Inquadramento diagnostico-clinico delle piastrinopenie

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La sottoscritta, Elena Rossi, in qualità di Relatore
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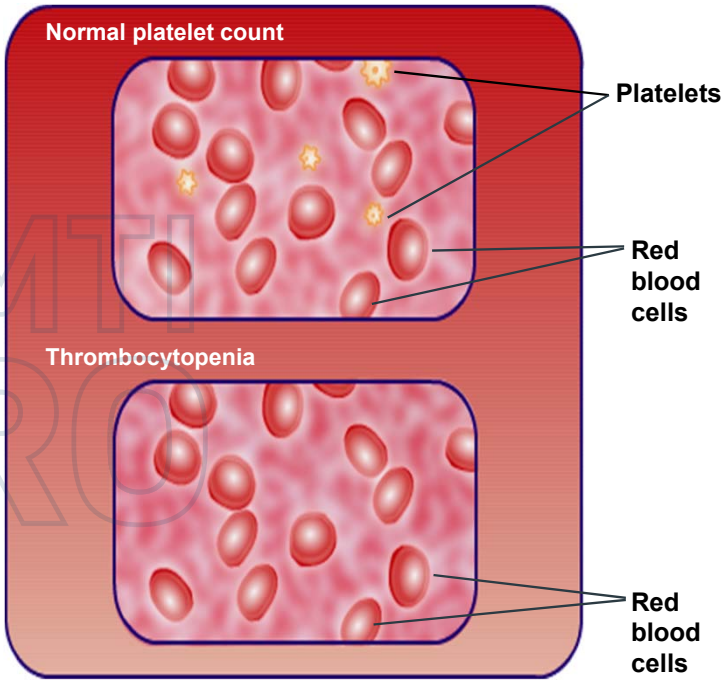
Immune thrombocytopenia

- Immune-mediated acquired disease of adults and children[1]
- ITP is defined as a platelet count less than 100 × 10^9/L, in the absence of other causes or disorders that may be associated with thrombocytopenia[2]
- Currently no definitive diagnostic criteria exist for primary ITP
  - Considered a diagnosis of exclusion
  - Thrombocytopenia may occur secondary to other conditions, such as lupus, leukemia, HIV, and HCV[3]
- Although the exact pathology behind ITP remains unclear, recent advances have indicated two broad routes
  - Increased platelet destruction[4]
  - Decreased platelet production[5]

HCV, hepatitis C virus; HIV, human immunodeficiency virus;
ITP, immune thrombocytopenia

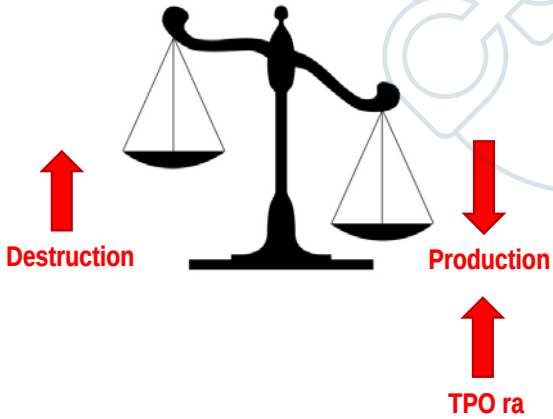


1. Rodeghiero F, *et al. Blood* 2009;113:2386–2393;
2. Neunert C, *et al. Ann Hematol* 2010;89:47–5; ;
3. Cines DB, Blanchette V. *N Engl J Med* 2002;346:995–1008;
4. Cooper N, *et al. Br J Haematol* 2006;133:364–374;
5. Gernsheimer T. *Eur J Haematol Suppl* 2008;80:3–8.

Immune ThrombocytoPenia: ITP

Pathogenetic mechanism

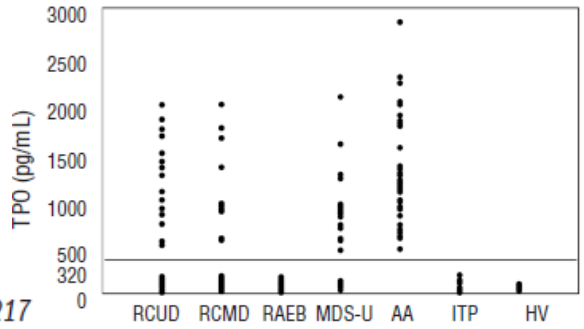
In contrast with the classical view of an increased platelets destruction not compensated by an increased platelets production (kinetic studies with 51Cr).



More recent kinetic analysis showed that platelets production in ITP is normal or reduced.

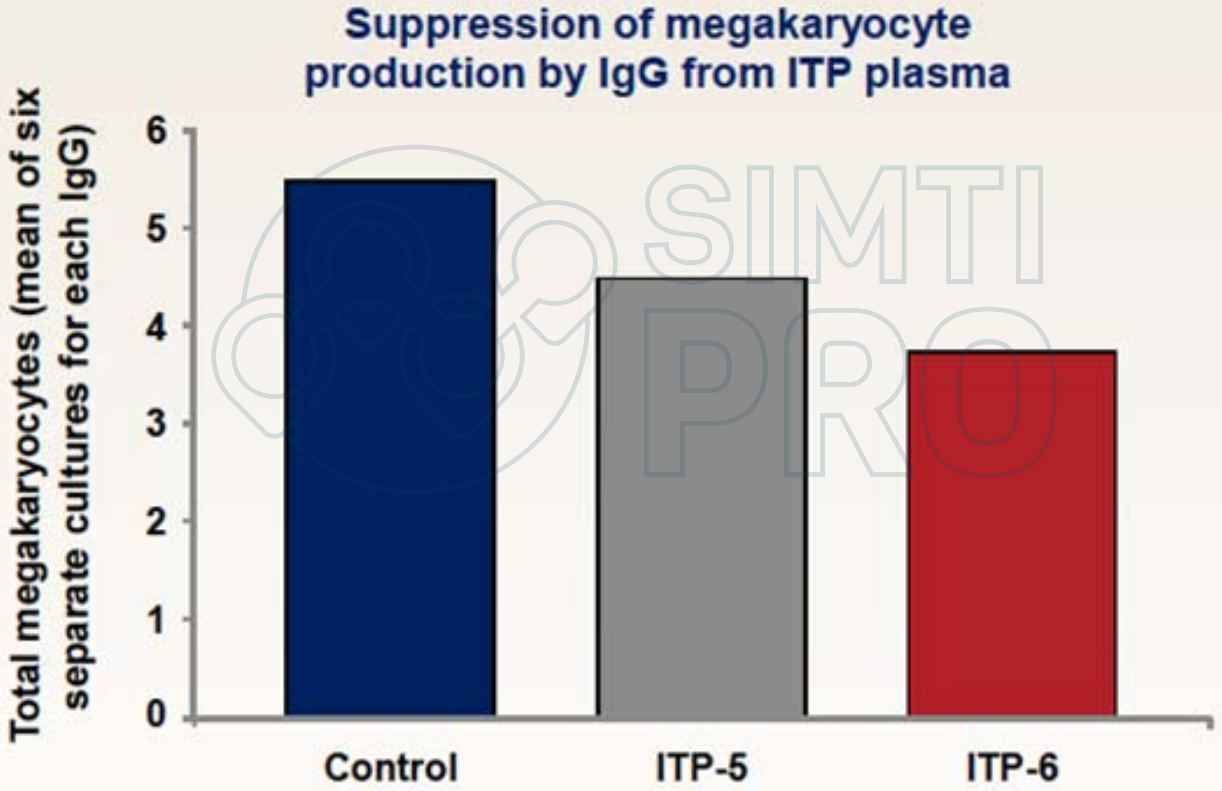
Therefore the pathogenetic mechanism of ITP is sustained by two factors:

- Increased platelets destruction
- Suppressed platelets production



Increased plasma thrombopoietin levels in patients with myelodysplastic syndrome: a reliable marker for a benign subset of bone marrow failure *Haematologica 2013;98. doi:10.3324/haematol.2012.066217*

Megakaryocyte growth and maturation in vitro is inhibited by platelet autoantibodies from patients with ITP

