Chronic ITP ,pathophysiology and epidemiology

Abolghasemi H
Professor of pediatrics
hematologist oncologist

IPHOS Webinar

NOVARTIS

Definition

- **Chronic** – i.e. ITP has lasted more than 12 months
- **Severe** – i.e. bleeding symptoms that mandate treatment (not just a very low count)
- Chronic severe ITP is very rare: perhaps 1 in 1 million
- Most children with ITP recover without any specific therapy within a few weeks

NOVARTIS

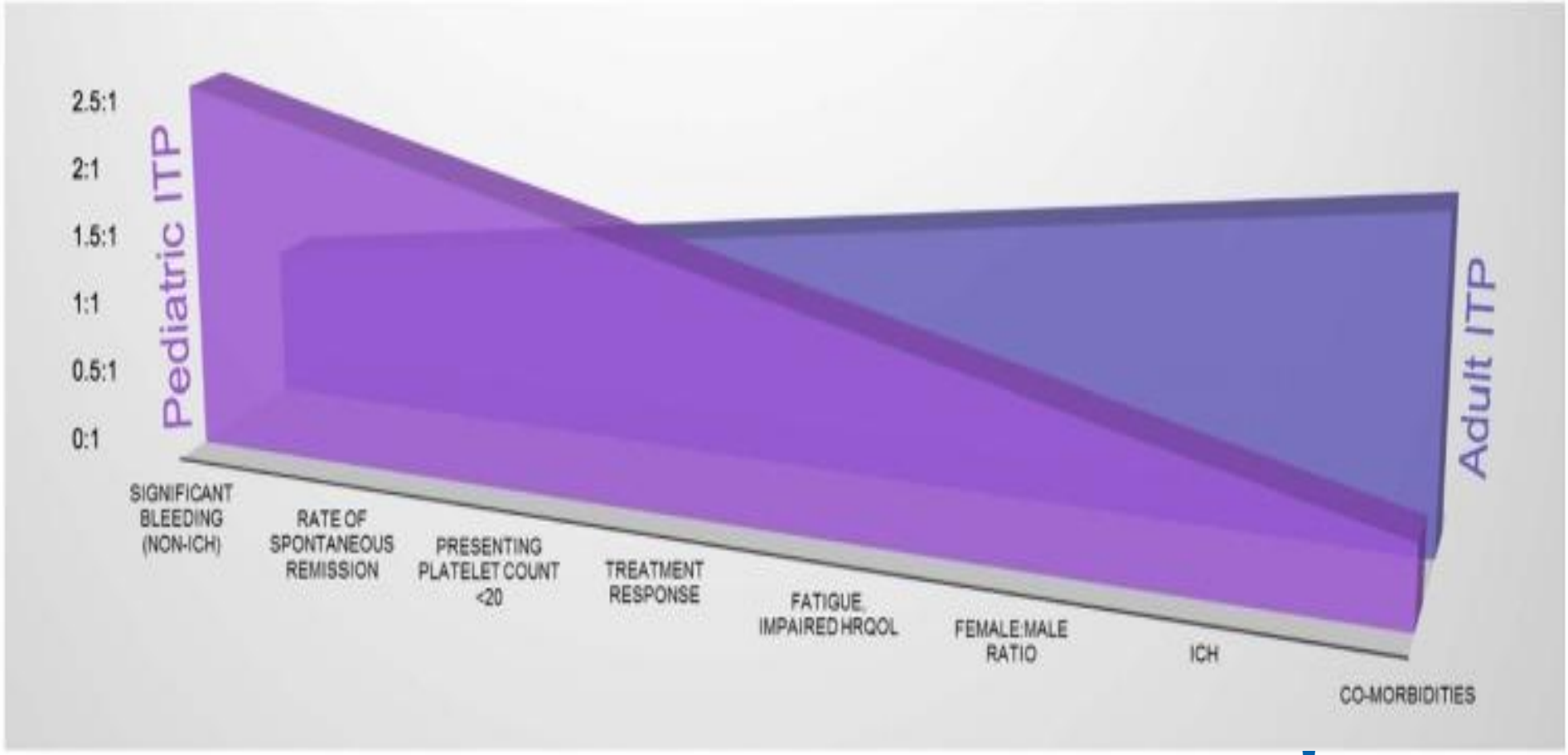
ITP prevalence

Immune thrombocytopenia (ITP) is one of the most common acquired bleeding disorders, occurring in ~5 to 10 per 100 000 children per year and 3.3 per 100 000 adults per year

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6246008/

NOVARTIS

Characteristic differences and similarities between pediatric and adult ITP



ITP = Immune Thrombocytopenia; ICH = Intracranial Hemorrhage; HRQoL = Health-Related Quality of Life

NOVARTIS

Features	Acute ITP	Chronic ITP
Peak incidence (age)	2 - 6 years	20 - 40 years
Sex predilection	None	3:1 female:male
Antecedent infection	Common 1-3 weeks before	Unusual
Onset of bleeding	Abrupt	Insidious
Platelet count microliters	<20,000/microliters	30-80,000/
Eosinophlia/lymphocytosis	Common	Rare
Duration	2-6 weeks; rarely longer	Months or years
Spontaneous remission	Occurs in 80% of the cases	Uncommon

