CESENA 28 maggio 2016
Sala Malatesta, Unaway Hotel

Le piastrinopenie “severe” non autoimmuni

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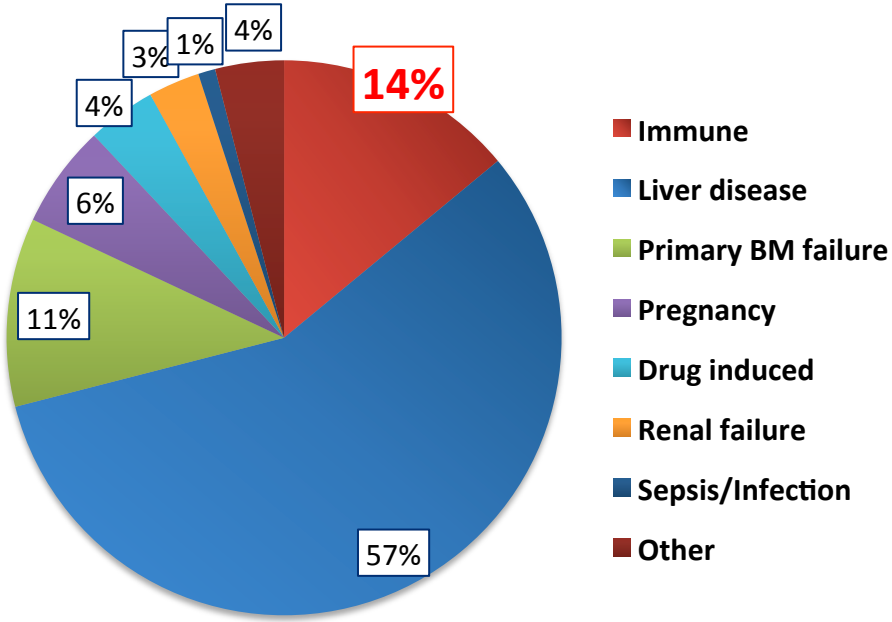
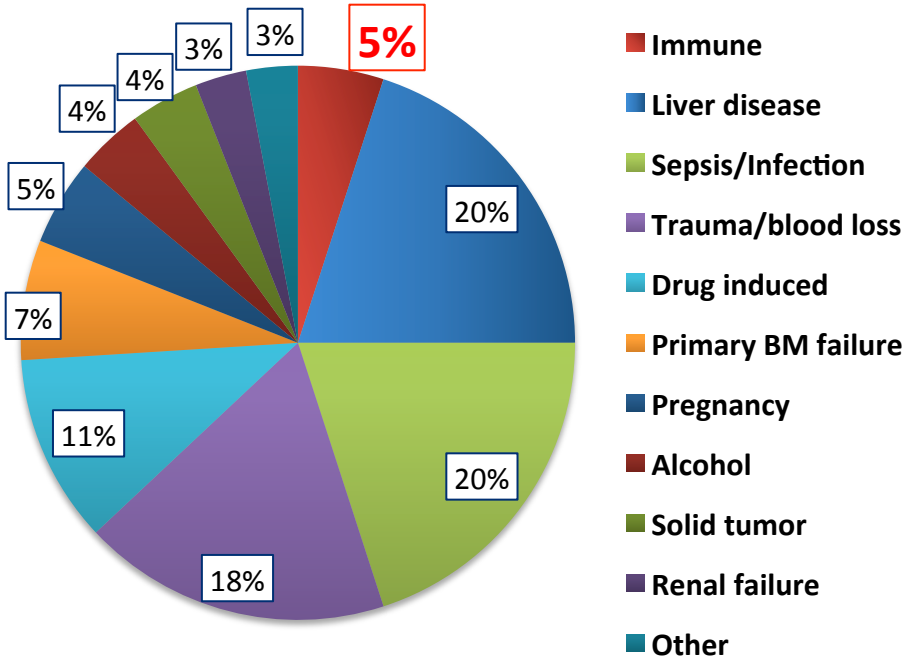
Non-immune Thrombocytopenia: The size of the problem

Causes of thrombocytopenia in outpatients (n=109)



Causes of thrombocytopenia in inpatients (n=114)



86% of outpatients and **95%** of inpatients presented a **non-immune** cause of **thrombocytopenia**

Hancox SH & Smith BC. ***Q J Med*** 2013; 106:425–431

Le piastrinopenia ”severe” non autoimmuni

- Chronic liver disease-related thrombocytopenia
- Thrombotic microangiopathy
- Bone marrow failure
- Hereditary thrombocytopenias

Le piastrinopenia ”severe” non autoimmuni

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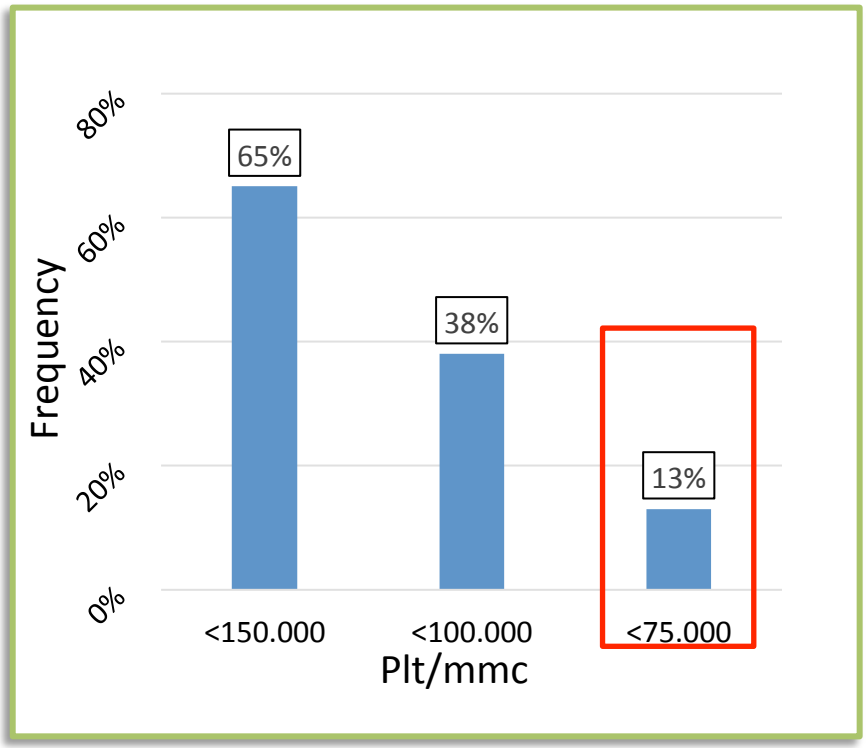
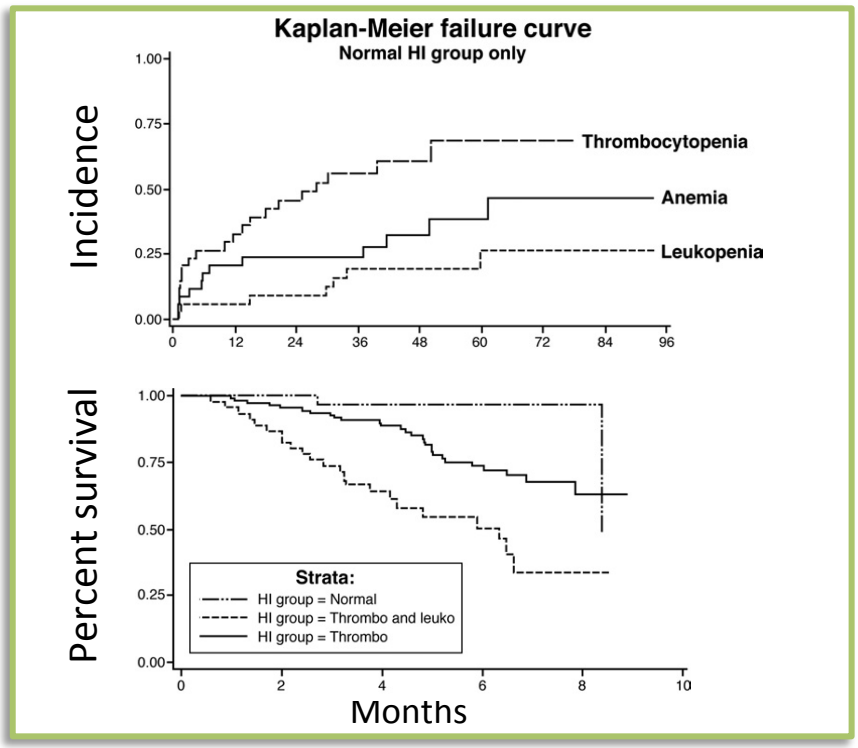
Thrombocytopenia in CLD: frequency

Thrombocytopenia is a well-known complication in chronic liver disease (CLD), with an **incidence of 65% to 85%** in patients with **cirrhosis**



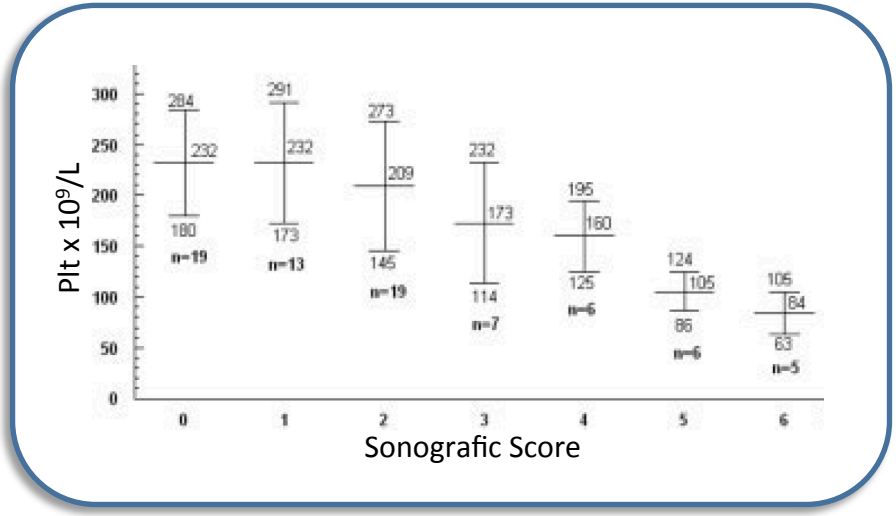


13% of patients present a **moderate to severe thrombocytopenia**, at cyrrhosis diagnosis