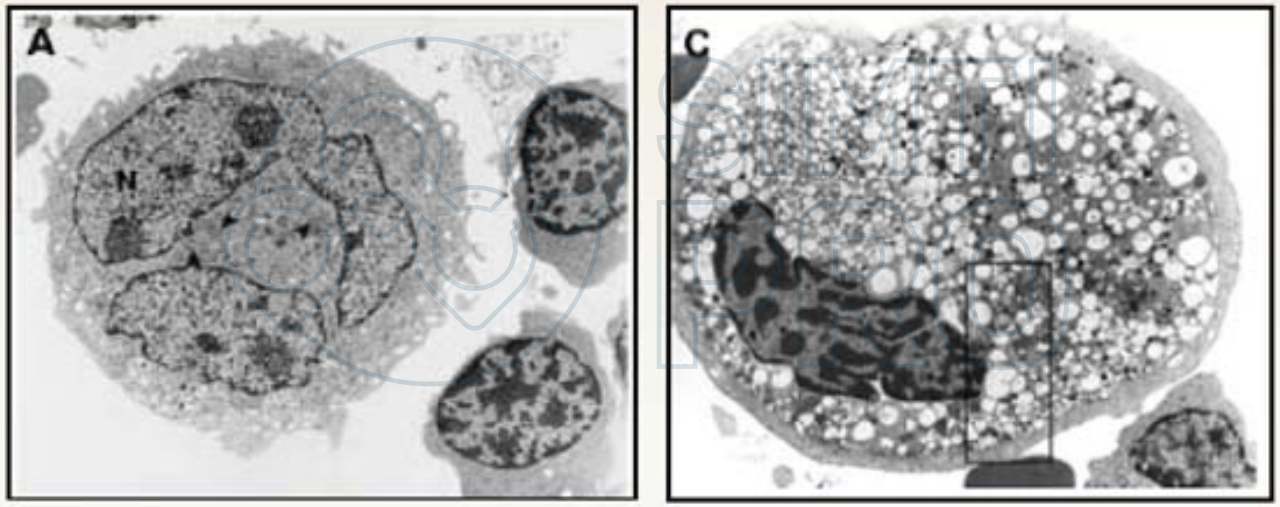


IgG, immuoglobulin G

Adapted from: McMillan R et al. *Blood* 2004;103:1364–1369

ITP autoantibodies stimulate apoptosis in megakaryocytes

Ultrastructure of normal and ITP megakaryocytes



Normal megakaryocyte

ITP megakaryocyte

Autoantibodies inhibit megakaryocyte growth in vitro and promote apoptosis resulting in impaired thrombopoiesis

Houwerzijl EJ et al. *Blood* 2004;103:500–506

ITP involves diverse autoimmune mechanisms

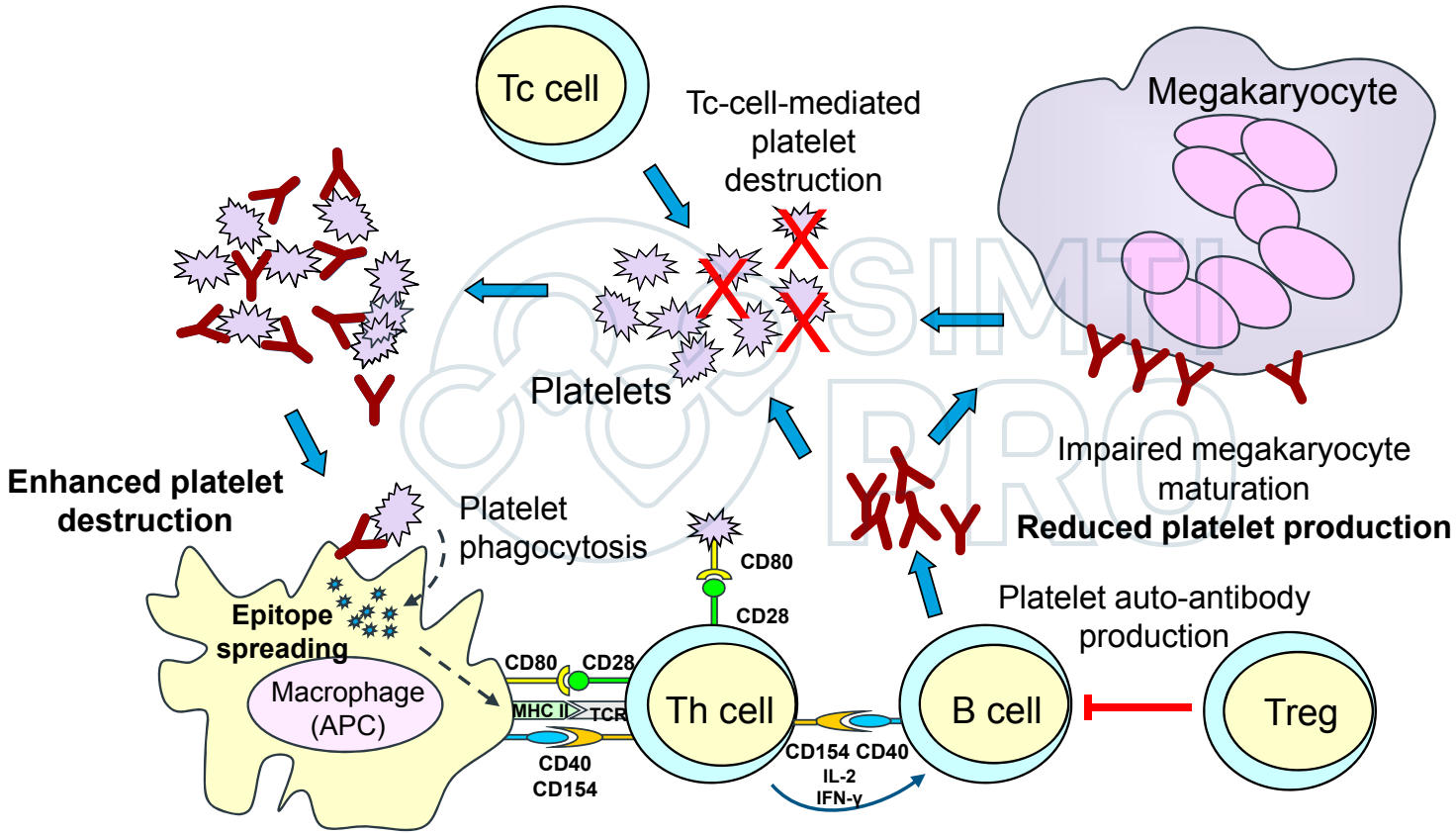
- Although the exact pathology behind ITP remains unclear, recent advances have indicated two broad routes

- Immune dysfunction may play a key role in these processes, including **B-cell abnormalities**, a **T-cell disorder**, **abnormality of thrombopoiesis**, or **increased mononuclear phagocyte activation**[1]

"Concepts… have shifted from the traditional view of increased platelet destruction mediated by auto-antibodies to more complex mechanisms where both impaired platelet production and T-cell-mediated effects play a role."[3]

1. Cooper N, *et al*. *Br J Haematol* 2006;133:364–374; 2. Gernsheimer T. *Eur J Haematol Suppl* 2008;80:3–8;
3. Provan D, *et al*. *Blood* 2010;115:168–186.

Underlying mechanisms of platelet destruction and production in ITP are complex



APC, antigen-presenting cell; CD, cluster of differentiation; IFN-γ, interferon gamma; IL, interleukin; MHC, major histocompatibility complex; TCR, t-cell receptor.

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

Immune ThrombocytoPenia: ITP

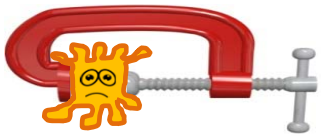
Pathogenetic mechanism

Primary event
Unknown (infections? Molecular mimicry? tissue damage? Genetic predisposition?)

Loss of self-tolerance
Mainly unknown (Treg deficit? Inflammatory cytokines production? Autoimmune mechanism)

Th1 and cytotoxic autoreactive T cells activation
Process speed up (APC potentiation? Lipopolysaccharids release?)

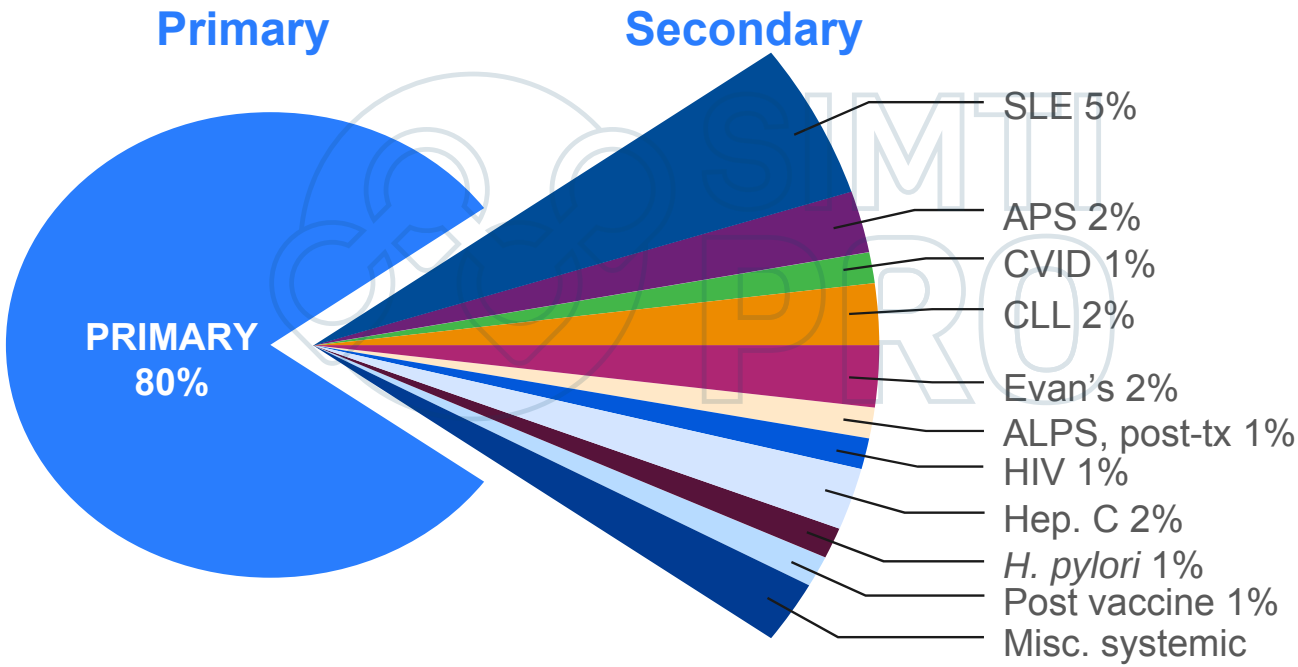
Massive IgG auto antibodies production
Process speed up (APC potentiation? Lipopolysaccharids release?)