ITP: Idiopathic thrombocytopenia purpura

Epidemiology

- One of the most well-documented epidemiological distinctions between childhood and adult ITP is the predominance of females among adults affected with ITP. This female predominance (~2:1 ratio) is consistently documented throughout the literature.
- The increased percentage of female patients in the adult ITP population is generally thought to be related to the increased incidence of systemic autoimmune disease in adult females.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6246008/

NOVARTIS

Rates of spontaneous remission in children and adults with ITP

- Time point (mo) Children (%) Adults (%)
- 6 1559/2233 (70) 145/324 (45)
- 12 1160/1639 (71) 133/271 (49)
- 24 744/1045 (71) 111/197 (56)
- Data are from the PARC-ITP study.6 Numbers at each time point included only those prospectively enrolled patients with data available at the specified time point and did not include patient lost to follow-up

- Schifferli A, Holbro A, Chitlur M, et al. ; Intercontinental Cooperative ITP Study Group (ICIS). A comparative prospective observational study of children and adults with immune thrombocytopenia: 2-year follow-up. Am J Hematol. 2018;93(6):751-759

NOVARTIS

Studies reporting ICH in children and adults with ITP

First author, year	Methodology	Subjects	ICH incidence (%)	ITP phase at ICH	Platelet count at ICH ($\times 10^9$/L)
Lilleyman, 1994	Retrospective	Children	14/~11 000 (~0.1)	72% ND, 14% P, 14% C	<15
Iyori, 2000	Retrospective	Children	4/772 (0.5)	75% ND, 25% C	<10
Kühne, 2001	Prospective	Children	2/1 496 (0.1)	ND*	
Neunrt, 2008[3]2013	Prospective	Children	1/863 (0.1) [0-28 d]; 0/854 (0) [6-24 mo]	100% ND, 0% P/C	<20
Choudhary, 2009	Retrospective	Children	17/750 (2.3)	59% ND, 41% C	Median, 12 (range, 20-50

NOVARTIS

Bone marrow aspiration

- the most recent ASH evidence-based practice guidelines for ITP recommend against routine bone marrow examination in children (even prior to corticosteroid therapy or splenectomy) and adults (irrespective of age) with typical features of ITP

- Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA.; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117(16):4190-4207.

NOVARTIS

Bone marrow aspiration

- the international consensus guidelines published in 2010 recommend consideration of bone marrow examination only for patients aged >60 years old, prior to splenectomy, or in other atypical circumstances (ie, relapse following remission or first-line treatment failure

- Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168-186

NOVARTIS

What is refractory ITP?

- An International Working Group (IWG) defined refractory ITP as disease that does not respond to or relapses after splenectomy and that requires treatment to reduce the risk of clinically significant bleeding.
- It may not be applicable to children; In these patients, avoidance of splenectomy may be desirable or even necessary.
- Indeed, the IWG acknowledged that it was unable to achieve consensus on the definition of refractory disease in children .

- **Adam Cuker and Cindy E. Neunert. How I treat refractory immune thrombocytopenia . , BLOOD, 22 SEPTEMBER 2016 x VOLUME 128**

NOVARTIS

Pathophysiology of chronic ITP

- The pathophysiology of chronic ITP is heterogeneous and complex.
- In chronic ITP, platelet membrane glycoproteins (GPs), become antigenic and stimulate the immune system to produce autoantibodies.
- The platelet-directed autoantibodies are more commonly directed against platelet GP IIb-IIIa and/or GPIb-IX
- In addition to the antibody-mediated destructive process, a perturbation in T-cell homeostasis also plays a role in the pathogenesis of chronic ITP.

- **Spotlight on romiplostim in the treatment of children with chronic immune thrombocytopenia: design, development, and potential place in therapy Drug Design, Development and Therapy 2017:11**

NOVARTIS

Pathophysiology of chronic ITP

- Platelet production is also suboptimal in chronic ITP patients. Megakaryocytes express GPIIb-IIIa and GPIb-IX, which are targets for autoantibodies.
- These autoantibodies inhibit megakaryocyte growth as documented by morphologically abnormal megakaryopoiesis and the ability of ITP plasma to inhibit megakaryopoiesis
- ***The suboptimal platelet production in ITP that is mediated by the presence of autoantibodies directed against platelet antigens provides support for the use of TPO mimetic agents in the treatment of children with chronic ITP***

- **Spotlight on romiplostim in the treatment of children with chronic immune thrombocytopenia: design, development, and potential place in therapy Drug Design, Development and Therapy 2017:11**

