SABATI EMATOLOGICI DELLA ROMAGNA

Cesena 28 maggio 2016

L'ematologo di fronte alla piastrinopenia, oggi

Diagnostica delle piastrinopenie

Marco Ruggeri, UOC Ematologia -Vicenza-

Definition of Isolated Thrombocytopenia (IT)

IT is a clinical condition characterized by:

- a low platelet count
- absence of any abnormalities of red and white blood cells
- no signs or symptoms of systemic illness

Stasi R ASH 2012

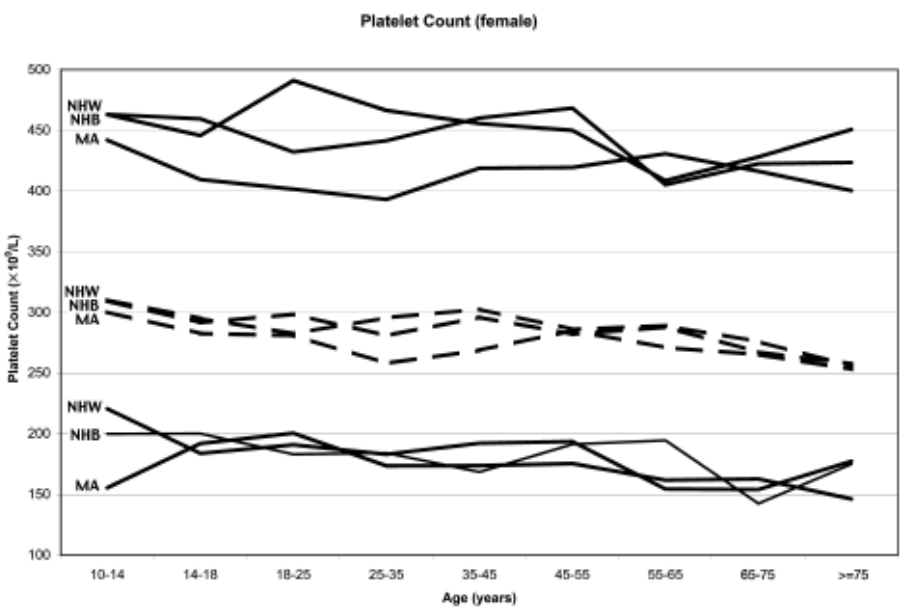
Laboratory Hematology 10:42-53

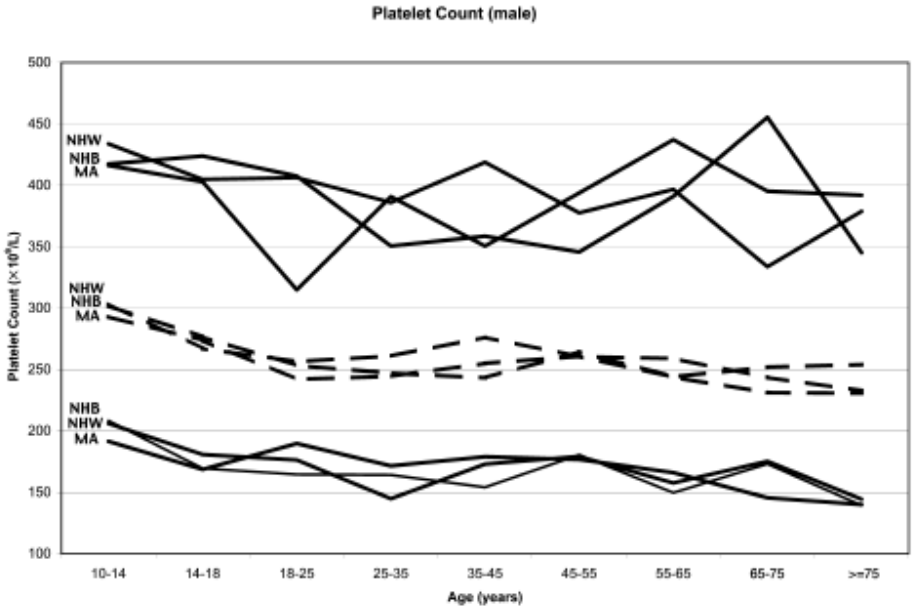
doi: 10.1532/LH96.04010

ISLH
Official Publication

Complete Blood Count Reference Interval Diagrams Derived from NHANES III: Stratification by Age, Sex, and Race

Calvino Ka-Wing Cheng,[1,2] Julie Chan,[2] George S. Cembrowski,[1,2]
Onno W. van Assendelft[3]





However…

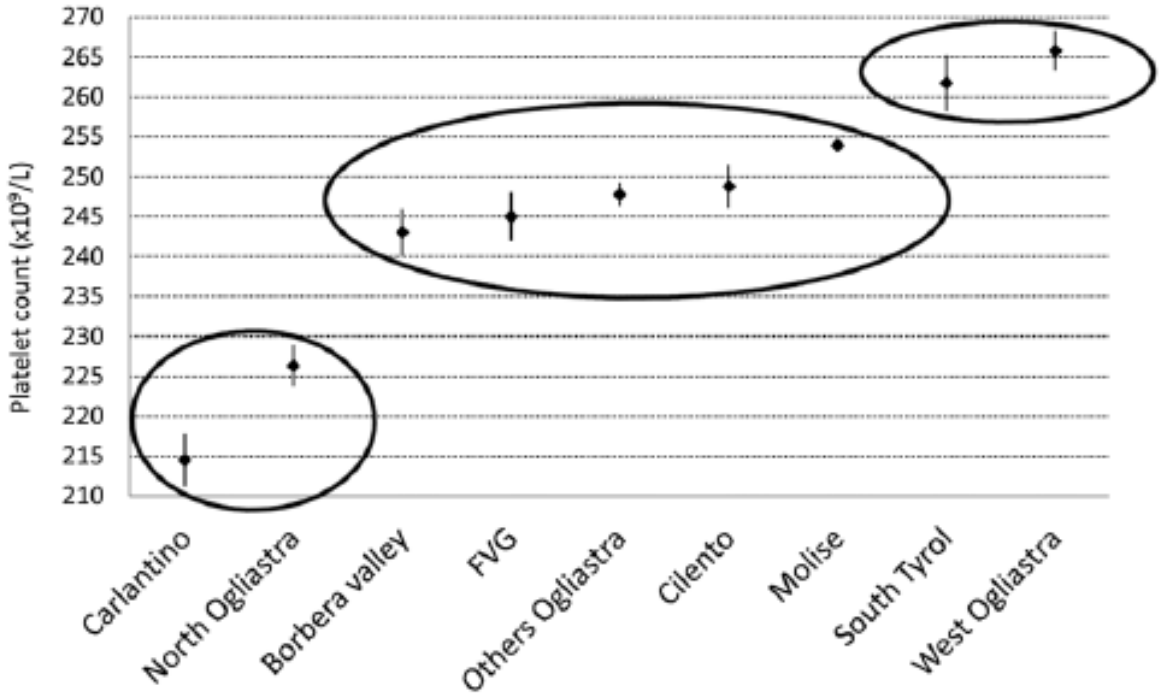
An International Working Group[1] suggested that a platelet count less than **100 x 10^9/L** could be more appropriate as a threshold for diagnosis of thrombocytopenia:

- By definition, 2.5% of the normal population have count below 150 x 10^9/L.
- Two prospective cohorts[2,3] of otherwise healthy subjects with a platelet count between 100 and 150 x 10^9/L showing that the 10-year probability of developing more severe thrombocytopenia is very low.
- This cut-off level could avoid inclusion of most women with pregnancy-related thrombocytopenia, a physiologic phenomenon.
- In non-western population a platelet count between 100 and 150 x 10^9/L are found in healthy people
- This pre-defined cut-off seems more practical than local range, allowing comparison across studies

[1]Rodeghiero F et al, Blood 2009
[2]Zimmer J et al, Plos Medicine 2006
[3]Stasi R et al, Plos Medicine 2006

On the other hand…

Local normal ranges should be calculated in case that epidemiologic evidences show the presence of a very wide age-, sex- and origin-related variability of platelet count[1]



[1]Biino G et al, Plos One 2013

On the other hand…

Table 3. Age-, sex- and, population-specific* reference intervals with 95% CI for platelet count.

