Thrombotic Microangiopathies
&
Immune Thrombocytopenic Purpura

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Clinica Luganese Moncucco / MC
CH - 25.09.2024

Thrombotic Microangiopathies (TMA)

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Thrombotic microangiopathies (TMAs)

- **Widespread ischemic damage**

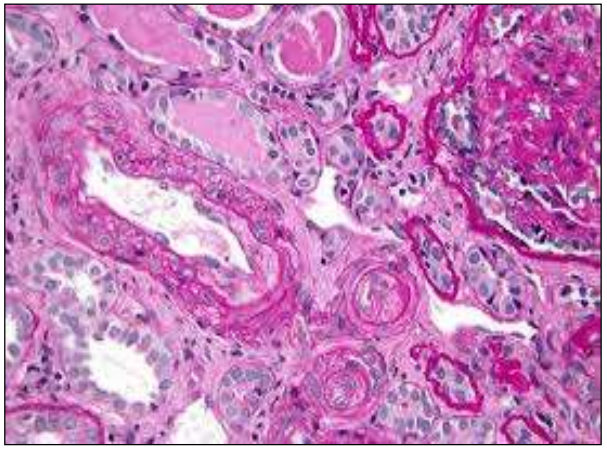
  (due to microthrombosis in arterioles)

- **Thrombocytopenia**

  (due to platelet trapping)

- **Microangiopathic hemolytic anemia**

  (due to red blood cell fragmentation)

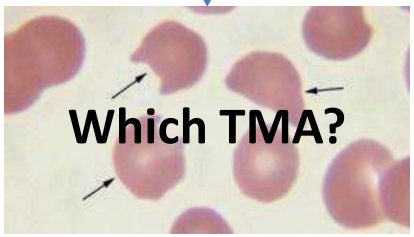


George JN, Blood 2010

From TMA suspicion to differential diagnosis…

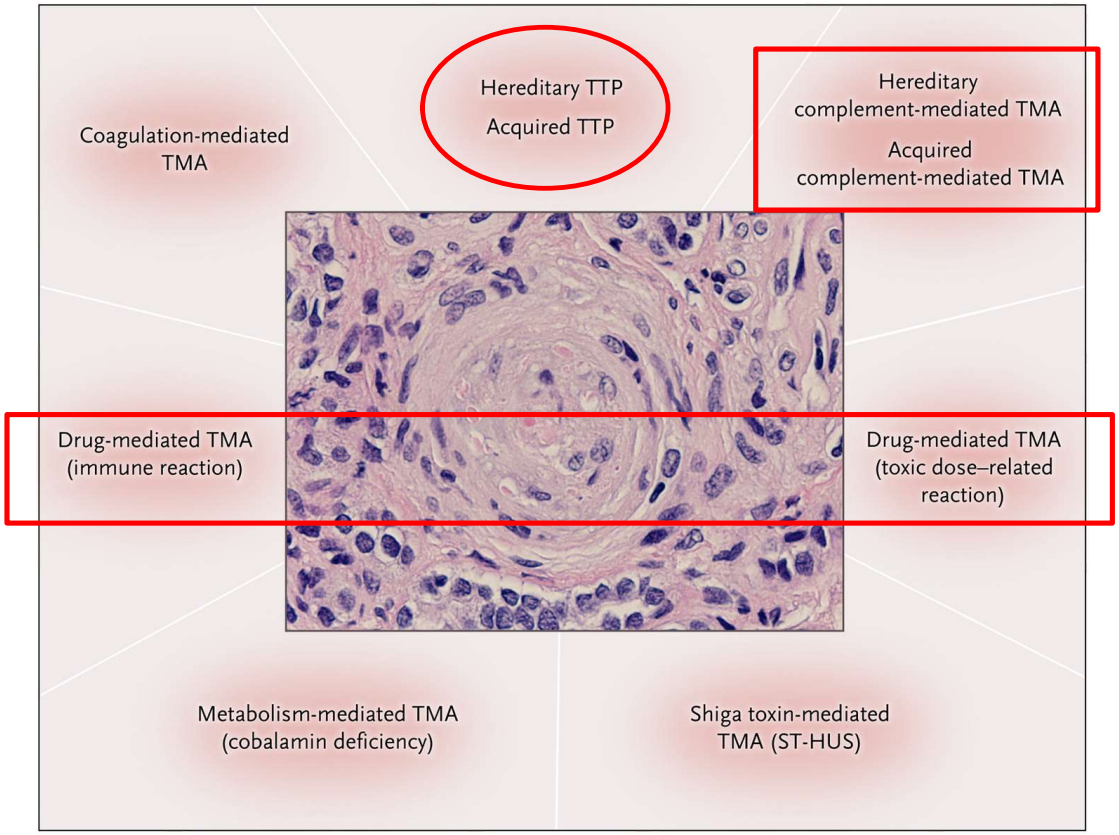
ANEMIA
+
LOW PLATELETS

- MCV normal / ↑
- ↑ Reticulocytes
- **↑ LDH**
- ↑ bilirubin (indirect)
- ↓ haptoglobin
- COOMBS TEST: **negative**
- Peripheral blood smear: **schistocytes > 1%**



TMAs: one term, many diseases

Represent the final common pathway
of a multitude of clinical syndromes:



George JN, NEJM 2014

Thrombotic Thrombocytopenic Purpura (TTP)

- Clinical features: “PENTAD”
- Thrombocytopenia
- Microangiopathic hemolytic anemia
- Neurological signs
- Renal impairment
- Fever

Thrombocytopenia	Epistaxis, bruising, petechiae, gingival bleeding, haematuria, menorrhagia, gastrointestinal bleeding, retinal haemorrhage and haemoptysis
Central neurological – often flitting and variable 70–80%	Confusion, headache, paresis, aphasia, dysarthria, visual problems, encephalopathy, coma (10%)
Fever (>37·5°C)	
Non-specific symptoms	Pallor, jaundice, fatigue, arthralgia or myalgia
Jaundice	Resulting from microangiopathic haemolytic anaemia
Renal Impairment	Proteinuria, microhaematuria
Cardiac	Chest pain, heart failure, hypotension
Gastro-intestinal tract	Abdominal pain

Scully, BJH 2012

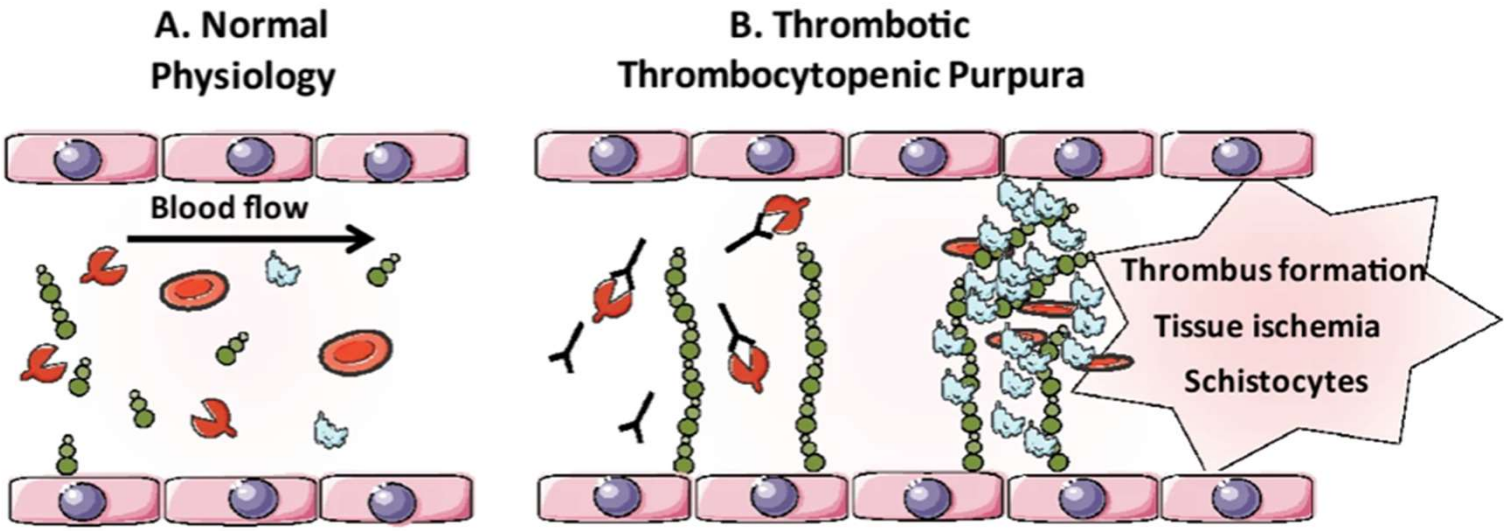
TTP epidemiology

- Rare: 5-11 cases / million people / year
- M:F ratio 1:3
- Peak of incidence: III-IV decades
- Mortality reduced from 90% to 10-20% with appropriate therapy
- Risk of recurrence: 30-35% (acquired form)

Peyvandi, Haematologica 2010

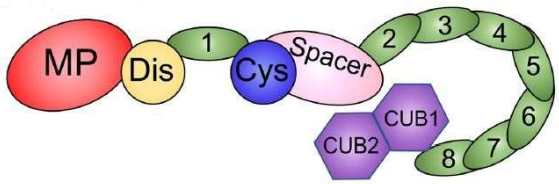
TTP pathophysiology

- **ADAMTS13 deficiency** - *A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13*



Azoulai E. et al , Intensive Care Medicine, 2019

ADAMTS13

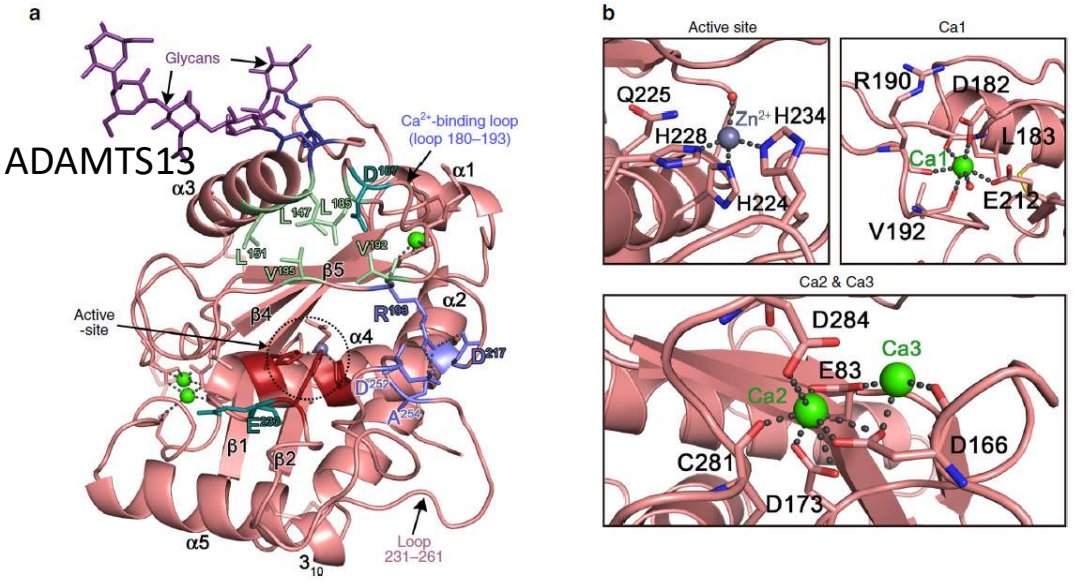


- **Metalloprotease**, 1427 amino acids
- Primarily synthesized in hepatic stellate cells, endothelial cells and platelets
- Half-life of 2-3 days

- **No activation required, no inhibitors**

Furlan M et al. Blood 1996; Tsai HM Blood 1996; Zheng XL et al. JBC 2001; Levy GG et al. Nature 2001; Fujikawa K et al. Blood 2001; image adapted from Petri A et al. Nat Comm 2019

ADAMTS13 - Zn2+, Ca2+-dependent metalloprotease

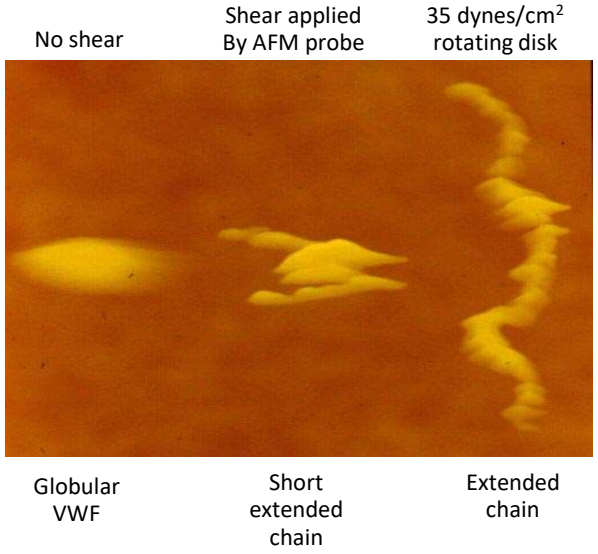


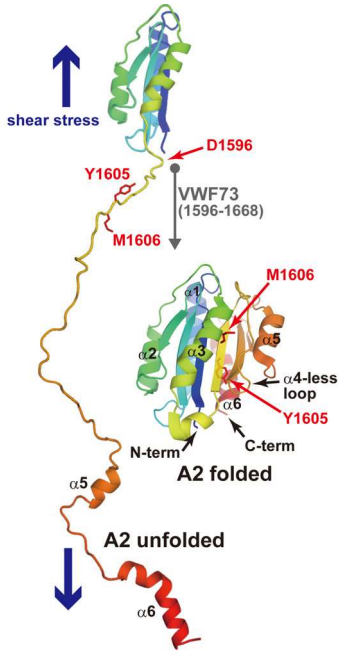
Petri A et al. Nat Comm 2019

ADAMTS13 cleaves VWF under high shear

Cleaves VWF in the A2 domain (Tyr1605–Met1606) **under high shear**

Limits platelet-rich thrombus formation in the small arteries by cleaving ultra large (UL) VWF multimers under high shear stress