NOVARTIS

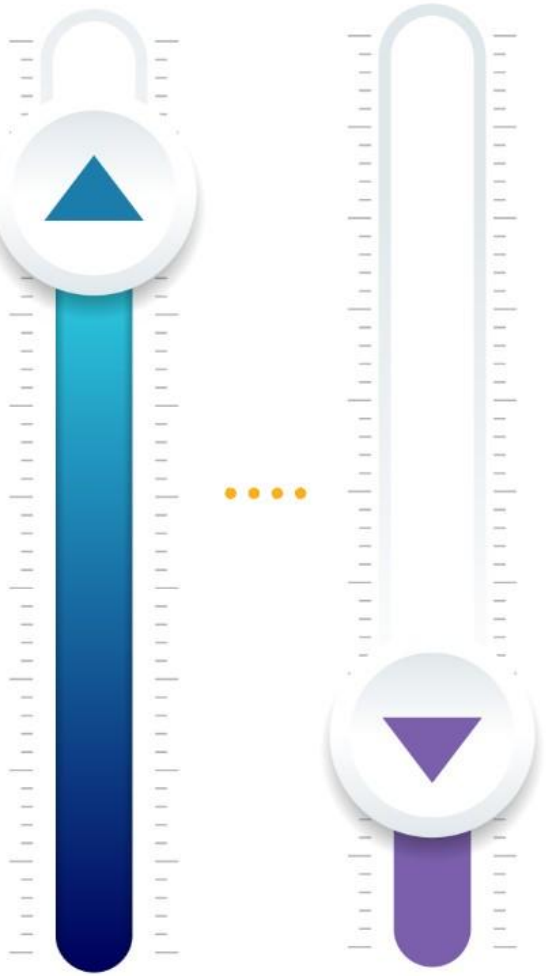
ITP IS CAUSED BY LOWER PRODUCTION AND HIGHER DESTRUCTION OF PLATELETS

ITP effector immunity is primarily composed of antibodies and T cells

Increased platelet destruction (spleen)

Antiplatelet immunity (Ab + T cell)

Healthy (normal platelet counts)



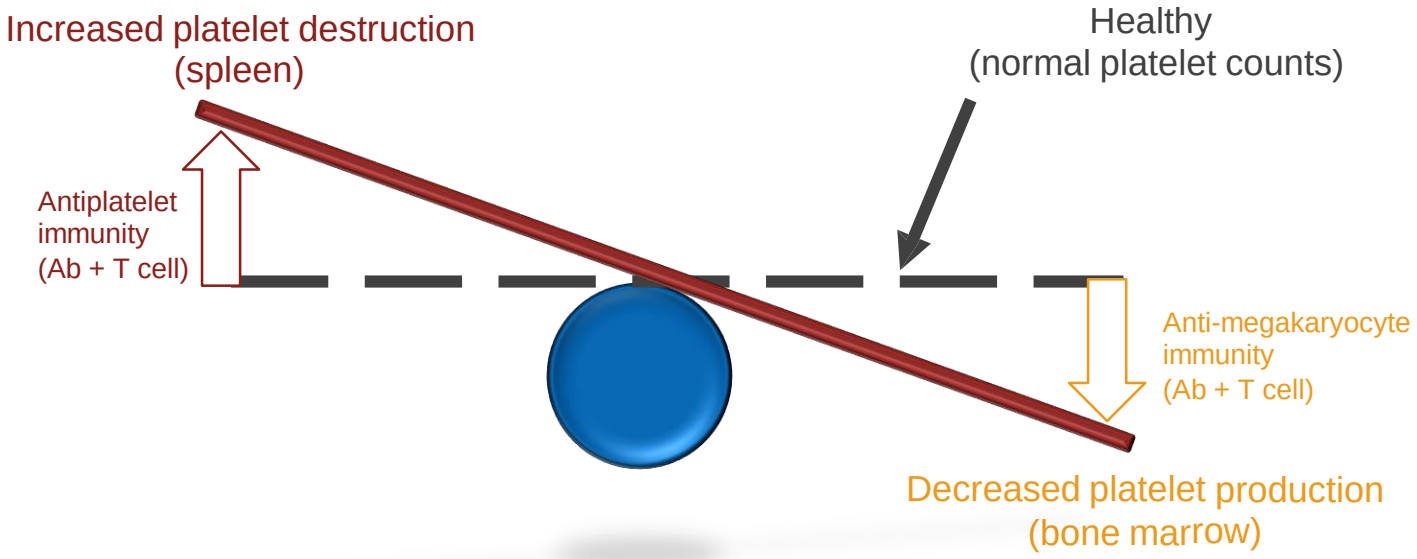
Decreased platelet production (bone marrow)

Anti-megakaryocyte immunity (Ab + T cell)

Nugent D *et al. Br J Haematol* 2009;146:585–596
Ab, antibody; ITP, immune thrombocytopenia

NOVARTIS

ITP: Acquired disorder of autoimmune-mediated platelet destruction and reduced platelet production



Platelet destruction and suppressed platelet production in ITP appear to be mediated by autoantibodies and cytotoxic T lymphocytes[1]
ITP presents clinically with varying degrees of petechiae, purpura, and mucosal bleeding.[2] Symptoms generally appear when platelet counts fall to <30 ·10^9/L[3,4]