50% of patients with normal hematological parameters are expected to **develop thrombocytopenia within 2 years** from diagnosis

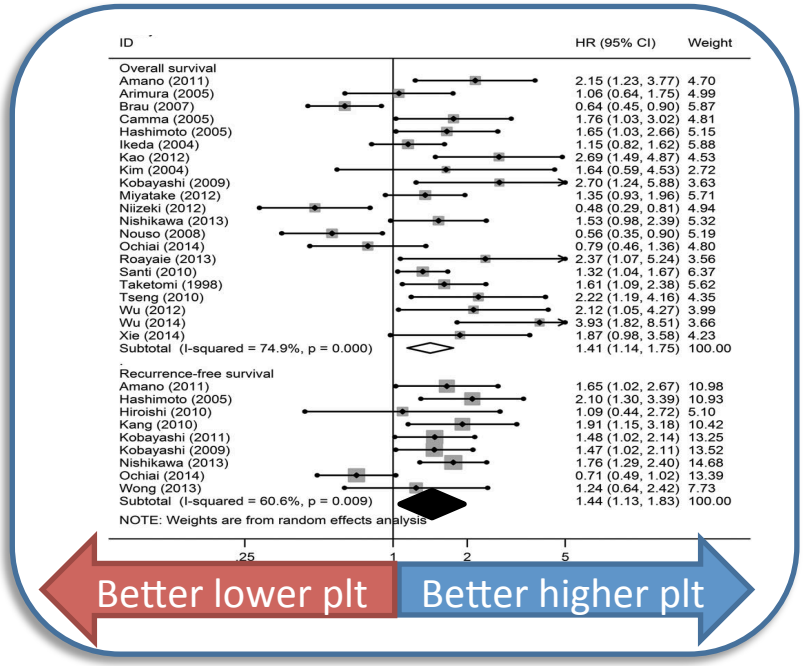
Afdhal et al. ***Journal of Hepatology*** 2008;48:1000-1007; Qamar AA ***Clin Gastroent And Hepat*** 2009;7:689-695

Thrombocytopenia in CLD: prognostic value



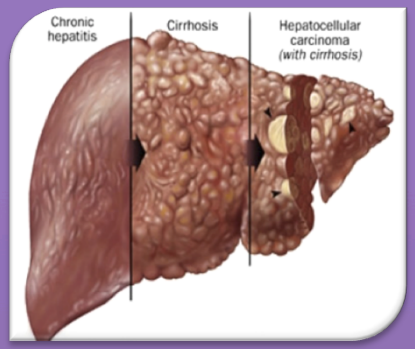
Platelet counts decreased according to **increased** pathologic **fibrosis US scores** for liver parenchyma disease and significantly correlated with **esophageal varices** and **HCC development**

A low level of PLT was found to be significantly associated with a **poor survival** of HCC, irrespective of the therapy used

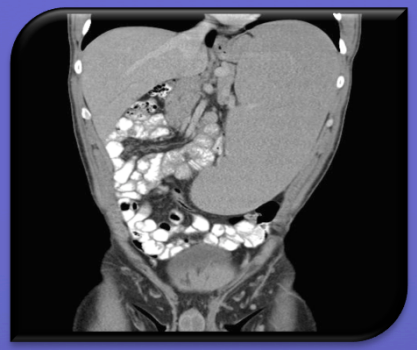


Pang Q et al. ***World J Gastroenterol*** 2015; 21: 5607-21; Lu SN et al. ***Cancer*** 2006;107:2212-22

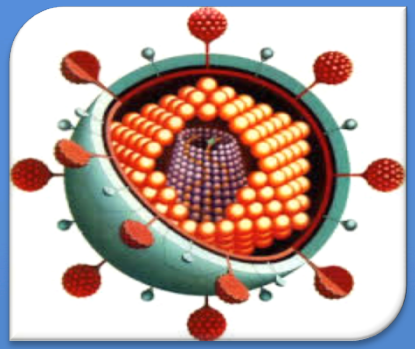
Thrombocytopenia in CLD: causes



- **TPO** production
- Hepatic **fibrosis**



- Portal **hypertension**
- **Plasma** expansion
- **Sequestration**



- **Myelosuppression**
- **Autoimmunity**

- **Alcohol** abuse
- **Interferon-α**
- **Chemotherapy** (HCC)

THROMBOCYTOPENIA

Giannini EG ***Aliment Pharmacol Ther*** 2006; 23, 1055-65; Afdhal et al. ***Journal of Hepatology*** 2008;48:1000-1007

Thrombocytopenia in CLD: clinical aspects

Along with thrombocytopenia, individuals with CLD have **abnormalities** in **tests of coagulation** (prolongations of PT, INR and aPTT).
Patients with CLD have an **increased risk** of **spontaneous bleeding** (e.g. variceal bleeding), or during or after **invasive procedure (liver biopsy)**.

TPO-receptor agonist	Setting	Endpoint	Results
Eltrombopag			
Phase II	HCV	Initiate IFN	71-91% started IFN
Phase III (ELEVATE)	HCV	Invasive procedures	72% transfusion-free
Phase III (ENABLE-I/II)	HCV	Initiate IFN	94-95%started IFN
Avatrombopag			
Phase II	Any	Invasive procedures	49% obtained >50 $x10^9$/L
Romiplostim			
Pilot study	Any	Invasive procedures	94% reached >70 $x10^9$/L

McHutchchison JG et al. ***N Engl J Med*** 2007;357(22):2227–36. Afdhal NH et al. ***N Engl J Med*** 2012;367(8):716–24; Afdhal NH et al. ***Gastroenterology*** 2014;146(2):442–52 e1. Terrault NA et al. ***J Hepatol***. 2014;61(6):1253–9. Moussa MM et al. ***J Gastroenterol Hepatol***. 2013;28(2):335–41.

Le piastrinopenia ”severe” non autoimmuni

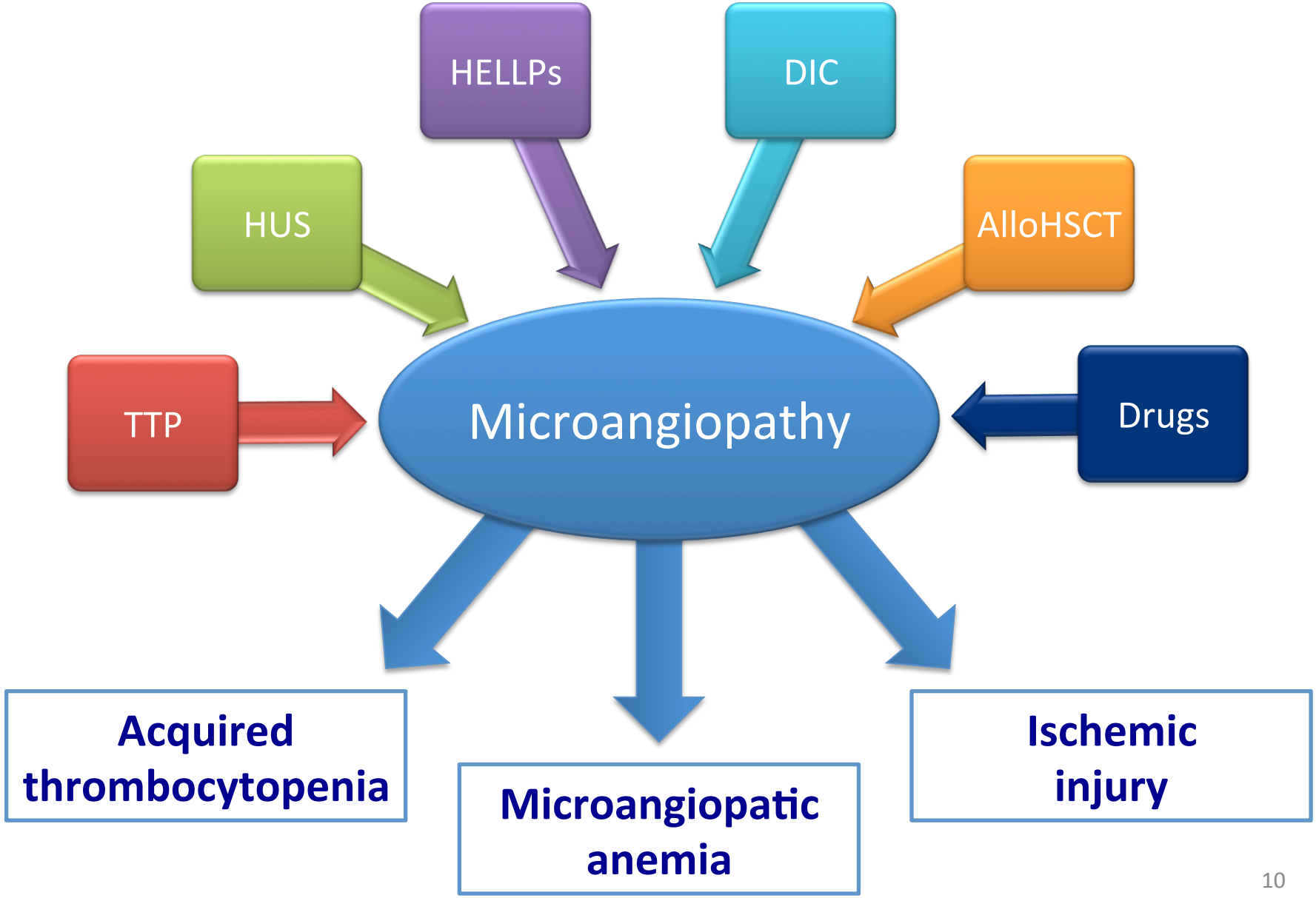
Chronic liver disease-related thrombocytopenia

Thrombotic microangiopathy

Bone marrow failure

Hereditary thrombocytopenias

Thrombotic thrombocytopenia



Differential diagnosis of TMAs

	TTP	HUS	DIC	HELLPs
Anemia	+	+	+	+
Thrombocytopenia	+	+	+	+
Renal Failure	-/+	**++**	-/+	-
Neurological symptoms	**++**	-/+	-	-
Liver abnormalities	-	-	-/+	**++**
Coagulation	**Normal**	**Normal**	**Defective**	**Defective**

George JN & Nester CM ***NEJM*** 2014; 371:654-66

Thrombotic thrombocytopenic purpura (TTP)

Thrombotic thrombocytopenic purpura is a thrombotic microangiopathy caused by severely **reduced activity** of the von Willebrand factor-cleaving protease **ADAMTS13**.
TTP can be acquired, due to an **autoantibody inhibitor** or **hereditary**, due to inherited mutations in ADAMTS13.

