danazol, mycophenolate mofetil
2
Thrombopoietin, thrombopoietic agents, corticosteroids
TPO mimetic

Table 3. Definitions of response to treatment by ITP*

Complete response (CR)	A platelet count $\geq 100 \times 10^9$/L measured on 2 occasions $>$ 7 days apart and the absence of bleeding.
Response (R)	A platelet count $\geq 30 \times 10^9$/L and a greater than 2-fold increase in platelet count from baseline measured on 2 occasions $>$ 7 days apart and the absence of bleeding.
No response (NR)	A platelet count $< 30 \times 10^9$/L or a less than 2-fold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on 2 occasions more than a day apart.
Loss of complete response	A platelet count $< 100 \times 10^9$/L measured on 2 occasions more than a day apart and/or the presence of bleeding.
Loss of response	A platelet count $< 30 \times 10^9$/L or a less than 2-fold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on 2 occasions more than a day apart.

Overall Management

- Goal of therapy
  - To achieve a hemostatic platelet count of 30×10^9/L
  - **DO NOT TARGET A NORMAL PLATELET COUNT**
  - Improve platelet count while minimizing treatment-related morbidity

- Recent literature suggests the potential for aggressive therapy at the time of diagnosis to alter the natural history of ITP

Treatment type	Initial Response (days)	Peak Response (days)
Anti D	1-3	3-7
IVIg	1-3	2-7
Prednisone	4-14	7-28
Dexamethasone	1-14	4-28
Danazol	14-90	28-180
Rituximab	7-56	14-180
Splenectomy	1-56	7-56
Eltrambopag	7-28	14-90
Romiplostim	5-14	14-60
Anti D	1-3	3-7
Azathioprine	30-90	30-180
Vinblastine	7-14	7-42
Vincristine	7-14	7-42

Platelet Thresholds

Setting	Platelet count
Neurosurgery CNS trauma	<100 x 109/L
Epidural catheter insertion or removal	<50 – 80 x 109/L
Significant microvascular bleeding Surgery Lumbar puncture	<50 x 109/L
Vaginal delivery	<50 x 109/L
Thrombocytopenia with fever or coagulopathy	<20 x 109/L
Thrombocytopenia due to marrow failure	<10 x 109/L

Canadian Blood Services, “Bloody Easy” , Br J of Haematol 2003;122:10-23

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Case 1 – H.T.

Case 1 – H.T.

- 24 yo F
- Presented 2014 – following sudden drop platelet coincided with Doxycycline acne
- 2 courses Pred – declined further courses – perceived associated weight gain
- W/U no secondary causes – presumptive Dx primary ITP

- Recurrent drop in plt to 30-40 – assoc with Menorrhagia
- Referral to Gyne - transexamic acid – later disclosed not using (cost), declined Mirena

- Fe deficiency with intermittent anemia – resolved with supplement

- Recurrent URTI S/S with chronic sinus congestion – infx - drops in plt

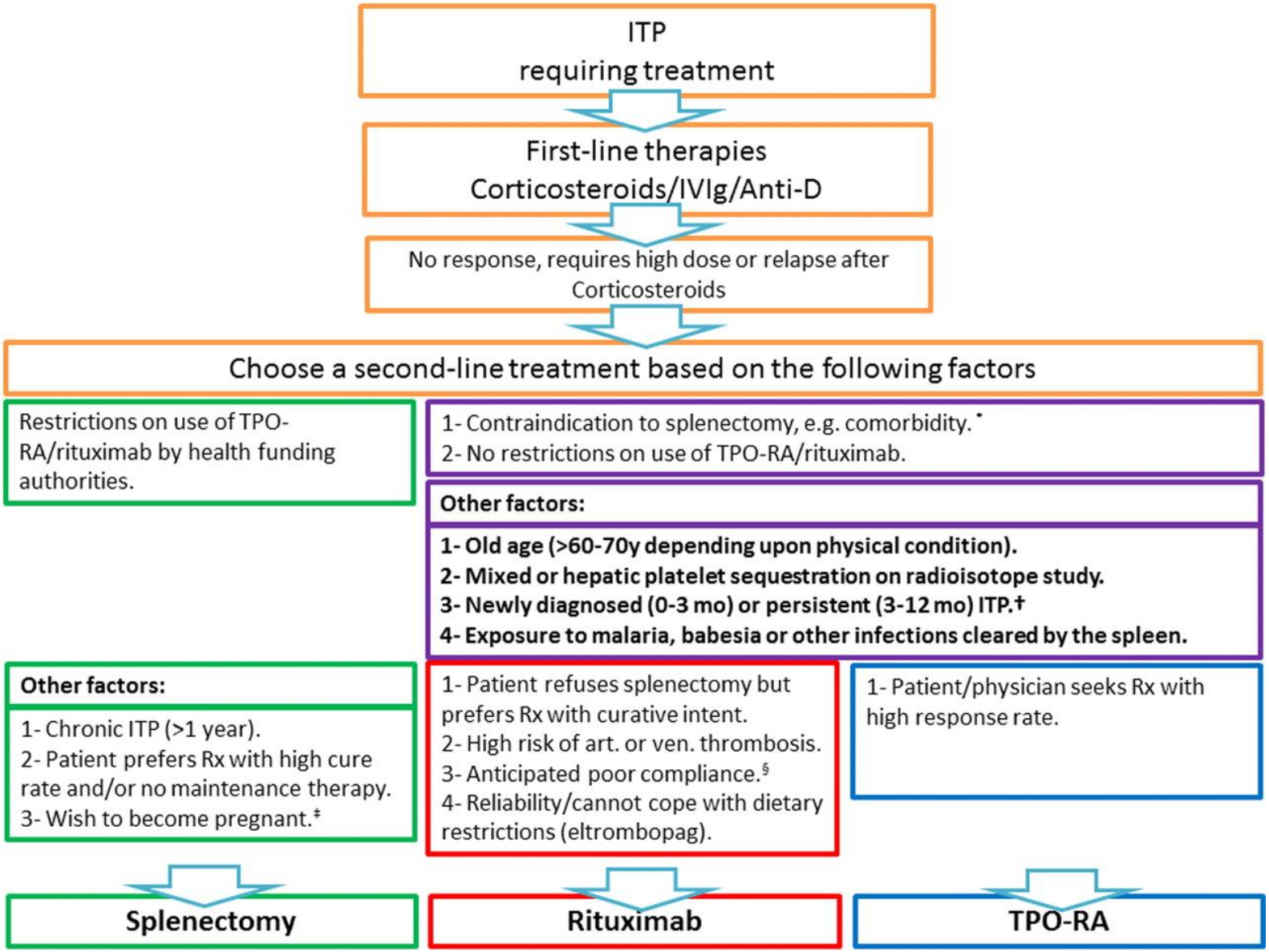
Case 1 – H.T.

