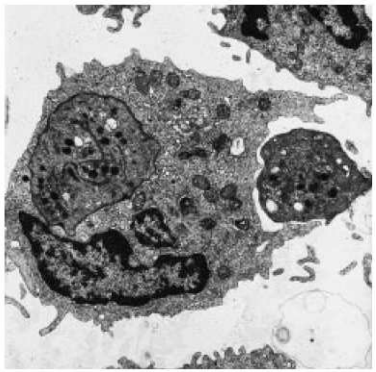
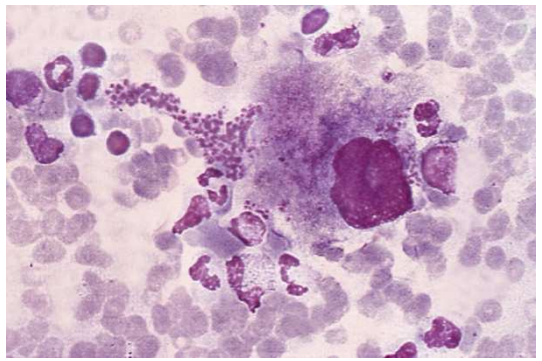
Corso di Ematologia di Laboratorio Istituto Tumori, Milano 11-12 novembre 2010





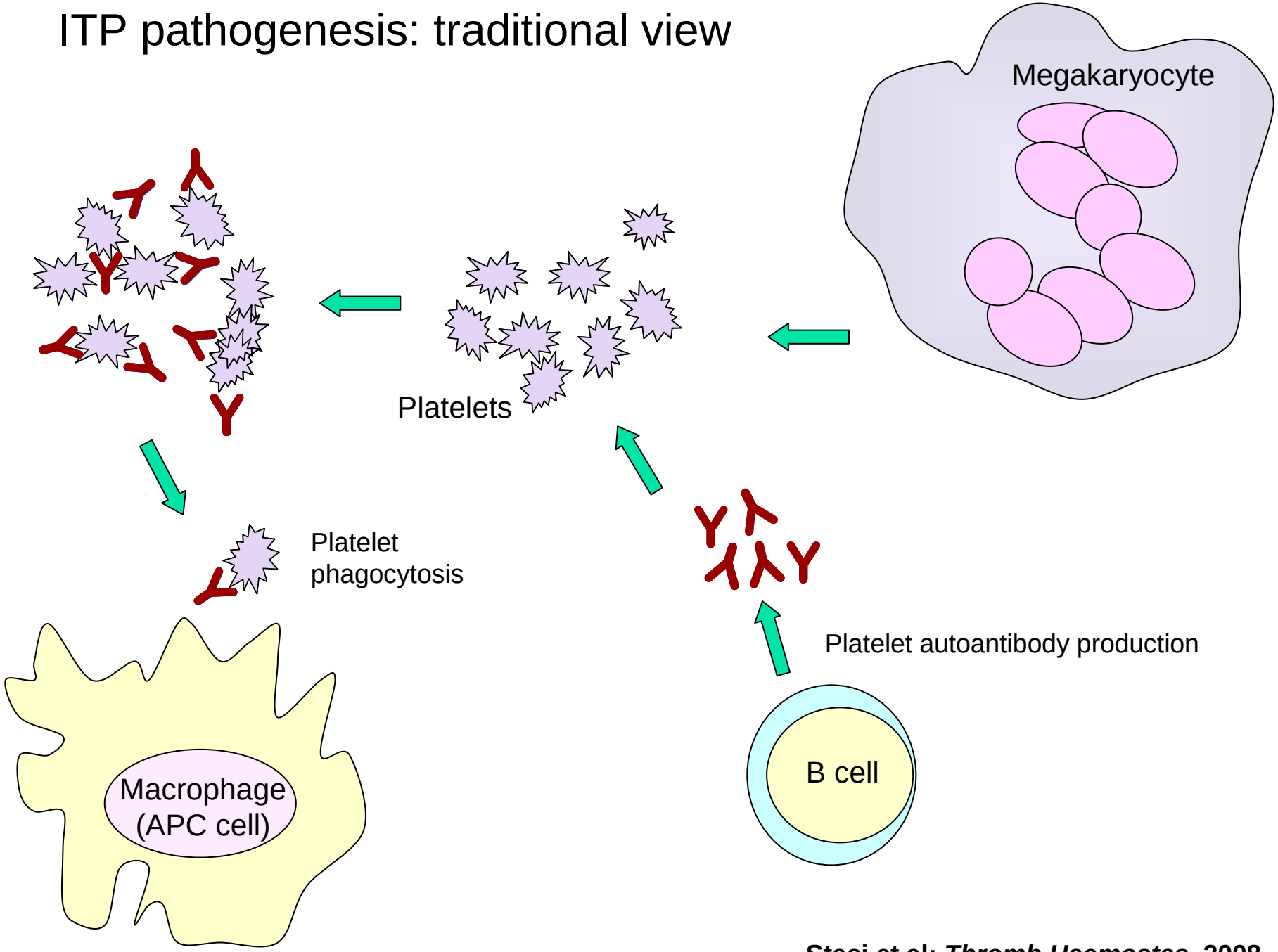
Piastrinopenie Immuni: dalla patogenesi alla standardizzazione del percorso diagnostico e terapeutico

Marco Ruggeri

UO Ematologia, Ospedale San Bortolo, Vicenza

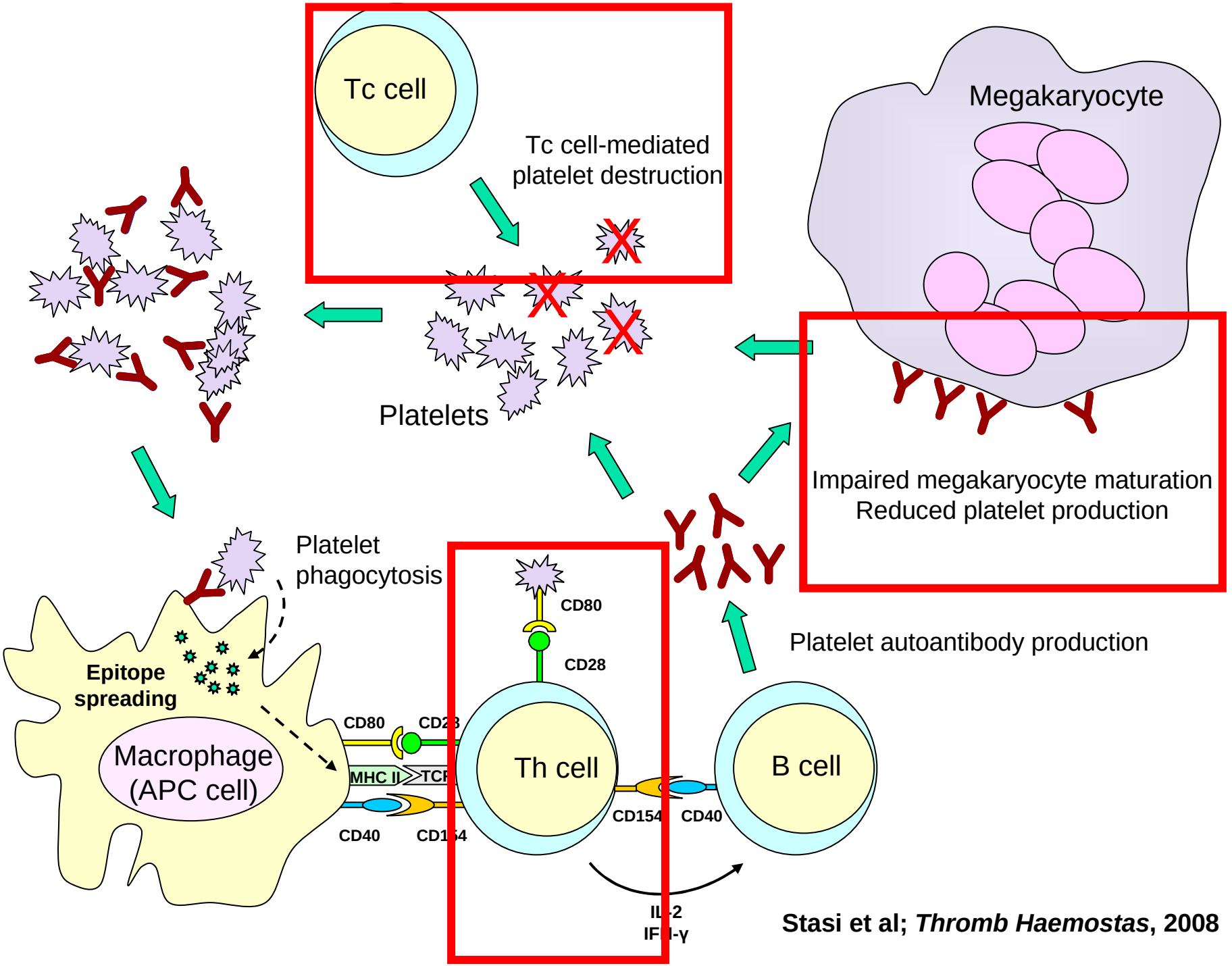
ITP is an autoimmune syndrome

ITP pathogenesis: traditional view



Stasi et al; *Thromb Haemostas*, 2008

Concepts surrounding the mechanisms of thrombocytopenia in ITP have shifted from the traditional view of increased platelet destruction mediated by autoantibodies to more complex mechanisms in which both **impaired platelet production** and **T cell–mediated effects** play a role



Stasi et al; *Thromb Haemostas*, 2008

Mechanisms of thrombocytopenia: great heterogeneity!

Autoimmune mechanisms:

1.Increased platelet destruction

-Antiplatelet antibodies secretion by autoreactive B lymphocytes (> 80% initial response rate to IVIg and splenectomy)

-Dysfunctional cellular immunity (autoreactive T cells)

-T cell- mediated cytotoxicity

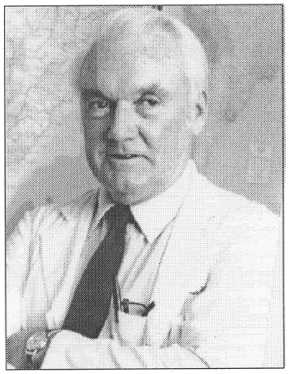
-Natural killer activation

2.Impaired thrombopoiesis

-Autoantibody suppression of megakaryopoiesis and thrombopoiesis

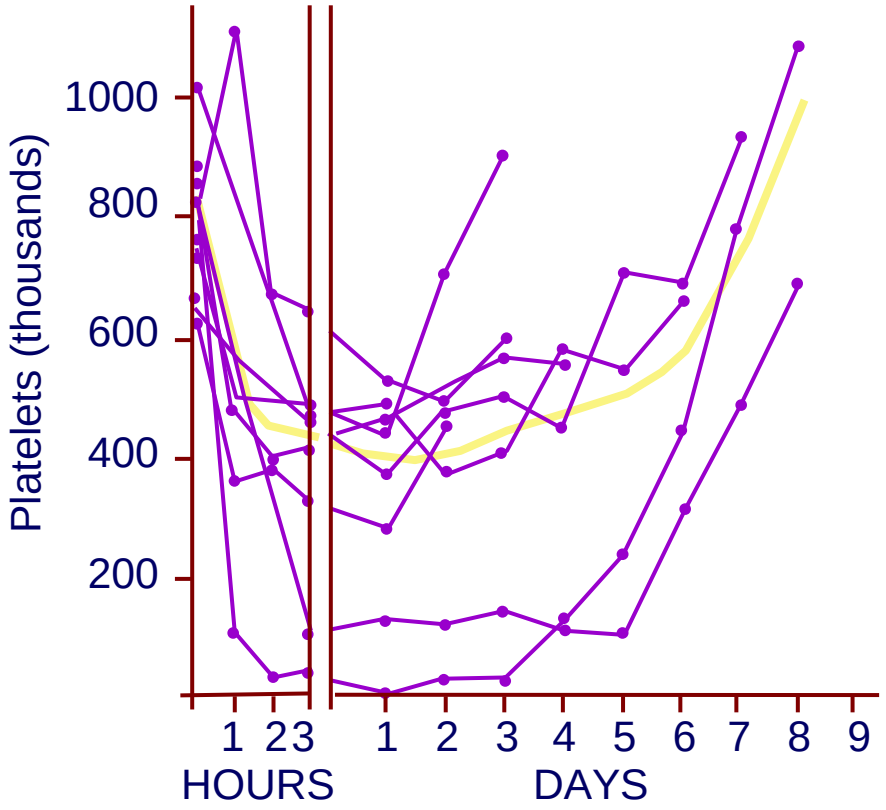
Evidence for increased platelet destruction ITP

Harrington's classic experiment



Biography: Dr. William J Harrington, Sr. (Sept. 21, 1923 - Sept 4, 1992)

- Blood from patients with chronic ITP injected into 10 normal volunteers
- Thrombocytopenia immediately observed in 8 subjects
- Due to an antiplatelet "factor" in the globulin fraction of plasma



Harrington et al; *J Lab Clin Med*, 1951

SIMILARITIES BETWEEN KNOWN ANTIPLATELET ANTIBODIES AND THE FACTOR RESPONSIBLE FOR THROMBOCYTOPENIA IN IDIOPATHIC PURPURA. PHYSIOLOGIC, SEROLOGIC AND ISOTOPIC STUDIES

N. Raphael Shulman, Victor J. Marder, Roy S. Weinrach
Clinical Hematology Branch, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

Shulman, N.R., Marder, V.J. & Weinrach, R.S. (1965) Similarities between known antiplatelet antibodies and the factor responsible for thrombocytopenia in idiopathic purpura. Physiologic, serologic and isotopic studies. *Annals of the New York Academy of Science*, **124**, 499–542.