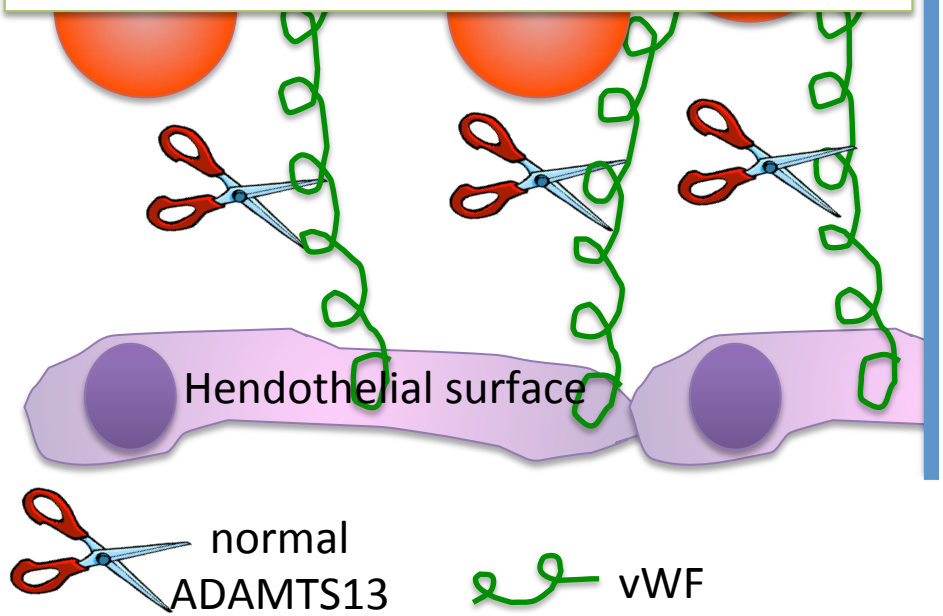
	Hereditary TTP (Upshaw-Shulman syndrome)	Acquired TTP
Frequency	1%	99%
Ethiology	ADAMTS13 gene mutations	Anti-ADAMTS13 antibody inhibitor
Epidemiology	5-10 cases per 1.000.000 adults per year	
ADAMTS13 activity	<5%	<5%
ADAMTS13 inhibitor	No	Yes

Shenkman B & Einav Y. ***Autoimmunity Rev*** 2014; 13:584-586

Normal Hemostasis

When **ADAMTS13 activity** is reduced **ultralarge vWF accumulate** on the endothelial surface, where platelets attach and accumulate

This leads to the formation of **platelet and vWF microthrombi**, which cause **platelet consumption** and **red blood cells fragmentation**



ADAMTS13 is a **protease**, which cleaves **ultralarge** von Willebrand factor (**vWF**), produced by the endothelial surface

This normal cleaveage **prevents ultralarge multimers** from **accumulating**, expecially in areas of high shear stress (small arterioles and capillaries)

TTP – clinical manifestations

TTP usually presents as severe microangiophatic **hemolitic anemia** and **thrombocytopenia** in a previously **healthy individual**. Importantly, however, **not all** patients with TTP are **critically ill**.

Low platelets	Anemia	Neurologic dis.	Renal failure	Fever
Purpura	Fatigue	Visual disturbance	Oliguria	50%
Petechiae	Difficulty concentrating	Confusion	Hypertension	
Epistaxis	Dyspnea	Paresthesia	Water retention	
Metrorrhagia	Pallor	Convulsions	5-10%	
Cerebral hemorrhage	Palpitations	Coma		
100%	90%	50-75%		

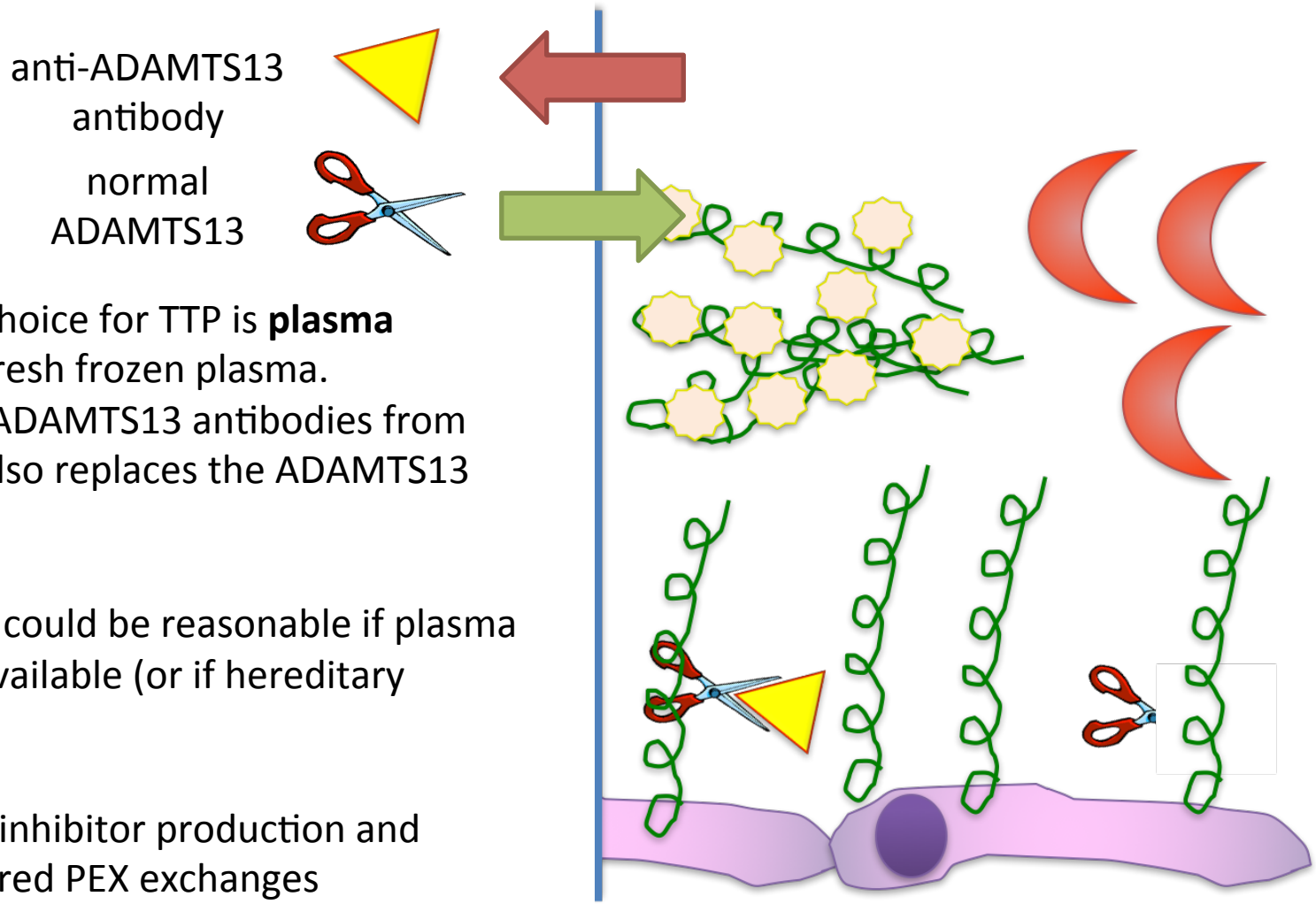
The complete **pentad** is rare, being present in only **5-40% of patients** at diagnosis.

On the contrary, **gastrointestinal symptoms** are **common** (nausea, vomiting, or diarrhea), probably related to **visceral ischemia**

George JN. ***Blood*** 2010; 116:4060-9

TTP – treatment

TTP is a **medical emergency** that is almost always fatal if appropriate **treatment** is not initiated **promptly**. Therapy should not be delayed while awaiting the results of ADAMTS13 activity levels or inhibitor testing.



The therapy of choice for TTP is **plasma exchange** with fresh frozen plasma.
It removes anti-ADAMTS13 antibodies from the blood and also replaces the ADAMTS13 enzyme.