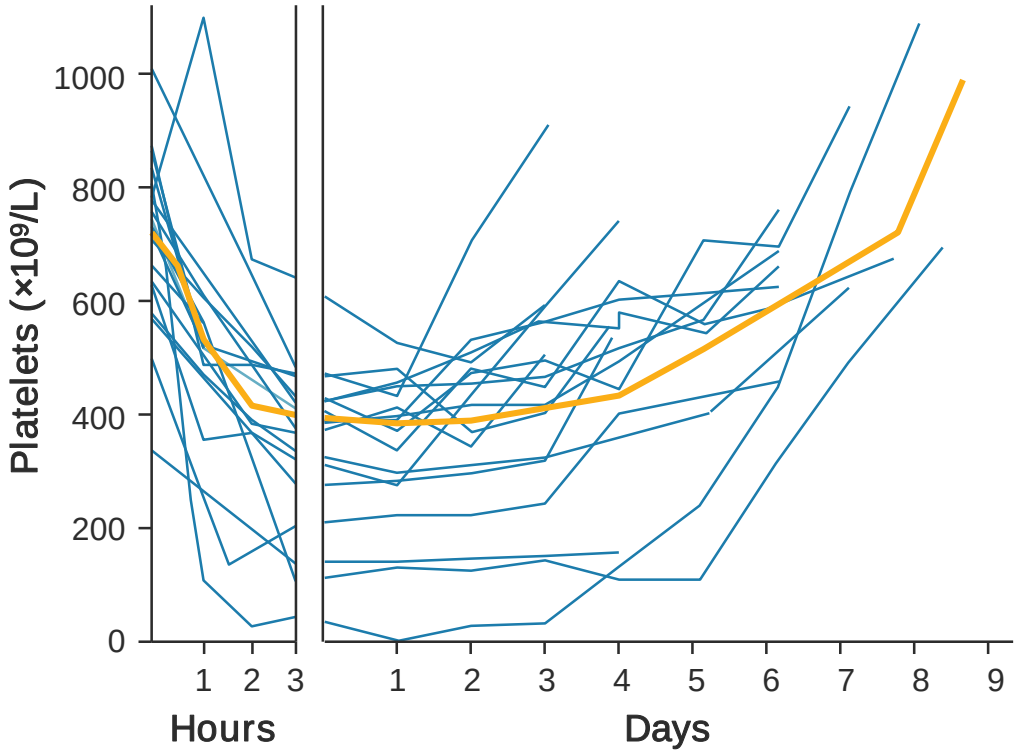
1. Nugent D *et al. Br J Haematol* 2009;146:585–596;
2. Cines DB *et al. Annu Rev Med* 2005;56:425–442;
3. Cooper N. *Br J Haematol* 2017;177:39–54;
4. Provan D *et al. Blood* 2010;115:168–186

Ab, antibody

NOVARTIS

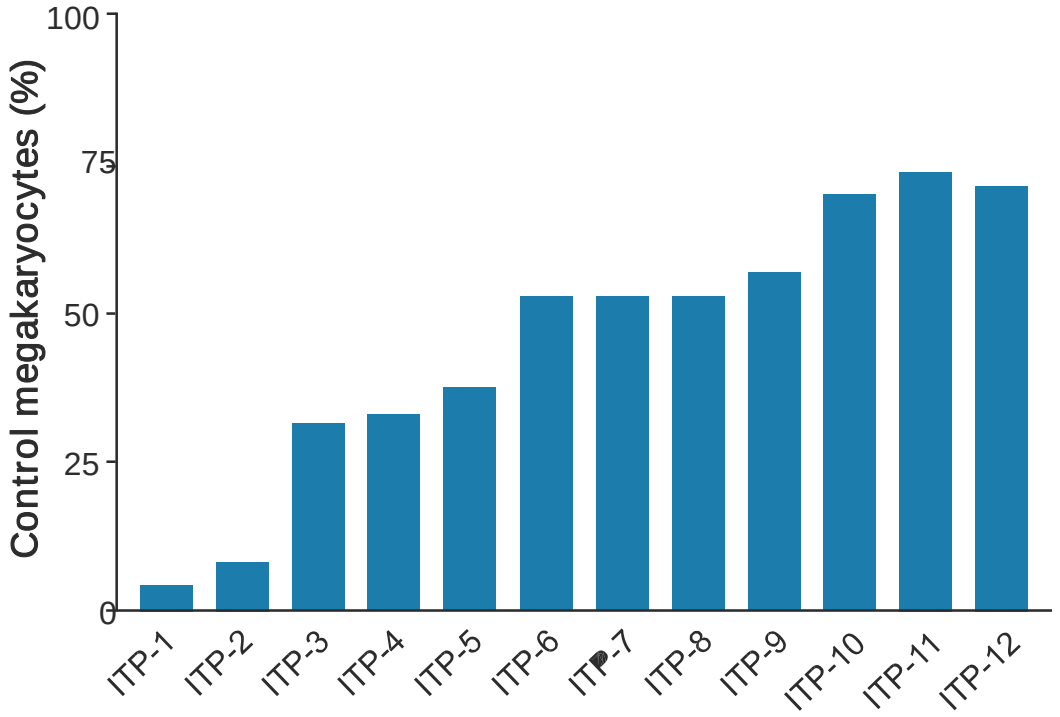
EVIDENCE THAT ITP IS A B CELL DISEASE

Antiplatelet antibodies: 1951[1]