Clinical Manifestations
Megakaryocytes inhibition and platelets distruction

Not all ITP is Primary ITP

Estimated fraction of the various forms of secondary ITP based on clinical experience

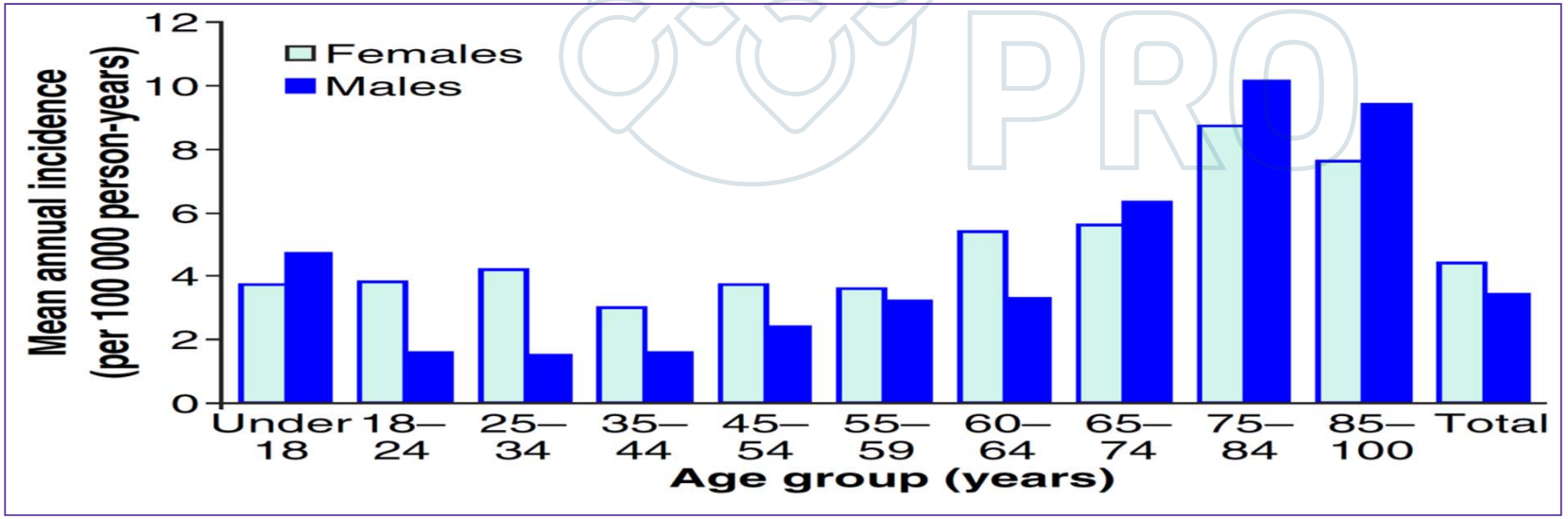


Cines DB et al. Blood 2009;113:6511–6521

ALPS, autoimmune lymphoproliferative syndrome; APS, antiphospholipid syndrome; CLL, chronic lymphocytic leukemia; CVID, common variable immune deficiency; posttx, post–bone marrow or solid organ transplantation; SLE, systemic lupus erythematosus

Incidenza della PTI

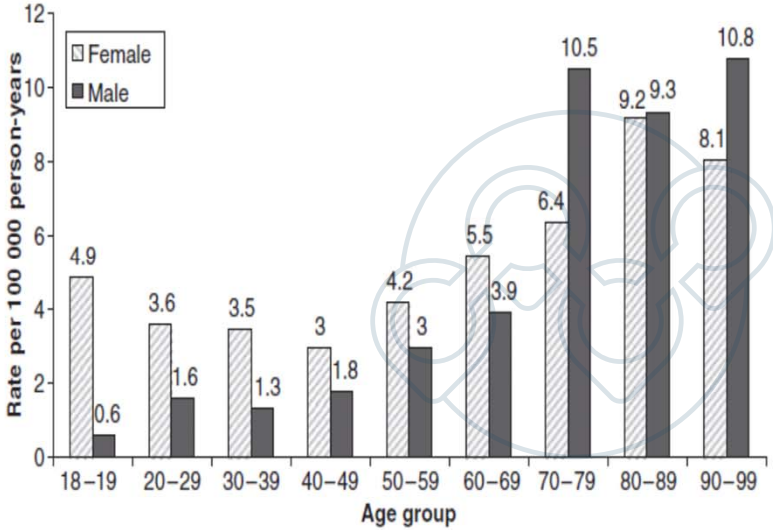
- In Europa, il numero stimato di pazienti adulti/anno con nuova diagnosi di PTI va da **1 a 4 per 100.000** persone[1]
- **L'incidenza tende ad aumentare con l'età**; con l'aumentata aspettativa di vita, anche il numero di pazienti con PTI e conseguenti comorbidità è destinato ad aumentare[1]
- In uno studio danese, il tasso di incidenza è più che raddoppiato nei pazienti di età > 60 anni rispetto ai pazienti più giovani; i risultati sono stati confermati da uno studio di coorte condotto in UK, con la più alta incidenza di PTI osservata nei pazienti > 60 anni[1]



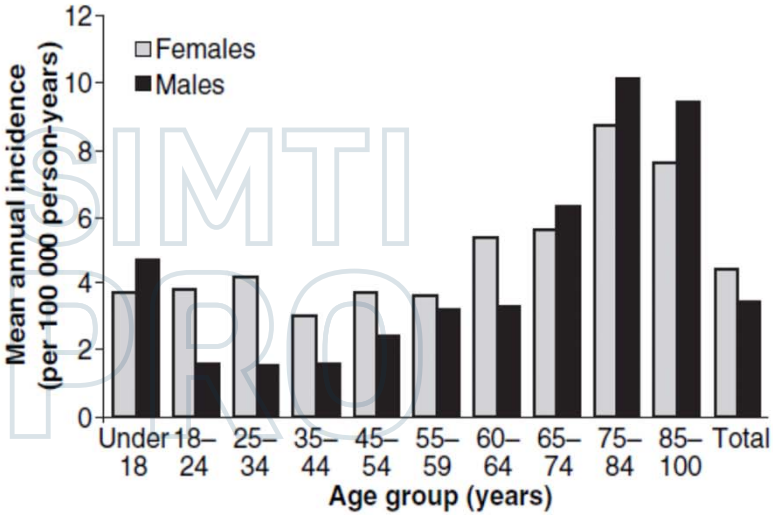
Studio UK -Distribuzione della PTI per fasce d'età: 1990-2005[2]

1. Michel M. *Eur J Haematol* 2009; 82 (suppl. 71): 3-7

2. Schoonen et al. *Br J Haematol* 2009;145; 235-244



Abrahamson et al, Eur J Hematol 2009



Schoonen et al, Br J Haematol 2009

Epidemiology

- Definition: platelets < 50 x 10^9 /L - < 100 x 10^9 /L and exclusion of other diseases causing thrombocytopenia

- Incidence:
  5 new cases / 100.000 / year (children)
  2 new cases / 100.000 / year (adults)

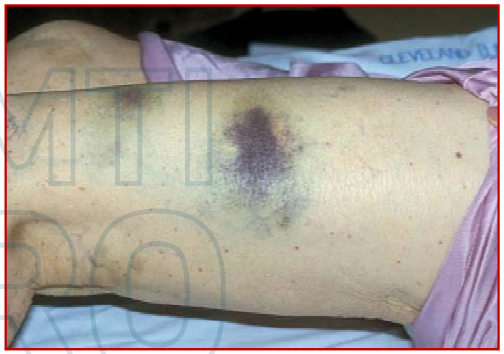
- Prevalence:
  7 cases / 100.000 (children)
  23 cases / 100.000 (adults)

Fogarty & Segal, Curr Opin Hematology 2007
Feudjo-Tiepe et al, J Thromb Haemost 2008
Abrahamson et al, Eur J Haematol 2009

