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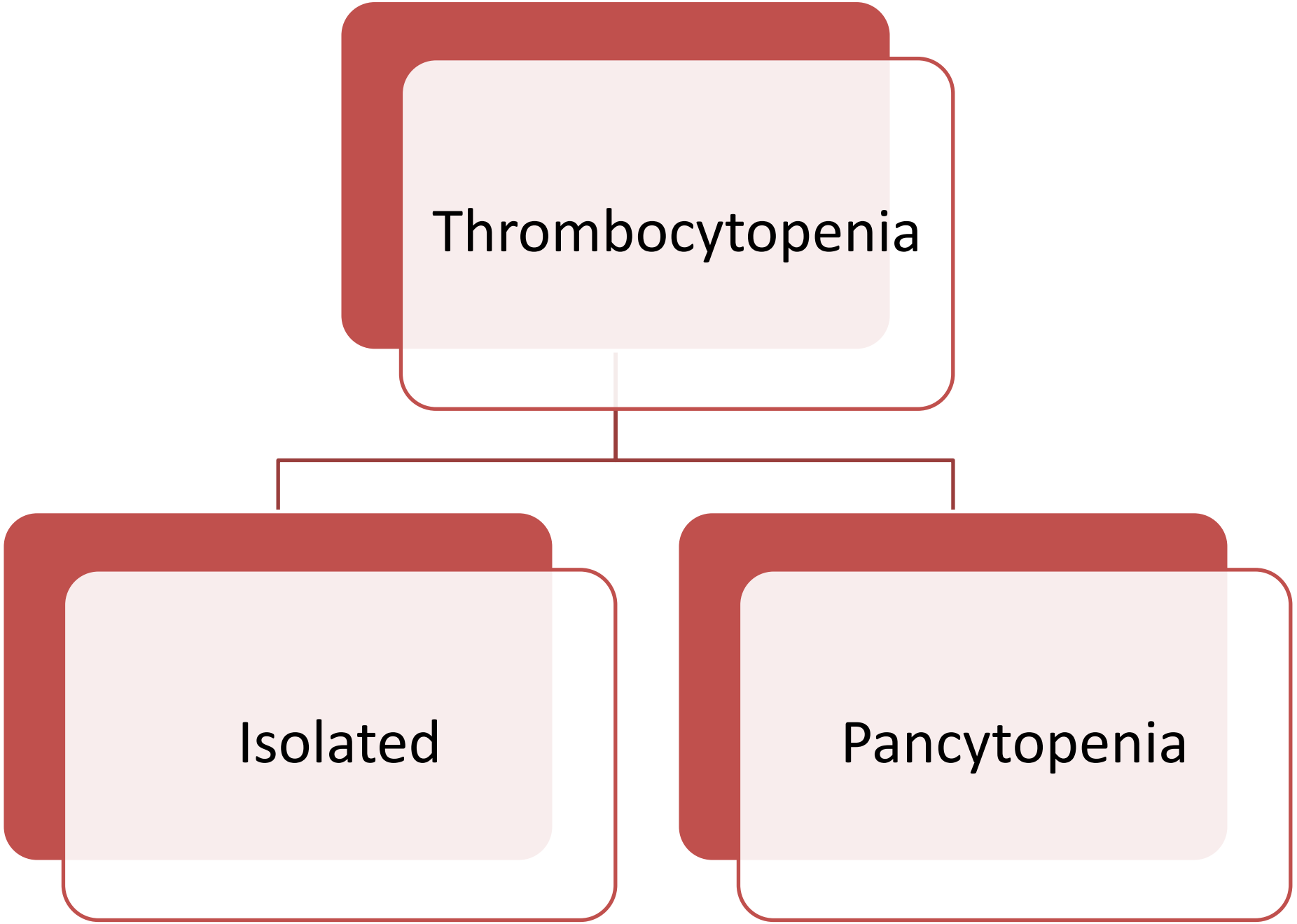
BHS course

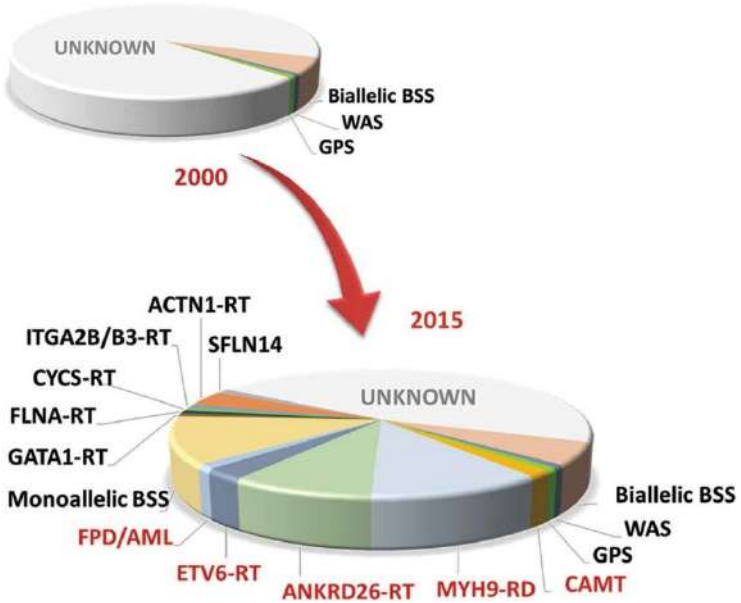
19 november 2022

ISOLATED THROMBOCYTOPENIA


Thrombocytopenia
Isolated
Pancytopenia

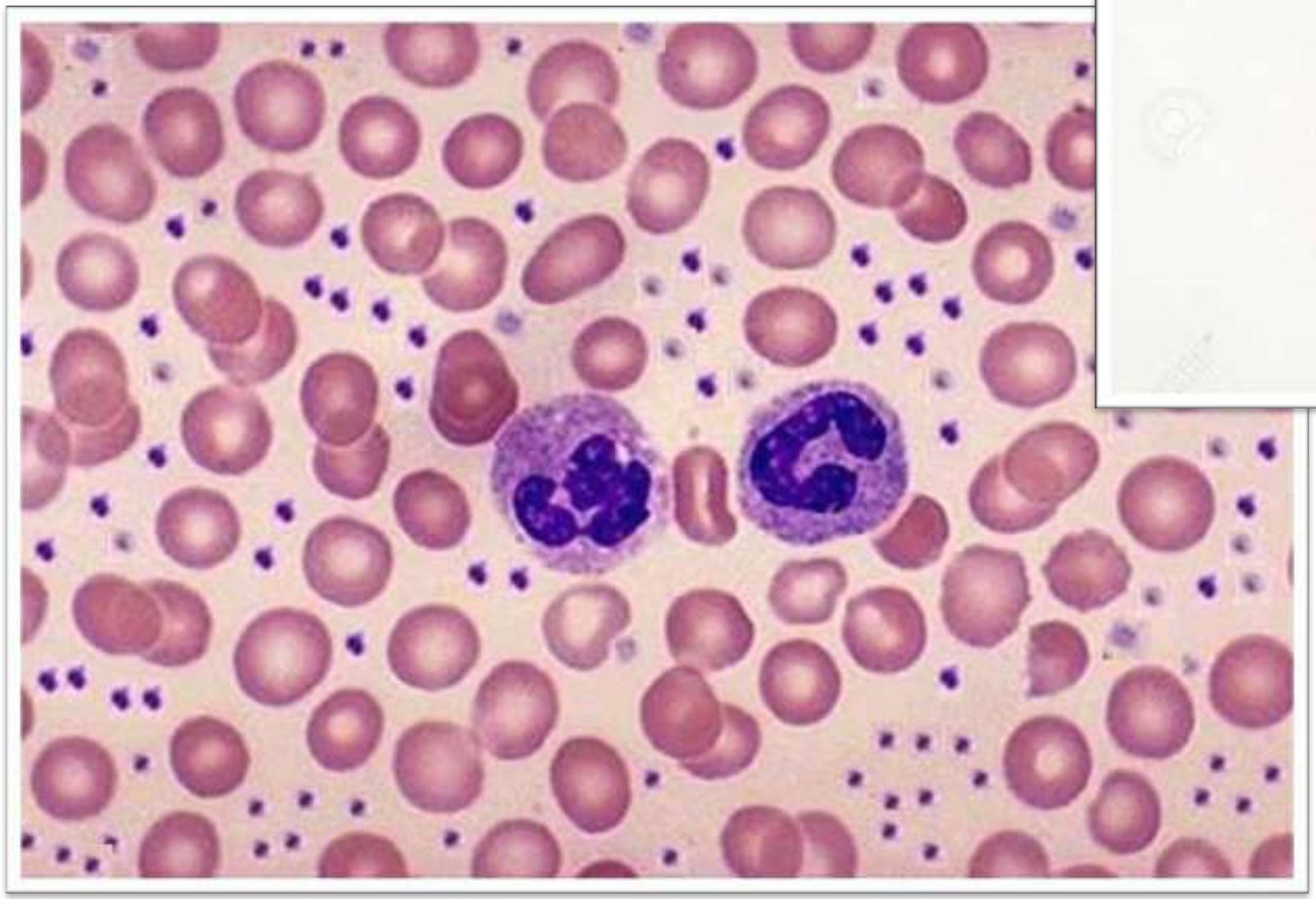
Thrombocytopenia

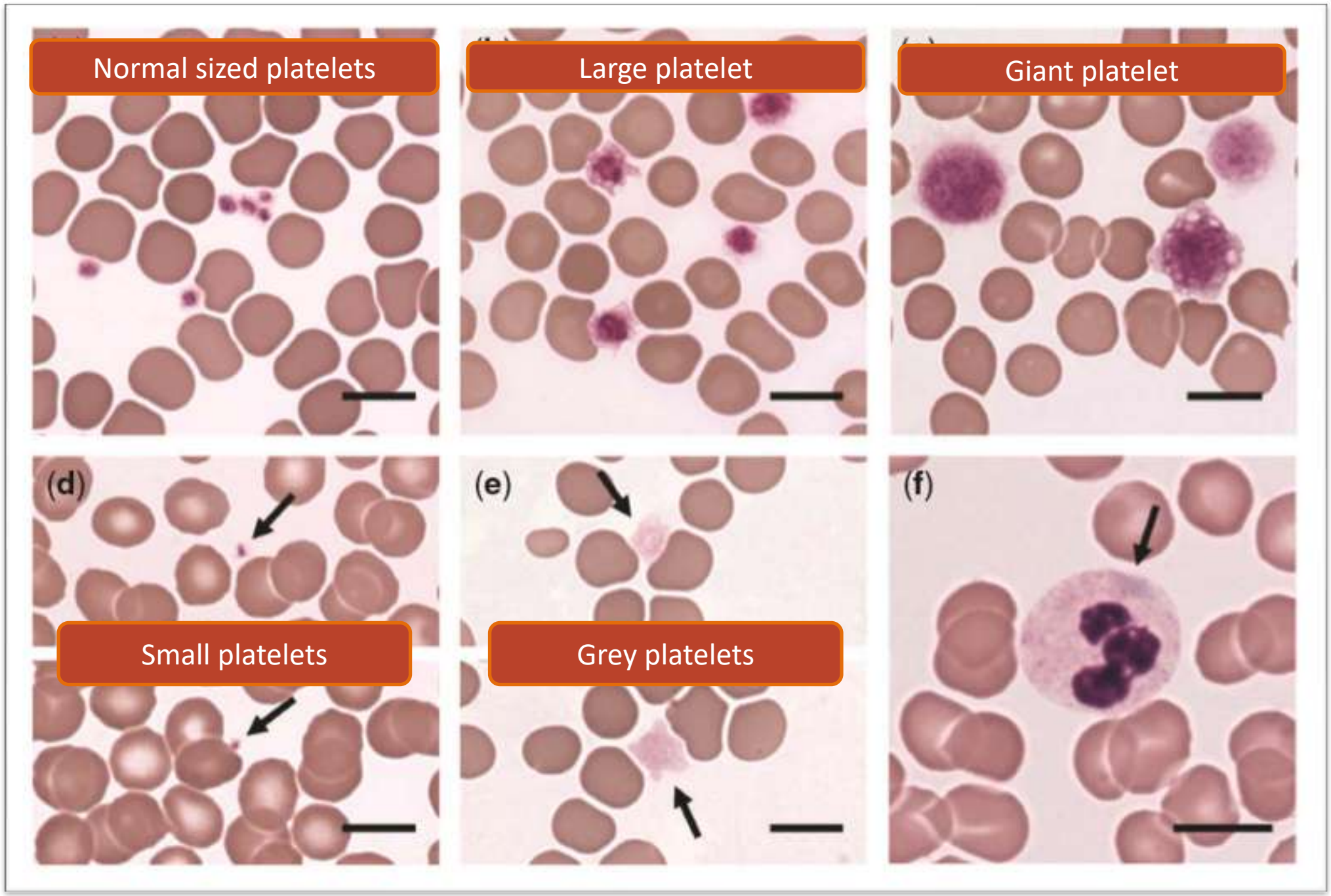
- Isolated
  - Acquired
  - Hereditary
    - Wiskott Aldrich S
    - TAR
    - Bernard Soulier
    - Grey platelet S
    - MYH9 related
    - FTLS
    - VCF
    - Di George
- Pancytopenia
  - Hereditary
    - Fanconi
    - Dyskeratosis congenita
    - CAMT
  - Acquired



- PLATELET SIZE
- MODE OF INHERITANCE (AD/AR)
- ASSOCIATED FEATURES (SYNDROMIC OR NOT)

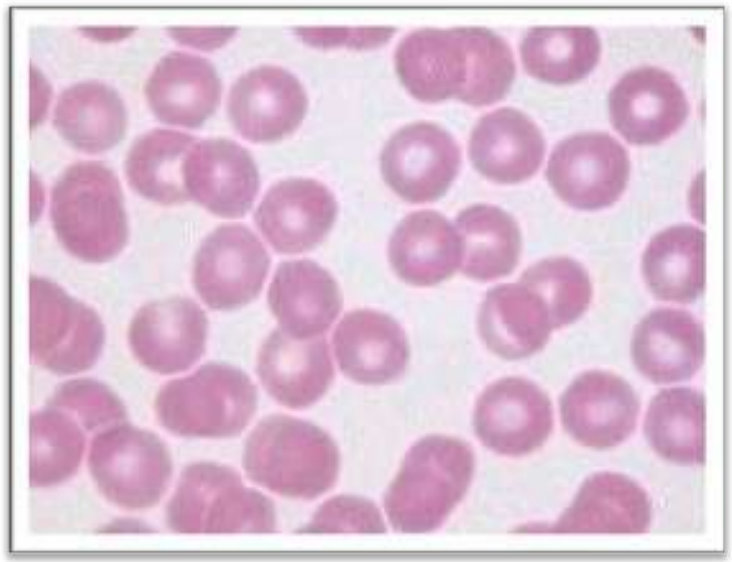
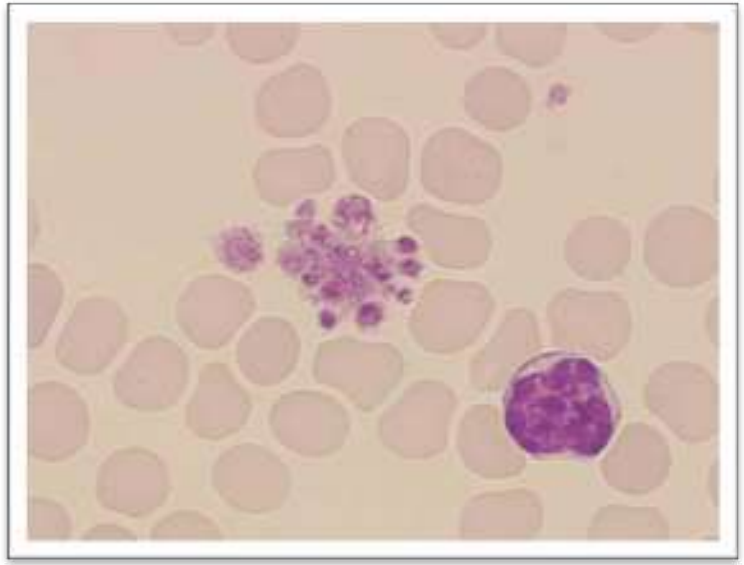
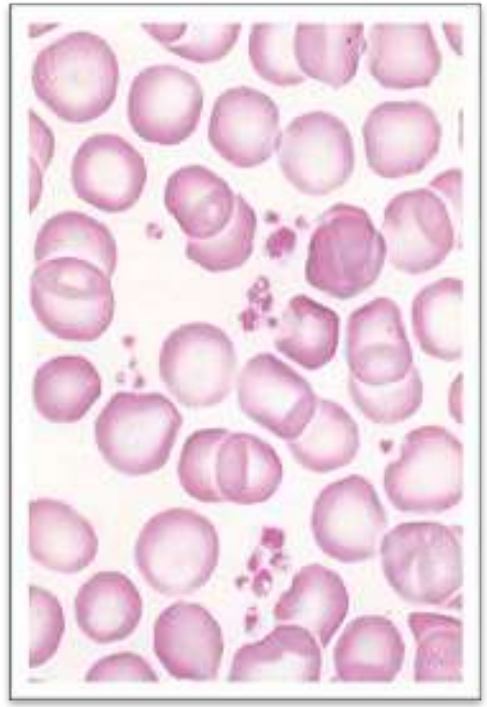
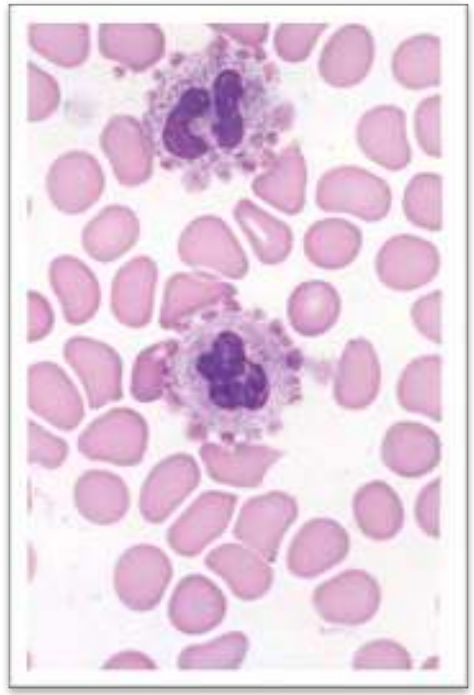
Peripheral Blood smear



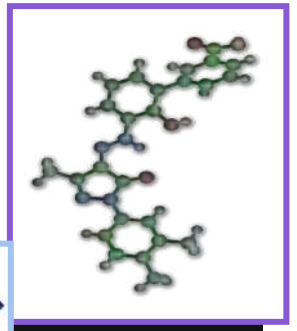

Normal sized platelets
Large platelet
Giant platelet
(d)
Small platelets
(e)
Grey platelets
(f)

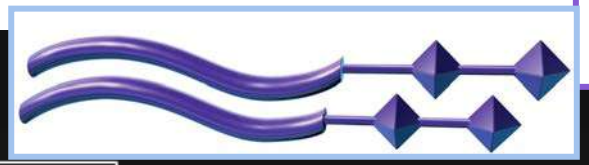
Exclusion of pseudo-thrombocytopenia or spurious thrombocytopenia

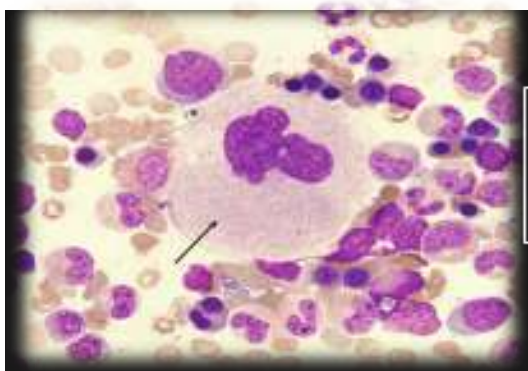
- In vitro agglutination of platelets when blood is collected in EDTA tubes (2% of all thrombocytopenias detected on EDTA blood) (max 0.2% of all EDTA samples in a hospitalized population)
- Measure platelets on blood collected in citrate or heparine tubes
- Look for agregates on the peripheral blood smear