Platelet count after infusion with patient plasma

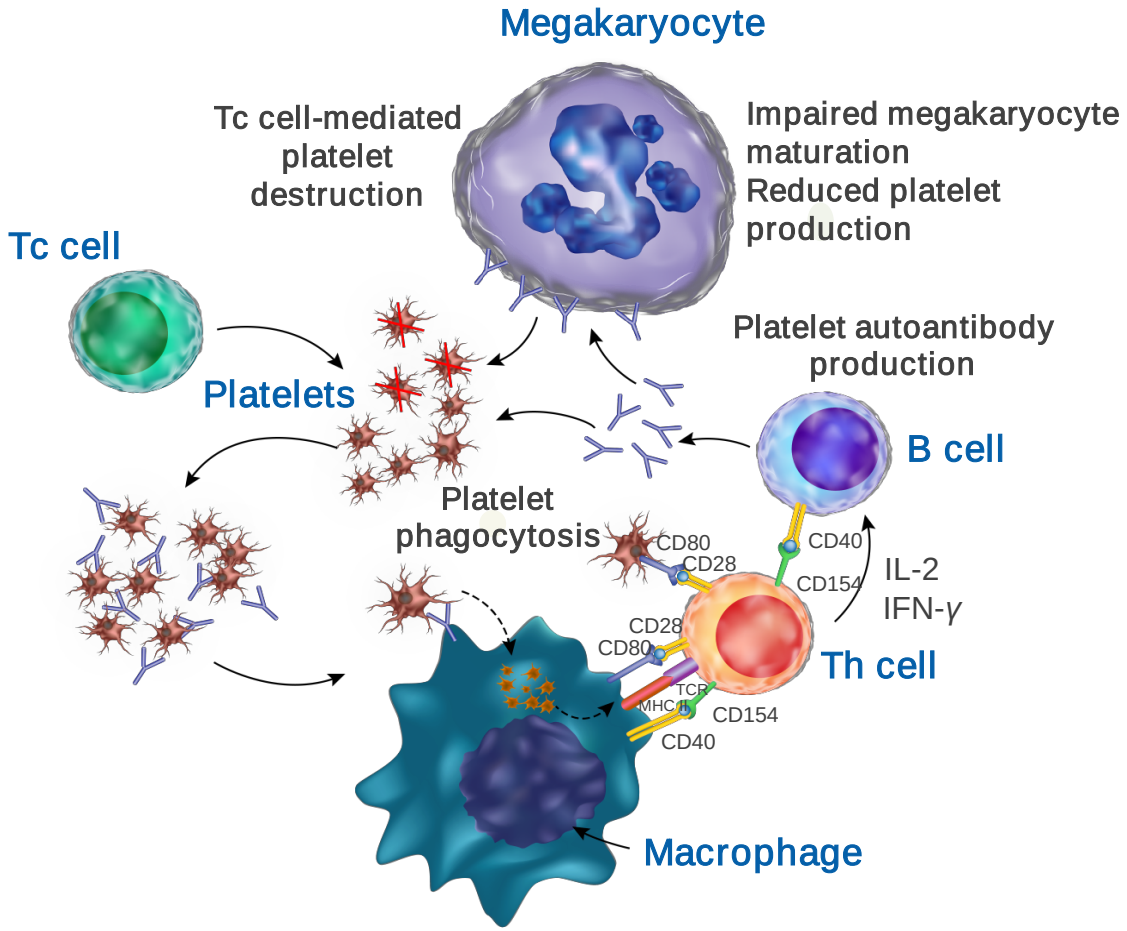
Inhibition of megakaryocytes by plasma from ITP patients: 2004[2]



1. Harrington WJ *et al. J Lab Clin Med* 1951;38:1–10; 2. McMillan R *et al.* Suppression of *in vitro* megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. *Blood* 2004;103:1364–1369. Republished with permission of American Society of Hematology, permission conveyed through Copyright Clearance Center, Inc

