

2019



Progetto Ematologia Romagna

Si può ancora morire per un sanguinamento difficilmente controllabile? Utilità e limiti del laboratorio

Pievesestina (FC) 21-9-2019

Giovanni Poletti

Laboratorio AUSL Romagna Patologia Clinica - Ematologia

Laboratorio SI

**Valutazione del
rischio emorragico**



Prevenire un'emorragia in un
soggetto a rischio



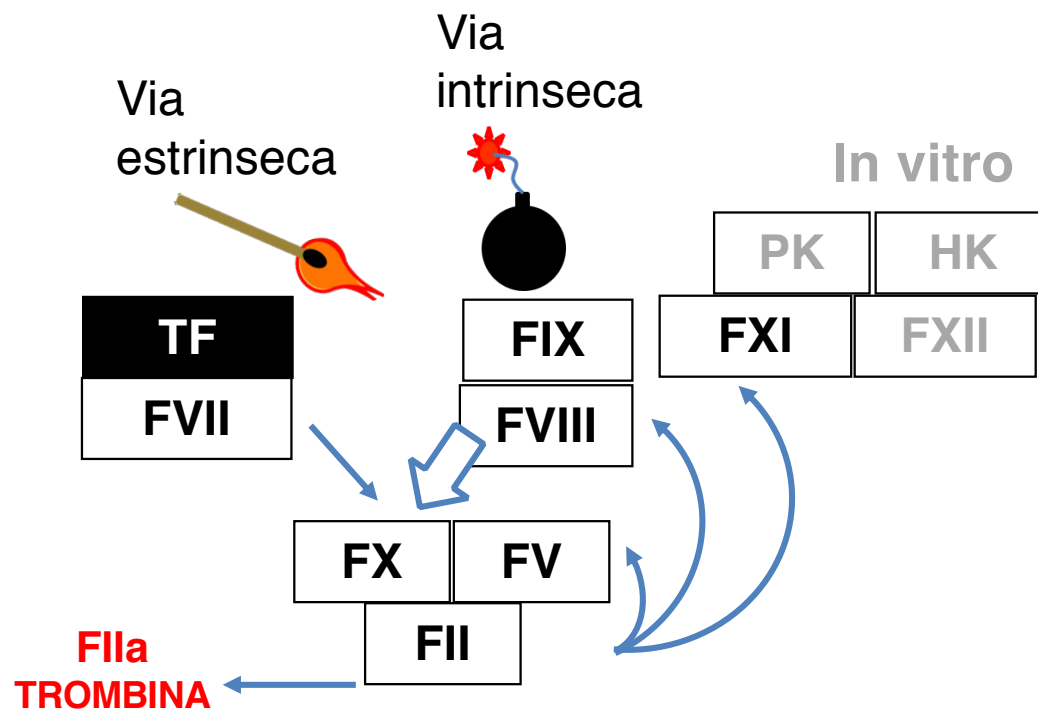
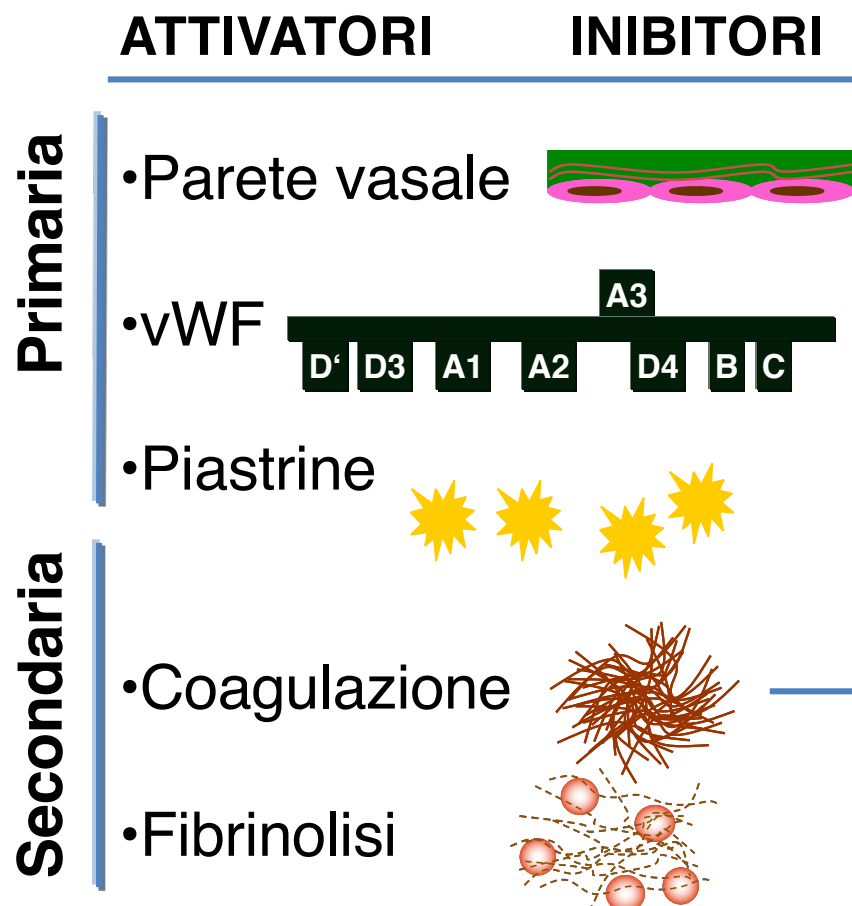
**Emorragia maggiore o
comunque sproporzionata
alla causa**