The history of platelets, megakaryocytes and thrombopoietin







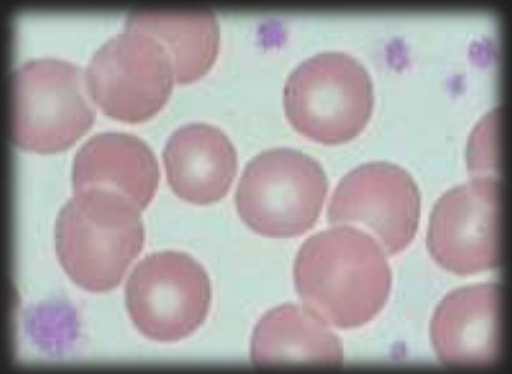
1890 Howell Names Megakaryocytes

1958 Kelemen Coined Thrombopoietin

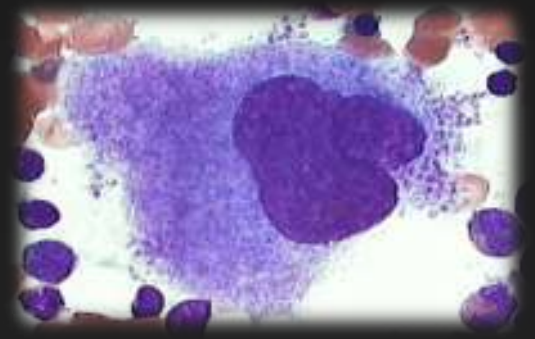
TPO Mimetics Reach the Clinic

1800 | 1900 | 2000

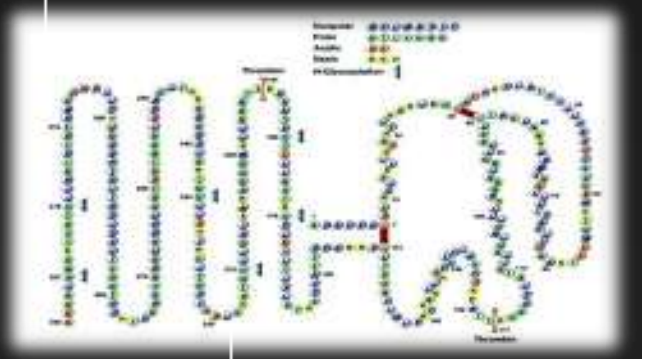
1841 Addison Describes Platelets



1882 Bizzozero Names platelets



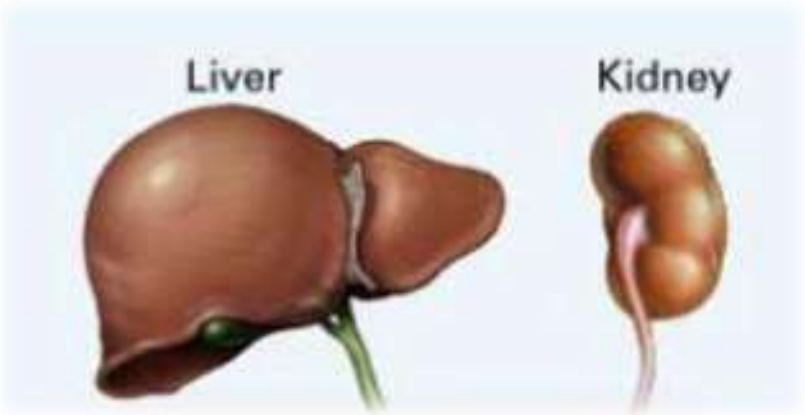
1906 Wright Discovers that Megakaryocytes are the precursors of platelets

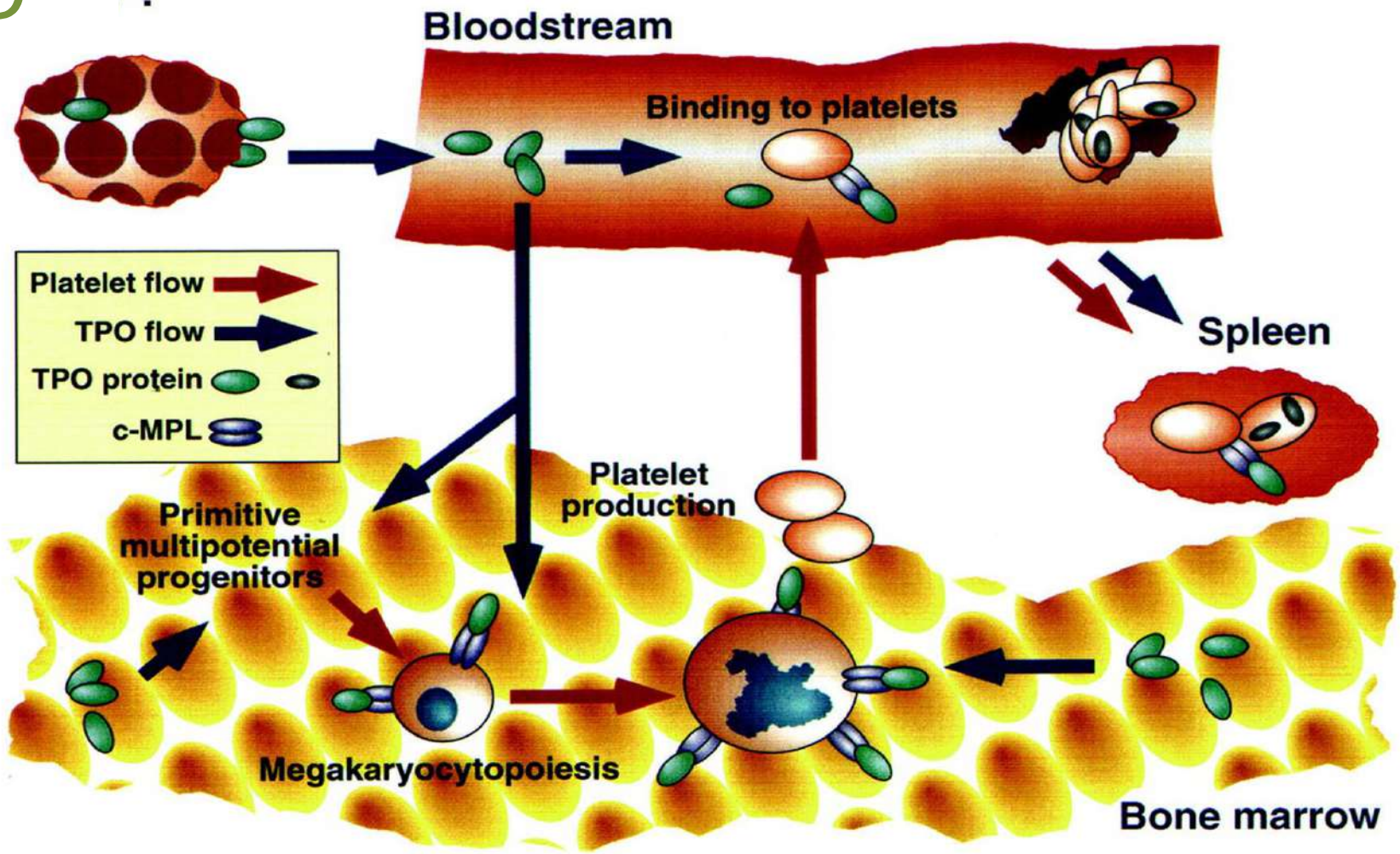


TPO Induces Megakaryocyte and Platelet Production

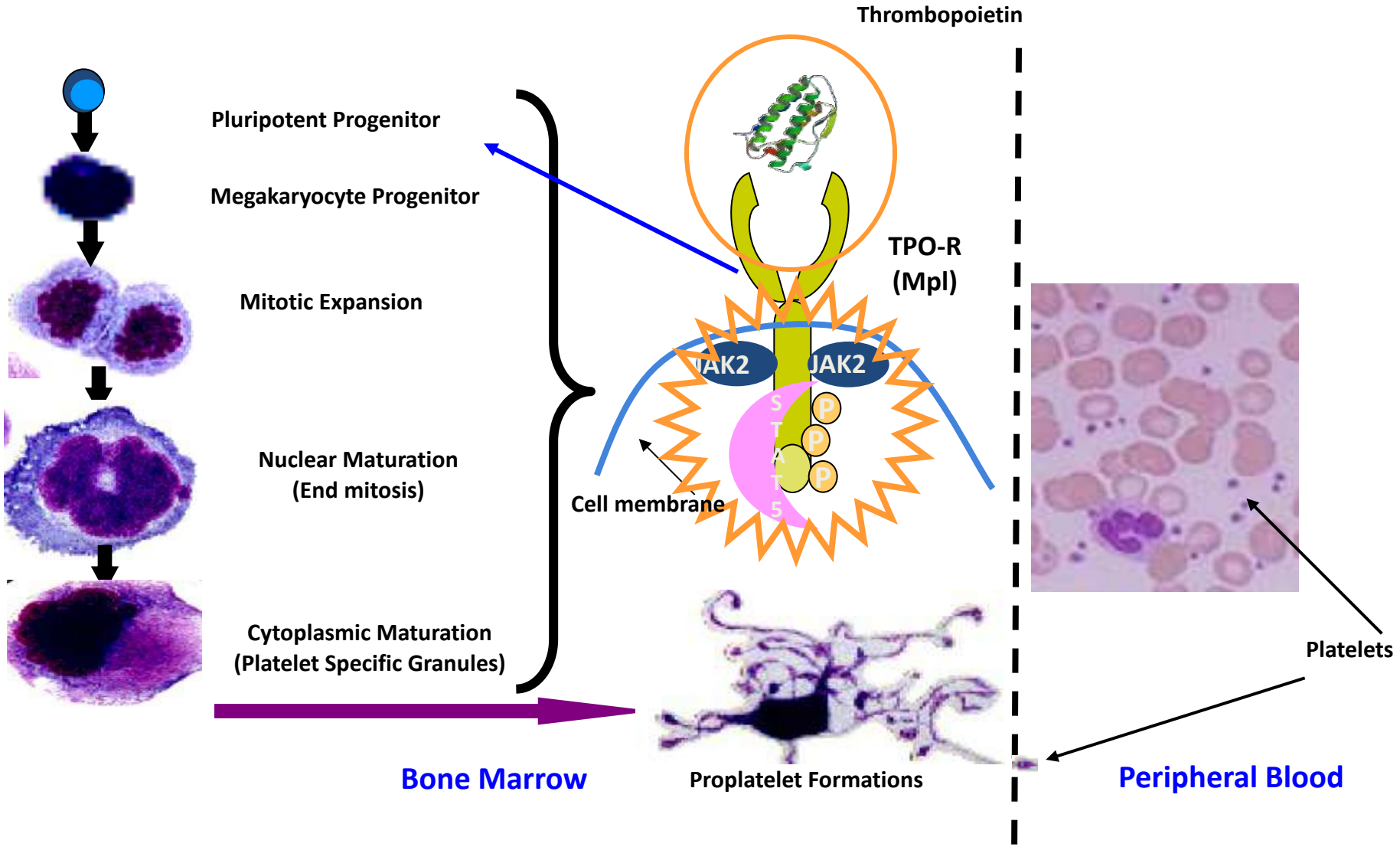
Thrombopoietin production: constitutive or regulated?

TPO

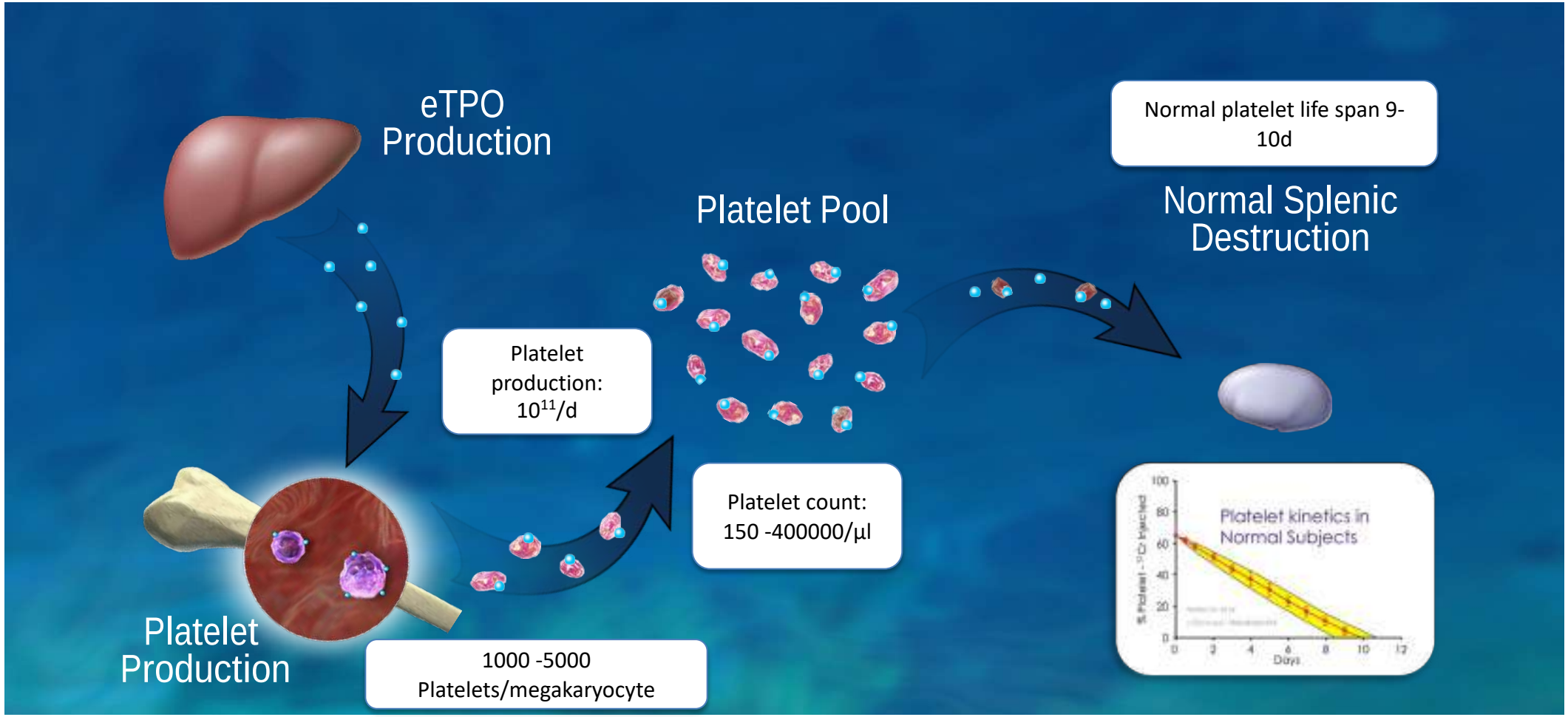




Thrombopoietin signaling & megakaryocyte maturation



Platelet homeostasis



- Endogenous thrombopoietin (eTPO)
- Megakaryocyte precursor
- Megakaryocyte
- Platelet

[1]Kuter et al PNAS 91:1994; [2]Stoffel et al Blood 1996;
[3]Gurney et al Science 1994; [4]de Sauvage et al JEM 1996

AMGEN

Causes of thrombocytopenia

Peripheral destruction

- **Autoimmune**
  - **Primary ITP**
  - **Secondary ITP**
- **Drug induced: HIT,…**
- Alloimmune: posttransfusion, neonatal
- Pregnancy induced
- TTP-HUS
- DIC
- Hemangiomas
- …

Insufficient production

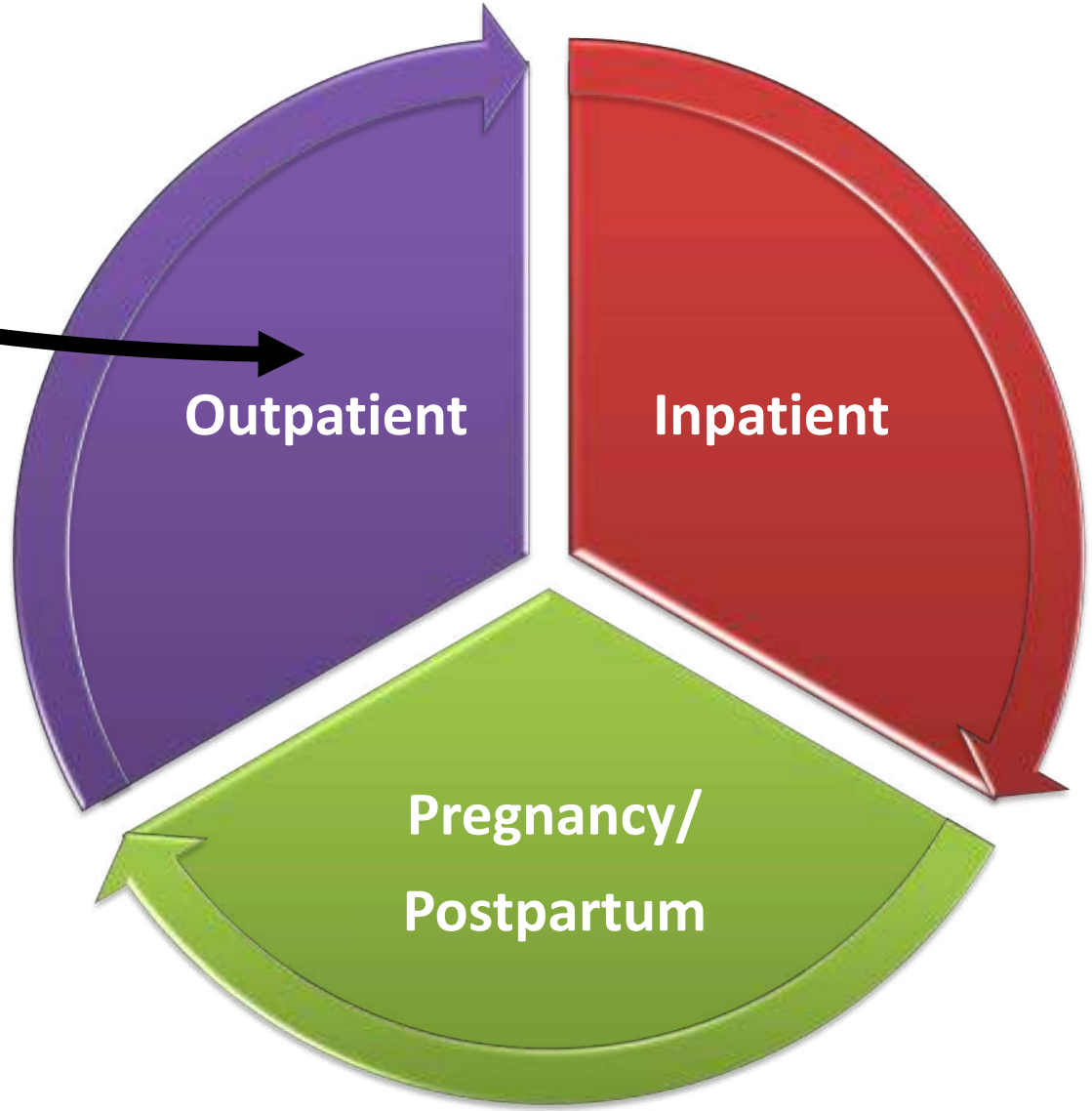
- AA
- **MDS**
- Myelofibrosis
- Bone marrow invasion
- Bone marrow toxicity
- Megaloblastic anemia
- **Hereditary disorders**
- …

others

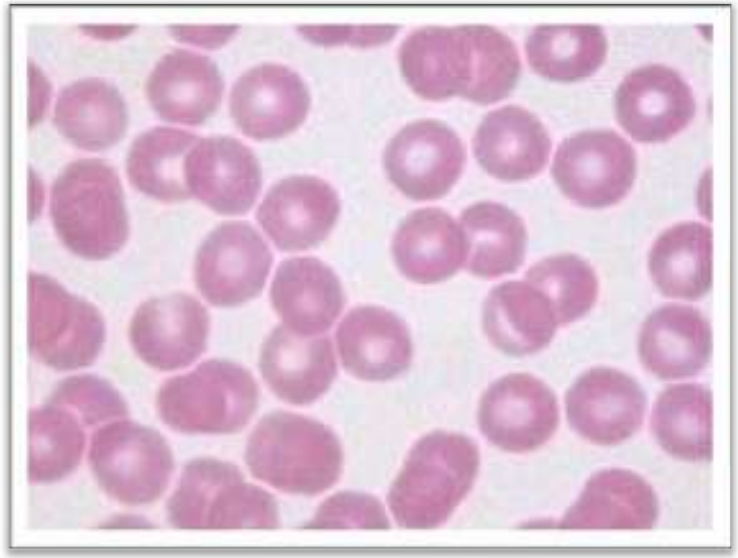
- Platelet sequestration due to hypersplenism
  - *Portal hypertension (cardiac, cirrhosis, V. Porta or V. Cava thrombosis*
  - *Gaucher*
  - *Myelofibrosis*
  - *Viral infections*
  - *…*
- Dilution due to massive transfusion