Clinical Presentation of ITP

- Depending on the severity of thrombocytopenia, the clinical presentation of ITP varies[1]
  - Intracerebral hemorrhage is the most feared complication
  - Most patients are asymptomatic but may complain of fatigue and bruising easily
  - As platelet counts fall, symptoms become more severe and may include:
    - Purpuric skin lesions
    - Cutaneous bleeding
    - Epistaxis
    - Gingival or gastrointestinal bleeding
    - Hematuria or menorrhagia
  - Risk of thromboembolic events is increased, although further work will be needed to determine the cause of this observation[2]

Purpura (reddish purple spots)*



Petechiae†

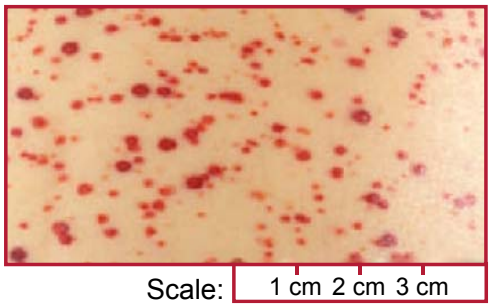


*Photo sourced from: Deitcher S. In: Armitage JO, ed. Atlas of Clinical Hematology. Philadelphia: Current Medicine, 2004;
†Image sourced from: http://www.slideserve.com/carter/supplemental-appendix-4. Accessed December 2015.
1. Cines DB, McMillan R. *Annu Rev Med* 2005;56:425–442; 2. Sarpatwari A, *et al. Haematologica* 2010;95:1167–1175.

Bleeding
Clinical Correlation - PLT Numbers

PLT Count	Spontaneous Bleed	Post Trauma Bleed
>50K/ml	*No*	*Rare*
30 – 50K/ml	*Rare*	*Occasional*
10 – 30K/ml	*Occasional*	*Always*
10K/ml	*Frequent*	*Always*

BT prolongation proportional to PLT count IF no complicating factors.

Mortality

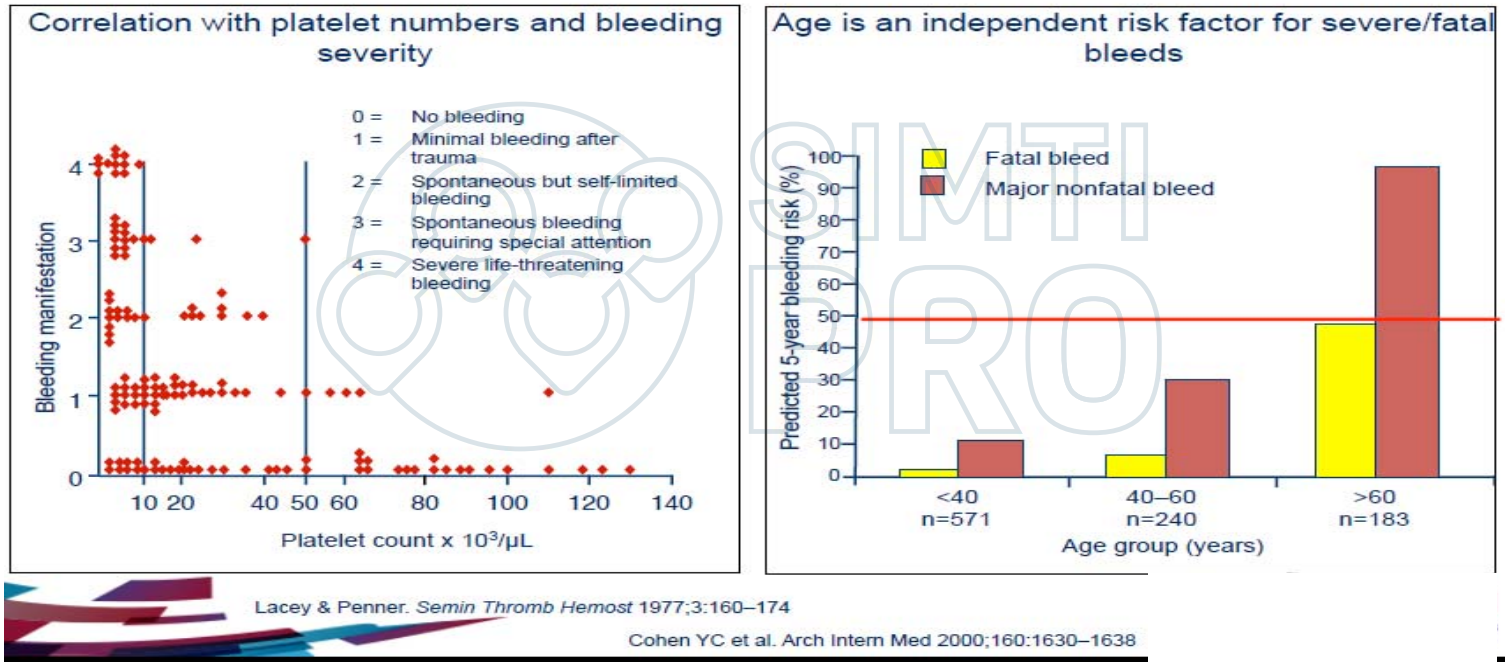
Table IV. Number of deaths among patients with incident ITP and comparison subjects.

Age group (years)	Deaths among ITP patients [N deaths/N total, (%)]	Deaths among comparison subjects [N deaths/N total, (%)]
<18	2/257 (0·8)	1/1285 (0·1)
18–64	22/534 (4·1)	45/2670 (1·7)
65–100	115/354 (32·5)	423/1747 (24·2)
Overall	139/1145 (12·1)	469/5702 (8·2)

13% of the recorded deaths were related to bleeding; the platelet count was low in 40% of them (= 5.2% of deaths)
The age- and sex-adjusted hazard ratio of death compared to age- and sex matched subjects was1.6 (95% CI: 1.3–1.9)

Schoonen et al, BJH 2009

Bleeding risk in adult patients



Courtesy of W. Barcellini

blood 1991 77: 31-33

High risk of severe bleeding in aged patients with chronic idiopathic thrombocytopenic purpura

S Cortelazzo, G Finazzi, M Buelli, A Molteni, P Viero and T Barbui

Table 2. Subgroup Analysis of the Odds of Hemorrhage in 117 Patients With ITP

Category	No. of Patients	Total Person-Years of Observation	No. of Events	Person-Time Incidence Rates	Odds Ratio	*P* Value
Age (y)						
<40	54	257	1	0.4	1.0*	—
40-60	32	177	2	1.1	2.8	NS
>60	31	67	7	10.4	28.9	<.010
Previous hemorrhagic events						
No	111	468	4	0.8	1.0*	
Yes	6	33	6	18.2	27.5	<.0005
Hypertension						
No	99	432	8	1.8	1.0*	
Yes	18	69	2	2.9	1.6	NS
Overt coexistent organic lesion						
No	96	409	7	1.7	1.0*	
Yes	21	92	3	3.3	1.9	NS

Guidelines for diagnosis of ITP

- ITP remains a **diagnosis of exclusion** of other conditions or factors that cause thrombocytopenia[1]
- **Assessment of the following is needed to diagnose ITP:**[1]
  - Patient and family history
  - Physical examination
  - Complete blood count
  - Peripheral blood film
  - Other laboratory investigations

  Results do not suggest other etiologies for thrombocytopenia[1]
- Bone marrow aspirate recommended on elderly patients only
- There is no robust clinical or laboratory test that can establish a diagnosis with accuracy[1]
- A platelet count <100 × 10^9/L has been defined as the threshold for diagnosis[2]

1. Provan D, *et al. Blood* 2010;115:168–186; 2. Rodeghiero F, *et al. Blood* 2009;113:2386–2393.

Williams – Hematology
Classification of thrombocytopenia I

CLASSIFICATION OF THROMBOCYTOPENIA

- Pseudo-thrombocytopenia
  - Platelet agglutination
  - Platelet satellitism
  - Antiphospholipid antibodies
  - GpIIa-IIIa antagonists
  - Giant platelets
  - Miscellaneous associations
- Impaired platelet production
  - Congenital
    - Autosomal dominant
      - MYH9-related
        - May-Hegglin anomaly
        - Fechtner syndrome
        - Epstein syndrome
        - Sebastian syndrome
      - Mediterranean macrothrombocytopenia
      - Familial platelet syndrome with predisposition to acute myelogenous leukemia
      - Thrombocytopenia with linkage to chromosome 10
      - Paris-Trousseau syndrome
      - Thrombocytopenia with radial synostosis
    - Autosomal recessive
      - Congenital amegakaryocytic thrombocytopenia
      - Thrombocytopenia with absent radius (TAR) syndrome
      - Bernard-Soulier syndrome (see Chap. 112)
      - Gray platelet syndrome (see Chap. 112)
    - X-linked thrombocytopenias
      - Wiskott-Aldrich syndrome
      - X-linked thrombocytopenia
      - X-linked thrombocytopenia with dyserythrocytosis