Monitorare l'evento acuto e
individuare il difetto nei casi dubbi



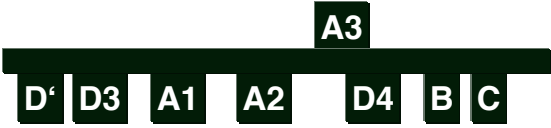
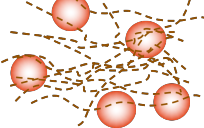
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Emorragia: i Test

EMOSTASI		Base	2 Livello
Primaria	• Parete vasale 	/	NON IN CONTESTI URGENTI
	• vWF 		vWF panel
	• Piastrine 	Emogramma	Blood smear
Secondaria	• Coagulazione 	PT/INR APTT	Fattori
	• Fibrinolisi 	Fibrinogeno	D-Dimero

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TEST GLOBALI

bjh guideline

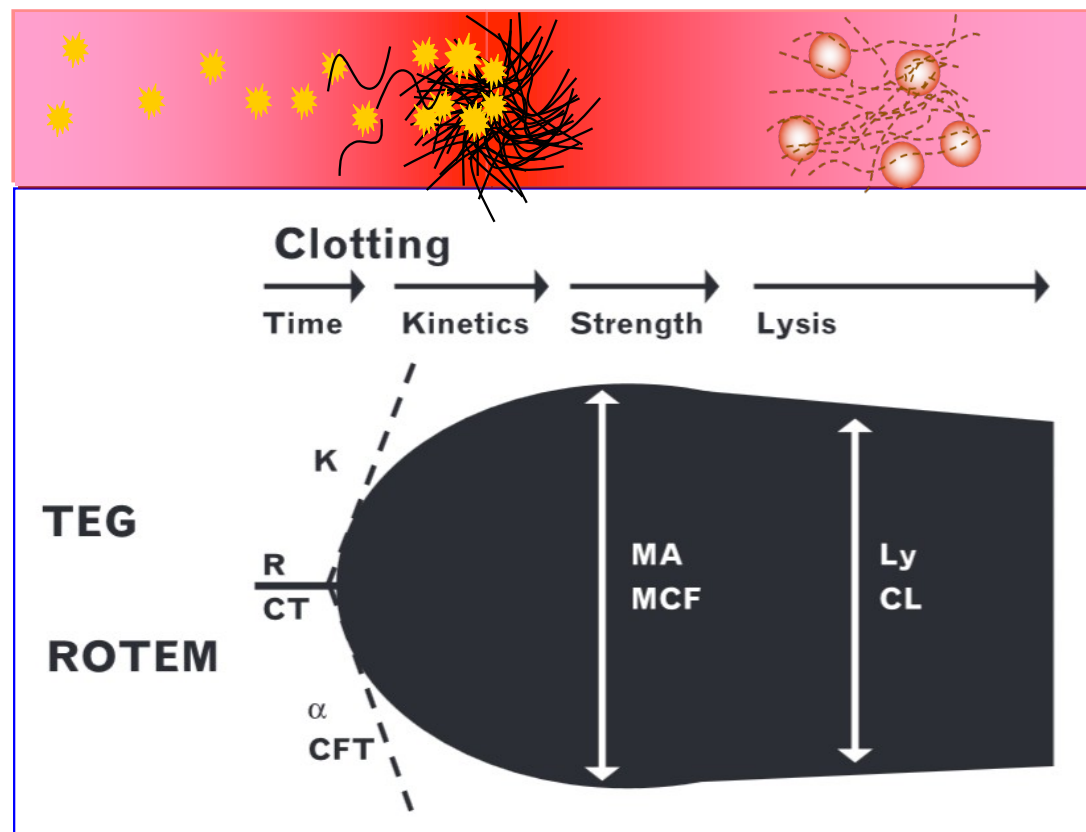
The use of viscoelastic haemostatic assays in the management of major bleeding