Outpatient

- ITP
- DITP
- Connective tissue disorders
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Antiphospholipid syndrome
- Infections
  - CMV
  - Hepatitis C virus
  - *H. pylori*
  - HIV
  - Other recent viral infections
- Vaccinations
- Myelodysplastic syndromes
- Congenital thrombocytopenia
- Common variable immunodeficiency



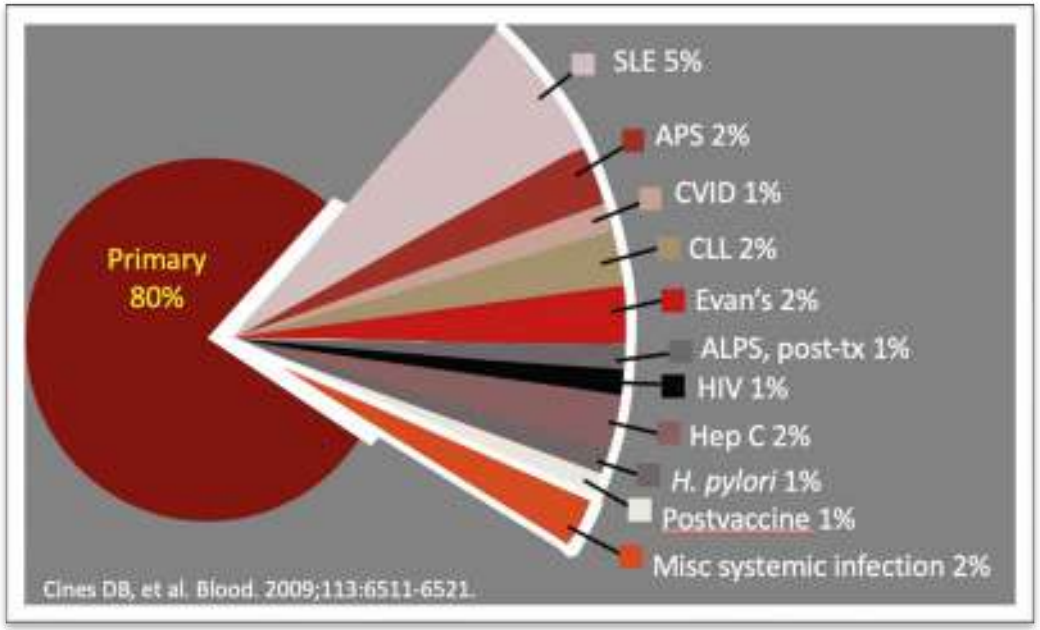
Definition:
Primary Immune Thrombocytopenia



- **Primary:** no obvious initiating and/or underlying cause
  - *Avoid idiopathic*
  - *Approach to secondary ITP differs in a number of cases!!!*

- **Immune:** immune-mediated pathogenesis

- **(Isolated) thrombocytopenia**
  - *Threshold platelets for ITP-diagnosis* ***≤100000/µl*** *instead of* 150000/µl
  - *Avoid Purpura (Bleeding symptoms frequently absent or minimal at the onset of disease)*
  - *Normal complete blood count and peripheral smear*



Rodeghiero et al, Blood 2009

Diagnostic work-up: History

- Personal and familial history
- Recent infections
- Vaccinations (>MMR, < H. Influenzae, pneumococci, Hep B,..)
- Malignancies
- Pregnancy
- Recent travels
- Recent transfusions
- Alcohol abuse
- Dietary habits, beverages, herbal preparations
- Risk factors for HIV and viral hepatitis
- Medication: especially those started 1 to 2 weeks before the onset of thrombocytopenia, recent exposure to heparine

Diagnostic work-up: clinical examination

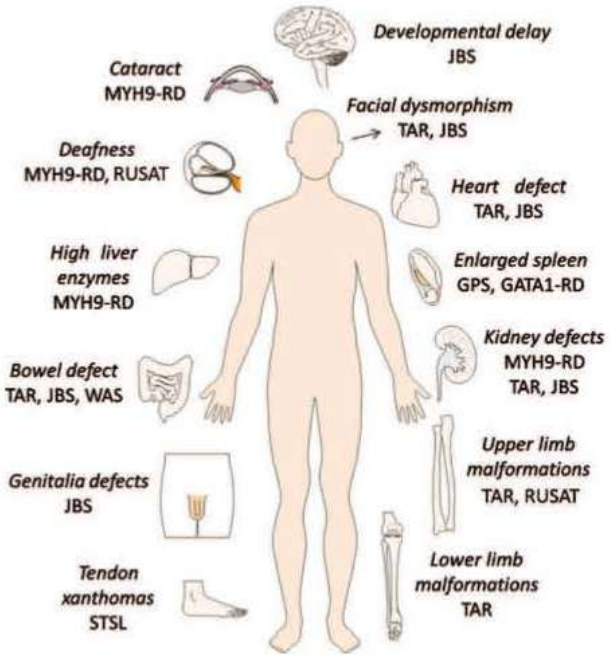
with special attention to:

- **Bleeding signs:**

  petechiae, purpura, ecchymoses

- **Lymphadenopathies**
- **Spleno- , hepatomegaly**

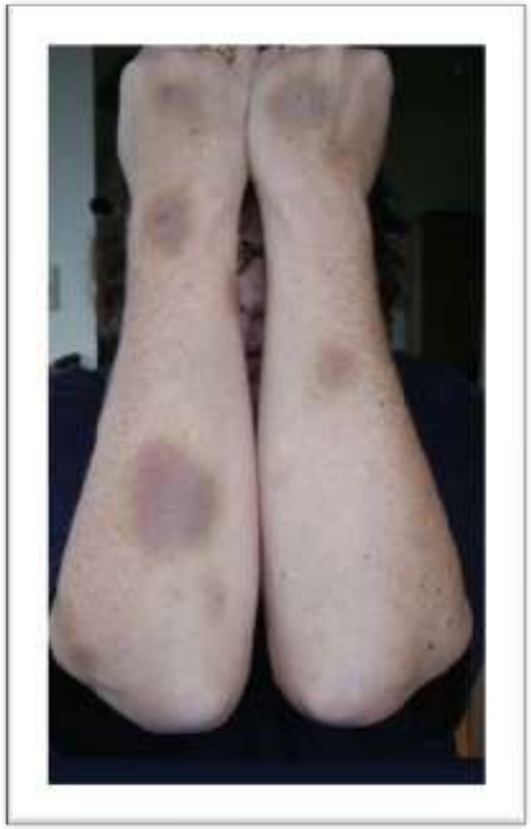
- **Skeletal abnormalities**
- **Dysmorphy**
- **Skin abnormalities**