Siedlecki et al. Blood 1996, Akiyama M et al. PNAS 2009

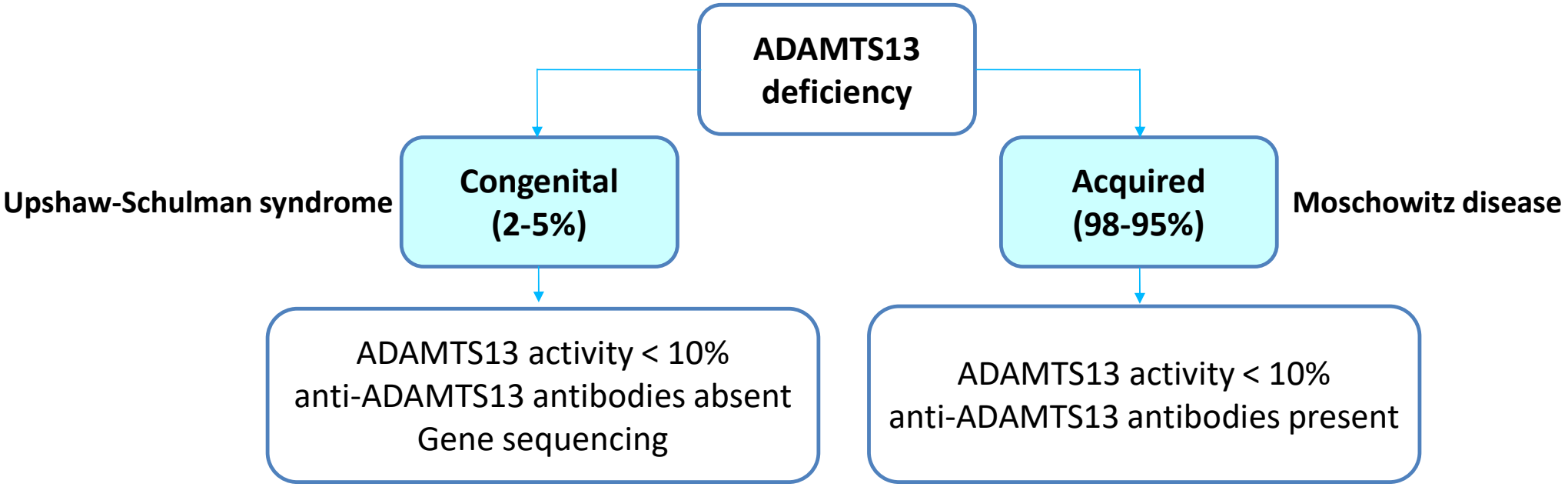
ADAMTS13 deficiency and TTP

- **Normal activity levels:** 40-160%
- **Mild-moderate deficiency:** 10%-40%
- **Severe deficiency:** < 10%

require anti-ADAMTS13 IgG auto Ab

diagnostic of TTP

Diagnostic flow-chart



The PLASMIC score

- Pre-test probability of severe ADAMTS13 deficiency (≤10% activity)
- 5 independent predictors
- Together with clinical judgment, it may facilitate treatment decisions in patients for whom timely results of ADAMTS13 activity testing are unavailable

PLASMIC score	
Platelet count	<30 g/l (+1)
Serum creatinine level	<2 mg/dL (+1)
Hemolysis Indirect bilirubin >2 mg/dL Or reticulocyte count >2.5% Or undetectable haptoglobin	+1
No active cancer in previous year	+1
No history of solid organ or stem cell transplantation	+1
INR <1.5	+1
MCV <90 fL	+1
Prediction of severe ADAMTS13 deficiency (activity <10%) based on score[a]	

Score	Risk category	Risk of severe ADAMTS13 deficiency (≤ 10%)
0-4	Low	4.3%
5-6	Intermediate	56.8%
7	High	96.2%

Bendapudi PK, et al. Lancet Haematol. 2017 Apr;4(4):e157-e164

The French score

French score	
Platelet count	<30 g/l (+1)
Serum creatinine level	<2.25 mg/dl (+1)
Prediction of severe ADAMTS13 deficiency (activity <10%) based on score[a]	0: 2% 1: 70% 2: 94%

The French score assumes that there is NO HISTORY OF OR CLINICAL EVIDENCE FOR associated cancer, transplantation, or disseminated intravascular coagulopathy; so these items are intrinsic to the score.

→ Platelet count < 30 g/l and creatinine <2 mg/dl: consistently associated with ADAMTS13 <10%

Coppo P, et al. *PLoS One*. 2010;5(4):e10208.

ADAMTS-13 Testing

Pre-analytical variables

- Citrated plasma/or serum
- Platelet poor plasma (centrifugation at >2000g for 15min)
- Centrifugation to separate plasma should occur as soon as possible
- Store frozen at < -40°C until testing
- Use dry ice for shipment to another site
- Avoid repeated freezing-thawing cycles
- Blood samples collected before initiating plasma therapy to avoid
  - donor plasma interference
  - ADAMTS13 Ab dilution
- However, in a series of 18 aTTP patients, >75% still showed <10% ADAMTS13 activity immediately before the fourth exchange procedure

Wu N et al. Transfusion 2015

Assays

Assay	Analyte	Clinical utility
ADAMTS13 **activity**	Functional assay; measure the ability of plasma ADAMTS13 to cleave VWF	Pivotal for diagnosis and management
ADAMTS13 **antigen**	Measure the concentration of plasma ADAMTS13 antigen	Rather useless for diagnosis
Anti-ADAMTS13 **antibodies**		
Anti-ADAMTS13 IgG	Measure the concentration of anti-ADAMTS13 IgG in plasma	Support TTP diagnosis and discriminate between acquired and congenital TTP
ADAMTS13 inhibitor	Functional assay; measure the concentration of antibodies neutralizing ADAMTS13 activity	

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Activity assays

	FRET	**Chromogenic ELISA (TECHNOZYM® by Technoclone)**
Substrate	FRETS-VWF73	GST-VWF73
Detection method	Fluorescence emitted after cleavage of FRETS-VWF73 by ADAMTS13; kinetic	Chromogenic immunoassay using specific mAb to detect ADAMTS13-generated fragment; endpoint

Kokame K et al. BJH 2005; Palla R et al. TH 2011; Joly B et al. TR 2014; Valsecchi C et al. TH 2019

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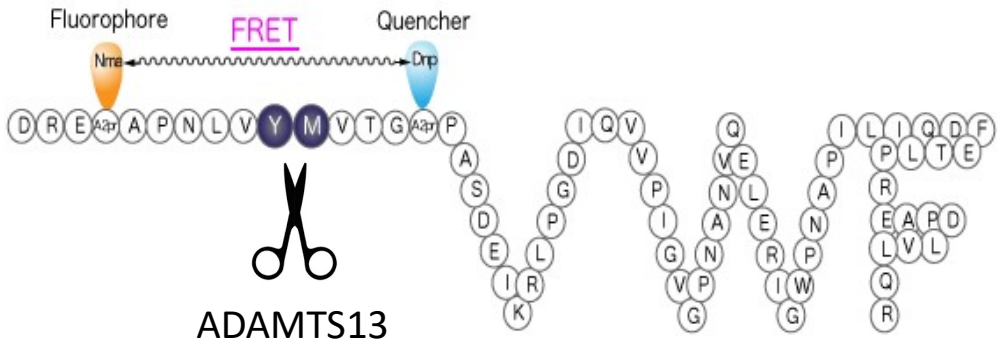
ADAMTS13 present → Emission at 440 nm



Kokame K et al. BJH 2005; Kremer Hovinga JTH 2006; Palla R et al. TH 2011

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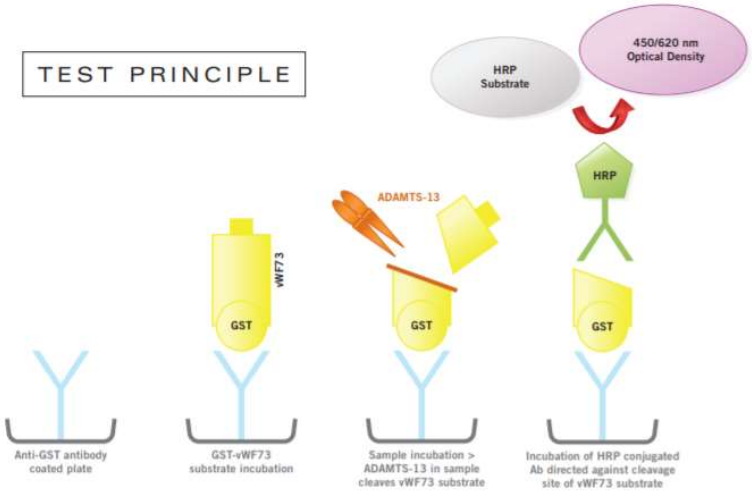
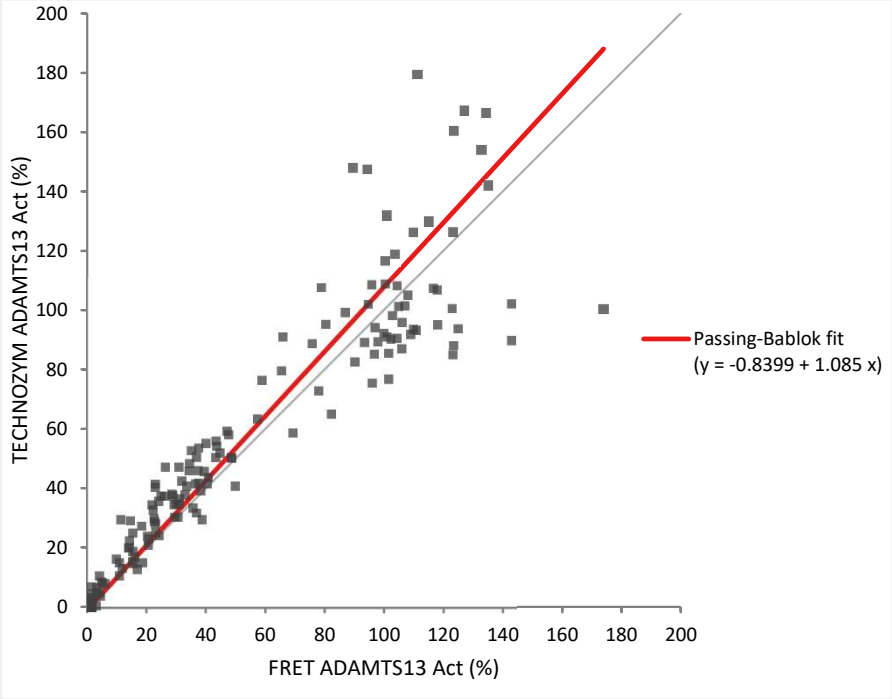


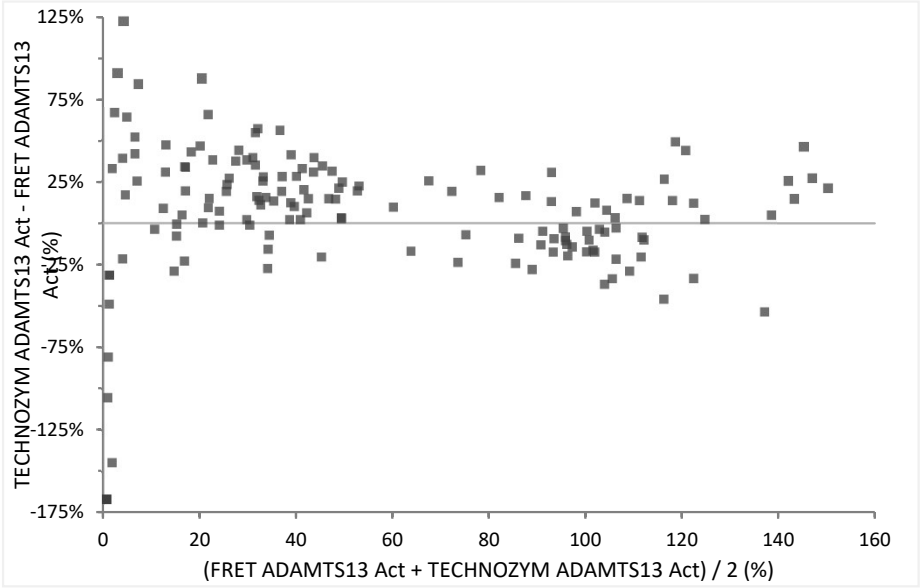
Kato S et al. Transfusion 2006; Joly B et al. TR 2014; https://www.technoclone.com/en/product/adamts13-chromogenic-elisas

Comparative study: FRET vs chromogenic ELISA

Regression plot



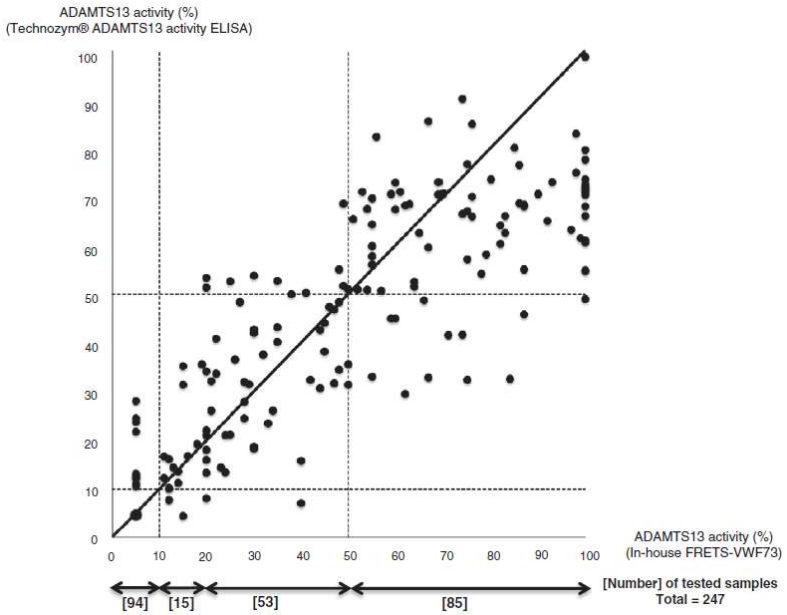
Difference plot



Valsecchi C et al. TH 2019, and unpublished data

Comparative study: FRET vs chromogenic ELISA

247 samples (healthy and TMA)



- Reasonable agreement (correlation r^2 0.59)
- Chromogenic ELISA (Technozym, Technoclone) provided **false negative results** in ~12% of acute TTP patients:

Patient	ADAMTS13 activity IH Frets-VWF73	ADAMTS13 activity Chr-VWF73
Congenital TTP (USS)	<10%	11%
Acquired TTP – idiopathic form	<10%	11%
Acquired TTP – secondary form	<10%	12%
Acquired TTP – secondary form	<10%	12%
Congenital TTP (USS)	<10%	13%
Acquired TTP – idiopathic form	<10%	13%
Acquired TTP – secondary form	<10%	13%
Acquired TTP – secondary form	<10%	22%
Acquired TTP – secondary form	<10%	24%
Acquired TTP – secondary form	<10%	25%
Acquired TTP – secondary form	<10%	28%
Other TMA	12%	<10%
Other TMA	15%	<10%
TTP remission	20%	<10%
Other TMA	40%	<10%

Joly B et al. TR 2014

Interferences

- Bilirubin
- Hemoglobin
- Lipaemia - might interfere, but no data available

Interferences: bilirubin

FRETS-VWF73

Unconjugated bilirubin interferes with fluorogenic FRETS-VWF73 assay

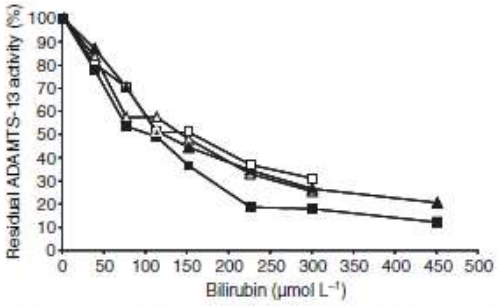


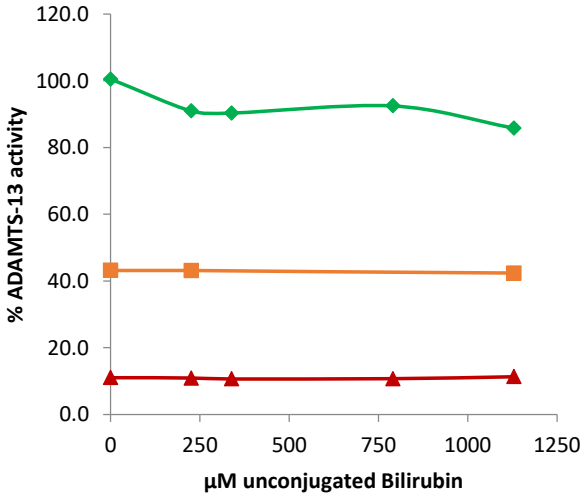
Fig. 1. Interference of bilirubin with ADAMTS-13 activity determination by the FRETS-VWF73 assay. Residual ADAMTS-13 activity as a function of bilirubin plasma concentration, expressed as percentage of starting ADAMTS-13 activity. Triangles display a starting ADAMTS-13 activity of 50% and squares of 25% of normal human plasma (NHP) (mean of two independent experiments each). Experiments in the presence of synthetic bilirubin are represented by filled and those in hyperbilirubinemic patient's plasma by open symbols.