A British Society for Haematology Guideline

Nicola S. Curry,^{1,2}  Ross Davenport,³ Sue Pavord,^{1,2} Susan V. Mallett,⁴ Dianne Kitchen,⁵ Andrew A. Klein,⁶ Helena Maybury,⁷ Peter W. Collins⁸ and Mike Laffan⁹

¹Department of Haematology, Oxford University Hospitals NHS Foundation Trust, ²NIHR BRC, Blood Theme, Oxford University, Oxford, ³Centre for Trauma Sciences, Blizard Institute, Queen Mary University of London, ⁴Department of Anaesthesia, Royal Free London NHS Foundation Trust, London, ⁵UK NEQAS for Blood Coagulation, Sheffield, ⁶Department of Anaesthesia and Intensive Care, Royal Papworth Hospital, Cambridge, ⁷Department of Obstetrics, Leicester Royal Infirmary, Leicester, ⁸Department of Haematology, School of Medicine, Cardiff University, Cardiff, and ⁹Department of Haematology, Imperial College and Hammersmith Hospital, London, UK

British Journal of Haematology, 2018, **182**, 789–806



PT APTT Fibrinogeno : test coagulativi

v. estrinseca

v. intrinseca

PT

-
-
-
-
-
-
FVII
FX
FV
FII

HMWK
PK
FXII
FXI

FIX
FVIII
-
FX
FV
FII

Fibrinogeno

APTT

Attivatore
Fosfolipidi
Ca++



Fibrina



TF
Ca++

Fibrinogeno



Trombina



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PT APTT: interpretazione

PT	APTT
-	HMWK
-	PK
-	FXII
-	FXI
-	FIX
-	FVIII
-	-
FVII	-
FX	FX
FV	FV
FII	FII
Fibrinogeno	Fibrinogeno

- Diversa sensibilità dei fattori ai due test
- Diverso significato clinico delle carenze fattoriali
- Esistono inibizioni aspecifiche che allungano i test ma i soggetti non sanguinano (Es LAC)



In caso di PT e/o aPTT allungati senza causa o in modo sproporzionato alla causa: dosare i fattori



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PT APTT: interpretazione

PT			APTT
-		HMWK	- I due test non vedono difetti come FXIII, a2-AP, vwF (lieve-moderato), Anticoagulanti naturali.. - L'allungamento causato da DOAC, LMWH non indica il livello di anticoagulazione - APTT corto con Emicizumab in Emofilia A
-		PK	
-		FXII	
-		FXI	
-		FIX	
-		FVIII	
FVII		-	
FX		FX	
FV		FV	
FII		FII	
Fibrinogeno		Fibrinogeno	