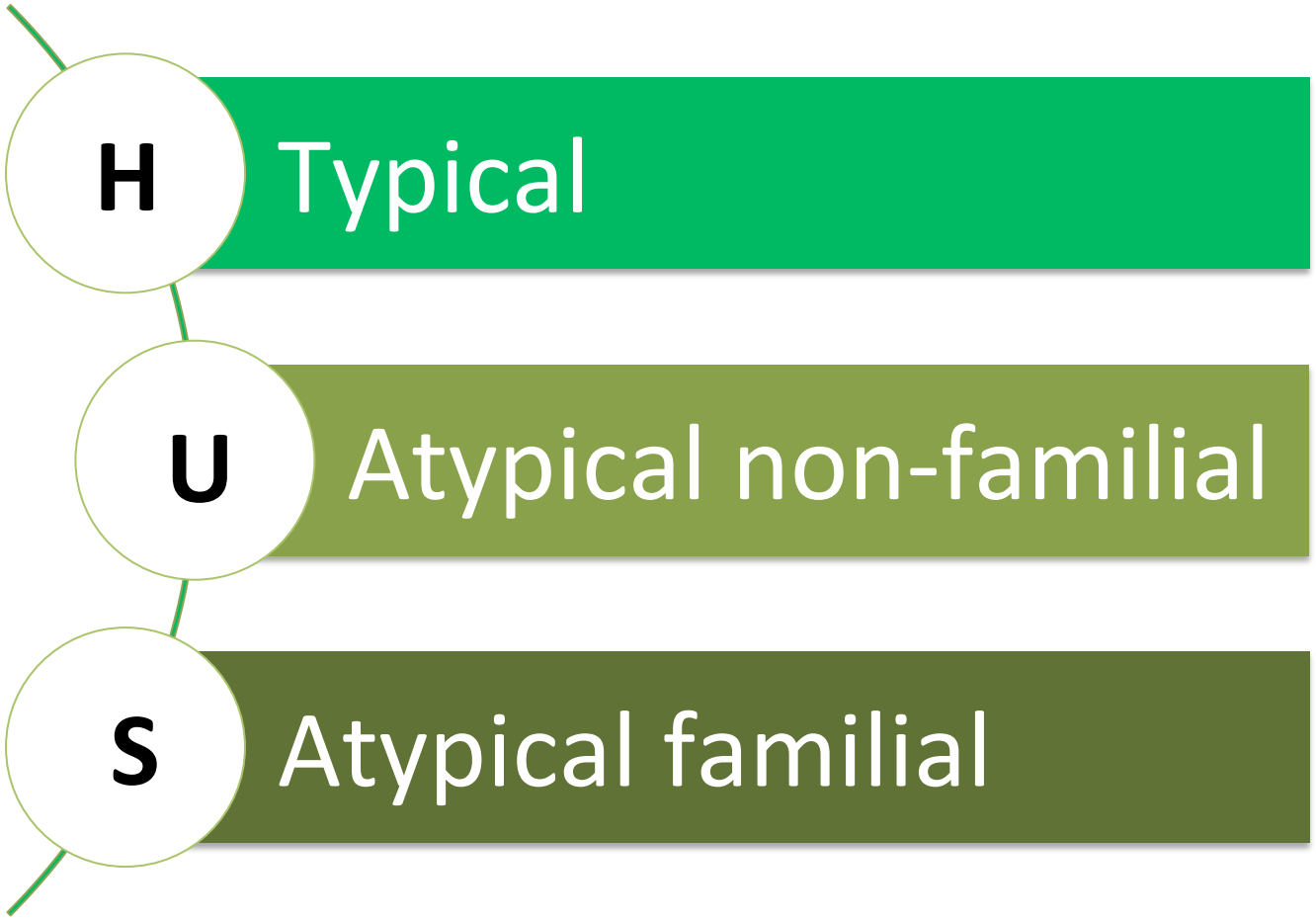
Plasma infusion could be reasonable if plasma exchange isn't available (or if hereditary disease)

Steroids reduce inhibitor production and number of required PEX exchanges

George JN. ***Blood*** 2010; 116:4060-9

Hemolitic-uremic syndrome (HUS)

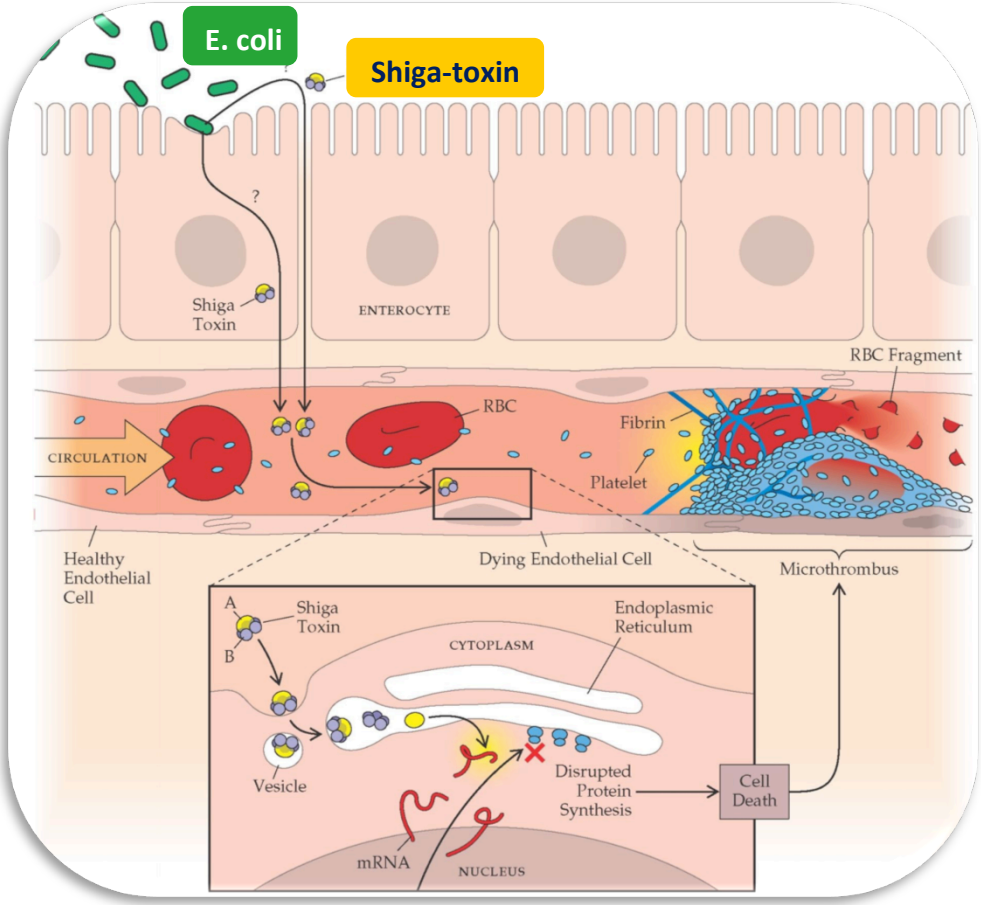
Hemolytic uremic syndrome (HUS) is characterized by generalized thrombotic microangiopathy (TMA) and the clinical **triad of thrombocytopenia**, **microangiopathic anemia**, and **acute renal failure**



Cheung V & Trachtman H ***Front Med*** 2014;42:1:7

Shiga-toxin associated HUS (typical HUS)

Typical HUS is caused by **Shiga-toxin producing bacteria** (e.g. more often E. coli O157:H7, but also Shighella dysenteriae).



Most cases occur in **children** under 5 years old

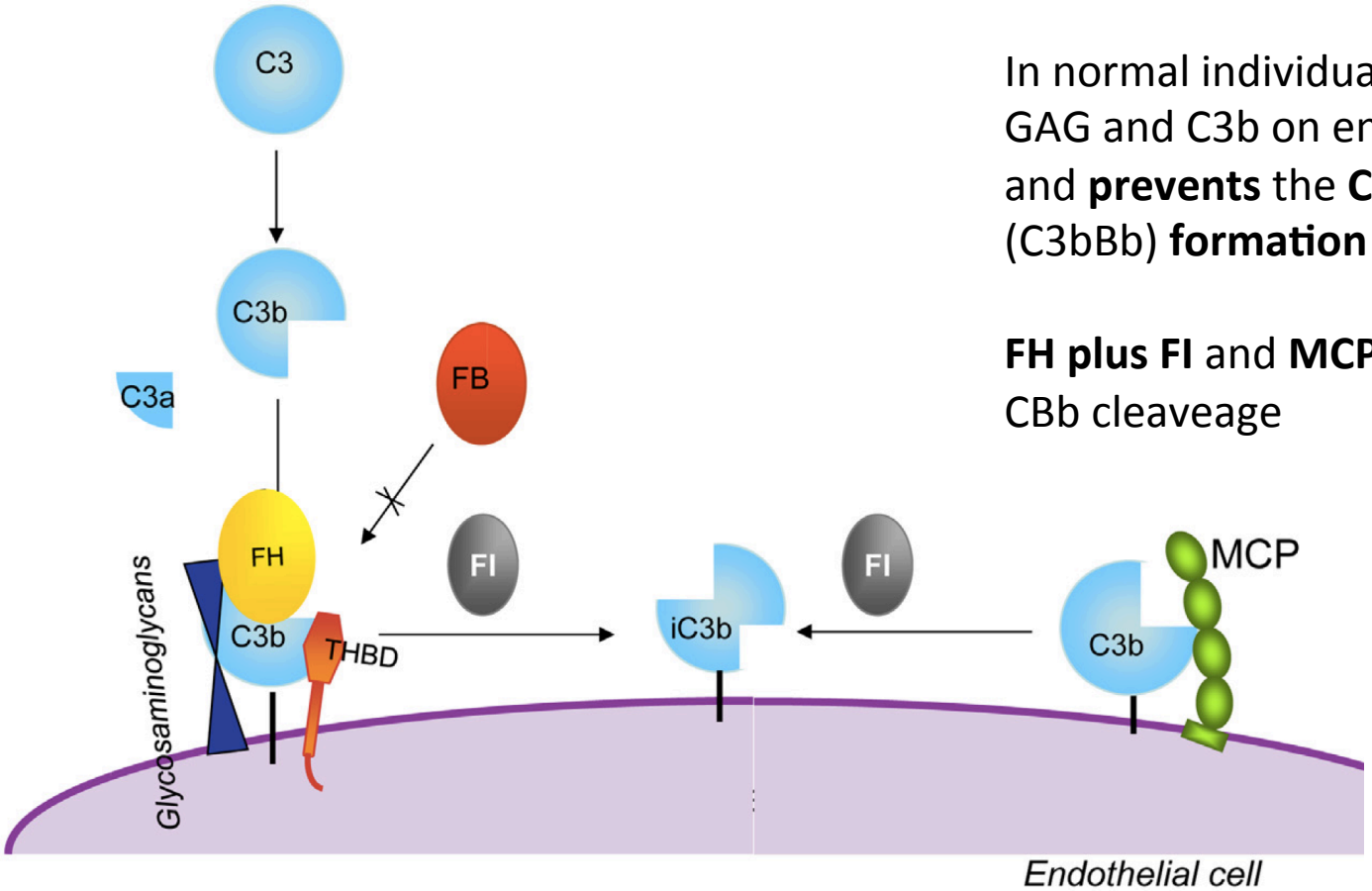
After a 2-5 day incubation period, **profuse (bloody) diarrhea** develops 3-15 days later features of **HUS** arise

There is **no direct treatment**.
Medical **management is supportive** (fluid and electrolyte management, medication for hypertension), focusing on stabilizing the patient until natural **disease resolution occurs (>80%)**

Keir LF. ***Hematol Oncol Clin N Am*** 2015;29:525-539

Alternative complement pathway

Complement is part of **innate immune system** and plays a fundamental role in the clearence of immune complexes and cell debris. The alternative pathway is responsible for **immune defence** angainst **bacteria** and **viruses**



In normal individuals **factor H** binds to GAG and C3b on endothelial surface and **prevents** the **C3-convertase** (C3bBb) **formation**