Williams – Hematology
Classification of thrombocytopenia I

- Acquired
  - Marrow infiltration (see Chap. 42)
  - Infectious disease
    - HIV (see Chap. 83)
    - Parvovirus (see Chap. 34)
    - Cytomegalovirus (see Chap. 34)
    - Others
  - Radiotherapy and chemotherapy (see Chap. 19)
  - Folic acid and vitamin B_{12} deficiency (see Chap. 39)
  - Paroxysmal nocturnal hemoglobinuria (see Chap. 38)
  - Acquired aplastic anemia (see Chap. 33)
  - Myelodysplastic syndromes (see Chap. 86)
  - Acquired pure megakaryocytic thrombocytopenia
- Accelerated platelet destruction
  - Immune-mediated thrombocytopenia
    - Autoimmune thrombocytopenic purpura
      - Idiopathic
      - Secondary (infections, pregnancy-related, lymphoproliferative disorders, collagen vascular diseases)
    - Alloimmune thrombocytopenia
      - Neonatal thrombocytopenia
      - Posttransfusion purpura
  - Nonimmune thrombocytopenia
    - Thrombotic microangiopathies
      - Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome
      - Disseminated intravascular coagulopathy
      - Kasabach-Merritt syndrome
    - Platelet destruction by artificial surfaces
    - Hemophagocytosis
- Abnormal platelet distribution or pooling
  - Splenomegaly (see Chap. 55)
  - Hypersplenism (see Chap. 55)
  - Hypothermia
  - Massive transfusion
- Drug-induced thrombocytopenia
  - Heparin-induced thrombocytopenia (HIT) (see Chap. 124)
  - Other drug-induced thrombocytopenias

Table 1. Recommendations for the diagnosis of ITP in children and adults (See appendix II)

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

**Quantitative immunoglobulin level measurement should be considered in children with ITP and is recommended in those children with persistent or chronic ITP as part of reassessment evaluation*

***Recommended by the majority of the panel for adult patients regardless of geographic locale*

Rh, rhesus; *H. pylori*, *Helicobacter pylori*; HIV, human immunodeficiency virus; HCV, hepatitis C virus; PCR, polymerase chain reaction; CMV, cytomegalovirus; TPO, thrombopoietin; PalgG, platelet associated immunoglobulin G

Blood 115: 168; 2010

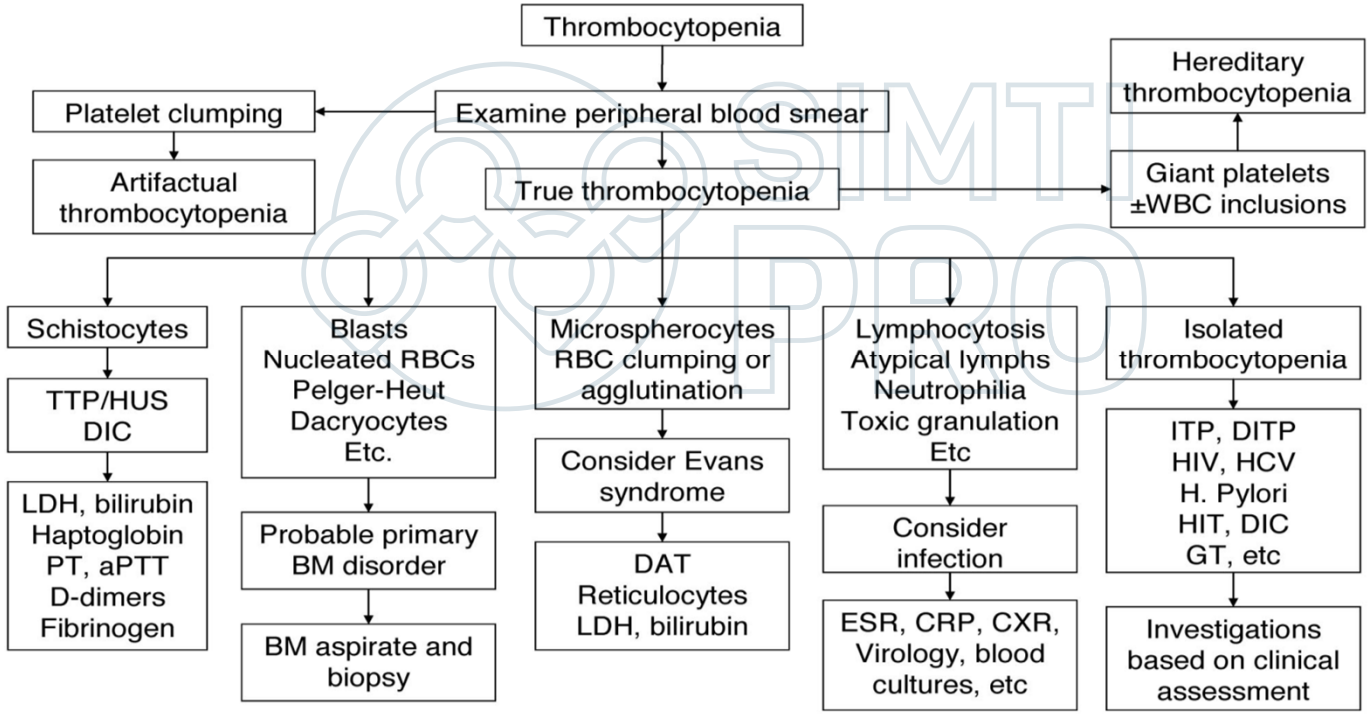
How to approach thrombocytopenia

Roberto Stasi[1]

[1]*Department of Haematology, St Georges Hospital, London, United Kingdom*

Thrombocytopenia is a common hematologic finding with variable clinical expression. A low platelet count may be the initial manifestation of infections such as HIV and hepatitis C virus or it may reflect the activity of life-threatening disorders such as the thrombotic microangiopathies. A correct identification of the causes of thrombocytopenia is crucial for the appropriate management of these patients. In this review, we present a systematic evaluation of adults with thrombocytopenia. The approach is clearly different between outpatients, who are frequently asymptomatic and in whom we can sometimes indulge in sophisticated and relatively lengthy investigations, and the dramatic presentation of acute thrombocytopenia in the emergency department or in the intensive care unit, which requires immediate intervention and for which only a few diagnostic tests are available. A brief discussion of the most common etiologies seen in both settings is provided.

Algorithm for workup of thrombocytopenia based on observation of the peripheral blood film



Hematology 2012

The decision to treat and to manage ITP [1,2]

Presence of active bleeding

Platelet count In patients with platelet counts > 30 × 10^9/L, treatment is not usually indicated unless the patient has other risk factors (e.g. bleeding or surgery)[3]

Patient age

Patient lifestyle and activity – related to risk of bleeding

Presence of additional risk factors for bleeding (e.g. uremia, chronic liver diseases)

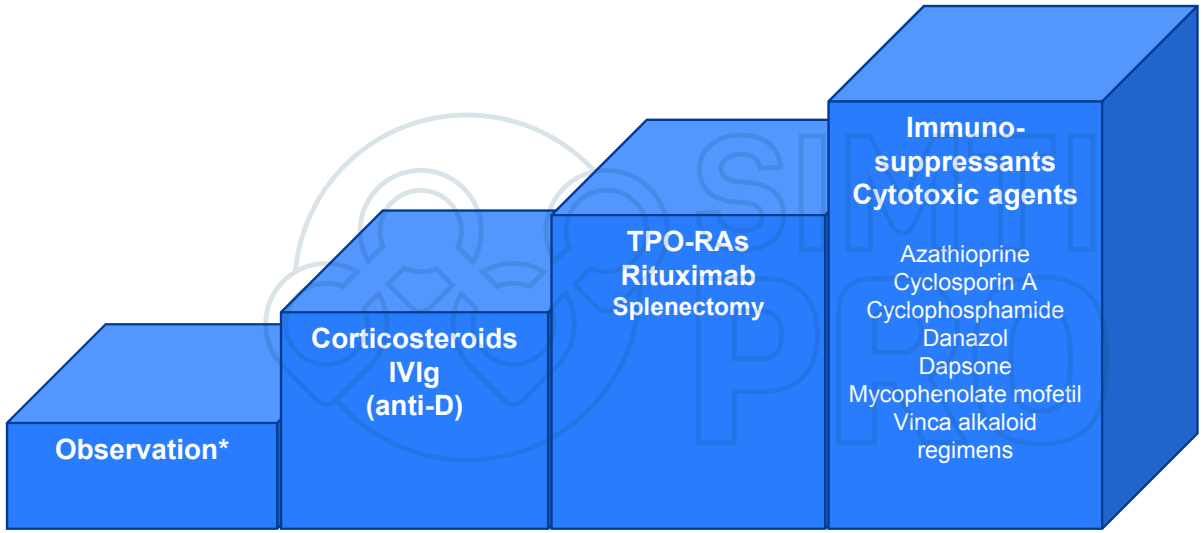
Predictable AEs of the offered treatment

Patient preferences (accessibility, expectations, tolerance, concerns)

Treatment should always be tailored to the individual patient[1,3]

1. Stasi R, Provan D. *Mayo Clin Proc* 2004;79:504–522; 2. Provan D, *et al. Blood* 2010;115:168–186;
3. Matzdorff A, *et al. Semin Hematol* 2013;50(Suppl 1):S12–S17. 3. Provan D, *et al. Blood* 2010;115:168–186.