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Test della coagulazione: significato emorragico

1. informazione predittiva di emorragia in pochi casi
(Es Emofilia A, B)
2. Nei setting clinici complessi i test non sono
predittivi di rischio emorragico in quanto valutano
parzialmente l'emostasi



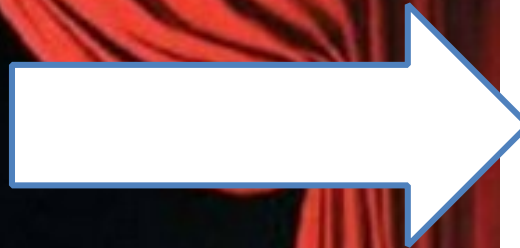
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Il contesto clinico è fondamentale per interpretare i test

**Cirrosi
Trauma
Chirurgia
Leucemia
Gravidanza
Anticoagulazione
Soggetto anziano
Malattie autoimmuni**

...

**Soggetto in precedente pieno
benessere**



**difetti isolati o
variabilmente combinati**

Parete vasale
Piastrine
Coagulazione
Fibrinolisi





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Difetti emorragici con test di base normali

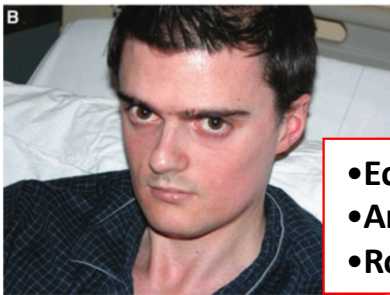
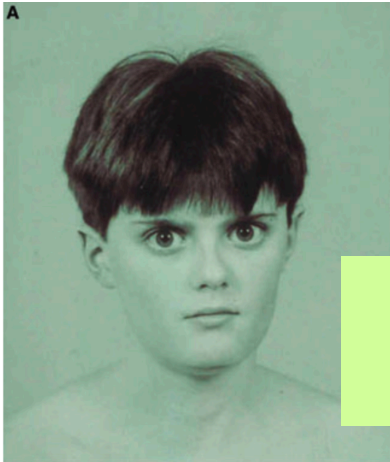
I difetti della parete vasale

FXIII

Piastrinopatie

α 2-antiplasmina

VWD (lieve-moderato)

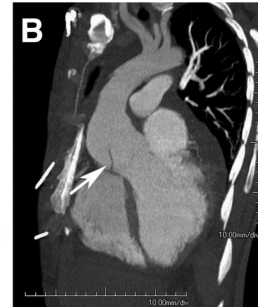
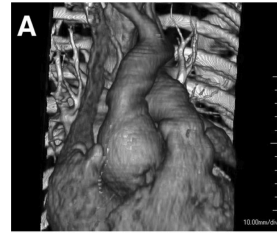


Sindrome di Ehlers-Danlos

- Ecchimosi, ematomi
- Aneurismi arteriosi
- Rottura d'organo (utero, intestino...)

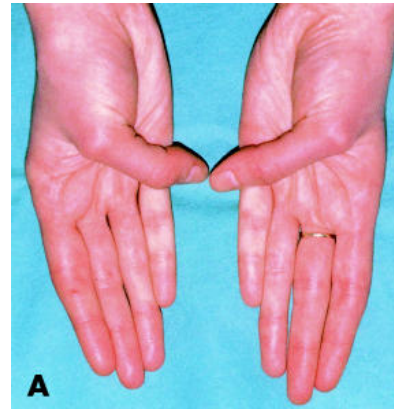


BJH 2004; 127:491-500



Sindrome di Marfan

- Ectasia aortica
- Rottura dell'aorta



A



B



Heart 2002;88:97-103



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Teleangiectasia emorragica ereditaria (HHT) (Osler-Weber-Rendu disease)



- Epistassi
- Teleangiectasie
- Malformazioni AV (fegato, polmone, cervello)
- Storia familiare