	Low platelets areas					Medium platelets areas					High platelet areas				
Age	**n**	**Mean (SD)**	**2.5th–97.5th**	**2.5th (95%CI)**	**97.5th (95%CI)**	**n**	**Mean (SD)**	**2.5th–97.5th**	**2.5th (95%CI)**	**97.5th (95%CI)**	**n**	**Mean (SD)**	**2.5th–97.5th**	**2.5th (95%CI)**	**97.5th (95%CI)**
<15 years															
All	426	277 (65.7)	165–412	144–176	396–441	995	301 (72.8)	179–459	162–185	441–484	281	322 (66.6)	196–473	181–218	452–503
15–64 years															
Men	1032	212 (52.6)	120–343	112–128	320–359	11614	239 (58)	143–362	141–146	358–366	1143	253 (54.9)	157–369	151–161	361–388
Women	1347	234 (54.2)	136–358	128–141	345–363	13577	265 (65)	157–405	156–160	401–410	1434	284 (68.6)	176–436	170–184	422–457
>64 years															
Men	279	201 (54.4)	112–332	73–123	304–363	3746	220 (59.5)	123–350	119–127	344–360	278	239 (58.8)	133–361	97–144	337–420
Women	408	217 (50.9)	119–325	103–133	307–349	4013	247 (61.4)	143–381	138–147	375–394	414	254 (60.5)	144–396	124–164	366–441

[1]Biino G et al, Plos One 2013

Classification of thrombocytopenias

1. Reduced platelet production

Inherited

- MYH9 related thrombocytopenia
- Bernard-Soulier syndrome
- Di George syndrome
- Jacobsen syndrome
- Gray platelet syndrome
- Congenital amegakaryocytic thrombocytopenia
- TAR syndrome
- Wiskott – Aldrich syndrome
- X-linked thrombocytopenia
- GATA 1 mutation

Acquired

- Primary bone marrow disease (leukemia,myeloma, advanced lymphoma)
- Solid tumors with bone marrow metastases
- Paraneoplastic syndromes
- Infection
- Chemotherapy
- Nutritional deficiences
- Selective megakaryocyte aplasia

Classification of thrombocytopenias

2. Accelerated, non immune platelet distruction

- Thrombotic thrombocytopenic purpura
- Disseminated intravascular coagulation
- Drug-induced

3. Accelerated, immune platelet distruction

- Immune thrombocytopenia
- Neonatal alloimmune thrombocytopenia
- Post-transfusion purpura
- Drug-induced thrombocytopenia

Mostly syndromic TCP

Table 1. Clinical scenarios and most common causes of thrombocytopenia

	Inpatient		
Outpatient	**Multisystem illness/ICU**	**Cardiac patient**	**Pregnancy/postpartum**
ITP	Infections	HIT	GT
DITP	TTP/HUS	Cardiac bypass	ITP
Infections	DITP	GPIIb/IIIa inhibitors	HELLP syndrome
HIV	DIC	Other DITP	Preeclampsia
Hepatitis C virus	Liver disease	Dilutional	Abruptio placentae
Helicobacter pylori	HIT		TTP/HUS
CMV	MAS		
Other recent viral infections	BM disorders		
Connective tissue disorders	CIT		
Systemic lupus erythematosus			
Rheumatoid arthritis			
Antiphospholipid syndrome			
Vaccinations			
Myelodysplastic syndromes			
Congenital thrombocytopenia			
Common variable immunodeficiency			

TTP/HUS indicates thrombotic thrombocytopenic purpura/hemolytic uremic syndrome; MAS, macrophage activation syndrome (including hemophagocytic syndrome); CIT, chemotherapy-induced thrombocytopenia; HELLP, hemolysis, elevated liver enzymes, and low platelets.

Stasi R ASH 2012

Cohort form Hematology Department San Bortolo Hospital Vicenza

(years 1997-2006)

	Outpatients (thrombocytopenia < 100 x 10^9/L)	**1.278**	**%**
PLT < 50 x 10^9/L PLT > 50 x 10^9/L	**ITP ≥ 3 Follow Up (FU)**	**264 (190) (74)**	**20,6**
	ITP ≤ 2 FU	**398**	**31,1**
	«Gestational» TCP	**124**	**9,7**
	ITP HCV + or HBV+	**80**	**6,2**
	Heparin-induced TCP	**31**	**2,4**
	Drug-induced TCP	**9**	**0,7**
	TCP in infections	**19**	**1,4**
	Other	**173**	**13,5**
	TCP without FU (trivial)	**180**	**14**

Initial diagnostic work-up of patients with IT

- Family history
- Patient history
- Physical examination (bleeding?)
- Complete blood count and reticulocyte count
- Peripheral blood film
- Liver and renal biochemistry

A « minimalistic» approach could be adequate in the majority of the cases

Examples of differential diagnosis 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
- Drugs, 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 (family history)

Heparin - induced thrombocytopenia

4Ts	Points* 2	1	0
Thrombocytopenia	Platelet count decrease > 50% and platelet nadir > 20 × 10^9/L	Platelet count decrease 30-50% or platelet nadir 10-19 × 10^9/L	Platelet count decrease < 30% or platelet nadir < 10 × 10^9/L
Timing of platelet count decrease	Clear onset between d 5 and 10 or platelet decrease ≤ 1 d (prior heparin exposure within 30 d)	Consistent with d 5-10 decrease, but not clear (eg, missing platelet counts); onset after d 10; or decrease ≤ 1 d (prior heparin exposure 30-100 d ago)	Platelet count decrease < 4 d without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction postintravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; non-necrotizing erythematous) skin lesions; Suspected thrombosis (not proven)	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

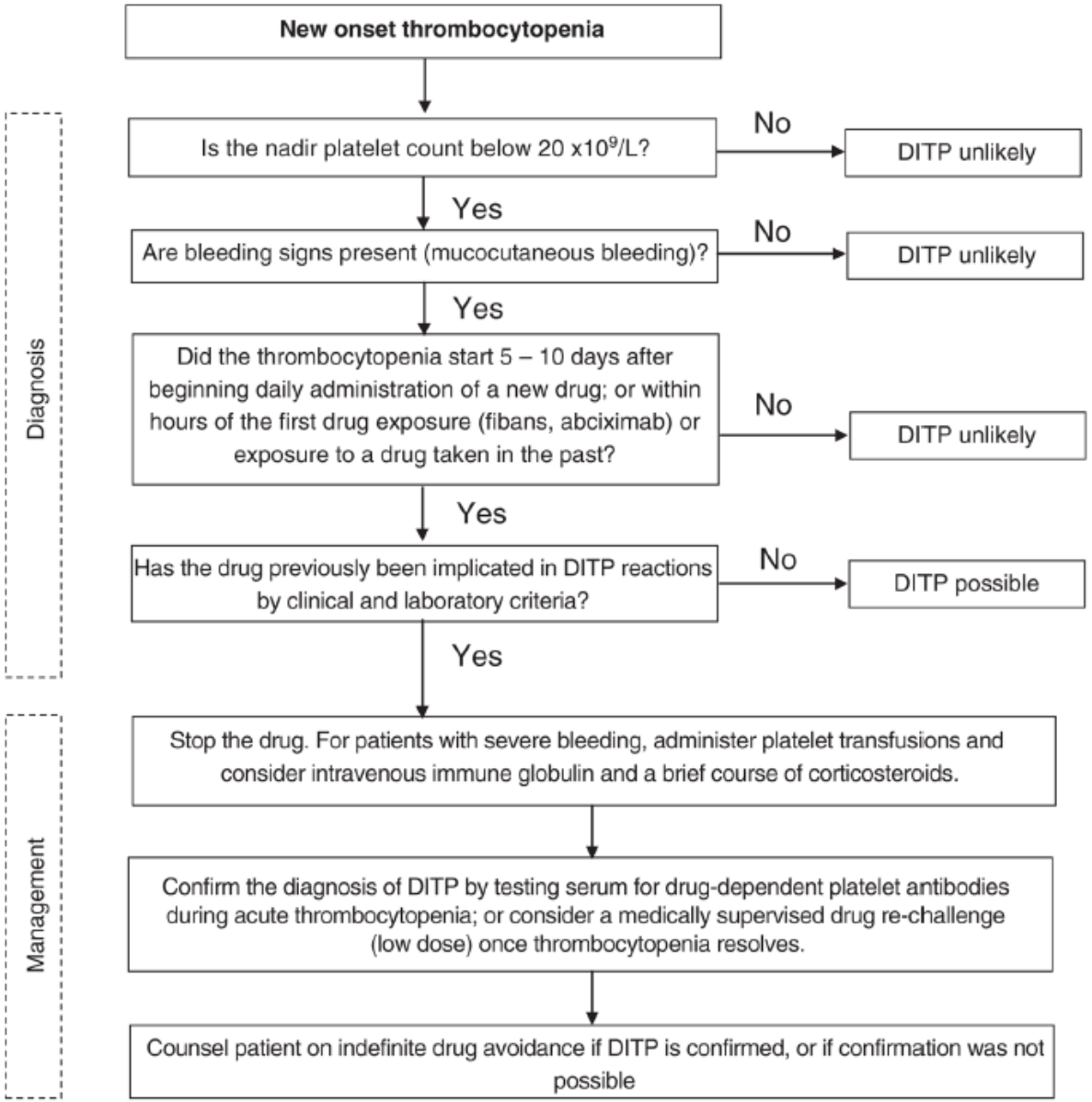
The 4 T pre-test probability of HIT= 0-3: low; 4-5: intermediate; 6-8 high