- Platelet as low as 16 since last wean of Prednisone
- responds to IVIg 1G/kg daily x 2 (approx q6 weeks)
- A neg, DAT negative
- Given Rx Danazol – did not start - side effect profile
- Declines referral for Rituxan
- Declines Romiplostim

- Bone marrow Bx – megakaryocytic thrombocytopenia
- Previous imaging with US - spleen size normal – no obvious accessory spleen

- ?splenectomy

Suggested treatment algorithm for ITP.



Waleed Ghanima et al. Blood 2012;120:960-969

Splenectomy

- Mortality
  - Open splenectomy 1%
  - Laparoscopic splenectomy 0.2%
- 4% complications
  - pneumonia, pleural effusion
  - bleeding
  - thrombosis
  - hernia, intra-abdominal adhesions
  - nerve palsies
- 1-2% lifetime risk of overwhelming sepsis

Overwhelming Post-Splenectomy Infection (OPSI)

Risk:

- 1-2% lifetime risk
- 0.2-0.4% annual risk
- Risk highest in first year (adults ~1%, children ~5%)
- Mortality approaches 40%

OPSI

- **Encapsulated** bacteria
- **Strep pneumoniae** most common
  - Recovered in 50-90% of isolates
- H. Influenza B
- Neisseria Meningitides risk
- Strep B, Staph Aureus, E. coli, Salmonella

OPSI

Immunizations

- 14 days prior to surgery

- Polyvalent Pneumococcal
  - pneumovax protects against 75% active organisms
  - Revaccination Every 5 -10 years
- Quadrivalent meningococcal polysaccharide
  - unclear in adult population but recommended
  - Revaccination Every 5 -10 years
- H. influenzae type b
  - AB titres can be monitored to assess need for booster doses

- Should also receive annual influenza vaccine

OPSI

Counselling and Antibiotics

- Discharge patients with a supply of oral antibiotics with clear instructions to initiate therapy with onset of infective symptoms while seeking medical aid.
- Warn all patients regarding OPSI risk.
- Seek immediate care if develop febrile illness.
- Long term prophylactic antibiotics remains controversial – not recommended
  - promotes resistant strains.
- Beware dog bites - capnocytophaga canimorus
- If travelling to malarial areas - **need prophylaxis**

Refractory ITP

- **Refractory ITP = chronic ITP post-splenectomy**
- ?accessory spleen
- Withhold any treatment unless thrombocytopenia severe and bleeding clinically important problem

- With Splenectomy
  - Generally ~40-50% response rates **though only 10-25% sustained response**
  - patients unresponsive to therapy with platelet counts <30
  - high rate of bleeding-related mortality (36.7%)
  - Fewer patients died from ITP treatment complications (6.7%)

- Generally require >3 months to see effect

Case 2 – S.G.

Thrombosis and ITP

- paradoxical development of thrombosis in patients with ITP have not been defined
- The mechanisms unknown - incidence of antiphospholipid antibodies (APLA) appears to be increased in patients with ITP
- Low and fluctuant platelet counts make management challenging

Case 2 – S.G.