- >100 umol/l (5.85 mg/dl)
- Due to fluorescence quencing

Meyer et al. JTH 2007

TECHNOZYM® ADAMTS13 Activity ELISA

No interference of unconjugated bilirubin during measurement independent of ADAMTS-13 concentration range



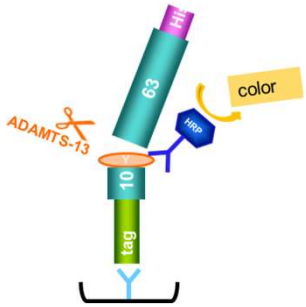


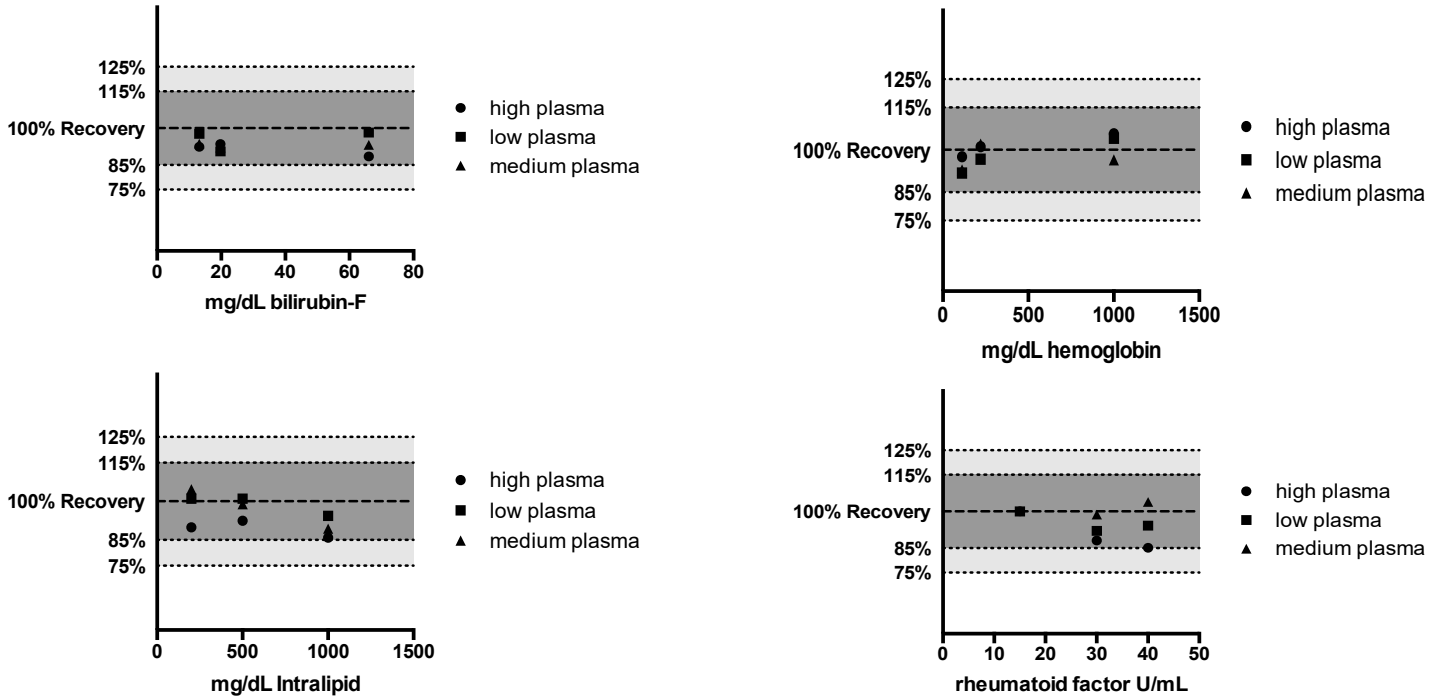
Plate is washed

Interferences: hemoglobin

- Haemoglobin binds to the VWF A2 domain and prevent cleavage by ADAMTS13 in vitro

Studt JD et al. Blood 2005; Zhou Z et al., TH 2009; Muia J et al. JTH 2013

Interferences - TECHNOZYM® ADAMTS-13 Activity ELISA



No interference of hemolysis, lipemia, conjugated bilirubin and rheumatoid factor

https://docs.google.com/viewer?url=https%3A%2F%2Fdiapharma.com%2Fwp-content%2Fuploads%2F2017%2F06%2F5450701_Technozym_ADAMTS-13_Activity_Assay_Technical_Tips_ML-00-00292REV02.pptx

Most popular ADAMTS13 activity assays: pros & cons

Pros

- High analytical sensitivity
- High analytical specificity
- High precision
- (Some degree of) Standardization
- CE marked IVD-certified (Technozym assay)

Cons

- Discrepancies
- Interferences
- **Long turnaround time**
- **Require trained lab staff**

→**Available in few specialized hospitals**

→**Not really suitable for emergencies**

More recent (and rapid) ADAMTS13 activity assays

- HemosIL AcuStar ADAMTS13 Activity assay (IL-Werfen)
- Technoscreen® ADAMTS13 Activity assay (Technoclone)

	FRET (in-house)	ELISA (kit TECHNOZYM®)	HemosIL AcuStar (under development)
Substrate	FRETS-VWF73	GST-VWF73	VWF73
Detection method	Fluorescence emitted after cleavage of FRETS-VWF73 by ADAMTS13	Chromogenic immunoassay using specific mAb to detect ADAMTS13-generated fragment	Chemiluminescent immunoassay using specific mAb to detect ADAMTS13-generated fragment
Limit of Detection	3.3%	0.002 IU/mL (0.2%)	0.2%
Assay range	3.3 – 105% (can be extended to values >100% by sample dilution)	0.003 – 1.05 IU/mL (0.3 – 105%) (can be extended to values >100% by sample dilution)	0.2 – 150.0% (no sample dilution required)
Intra-assay precision (CV) Inter-assay precision (CV)	6.0% 9.5%	≤ 5.4% ≤ 8.0%	≤ 4.4% ≤ 5.1%
Normal range	45 – 147%	0.40 – 1.30 IU/mL (40 – 130%)	67 – 129%
Assay length	~ 2 hours	~ 4 hours	33 minutes
Instrument	Spectrofluorometer (not automated)	Spectrophotometer (not automated)	ACL AcuStar™ (fully automated)

ADAMTS13 testing – practical approach

- ADAMTS13 activity
  - FRET (in-house) for routine
  - Technozym ADAMTS13 Activity assay for night/weekend emergencies
- ADAMTS13 antigen (in-house ELISA)
- Anti-ADAMTS13 antibodies
  - Anti-ADAMTS13 IgG (Technozym ADAMTS13 Inhibitor ELISA)
  - Anti-ADAMTS13 IgA/M
  - Neutralizing ADAMTS13 activity (mixing assay)
  - ADAMTS13-specific immune complexes

ADAMTS13 testing – practical approach

- Collect blood sample as soon as TTP is suspected
- Test ADAMTS13 activity as soon as possible (treatment is initiated REGARDLESS of ADAMTS13 testing results)
- Test anti-ADAMTS13 antibodies if ADAMTS13 activity is below the low limit of the normal range
- If congenital TTP is suspected based on patient history, presentation, response to therapy and ADAMTS13 results (activity <10%, negative antibodies, ideally in at least two occasions far from acute TTP therapy), perform ADAMTS13 genetic analysis and measure ADAMTS13 antigen

From **ACUTE PHASE**

Disease duration is variable

Clinical response usually achieved after 9-16 days of PEX

Mortality highest in the first days from disease onset

Risk of **exacerbation** (new clinical signs and symptoms within 30 days after normalisation of PLT count)

Still 10% mortality despite PEX

To **REMISSION PHASE**

TTP: risk of recurrence

Almost **1/3 of patients** who survive the first acute episode of TTP will relapse (after 1 month – many years) and will develop a **chronic recurrent form** of TTP

Zhan H et al Transfusion, 2010

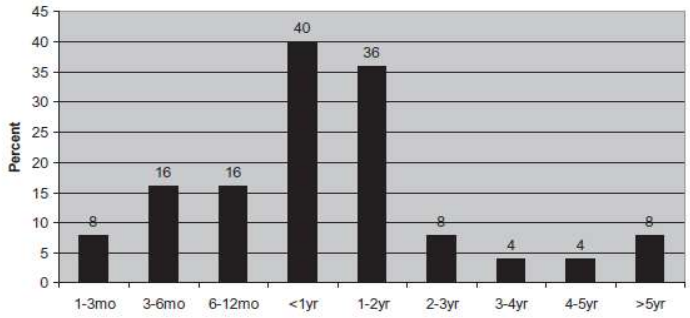


Fig. 2. Time to relapse in patients who achieved remission on their initial presentation of TTP.

Risk factors for recurrence?

- Low ADAMTS13 levels (<10%) in remission phase
- Infections
- Surgery
- Some drugs (estrogens, thyenopiridines, quinine, etc.)
- Pregnancy

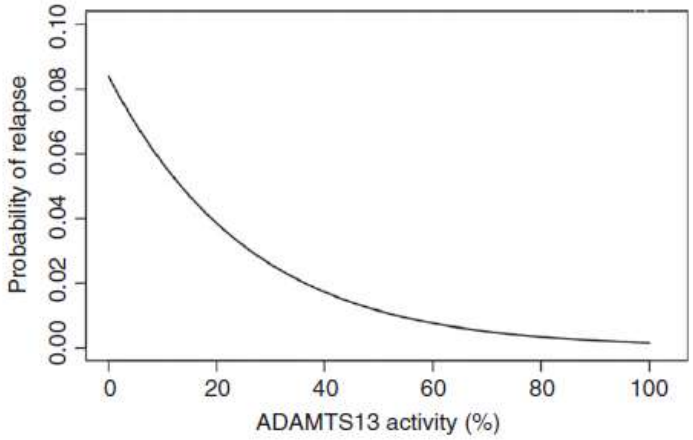
Acquired TTP and ADAMTS13 levels in remission phase

3-fold higher risk of relapse in patients with **ADAMTS13 <10%** or positive Ab **antiADAMTS13** during remission

Peyvandi et al JTH, 2008

Lower ADAMTS13 activity were significantly associated with higher risk of relapse in the 3 months after remission

Jin et al BJH, 2008; Yang et al, ISTH 2015



Acquired TTP: preventive therapy

- Patients treated with RTX during acute phase had a significantly reduced relapse rate compared with the hystorical control (10 vs 57%)

•Scully et al, Blood 2011

- Relapse-free survival was longer in patients treated with preemptive infusion of RTX during remission phase

•Hie et al, Blood 2014

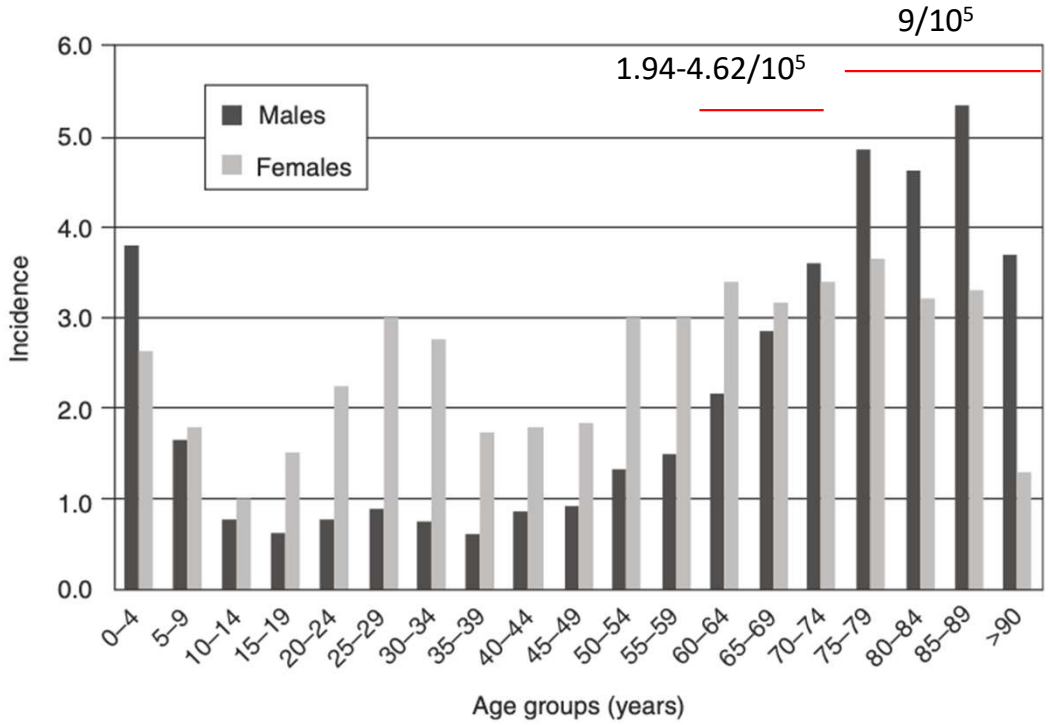
TREATMENT OPTIONS

- RITUXIMAB
- Other immunosuppressive therapy: CSA, Azatiophrine
- (Splenectomy)