There is good evidence that a humoral factor is involved in the pathogenesis of idiopathic thrombocytopenic purpura (ITP), for children of mothers with ITP are sometimes thrombocytopenic at birth,[1] and the plasma of some patients with ITP causes thrombocytopenia when infused into normal individuals.[2] That the ITP humoral factor may be an antibody, is suggested by similarities between ITP and thrombocytopenia caused by heterologous antibodies in animals,[3-5] and by drug antibodies or isoantibodies in man.[6-9] Evidence for the immune nature of ITP has remained circumstantial, however, because there has been no satisfactory immunologic technique for characterizing the factor in ITP plasma that causes thrombocytopenia in homologous recipients and no proof that the ITP factor affects autologous platelets.

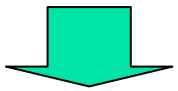
The present report concerns direct evidence that the ITP factor destroys autologous platelets and is most likely an antibody. Although *in vitro* tests for antibody were negative with the ITP plasmas used, the ITP humoral factor appeared to be species specific, was adsorbed by platelets, and was found in the 7S gamma globulin fraction of plasma. The thrombocytopenic effects of ITP plasma were found to be quantitatively, as well as qualitatively, similar to those of known antiplatelet antibodies. Studies of experimental thrombocytopenia provided information on platelet production and reserve, on mechanisms of destruction of normal and immunologically altered platelets, and on the nature of the response to splenectomy and corticosteroid therapy in ITP.

Materials and Methods

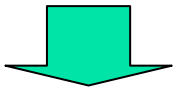
General Techniques

Methods used to prepare platelets and to measure complement fixation, agglutination, inhibition of clot retraction and anti-globulin consumption with sera containing drug antibodies or isoantibodies have been described before.[4,10] These same tests were used with ITP sera. In addition, the agglutination techniques of Harrington *et al.*[6] and of Dausset and Malinvaud[7] were used. Harrington's technique is essentially an overnight incu-

- Severity of post-transfusion thrombocytopenia was dose-depending



- The plasma factor that caused thrombocytopenia could be absorbed by platelet



- The plasma factor was present in IgG rich fraction = antiplatelet autoantibody

Phagocytosis of Antibody-Coated Platelets by Human Granulocytes

Handin et al; N Engl J Med, 1974

Methods:

Normal human platelets exposed to a variety of serums containing anti-platelet antibodies, incubated with autologous granulocytes

Phagocytosis was observed microscopically, by uptake of 51Cr-labeled platelets, and by initial rate of reduction of nitroblue tetrazolium.

Results:

- Phagocytosis and the initial rate of dye reduction were increased *as compared to control serums*, by serums from:
  - -14 patients with idiopathic thrombocytopenic purpura,
  - -13 patients refractory to platelet transfusion
  - -rabbits immunized with washed human platelets

- The opsonic activities of serums from patients with idiopathic thrombocytopenic purpura persisted after treatment with steroids or splenectomy.

Assay for antibodies specific for platelet glycoprotein IIb/IIIa and Ib/IX

- Mueller-Eckhardt C, Kayser W, Mersch-Baumen K, Mueller- Eckhardt G, Kugel HG, Graubner M: The clinical significance of platelet-associated IgG: A study on 298 patients with various disorders. Br J Haematol 46:123, 1980
- Kelton JG, Powers PJ, Carter CJ: A prospective study of the usefulness of the measurement of platelet-associated IgG for the diagnosis of idiopathic thrombocytopenic purpura. Blood 60: 1050, 1982
- Sinha RK, Kelton JG: Current controversies concerning the measurement of platelet-associated IgG. Transfus Med Rev 4:121, 1990
- McMillan R, Tani P, Millard F, Berchtold P, Renshaw L, Woods VL Jr: Platelet-associated and plasma anti-glycoprotein autoantibodies in chronic ITP. Blood 70:1040, 1987
- Kiefel V, Santoso S, Weisheit M, Mueller-Eckhardt C: Monoclonal antibody-specific immobilization of platelet antigens (MAIPA): A new tool for the identification of platelet-reactive antibodies. Blood 70:1722, 1987
- McMillan R: Antigen-specific assays in immune thrombocytopenia. Transfus Med Rev 4:136, 1990
- Kiefel V, Santoso S, Kaufmann E, Mueller-Eckhardt C: Autoantibodies against platelet glycoprotein Ib/IX: A frequent finding in autoimmune thrombocytopenic purpura. Br J Haematol 79:256, 1991

T-cell abnormalities in ITP

- Increase ratio Th1/Th2
  - -↑ IL-2 and INF-γ⇨ B cell differentiation and antibodies production
  - -↓ IL-10)
- ↑ release of TGF-β1
  - -a potent inhibitor of MKC maturation
- Defective T regulatory cells CD4+ CD 25+
  - -deficiency in peripheral tolerance
- ↑ cytotoxic genes, such as granzyme A, B and perforin
  - -direct cytotoxic effect of T cell

T-cell abnormalities in ITP: role of anti-CD 20 antibodies

<u>T cell abnormalities (pretreatment vs control group):</u>

↑ Th1/Th2 (CD4+)	(p< 0.001)
↑ Tc1/Tc2 (CD8+)	(p<0.001)
↑ Fas expression ligand	(p<0.001)
↑ Bcl-2 mRNA expression	(p=0.003)
↓Bax mRNA expression	(p=0.025)

All reverted in responders (at 3 and 6 months); unchanged in nonresponders

Stasi et al; *Blood,* 2007

Evidence for decreased platelet production

Kinetics studies

At stable platelet counts:

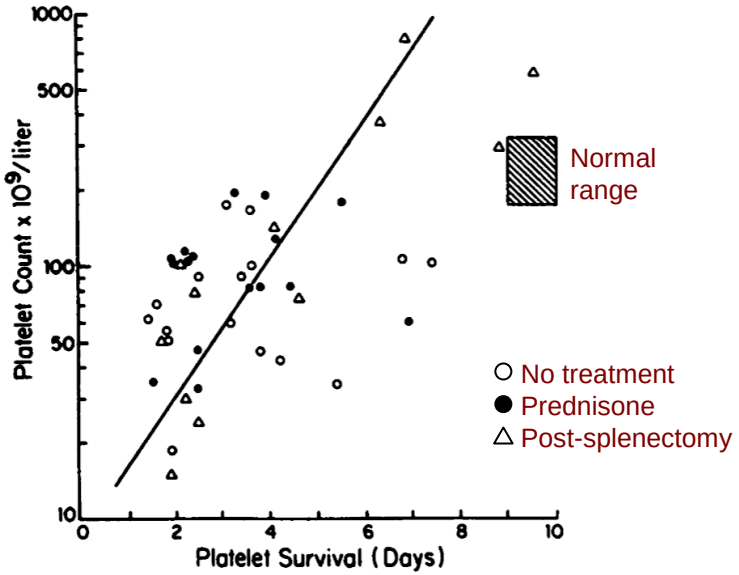
Platelet Turnover = Platelet Destruction = Platelet Production

$$\text{Platelet Turnover} = \frac{\text{Platelet Count}}{\text{Platelet Survival}} \times \frac{90}{\text{Platelet Recovery}}$$

Mechanism of Thrombocytopenia in ITP

Decreased platelet survival

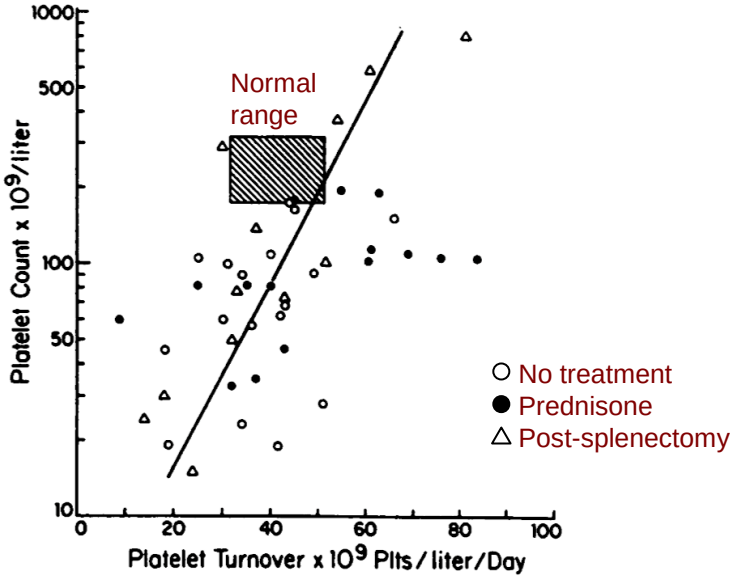
Radiolabeled autologous platelets



Homologous platelets are cleared much faster (minutes-hours)

Impaired platelet production

Production ≈ Platelet count / Platelet survival



Most patients have inappropriately low or normal rates of platelet production

Ballem PJ et al; *J Clin Invest* 1987

Morphological studies

1.Dameshek et al, 1946; Diggs et al, 1948 (examination by light microscopy):

- abnormal thrombopoiesis, including normal or increased megakaryocyte numbers with a larger percentage of younger forms lacking cytoplasmic granularity or evidence of platelet formation
- degenerative changes in both nuclei and cytoplasm

2.Pisciotta et al, 1953 (phase contrast studies):

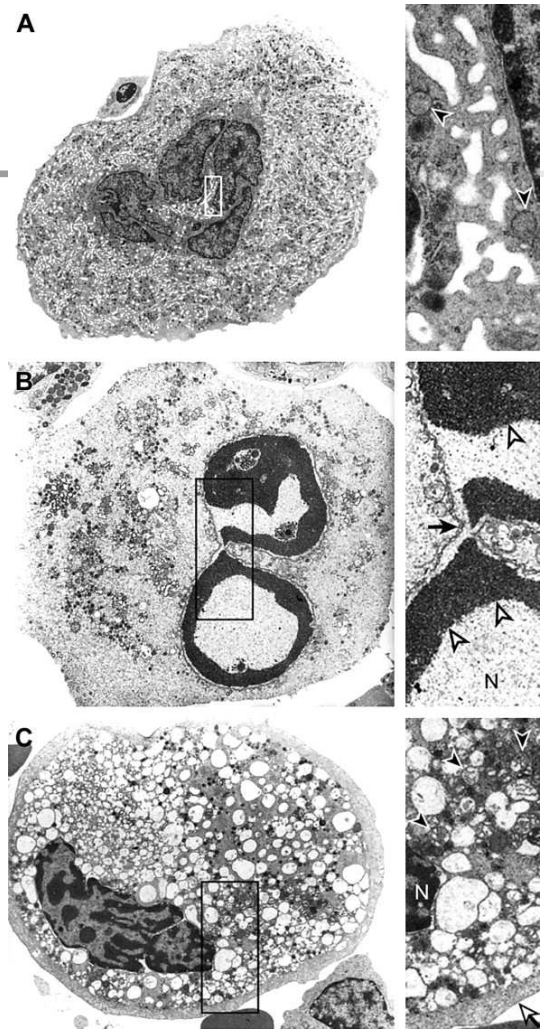
- confirmed these findings and also showed that infusing healthy controls with plasma from ITP patients produced these same abnormalities in megakaryocytes

3.Stahl et al, 1986 (electron microscopy studies):

- confirmed the presence of abnormal megakaryocytes, as shown by markedly distended demarcation membranes, vacuolized cytoplasm, swollen mitochondria, and disrupted peripheral zone

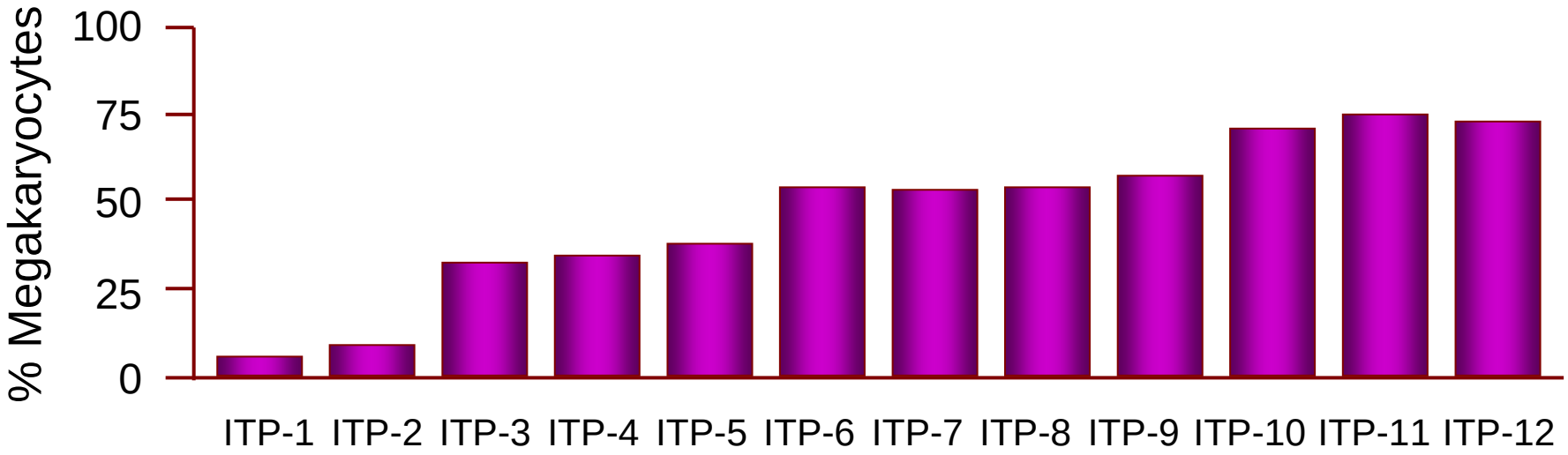
Ultrastructure of megakaryocytes in healthy control and ITP