FH plus FI and **MCP plus FI** mediate CBb cleaveage

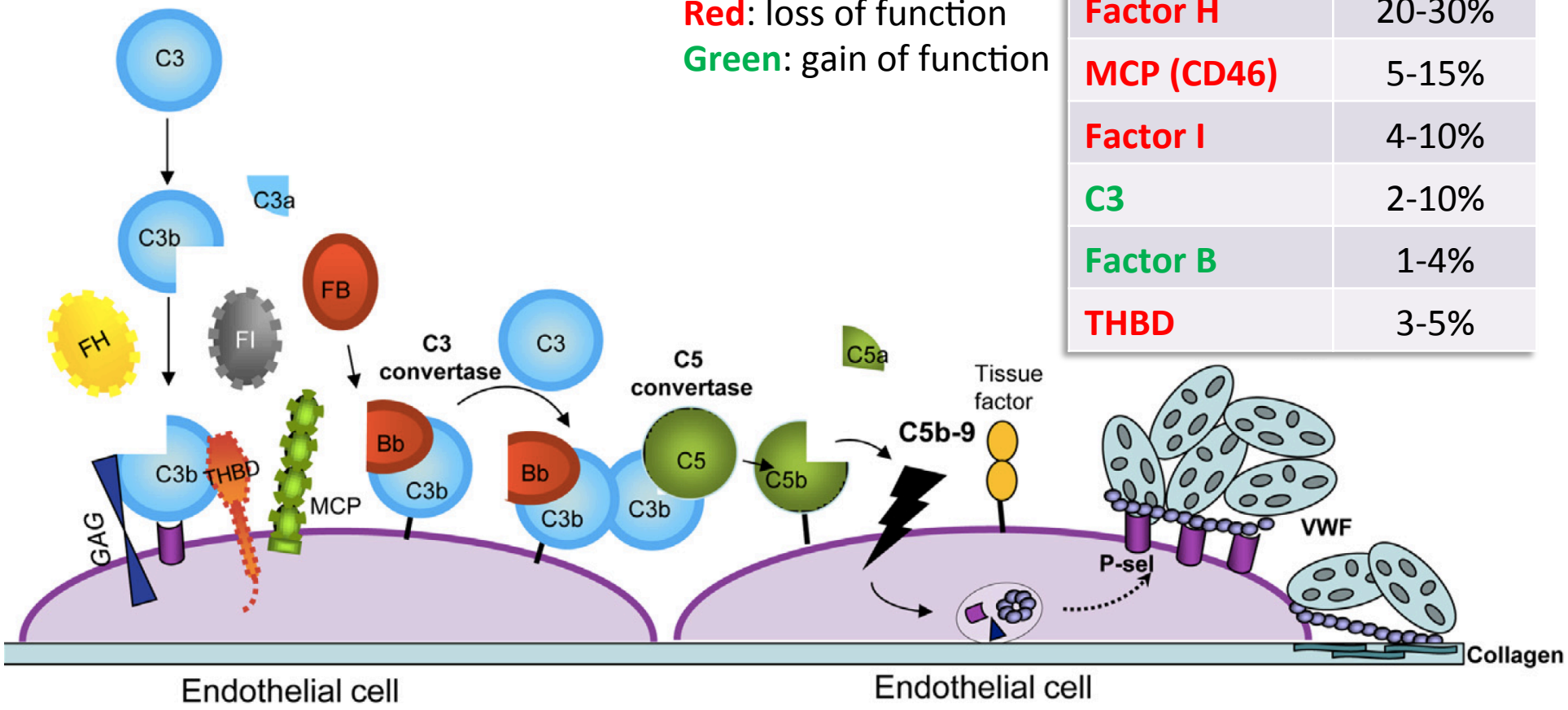
Noris M & Remuzzi G ***Am J Kidney Dis*** 2015; 66:359-375

Atypical HUS (complement-mediated HUS)

Atypical HUS is a rare disorder (incidence 0.5-2 per million persons). Most complement-mediated HUS cases are due to **gene mutations of complement factors**. Antibodies against complement proteins have been implicated in 6-10% of patients.

Red: loss of function
Green: gain of function

Gene mutated	Frequency
Factor H	20-30%
MCP (CD46)	5-15%
Factor I	4-10%
C3	2-10%
Factor B	1-4%
THBD	3-5%

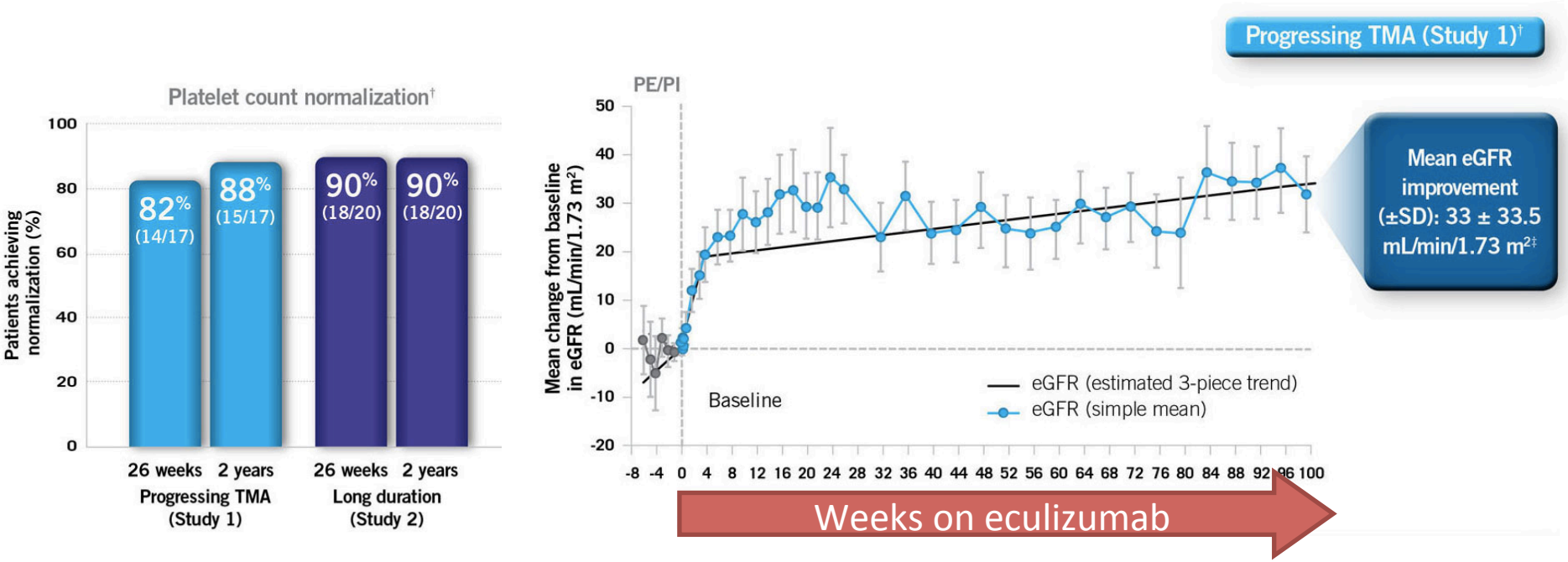


Noris M & Remuzzi G ***Am J Kidney Dis*** 2015; 66:359-375

Atypical HUS – prognosis and treatment

The natural course of this disease is variable, up to **60-70%** of patients progresses to **end-stage renal disease or death** within one year of presentation. In addition, there is a high rate of recurrent disease in patients who undergo **renal transplantation**.

Treatment options include: **supportive therapy**, **plasma** infusion/exchange (plus steroids in antibody-mediated aHUS) and **eculizumab** (anti-C5 antibody)



Legendre CM et al. ***N Engl J Med*** 2013;368:2169-81.

Le piastrinopenia ”severe” non autoimmuni

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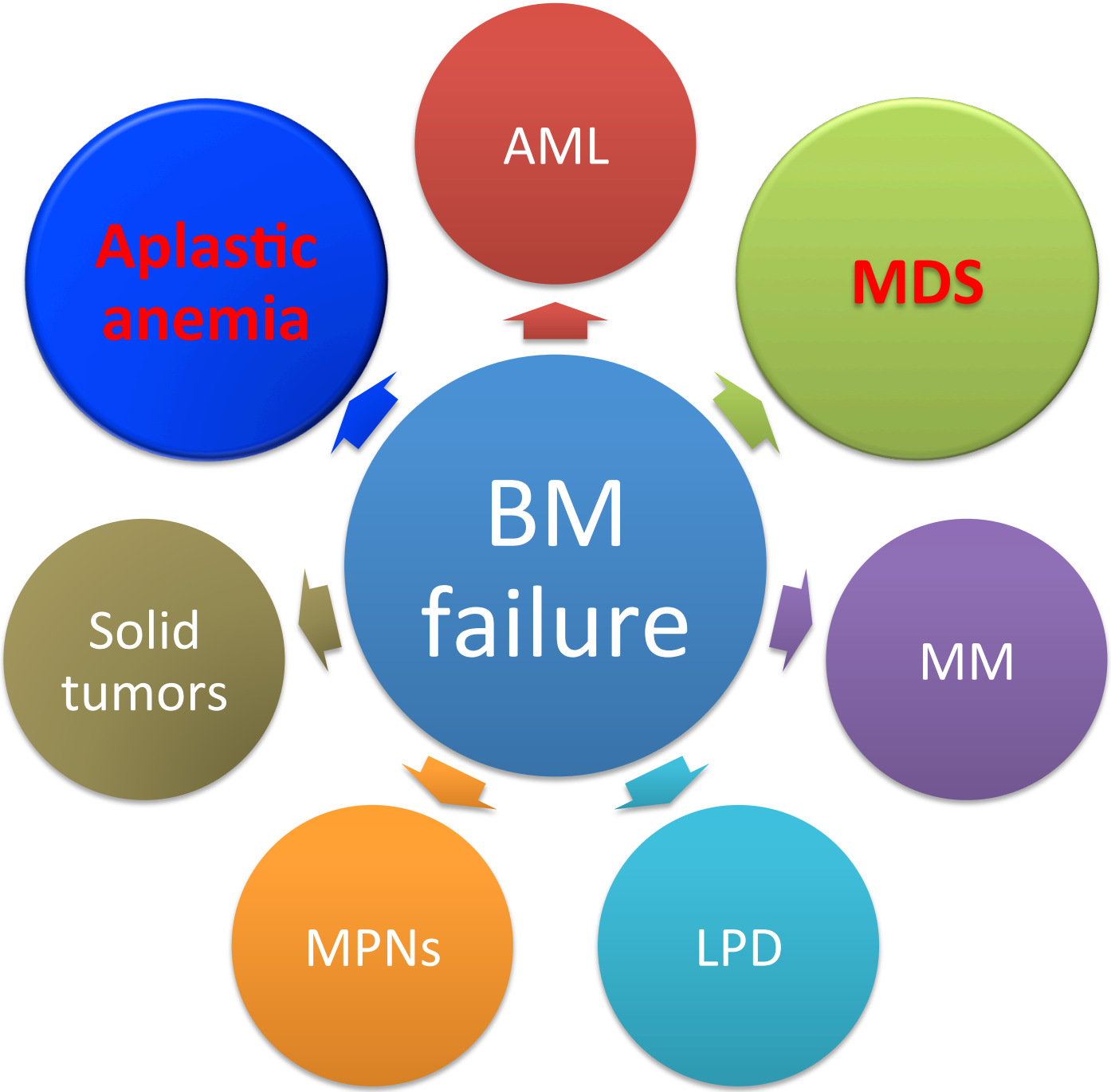
Thrombotic microangiopathy