Staircase model of ITP treatment



*Children and patients with relatively high platelet counts.
IVIg, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist.
Arnold DM, Kelton JG. *Semin Hematol* 2007;44(Suppl 5):S12–S23; Provan D, *et al. Blood* 2010;115:168–186; Neunert C, *et al. Blood* 2011;117:4190–4207.

blood

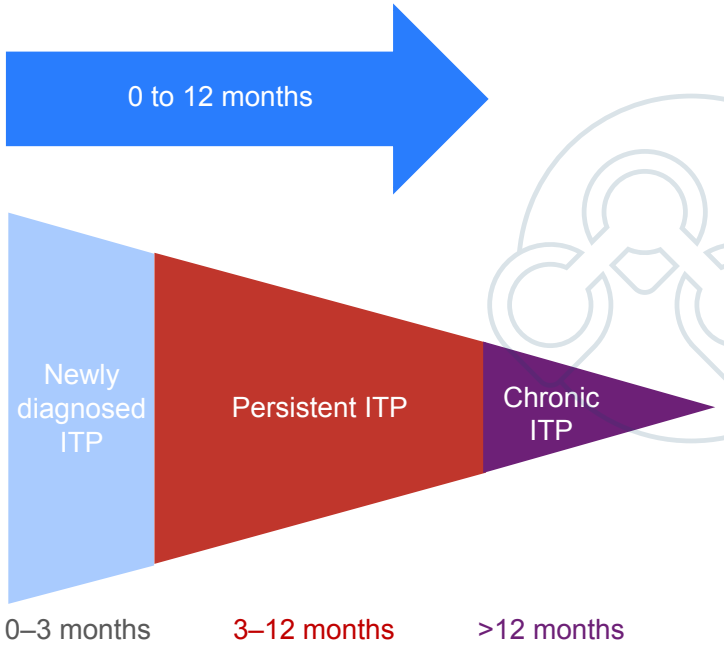
2009 113: 2386-2393
Prepublished online Nov 12, 2008;
doi:10.1182/blood-2008-07-162503

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

ITP terminology, duration and classification

Possibility of spontaneous remission:



Terminology	Definition
ITP	Immune thrombocytopenia (rather than idiopathic or immune thrombocytopenic purpura)
Platelet threshold for ITP diagnosis	$<100 \times 10^9$/L
Primary ITP	ITP with no associated cause (diagnosis of exclusion)
Secondary ITP	ITP in the setting of an underlying cause such as drugs, HIV, or SLE
Newly diagnosed ITP	Designation for patients at diagnosis (rather than "acute" ITP).
Persistent ITP	Sustained or recurrent thrombocytopenia lasting 3-12 months
Chronic ITP	Thrombocytopenia lasting >12 months
Complete response	Achievement of a platelet count of $\geq 100 \times 10^9$/L in the absence of bleeding
Response	Achievement of a platelet count of $\geq 30 \times 10^9$/L and at least a twofold increase from baseline in the absence of bleeding
Refractory ITP	Failure to achieve a response or relapse after splenectomy* and requirement for treatment(s) to minimize the risk of clinically significant bleeding.

Rodeghiero F, *et al. Blood* 2009;113:2386–2393; Vicenza Consensus Conference, 2009.

What is primary ITP

- Definition:
  - autoimmune disorder
  - isolated thrombocytopenia – platelet count $<100 \times 10^9/L$
  - absence of other causes or disorders
- Diagnosis:
  - one of exclusion
  - no robust clinical or laboratory parameters establish diagnosis with accuracy
- Main clinical problem:
  - increased risk of bleeding
  - bleeding symptoms not always present

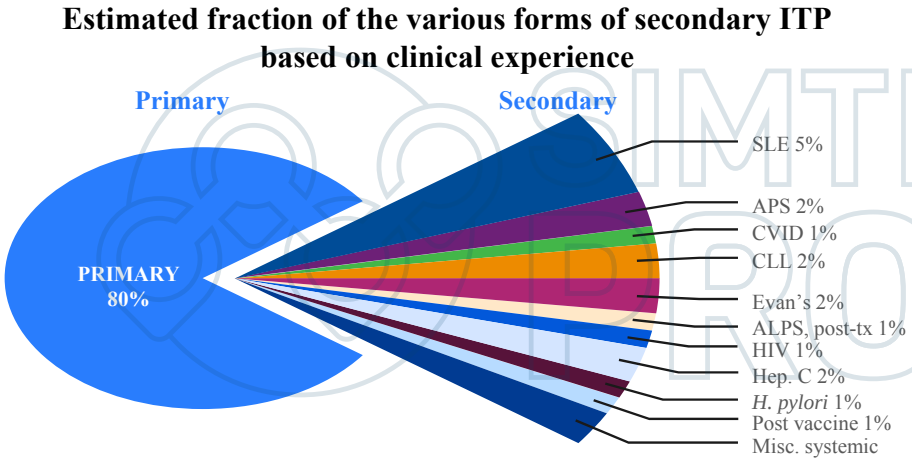
- **Secondary immune thrombocytopenia:**
  - all forms of immune-mediated thrombocytopenia, except primary ITP

Secondary ITP	All forms of immune-mediated thrombocytopenia except primary ITP*

*The acronym ITP should be followed by the name of the associated disease (for thrombocytopenia after exposure to drugs, the terms "drug-induced" should be used) in parentheses: for example, "secondary ITP (lupus-associated)," "secondary ITP (HIV-associated)," and "secondary ITP (drug-induced)." For manuscript titles, abstracts, and so on, definitions such as lupus-associated ITP or HIV-associated ITP can also be used.

Blood 2009; 113: 2386

Not all ITP is Primary ITP



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

ALPS, autoimmune lymphoproliferative syndrome; APS, antiphospholipid syndrome; CLL, chronic lymphocytic leukemia; CVID, common variable immune deficiency; posttx, post–bone marrow or solid organ transplantation; SLE, systemic lupus erythematosus

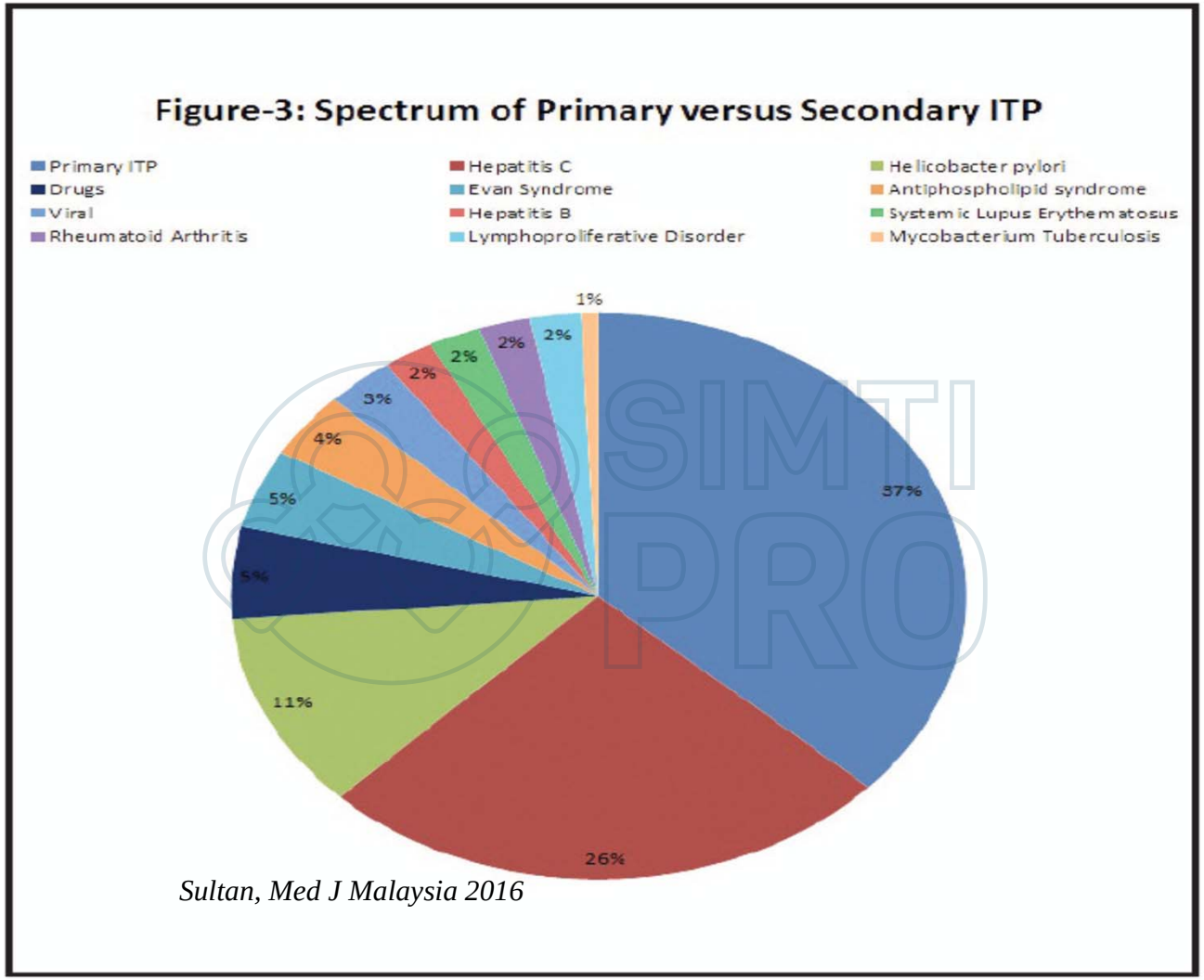


Fig. 3: Spectrum of primary versus secondary ITP.