Lo GK et al, JTH 2006

Drug-induced TCP

A challenging clinical problem:

- Under-recognized
- difficult to diagnose
- associated with severe bleeding complications (also death)
- Un-necessary treatment



Diagnosis and management of patients with suspecet DITCP, from **Arnold DM et al, Transfus Med Rev 2013**

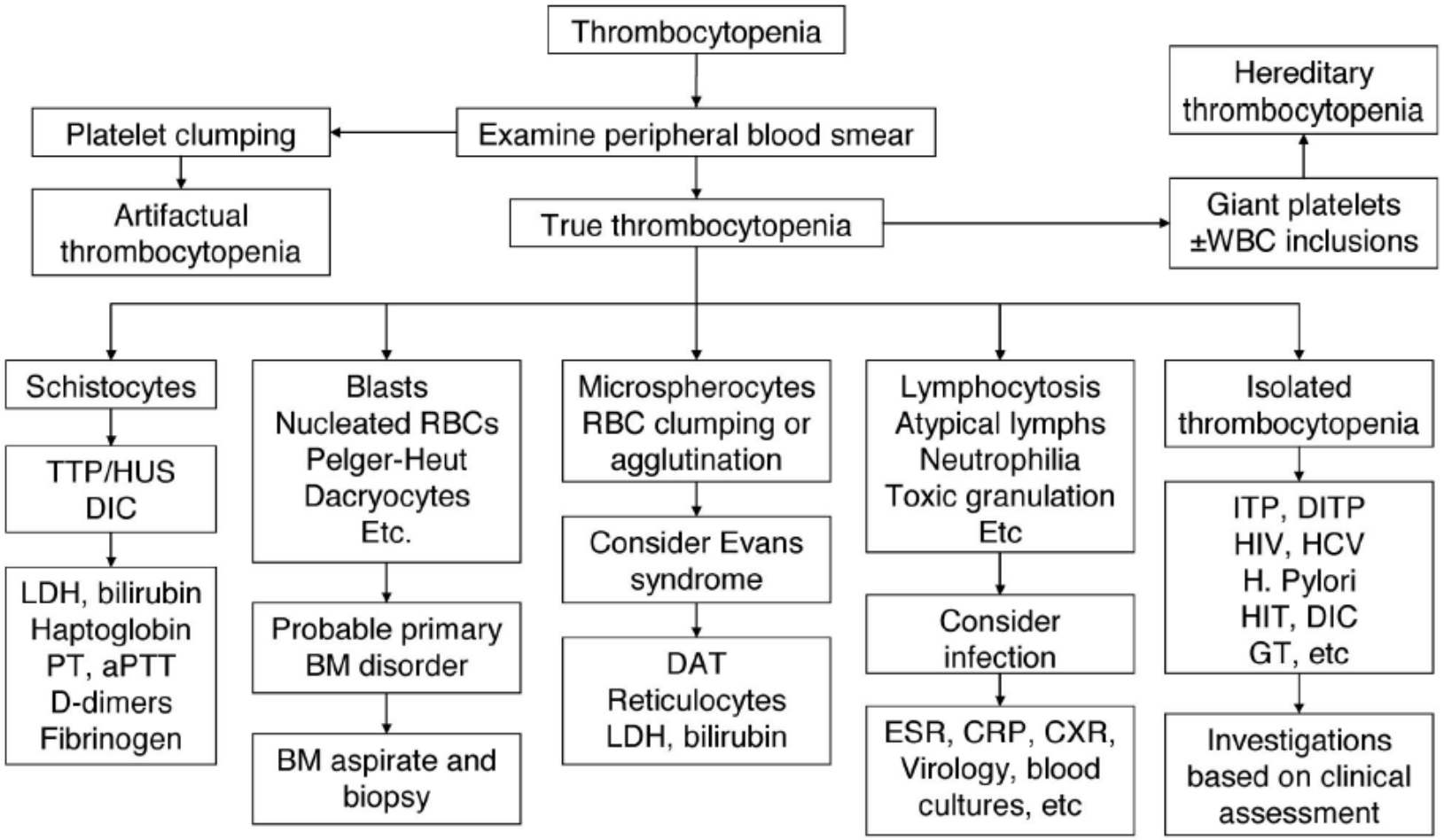
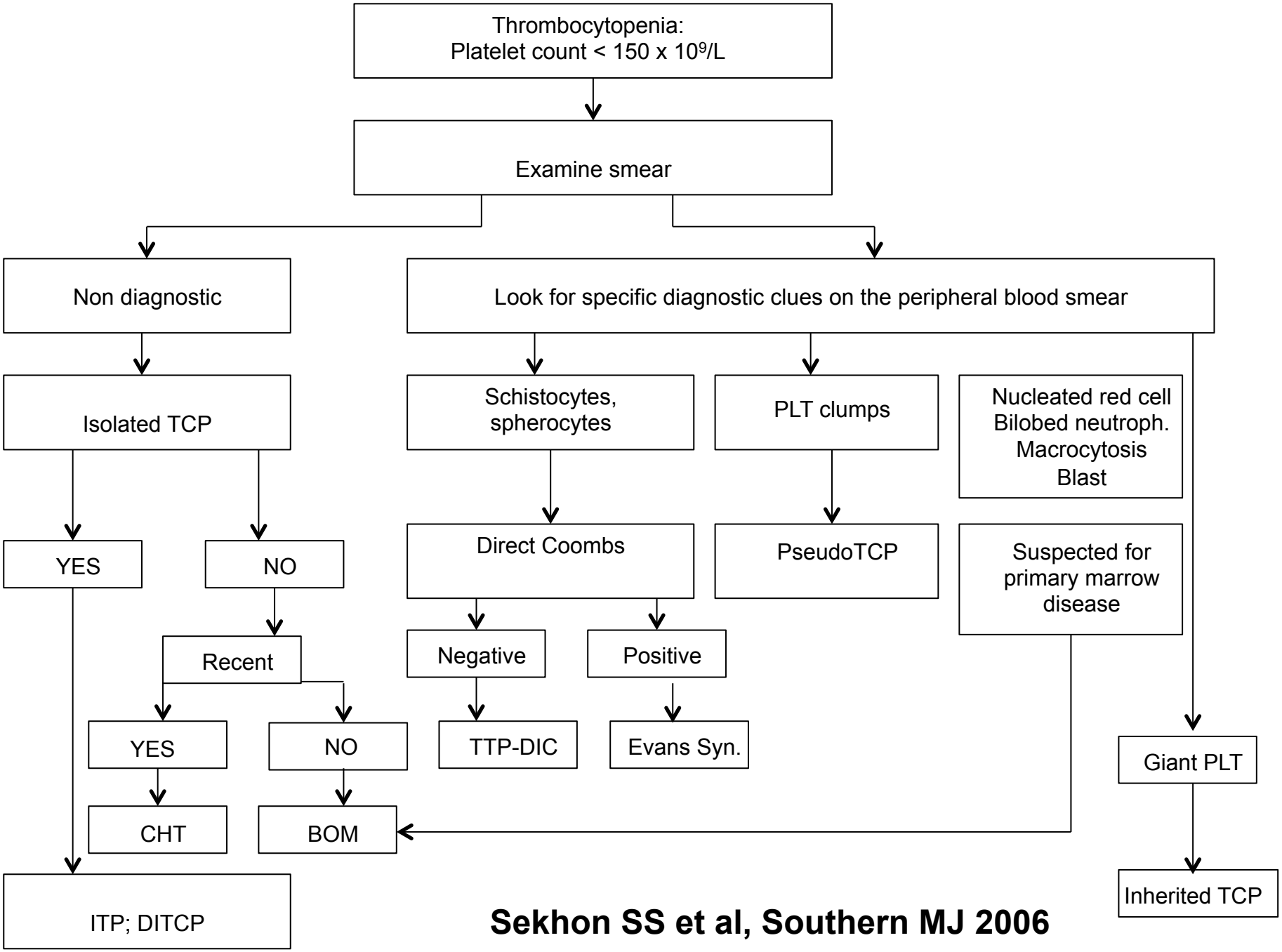


Figure 1. Algorithm for workup of thrombocytopenia based on observation of the peripheral blood film. TTP/HUS indicates thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

Stasi R ASH 2012



Sekhon SS et al, Southern MJ 2006

Examples of differential diagnosis identified by blood film examination

Table 2. Morphologic aspects of the peripheral blood smear of particular relevance to the diagnosis of thrombocytopenia

Platelets

Platelet clumping

Platelet clumping caused by EDTA-dependent platelet autoantibodies is a common cause of artifactual thrombocytopenia. It occurs in about 1 in 1000 normal adults and is not associated with bleeding or thrombosis.