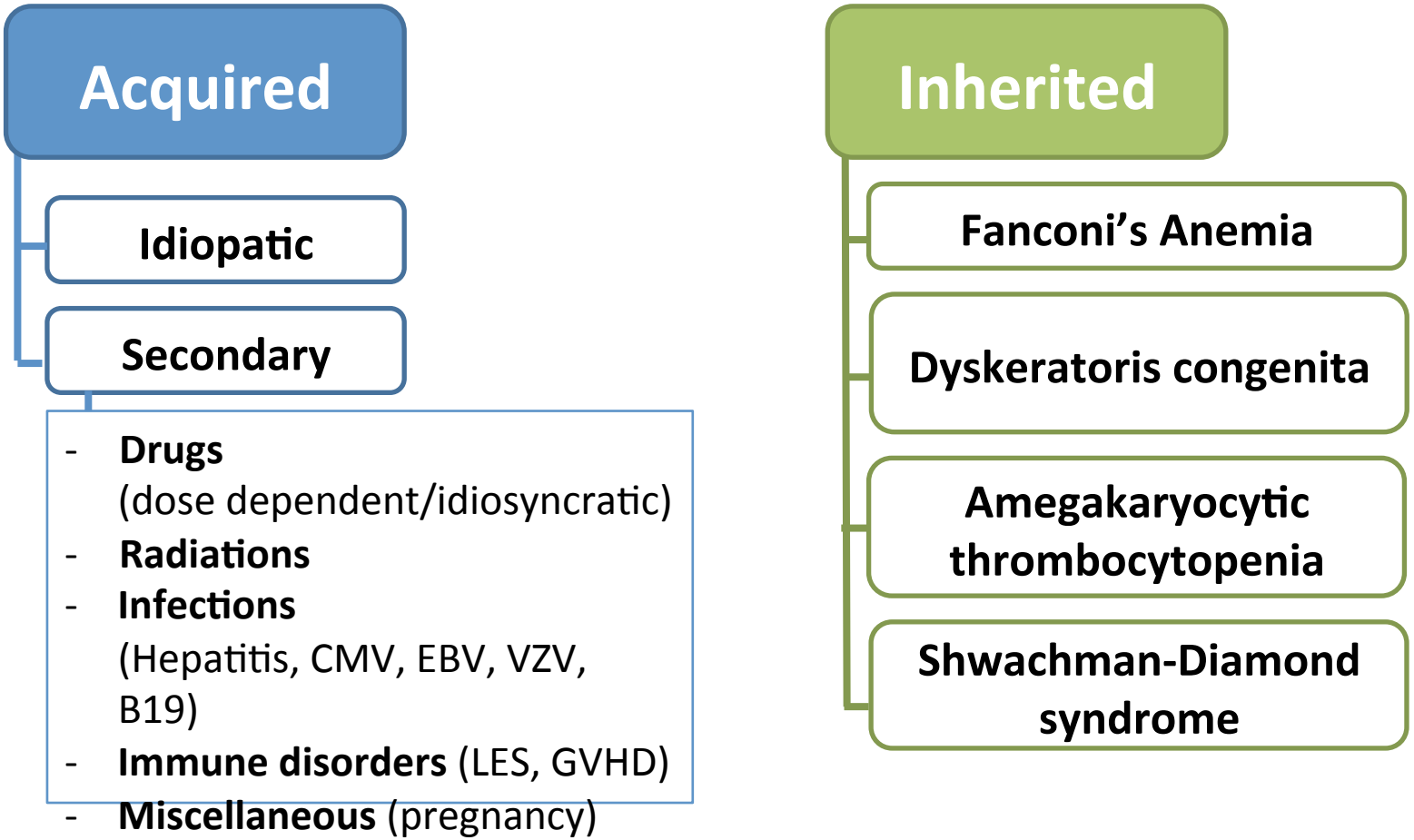
Bone marrow failure

Hereditary thrombocytopenias


AML
Aplastic anemia
MDS
BM failure
Solid tumors
MM
MPNs
LPD

Aplastic anemia

Aplastic anemia is a disorder characterized by diminished or **absent hematopoietic precursors** in the bone marrow. In about 10-20% of cases an **isolated thrombocytopenia** may precede the trilinear **cytopenia**.

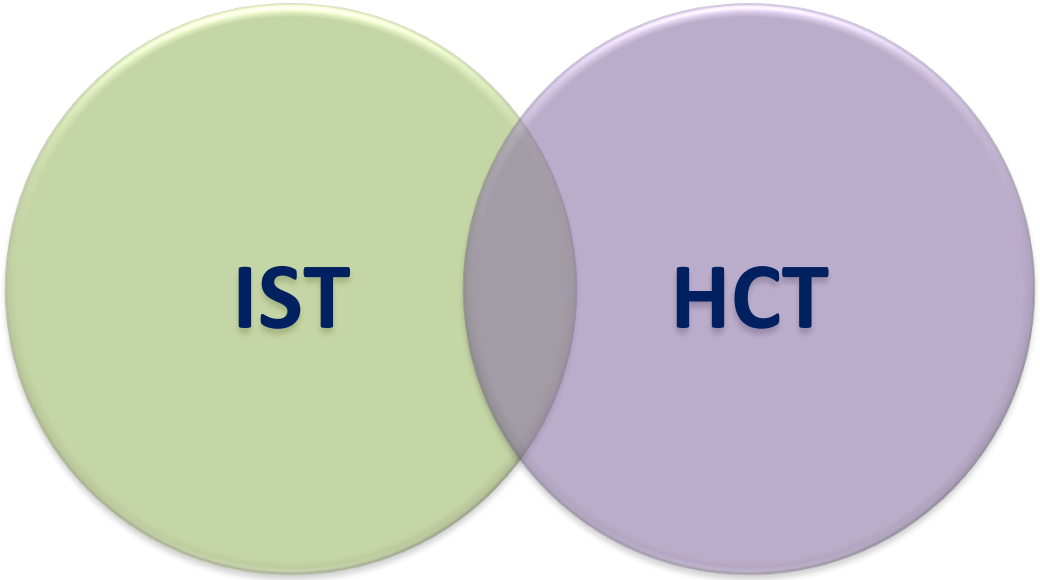


Scheinberg P & Young NS. ***Blood*** 2012;120: 1185-1196

Aplastic anemia - treatment

The **pathogenesis** of aquired idiopatic **aplastic anemia** has always been associated with possible **immunomediated** mechanisms, as shown by response to **immunosuppressive therapy (IST)**.

- **Age**
- **Comorbidities**
- Grade of **severity**
- Availability of an appropriate **donor**



Immuno suppressive therapy with **ATG** (horse>rabbit) plus **CyA** and **steroids** represent the standard first-line treatment, with about **60-65%** of patients achieving a **clinical response (about 10%** obtaining a **complete remission)**

Peinemann F & Labeit AM. ***BMJ Open***. 2014;4:e005039; Scheinberg P et al. ***N Engl J Med*** 2011;365:430-8.

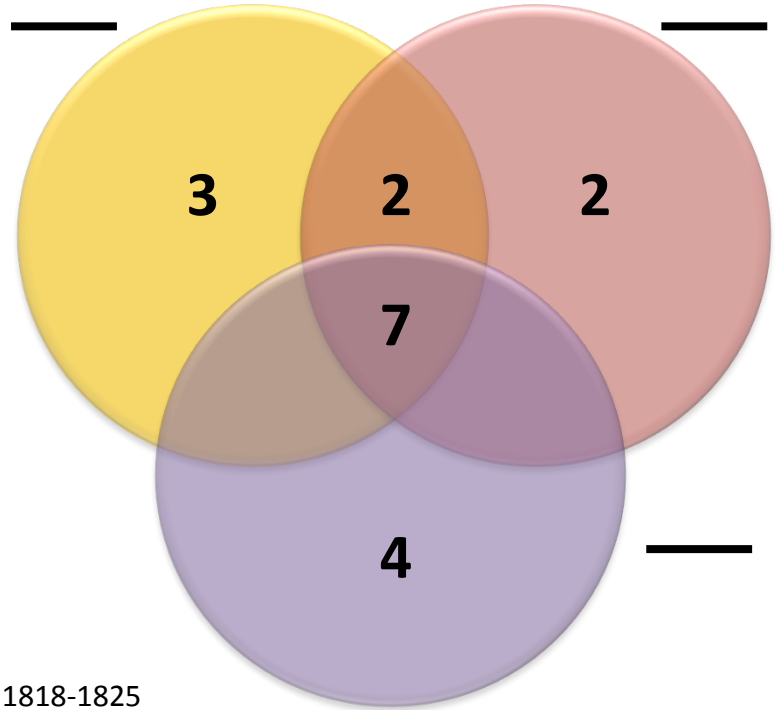
Aplastic anemia – TPO receptor agonists

Characteristics	Total (43)
Age, median (range)	44 (17-44)
≧ 2 prior IST	84%
RBC-transfusion dependent	86%
PLT-transfusion dependent	91%