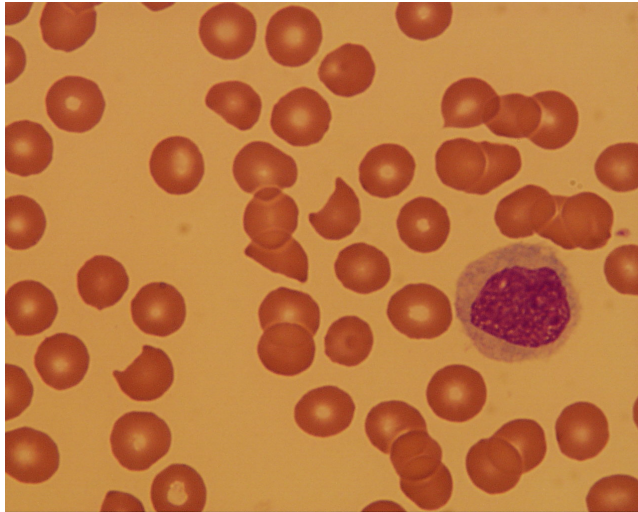
Amiloidosi



- Rottura spontanea della milza
- Emorragia cerebrale



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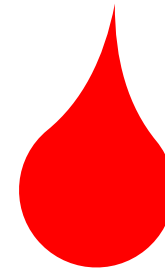
Piastrinopenie

Includere sempre lo striscio di s.p. nel work-up diagnostico

Plt: 15.000/uL

HIT

ITP





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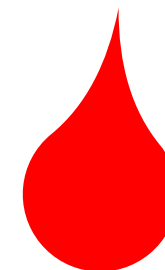
PTINR: 4.0

FVII: 10%

Cirrosi

VKA

Trauma





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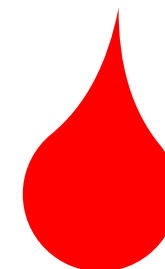
APTT: 3.0

LAC

FXII: 10%

UFH

FVIII: 1%





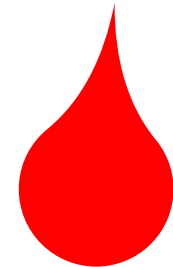
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Fibrinogeno: 80 mg/dl

Difetto
congenito

rtPA

DIC





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ISOLATO APTT ALLUNGATO



Dosaggio Fattori

Emofilia A (FVIII)
vs
Emofilia B (FIX)

Emofilia acquisita FVIII

Journal of Thrombosis and Haemostasis, 10: 622–631

DOI: 10.1111/j.1538-7836.2012.04654.x

ORIGINAL ARTICLE

Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2)

P. KNOEBL,* P. MARCO,† F. BAUDO,‡ P. COLLINS,§ A. HUTH-KÜHNE,¶ L. NEMES,** F. PELLEGRINI,†† L. TENGBORN,‡‡ and H. LÉVESQUE,§§ ON BEHALF OF THE EACH2 REGISTRY CONTRIBUTORS¹

*Division of Hematology and Hemostasis, Department of Medicine 1, Medical University of Vienna, Vienna, Austria; †Unidad de Hemostasia y Trombosis, Servicio de Hematología, Hospital General Universitario, Alicante, Spain; ‡Thrombosis Hemostasis Unit, Niguarda Hospital, Milan, Italy; §Arthur Bloom Haemophilia Centre, School of Medicine, University Hospital of Wales, Cardiff University, Cardiff, UK; ¶SRH Kurpfalzkrankenhaus Heidelberg GmbH and Hemophilia Center, Heidelberg, Germany; **National Hemophilia Center and Hemostasis Department, State Health Centre, Budapest, Hungary; ††Unit of Biostatistics, Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti, Italy; ‡‡Clinical Coagulation Research Unit, Skåne University Hospital, Malmö, Sweden; and §§Department of Internal Medicine, Rouen University Hospital, Rouen Cedex, France