Apoptosis abnormalities present in 78% of MKC, reversed by *in vivo* steroids or Ig therapy



Houwerzijl et al; *Blood,* 2004

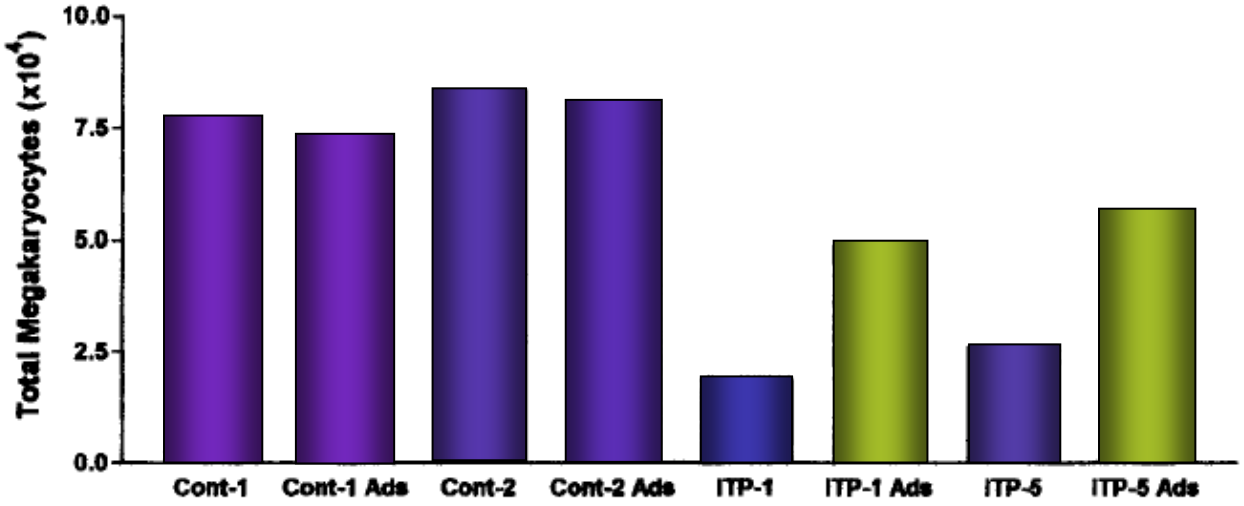
Suppression of megakaryocyte production by ITP plasma



Plasma form 12/18 ITP patients (67%) suppress (from 25% to 95%) in vitro MKC production

McMillan et al; *Blood*, 2004

Suppression of megakaryocyte production by ITP plasma



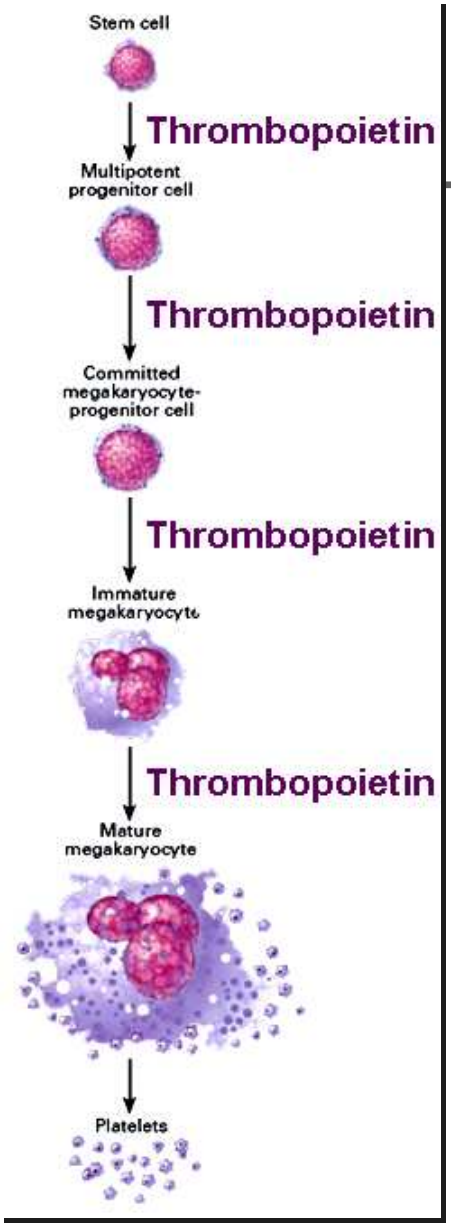
Effect of autoantibody adsorption with immobilized GPIIb - IIIa

McMillan et al; *Blood,* 2004

Non-immune mechanisms

Thrombopoietin dysregulation

Thrombopoietin (TPO) involved at all stages

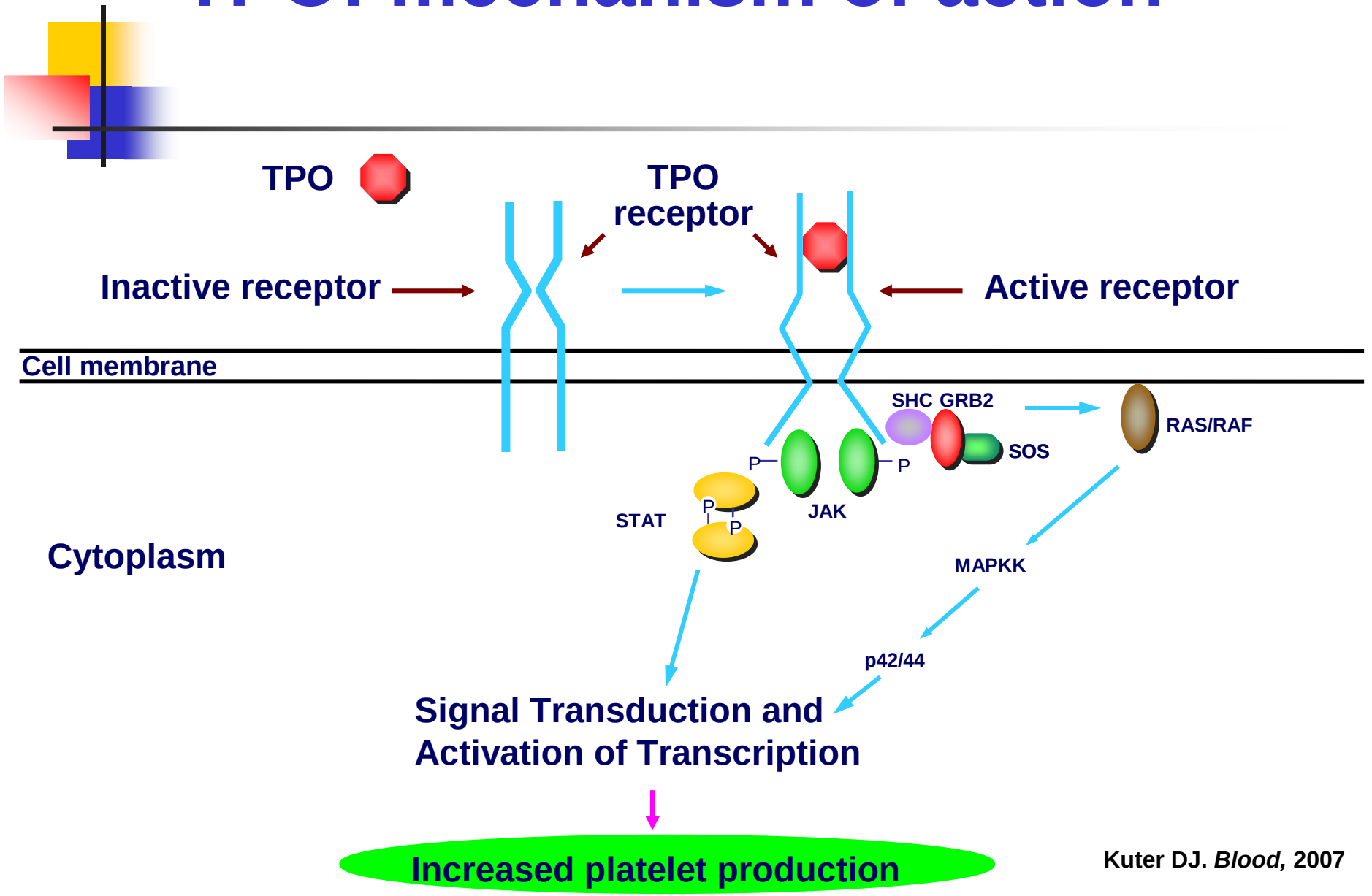


Stimulates platelet production by promoting:

- Proliferation
- Survival
- Differentiation of megakaryocyte precursors into mature megakaryocytes