Table 1 Primary and secondary ITP at hospital discharge

	N	(%)
Primary ITP	68	(86.1)
Secondary ITP	11	(13.9)
Infective diseases		
HIV infection	3	
Immune diseases		
Rheumatoid arthritis	1	
Systemic lupus erythematosus	1	
Lymphoproliferative disorders		
Non-Hodgkin's lymphoma	2	
Waldenstrom's macroglobulinaemia	1	
Castleman's disease	1	
Chronic liver diseases		
Primary biliary liver cirrhosis	1[a]	
Posthepatitis liver cirrhosis	1[b]	
Total	79	(100)

[a] Complicated by cytomegalovirus (CMV) infection. [b] Associated with the presence of HBs antigen and anti-δ, anti-HCV, and anti-HIV antibodies.

Cirasino et al, Blood Coag Fibrin 2011

Table 2 Primary and secondary ITP after data review

	N			(%)
Primary ITP	49			(62)
Isolated ITP		41		
ITP associated with noncausative conditions:		8		
H. pylori infection without prolonged CR of ITP after *H. pylori* eradication			4	
Lymphoproliferative conditions in verified CR without BM and/or PBSCT			1	
Nonhaematological cancers			3	
Secondary ITP and/or ITP associated with conditions with a possible causative role:	30			(38)
Infections:		14		
H. pylori infection with prolonged CR of ITP induced by *H. pylori* eradication			1[a]	
HIV infection			4	
Isolated				1
Associated with HCV infections, independently by the presence or not of chronic liver disease				3
HCV infection			7	
Isolated and without evidence of chronic liver disease				3
Associated with chronic liver disease (chronic hepatitis and/or liver cirrhosis) but not with HIV infection (see above for the last condition)				4
Other infections non associated with other putative conditions:			2	
Cytomegalovirus infection				1[a]
Epstein–Barr virus infection				1[a]
Herpes simplex genitalis				0[b]
Immune diseases:		7		
IgA selective defect			1	
Antiphospholipid syndrome			2[a]	
Primary Evans' syndrome			1[c]	
Rheumatoid arthritis			1	
System lupus erythematosus			1	
Primary biliary cirrhosis			1	
Post-transplantation		5		
After allogeneic BMT for acute myeloid leukaemia				2
After autologous BMT for Hodgkin's lymphoma				2
After liver transplantation for HBV and HDV associated liver cirrhosis				1
Lymphoproliferative diseases:		4		
Non-Hodgkin's lymphoma			2	
Castleman's disease			1	
Waldenstrom's macroglobulinaemia			1	
Total ITP	79			(100)

BM, bone marrow; BMT, bone marrow transplantation; CR, complete remission; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; NHL, non-Hodgkin's lymphoma; PBSCT, peripheral stem cell transplantation. [a] Recognized during the follow-up. [b] Herpes simplex genitalis was present in one case of ITP which occurred in an allogeneic BMT for AML. [c] Two cases of secondary Evans' syndrome were, respectively, observed in a patient with primary biliary cirrhosis associated with cytomegalovirus infection and in a patient with Castleman's disease. The patient who was considered to have a primary Evans' syndrome also had a T-cell receptor (TCR)-gamma rearrangement without evidence of lymphoma. At data review we included this case in the secondary forms of ITP according to the classification of secondary ITP proposed by Cines *et al.* [8].

Cirasino et al, Blood Coag Fibrin 2011

Table 1. Demographic and Clinical Characteristics of Patients With Primary or Secondary Immune Thrombocytopenic Purpura.

	Immune Thrombocytopenia Purpura			
	Primary ($n = 38$)	Secondary ($n = 29$)	Total ($N = 67$)	*P* Value
Gender				.503
Female	26 (68.4)	22 (75.9)	48 (71.6)	
Male	12 (31.6)	7 (24.1)	19 (28.4)	
Age (years)				.027
<30	24 (63.2)	10 (35.7)	34 (51.5)	
≥30	14 (36.8)	18 (64.3)	32 (48.5)	
Initial platelet count				<.005
0-10 × 10^9/L	28 (73.7)	3 (10.3)	31 (46.3)	
11-30 × 10^9/L	10 (26.3)	6 (20.7)	16 (23.9)	
>30 × 10^9/L	0	20 (69.0)	20 (29.9)	
Splenectomy				.039
No	26 (68.4)	26 (89.7)	52 (77.6)	
Yes	12 (31.6)	3 (10.3)	15 (22.4)	
Purpura				<.005
No	5 (13.2)	25 (86.2)	30 (44.8)	
Yes	33 (86.8)	4 (13.8)	37 (55.2)	
Response to treatment (steroids)				<.005
No	0	23 (79.3)	23 (34.3)	
Yes	38 (100.0)	6 (20.7)	44 (65.7)	
Antinuclear antibody				<.005
Negative	36 (94.7)	17 (58.6)	53 (79.1)	
Positive	2 (5.3)	12 (41.4)	14 (20.9)	

Ayesh et al, Clin Applied Thromb Hemostas 2013

Table I: Clinical manifestations of primary versus secondary ITP

Parameters	Primary ITP n= 147	Secondary ITP n= 270	P- value
Mean age	37.5±14.8	42.8±14.5	0.04
Male; female	1.5 : 2	2: 3	-
Asymptomatic	38.8%	65.6%	0.004
Symptomatic	61.2%	34.4%	0.004
Dry purpura	57.1%	26.7%	0.001
Wet purpura	49.0%	25.6%	0.008
Epistaxis	40.8%	13.3%	0.001
Gum bleeding	32.7%	11.1%	0.003
Bruises	6.1%	2.2%	0.3*
Mennorhagia	6.1%	5.6%	1.0*
Hematuria	4.0%	2.2%	0.6*
Melena	2.0%	2.2%	1.0*

Table II: Laboratory attributes of primary versus secondary ITP

Parameters	Primary ITP n= 147 Mean±SD	Secondary ITP N= 270 Mean±SD	P- value
Hemoglobin (gm/dl)	12.2± 1.4	11.3 ±1.8	0.01
Hematocrit (%)	38.2±1.7	30.5±2.3	0.001
TLC (10^9/l)	8.3 ± 2.8	6.6± 2.8	0.002
Platelets (10^9/l)	31.5±21.9	54.1± 26.9	0.000
MPV (fl)	12.8±1.4	9.6±0.9	0.001
MCV (fl)	83.1± 8.7 fl	86.6 ±8.9 fl	0.06 *

Sultan, Med J Malaysia 2016

Table 5

Immunological characteristics in AIF-ITP and pITP patients.

	AIF-ITP	pITP	*P*
Subjects, n	31	12	
PAIG	18/26 (69.20%)	7/10 (70.00%)	1.097
ANA	22/31 (71.00%)	0/12 (0.00%)	0.000*
Ds-DNA	1/31 (3.20%)	0/12 (0.00%)	1.063
SSA	13/31 (41.90%)	0/12 (0.00%)	0.091
SSB	2/31 (6.50%)	0/12 (0.00%)	1.030
Ro-52	9/31 (29.00%)	0/12 (0.00%)	0.374
RNP	3/31 (9.70%)	0/12 (0.00%)	1.165
ACA	6/31 (22.20%)	0/12 (0.00%)	1.047
β2-GP1	6/31 (22.20%)	0/12 (0.00%)	0.873
Low C3	20/31 (64.50%)	1/12 (8.30%)	0.034*
Low C4	1/31 (3.20%)	0/12 (0.00%)	1.000
IgG	14.49 ± 0.83	13.89 ± 1.07	1.292
IgA	2.11 ± 0.15	2.01 ± 0.24	1.313
IgM	1.19 ± 0.12	1.20 ± 0.18	1.303
CRP	4.30 ± 1.18	8.99 ± 5.54	1.114

Data are presented as mean ± s.d. or n (%), *P*, comparison of AIF-ITP with pITP.
β2-GP1 = β2-glycoprotein 1, ACA = anticardiolipin antibodies, AIF = autoimmune featured, ANA = antinuclear antibodies, CRP = C reactive protein, pITP = primary immune thrombocytopenia.
* $P < 0.05$.