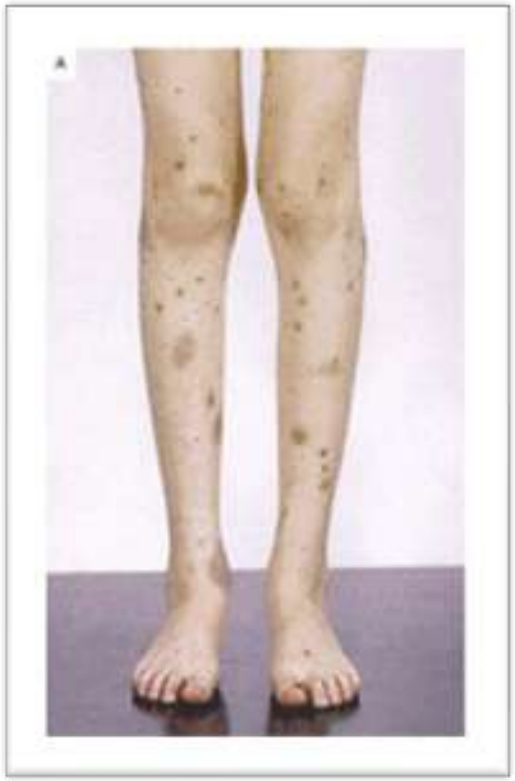


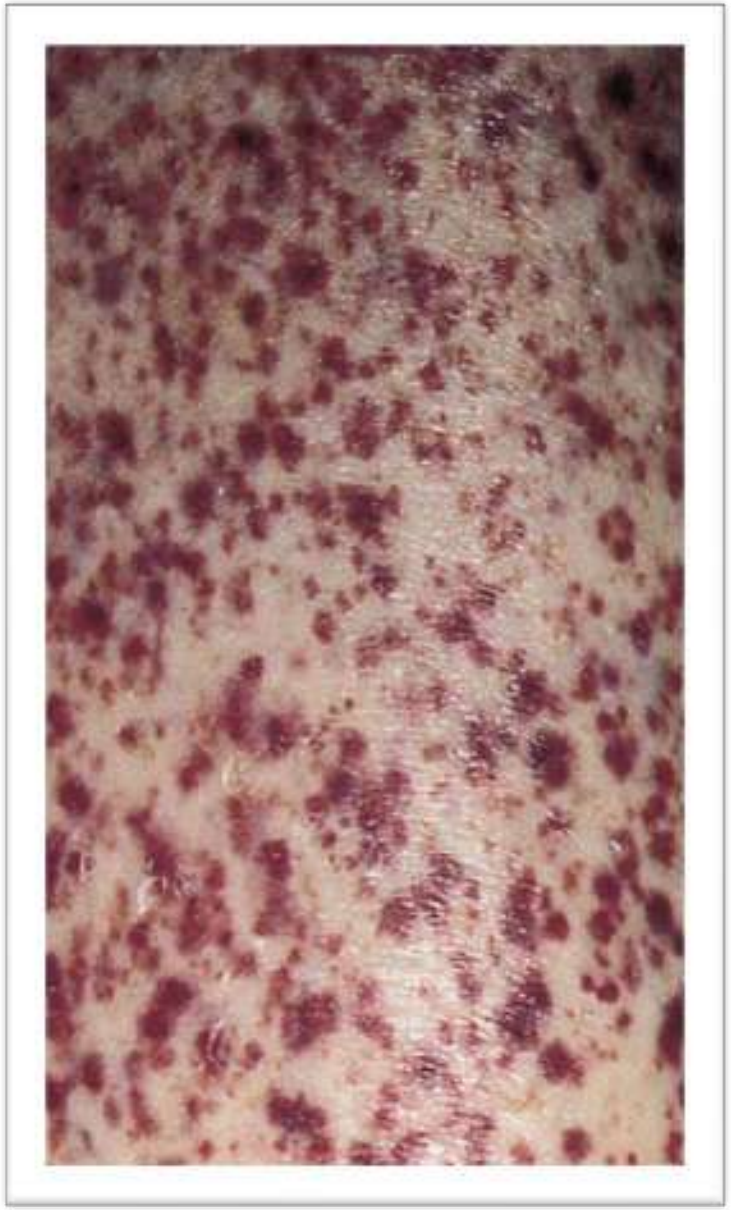
Bleeding symptoms

"Dry" purpura vs…

Petechiae
Purpura
Bruises

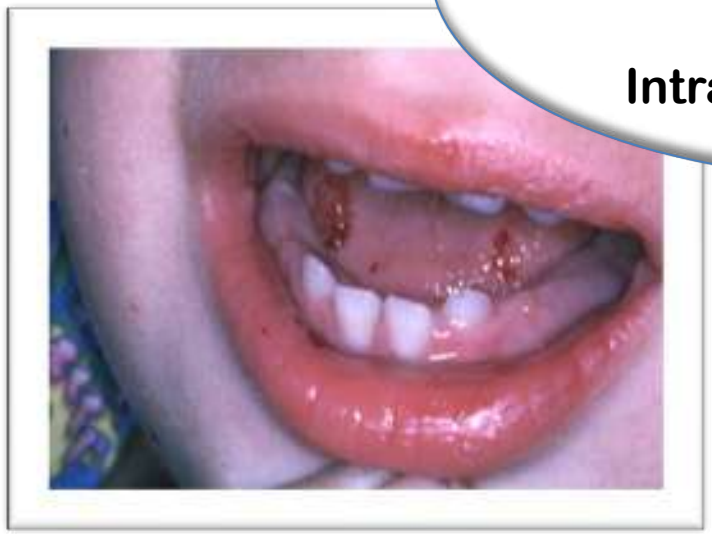


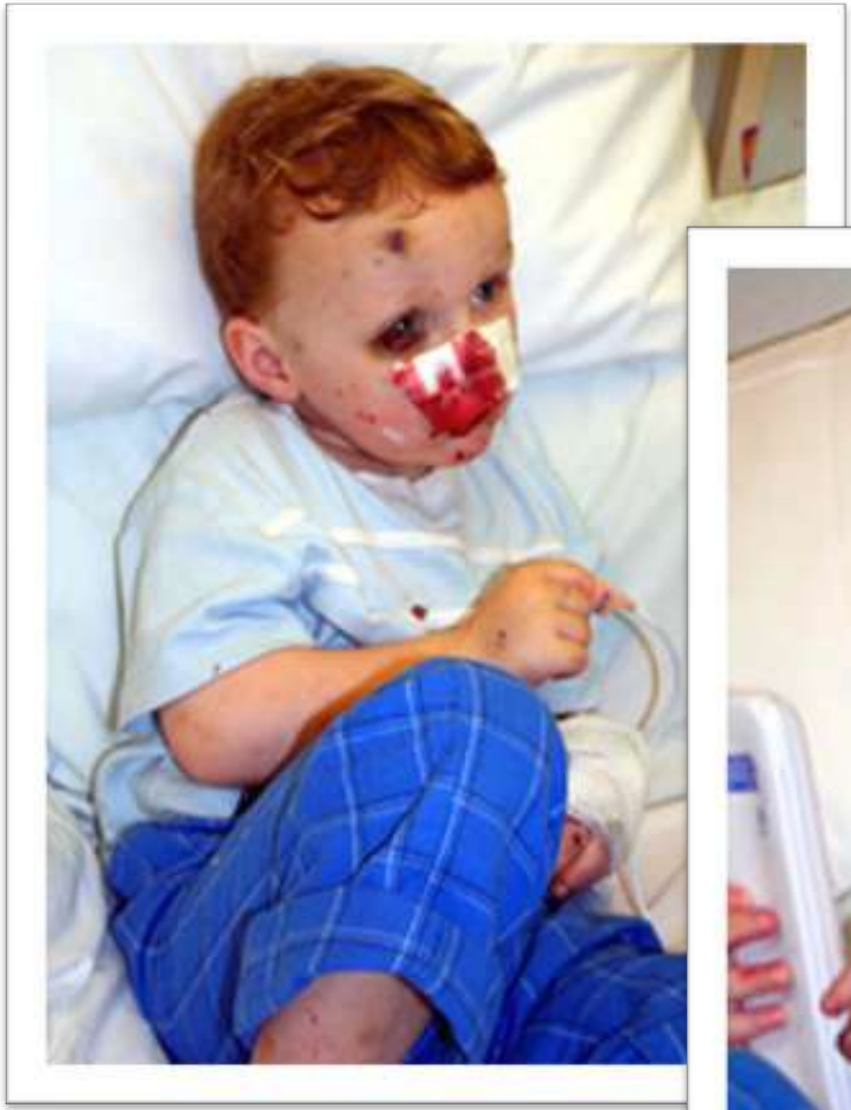


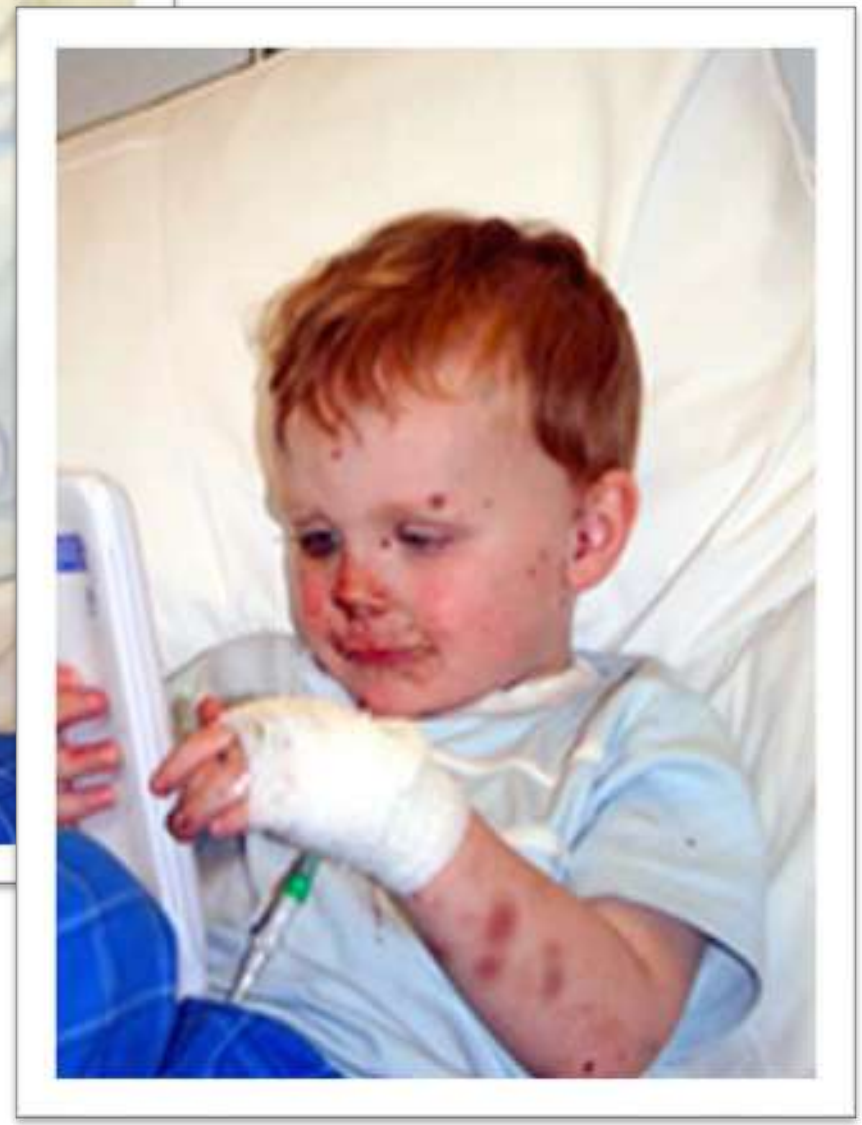


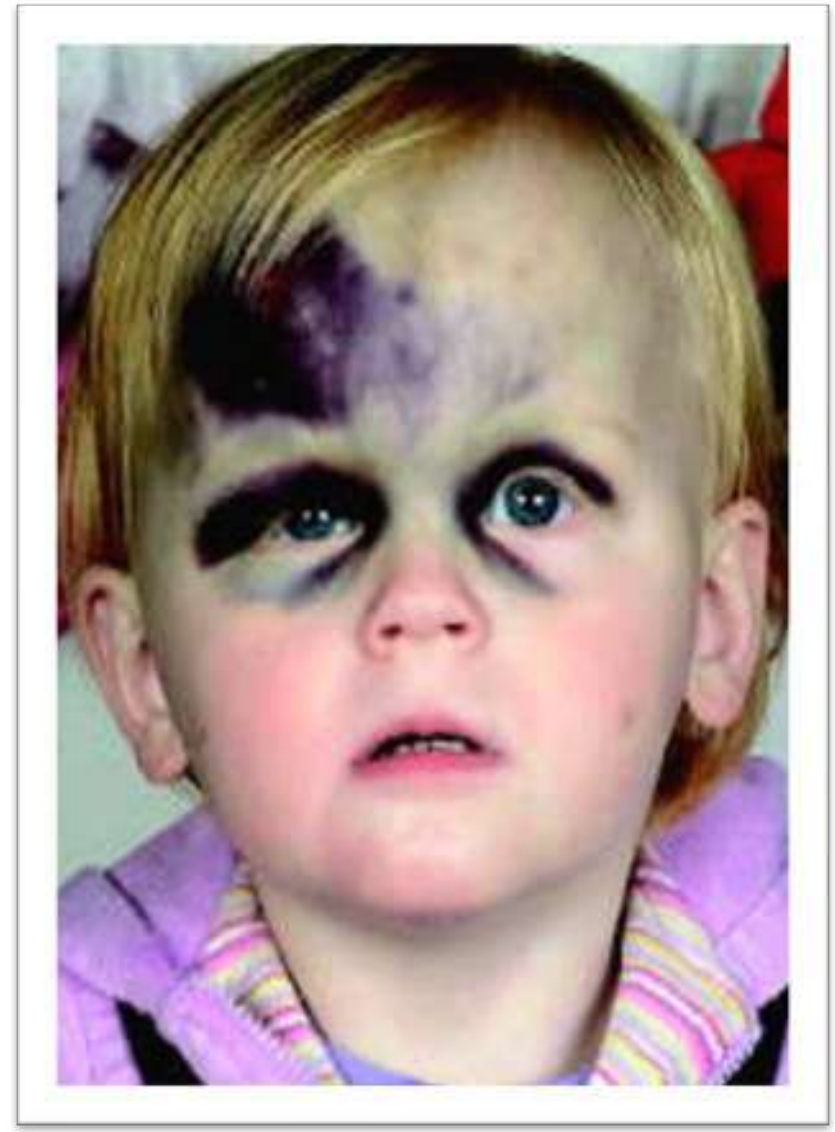
Bleeding symptoms
… vs "Wet" purpura

Mucous membrane bleeding
Epistaxis
Gingival
UG-GI tract
Intracerebral bleeding



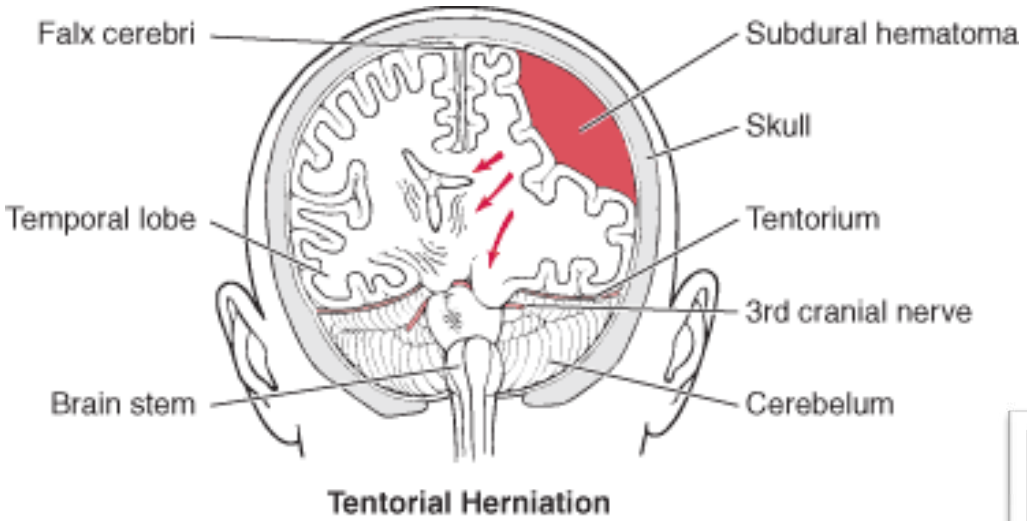




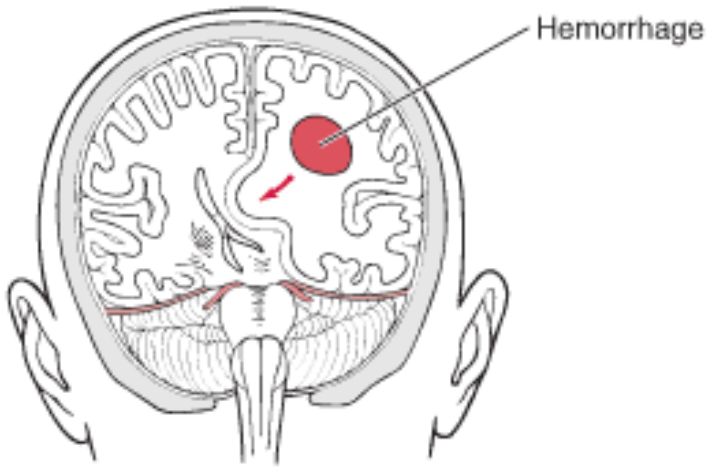


Wet purpura:

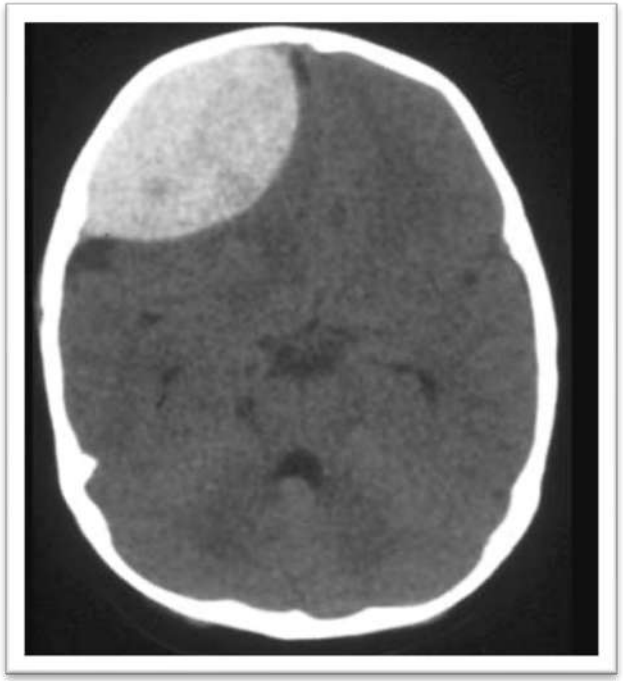
…intracranial bleeding

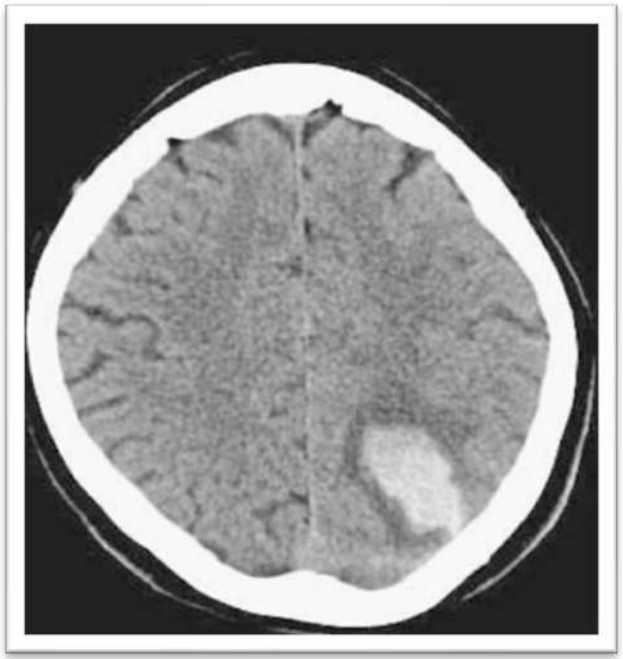


Tentorial Herniation

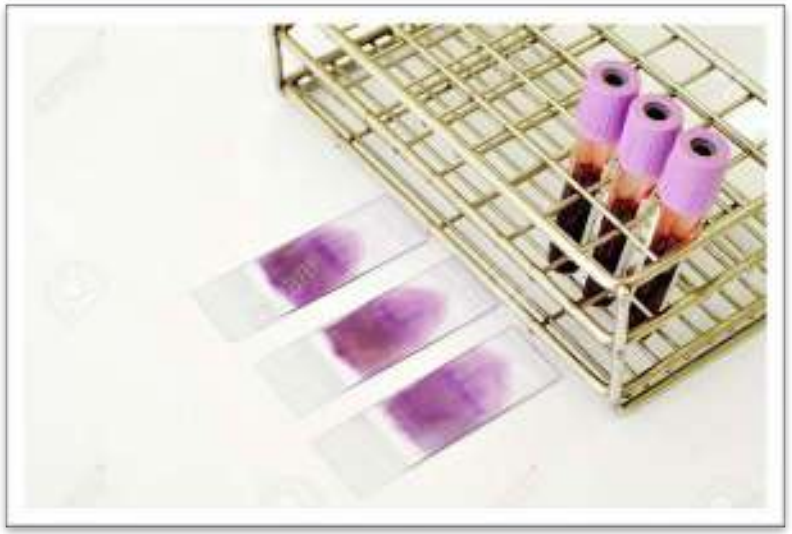


Subfalcine Herniation





Diagnostic work-up: laboratory



- Complete blood count & Blood smear
  - **Isolated vs pancytopenia**
  - **With neutrophilia or lymphocytosis**
  - **True vs pseudo**
  - **Platelet morphology: giant platelets, vs microthrombocytes**
  - **Toxic granulation in the neutrophils**
  - **Pelger Huet, blasts**
  - **Atypical lymphocytes**
  - **Fragmentocytes**
  - **Tear drops, nucleated red blood cells**

- Additional investigations
  - **LDH**
  - **Coombs, hapto, bilirubin**
  - **Renal function**
  - **Coagulation**
  - **Liver function**
  - **Virus serology,**
  - **Bone marrow examination**

Diagnostic work up ITP

Basic evaluation

- **Personal and family history**
- **Clinical examination**
- **Full blood count with reticulocytes and Coombs**
- **Peripheral blood film!!!**
- **Immunoglobulins**
- **Blood group ?**
- **HIV, hep C, H pylori ?**
- **Bone marrow in selected patients**

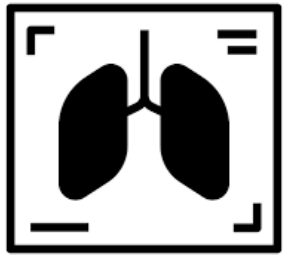
MANDATORY!!!

Potential utility

- Antiplatelet antibodies
- **Antiphospholipid antibodies**
- **Thyroid function and antithyroid antibodies**
- pregnancy test
- **Antinuclear antibodies**
- PCR for CMV and parvovirus
- **Hep B**
- **Chest radiograph**
- **Abdominal ultrasound**
- **Biological fitness**

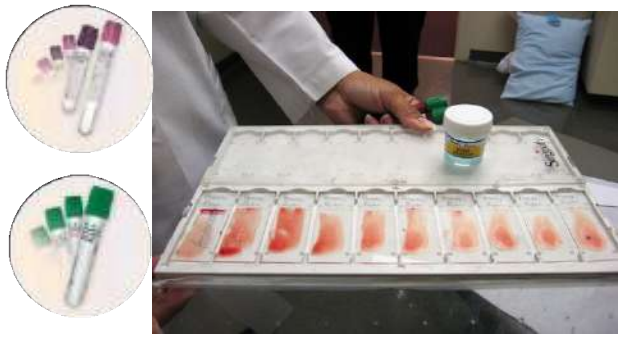
Unproven benefit

- Thrombopoitin
- Reticulated platelets
- Bleeding time
- Platelet survival time
- Serum complement



Bone marrow examination

Basic evaluation or potential utility?



Provan et al,
Blood Adv 2019

Bone marrow aspirate and biopsy

- Cytology
- Immunophenotyping
- Karyotyping
- NGS panels for MDS, inherited thrombocytopenia and bone marrow failure syndromes

ONLY IN PATIENTS WITH ABERRANT PHYSICAL EXAMINATION

or

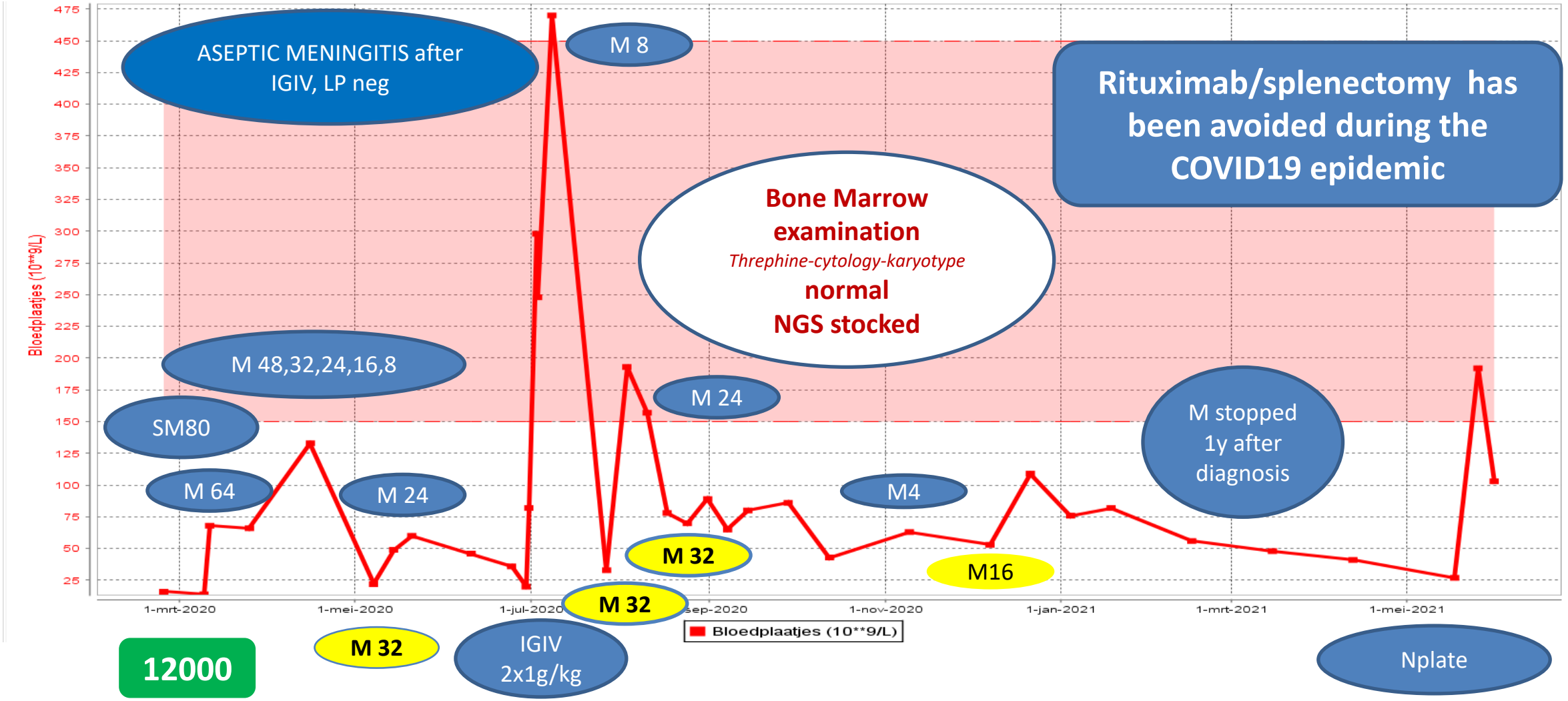
BLOOD SMEAR ABNORMALITIES

or

REFRACTORY TO TREATMENT

If it looks/feels like ITP- no need !!!!

Case: ♀ 64y
Frontline ITP treatment: steroids



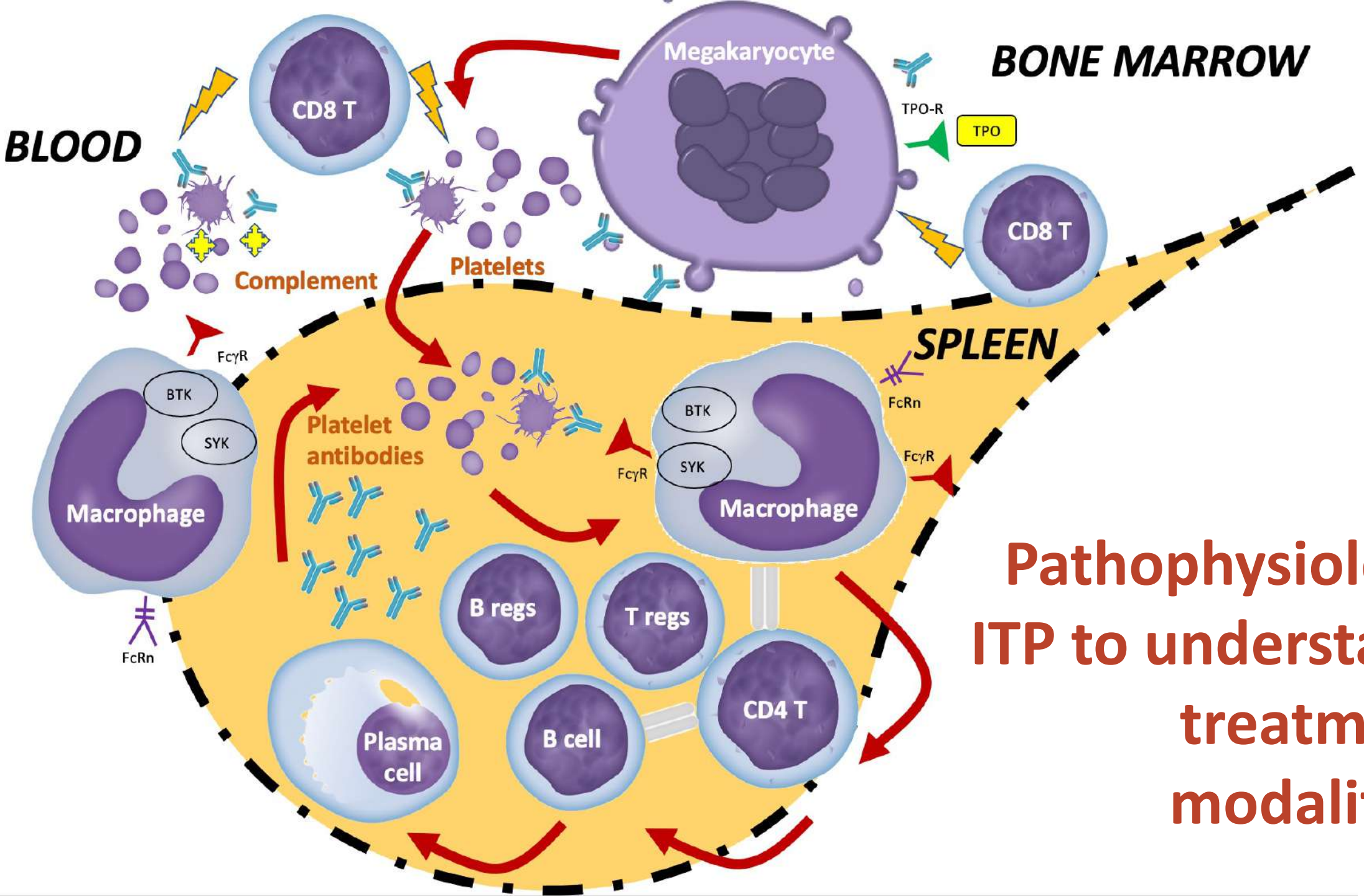
Primary ITP is a diagnosis of exclusion!