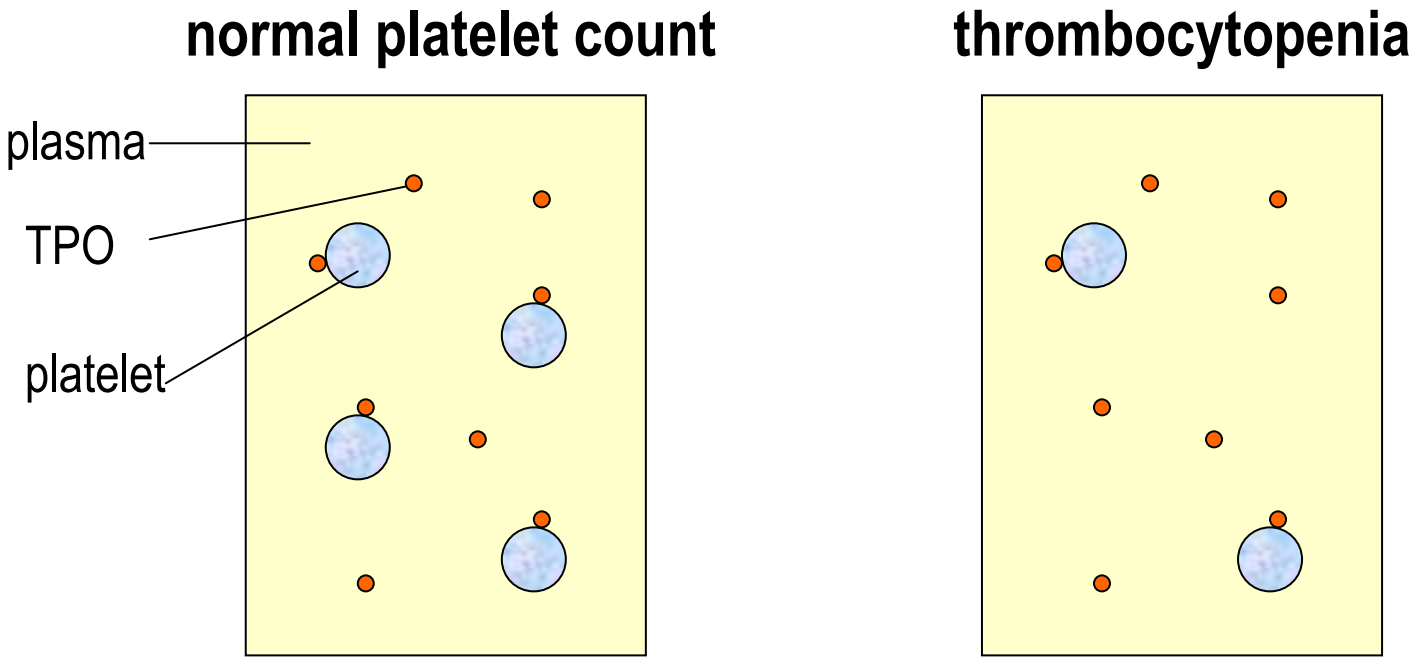
Platelet release

TPO: mechanism of action



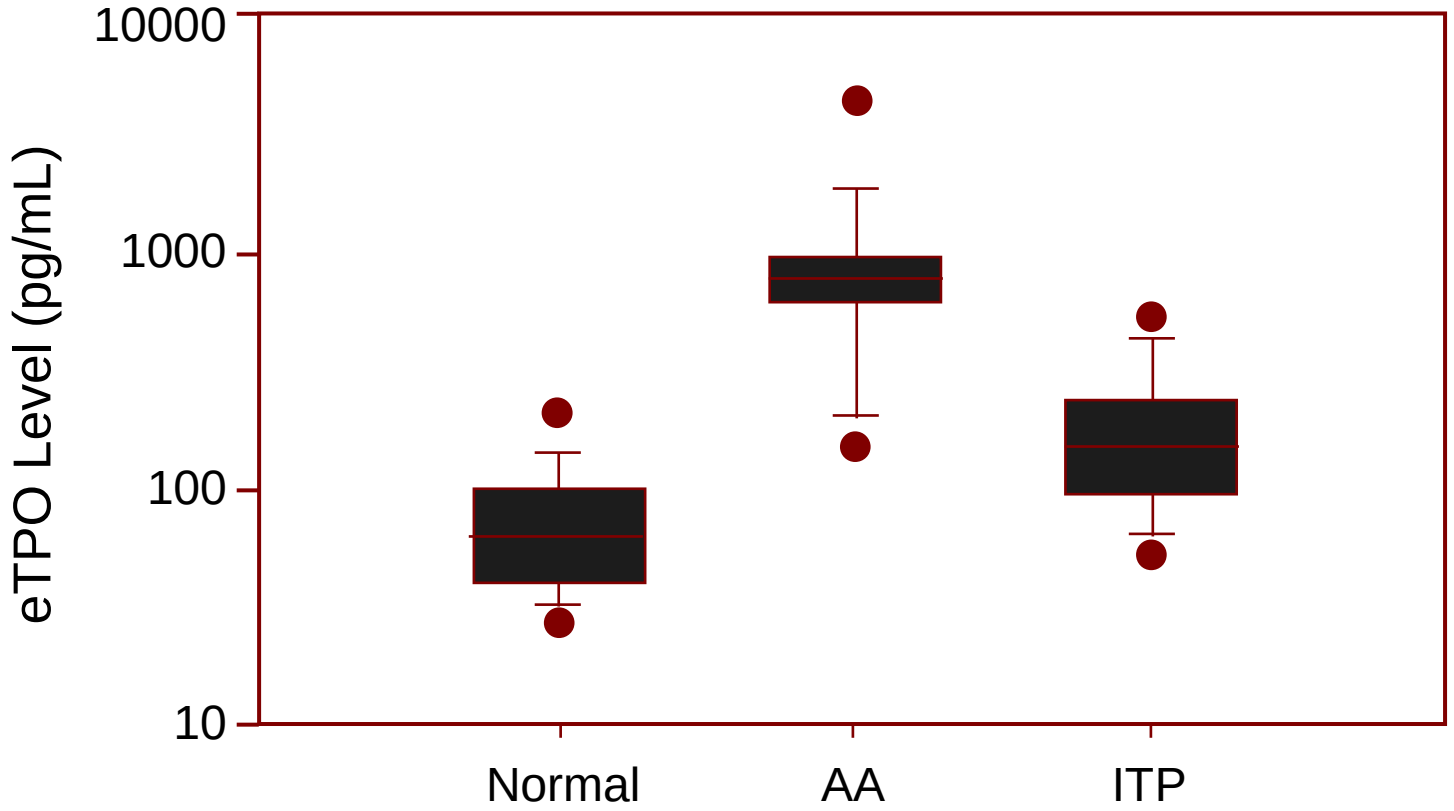
Kuter DJ. *Blood*, 2007

TPO levels are inversely proportional to the platelet count



[TPO] total	normal	normal
[TPO] free	normal	increased

Endogenous thrombopoietin concentrations are minimally elevated in patients with ITP



Nichol JL. In: Kuter DJ et al, eds. *Thrombopoiesis and Thrombopoietins: Molecular, Cellular, Preclinical and Clinical. 1996;Mukai Thromb Haemost.*

Proposed feedback mechanism of TPO

TPO levels are inversely related to the platelet and megakaryocyte mass, because these cells bind and degrade TPO

- In steady state, plasma concentrations of platelet-bound TPO and free TPO are fixed
- When platelet and megakaryocyte mass ↓, free TPO ↑
- In ITP there is increased megakaryocyte mass and accelerated removal of TPO by the increased platelet turnover

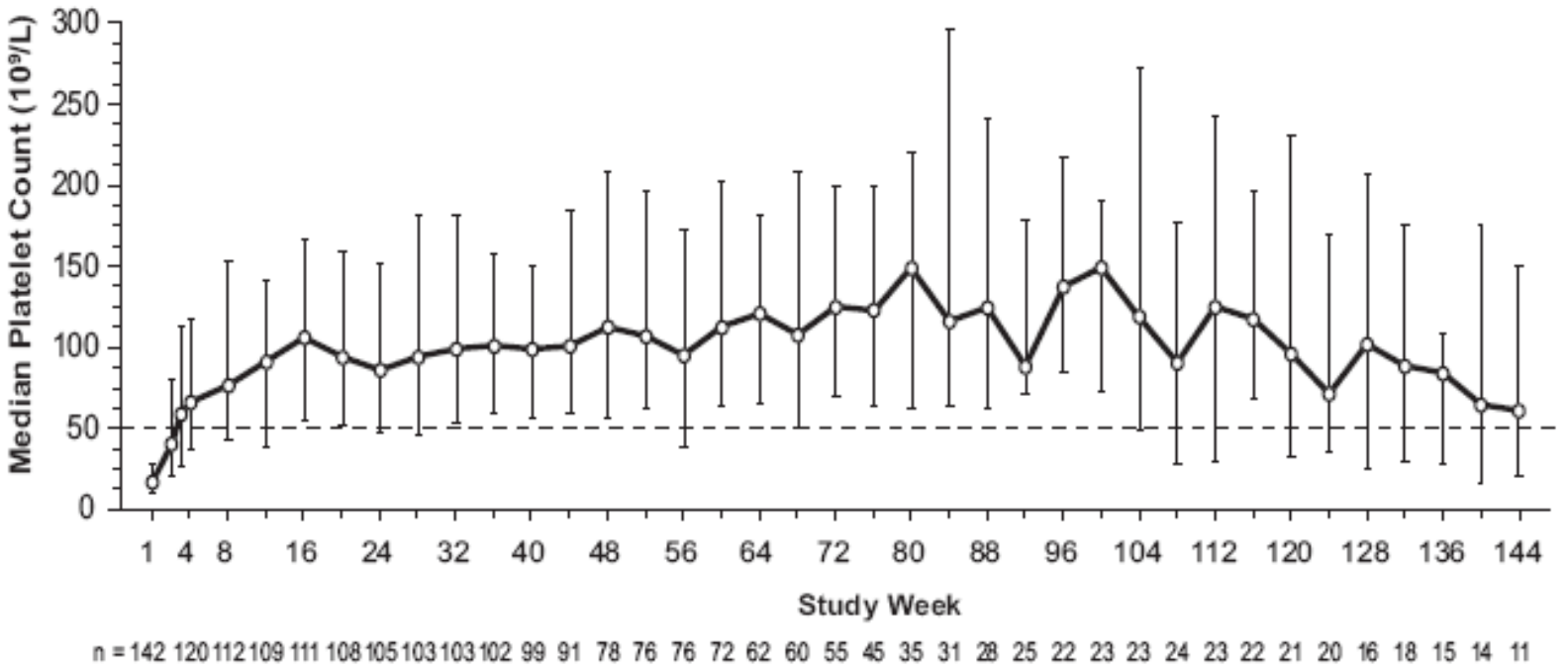
Free TPO is not sufficiently increased to compensate for thrombocytopenia

blood

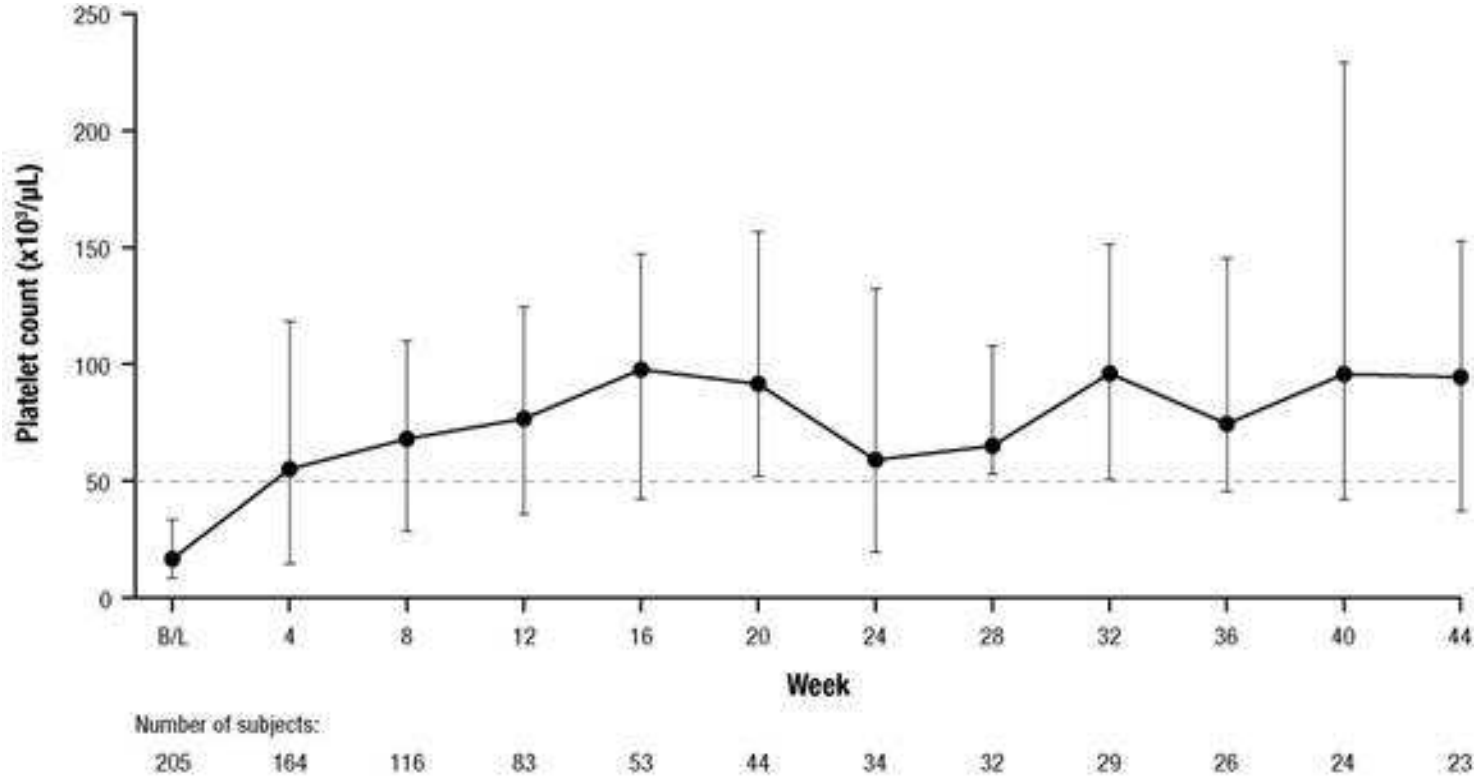
2009 113: 2161-2171
Prepublished online Nov 3, 2008;
doi:10.1182/blood-2008-04-150078

Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP

James B. Bussel, David J. Kuter, Vinod Pullarkat, Roger M. Lyons, Matthew Guo and Janet L. Nichol

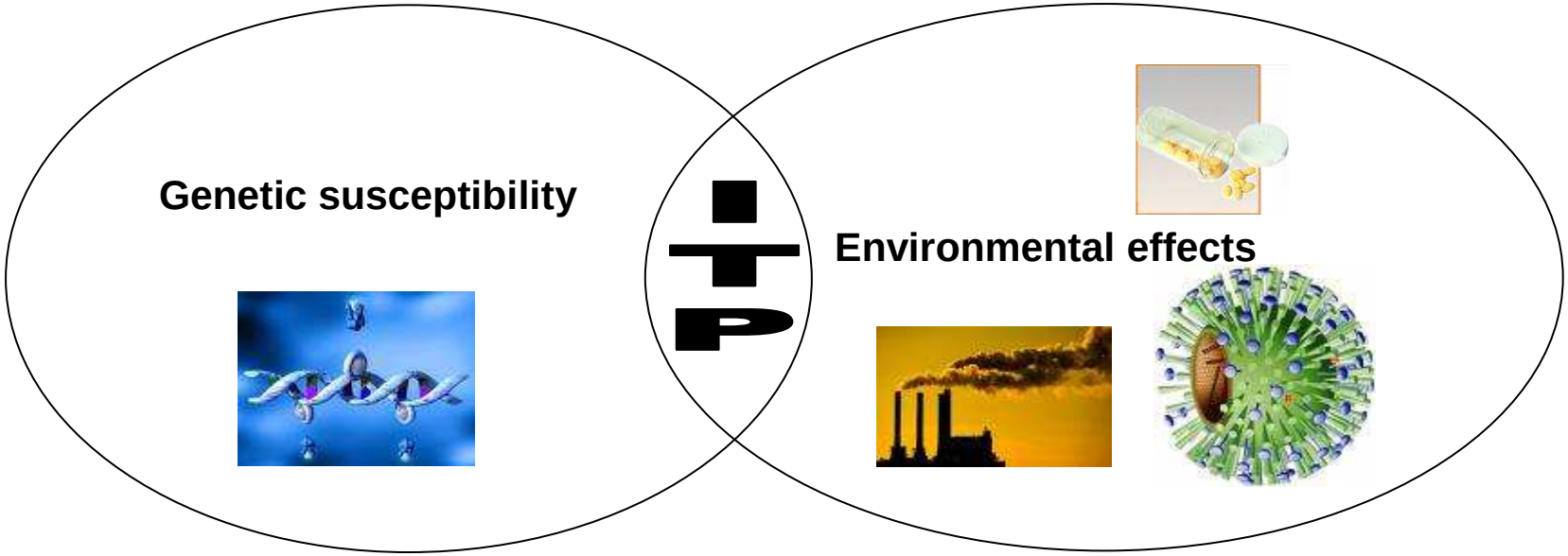


Platelet count in ITP patients treated with Eltrombopag
EXTEND study Bussel et al, abstract ASH 2009



Pathogenesis of ITP

Precipitating events?