NOVARTIS

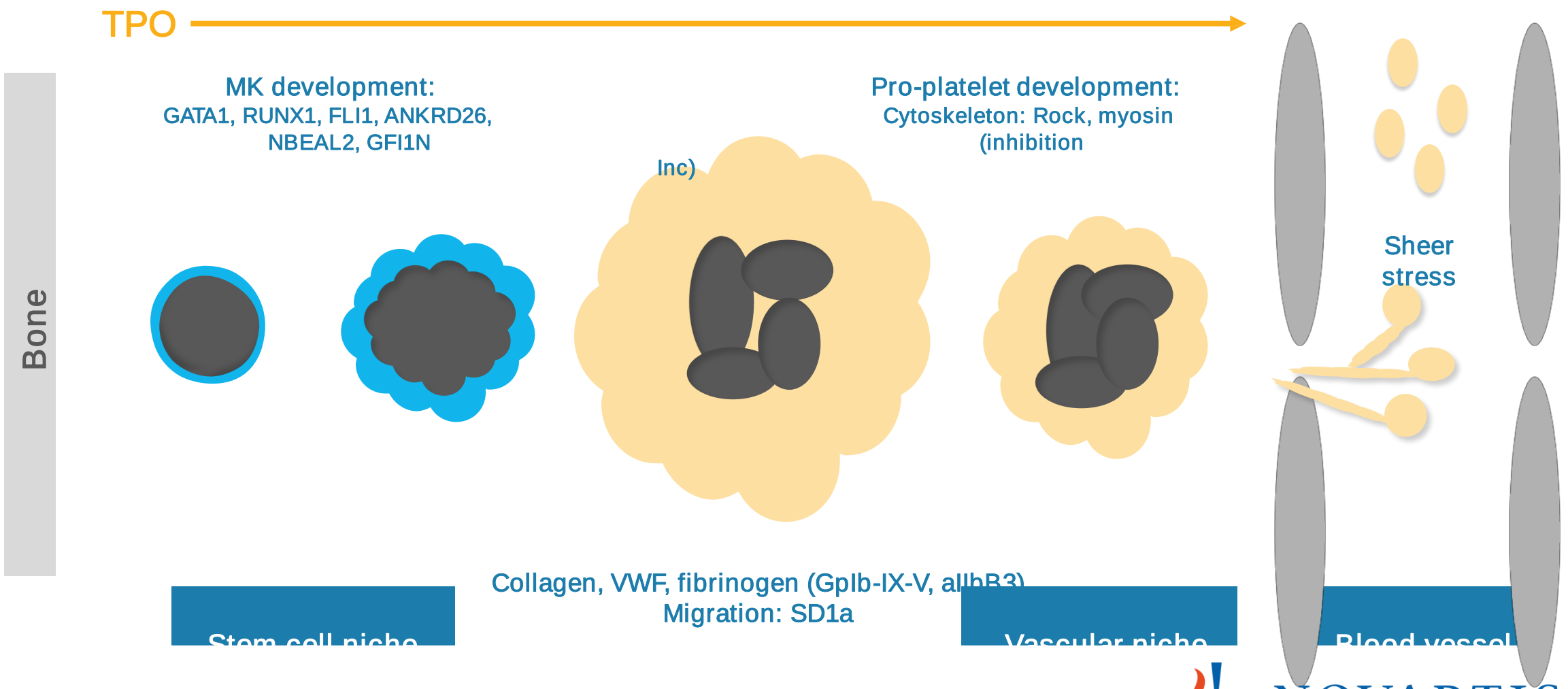
Pathophysiology of ITP



CD, cluster of differentiation; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; Tc, cytotoxic T cell; TCR, T cell receptor

Adapted from Stasi R *et al. Thromb Haemost* 2008;99:4–13

MANY FACTORS HELP MAKE PLATELETS



Br J Haematol 2014;165:179–192. Republished with permission of John Wiley & Sons ©2014 John Wiley & Sons Ltd
Adapted from Pecci A & Balduini CL. Lessons in platelet production from inherited thrombocytopenias.

MK, megakaryocyte; TPO, thrombopoietin; VWF, von Willebrand factor

The clinical manifestations of ITP vary between patients

Bleeding[1]

Most common manifestation (bleeding of skin, oral cavity or GI tract)

Purpura may appear without precipitating event

ICH is the most feared complication

Fatigue[2]

Affects up to 39% of adults and ~22% of children with ITP

Impaired HRQoL[3]

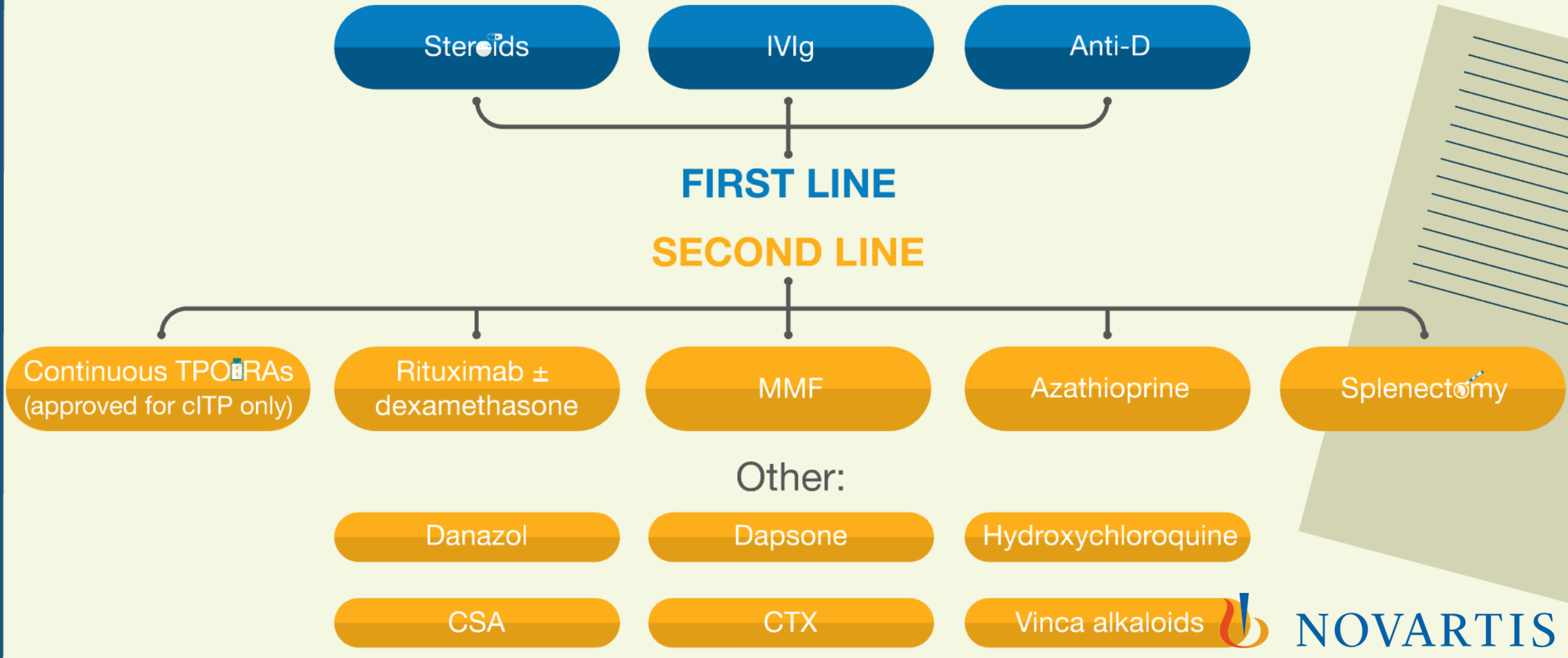
Clinically meaningful impairments in physical and mental HRQoL