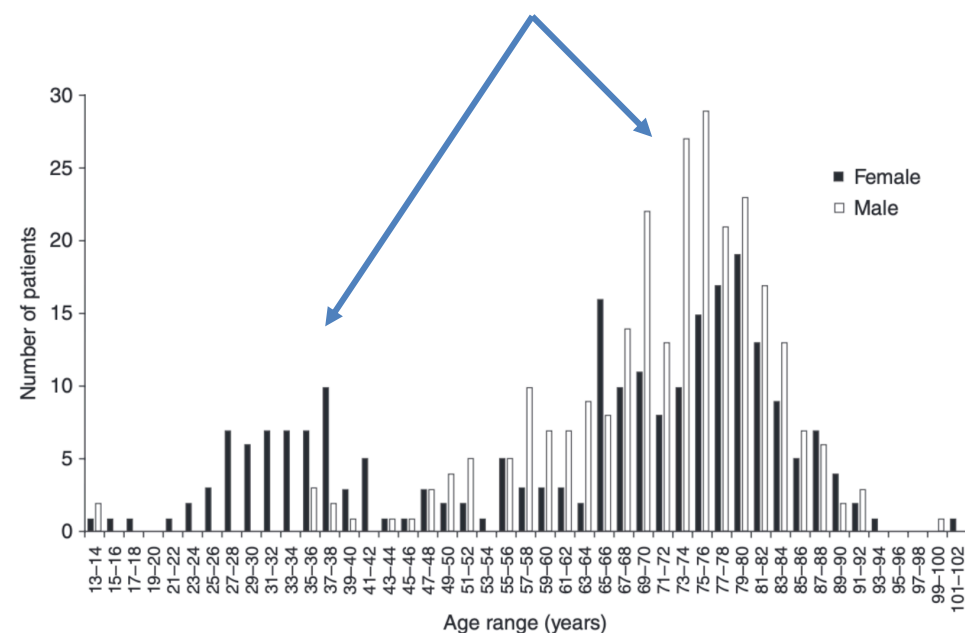


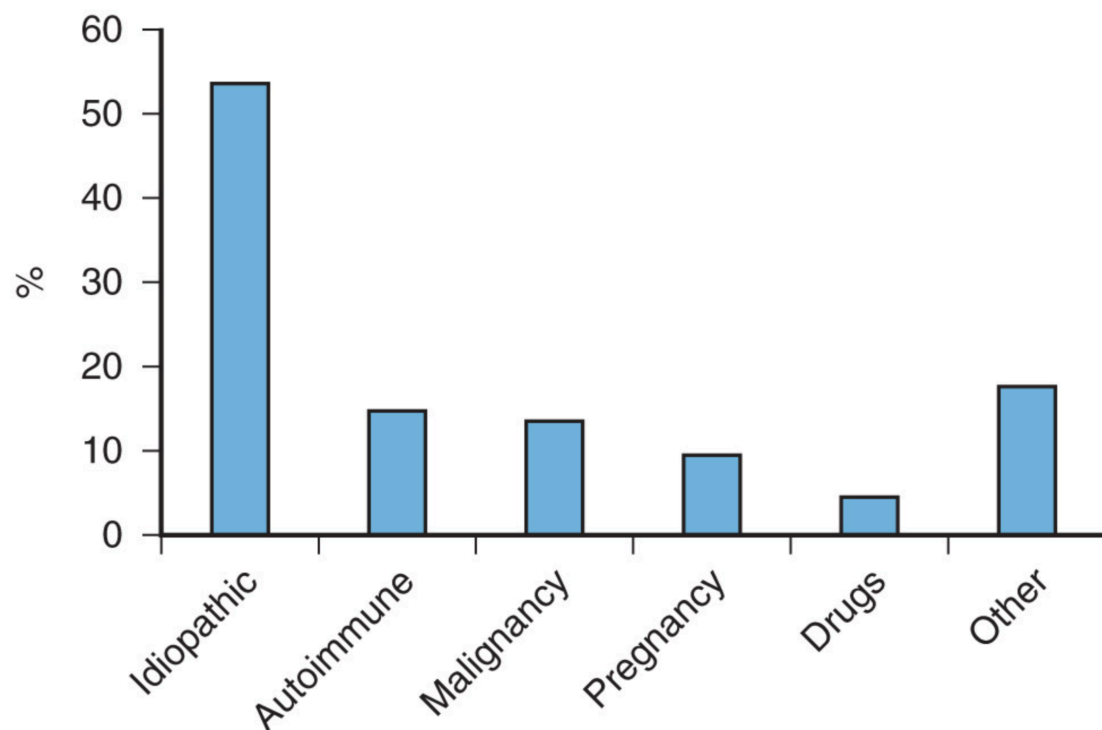
Fig. 1. Histogram of age at diagnosis according to gender.