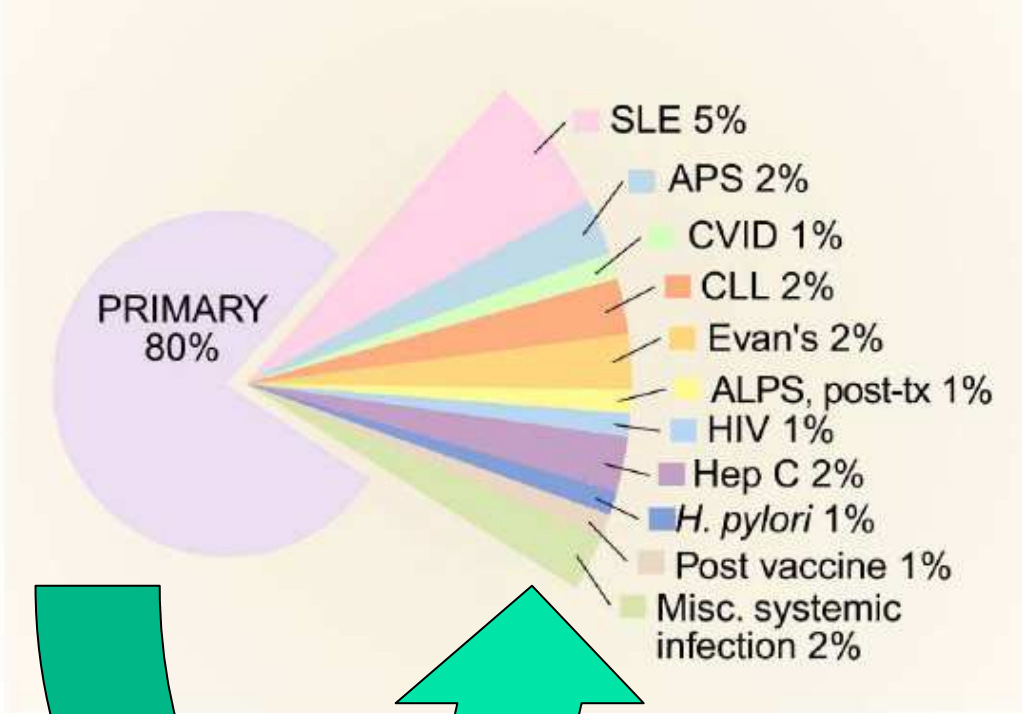
Heterogeneity of Primary ITP

blood

Prepublished online Apr 24, 2009;
doi:10.1182/blood-2009-01-129155

The ITP syndrome: pathogenic and clinical diversity

Douglas B. Cines, James B. Bussel, Howard A. Liebman and Eline T. Luning Prak



Increase identification of inciting events and immune defects

Loss of self-tolerance in secondary ITP

blood
Prepublished online Apr 24, 2009;
doi:10.1182/blood-2009-01-129155

The ITP syndrome: pathogenic and clinical diversity

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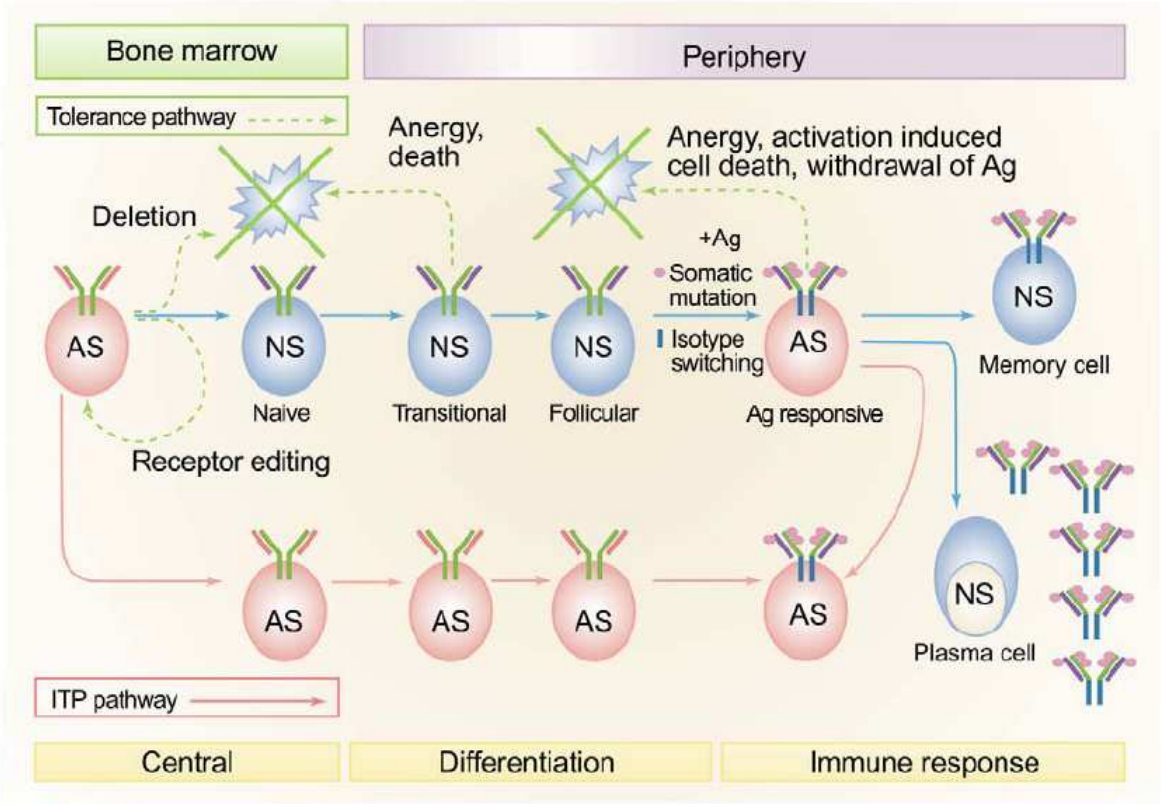

blood

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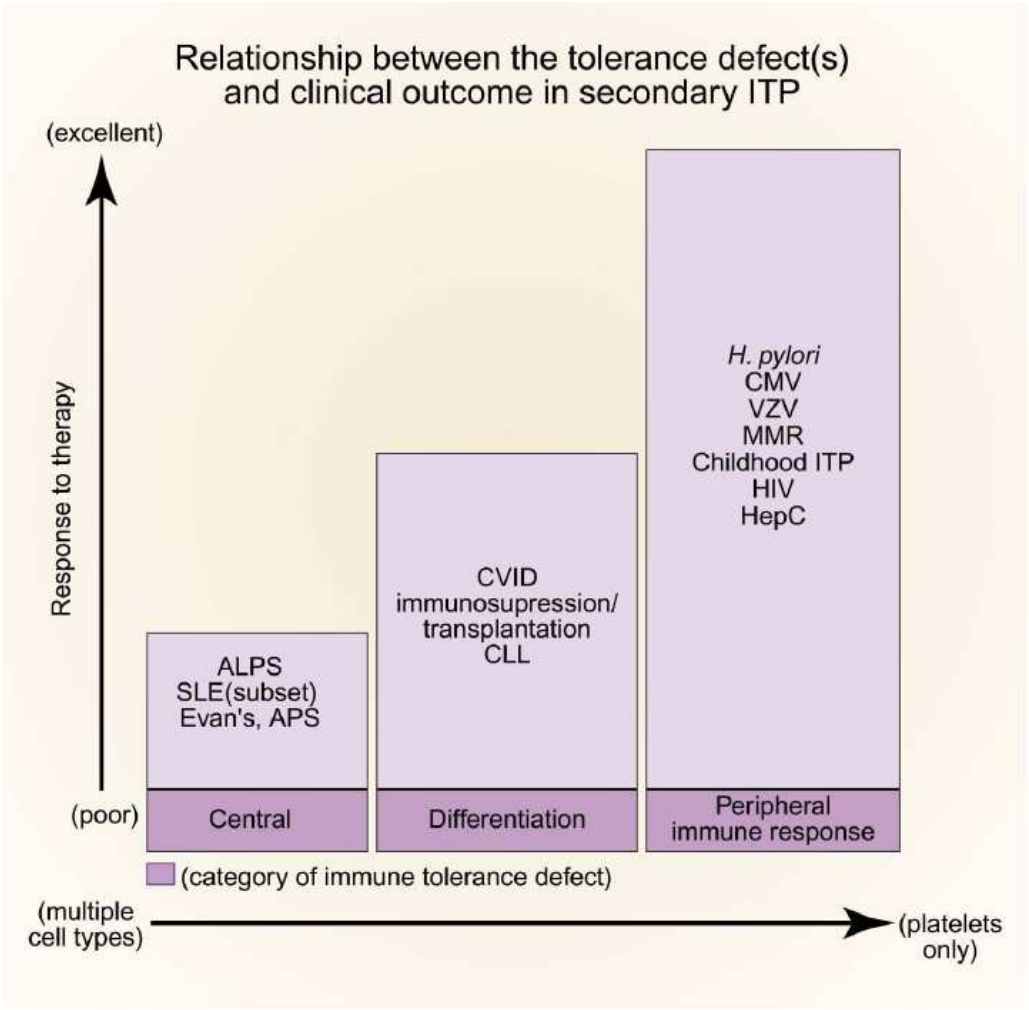


Central tolerance defect

More cell types involved: less responsive to therapy

Peripheral tolerance defect

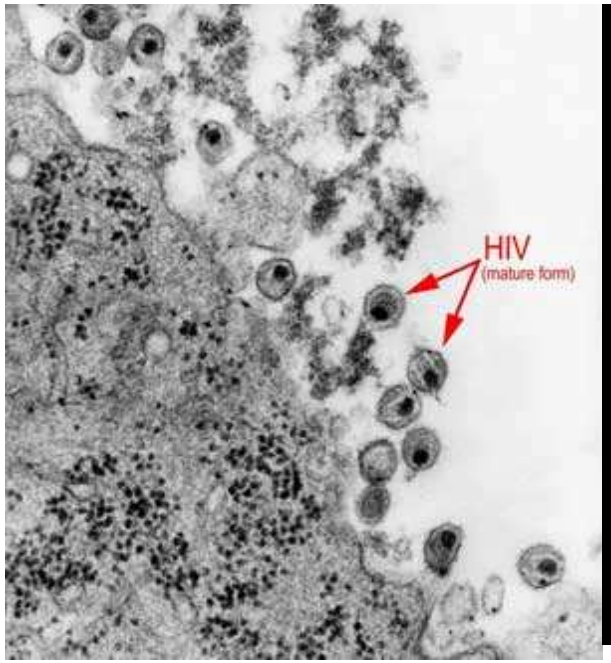
More platelet-specific: more responsive to therapy

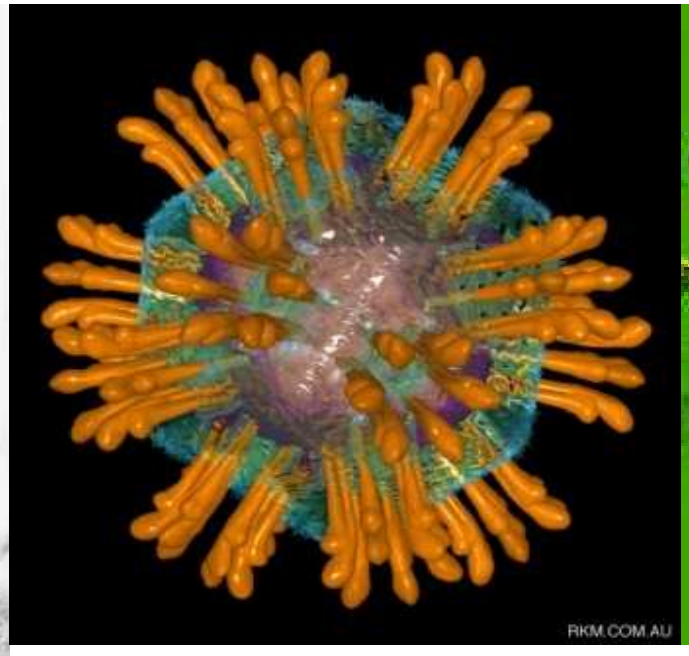
Immune thrombocytopenia post-infection

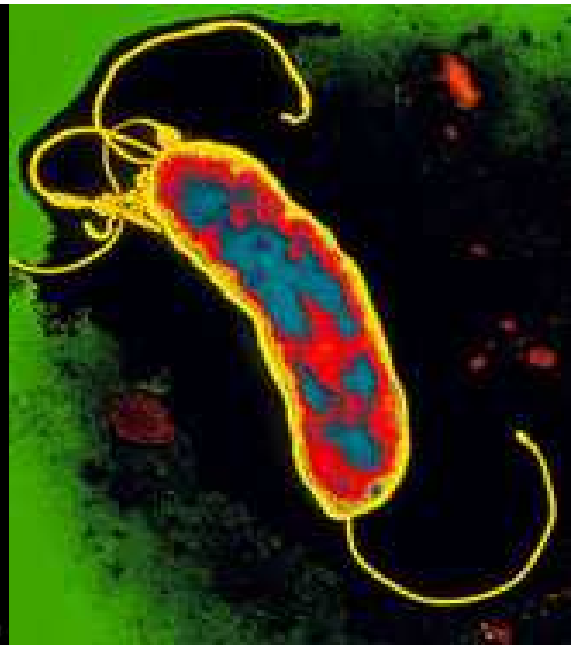
HIV

HCV

H.pylori







Pathophysiology ITP in HIV infection

- Immune complex disease

  (platelet “innocent bystanders”)