Higher fatigue severity associated with worse HRQoL

1. Neunert C *et al. Blood* 2011;117:4190–4207; 2. Newton JL *et al. Eur J Haematol* 2011;86:420–429; 3. Efficace F *et al. Am J Hematol* 2016;91:995–1001

GI, gastrointestinal; HRQoL, health-related quality of life; ICH, intracranial hemorrhage

CURRENT TREATMENT OPTIONS FOR PATIENTS WITH ITP

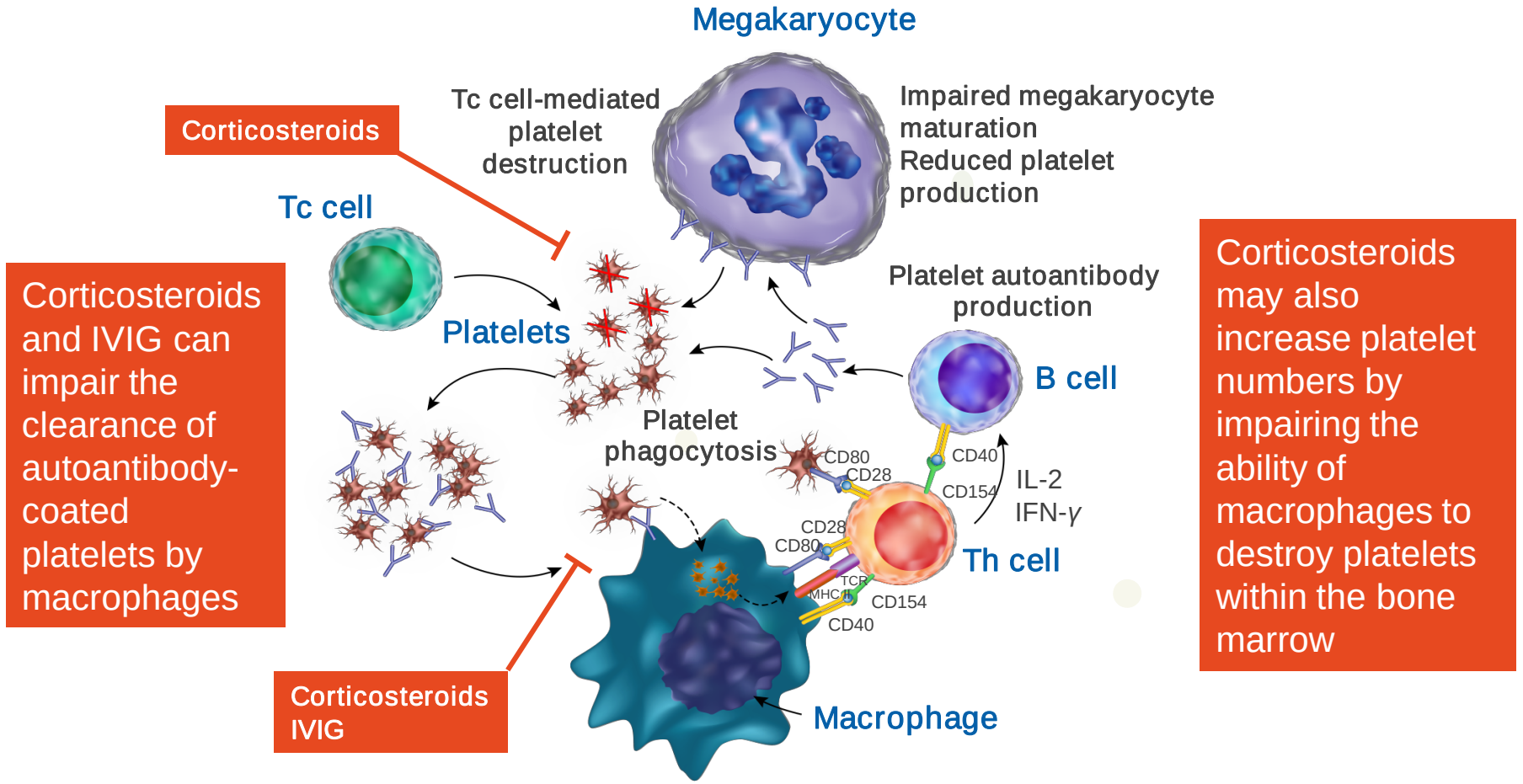


Modified from Cooper N. *Br J Haematol* 2017;177:39–54; Provan D *et al. Blood* 2010;115:168–186

cITP, chronic ITP; CSA, cyclosporine; CTX, cyclophosphamide; MMF, mycophenylate mofetil