Immune Thrombocytopenic Purpura (ITP)

Clinica Luganese Moncucco / MC
CH - 13.09.2023

Epidemiology



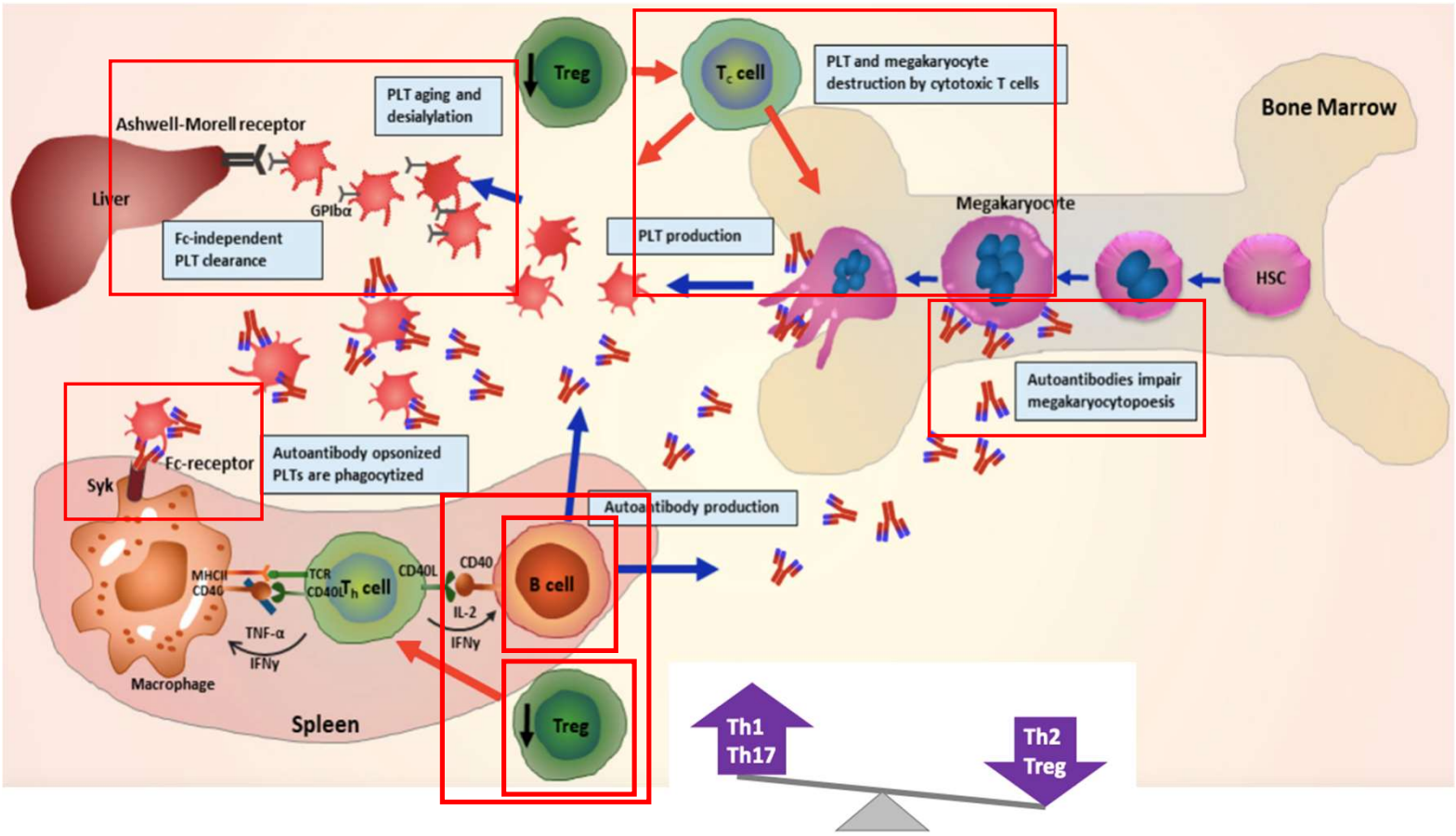
>65aa

2004 → 461 million

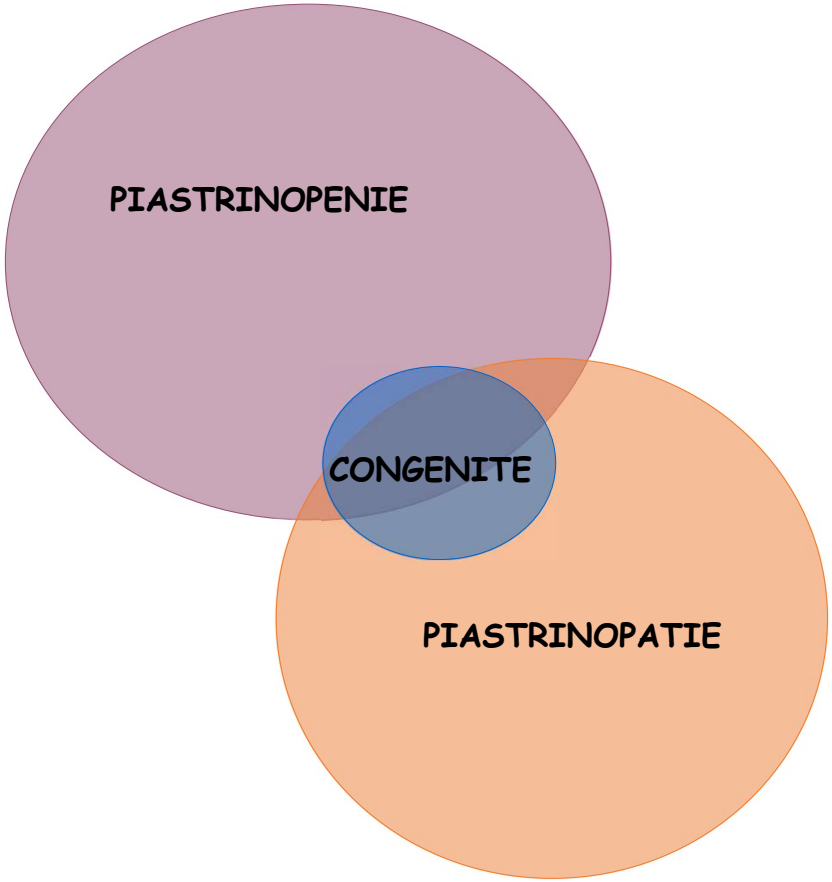
2050 → >2 billion

Kurata Y et al. Int J Hematol. 2011;93:329–35

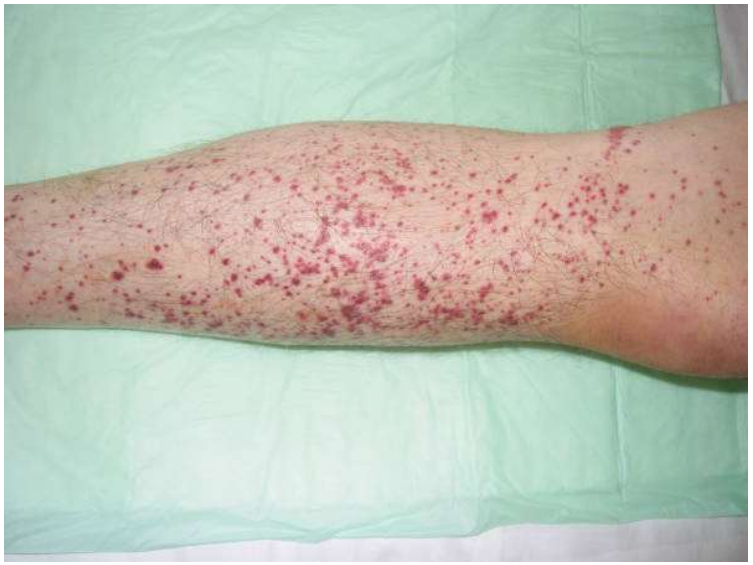
Pathophysiology



Patologia piastrinica emorragica

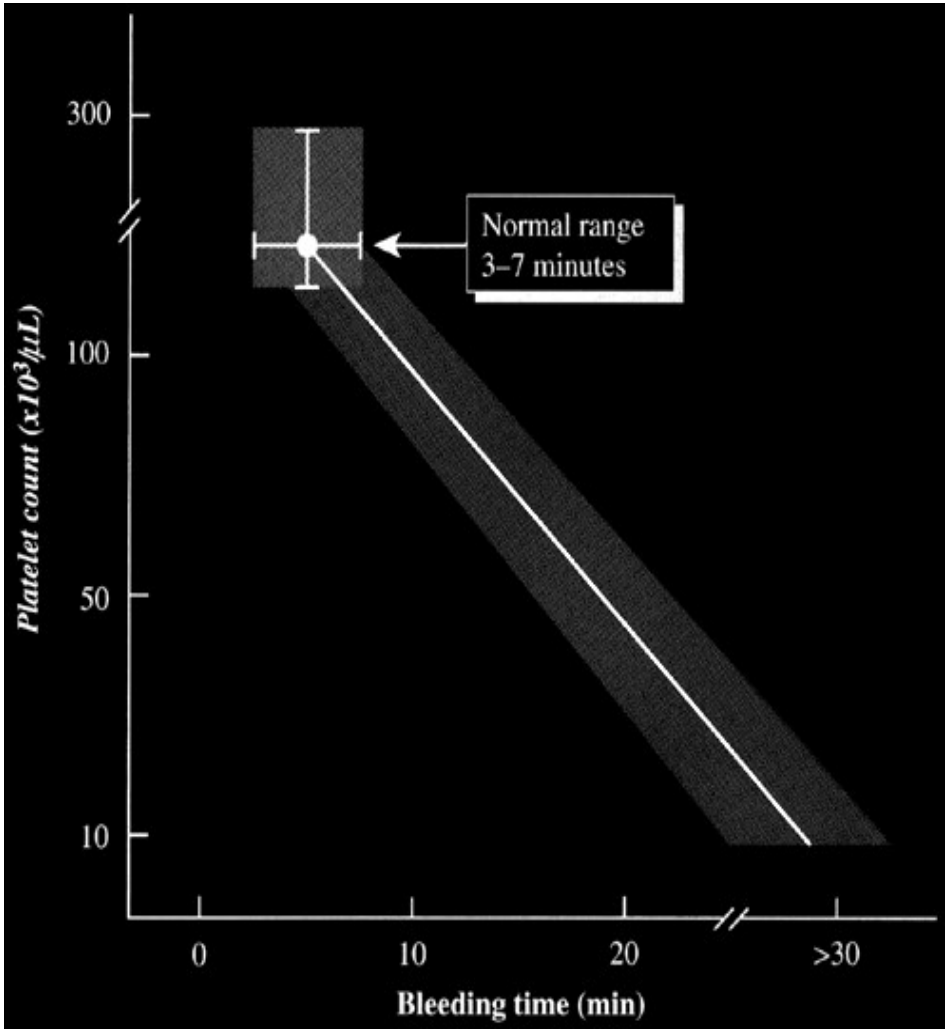


Difetto vaso-piastrinico – dell'emostasi primaria

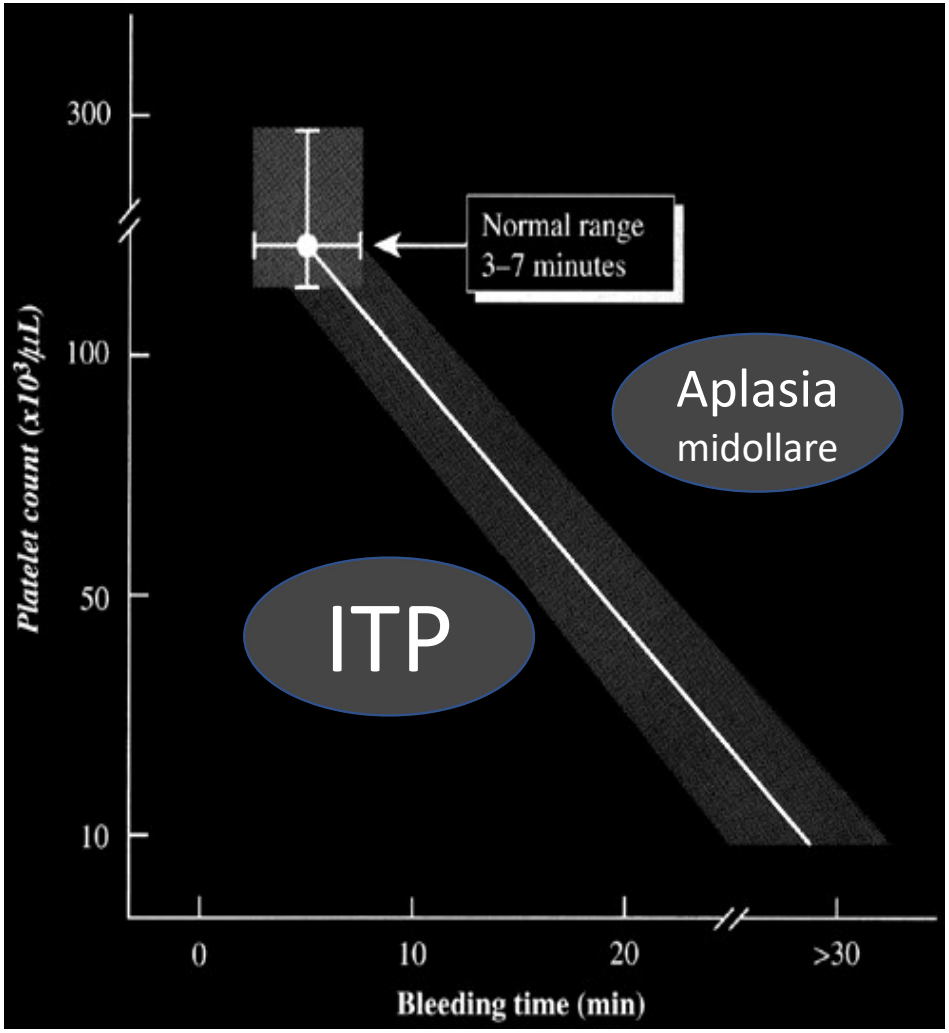


- Sanguinamento di tipo mucoso (epistassi, gengivorragia, GI, GU)
- Sanguinamento cutaneo (petecchie, porpora, ecchimosi)
- Sanguinamento immediato (in seguito a soluzione di continuo)
- Aggravato/slatentizzato da uso di FANS
- Emostasi locale efficace

Quando diventa sintomatica?