Platelet size and granularity

Consistently large platelets suggest hereditary macrothrombocytopenia. Large platelets with a gray color on Wright-Giemsa stain define the gray platelet syndrome, an autosomal-dominant macrothrombocytopenia associated with bleeding tendency due to absent or greatly reduced α-granules.

In thrombocytopenia due to peripheral destruction, large platelets or giant platelets are often seen in addition to platelets of normal size.

When thrombocytopenia is due to reduced platelet production (eg, after chemotherapy), platelets are of normal size. In myelodysplastic syndromes, platelets have variable size (giant platelets may be seen) and are frequently hypogranular. In Wiskott-Aldrich syndrome, and X-linked thrombocytopenia, both caused by mutations of the WAS gene, platelets are small.

WBCs

Leukemic cells

Malignant hematological disorders (leukemias and lymphomas) are often associated with thrombocytopenia, which is almost never an isolated finding.

Other abnormalities of WBCs, including leukocyte inclusions

A constellation of nonspecific abnormalities of WBCs are common to many conditions (eg, neutrophilia, lymphocytosis, leukopenia, etc) and may be associated with thrombocytopenia. The presence of hypolobulated neutrophils (Pelger-Huët anomaly) suggests a myelodysplastic syndrome. Dark coarse granules (toxic granulations) found in neutrophils suggest sepsis. Atypical lymphocytes suggest viral infection. The presence of WBC inclusions ((Döhle-like bodies)) should be investigated carefully when platelets are mostly large (MYH9-related congenital macrothrombocytopenia).

RBCs

Schistocytes

The presence of RBC fragments known as schistocytes is indicative of a thrombotic microangiopathy (TTP/HUS) or DIC.

Size and other morphological features

Microspherocytes may suggest Evans syndrome, but may also be present along with shistocytes in thrombotic microangiopathies. Macrocytosis (and hypersegmentation of neutrophils) suggest vitamin B12 or folate deficiency. Dacryocytes (teardrop-shaped cells) suggest myelofibrosis. Nucleated RBCs suggest hemolytic anemia, myelofibrosis, or an infiltrative process of the BM.

Parasites

The presence of intracellular parasites (eg, in malaria) is diagnostic of infection.

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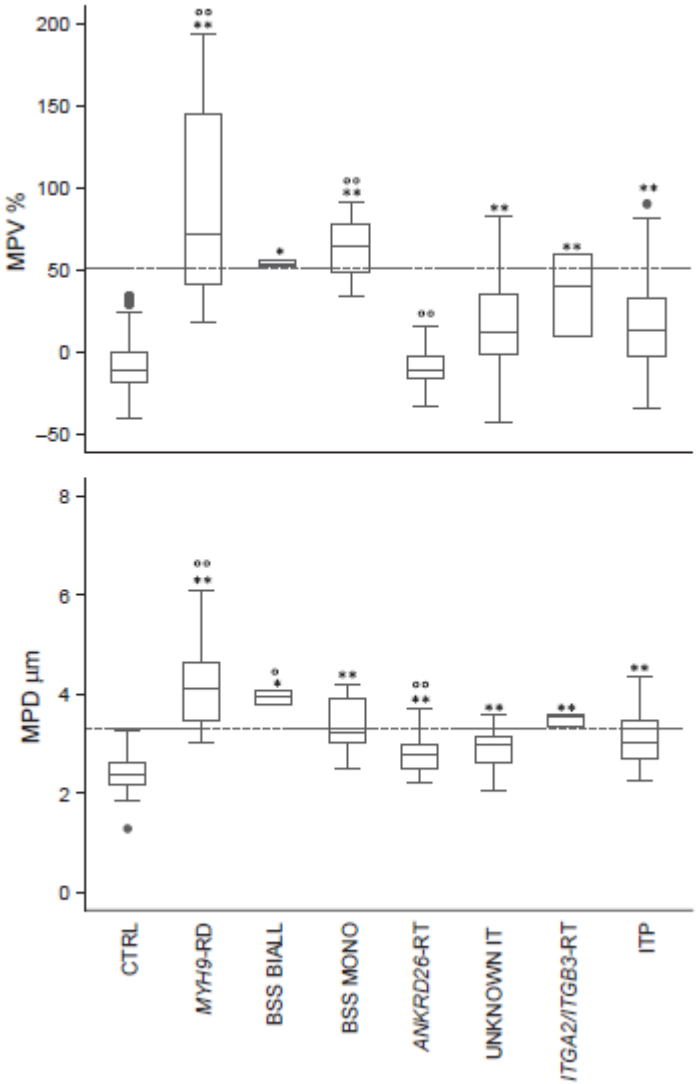
Platelet size for distinguishing between inherited thrombocytopenias and immune thrombocytopenia: a multicentric, real life study



Noris P et al, BJH 2013

blood

2009 113: 2386-2393
Prepublished online Nov 12, 2008;
doi:10.1182/blood-2008-07-162503

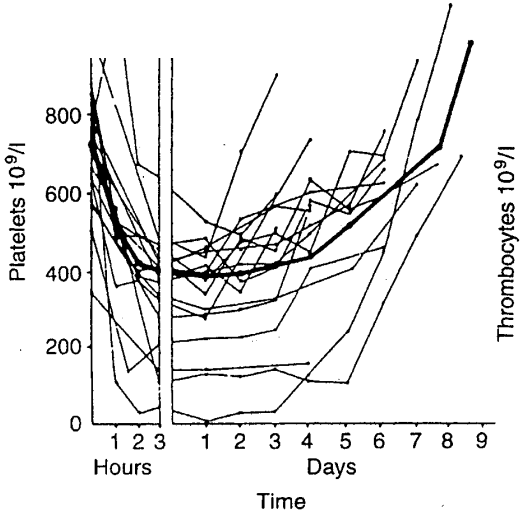
Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group

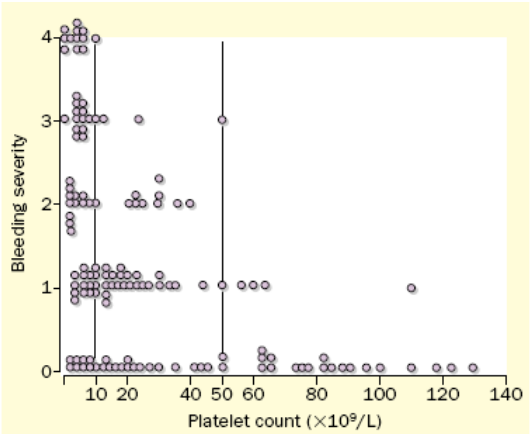
Francesco Rodeghiero, Roberto Stasi, Terry Gernsheimer, Marc Michel, Drew Provan, Donald M. Arnold, James B. Bussel, Douglas B. Cines, Beng H. Chong, Nichola Cooper, Bertrand Godeau, Klaus Lechner, Maria Gabriella Mazzucconi, Robert McMillan, Miguel A. Sanz, Paul Imbach, Victor Blanchette, Thomas Kühne,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

Primary Immune **T**hrombocyto**P**enia

(no longer **I**diopathic **T**hrombocytopenic **P**urpura)