NOVARTIS

Corticosteroids and IVIG are the first-line treatment for ITP



Corticosteroids and IVIG can impair the clearance of autoantibody-coated platelets by macrophages

Corticosteroids may also increase platelet numbers by impairing the ability of macrophages to destroy platelets within the bone marrow

IVIG, intravenous immunoglobulin

Adapted from Stasi R *et al. Thromb Haemost* 2008;99:4–13

NOVARTIS

Corticosteroids and IVIG elicit a platelet response in most patients

Treatment	Approximate response rate	Approximate time to response
Corticosteroids		
Dexamethasone	Up to 90% of patients respond initially	Several days to several weeks
Methylprednisolone	As high as 95%	~5 days
Prednis(ol)one	70–80% of patients respond initially	Several days to several weeks
IVIG	Up to 80% of patients respond initially, half achieve normal platelet count	Many respond in 24 hours, typically 2–4 days

A good response rate is generally achieved within days in the majority of patients, although the various response rate criteria between studies make direct comparison between individual treatments difficult

Provan D *et al. Blood* 2010;115:168–186

Treatment

- Children with ITP have an excellent chance of recovery with or without treatment.
- Typically, bleeding signs subside within weeks, and the platelet count returns to normal in a few weeks to months.
- Overall, 70% to 80% of children diagnosed with ITP will go into complete remission within a few months .
- Remission rate of 87%, achieved by watchful waiting without specific therapy 6 months after initial presentation

NOVARTIS

Predictors of chronic ITP

- A recent systematic review and meta-analysis identified following predictors of chronic ITP in children:
- older age, insidious onset, no preceding infection or vaccination, mild bleeding, and higher platelet counts at presentation (> 20 x 109/L)
- two genetic biomarkers have been suggested as predictors of chronic disease: overexpression of vanin-1 (VNN-1), an oxidative stress sensor, and the Q63R missense variant of the gene encoding the cannabinoid receptor type 2

NOVARTIS

Watchful waiting

- The self-limited nature of childhood ITP and very low incidence of severe bleeding is the basis of a non-interventional strategy.
- Pharmacotherapy has proven to be mostly effective in raising the platelet count in a short period of time
- it has never been demonstrated that the fast platelet response is of clinical significance
- ASH practice guidelines recommend that children with no bleeding or mild bleeding (defined as skin manifestations only), be managed with observation alone regardless of platelet count .
- This “watch and see” strategy is now accepted by many experts.

NOVARTIS

- ITP treatment may be conceptually divided into rescue therapy and maintenance therapy.
- The objective of rescue therapy is a swift rise in platelet count in a patient with active hemorrhage, a high risk for bleeding, or need for a critical procedure.
- In selecting rescue therapy, a premium is placed on rapidity of response with relatively less regard for durability of response, patient convenience, or safety and tolerability with long-term use.
- Maintenance therapy, in contrast, is given with the goal of achieving a sustained platelet response while minimizing short- and long-term treatment-related toxicity.

NOVARTIS

Platelet transfusion

- From 2010 to 2014, there were 78,376 admissions with ITP as the primary admission diagnosis . Overall, 27% admissions with ITP as primary (children 4%) and 15% admissions with ITP as one of all the diagnoses documented at least one platelet transfusion.

- In conclusion, this study demonstrates that the majority of ITP hospitalizations reporting platelet transfusions were restricted to adults and did not meet the criteria for administering platelets based on current guidelines.
- Platelet transfusions were not related to improved mortality outcomes and given the added risks and costs of what could possibly be unnecessary platelet transfusions

- Ruchika Goe etal. From the 1 Department of Pathology, Johns Hopkins University, Baltimore, Maryland; 2 Division of Hematology Oncology Platelet transfusion practices in immune thrombocytopenia related hospitalizations. Volume 59, January 2019 TRANSFUSION

NOVARTIS

Table 1. Goals and standard treatment options for rescue and maintenance therapy

	Rescue therapy	Maintenance therapy
Goals of treatment	Rapid platelet response	Durable platelet response
	Short-term safety	Long-term safety and tolerability
		Patient convenience
Desired time to response	Hours to days	Days to weeks
Standard treatment options	Corticosteroids	Splenectomy
	IVIG	
	Anti-D*	

IVIG, intravenous immunoglobulin G.

*Indicated only in Rh(D)-positive, nonsplenectomized patients.

Case Presentation

A 10-year-old male was diagnosed with primary immune thrombocytopenia (ITP) 5 months ago when he presented with epistaxis, petechiae, bruising, and a platelet count of 5 000 . He responded transiently to Intravenous immunoglobulin G (IgG), but epistaxis recurred 2 weeks later. He subsequently received a short course of oral corticosteroids to which he had a temporary response in platelet count and cessation of epistaxis. Since discontinuing corticosteroids, he has had only occasional bruising and petechia. His platelet count is currently 13 000 . He states that ITP is not interfering with activities.

NOVARTIS

- Besides bleeding manifestations and platelet count
- age
- physical activities
- health- related quality of life
- potential co-morbidities and co-medications
- duration of the disease
- geographic distance from a tertiary care center
- patient’s and parents preferences
- time lost from school due to hospital visits
- psychosocial impact and economic aspects

NOVARTIS

Thank you