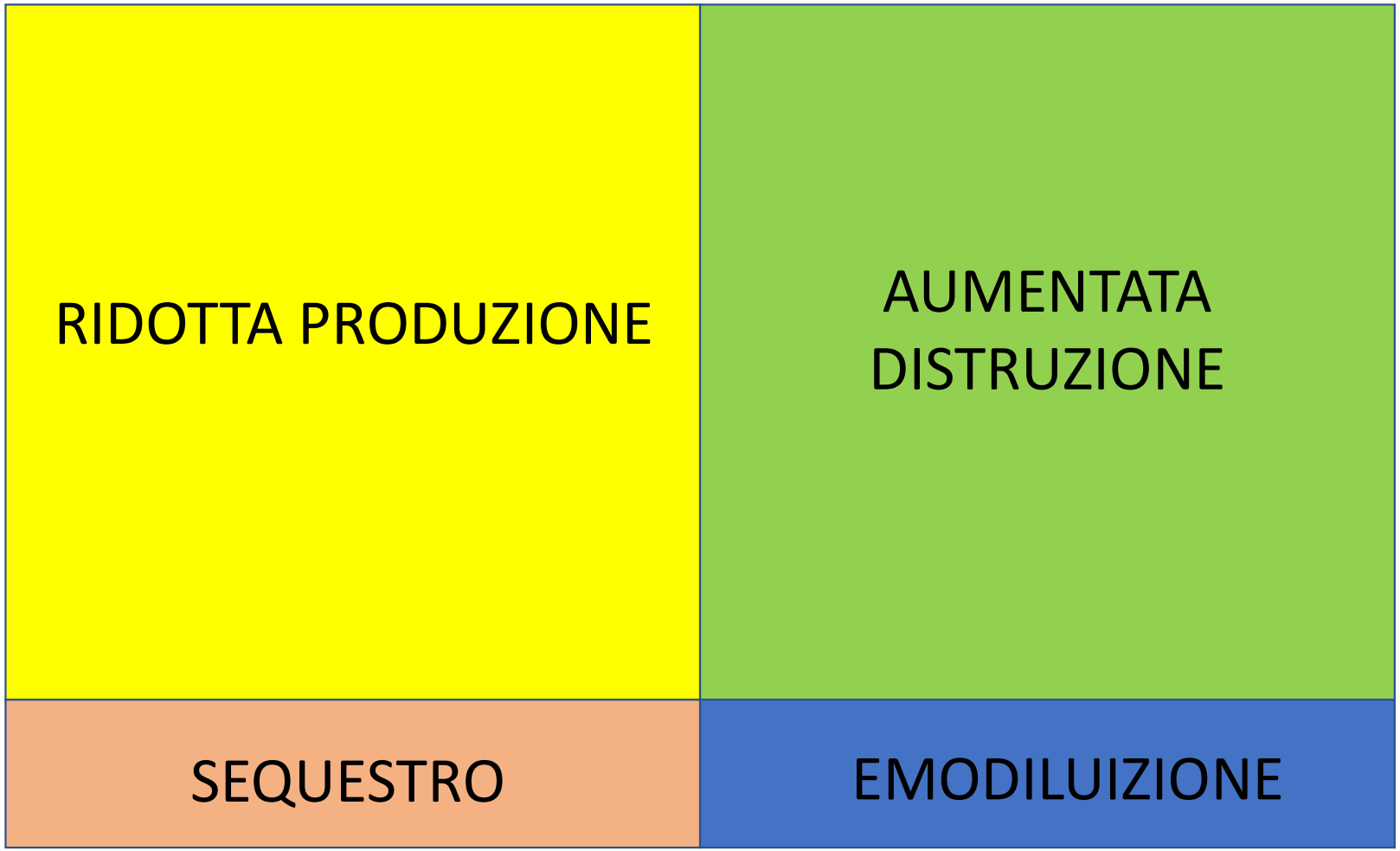


Dipende anche dall'eziologia

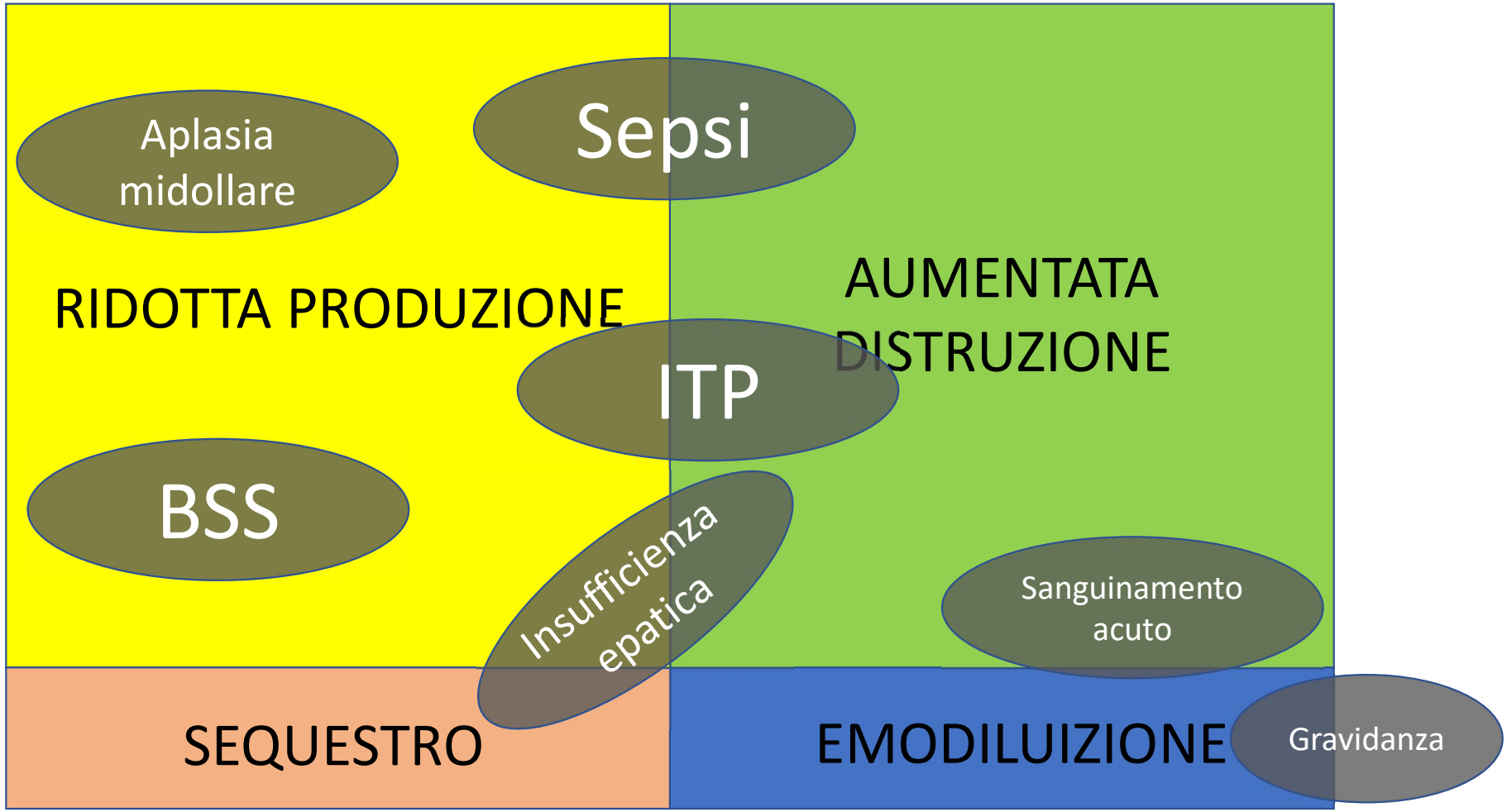


PIASTRINOPENIE

Cause


RIDOTTA PRODUZIONE
AUMENTATA DISTRUZIONE
SEQUESTRO
EMODILUIZIONE

Cause


Aplasia midollare
Sepsi
RIDOTTA PRODUZIONE
AUMENTATA DISTRUZIONE
ITP
BSS
Insufficienza epatica
Sanguinamento acuto
SEQUESTRO
EMODILUIZIONE
Gravidanza

Diagnosi – Esami di laboratorio

-Emocromo (in citrato)

-Striscio di sangue periferico

-Funzione epato-renale

-PT, PTT, fibrinogeno, DD

-LAC, ACA e anti-b2gp1 IgG/M

-HIV, HBV, HCV, CMV, EBV

-EFS, ANA, ENA, FR, C3, C4

-IgG, IgA, IgM

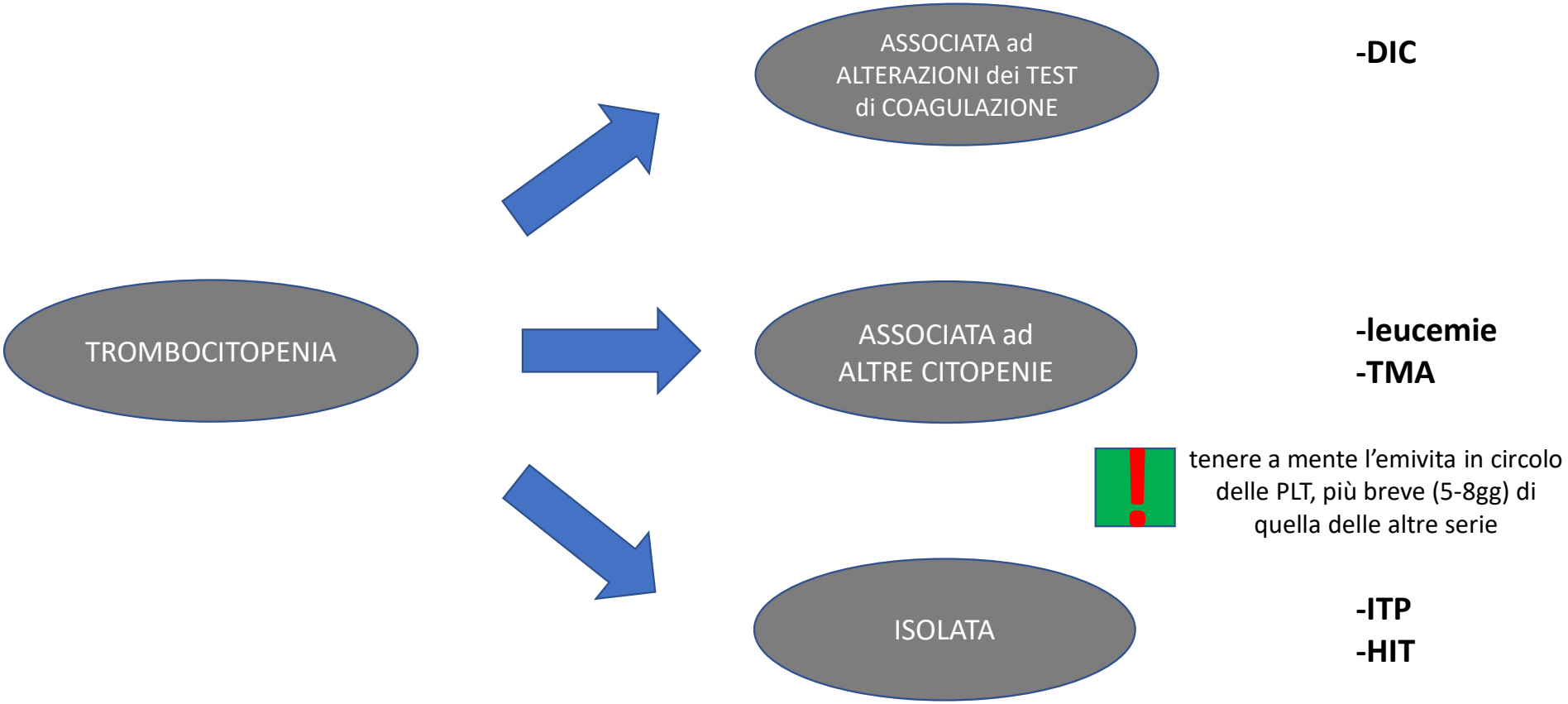
-TSH

-Fe, Tfr, TSAT, ferritina
folati, B12

-Ag fecale HP

-(anticorpi anti-piastrine)

Diagnosi – Esami di laboratorio



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-Ag fecale HP

-(anticorpi anti-piastrine)

ANEMIA vs TROMBOCITOPENIA

RETICOLOCITI	PIASTRINE RETICOLATE test non standardizzato
MCV	MPV variabilità preanalitica
TEST di COOMBS	ANTICORPI ANTIPIASTRINE bassa sensibilità

Diagnosi – Esami di laboratorio

-Emocromo (in citrato)

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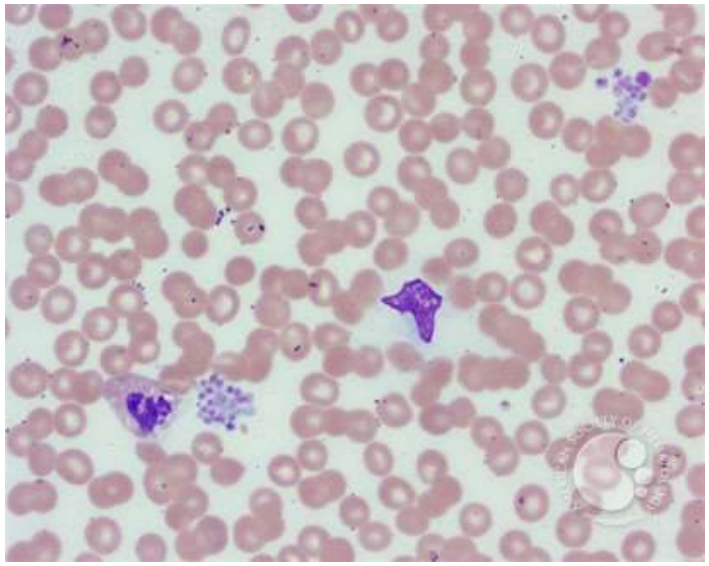
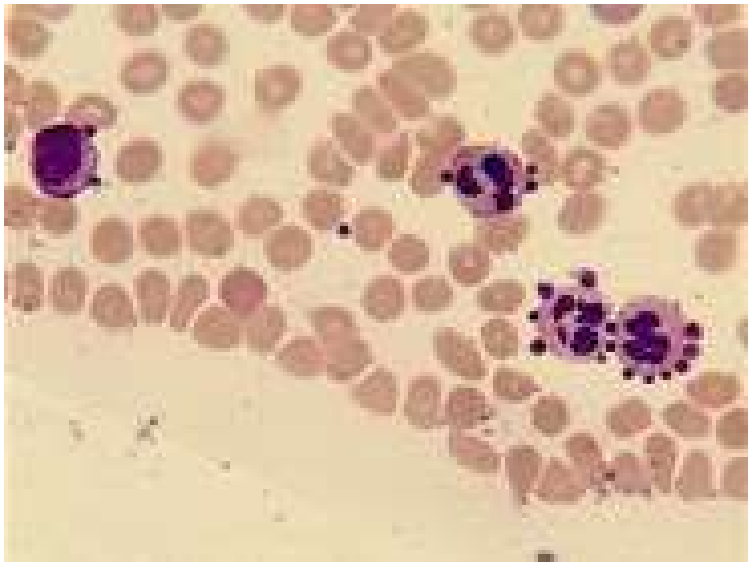
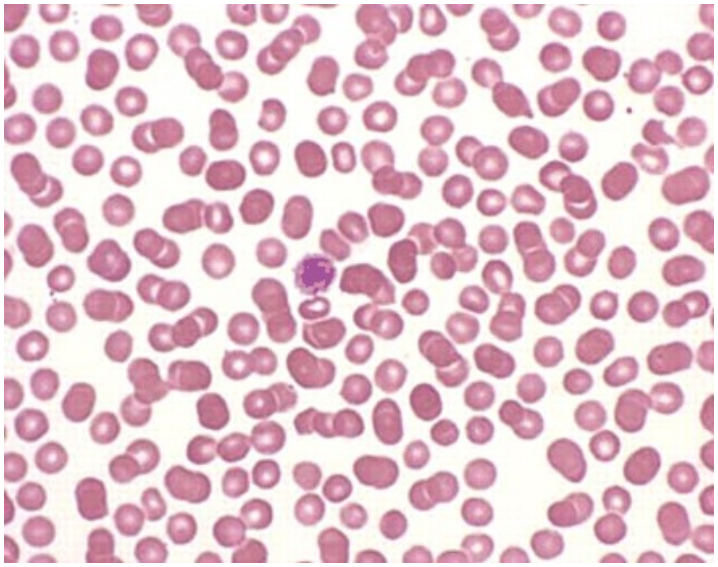
Striscio di sangue periferico