- 34 yo F
- ITP Dx 2007 (plt 60-80, as low as 20)
- Unprovoked PE July 2009 (warfarin with unstable INR, often subtherapeutic – menorrhagia)
- G3A1L2 – no VTE/preterm delivery
- Recurrent PE and DVT when sub therapeutic INR
- APLA neg
- Remnant DVT right leg - SFV
- Rivaroxaban 20 mg po daily

Case 2 - S.G.

- Platelet drop 30s – interruption of A/C for IVIg and prednisone (with a slow wean)
- 4 days later– ER – occlusive thrombus right leg SFV
- Chest pain and SOB – PE on CTA
- Restarted Rivaroxaban – plt 40 (counseled)
- No further interruptions
- Age related malignancy screening delayed – unable to interrupt therapy (endometrial Bx, Colonoscopy), mammogram neg, PAP normal
- Started smoking again

Case 2 – S.G.

- Started Danazol prior to wean off prednisone
- Once off Pred - multiple arthralgias and myalgias
- Autoimmune W/U neg, ESR elevated
- Weaning Danazol to lowest effective dose
- Colonoscopy neg
- Gyne W/U neg
- Platelets 50-80 on 100mg BID Danazol – acne, but menorrhagia better
- Arthralgias improving without intervention

What were our other options?

- Anti D
- Rituxan
- Anti TPO
- Splenectomy
- IVC filter in case plt drop again

Case 3 - N.C.

ITP and Pregnancy

- ITP occurs in 1-2 in 1000 pregnancies

- the most common cause of isolated thrombocytopenia in the first and early second trimesters

- There are variable reports of exacerbation of ITP during pregnancy or in the postpartum period

- Approximately half of patients with a prior diagnosis of ITP experience a progressive decline in platelet count during pregnancy

Causes in Pregnancy

Pregnancy Specific

Isolated thrombocytopenia

- Gestational thrombocytopenia (70%-80%)

Thrombocytopenia associated with systemic disorders

- Preeclampsia (15%-20%)
- HELLP syndrome (< 1%)
- Acute fatty liver of pregnancy (< 1%)

Not Pregnancy Specific

Isolated thrombocytopenia

- Primary immune thrombocytopenia– ITP (1%-4%)
- Secondary ITP (< 1%)*
- Drug-induced thrombocytopenia (< 1%)
- Type IIb VWD (< 1%)
- Congenital (< 1%)

Thrombocytopenia associated with systemic disorders

- TTP/HUS (< 1%)
- SLE (< 1%)
- Antiphospholipid antibody syndrome (< 1%)
- Viral infections (< 1%)
- Bone marrow disorders (< 1%)
- Nutritional deficiency (< 1%)
- Splenic sequestration (liver diseases, portal vein thrombosis, storage disease, etc; < 1%)

ITP and Pregnancy

Differentiating ITP from Gestational Thrombocytopenia (GP):

- **Whenever plt count <50 in absence of OBS complication = ITP**
- thrombocytopenia pre-pregnancy = consider ITP
- women with no history of ITP, platelet counts below 100 × 10^9/L early in pregnancy and declining as gestation progresses are more consistent with ITP than with GT

- The situation becomes more complicated if a low platelet count is detected during the third trimester

- no clear lower limits of the platelet count in GT
- Platelet count 50-70 - diagnosis remains uncertain

Case 3 – N.C.

- 33 yo F - G2P1 26w gestation
- ITP in first pregnancy (Dec 2013)
  - 36 4/7 gestation- plt count 80 – monitored weekly
    - Stable 70-80, asymptomatic
  - Presented 41w gestation - induced (plts 42)
  - failure to progress – plt drop (30) – treated with IVIg (Ig/kg 2 days), prednisone (1mg/kg po daily)
  - platelets for C Section – no bleeding complications

Case 3 – N.C.

- Plan:
  - Contacted office at discovery of 2nd pregnancy
  - Monthly monitoring now moved to q 2 weeks
  - Reliable to present to ER/mat
  - Planned C Section – allows for management of platelets at delivery and days preceding
  - Close consultation with Gyne
  - Current platelet count 80-90

Pregnancy and ITP

- ? Gestational thrombocytopenia
  vs ITP

- consider ITP if plt count < 70 or if occurs before 3rd trimester
- Don’t forget about non-pregnancy causes
- pregnancy causes - HELLP syndrome

ITP in Pregnancy

- Management should be based on platelet count
  - Plt >50 – observe, IVIg pre-delivery if plt 70-80 (for epidural option)
  - Plt<20-30 – IVIg and prednisone (plts if bleeding or delivery)
  - Splenectomy – severe cases

- No need to deliver via C-section – base on obstetrical considerations only
  - may be indicated if fetal platelet count **known to be <20,000**

- Have platelets available if maternal platelet count <20

Summary

- ITP – rarely associated with bleeding (plt <10)
- Drop in platelet counts are expected in pregnancy for those with ITP – planned delivery recommended
- ITP association with increased VTE risk
- Heterogeneous group of patients – different presentations and response to therapies
- Personalized approach to management is recommended


QUESTIONS?