No reliable test exist that can be used to establish diagnosis of ITP

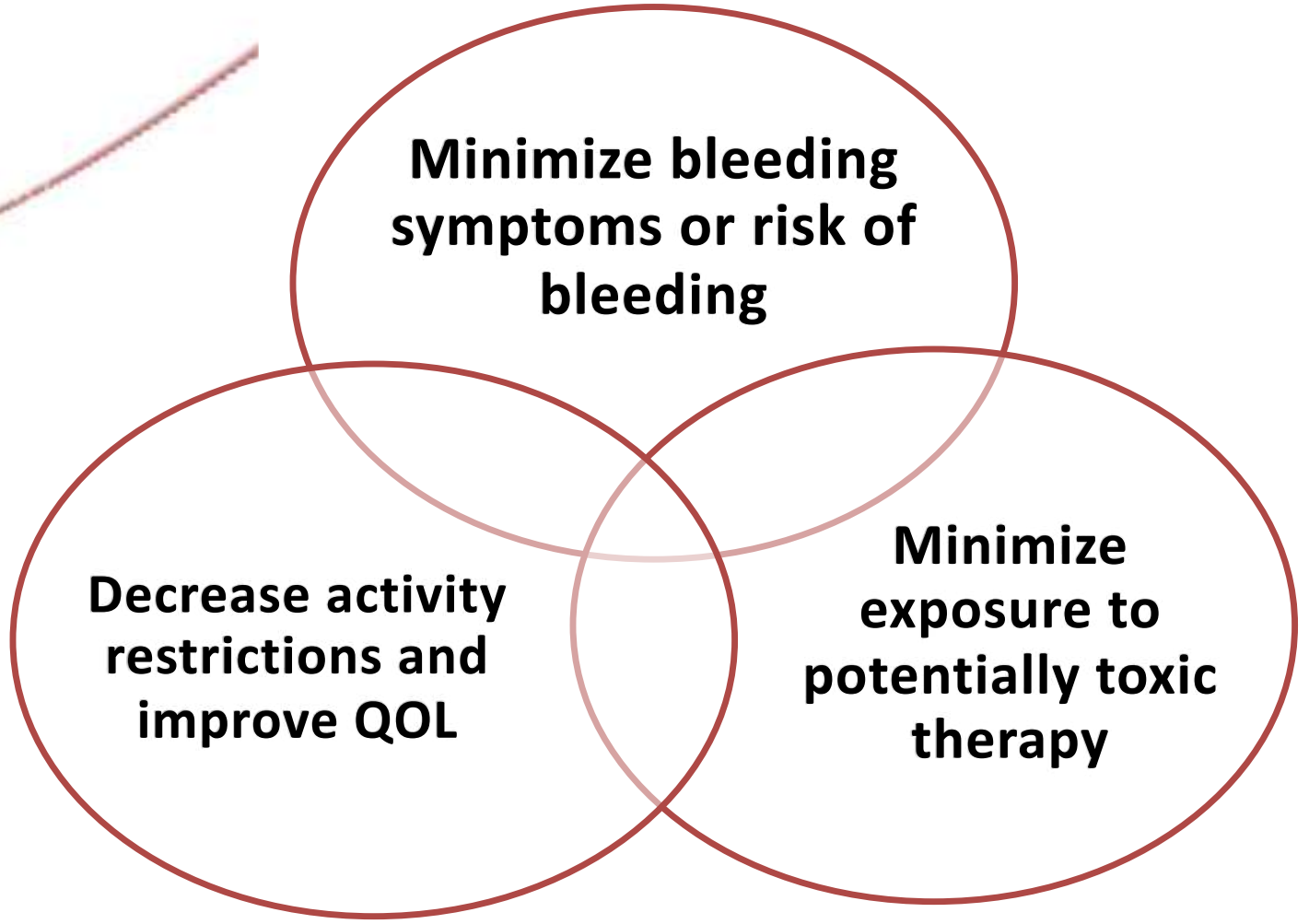
Misdiagnosis expected in 1/7!!!

If a patient fail to respond to appropriate treatment, reassessment of diagnosis ITP is important

In refractory patients (≥2 previous treatments): MISDIAGNOSIS OF ITP IN 50%

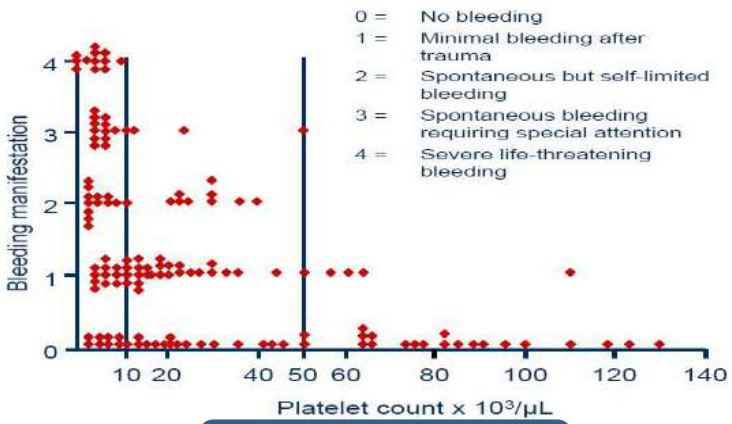


Pathophysiology ITP to understand treatment modalities

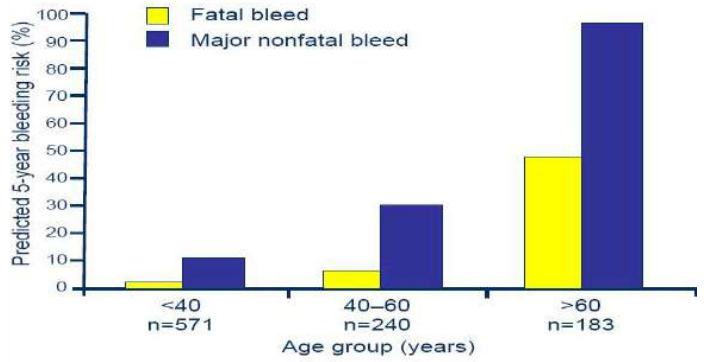


ITP: Goals of treatment

Indications for initiation of treatment



Hematuria!



Provan et al, Blood Adv 2019
Neunert et al, Blood Adv 2019

Active bleeding OR platelets <10000/µl

- treatment is **obligatory**

No or mild bleeding AND platelets 10-30000/µl

- **treatment is a potential option**
- (evaluation of patient characteristics)

No bleeding AND platelets >30000/µl

- **no need for treatment** unless special circumstances

Safe platelet count for medical interventions in patients with low platelets

these thresholds, adapted from safe platelet counts in patients with platelet production problems, are mainly based on « expert opinion » rather than « evidence-based data » and must be individualized to the patient bleeding history

Dental care	**≥ 10-20 x 10^9/L**
Extractions (simple)	**≥ 30 x 10^9/L**
Extractions (complex, molar)	**≥ 50 x 10^9/L**
Lumbar puncture: elective	**≥ 40-50 x 10^9/L**
vital indication	**≥ 20 x 10^9/L**
Central venous catheter insertion	**≥ 20 x 10^9/L**
GI endoscopy with biopsy	**≥ 20 x 10^9/L**
Bronchoscopy	**≥ 20 x 10^9/L**
Bronchoscopy with biopsy	**≥ 50 x 10^9/L**
Joint puncture	**≥ 20 x 10^9/L**
Organ biopsy	**≥ 50 x 10^9/L** ***(<for bone marrow biopsy)***
Minor surgery	**≥ 50 x 10^9/L**
Delivery	**≥ 50 x 10^9/L**
Major surgery (including neurosurgery)	**≥ 80 x 10^9/L**
Epidural anesthesia	**≥ 70 x 10^9/L**
Major neurosurgery	**≥ 100 x 10^9/L**
Single antiplatelet or anticoagulant	**≥ 30-50 x 10^9/L**
Dual antiplatelet and anticoagulant	**≥ 50-70 x 10^9/L**

Matzdorff et al, Immunthrombozytopenie, Oncol Res Treat 2018

ITP: phases of disease

relevant for treatment and prognosis ????

Newly diagnosed ITP (<3mo)

(retrospective diagnosis)

Persistent ITP (3 to 12mo)

(time in which spontaneous remission can occur)

Chronic ITP (>12mo)

Rodeghiero et al, Blood 2009:113;2386-2393

When is hospitalization justified?

Not really, observe!

- Younger
- Well
- No bleeding

- No comorbidities
- Platelets > 20000/μl

Maybe yes, admit!

- Older
- Unwell
- Bleeding symptoms or history of bleeding
- Comorbidities
- Platelets < 20000/μl

Provan et al, Blood Adv 2019
Neunert et al, Blood Adv 2019

Treatment of ITP

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2019 guidelines for immune thrombocytopenia

Cindy Neunert,[1] Deirdra R. Terrell,[2] Donald M. Arnold,[3,4] George Buchanan,[5] Douglas B. Cines,[6] Nichola Cooper,[7] Adam Cuker,[8] Jenny M. Despotovic,[9] James N. George,[2] Rachael F. Grace,[10] Thomas Kühne,[11] David J. Kuter,[12] Wendy Lim,[13] Keith R. McCrae,[14]

REVIEW ARTICLE

blood advances

Updated international consensus report on the investigation and management of primary immune thrombocytopenia

Drew Provan,[1] Donald M. Arnold,[2] James B. Bussel,[3] Beng H. Chong,[4] Nichola Cooper,[5] Terry Gernsheimer,[6] Waleed Ghanima,[7,8] Bertrand Godeau,[9] Tomás José González-López,[10] John Grainger,[11] Ming Hou,[12] Caroline Kruse,[13] Vickie McDonald,[14] Marc Michel,[9] Adrian C. Newland,[1] Sue Pavord,[15] Francesco Rodeghiero,[16] Marie Scully,[17] Yoshiaki Tomiyama,[18] Raymond S. Wong,[19] Francesco Zaja,[20]

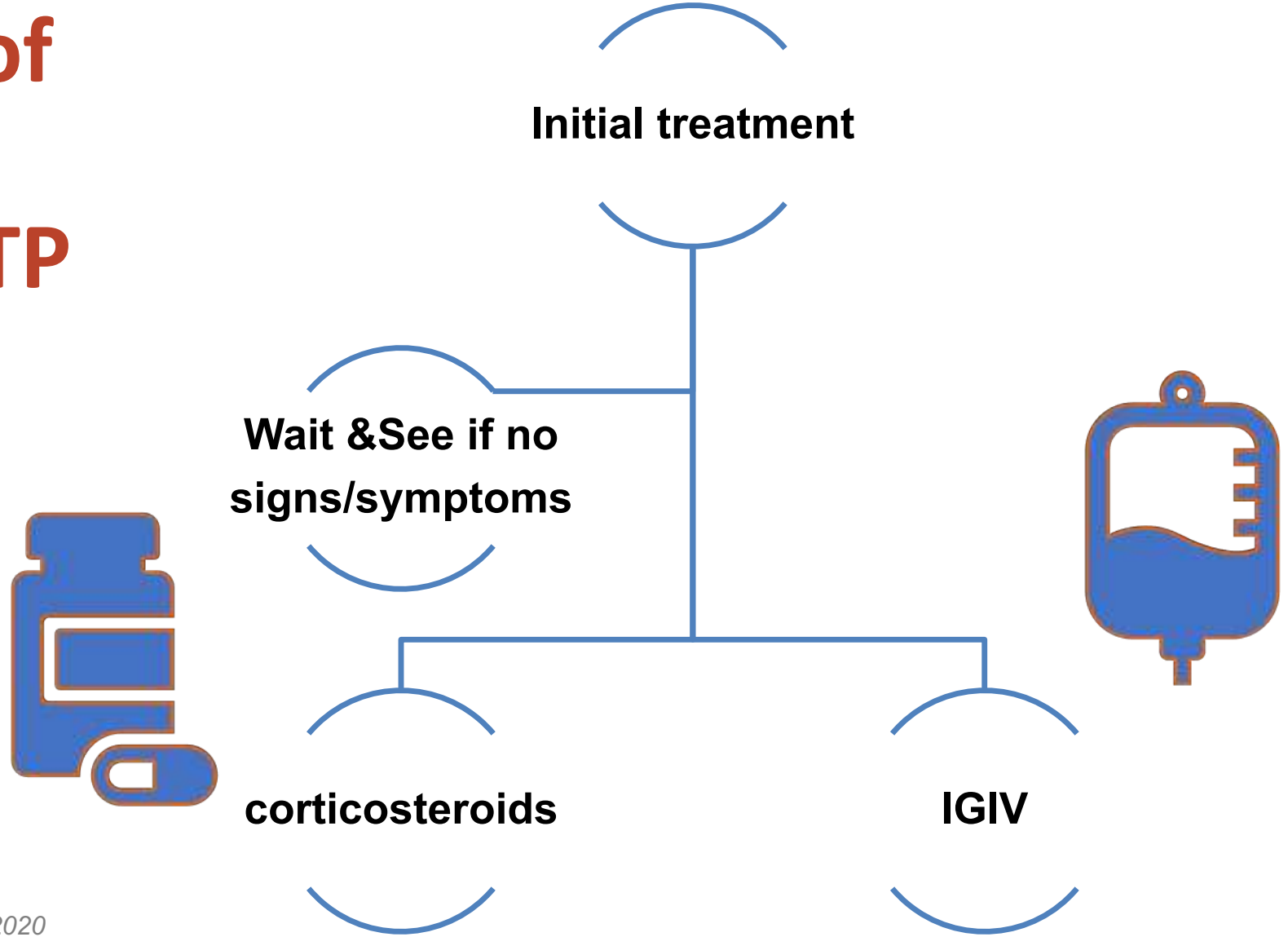
Primary immune thrombocytopenia in adults Belgian recommendations for diagnosis and treatment anno 2021 made by the Belgian Hematology Society

Janssens[a*], D. Selleslag[b], J. Depaus[c], Y. Beguin[d] and C. Lambert[e]

BHS
Belgian Hematology Society

Submitted nov 2020

Treatment of newly diagnosed ITP

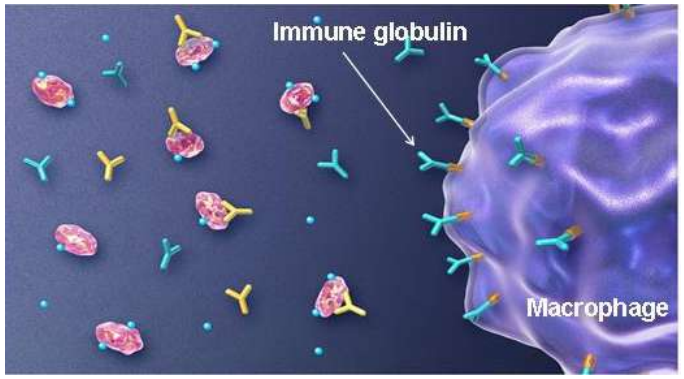


Janssens et al. Belg J Hematol 2020

Treatment of newly diagnosed ITP or initial treatment

Steroids

IGIV

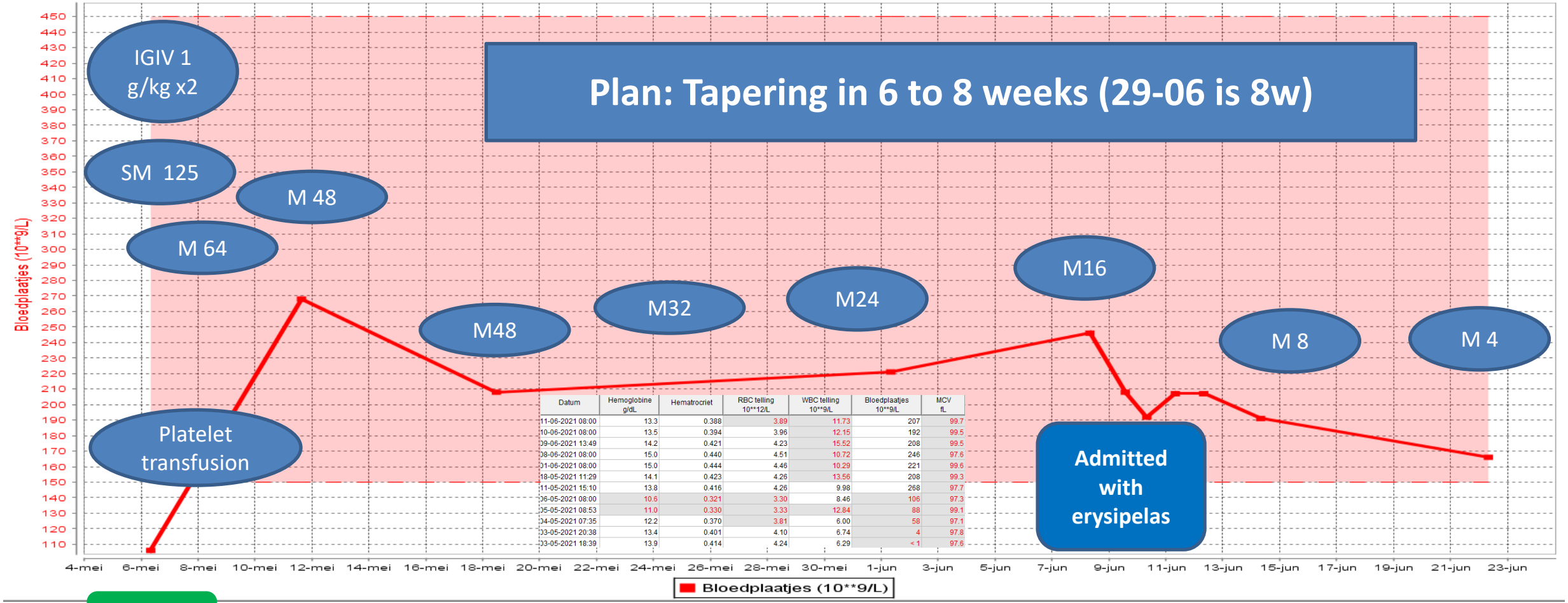


- No preference for (methyl)prednisolone or dexamethasone (D)
  Earlier & higher initial response without better sustained response for D
- Short term response: 75-80%
- Durable response: 30-50%
- Avoid long-term treatment (<8 weeks) (long-term side effects)!!!
- Can be repeated at relapse after a long-term treatment-free period
- More side effects compared with other therapies leading to dose reduction and treatment discontinuation
- Cheap

- Starting dose: 400 mg/kg/5 days or 1 g/kg/2days
- Short term response: ± 80%, rapid response
- Durable response: only a few, relapse between 14-28d
- Repeated infusions possible
- Expensive
- Drug shortage (sc IG no alternative for IV IG in ITP)