- Antigen mimicry

  (ab anti HIV cross-reacting with PLT GPIIIa and HIV GP160)

- Megakaryocytic apoptosis

  (direct infection of MKC)

Clinical manifestations of ITP in HIV infection

- Clinical picture often mild (minority of patients with plt count < 50 x 10^9/L); major bleeding rare
- Severe thrombocytopenia associated with advance HIV infection and additional cytopenias (often concomitant HBV and HCV hepatitis in i.v. drug users)
- Responsive to therapeutic intervention used in primary ITP (PDN, Ig ev, splenectomy)
- Zidovudine mono-therapy and HAART increase platelet count in 60%-70% HIV^+ITP (response more limited in HIV^+HCV^+ITP)

Pathophysiology of ITP in HCV infection

- Immune complex disease (platelet “innocent bystanders)
- Megakaryocytic apoptosis (direct infection of MKC)
- Hypersplenism
- Inadequate production of thrombopoietin

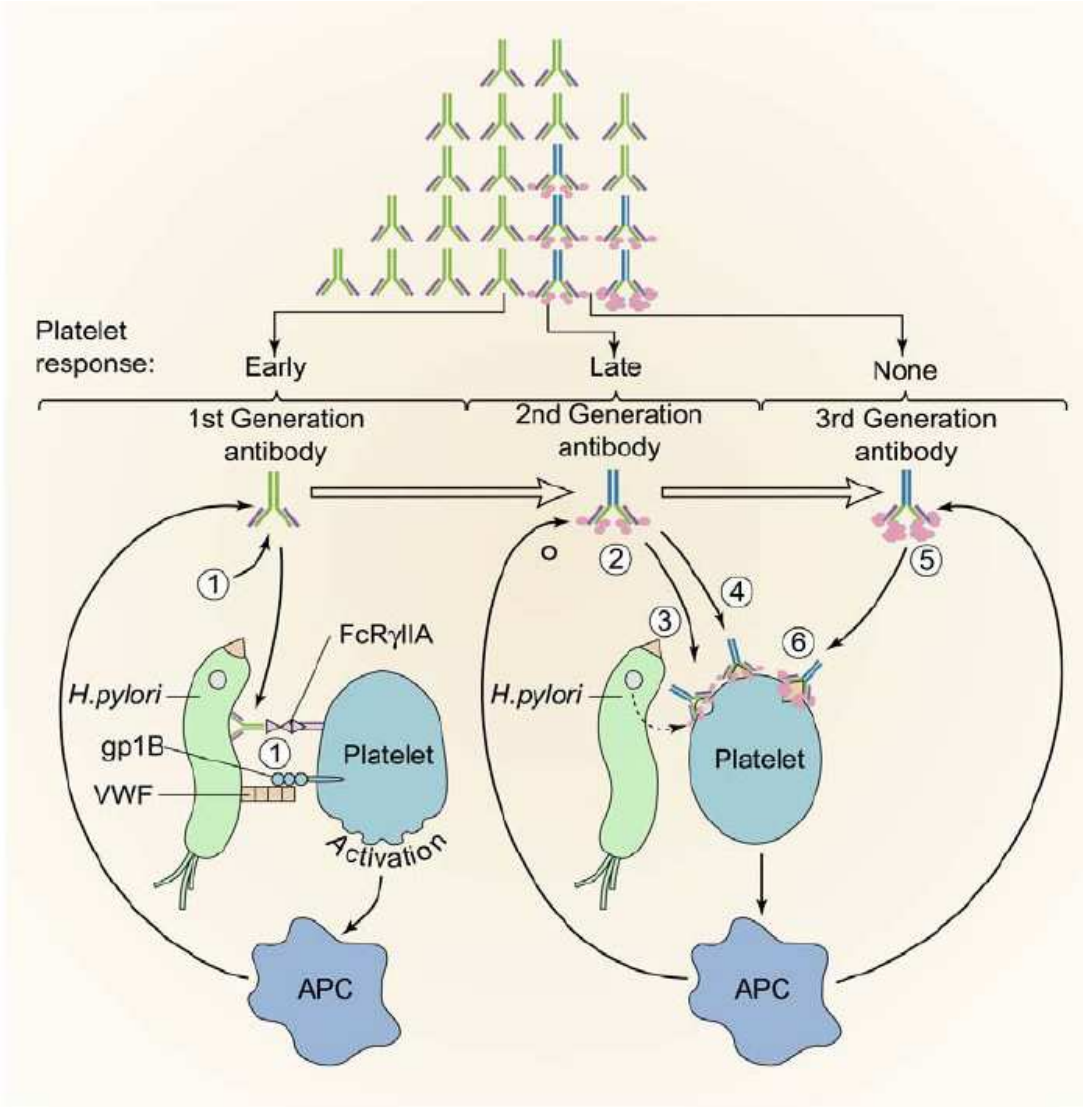
HCV^{+} vs. HCV^{-} ITP

- Older and equally distributed between the sexes
- Higher platelet counts
- More bleeding at higher platelet counts

Rajan S et al *Br J Haematol,* 2005

Pathogenesis of *H. pylori*-induced ITP

Cines DB et al. *Blood*, 2009



Great heterogeneity in terminology and clinical definitions in ITP

Criteria for eligibility

Ruggeri et al. Haematologica, 2007

- Literature search: papers on ITP in adults published from 2000 to 2005
- 10 or more patients described, aged > 18 years
- At least one of the following clinical definitions or decisional criteria was reported
  - Definition of ITP
  - Platelet cut-off for initial treatment
  - Platelet levels to define response (complete, partial, minimal, no response)
  - Timing to assess response
  - Bleeding score to assess the severity
  - Platelet level to define chronic phase
  - Timing to assess the chronic evaluation
  - Criteria for splenectomy
  - Criteria to define response to splenectomy
  - Criteria to define refractory disease
  - Criteria to define response to second line therapy

Major results

Clinical setting	Definition	N papers	Parameter (range)	Most agreed parameter	Agreement (N%)
Definition ITP	Platelet level Severe ITP	10 21	<150-<100 (x10^9/L PLT) <90 -<30 (x10^9/L PLT)	< 150 (x10^9/L PLT) <30 (x10^9/L PLT)	5(50) 8 (38)
Initial treatment	To start TX	23	< 50 -< 10 (x10^9/L PLT)	< 30 (x10^9/L PLT)	14 (60)
	CR	18	>150-> 100 (x10^9/L PLT)	>150 (x10^9/L PLT)	10 (56)
	PR	18	> 30-<150 (x10^9/L PLT)	>50 < 150 (x10^9/L PLT)	6 (33)
	NR	19	< 50 - < 20 (x10^9/L PLT)	< 50 (x10^9/L PLT)	10 (53)
	Timing	13	3 days-9 months	3-7 days	5 (38)
	Durable R	14	3 wks – 12 months	1 month	4 (29)
Chronic ITP	Platelet level	11	> 50 - < 150 (x10^9/L PLT)	< 50	4 (45)
	Time from diagnosis	25	3-6 months	> 6 months	**19 (76)**
Splenectomy	CR	24	> 50-> 150 (x10^9/L PLT)	> 150 (x10^9/L PLT)	13(54)
	PR	20	> 30- <150 (x10^9/L PLT)	> 50-<150 (x10^9/L PLT)	9(45)
	NR	16	< 50-<30 (x10^9/L PLT)	< 50 (x10^9/L PLT)	11(70)
	Timing	11	3 days – 6 months	1 month	2(18)
	Durable R	13	1 month-12 months	1 month	5(38)
Refractory ITP	Platelet level	7	< 20-<100 (x10^9/L PLT)	< 20 (x10^9/L PLT)	3 (43)
	To start TX	24	<10- <90 (x10^9/L PLT)	<30 (x10^9/L PLT)	11(45)
	CR	31	>100->150 (x10^9/L PLT)	>150 (x10^9/L PLT)	12(39)
	PR	27	>30-<150	>50-<150 (x10^9/L PLT)	5(16)
	NR	25	<50-<10	<50	10(40)

blood

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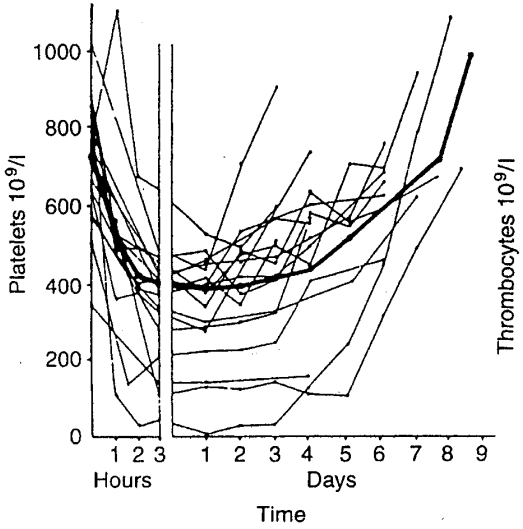
Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group

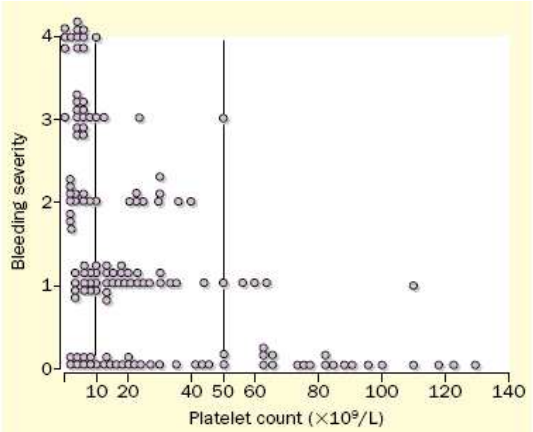
Francesco Rodeghiero, Roberto Stasi, Terry Gernsheimer, Marc Michel, Drew Provan, Donald M. Arnold, James B. Bussel, Douglas B. Cines, Beng H. Chong, Nichola Cooper, Bertrand Godeau, Klaus Lechner, Maria Gabriella Mazzucconi, Robert McMillan, Miguel A. Sanz, Paul Imbach, Victor Blanchette, Thomas Kühne, Marco Ruggeri and James N. George

Denomination of the disease

Primary **I**mmune **T**hrombocyto**P**enia
(no longer **I**diopathic **T**hrombocytopenic **P**urpura)

- Primary = absence of any initiating/underlying disease
- **I**mmune = immune-mediated pathogenesis
  (opposed to *Idiopathic*)
- Avoid **P**urpura: a minority of patients present bleeding at the onset of the disease
- **T**hrombocyto**P**enia: to save acronym ITP (utility in electronic database search)





Denomination of the disease: platelet threshold

Platelet threshold for diagnosis = **< 100 x 10^9/L**

(no longer < 130-150 x 10^9/L)

WHY?