Open-label, single center, **Phase II** trial assessing safety and efficacy of **eltrombopag** in IST-refractory SAA

18 out of 43 (40%) patients experienced an **hematological response** (5 patients mantained the response after discontinuation)

Platelet response
- increase >20 x10^9/L
- Transfusion-independence



Erythroid response
- increase by 1.5 g/dL for Hb <9 g/dL at start
- Reduction in the RBC-transfusions for 8 weeks

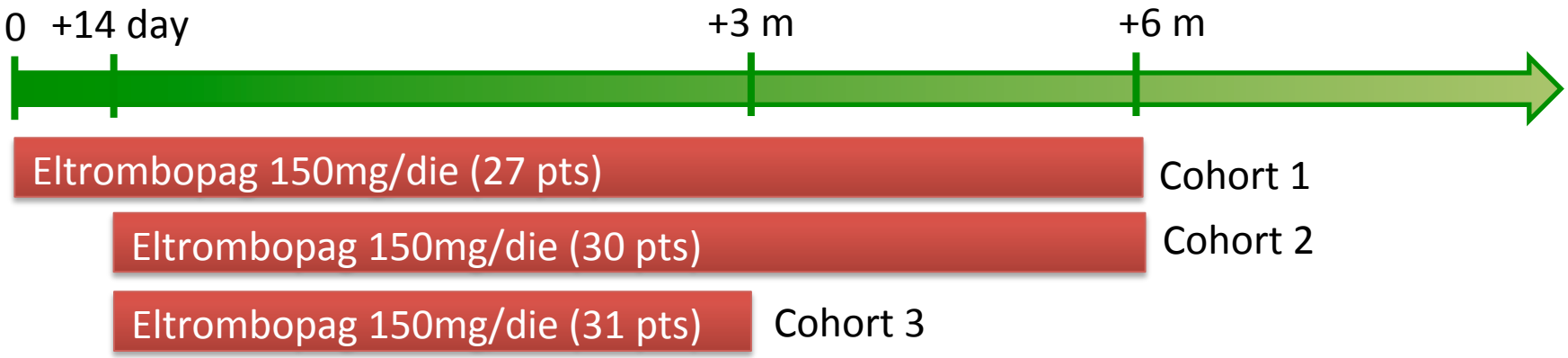
Neutrophil response
- increase by 100% for pre-treatment ANC <0.5 x10^9/L
- According CTCAE for >0.5 x10^9/L

Desmond R et al. ***Blood*** 2014;123:1818-1825

Eltrombopag in association to IST

88 patients with **treatment-naive SAA**, enrolled from July 2012 to October 2015 in a phase II trial

All patients received **hATG** 40 mg/Kg d1-4 and **CsA** for 6 months (blood levels 200-400)



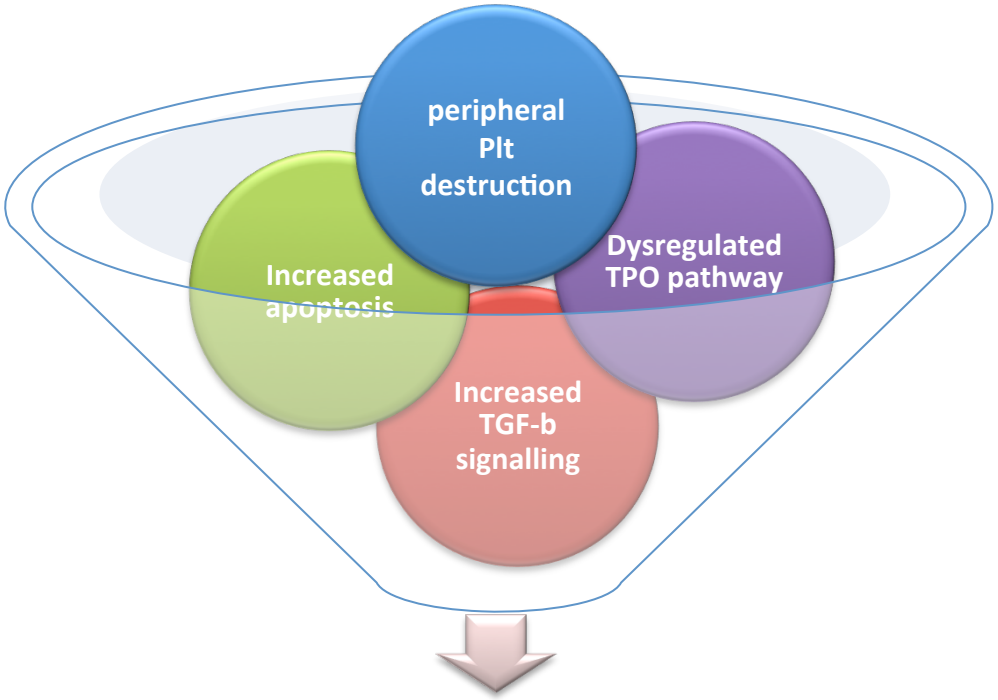
	3 months (82)	6 months (74)
ORR	**66 (80%)**	**63 (85%)**
PR	43 (52%)	34 (46%)
CR	23 (28%)	25 (34%)

Median time to response to ANC >500 was **35-47 days**, to platelet transfusion independence 32 days, to RBC-transfusion independence 42 days

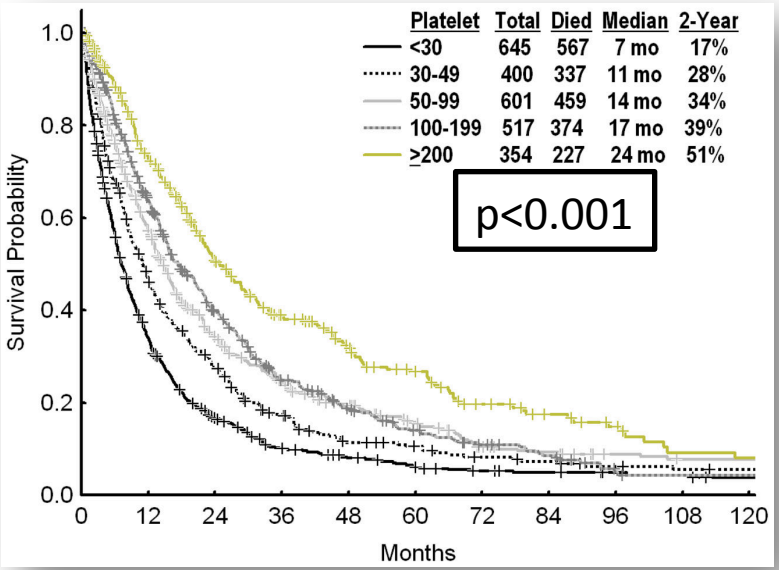
Townsley et al . ***ASH meeting abstract*** 2015

MDS with thrombocytopenia

An **isolated thrombocytopenia (IT)** may rarely represent the only clinical manifestation of MDS at diagnosis (5-10%). The estimated **prevalence of thrombocytopenia** in MDS, has been shown to range from **40 to 65%** at diagnosis. About **25%** of patients presents a severe thrombocytopenia (<30 x10^9/L).



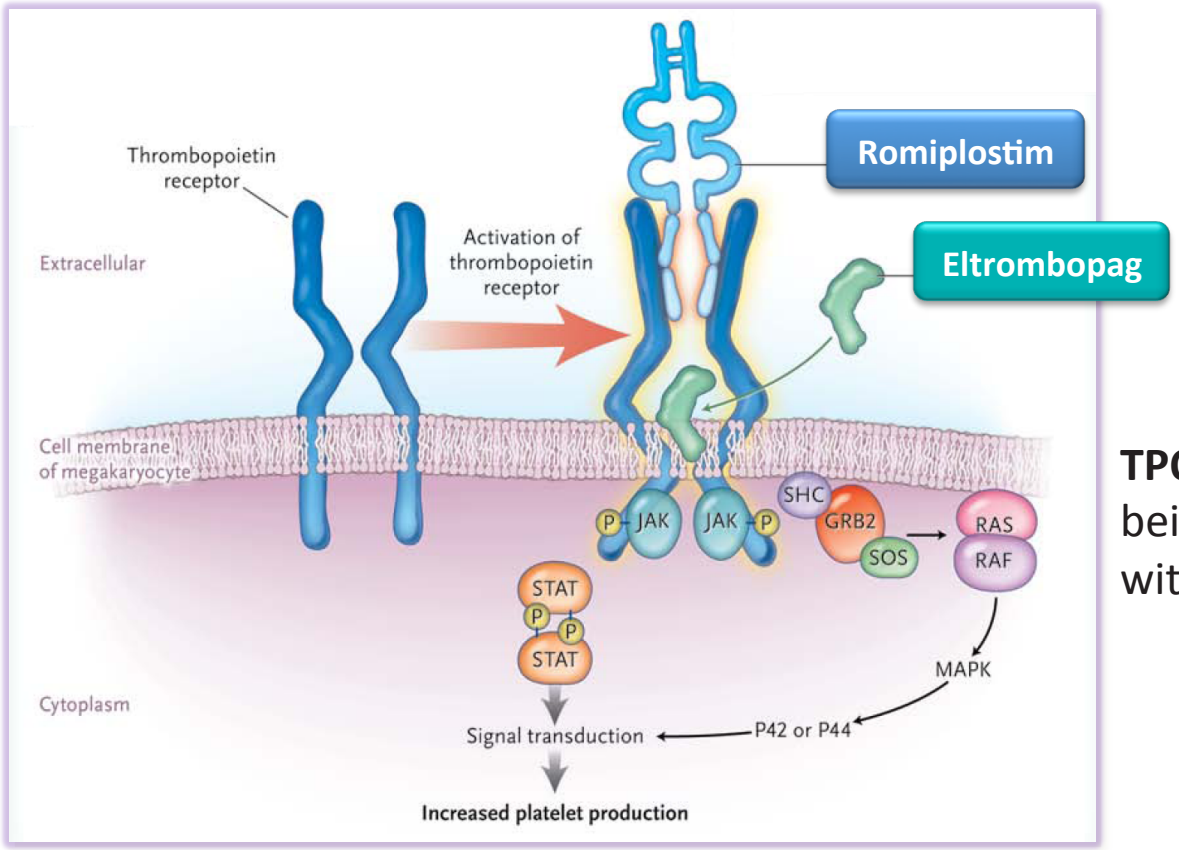
Hemorrhagic complications which are due to thrombocytopenia and platelet dysfunction, are important causes of **morbidity and mortality** in MDS patients