Provan et al, Blood Adv 2019
Neunert et al, Blood Adv 2019

Case, ♀ ,69y
Frontline ITP treatment: steroids

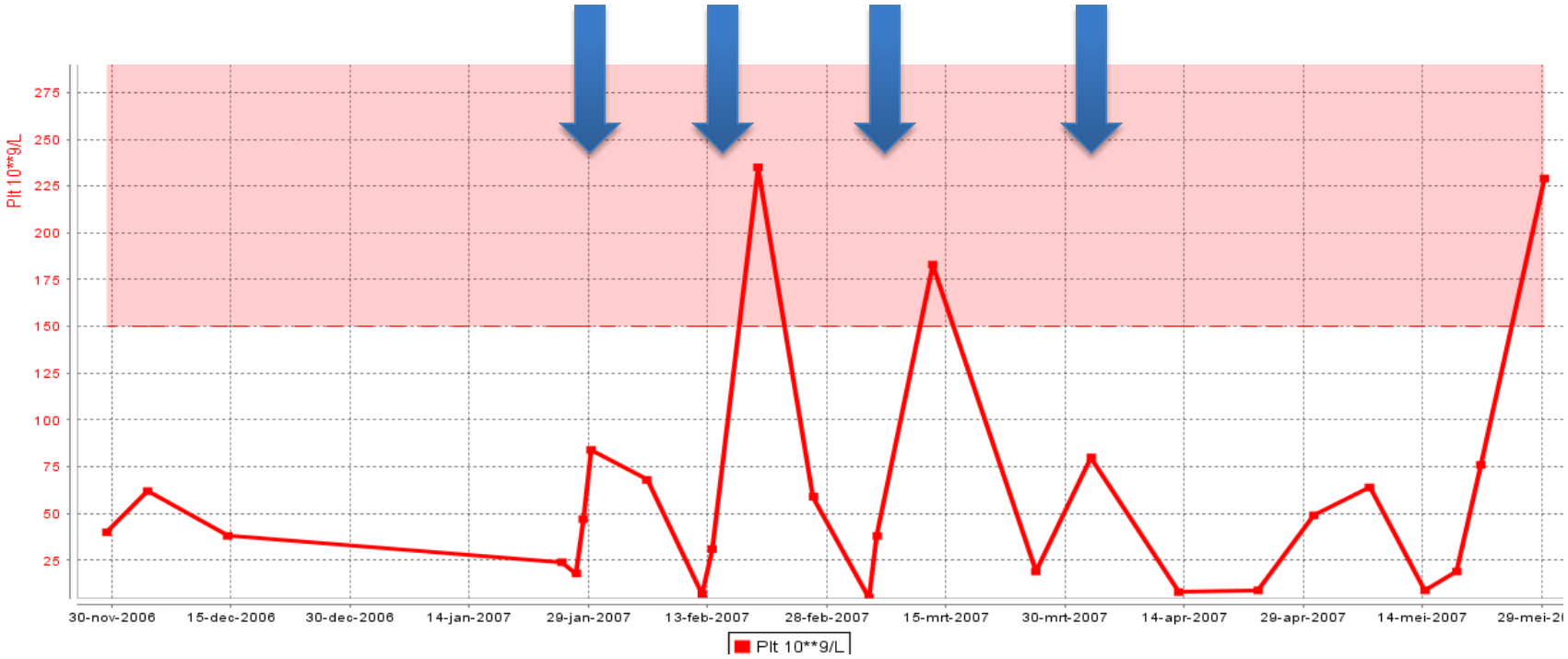


Datum	Hemoglobine g/dL	Hematocriet	RBC telling 10**12/L	WBC telling 10**9/L	Bloedplaatjes 10**9/L	MCV fL
11-06-2021 08:00	13.3	0.388	3.89	11.73	207	99.7
10-06-2021 08:00	13.5	0.394	3.96	12.15	192	99.5
09-06-2021 13:49	14.2	0.421	4.23	15.52	208	99.5
08-06-2021 08:00	15.0	0.440	4.51	10.72	246	97.6
01-06-2021 08:00	15.0	0.444	4.46	10.29	221	99.6
18-05-2021 11:29	14.1	0.423	4.26	13.56	208	99.3
11-05-2021 15:10	13.8	0.416	4.26	9.98	268	97.7
06-05-2021 08:00	10.6	0.321	3.30	8.46	106	97.3
05-05-2021 08:53	11.0	0.330	3.33	12.84	88	99.1
04-05-2021 07:35	12.2	0.370	3.81	6.00	58	97.1
03-05-2021 20:38	13.4	0.401	4.10	6.74	4	97.8
03-05-2021 18:39	13.9	0.414	4.24	6.29	< 1	97.6

<1000

Case, ♀ , °22-06-1934
IGIV for a cortico-refractory patient

- 11-2006: diagnosis of ITP
- 01-2007: platelets 16000/µl : Medrol 64 mg/d (corticorefractory)
- 02-2007: IGIV monthly (4x) with tapering of corticosteroids



Subsequent ITP treatment

Assess patient values and preferences!

Wait & see if no signs/symptoms

(consider thrombotic risk)
(consider durable response)

TPO-RAs

Rituximab

(consider risk of infection)
(avoid long-term treatment)

Splenectomy

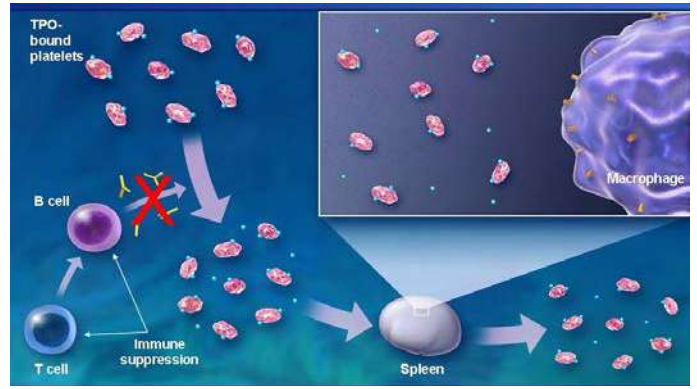
(consider in chronic ITP & a severe bleeding tendency)

Azathioprine
Cyclosporine A
Cyclophosphamide
Danazol
Dapsone
Mycophenolate mofetil
Vinca alkaloids

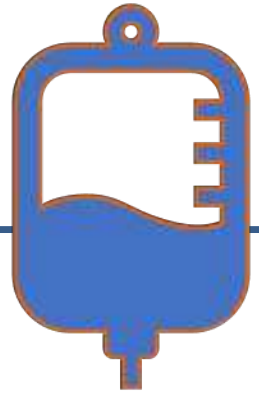
Provan et al, Blood Adv 2019
Neunert et al, Blood Adv 2019
Janssens,…,Lambert. Acta Clinica Belgica & BJH 2021

Subsequent ITP treatment

Rituximab as medical treatment



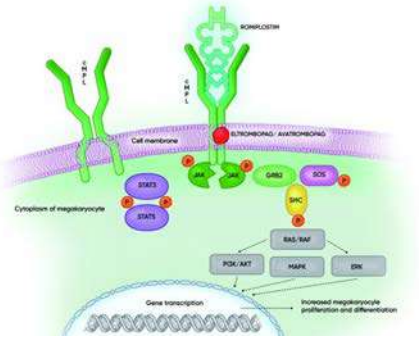
- **B-cell depletion and reduction of antibody formation**
- **Good short term-response (+/-60%), but modest long-term response (20-30%)**
- **Can be repeated in patients with a complete response and a long lasting response**
- **IV administration (lymphoma or rheumatoid arthritis regimen)**
- **Good safety with acceptable risk of infection (late onset neutropenia, hypogammaglobulinemia,…)**
- **Avoid in patients with a history of infections or previous prolonged treatment with immunosuppressive agents**
- **Relatively not expensive anymore**



Provan et al, Blood Adv 2019
Neunert et al, Blood Adv 2019

Subsequent ITP treatment

TPO-RAs as medical treatment

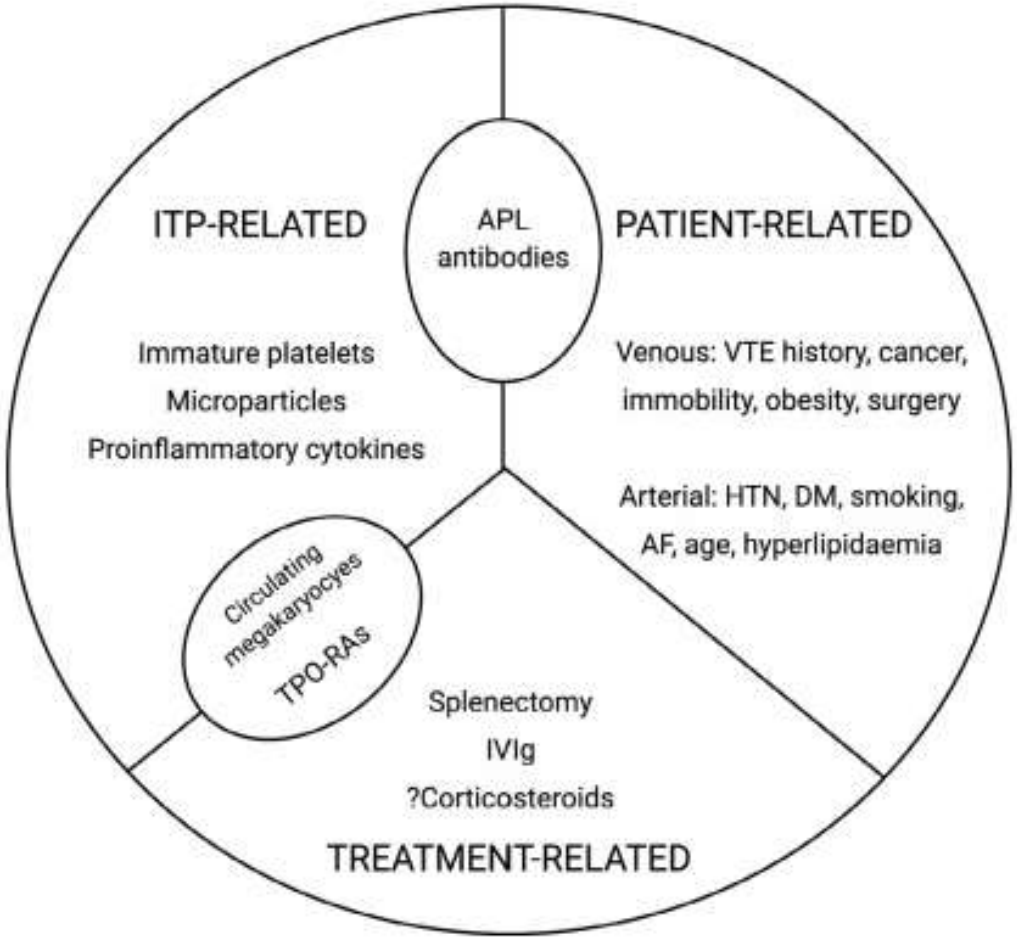


- **Stimulation of platelet production by megakaryocytes in the bone marrow**
- **Sustained platelet response in ≈ 80% of patients**
- **Response as long as therapy is maintained: Cavé compliance and adherence!!!**
- **… Spontaneous remission: 10 à 30% (BHS survey 22%)**
- **Very well tolerated (10-15% stop because of AEs)**
- **Reduction or discontinuation of concurrent treatment (corticosteroid, …)**
- **Reduction in need for rescue therapy (IGIV, splenectomy)**
- **Improvement of fatigue and health-related QOL**
- **Use TPO-R agonists carefully in patients with a history or risk factors for thrombosis (APS)**
- **Expensive (oral or subcutaneous agents)**

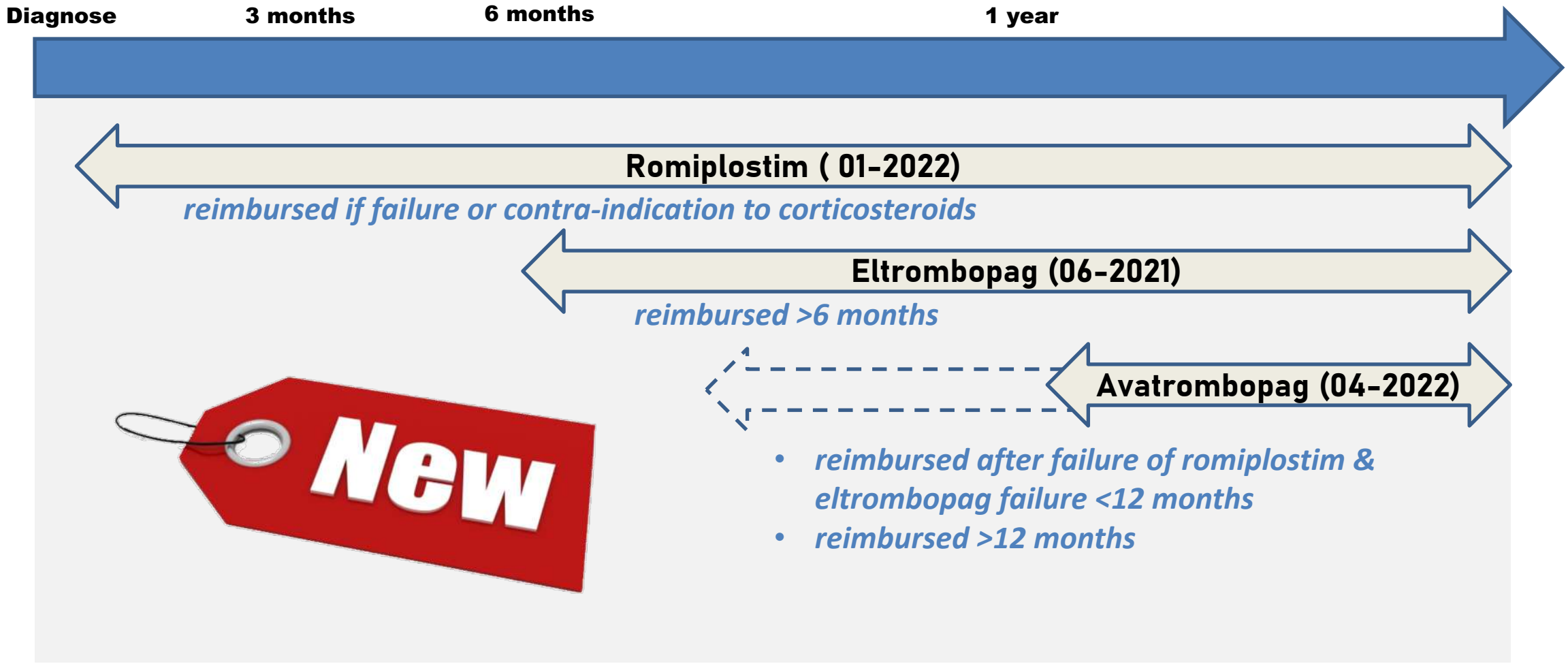
Provan et al, Blood Adv 2019
Neunert et al, Blood Adv 2019

TPO-RAs and thrombosis

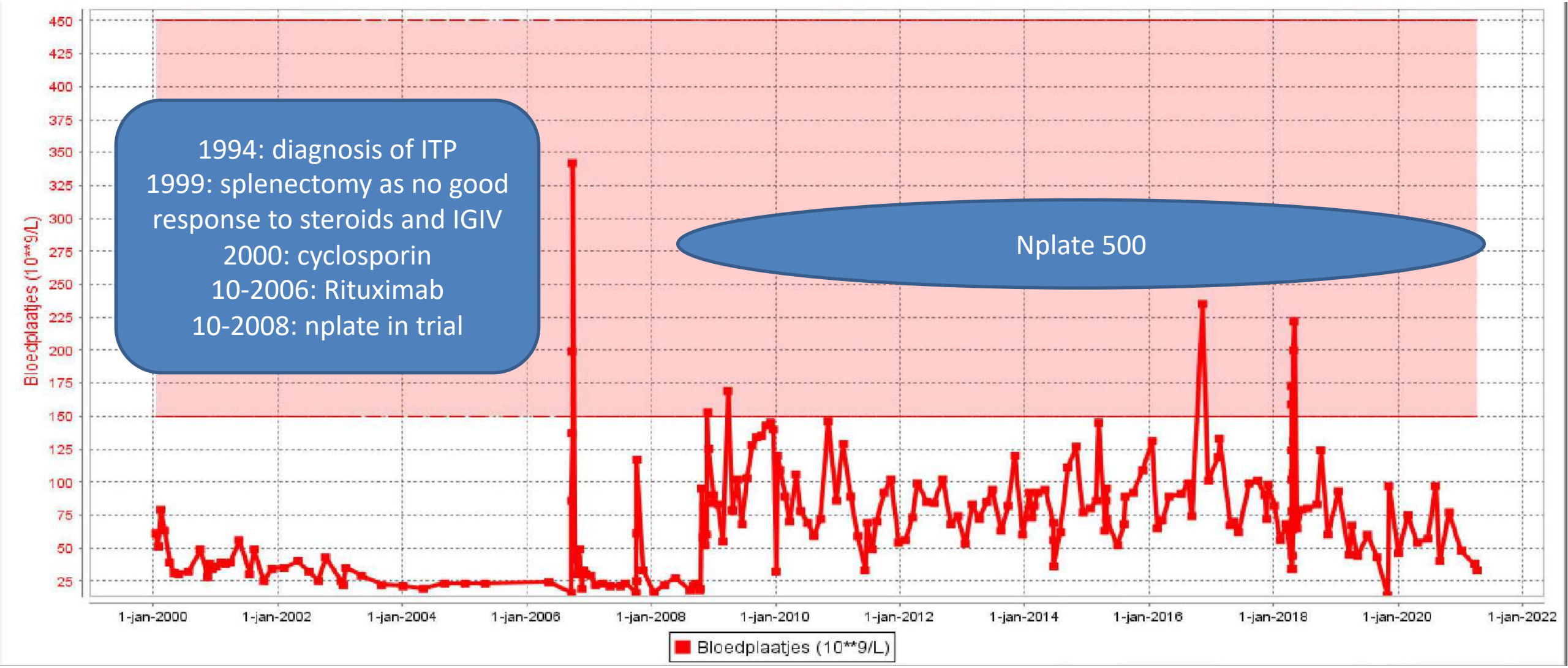
- Thrombosis
  - ITP is a procoagulant condition (more arterial thrombosis (AT) and venous thromboembolism (VTE))
  - TPO-RAs increase the risk of VTE and AT compared to ITP
  - Thrombosis not correlated with type, duration, dose of TPO-RA or platelet count
  - Splenectomy increases the risk of VTE.
  - TPO-RAs do not increase the thrombotic risk in splenectomized patients
  - **Careful consideration benefits vs. risk of thromboembolism**