- Primary = absence of any initiating/underlying disease (opposed to *Idiopathic*)
- **I**mmune = immune-mediated pathogenesis
- 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: secondary forms

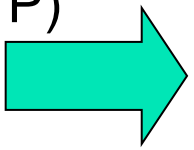
SECONDARY Immune ThrombocytoPenia (Secondary ITP)

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

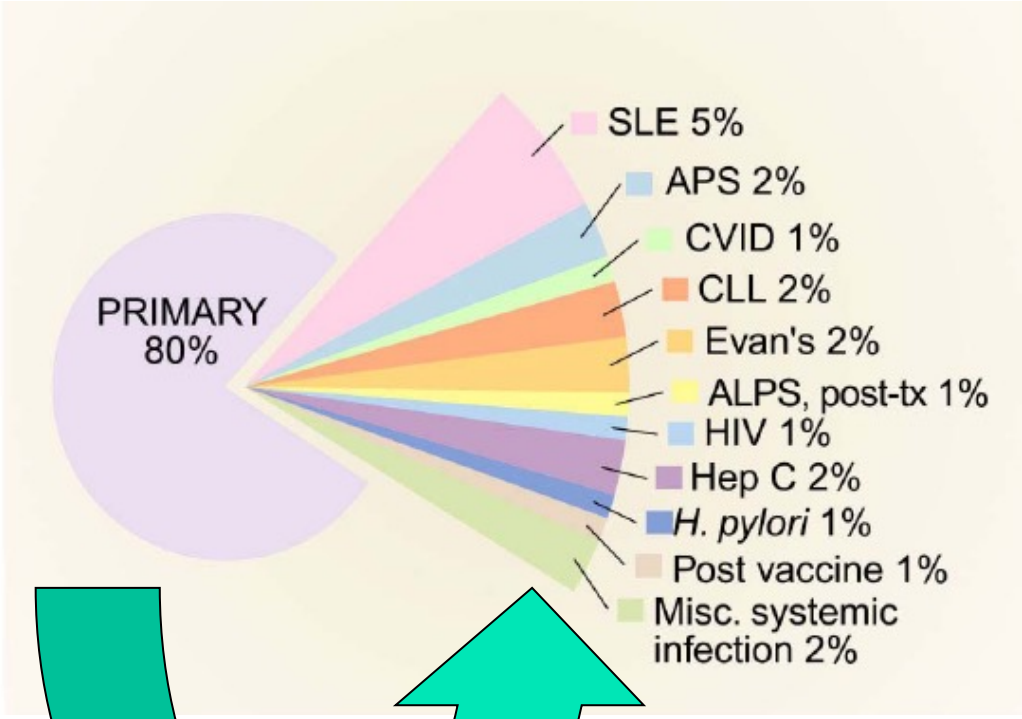
Heterogeneity of Primary ITP

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

International consensus report on the investigation and management of primary immune thrombocytopenia 2010 115: 168-186

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

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†		

Bone marrow examination

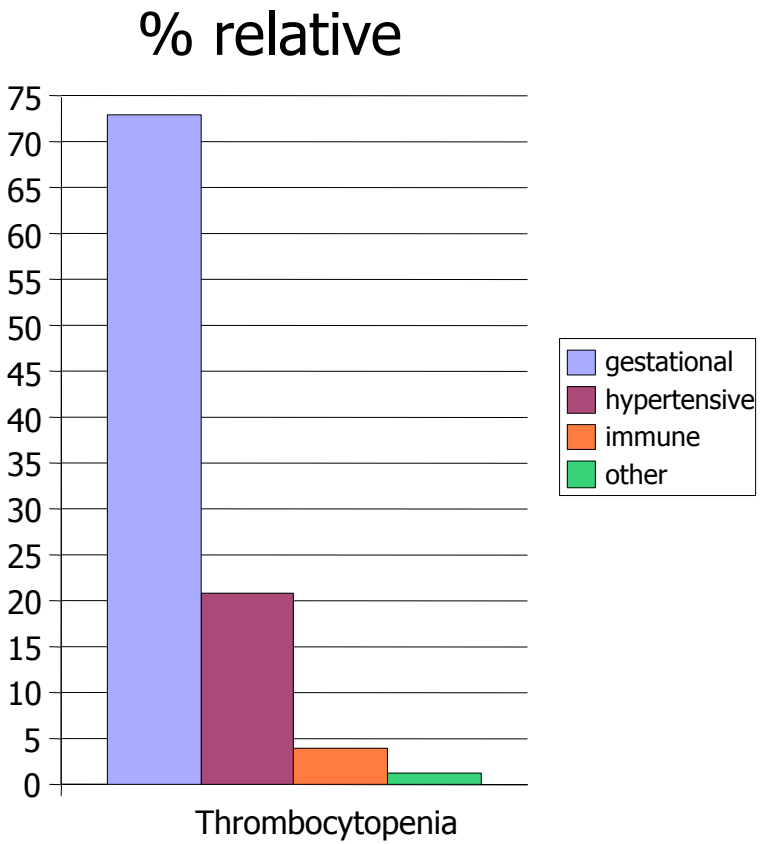
IWG 2010	ASH 2011
• Patients older than 60 years • Before splenectomy in adult • Before steroids in children	Not necessary in case of typical features

Rate of maternal low platelet count-associated diseases during pregnancy

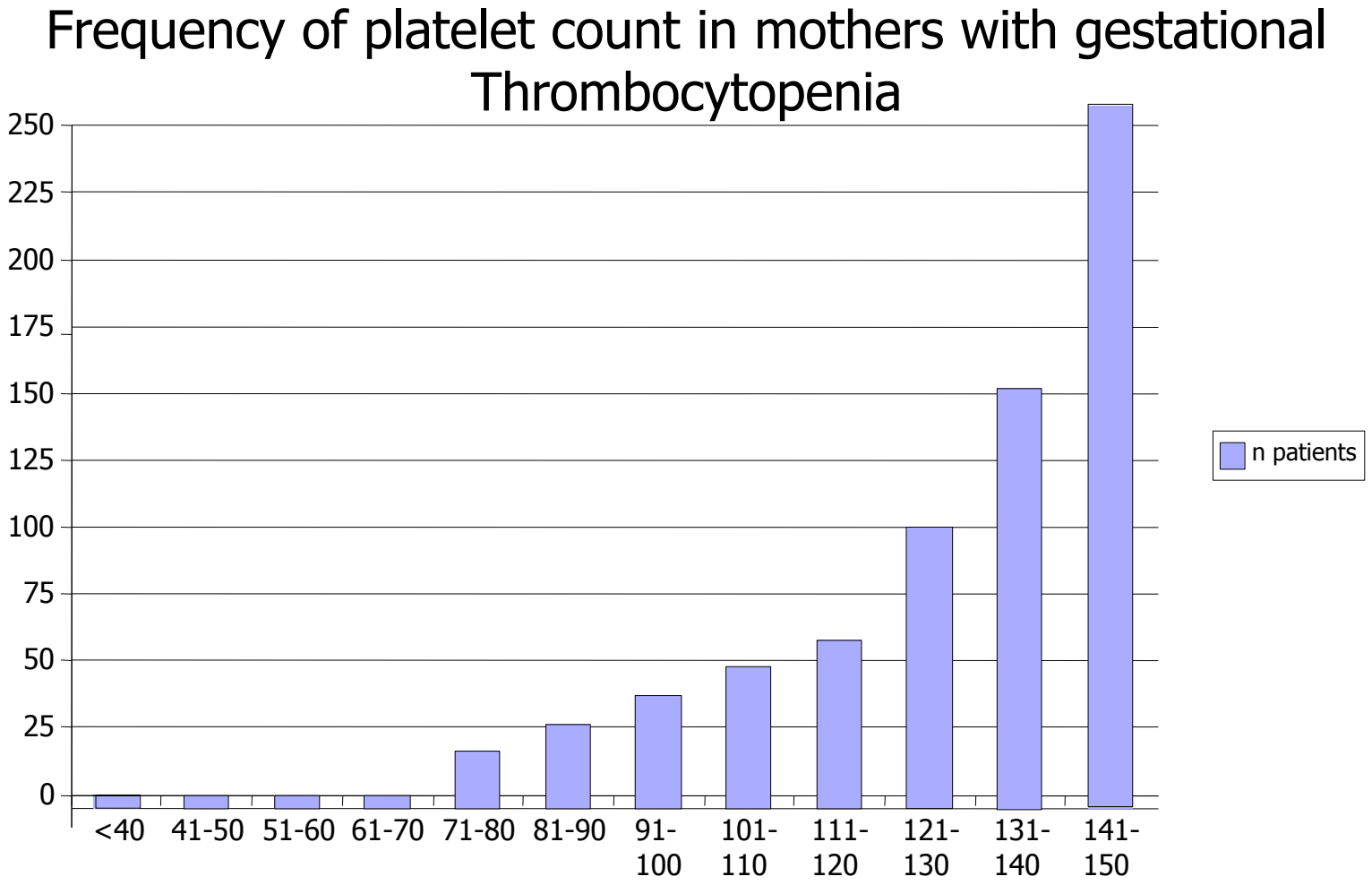
(Burrows and Kelton, NEJM 1993)