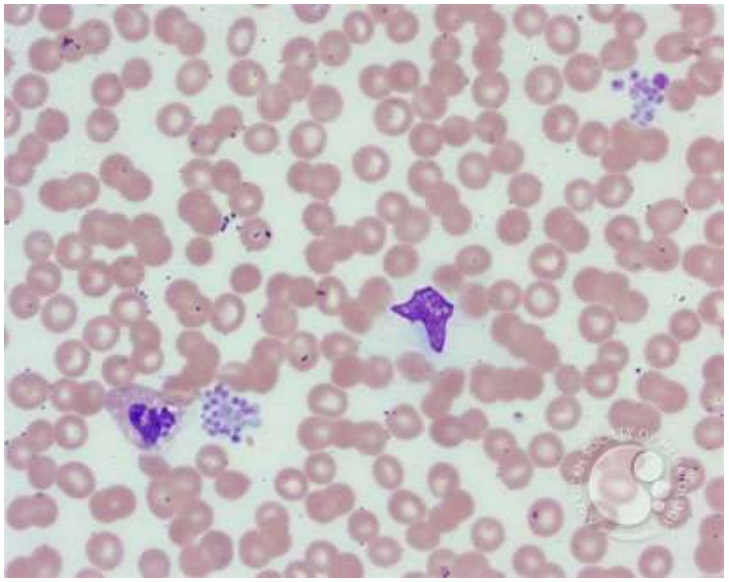


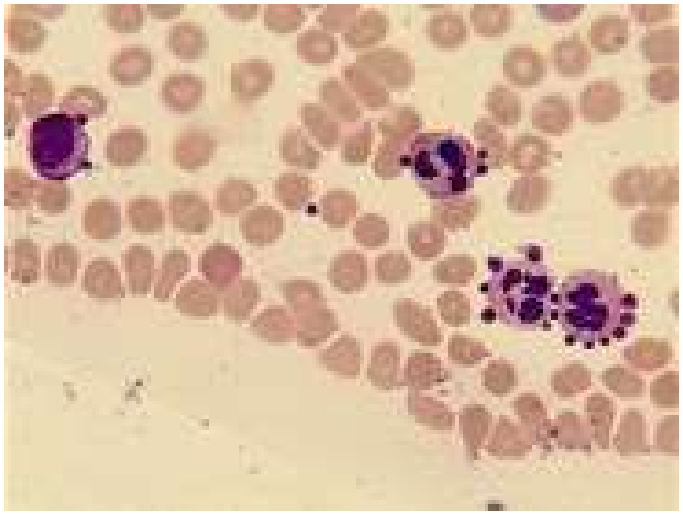
Pseudopiastrinopenia da EDTA



Piastrinopenia vera

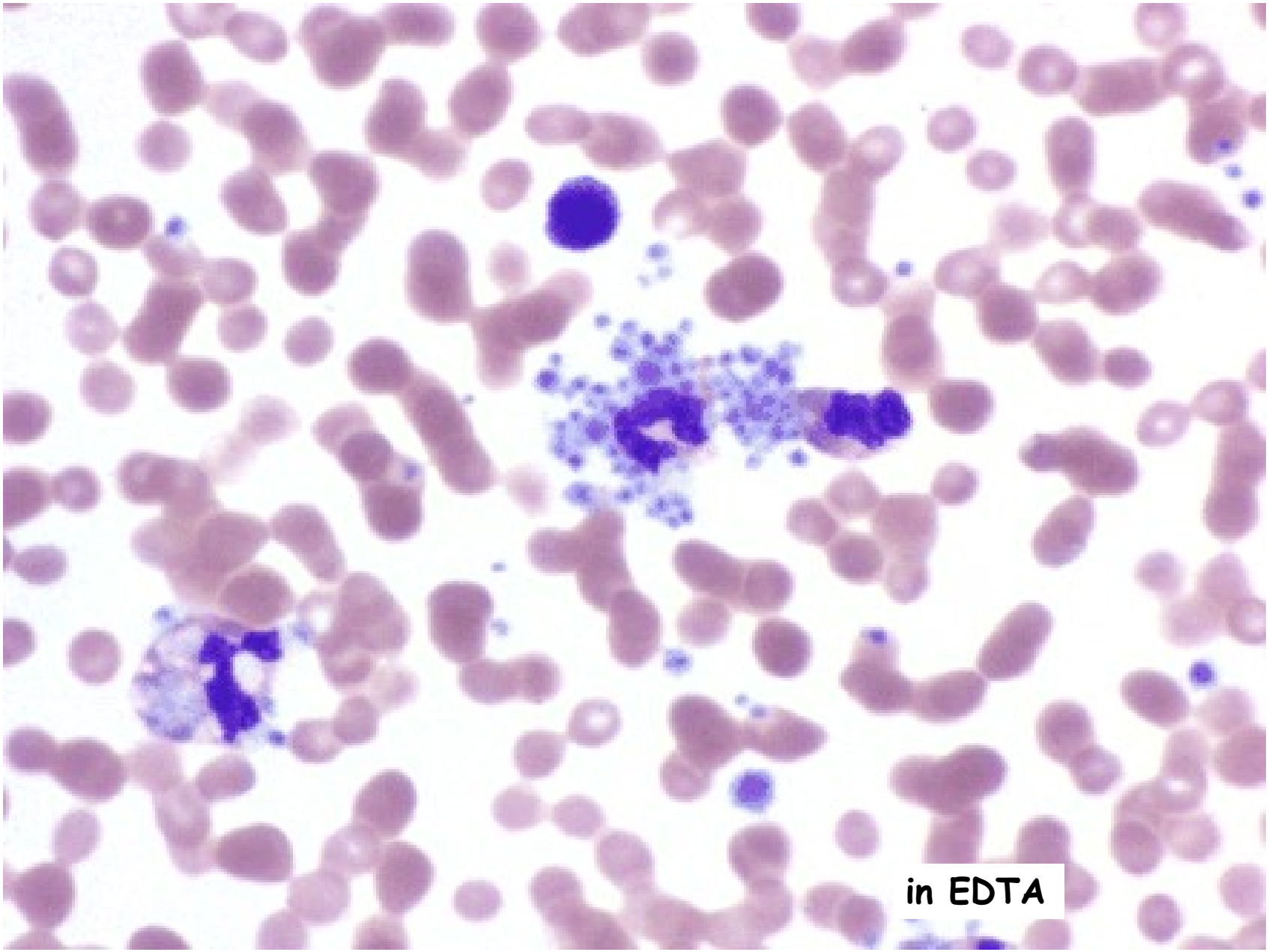
Pseudopiastrinopenia da EDTA

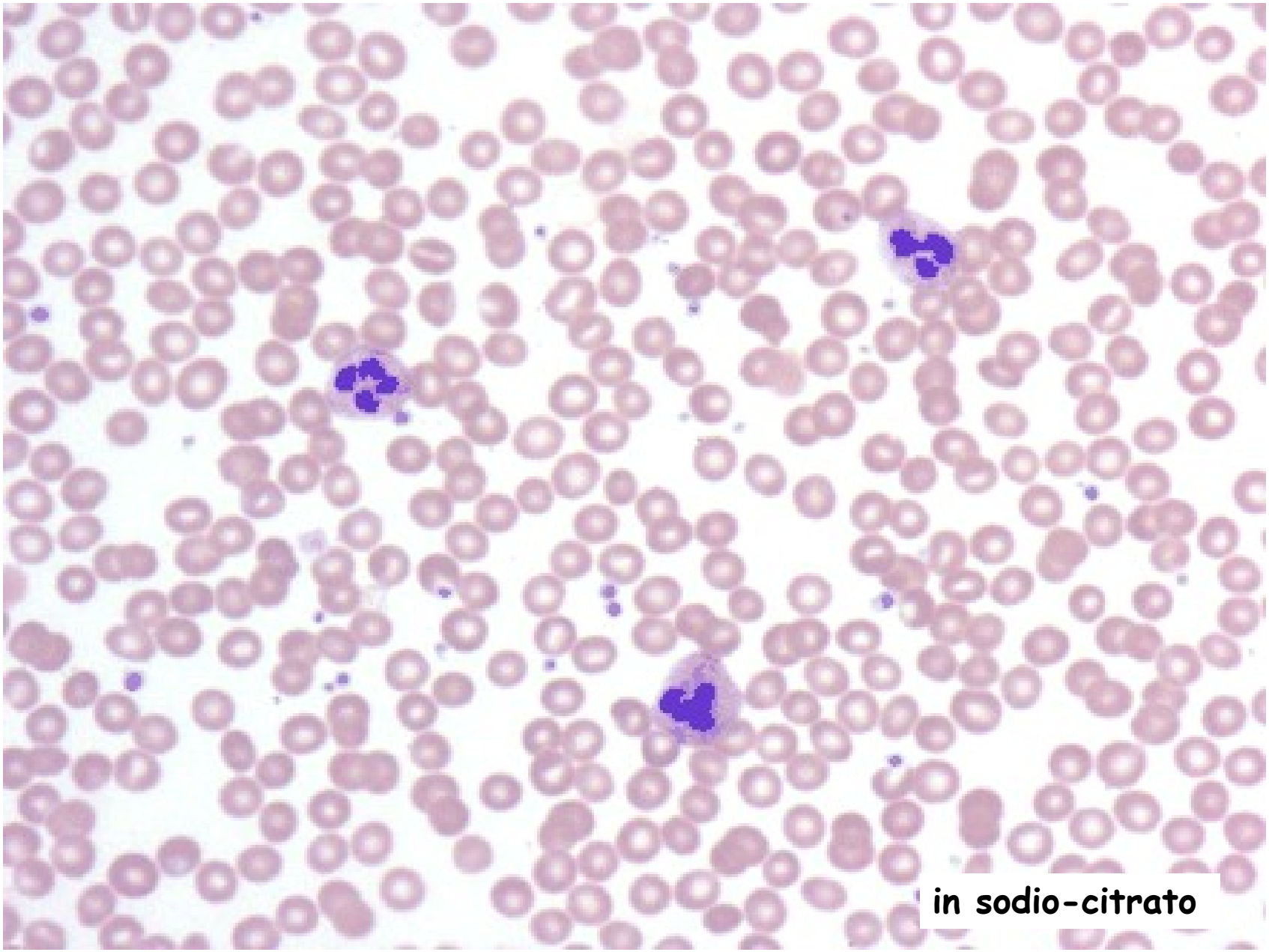




-osservare lo striscio

-confermare la conta piastrinica in un altro anticoagulante


in EDTA

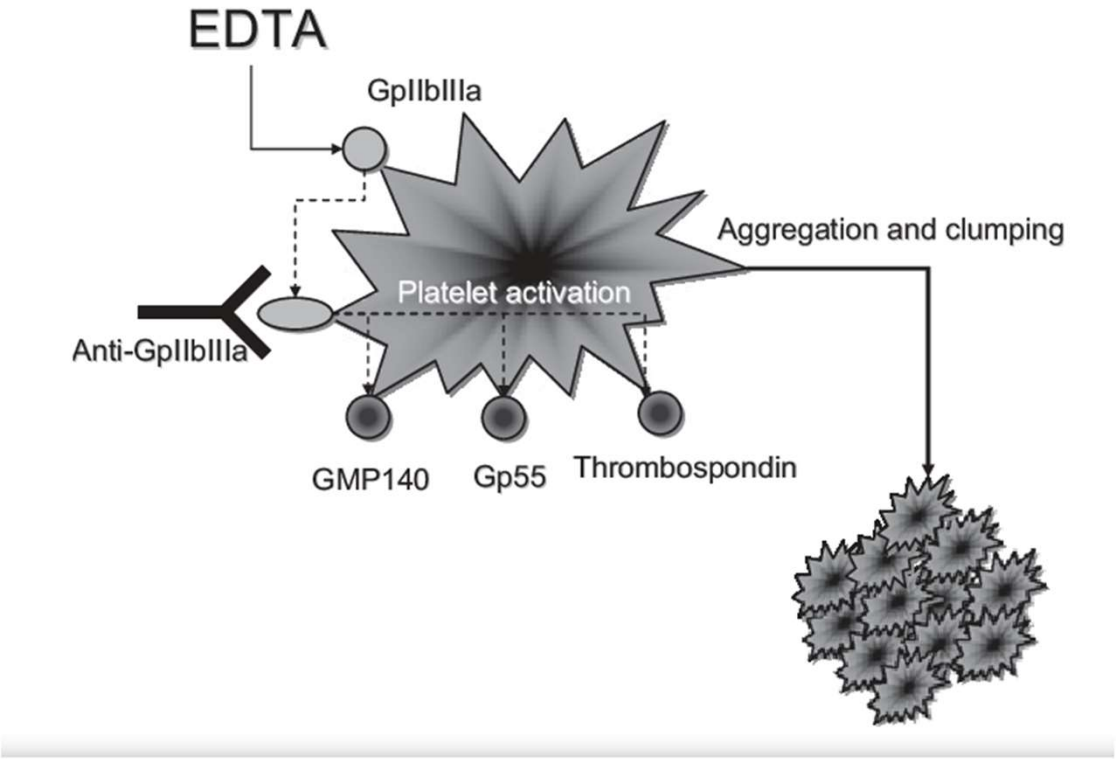

in sodio-citrato

Pseudopiastrinopenia da EDTA

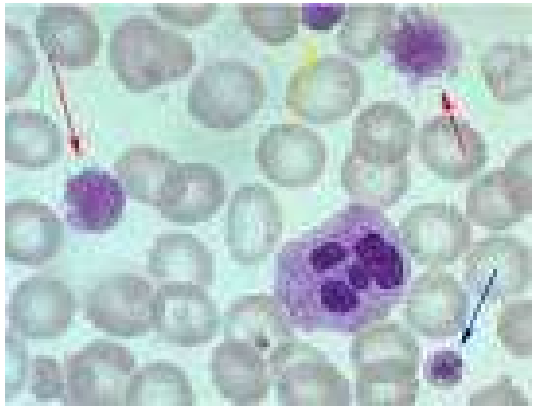
-in vitro phenomenon (also on Wright-Giemsa PS)