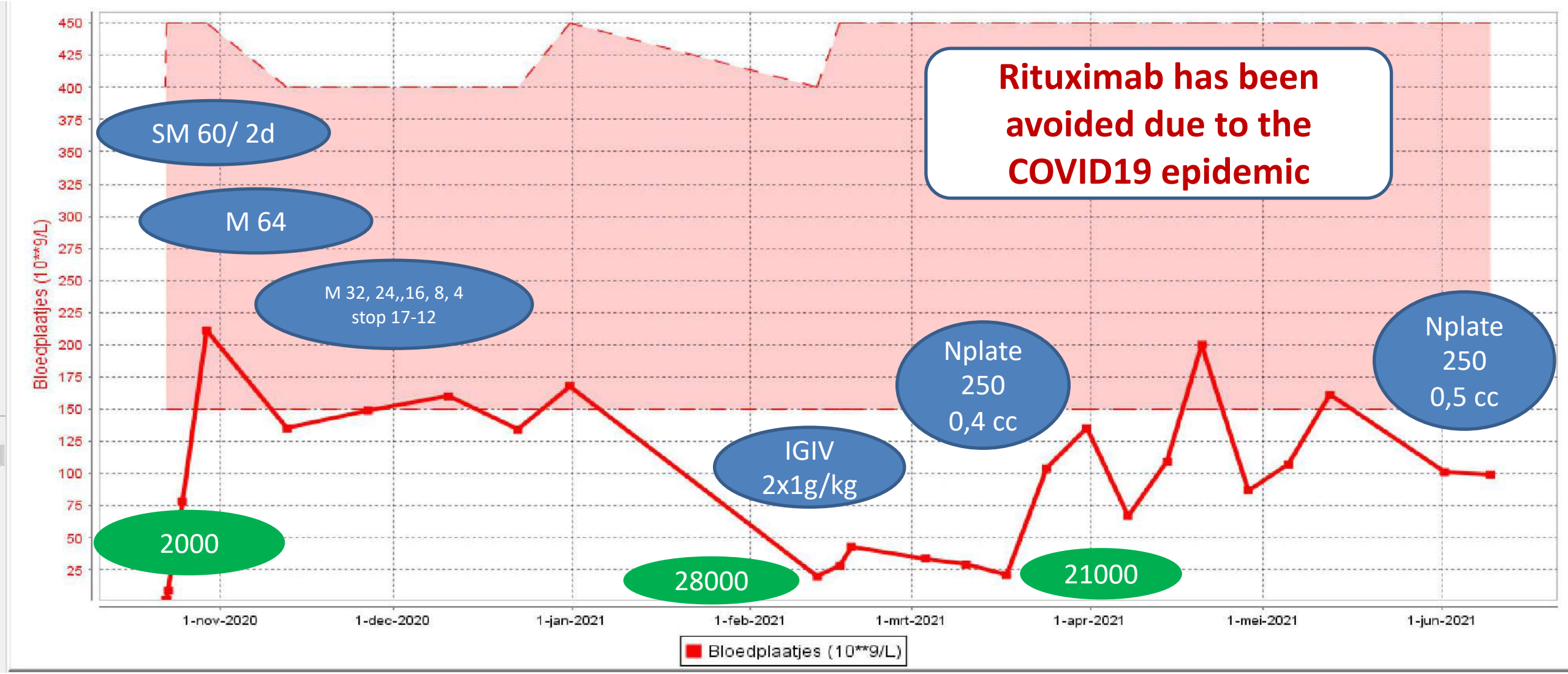
TPO-RAs in Belgium today 19-11-2022



Case, ♂,°1945, TPO-RAs in chronic ITP
Safe platelet counts for almost 13ys



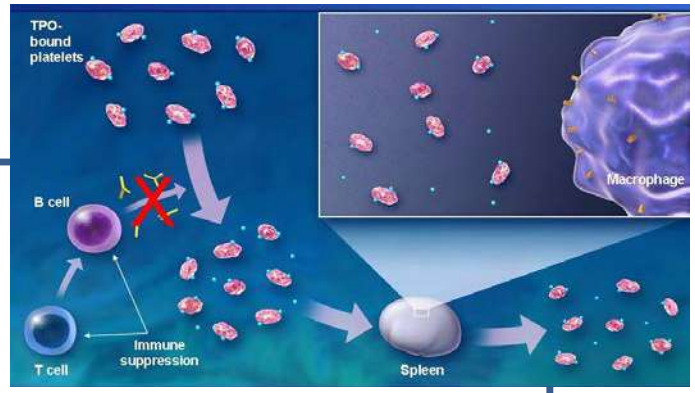
Case, ♀, 61y
Subsequent treatment 3-4mo after diagnosis



Subsequent ITP treatment

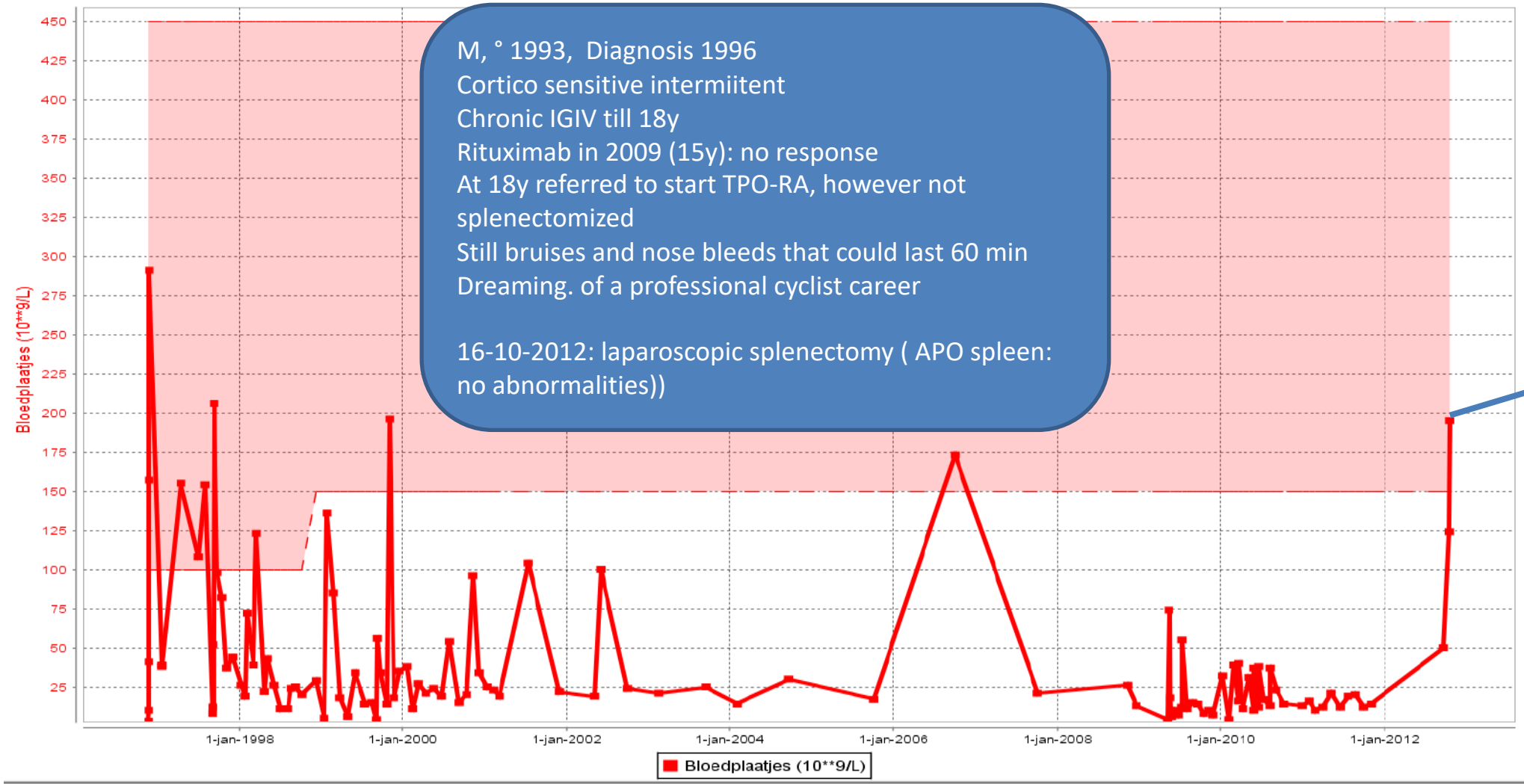
Splenectomy as surgical treatment

Provan et al, Blood Adv 2019
Neunert et al, Blood Adv 2019

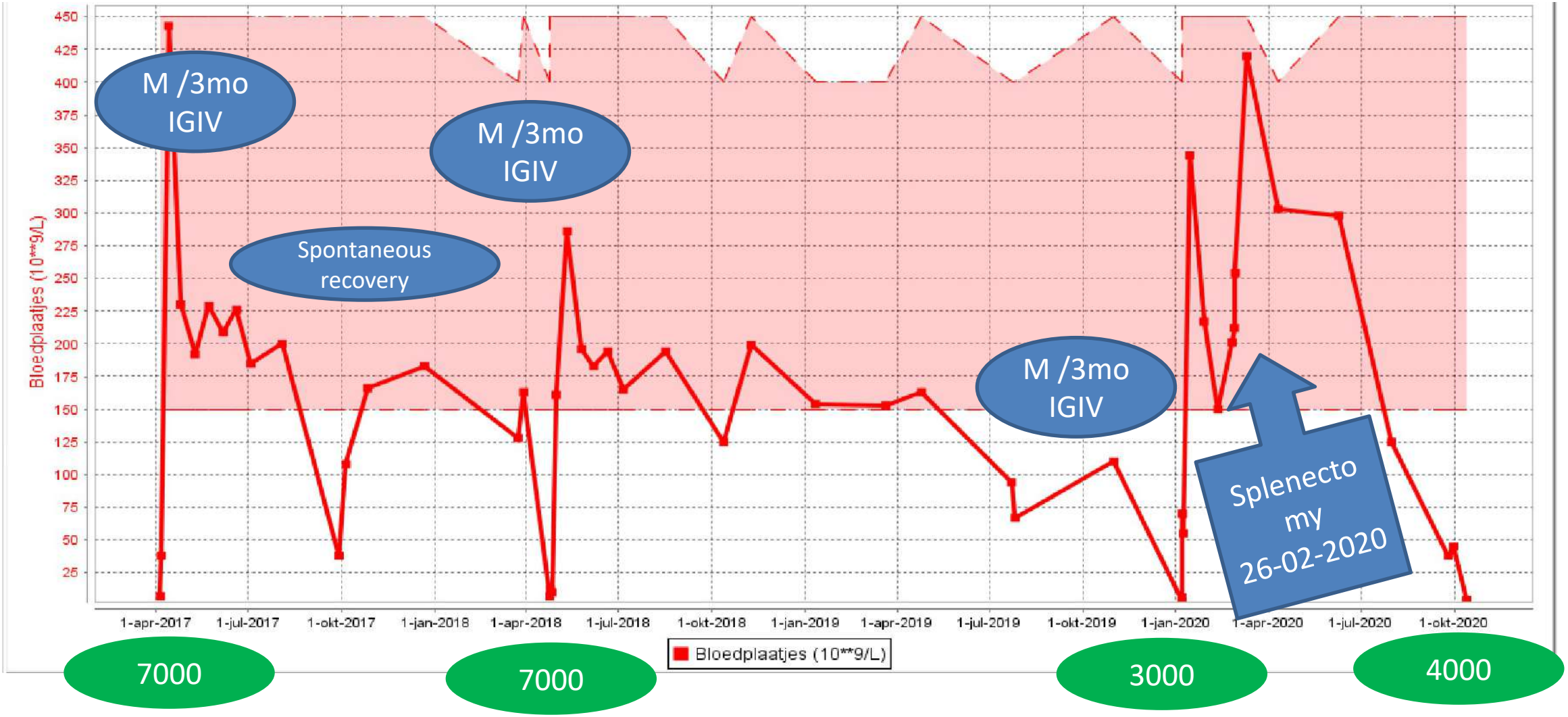


- **Removes primary site of platelet clearance and antibody production**
- **Effective and durable responses: 66% long-term normal platelets**
- **Laparoscopic splenectomy (morbidity 10%, mortality 0.2%)**
- **Overwhelming post-splenectomy infection: Vaccination and education of infection!!!**
- **Long-term vascular risks: DVT, …**
- **Postpone splenectomy at least 12 mo (spontaneous remission)**
- **Reasonable treatment option for patients with an active lifestyle, for those who desire freedom from medication and monitoring and for those who are not well responding to treatment**
- **Contra-indications for splenectomy (low platelets, geriatric prophile, comorbidities with increased perioperative risks)**
- **Cost affordable**
- **“Removal of a healthy organ” some patients refuse this irreversible treatment option**

Case,♂,°1993
Splenectomy, 15y after ITP diagnosis



Case, ♀, °1985
Splenectomy 34 mo after ITP diagnosis



7000

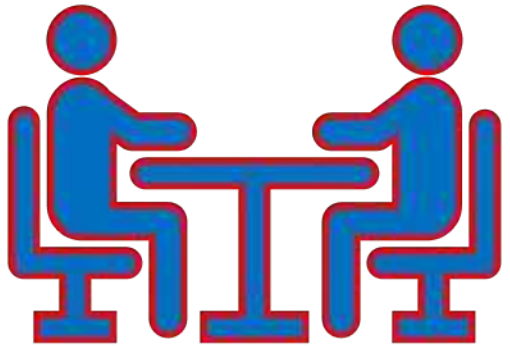
7000

3000

4000

Patient values and preferences

- Fear and anxiety or Acceptance of low platelets
- Fear and anxiety or Tolerance of minor bleeding signs
- Acceptance or not of fatigue
- Acceptance or not of activity restrictions
- Acceptance of chronic therapy
- Desire to avoid treatments with certain toxicities (steroids, splenectomy)
- Desire to live without ITP
- Desire to get pregnant
- …



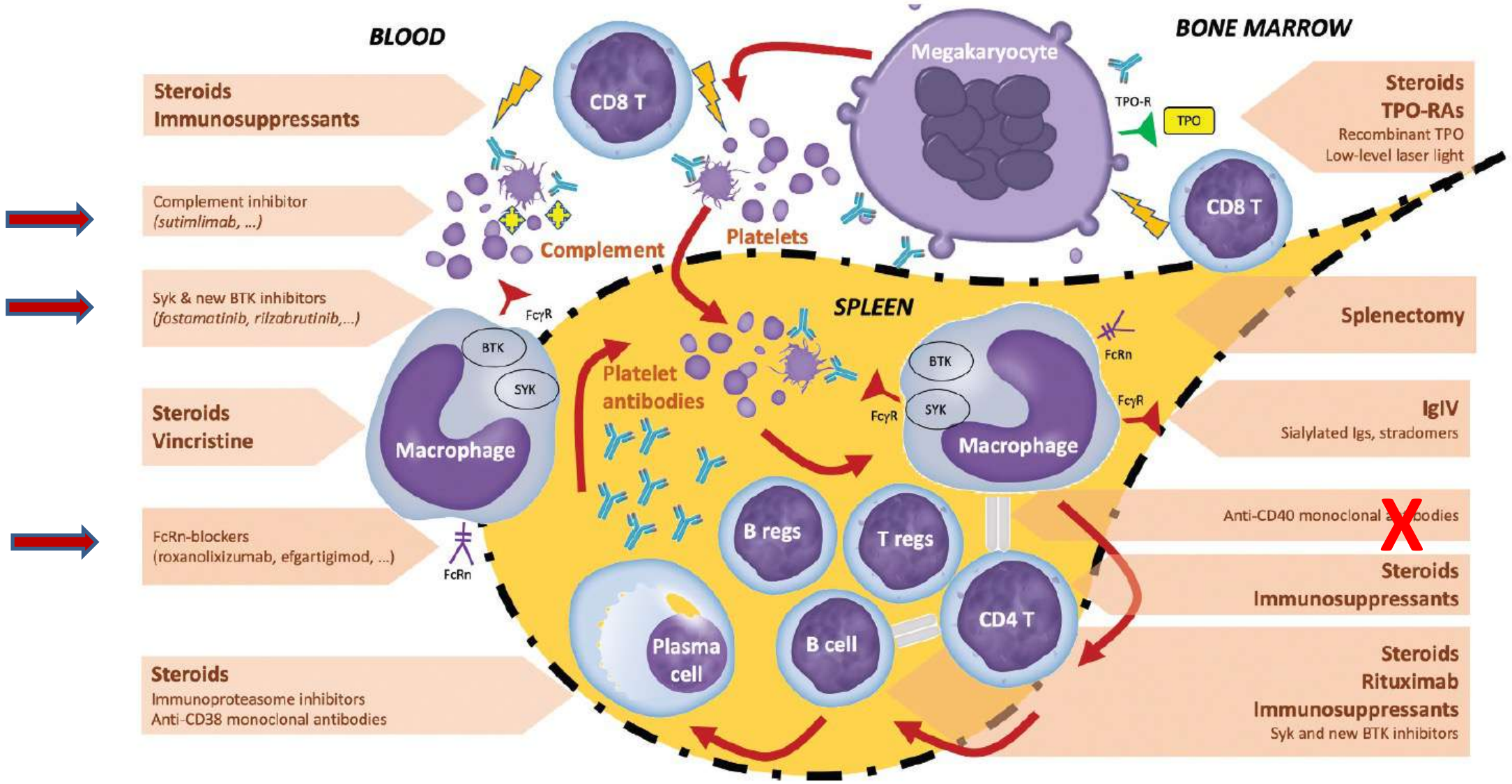
Treatment of persistent of chronic ITP

(immunosuppressive agents) after TPO-RA and rituximab and splenectomy

- Azathioprine, cyclophosphamide, cyclosporine A, danazol, dapsone, mycophenolate mofetil and vincristine have been used after treatment failure for decades.
  - Variable individual responses
  - Long-term side effects such as immune suppression

	Dose	Toxicities
Azathioprine	1-2 mg/kg/d po	Neutropenia, transaminase elevation, pancreatitie, etc.
Cyclophosphamide	1-2 mg/kg/d po 500-1000 mg 4wks IV	Nausea, vomiting, sterility, secondary acute myeloid leukemia, etc.
Cyclosporine	4-5 mg/kg/d po (through blood levels 100-200 ng/ml)	Renal insufficiency, hypertension, neuropathy, hypertrichosis, tremor, gingival hyperplasia, etc.
Danazol	400-800 mg/d po	Weight gain, hair loss, liver dysfunction, myalgia, amenorrhea, etc.
Dapsone	75-100 mg/d po	Abdominal distension, anorexia, nausea, hemolytic anemia if glucose 6-phosphate dehydrogenase deficiency, etc.
Mycophenolate mofetil	1000 mg bid po	Headache, anorexia, nausea, abdominal distention, etc.
Vincristine	1-2 mg/wk IV max for 6 wks	Neuropathy, constipation, hair loss, etc.
Vinblastine	5-10 mg/wk IV max for 6 wks	Neuropathy, constipation, hair loss, etc.

Mode of action of ITP treatments & Future options?