- more specific than 150 x 10^9/L (e.g. thrombocytopenia during pregnancy)
- in some non-western ethnicities PLT count ranged from 100 and 150 x 10^9/L in healthy people
- low risk of developing ITP in subjects with persistent PLT count between 100 and 150 x 10^9/L *
- uniform predefined cut-off is more convenient and comparable than local normal range

*Stasi et al. Plos Med 2006

Denomination of the disease: secondary forms

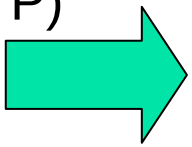
SECONDARY Immune ThrombocytoPenia (Secondary ITP)

All forms of immune-mediated thrombocytopenia except primary ITP

The acronym ITP should be followed by the name of the associated disease, e.g.:

Secondary ITP (Lupus-associated)
Secondary ITP (HIV-associated)
Secondary ITP (Drug-induced)

- Neonatal AutoImmnuneThrombocytoPenia (NAITP)
- Post Transfusion Purpura (PTP)
- Heparin Induced Thrombocytopenia (HIT)



maintain their standard denomination

Denomination of disease: grading of severity

Grading (mild, moderate, severe) usually correlated with platelet count

New proposal:

Severe ITP (in all phases of the disease):

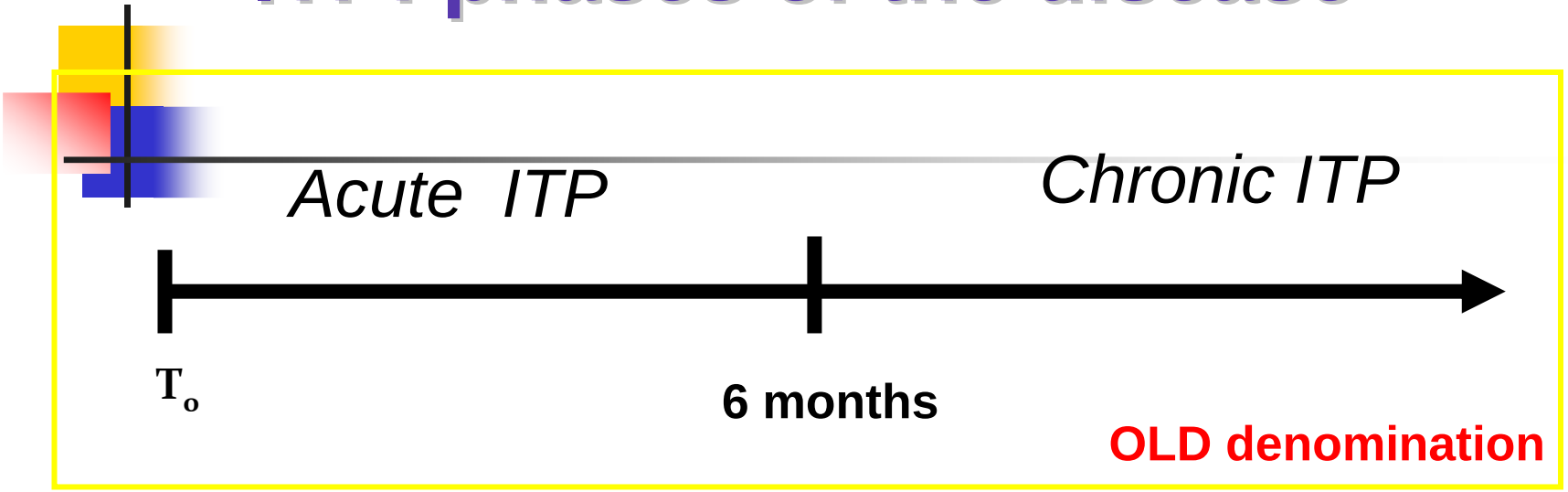
- presence of relevant bleeding, i.e. demanding active treatment
- no relationship with platelet count

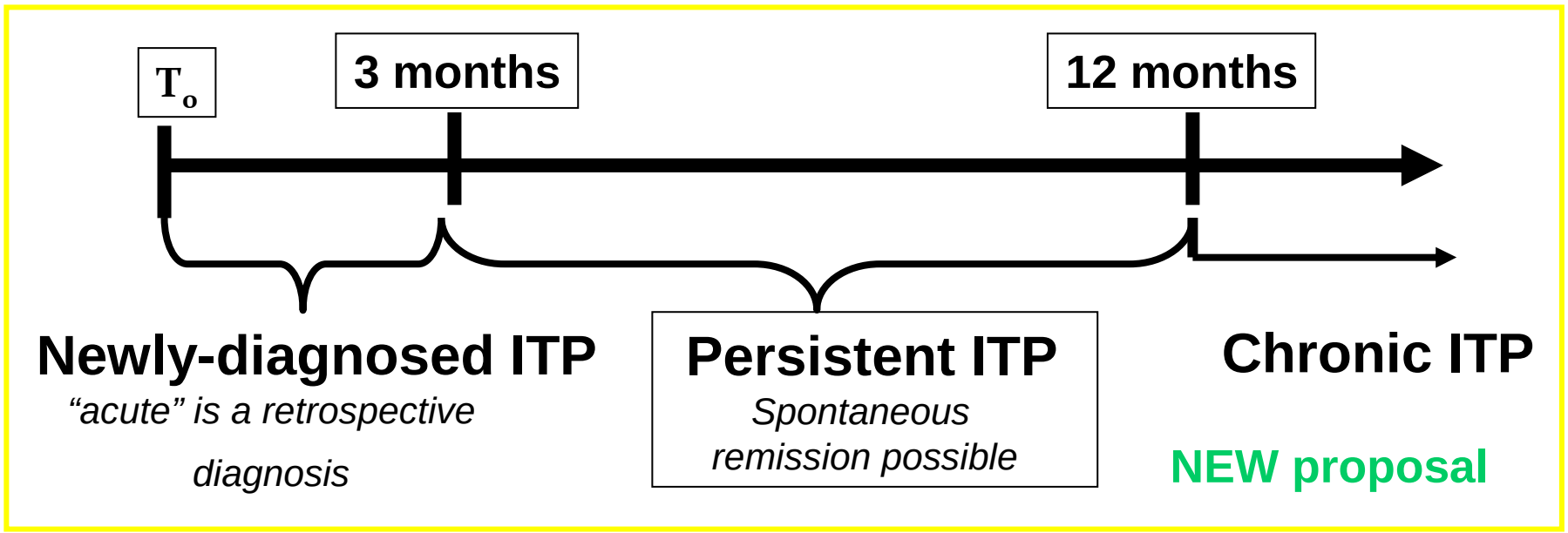
e.g. *asymptomatic* patient with platelet count : 2 x 10^9/L would not be classified as having “severe” ITP

Denomination of disease: clinical phases

- “Newly-diagnosed ITP” : all cases from diagnosis to 3rd month of disease duration
- “Persistent ITP” : 3 to 12 months from diagnosis
- “Chronic ITP” : thrombocytopenia lasting more than 12 months

ITP: phases of the disease





Therapeutic goals

Phase of disease	**Aim of treatment**
Initial treatment	Obtain a safe platelet count (rapidly) to reduce bleeding or bleeding risk
Persistent disease	Defer/avoid toxic Immunosuppression or splenectomy
Chronic disease	Curative aim (?)
Refractory patients *(after splenectomy)*	Minimize the risk of bleeding; to increase the PLT count is not the main goal

Definition of response 1

(applied to initial treatment, to therapy in chronic/persistent phase and after splenectomy)

3 characteristics:

a) Quality (platelet count increase and reduction/stopping of hemorrhage)

b) Timing of response assessment

c) Duration of the response

Definition of response 2

a) Quality of response*

- **Response (R):** platelet count ≥ 30 x 10^9/L and at least twofold increase the basal count **and** absence of bleeding

- **Complete response (CR):** platelet count ≥ 100 x 10^9/L **and** absence of bleeding

- **No response (NR):** platelet count < 30 x 10^9/L **or** less than doubling basal platelet count **or** bleeding

- **Loss of response:** platelet count below 100 x 10^9/L or bleeding (from CR); below 30 x 10^9/L or less than doubling basal platelet count or bleeding (from R)

*Platelet counts should be confirmed on at least 2 separate occasions (7 or more days apart) when used to define CR, R or NR.

Avoid “partial” and “minimal” response categories for their wide heterogeneity and marginal clinical relevance

Definition of response 3

b) <u>Timing of response after starting of treatment</u>:

AGENTS	TIME TO INITIAL RESPONSE (days)	TIME TO PEAK (days)
Prednisone	4-14	7-28
Dexamethasone	2-14	4-28
IVIg	1-3	2-7
Anti D	1-3	3-9
Rituximab	7-56	14-180
Splenectomy	1-56	7-56
VCR	7-14	7-42
Danazol	14-90	28-180
Azathioprine	30-90	30-180
Eltrombopag	7-28	14-90
Romiplostim	5-14	14-60

Definition of response 4

c) <u>Duration of response</u>:

1= From the time of response (CR or R) to loss

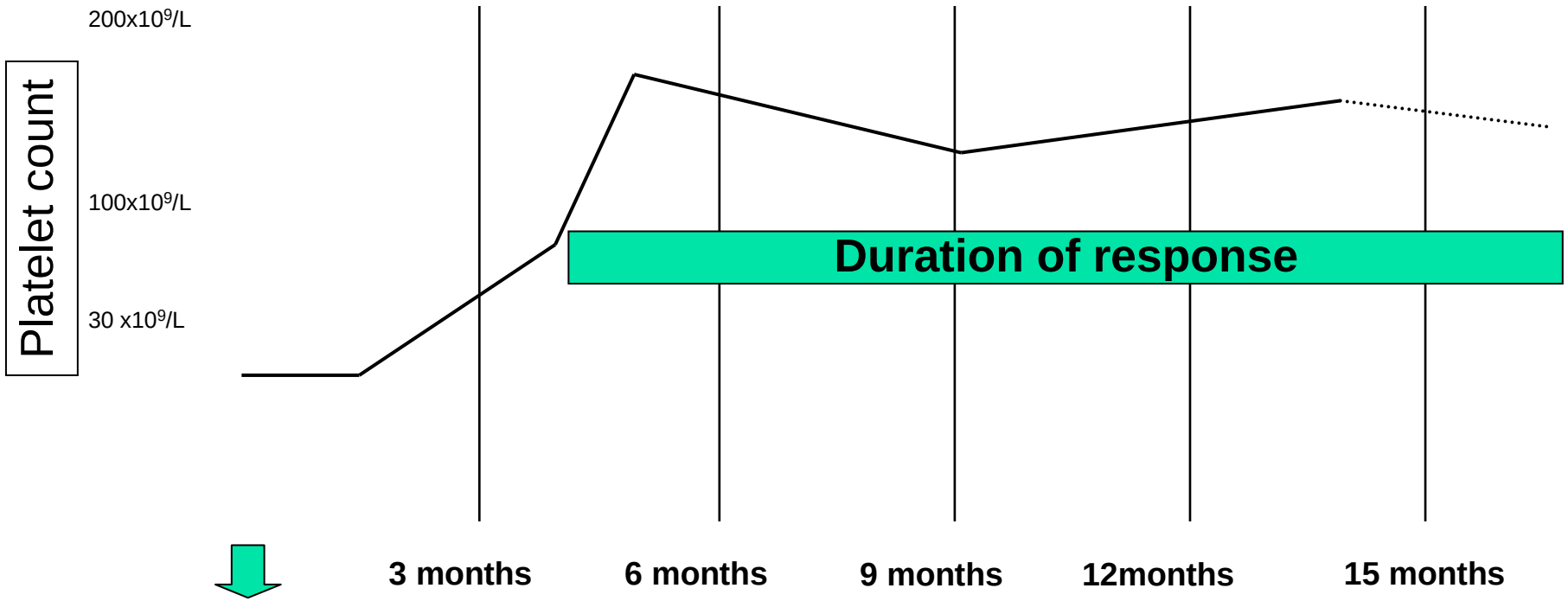
2= As proportion of the cumulative time spent within CR or R during the period of observation

The two definitions are not mutually exclusive

The first definition is more suitable for treatments aimed at inducing prolonged remission of the disease (e.g. splenectomy, rituximab)

The second one is more suitable to evaluate the overall benefit of continuous or intermittent repeated administration of agents requiring dose adjustments with anticipated temporary losses of CR or R (e.g. IVIg; TPO agonist)

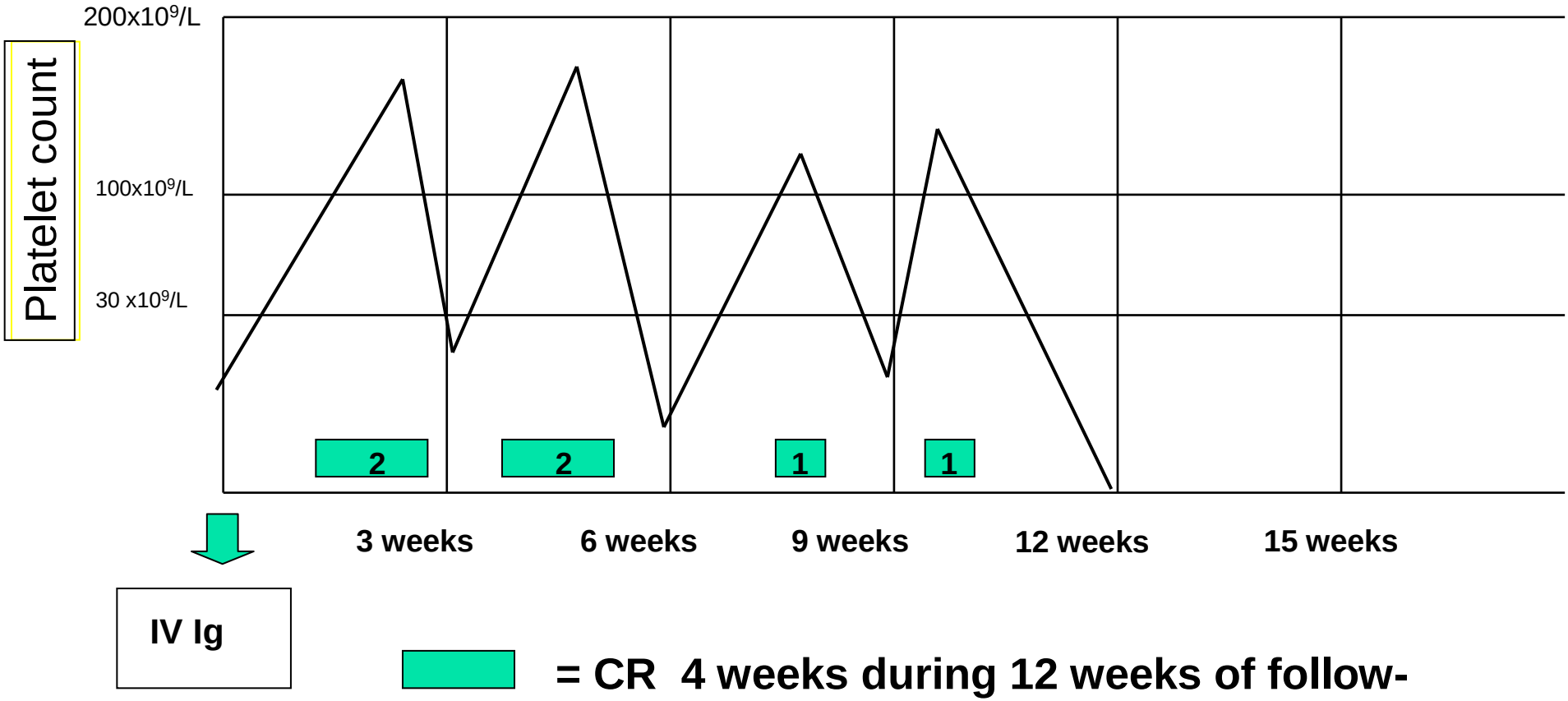
First modality to calculate the duration of response



e.g. Mabthera, splenectomy

CR: 12 months (from 4 to 16 months)