-0.07 to 0.20% of the general population
-0.1 to 2% of hospitalized patients

-EDTA-dependent autoAb:
-max activity at 0-4°C
-all Ig isotypes (++ IgG/M)

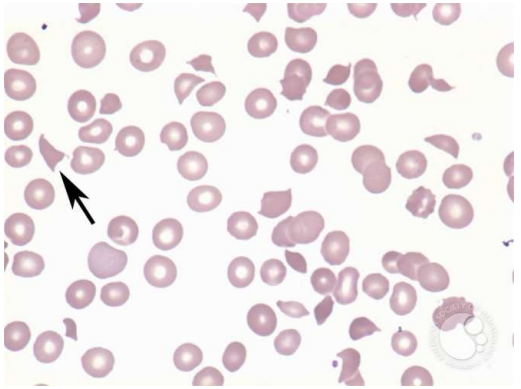


Striscio di sangue periferico



Sindrome di Bernard Soulier
- piastrine giganti

TMA
- schistociti



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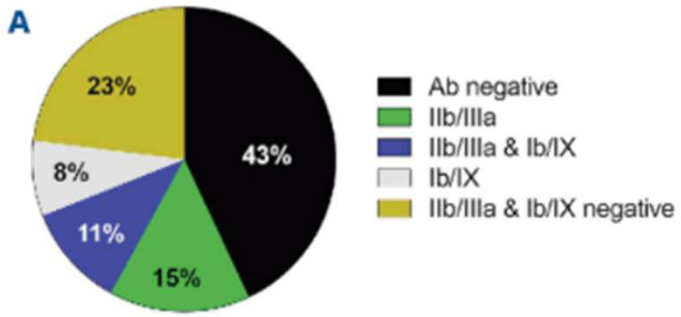
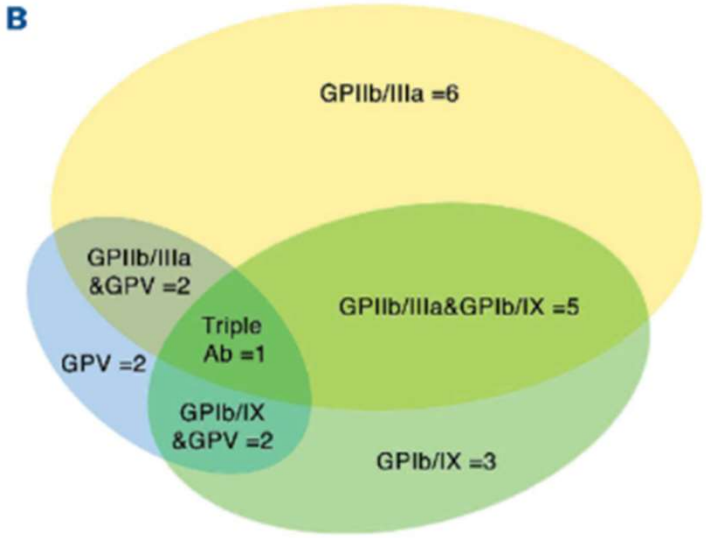
-(anticorpi anti-piastrine)

Anti-platelet antibodies

GP
IIb/IIIa
Ib/IX
V
Ia/IIa





Ib/IX
Abs to >1 GP

-lower PLT count
-lower resp to Tp

Anti-platelet antibodies

1) Measurement of **PAIgG** (Platelet-Associated total IgG)

-low spec
-should no longer be used !

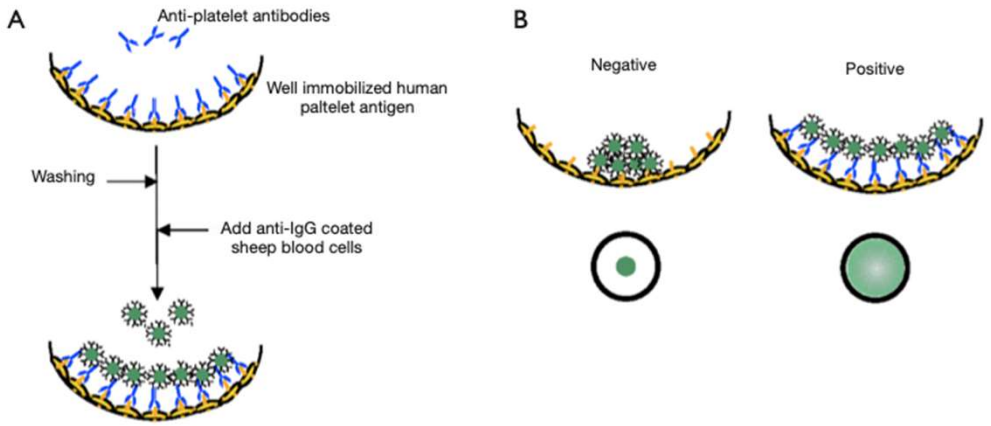
Radioimmunoassay

Immunofluorescence test

Mixed passive hemagglutination (MPHA)

Solid-phase RBC adherence (SPRCA)

Enzyme-linked immunosorbent assay (ELISA)



Anti-platelet antibodies

2) Antigen-capture assays

-spec 98% (false pos in MDS, lymphoma)
-sens 63%

Immunobead assay

Immunoblotting

Monoclonal antibody immobilization of platelet antigens (MAIPA)

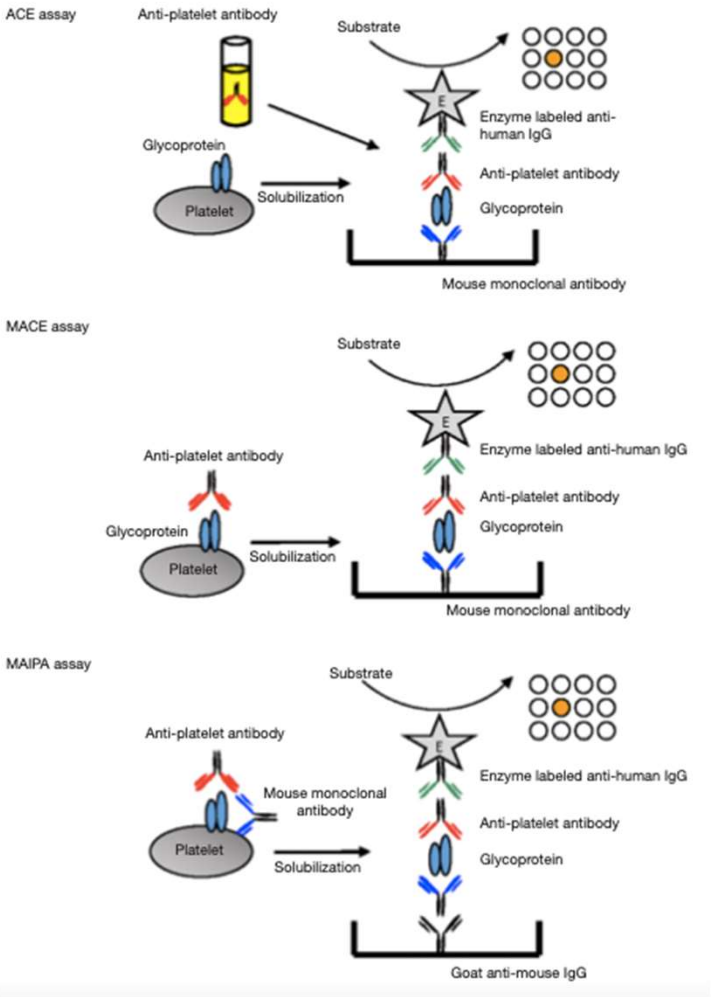
Antigen capture ELISA (ACE)

Modified antigen capture ELISA (MACE)

Anti-platelet antibodies

2) Antigen-capture assays

-spec 98% (false pos in MDS, lymphoma)
-sens 63%



Diagnosi – Esami di laboratorio

-IPF

-Bone marrow biopsy

-Next generation sequencing

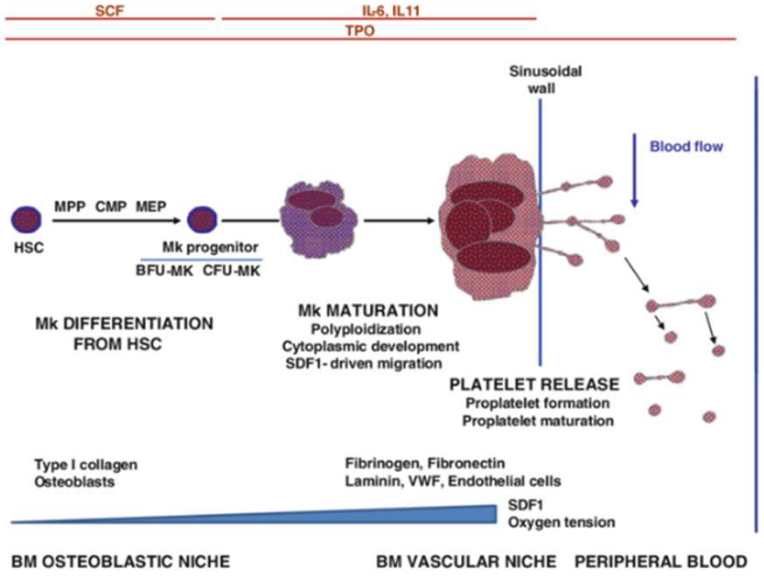
Immature Platelet Fraction (IPF)

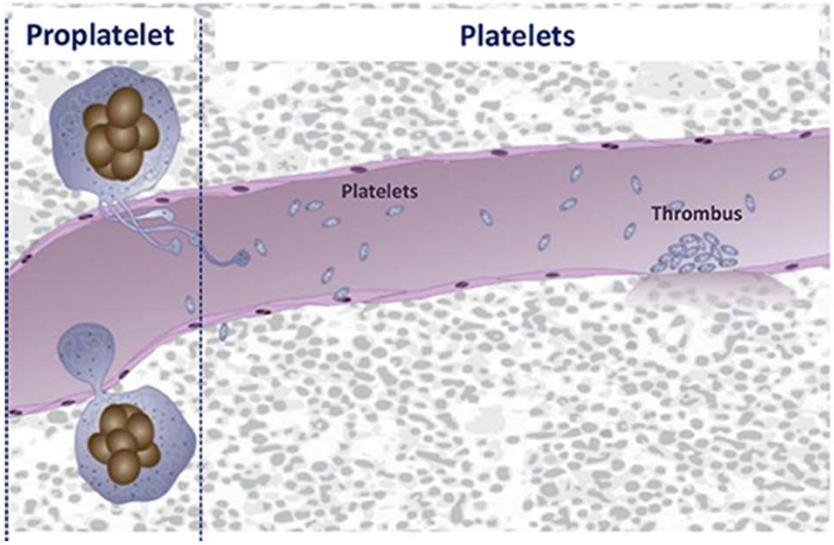
immature/reticulated (reticulocyte counterpart)/young platelets

1-2d old

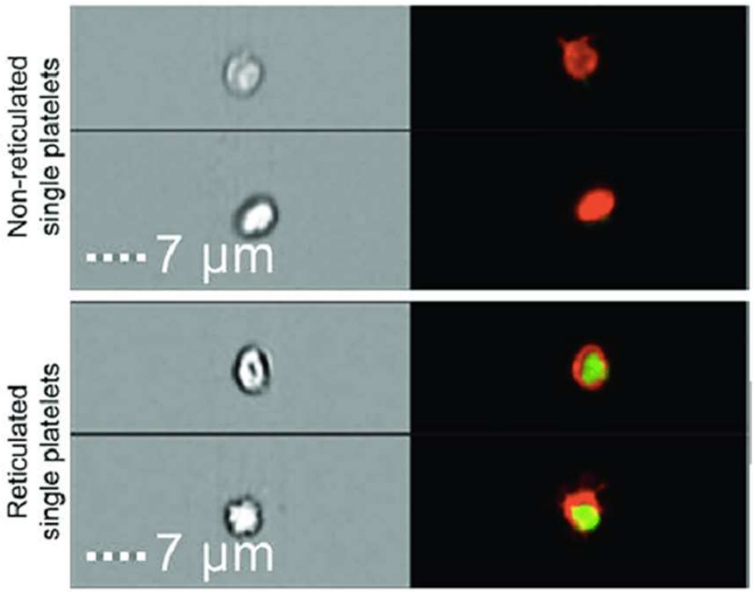
larger

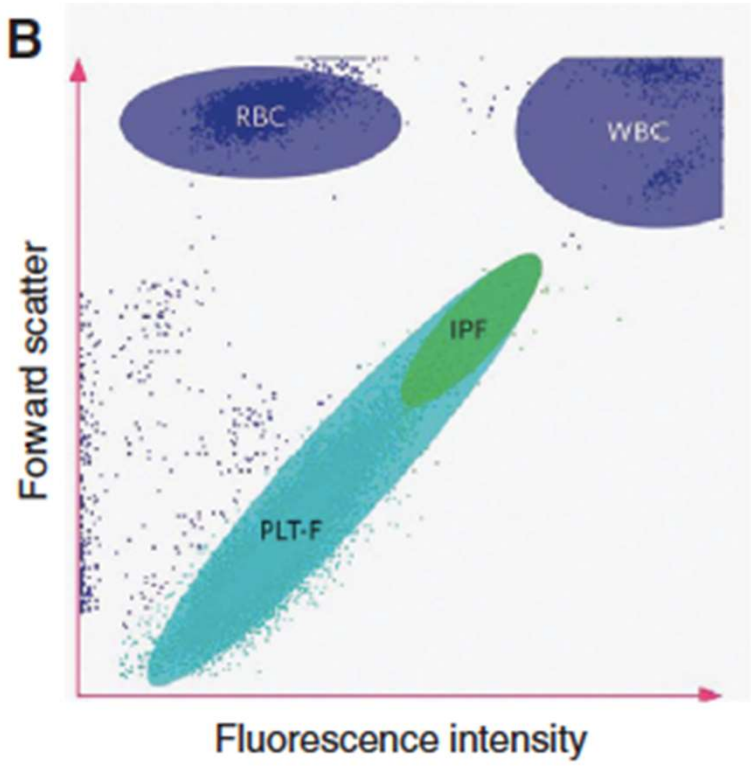
contain more RNA





Immature Platelet Fraction (IPF)