Platelet < 150 x $10^3/\mu L$ at partum

Type of disease	n.		% rel.	% ass.
Gestational	**756**	**73**		**4.8**
Hypertensive	**216**	**21**		**1.4**
ITP	**31**	**3**		**0.25**
LES	**8**	**0.8**		**0.005**
Other	**13**	**1.2**		**0.08**
Total:	**1027/15471**			**6.6**



Maternal platelet count in 756 gestational thrombocytopenia (Burrows and Kelton, 1993)



Cause of thrombocytopenia	Time of the most common onset	Grade of thrombocytopenia	Biochemical abnormalities	Clinical symptoms
Gestational	III trimester	mild	no	no
ITP	I-II trimester	mild to severe	no	bleeding in severe cases
Eclampsia	III trimester	mild to severe	DIC[4]) proteinuria	hypertension
HELLP[1]	III trimester	mild to severe	DIC, hemolytic anemia ↑ AST/ALT	no or complex presentation
TTP[2]	II trimester	mild	hemolytic anemia	fever, CNS[5]
HUS[3]	Post - partum	mild	hemolytic anemia	fever, renal failure
AFL[6]	III trimester	mild	DIC, hemolytic anemia, hypoglycemia	complex presentation

Recommendations for investigation of suspected ITP in pregnancy

- Patient history, physical examination, blood count and blood smear examination (Grade C recommendation)
- Bone marrow examination not recommended (Grade C recommendation)
- Recommended tests are:
  - Coagulation screening (prothrombin time, activated partial thromboplastin time, fibrinogen)
  - Liver function tests including bilirubin, albumin, total protein, transferases, gamma-glutamyl transferase and alkaline phosphatase
  - Anticardiolipin antibodies and lupus anticoagulant
  - SLE serology
  - Review of the peripheral blood smear and reticulocyte count
- Anti-platelet antibody testing does not predict neonatal thrombocytopenia unlike with alloimmune thrombocytopenia (Grade C recommendation)

Due sintomi da valutare nel work-out diagnostico

- Bleeding
- Fatigue

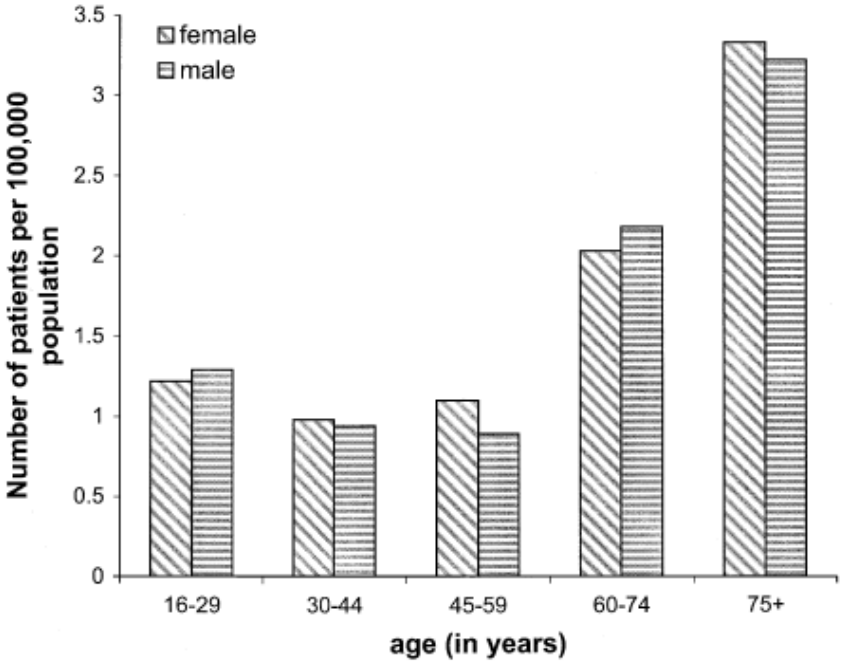
Bleeding at diagnosis of ITP

- 221 patients identified (139 women, 63%); median age 56 years
- Mean platelet count at diagnosis: 12 x 10^9/L
- 46 patients (21%) were asymptomatic; 25 (11%) with severe bleeding

Frederiksen et al, *Blood* 1999

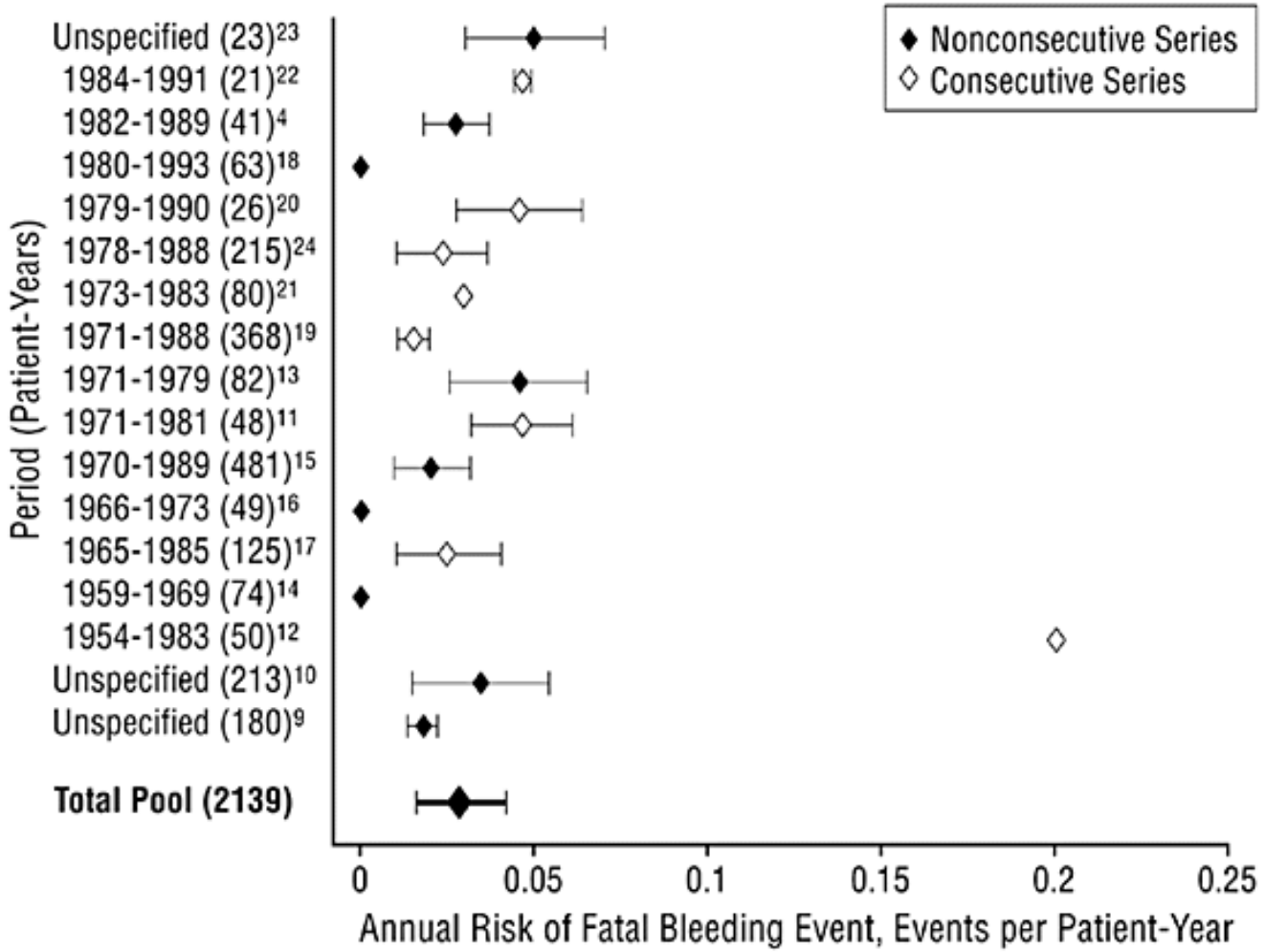
Bleeding at diagnosis of ITP

- Overall incidence: 1.6 x 10^5 –years (PLT < 50 x 10^9/L; bone marrow evaluation)
- 245 patients (134 women, 54%); median age 56 years
- 114 patients (46%) with PLT < 10 x 10^9/L at diagnosis; 30/245 (12%) with bleeding