Second modality to calculate the duration of response



*Including time to stable platelet count after stopping treatment

Refractory ITP 1

Definition

- Failed splenectomy (may not be applicable in children)
- Thrombocytopenia demanding treatment (for bleeding or risk of bleeding)

Possible to increase the platelet count temporarily with steroids or IV Ig
May be in persistent (early splenectomy) or chronic phase

NB - Secondary ITP and other causes of thrombocytopenia excluded with appropriate testing
- Accessory spleen excluded if patient has previously responded to splenectomy

Refractory ITP 2

Definition of response to therapy in Refractory ITP

Ability to maintain a platelet count sufficient to prevent *significant* bleeding
Aim is more to “treat the patient” than to “correct platelet count”

Definition of “on demand” therapy:

Any therapy used to increase the platelet count to safely perform invasive procedure or in case of major bleeding or trauma

Definition of response to “on demand” therapy

- Achievement of platelet count *sufficient* to safely perform invasive procedure or minimize risk after trauma
- Control bleeding

Definition of adjunctive therapy

Therapy that may decrease bleeding e.g. antifibrinolytic agents, DDAVP, recombinant F VIIa, fibrin sealants

blood

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International consensus report on the investigation and management of primary immune thrombocytopenia

Drew Provan, Roberto Stasi, Adrian C. Newland, Victor S. Blanchette, Paula Bolton-Maggs, James B. Bussel, Beng H. Chong, Douglas B. Cines, Terry B. Gernsheimer, Bertrand Godeau, John Grainger, Ian Greer, Beverley J. Hunt, Paul A. Imbach, Gordon Lyons, Robert McMillan, Francesco Rodeghiero, Miguel A. Sanz, Michael Tarantino, Shirley Watson, Joan Young and David J. Kuter

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Recommendations for the diagnosis of ITP in children and adults

Basic evaluation	Tests of potential utility in the management of an ITP patient	Tests of unproven or uncertain benefit
• Patient history	• Glycoprotein-specific antibody	• TPO
• Family history	• Antiphospholipid antibodies (including anticardiolipin and lupus anticoagulant)	• Reticulated platelets
• Physical examination	• Antithyroid antibodies and thyroid function	• PaIgG
• Complete blood count and reticulocyte count	• Pregnancy test in women of childbearing potential	• Platelet survival study
• Peripheral blood film	• Antinuclear antibodies	• Bleeding time
• Quantitative immunoglobulin level measurement*	• Viral PCR for parvovirus and CMV	• Serum complement
• Bone marrow examination (in selected patients; refer to text)		
• Blood group (Rh)		
• Direct antiglobulin test		
• *H pylori*†		
• HIV†		
• HCV†		

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Examples of differential diagnosis of ITP identified by patient history

- Previously diagnosed disease that may be associated with autoimmune thrombocytopenia (HIV, HCV, CMV; systemic lupus erythematosus; lymphoproliferative disorders; recent vaccination)
- Liver disease (including alcoholic liver cirrhosis)
- Drugs (prescription or non-prescription), alcohol abuse, consumption of quinine, exposure to environmental toxins
- Bone marrow diseases: myelodysplastic syndromes, leukemias, other malignancies, fibrosis, aplastic anemia, megaloblastic anemia
- Recent transfusions (possibility of post-transfusion purpura)
- Inherited thrombocytopenia: thrombocytopenia-absent radius (TAR) syndrome,radioulnar synostosis, congenital amegakaryocytic thrombocytopenia, Wiskott-Aldrich syndrome, MYH9-related disease, Bernard-Soulier syndrome, type IIB von Willebrand disease

Consistent with ITP	Not consistent with ITP
• Platelet morphology: o Thrombocytopenia o Platelets are larger than normal in patients with moderate thrombocytopenia or normal in size where the platelet count is >50 $x10^9$/L	• Platelet morphology: o Predominance of consistently giant (the size of RBCs or larger) o Agranular o Very small (or normal in size where the thrombocytopenia is severe)
• Normal red blood cell morphology: o Findings such as microcytosis and hypochromia should be readily explained by iron deficiency or thalassemia	• Abnormal RBC morphology including: o Marked poikilocytosis o Schistocytes o Polychromatophilia (unless in response to bleeding) o Macrocytes o Nucleated RBCs o RBC inclusions eg malaria
• Normal white blood cell (WBC) morphology: o Abnormalities readily explained by recent infection	• Leukocytosis or leukopenia: o Immature or abnormal cells, eg blasts (atypical lymphocytes and eosinophilia may occur in children with ITP) • Leukocyte inclusions: o Döhle bodies (together with giant platelets may suggest May-Hegglin Anomaly)

!

In this guideline all treatment options are listed alphabetically

No preference for a particular therapy, given the limited number of randomized clinical trials available

First line treatment

(initial treatment for newly diagnosed patients)

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Recommended treatment strategy	Approximate response rate	Approximate time to response	Toxicities	Duration of sustained response
Corticosteroids				
Dexamethasone 40 mg daily for 4 d every 2-4 wk for 1-4 cycles	Up to 90% of patients respond initially	Several days to several weeks	Vary with length of administration: mood swings, weight gain, anger, anxiety, insomnia, Cushingoid faces, dorsal fat, diabetes, fluid retention, osteoporosis, skin changes including thinning, alopecia, hypertension, GI distress and ulcers, avascular necrosis, immunosuppression, psychosis, cataracts, opportunistic infections, adrenal insufficiency; hypertension, anxiety. Tolerability decreases with repeated dosing. Possibly lower rate of adverse events when used as short-term bolus therapy	As high as 50%-80% reported, the latter with 3-6 cycles (during 2-5 y of follow-up)
Methylprednisolone 30 mg/kg/d for 7 d	As high as 95%	4.7 d vs 8.4 d (high-dose methylprednisolone [HDMP] vs prednisone)		23% of patients have sustained platelet count ($> 50 \times 10^9$/L) at 39 mo
Prednis(ol)one 0.5-2 mg/kg/d for 2-4 wk	70%-80% of patients respond initially	Several days to several weeks		Remains uncertain; estimated 10-y disease-free survival 13%-15%
IV anti-D				
50-75 μg/kg	Initial response rate similar to IVIg (dose dependent)	4-5 d	Common: hemolytic anemia (dose-limiting toxicity), fever/chills Rare: intravascular hemolysis, disseminated intravascular coagulation, renal failure, rare death	Typically last 3-4 wk but may persist for months in some patients
IVIg*				
0.4 g/kg/d for 5 d or infusions of 1 g/kg/d for 1-2 d	Up to 80% of patients respond initially; half achieve normal platelet counts	Rapid; many respond in 24 h; typically 2-4 d	Headaches common: often moderate but sometimes severe Transient neutropenia, renal insufficiency, aseptic meningitis, thrombosis, flushing, fever, chills, fatigue, nausea, diarrhea, blood pressure changes and tachycardia IVIg preparations may contain small quantities of IgA, which occasionally causes anaphylactoid reactions in patients with IgA deficiency; in these cases use IgA-depleted IVIg	Usually transient; platelet counts returning to pretreatment levels 2-4 wk after treatment; persists for months in a few patients

Corticosteroids standard treatment for adults with ITP who need treatment and do not have a relative contraindication to its use (e.g. diabetes, psychiatric disorders).

IVIg may be appropriate in patients with bleeding, at high risk of bleeding, or are unresponsive to prednisone or have contradictions to steroid

Second-line treatment options for adult ITP patients

Recommended treatment strategy	Approximate response rate	Approximate time to response	Toxicities	Duration of sustained response
Azathioprine 1-2 mg/kg (maximum: 150 mg/d)	Up to two-thirds of patients; 40% in anecdotal reports	Slow; may need to be continued for 3-6 mo	Low incidence and generally mild: weakness, sweating, transaminase elevations, severe neutropenia with infection, pancreatitis	Up to a quarter of patients off therapy maintain response
Cyclosporin A 5 mg/kg/d for 6 d then 2.5-3 mg/kg/d (titration to blood levels of 100-200 ng/mL)	Dose-dependent. High response rate (~50%-80%) in small series	3-4 wk	In most patients, the following are seen to some degree; moderate but transient: increase in serum creatinine, hypertension, fatigue, paresthesias, gingival hyperplasia, myalgia, dyspepsia, hypertrichosis, tremor	More than half of responders receiving low doses sustain remission (at least 2 y)
Cyclophosphamide (1-2 mg/kg orally daily for at least 16 wk) or IV (0.3-1 g/m^2 for 1-3 doses every 2-4 wk)	24%-85% of patients	1-16 wk	Most are mild to moderate: neutropenia, acute deep venous thrombosis, nausea, vomiting	Up to 50% show a sustained response
Danazol 200 mg 2-4 times daily	67% complete or partial response; 40% in anecdotal reports	3-6 mo	Frequent side effects: acne, increased facial hair, increased cholesterol, amenorrhea, transaminitis	46% remained in remission at a median of 119 ± 45 mo and mean duration of danazol therapy was 37 mo
Dapsone 75-100 mg	Response in up to 50% of patients	3 wk	Infrequent and treatable/reversible: abdominal distension, anorexia, nausea, methemoglobinuria, hemolytic anemia in those with G6PD deficiency. Severe: skin rash may require drug to be stopped	Sustained response in up to two-thirds of responders off therapy
Mycophenolate mofetil 1000 mg twice daily for at least 3-4 wk	Up to 75% of patients; complete response in up to 45%	4-6 wk	Mild and infrequent: headache (most common and dose-limiting), backache, abdominal distension, anorexia, nausea	Sustained for short time after treatment discontinuation
Rituximab 375 mg/m^2 weekly ×4 (lower doses may also be effective)	60% of patients; complete response in 40% of patients	1-8 wk	Low rate, usually mild-to-moderate first-infusion fever/chills, rash, or scratchiness in throat. More severe reactions include serum sickness and (very rarely) bronchospasm, anaphylaxis, pulmonary embolism, retinal artery thrombosis, infection, and development of fulminant hepatitis via reactivation of hepatitis B. Rare cases of progressive multifocal leukoencephalopathy.	Sustained response > 3-5 y in 15%-20% of responders. Responders may require retreatment months to years later
Splenectomy	80% of patients respond; approximately two-thirds achieve a lasting response	1-24 d	Hemorrhage, peripancreatic hematoma, subphrenic abscess, wound infection, death, pneumococcal infection, fever, overwhelming sepsis syndrome, thrombosis	Response sustained with no additional therapy in approximately two-thirds of patients over 5-10 y
TPO receptor agonist: eltrombopag 25-75 mg orally daily	Platelet responses (platelet count > 50 × 10^9/L on d 43 of study): 70% receiving 50-mg dose, 81% receiving 75-mg dose	By d 15, more than 80% of patients receiving 50 or 75 mg of eltrombopag daily increased platelet count	Adverse events in at least 20% of patients: headache Treatment-related serious adverse events: increased bone marrow reticulin, worsening thrombocytopenia upon discontinuation, thrombosis, liver function abnormalities in 13%	Up to 1.5 y with continual administration of the drug
TPO receptor agonist: romiplostim Doses 1-10 μg/kg subcutaneously weekly	Overall platelet response rate: non-splenectomized, 88%; splenectomized, 79%	1-4 wk (in patients with platelet count < 30 × 10^9/L to achieve > 50 × 10^9/L)	Adverse events in at least 20% of patients: headache, fatigue, epistaxis, arthralgia and contusion (similar incidence in placebo groups) Treatment-related serious adverse events: increased bone marrow reticulin, worsening thrombocytopenia upon discontinuation, thrombosis	Up to 4 y with continual administration of the drug
Vinca alkaloid regimens: vincristine total dose of 6 mg (1-2 mg per infusion weekly); vinblastine total dose of 30 mg (10 mg per infusion weekly), and some patients, vincristine and vinblastine infusions administered alternatively	Highly variable transient response in 10%-75% of patients	5-7 d	Neuropathy especially with repeated dose and in the elderly; neutropenia, fever, inflammation/thrombophlebitis at the infusion site	A normal platelet count was observed in 6 of 9 (9/12 had response) patients under long-term 3-36 mo monitoring; average, 10 mo

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Relevant factors that contribute to management decisions

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- The extent of bleeding or co-morbidities predisposing to bleeding
- Complications of specific therapies, activity and lifestyle
- Tolerance of side effects
- Potential interventions that may cause bleeding
- Accessibility of care
- Patient expectations
- Patient worry or anxiety about disease burden
- Non-ITP medications that may create a bleeding risk

- Platelet threshold ???? < 20-30 x 10^9/L