Immature Platelet Fraction (IPF)

IPF - ratio of immature PLT to total number of PLT

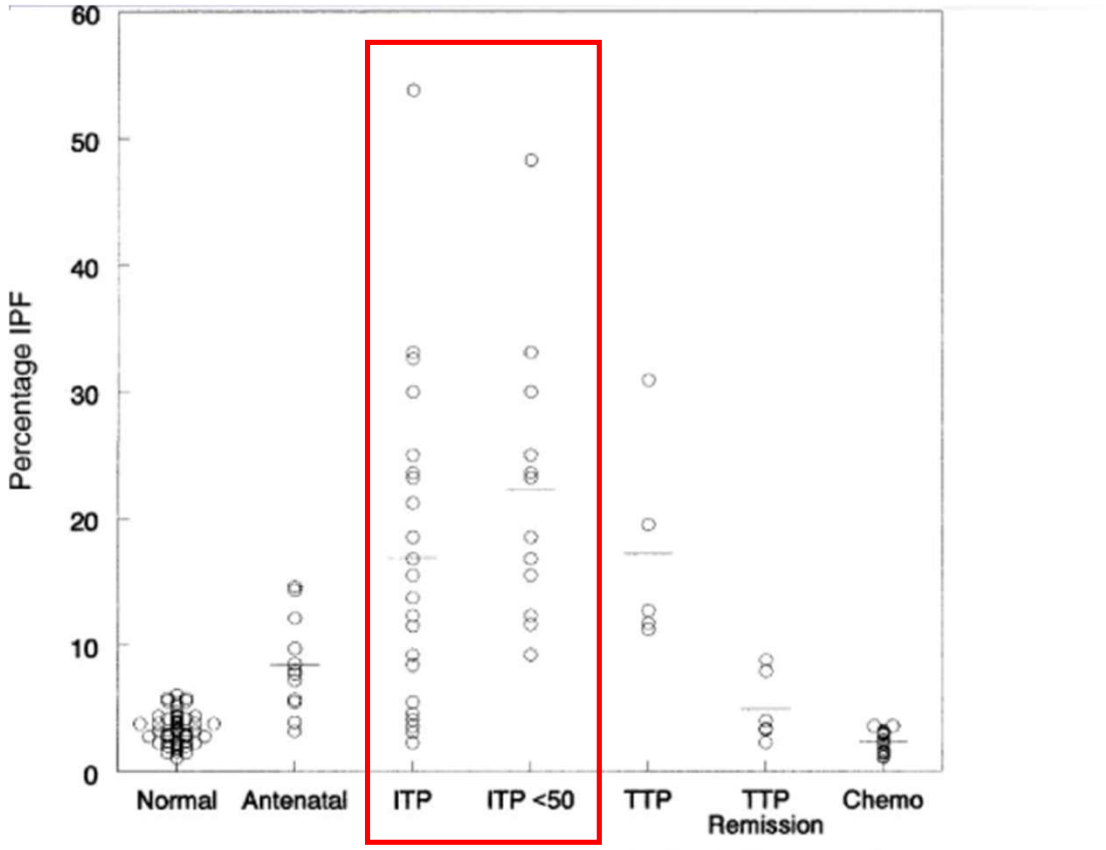
- measures PLT newly released from bone marrow
- a measure of the rate of thrombopoiesis

Immature Platelet Fraction (IPF)

Clinical conditions - IPF as <u>estabilshed</u> diagnostic or prognostic tool

Condition	Intended goal	References retPLT	References IPF
Low platelet count			
Thrombocytopenia of unknown etiology	Differentiating hypoproduction from accelerated destruction	[15, 63, 66, 84, 85]	[49, 55, 63, 66, 75]
Chemotherapy	Predicting platelet recovery	[86, 87]	[76]
Bone marrow or peripheral stem cell transplantation	Predicting platelet recovery	[17, 88–90]	[91–95]
Normal or high platelet count			
Thrombocytosis	Estimating platelet turnover	[22, 23, 96]	

Immature Platelet Fraction (IPF)



Briggs, C. et al., Br J. Haematol. *126*: 93, 2004

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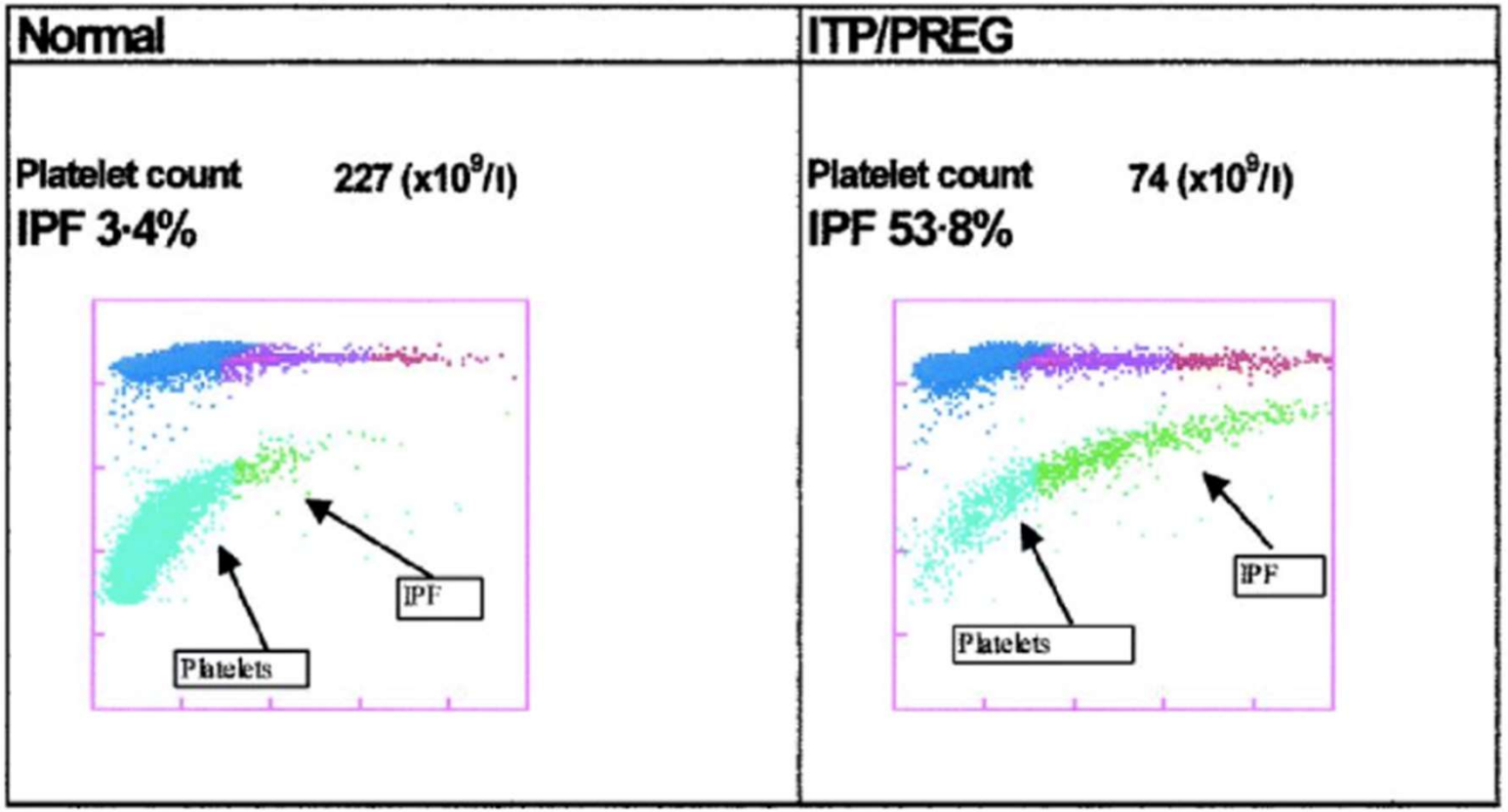

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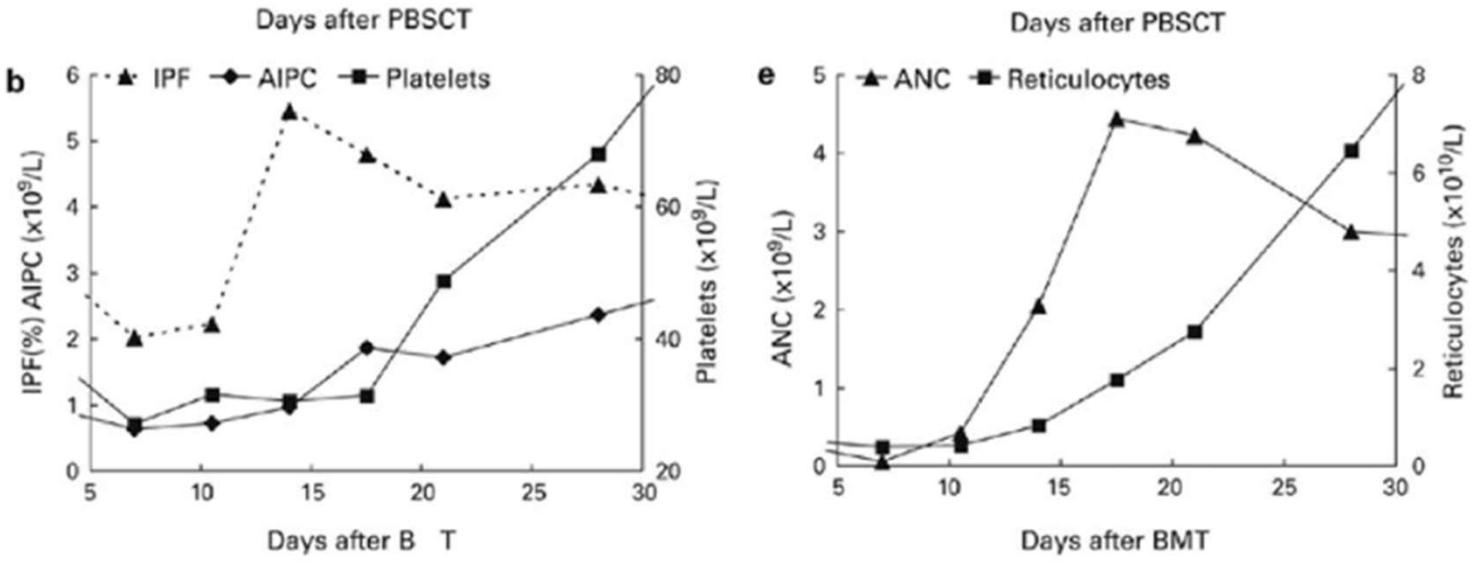


Takami, A. et al. Bone Marrow Transplantation *39*: 501, 2007

Diagnosi – Esami di laboratorio

-IPF

-Bone marrow biopsy

-Next generation sequencing

-to exclude other diagnosis

-not at diagnosis with typical presentation
-in older pts (MDS more frequent)

-at relapse before 2° line Tp

-can be performed with PLT>20k (prolonged compression)

Diagnosi – Esami di laboratorio

-IPF

-Bone marrow biopsy

-Next generation sequencing

-if suspect of hereditary PLTpenia (family history)
- -MYH9-associated PLTpenia
- -PLT-type (pseudo) vWD
- -BSS
- -GTA

Diagnosi – Esami di laboratorio

-IPF

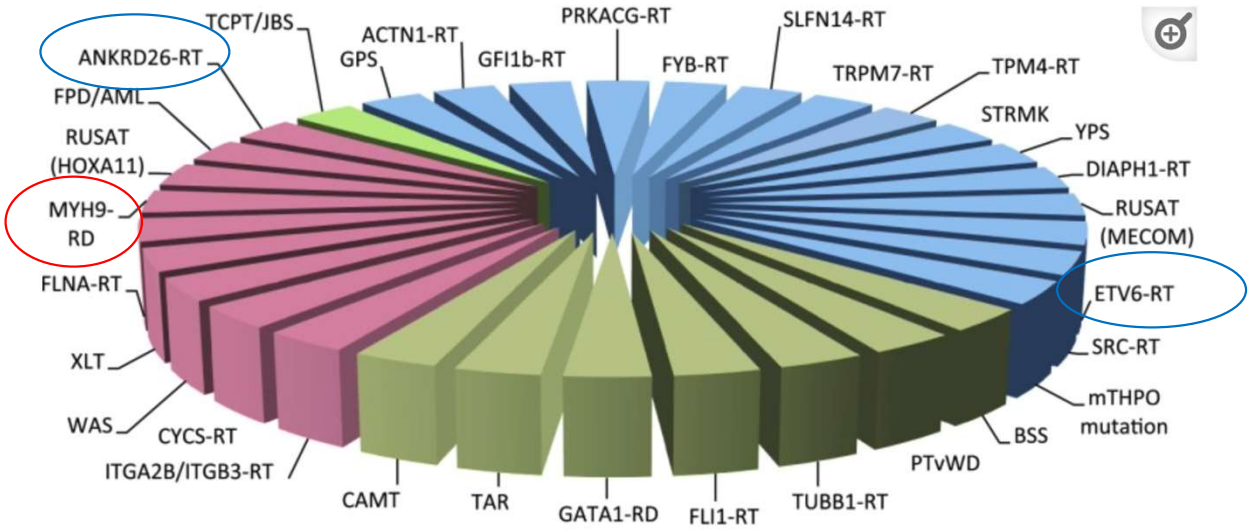
-Bone marrow biopsy

-Next generation sequencing

-if suspect of hereditary PLTpenia (family history)
- -MYH-associated PLTpenia
- -PLT-type (pseudo) vWD
- -BSS
- -GTA

-if poor or no resp to standard Tp
to identify genetic variant with a germline predisposition to cancer or hematologic neoplasia

Diagnosi – Esami di laboratorio



RUNX1

Diagnosi – Esami di laboratorio

Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder
Myeloid or lymphoid neoplasms with germline *RUNX1* mutation
Myeloid neoplasms with germline *ANKRD26* mutation
Myeloid or lymphoid neoplasms with germline *ETV6* mutation

important for:

-screening of related donor for HSC transplantation (use of related donor with the same germline mutation lead to donor-derived MDS or AML)

-counselling for family members

Thrombotic Microangiopathies
&
Immune Thrombocytopenic Purpura

Dr. Med. Capecchi Marco, MD PhD
Specialista in Ematologia

Clinica Luganese Moncucco / MC
CH - 25.09.2024