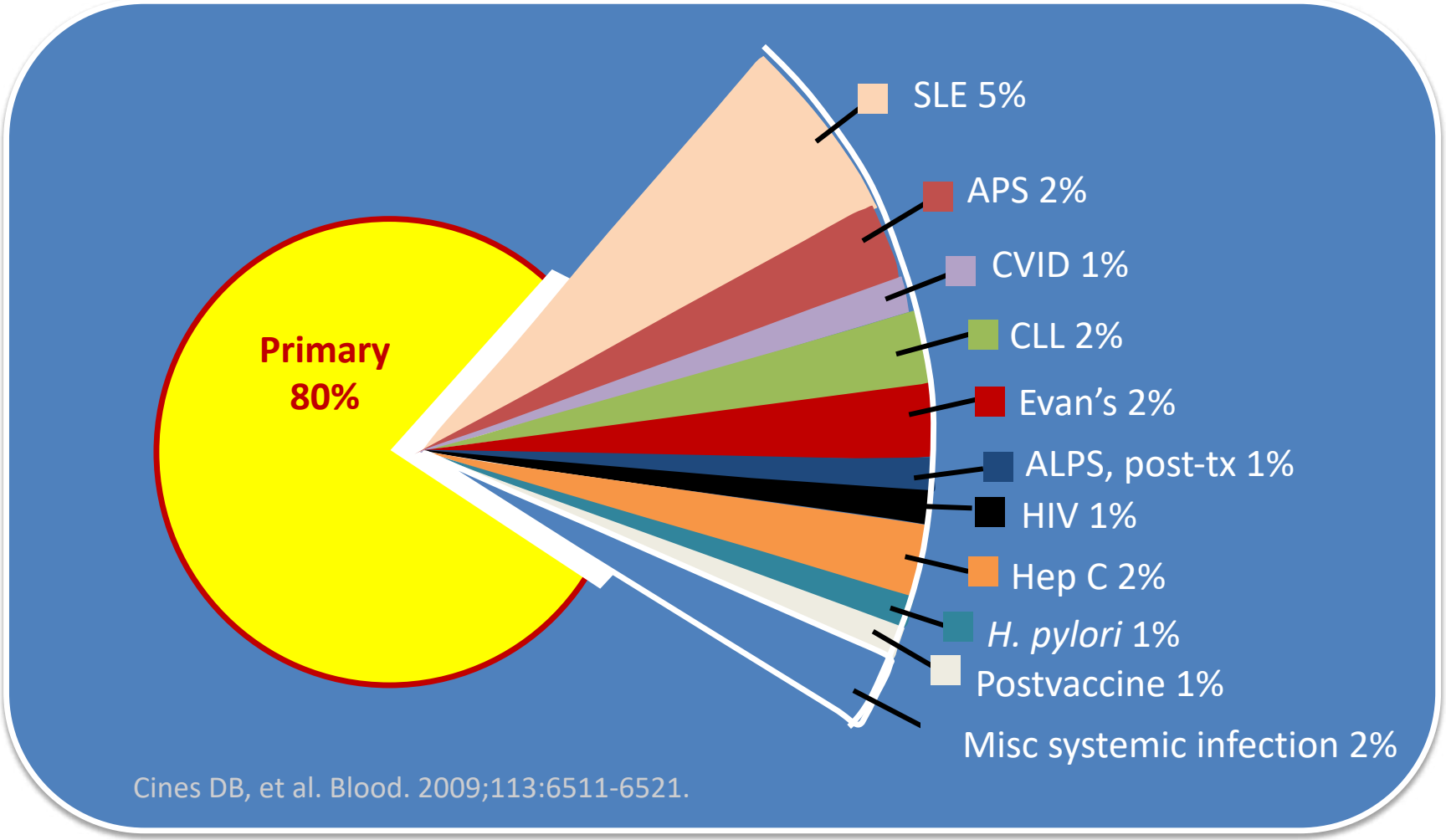


Janssens et al. Acta Clinica Belgica. 2021

Supportive care in ITP

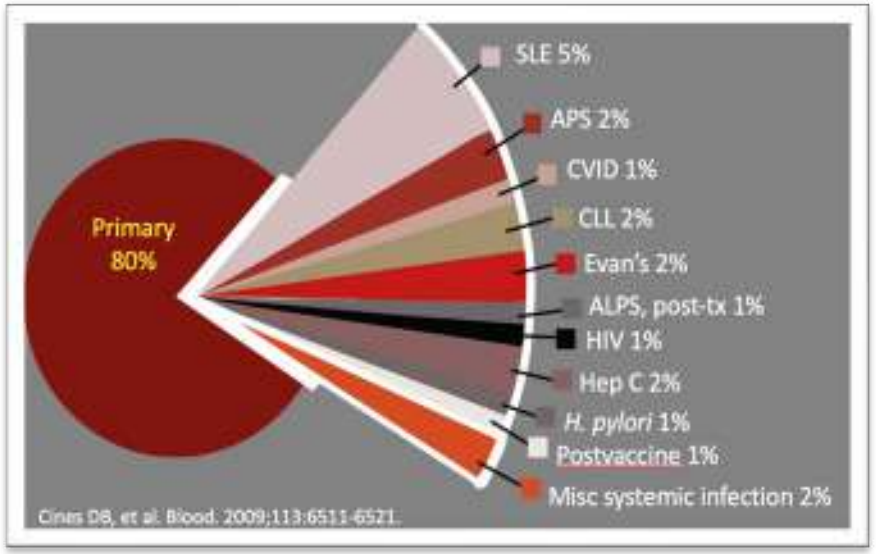
Antifibrinolytic agents (tranexamic acid : 3 g/day per os)
Oral iron supplements if iron deficient
Local application of adrenalin soaked nose pads
Nasal cauterisation
Hormone substitutes to prevent menorrhagia
Control of blood pressure
Avoid ASA, antiplatelet agents, nonsteroidal anti-inflammatory drugs, anticoagulation if appropriate

Secondary ITP



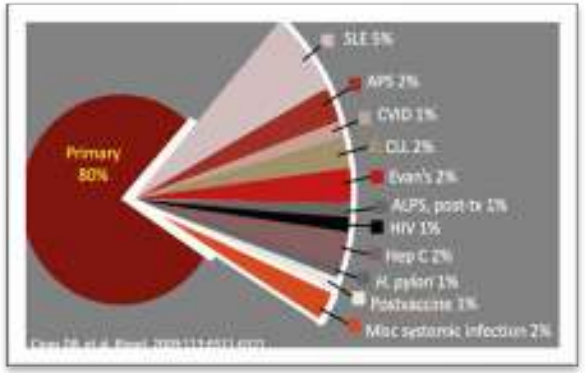
Cines DB, et al. Blood. 2009;113:6511-6521.

Autoimmune disease–related ITP +/- 8%



- **SLE**
  - 25% develop thrombocytopenia
  - 15-25% of ITP pat are pos for ANF
  - Bleeding risk? Activity of SLE? Vasculitis?
  - **Severe thrombocytopenia with active SLE: treat SLE**
  - **Severe thrombocycytopenia without active SLE:**
    - **treat as primary ITP; rituximab; splenectomy if refractory**
- **APS**
  - thrombopenia with thrombotic events and poor outcome of pregnancy
  - Lupus anticoagulans and anticardiolipin AB pos
  - +/- 40 (10-70)% of pat with ITP has APLAs
  - **treat as primary ITP, also good outcome with rituximab, avoid thombosis inducing therapies**
  - Aspirin ?
- **Thyroid disease** (hypothyroidism,thyrotoxicosis)
  - 25-50% ITP patients has antithyroid AB
  - Control of the underlying thyroid disease
- **CVID**
  - 10% develop ITP with or without AIHA
  - **Treat as primary ITP, avoid immunosuppressive agents, rituximab?**

Infection-related ITP +/-6%



Children:

- thrombocytopenia 1 to 4 weeks after an acute infection with mumps, rubella, EBV, CMV,…
- appears sudden and can be severe
- remits mostly in 2 to 4w

Adults:

- HIV, hep C, *H. Pylori*
- insidious onset, no tendency to remit spontaneously

Nagamine et al. J Hepatol 1996
Rajan et al. Br J Haematol 2005
Stasi, Sem Hematol, 2009

Hep C-related ITP

- US: prevalence of anti-HCV AB: 2%
- Platelets <150000/µl: 41% chronic Hep C (19% in chronic hep B)
- Platelets <50000/µl: +/- 9% chronic hep C
- Associated with cryoglobulins and anticardiolipin AB
- **Bleeding symptoms at higher platelet counts**
- Treatment
  - antiviral treatment
  - Corticosteroids (try to avoid: increase in viral load, elevation in transaminases)
  - IGIV
  - Splenectomy
  - TPO-R agonists

Infection-related ITP +/-6%

H. pylori-related ITP

- Prevelance depends on socio-economic conditions
- Prevalence in adult ITP: 20-80% (Japan 70%, Italy 50%, US 22%)

- Diagnostic methods:
  - **urea breath test and stool Ag test**: highest sensitivity and specificity
- Association with dyspepsia????
- Older than ITP without *H. Pylori*

- Eradication therapy: ORR 50 (14-100) % (higher ORR in Japan), persistent response 70%
- Higher ORR in ITP with a short duration and a higher platelet count >30000
- Platelet responses after 3d to 24 w (2 weeks in Italian trial)
- No responses to eradication therapy in pat *H. Pylori* neg

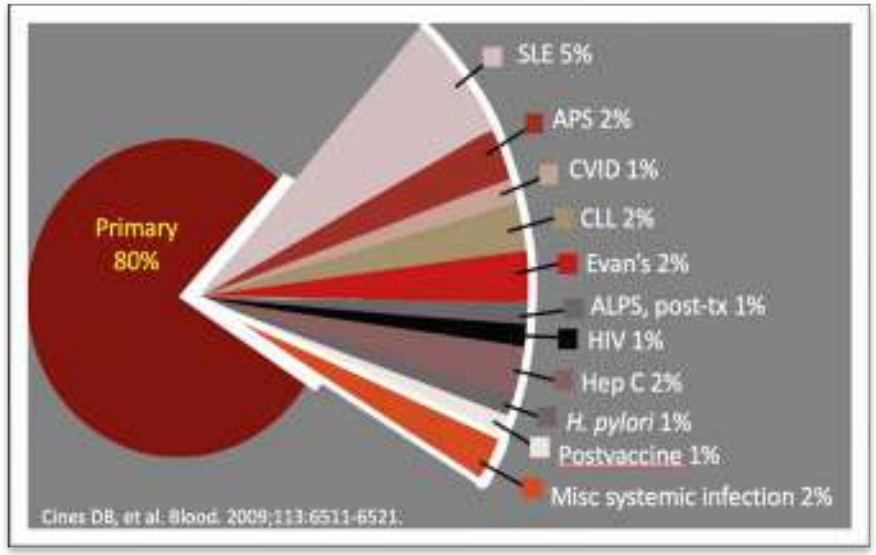
Stasi, Sem Hematol, 2009

HIV-related ITP

- Before HAART: 5 to 30% of HIV + patients develop thrombocytopenia (<150000/µl)
- Incidence of thrombocytopenia higher with an increase in immunosuppression
- If diagnosed before the stage of AIDS: thrombocytopenia mostly mild
- (can have additional bleeding problems: hemophilia, hep C, liver disease in drug addicts,…)

- Treatment
  - Antiretroviral therapy (can take weeks)
  - Corticosteroids, IGIV
  - Splenectomy
  - TPO-R agonists

Lymphoproliferative-related ITP +/-3%



Liebman, Sem Hematol,2009

ITP can occur in all lymphoproliferative disorders

Treatment ITP-CLL (1-5%) (can occur at any time in the course of CLL)

- **Corticosteroids, IGIV,** splenectomy
- **Rituximab monotherapy** or in combination with cyclophosphamide-dexamethasone
- Cyclosporine, Cellcept, Alemtuzumab
- TPO-R agonists
- **BTKi, Bcl-2i**

Treatment of ITP-Ho (0,2-1%) (can occur at any time in the course of Ho, also in remission)

- Ho treatment if active disease
- Corticosteroids, IGIV, splenectomy, TPO-RA
- Azathioprine

Treatment of LGL-thrombocytopenia (1% (severe)-20%(mild))

- Cytotoxic treatment against the LGL-clone
- Cyclosporine
- Alemtuzumab

ALPS

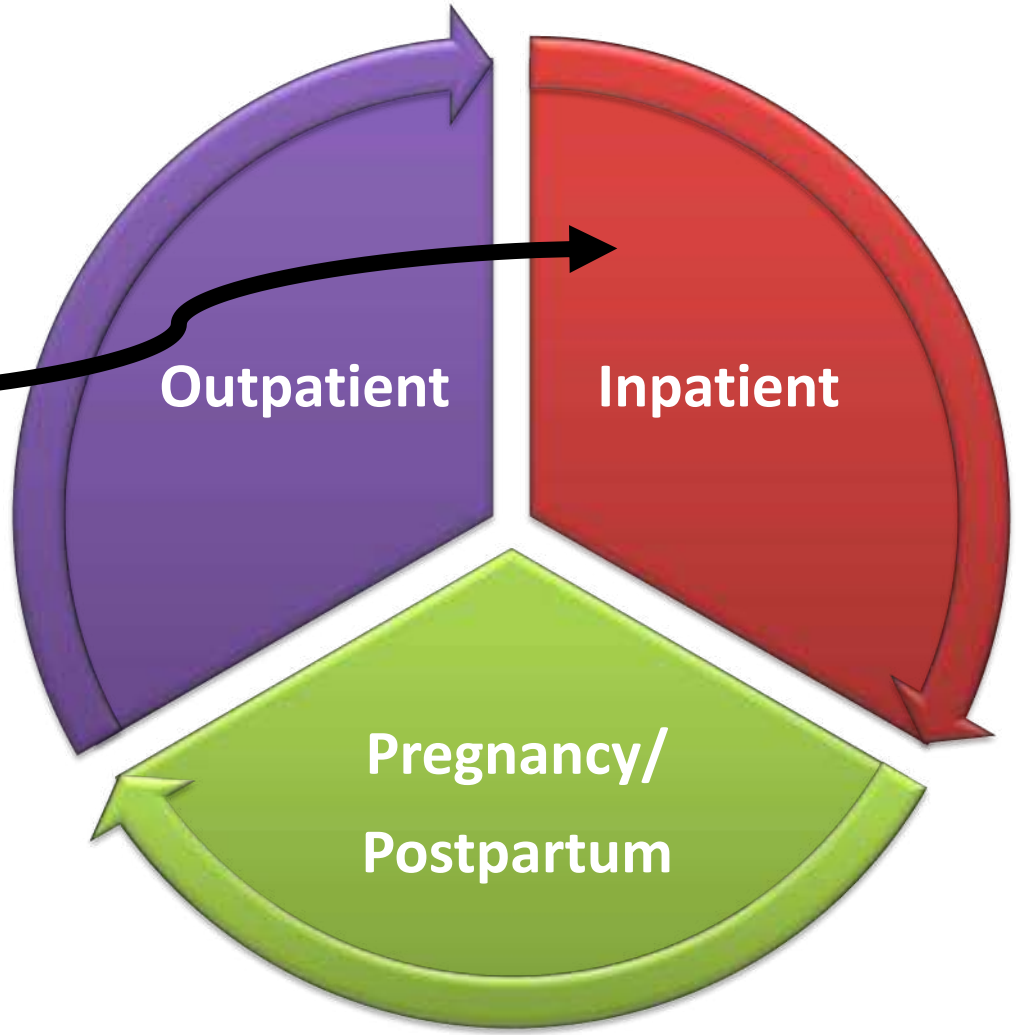
- Corticosteroids, IGIV
- Rituximab, Cellcept, SCT

Post-transplantation-related ITP

- Autologeous
- Allogeneic
- Post liver transplantation
- …

Inpatient	
Cardiac patient	Multi-system illness/ICU
• HIT • Cardiac bypass • GPIIb/IIIa inhibitors • Other DITP • Dilutional	• Infections • TTP/HUS • DITP • DIC • Liver disease • HIT • MAS • BM disorders • CIT

¼ critically ill patients at risk for DIT



>300 drugs suspected to induce thrombocytopenia

Drug-induced thrombocytopenia

- **Non-immune:**
  - **general myelosuppression** *(chemotherapy: platinum, gemcitabine)*
  - **dose dependent megakaryocyte suppression** *(linezolid given in high dose for >2w: +/- 30%, B-lactams, vancomycin, azathioprine, Bactrim, ganciclovir, foscarnet,…)*
  - **inhibition of megakaryocyte maturation** *(panobinostat, bortezomib)*
  - **inhibition of TPO signalling** *(selixinor)*
  - **Induction of apoptosis by inhibiton of Bcl-XL** *(navitoclax)*
  - **TTP-HUS: (***cyclosporin, tacrolimus, …)*

- **Immune mediated:** *(drugs, beverages (tonic water, bitter lemon), food (tahini & sesam seeds, lupus beans, Jui herbal (chinese) tea, herbal products,….*
  - **Ab that accelerate destruction,**
  - **Ab that increase platelet activation**

Arnold et al, Transfusion medicine reviews 2013
Danese et al, Sem Thrombosis & Hemostasis 2020

Platelets on the web
http://www.ouhsc.edu/platelets/ditp.html

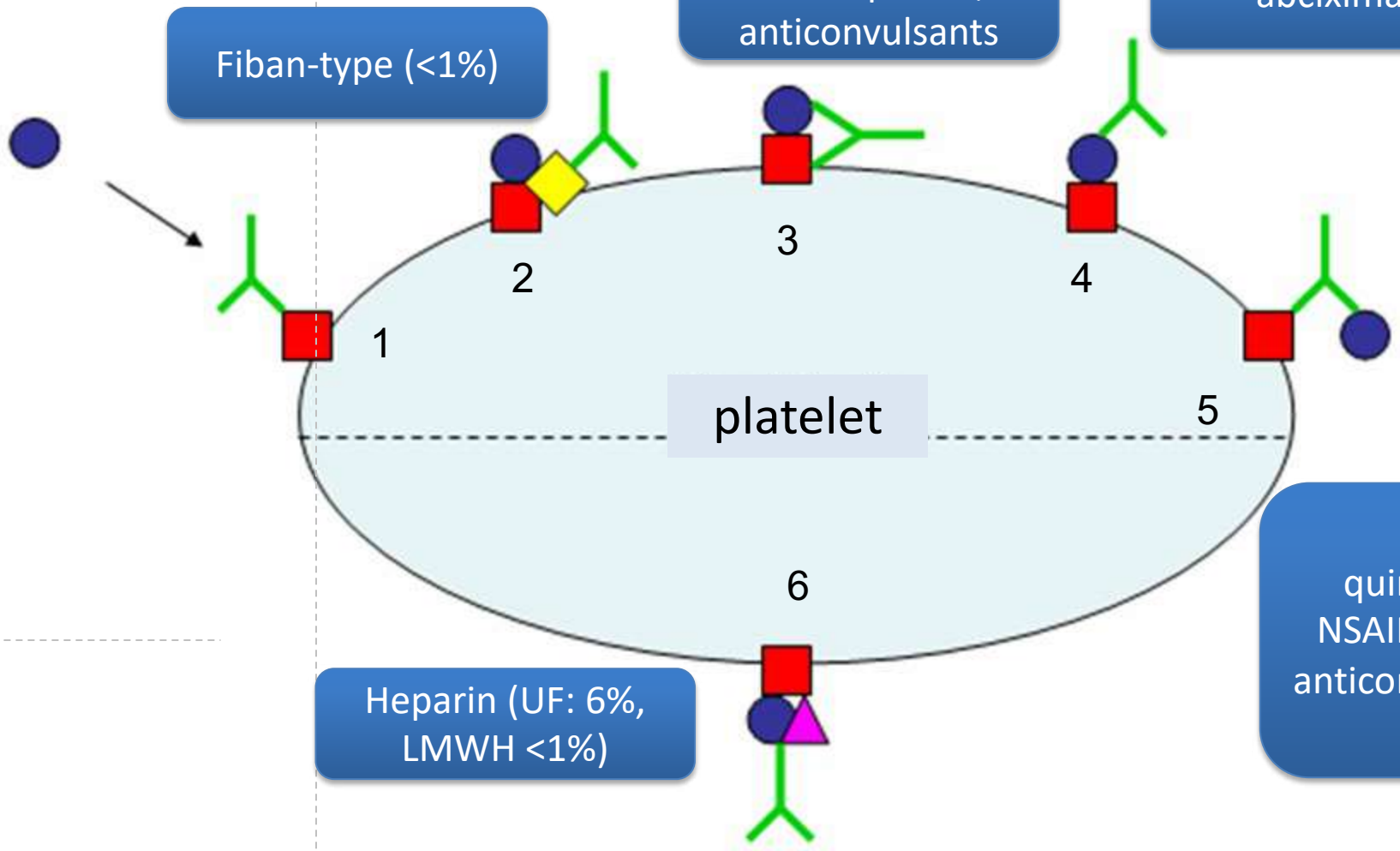
Drug-induced ITP

Gold (1%), procainamide, L-dopa, penicillamine, sulfamethoxazole, vaccinations

Fiban-type (<1%)

Penicillin, cefalosporine, anticonvulsants

abciximab



Mechanisms:

1 auto-antibodies

2 neo-epitope

3 hapteen

4 drug specific

5 quinine type

6 Immune complex

Heparin (UF: 6%, LMWH <1%)

quinine, NSAIM, AB, anticonvulsiva

FAB FC :immuunglobuline :(glyco)proteïne :drug (metabolite) :PF-4 :neo-epitope

Aster et al., NEJM 2007

Key messages and Conclusions

01

Exclude pseudothrombo-cytopenia

02

Be aware that even in adults a low platelet count could have a hereditary cause

03

Exclude thrombocyto-penia due to drugs, beverages, alcohol, herbal supplements,…

04

Not every ITP patient need treatment: balance bleeding and toxicity risk

05

Reconsider the diagnosis of ITP when the patient does not respond to treatment