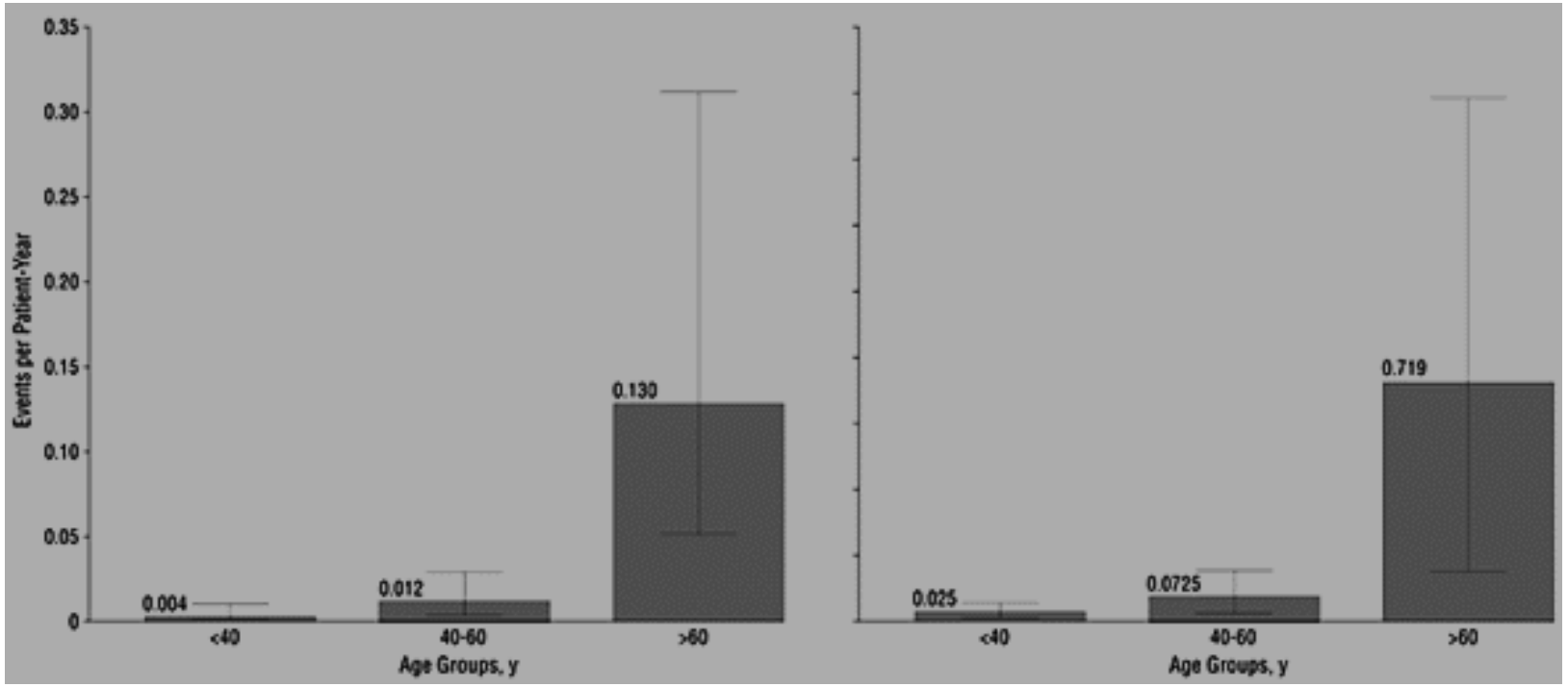
Neylon et al, *Br J Haematol* 2003

Annual rate of fatal haemorrhage among patients with persistent low platelet counts



Cohen, Y. C. et al. Arch Intern Med 2000;160:1630-1638.

Estimated annual rate of fatal and major nonfatal haemorrhages



Fatal haemorrhage

Non-fatal haemorrhage

Cohen, Y. C. et al. Arch Intern Med 2000;160:1630-1638.

Bleeding symptoms in clinical trials (initial treatment in newly diagnosis ITP patients)

Studies	Basal bleeding assessment	Score	Prognostic value (grade of severity and chance of response)	Decrease of bleeding as end point	Bleeding as adverse event
Mazzucconi, Haematologica 1985 (steroid 0.5 mg vs 1.5 mg)	No	No	No	No	No
Bellucci, Blood 1988 (steroid 0.25 mg vs 1 mg)	No	No	No	No	No
Godeau, Lancet 2002 (HD-MP vs Ig	Yes	Yes (clinical scoring system)	No	No	No
George, AJH 2003 SOC vs anti D	No	No	No	Yes (safety: clinical scoring system for major bleeding)	Yes
Cheng, NEJM 2003 (HD-DEXA)	No	No	No	No	No
Mazzucconi, Blood 2007 (HD-DEXA)	Yes	Yes (clinical scoring system; 5 grades)	No	No	No
Zaja, Blood 2010 (DEXA vs R-DEXA)	No	No	No	No	Yes

Bleeding symptoms in trials with Romiplostim

Studies	Basal bleeding assessment	Score	Prognostic value (grade of severity and chance of response)	Decrease of bleeding as end point	Bleeding as adverse event
Newland, BJH 2006	No	No	No	No	Yes
Bussel, NEJM 2006	No	No	No	No	Yes
Kuter, Lancet 2008	No	No	No	No	Yes
Kuter, NEJM 2010	No	No	No	No	Yes; score with 2-5 grades
Gernsheimer, JTH 2010	Yes, descriptive	Yes; Amgen adverse event grading scale	-.	-	Yes; descriptive, with grading and with platelet count correlation

Bleeding symptoms in trials with Eltrombopag

Studies	Basal bleeding assessment	Score	Prognostic value (grade of severity and chance of response)	Decrease of bleeding as end point	Bleeding as adverse event
Bussel, NEJM 2007	Yes	WHO (0-4 grades)	No; % of bleeding events during treatment are cumulatively reported	Yes; secondary	Yes
Bussel, Lancet 2009	Yes	WHO (0-4 grades)	No; % of bleeding events during treatment are cumulatively reported	Yes; secondary	Yes
Cheng, Lancet, 2010	Yes 77% placebo; 73% TPO	WHO (0-4 grades)	No; % of bleeding events during treatment are cumulatively reported	Yes; secondary	Yes

	Bleeding grade		
Site	0	1	2
Skin (physical examination)	None	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/ or diffuse petechiae
Oral (physical examination)	none	1 blood blister or >5 petechiae or gum bleeding that clears easily with rinsing	Multiple blood blisters and/or gum bleeding
Skin (history previous week)	none	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/ or diffuse petechiae
Oral (history previous week)	none	1 blood blister or >5 petechiae and/or gum bleeding <5 min	Multiple blood blisters and/or gum bleeding >5 min
Epistaxys	none	Blood when blowing nose and/or epistaxis <5 min (per episode)	Bleeding >5 min (per episode)
Gastrointestinal	none	Occult blood	Gross blood
Urinary	none	Microscopic (+ve dipstick)	Macroscopic
Gynecological	none	Spotting not at time of normal period	Bleeding >spotting not at time of period
Pulmonary	none	NA	YES
Intracranial haemorrhage	none	NA	YES
Subconjunctival haemorrhage	none	YES	NA