Table 1 Causes of Secondary Immune Thrombocytopenia[8–10]			
Autoimmune Disorders	**Infections**	**Drugs**	**Vaccinations**
• Systemic lupus erythematosus • Antiphospholipid syndrome	• Human immuno-deficiency virus • Hepatitis C virus • *Helicobacter pylori*	• Heparin • Penicillin • Nonsteroidal anti-inflammatory drugs	• Measles • Mumps • Rubella • Varicella

Khan et al, PT 2017

blood 1996 88: 3-40

Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology [see comments]

JN George, SH Woolf, GE Raskob, JS Wasser, LM Aledort, PJ Ballem, VS Blanchette, JB Bussel, DB Cines, JG Kelton, AE Lichtin, R McMillan, JA Okerbloom, DH Regan and I Warrier

New International ITP consensus

blood

Prepublished online Oct 21, 2009;
doi:10.1182/blood-2009-06-225565

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

Blood 115:168;2010

- 22 international ITP experts as authours
  - Diagnosis of ITP
  - Management of adult ITP
  - ITP in pregnancy
  - ITP in childhood

blood

Prepublished online Feb 16, 2011;
doi:10.1182/blood-2010-08-302984

Clinical guideline update on "Immune thrombocytopenia: an evidence based practice guideline developed by the American Society of Hematology"

Cindy Neunert, Wendy Lim, Mark Crowther, Alan Cohen, Lawrence Solberg, Jr. and Mark Crowther

Evaluation of Patient with Low Platelets

- History
  - Has the patient ever had a normal platelet count?
  - Carefully review medications, including OTC meds.
    - Antibiotics, quinine, anti-seizure medications
  - Ask about other conditions which may be associated with low platelets
    - Liver Disease/hepatitis
    - Thyroid Disease - both hypo- and hyper-
    - Infections: viral, rickettsial
    - Pregnancy
  - Ask about other conditions which may be associated with ITP
    - Lupus, CLL, lymphoma

Evaluation of Patient with Low Platelets

- Physical
  - Evaluate for lymphadenopathy and splenomegaly
  - Look for stigmata of bleeding
  - Blood blisters and oral petechiae, ie “Wet Purpura”
    - best harbinger of intracranial hemorrhage
- Laboratory Data
  - Other blood counts should be normal.
  - Check B12 and folate levels.
  - Look at peripheral smear to exclude pseudothrombocytopenia, also exclude TTP (especially if anemia also present.)
  - Send coagulation screens (PT/PTT) to exclude DIC
  - Send HIV, hepatitis serologies and TSH
- Consider doing a bone marrow biopsy
  - Megakaryocytes should be present.

Immune ThrombocytoPenia: ITP

Disease Severity (before)

- Mild
- Moderate
- Severe

Severe ITP (now)

Presence of bleeding symptoms at presentation sufficient to mandate treatment, or occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose

Platelets Count

Clinical Manifestations

Description of bleeding symptoms and signs of hemorrhages.

(is a very complex topic which requires a lot of time …. we fortunately don't have!)

- None of the few bleeding assessment tools available in the literature could be easily adopted and/or were validated for ITP.
- Terms such as "mild" or "moderate" ITP were discouraged because their vagueness.
- The IWG concluded that a new system based on the consensus of clinicians who are experts in adult and pediatric ITP should be proposed

To have a <u>single tool for both children and adults</u>

- to standardize description of the hemorrhages at presentation and during the different phases,
- to assess the overall impact of treatments,
- to correlate with QoL, platelet count, age, gender, etc.
- to be used in research studies.

blood®
2013 121: 2596-2606
doi:10.1182/blood-2012-07-442392 originally published online January 29, 2013

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

Francesco Rodeghiero, Marc Michel, Terry Gernsheimer, Marco Ruggeri, Victor Blanchette, James B. Bussel, Douglas B. Cines, Nichola Cooper, Bertrand Godeau, Andreas Greinacher, Paul Imbach, Mehdi Khellaf, Robert J. Klaassen, Thomas Kühne, Howard Liebman, Maria Gabriella Mazzucconi, Adrian Newland, Ingrid Pabinger, Alberto Tosetto and Roberto Stasi

- **Skin**

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Petechiae (does not include steroid–induced or senile purpura)	☐ No	☐ Less than or equal to 10 in a patient's palm-sized area in the most affected body area ☐ Any number if reported by the patient	☐ More than 10 in a patient's palm-sized area or more than 5 in at least 2 patient's palm-sized areas located in at least 2 different body areas, one above and one below the belt (in the most affected body areas)	☐ More than 50, if scattered both above and below the belt	

- **Mucosal**

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Epistaxis*	☐ No	☐ Lasting < 5 min ☐ Any episode if reported by the patient	☐ Lasting > 5 min or interfering with daily activities	☐ Packing or cauterization or in-hospital evaluation at the time of this visit ☐ Medical report describing packing or cauterization or in-hospital evaluation	☐ RBC transfusion or Hb drop > 2g/dL

- **Organ**

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Hematuria	☐ No	☐ Any episode if reported by the patient ☐ Microscopic (lab analysis)	☐ Macroscopic ☐ Described in a medical report	☐ Macroscopic, and requiring cystoscopy or other therapeutic procedures or in-hospital evaluation at the time of this visit ☐ An equivalent episode if described in a medical report	☐ RBC transfusion or Hb drop > 2g/dL

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HARMONIZATION OF TERMINOLOGY AND DEFINITIONS OF BLEEDING IN ITP

The term **"severe" ITP** should be used only in patients who have **"clinically relevant bleeding"**
The ability to maintain a platelet count sufficient to prevent **"clinically significant bleeding"** could be considered as response to treatment in refractory ITP.

Bleeding manifestation can generally be labeled <u>"severe or clinically relevant"</u> if:

- grade 3 for skin and/or
- grade 2 or higher for mucosal domains and/or
- higher than grade 1 for organ domain
  (S >2 and/or M >1 and/or O >1).

Immune ThrombocytoPenia: ITP

Initial treatment: When?

Children

- Generally only if severe hemorrhage is present
- Case-by-case assessment

Adults

- Confirmed platelet count < 20-30 $x10^9/L$
- Significant hemorrhage with any platelets count

Immune ThrombocytoPenia: ITP

Initial treatment: What to do?

Treatment targets

- Resolution and/or prevention of hemorrhagic manifestations
- Rapid platelets number increase
- Complete response or stable clinical response
- Postpone splenectomy
- QOL improvement

- Temporary platelets number increase

Evidence-based management of immune thrombocytopenia: ASH guideline update

Cindy E. Neunert[1] and Nichola Cooper[2]

[1]Department of Pediatrics, Columbia University Medical Center, New York, NY; and [2]Imperial College Health Care NHS Trust, Hammersmith Hospital, London, UK

In 1996 and 2011, the American Society of Hematology (ASH) supported efforts to create guidelines for the diagnosis and management of patients with immune thrombocytopenia (ITP). These guidelines used different approaches to arrive at recommendations for testing and treatment. Despite differences in methodology, in both cases there was a paucity of randomized trials to inform recommendations. As data on the diagnosis and management of ITP expands, the ASH Committee on Quality is dedicated to maintaining updated guidelines representing recent evidence and guideline methodology. Here, we will review the updated ASH guidelines on ITP with a focus on recommendations with new understanding and future research to close knowledge gaps.

Hematology 2018

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] and David J. Kuter[21]

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Table 3. Recommendations for the diagnosis of ITP in children and adults

Basic evaluation in all patients	Tests of potential utility in the management of an ITP patient	Tests of unproven or uncertain benefit*
Patient history	Glycoprotein-specific antibody (can be used in difficult cases, has poor sensitivity, and is not a primary diagnostic test)	TPO level
Family history	Anti-phospholipid antibodies (including anti-cardiolipin and lupus anticoagulant) if there are clinical features of antiphospholipid syndrome	Reticulated platelets/immature platelet fraction
Physical examination	Anti-thyroid antibodies and thyroid function	
CBC and reticulocyte count	Pregnancy test in women of childbearing potential	Bleeding time
Peripheral blood film	Antinuclear antibodies	Serum complement
Quantitative Ig level measurement†	Viral PCR for EBV, CMV, and parvovirus	
Blood group (Rh)	Bone marrow examination (in selected patients; refer to text)	
HIV‡	Direct antiglobulin test	
HCV‡	*H pylori*‡	
HBV		

CMV, cytomegalovirus; EBV, Epstein-Barr virus; PCR, polymerase chain reaction; PTT, partial thromboplastin time; Rh, rhesus; TPO, thrombopoietin.
*These tests have no proven role in the differential diagnosis of ITP from other thrombocytopenias and do not guide patient management.
†Quantitative Ig level measurement should be considered in children with ITP and is recommended in children with persistent or chronic ITP as part of the reassessment evaluation.
‡Recommended by the majority of the panel for adult patients in the appropriate geographic setting.