Al Ameri A et al. ***Clin Lymphoma Myeloma Leuk.*** 2011;11: 237–241; Li W et al. ***Leukemia*** 2016;30:536-44

MDS with thrombocytopenia - treatment

Managing thrombocytopenia in MDS remains **challenging**. Current treatment options for MDS with thrombocytopenia may include: platelet **transfusions**, **hypometilating agents** (ORR 35-40%), **immunosuppressive therapy** (ATG ± CyA, ORR 25-40%), **androgens** (danazole, ORR 20%)



TPO agonists are promising and are being tested in trials in combination with other agents

Li W et al. ***Leukemia*** 2016;30:536-44; Ades L et al. ***Lancet*** 2014; 383: 2239–52

Le piastrinopenia ”severe” non autoimmuni

Chronic liver disease-related thrombocytopenia

Thrombotic microangiopathy

Bone marrow failure

Hereditary thrombocytopenias

Hereditary thrombocytopenias

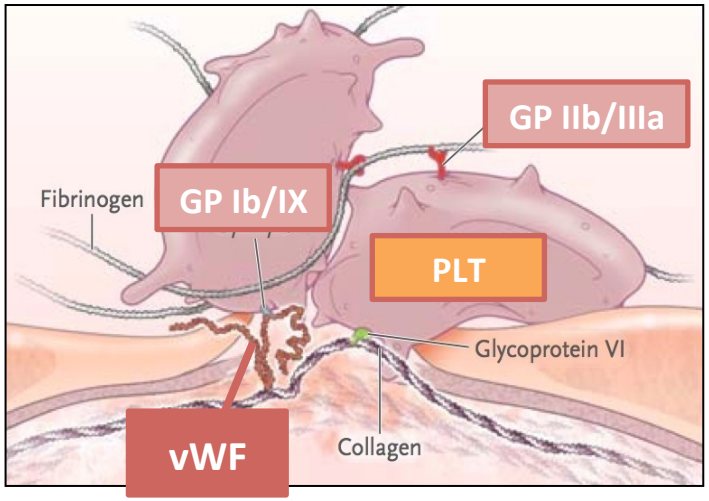
A **large number of rare inherited diseases** presents with **reduced platelet count**, and many also have impaired platelet function. These conditions arise from genetic defects of the **megakaryocyte lineage** that result in dysregulated thrombopoiesis

Small platelets (MPV <7 fL)	Normal-sized platelets (MPV 7 to 11 fL)	Large platelets (MPV >11 fL)
Wiskott-Aldrich syndrome	Congenital amegakaryocytic thrombocytopenia	Bernard-Soulier syndrome
X-linked thrombocytopenia	TAR syndrome	MYH9-related disorders
	Amegakaryocytic thrombocytopenia with radioulnar synostosis	DiGeorge syndrome
	ANKRD26-thrombocytopenia	Paris-Trousseau syndrome
		Gray platelet syndrome
		Platelet-type vWB disease
		Type 2B vWB disease

Kumar R & Kahr WH. ***Hematol Oncol Clin North Am*** 2013;27:465-94.

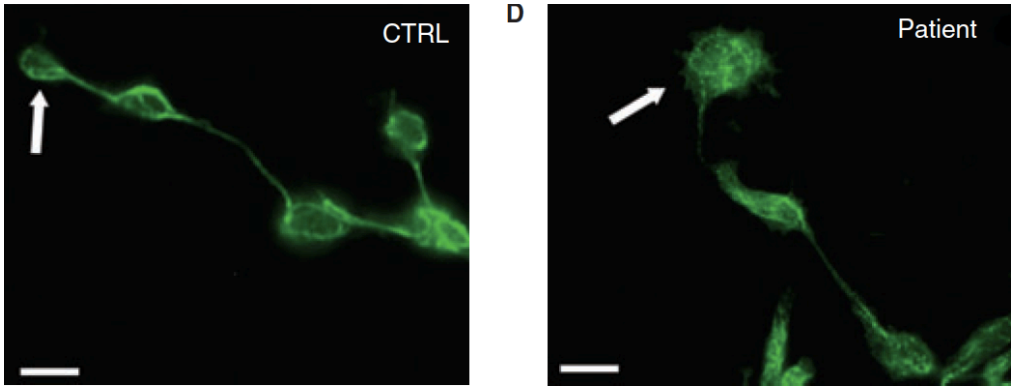
Bernard-Soulier syndrome

Bernard-Soulier syndrome (BSS) is a **autosomal recessive thrombocytopenia** induced by **mutations in GPIb** (alpha or beta) or **GPIX** resulting in quantitative or qualitative abnormalities affecting platelet adhesion. So far, **more than 50 different mutations** have been identified



Few **monoallelic mutations** of GP1BA or GP1BB have been reported to result in a mild form of BSS transmitted as an a autosomal dominant trait (e.g. **Bolzano variant**)

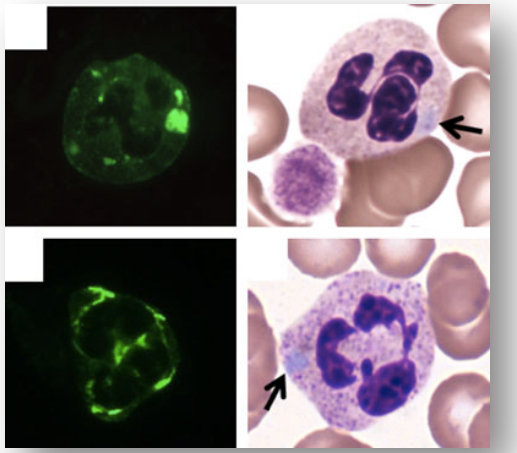
Unlike with biallelic BSS, **platelet aggregation** in response to ristocetin is completely **normal** or only marginally reduced



Balduini CL et al. ***Platelets*** 2016 [epub]; Balduini CL et al. ***JTH*** 2013;11: 1006-19; Balduini A et al. ***JTH*** 2009;7:478-484

MYH9-related disease

MYH9-RD is an **autosomal dominant** disorder presenting at birth as a **non-syndromic form** of macrothrombocytopenia. However, patients are exposed to an increased risk of sensorineural **deafness**, **cataract**, alteration of **liver** enzymes, and/or a **glomerulonephritis**



Individuals with MYH9-RD have characteristic inclusion **(Dohle-like) bodies** in the cytoplasm of neutrophils containing wild-type and mutant myosin-9

Hemorrhagic manifestations are proportional to the grade of thrombocytopenia

	Hearing loss	Cataract	Renal defect	Leukocytes inclusion
May Hegglin	N	N	N	Y
Sebastian syndrome	N	N	N	Y
Fechtner syndrome	Y	Y	Y	Y
Epstein Syndrome	Y	N	Y	N

Strong correlations between genotypes and phenotypes have been identified. Patients with mutations in the **motor domain** generally have a **serious form of the disease**

Balduini CL et al. ***Platelets*** 2016 [epub]; Balduini CL et al. ***Haematologica*** 2002; 87:860-880; Balduini CL et al. ***JTH*** 2013;11: 1006-19

Hereditary thrombocytopenias – therapy

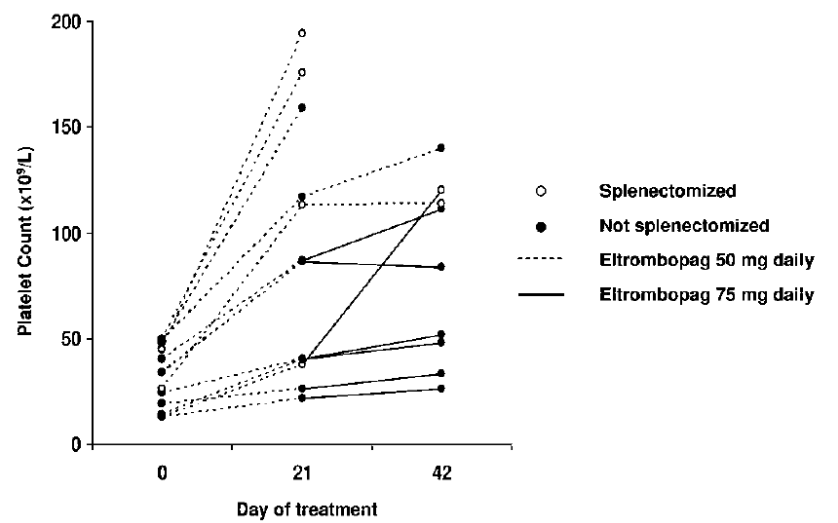
Inherited thrombocytopenias identified in adults **do not** usually show **spontaneous bleeding**

Prevenction of bleeding:

- **Avoid** NSAID, some antibiotics, cardiovascular agents, psychotropic agents, and oncologic agents,anesthetics, antihistamines
- **Prevent the need for medical interventions** (e.g. dental care)

In cases of **surgery**:

- **Maintain a safe platelet count by transfusion**
- **Desmopressin**



12 patients with MYH9-RD and platelets below 50 x10^9/L treated with eltrombopag

ORR 91% (11/12)

Balduini CL et al. ***JTH*** 2013;11: 1006-19; Pecci A et al. ***Blood*** 2010;16:5832-5837

Conclusions

- **Non immuno-mediated thrombocytopenia** represents the **most frequent cause** of thrombocytopenia in adults
- **Chronic liver disease** is the **leading cause** of non-immune thrombocytopenia. Thrombocytopenia does correlate with **disease severity** and **outcome**. It can interfere with invasive procedures and disease treatment
- **Platelet consumption** is the result of thrombotic **microangiopathy**. The appropriate treatment have to be started as soon as possible to improve outcome
- **Hematological neoplasms** are frequently associated to **thrombocytopenia**, that can represent the **first sign** of disease
- **Hereditary thrombocyopenias** should be taken into account in **differential diagnosis with ITP**, in particular in patients not responding to first-line steroid treatment
- **Thrombopoietin receptor agonists** represent intriguing **therapeutic option** in most non-immune thrombocytopenia

GRAZIE!

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