Page et al, Br J Haematol, 2007

Bleeding score	
Signs	**Point**
Cutaneous bleeding*	
Localized petechial purpura (legs)	1
Localized ecchymotic purpura	2
locations of petechial purpura (ie, legs & chest)	2
Generalized petechial purpura	3
Generalized ecchymotic purpura	4
Mucosal bleeding	
Unilateral epistaxis	2
Bilateral epistaxis	3
Hemorrhagic oral bullae, spontaneous gingival bleeding or both	5
Gastrointestinal Bleeding *	
Gastrointestinal hemorrhage without anemia	4
Gastrointestinal hemorrhage with acute anemia (> 2 g Hb per 24 h) and/or shock	15
Urinary Bleeding *	
Macroscopic hematuria without anemia	4
Macroscopic hematuria with anemia	10
Genital Bleeding*	
Major meno-/metrorrhagia without anemia	4
Major meno-/metrorrhagia with anemia	10
Central nervous system bleeding and/or life-threatening hemorrhage	15

Khellaf et al, Blood 2011

blood
2009 113: 2386-2393
doi:10.1182/blood-2008-07-162503 originally published online November 12, 2008

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

,

blood
2013 121: 2596-2606
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doi:10.1182/blood-2012-07-442392

Standardization of bleeding assessment in immune thrombocytopenia: report from the International Working Group

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Principles governing ITP Bleeding Assessment Tool (ITP-BAT)(SMOG system)

3 domains and 19 different bleeding manifestations:

- Skin
  - Petechiae, ecchymoses, subcutaneous hematomas, bleeding from minor wounds
- Mucosal (visible)
  - Epistaxis, gum bleeding, hemorrhagic bullae or blisters, bleeding after bites to lip or tongue or after deciduous teeth loss, subconjunctival hemorrhage
- Organ
  - Gastrointestinal bleeding (not explained by visible mucosal bleeding or lesion), lung bleeding, hematuria, menorrhagia, intramuscular hematomas, hemarthrosis, ocular bleeding, intracranial bleeding, other internal bleedings, bleeding after surgery or invasive procedures or hemostatic challenges
- Grade: 0 – 4 (max grade 3 for skin and some mucosal)
- Grade 5 : fatal bleeding

Principles governing ITP-BAT: grading scale

Grade 0	**no bleeding**
Grade 1	all episodes referred by the patients or assessed directly but without need of care (exceptions in skin)
Grade 2 & 3	Bleeding interfering with daily activities or with need of direct medical intervention
Grade 4	requirement of blood transfusion, hospitalization or surgical intervention*
Grade 5	any fatal bleeding

Principles governing ITP-BAT:

Worst episode for each bleeding and each domain

- For each of the 19 bleeding manifestations the worst episode during the observation period should be recorded and graded

- For each domain (Skin, Mucosal, Organ) the worst bleeding episode is then chosen, graded and reported in the SMOG index

Example: if during the period under evaluation the highest grade is 2 for the skin domain, 2 for the mucosal domain, and 0 for the organ domain, the index is S2M2O0

Definition of bleeding manifestations based on physical examination

Site of bleeding	Manifestation	Definition
Skin (epidermis and dermis)		
	Petechiae	Red (recent) or purplish (a few days old) discoloration in the skin with a diameter of 0.5-3 mm that does not blanche with pressure and is not palpable
	Ecchymosis (purpuric macule, bruises, or contusions)	Flat, rounded, or irregular red, blue, purplish, or yellowish green patch, larger than a petechia. Elevation indicated spreading of an underlying hematoma into the superficial layers of the skin
Skin (subcutaneous tissue)		
	Hematoma	Bulging localized accumulation of blood, often with discoloration of overlying skin
Visible mucous membranes		
	Petechiae, purpuric macules, and ecchymosis	Same as for skin
	Bulla, vesicle, and blister	Visible raised, thin-walled, circumscribed lesion containing blood. Each bulla (>5 mm) is larger than a vesicle. Bullae, vesicles, and blisters should be counted together as bulla
	Epistaxis	Any bleeding from the nose may be anterior or posterior and unilateral or bilateral
	Gingival bleeding	Any bleeding from the gingival margins
	Subconjunctival hemorrhage	Bright red discoloration underneath the conjunctiva at onset; may assume the appearance of an ecchymosis over time
Muscles and soft tissues		
	Hematoma	Any localized collection of blood visible, palpable, or revealed by imaging. May dissect through fascial planes

Fatigue

Definition:

Extreme and persistent tiredness, weakness or exhaustion (mental, physical or both) experienced in the absence of any excessive expenditure of energy.

Often associated with decreased functioning

Dittner, 2004

Fatigue

Measured in ITP patients using self – assessment scale:

1. ITP – PAQ (romiplostim trials)

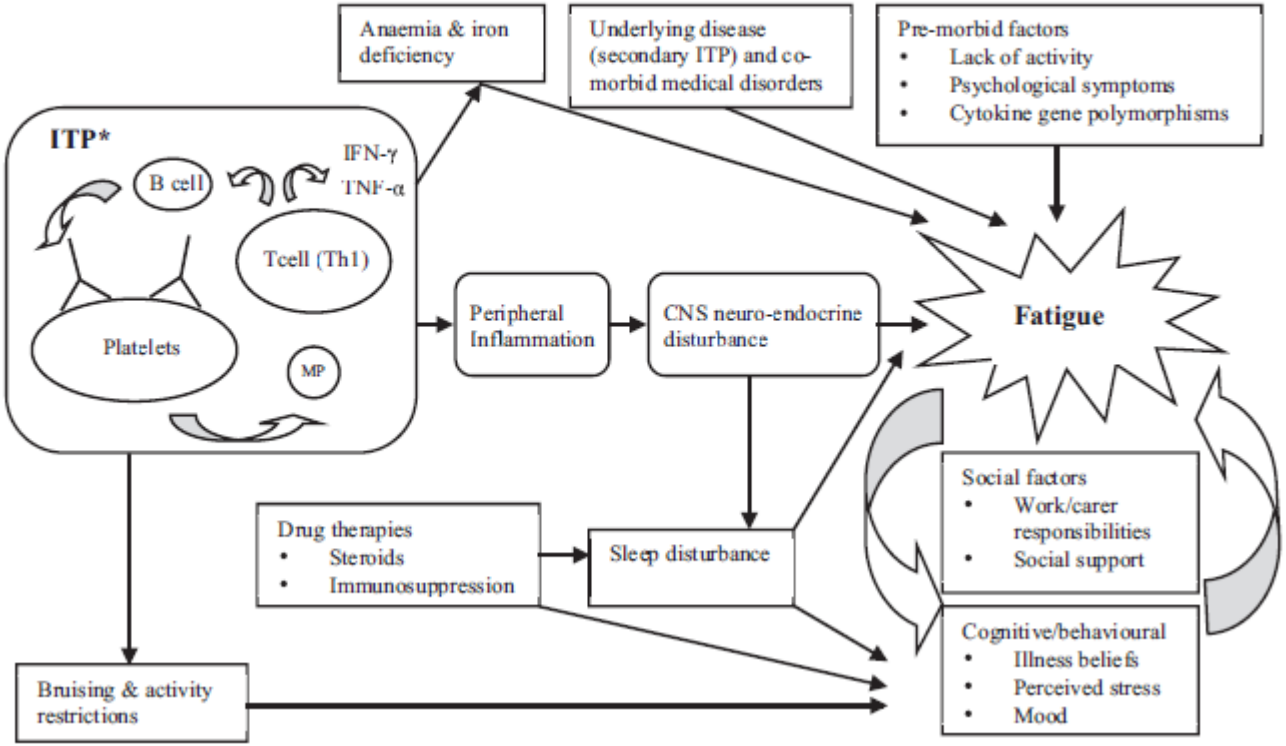
2. FACIT-F questionnaire (eltrombopag trials)

Mathias, 2007
Hill, 2015

Fatigue in ITP patients

Author	N° patients	% with significant fatigue	Association with platelet count
Sarpatwari 2010	790	12.5%	No
Newton 2011	585 UK 93 USA	39% UK 22% USA	Yes

Fatigue in ITP patients



Hill, 2015

Take-home messages

- A cut-off platelet count of 100 x 10^9/L is suggested to define a condition of “thrombocytopenia” in IT; in special circumstances (“epidemiologic evidence” from local population) a local range calculation could be desirable
- In patient with a “true” isolated thrombocytopenia, a “ minimalistic” diagnostic approach could be sufficient in the majority of the cases, as initial work-up
- In patients with drug- induced-TCP no need of further examinations after resolution
- In patients with inherited TCP participation to cooperative studies is recommended, with molecular diagnostic definition
- In patients with ITP and abnormal behavior or need of long-term follow-up, investigation in depth is recommended
- Specific score for bleeding symptoms should be used to assess the severity of disease
- Fatigue is established in a significant proportion of ITP patients; need to know more