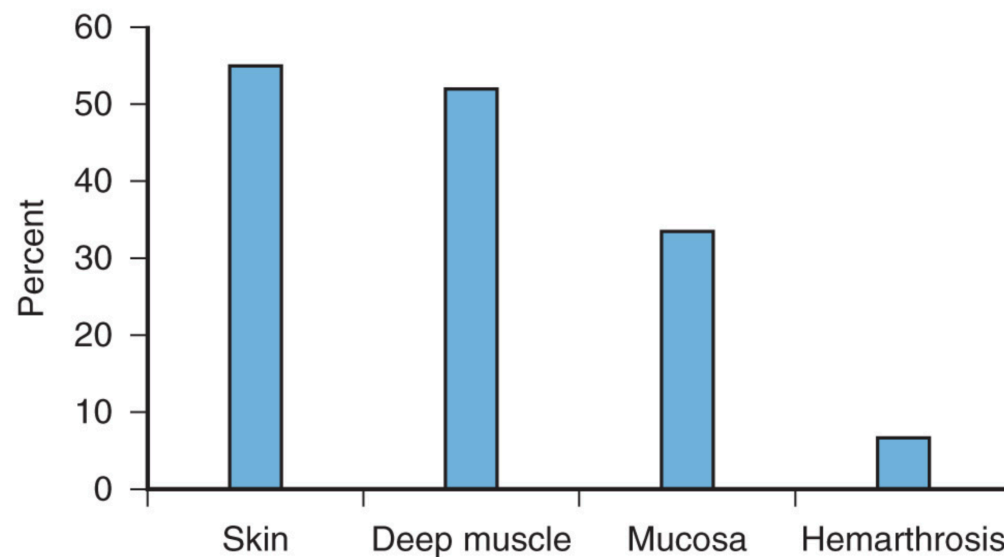
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Inibitori Acquisiti del FVIII: clinica

Setting



Emorragie



JTH 2012;10:622-631

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Gravità della patologia

JTH 2012;10:622-631

Table 7 Outcome and adverse events

	All patients entered*	Entire collective
No. of patients [n (%)]	331 (66.1%)	501 (100%)
Observation time [median, IQR; (days)]	258 (74–685)	318 (111–759)
Survival		
Alive at final follow-up	191 (57.7%)	340 (67.9%)
Death reported	87 (26.3%)	100 (20%)
Unknown survival state	47 (14.2%)	34 (6.8%)
Remission		
Complete remission [n/total (%)]	237 (71.6%)	365 (72.6%)
Stable remission on IST [n/total (%)]	39 (11.8%)	63 (12.6%)
No remission and off IST	33 (10.0%)	47 (9.4%)
Unknown remission state	22 (6.7%)	26 (5.2%)
Cause of death [n (%)]		
Fatal bleeding	15 (17.2% of deaths) (4.5% of group)	16 (16% of deaths) (3.2% of group)
Hemostatic therapy	0 (0%)	0 (0%)
IST complications	14 (16.1% of deaths) (4.2% of group)	16 (16% of deaths) (3.2% of group)
Underlying disease	40 (46% of deaths) (12.1% of group) (4.8% of patients receiving IST)	45 (45% of deaths) (9.0% of group) (3.3% of patients receiving IST)
Unknown/other	33 (37.9% of deaths) (10.0% of group)	39 (39% of deaths) (7.8% of group)
Adverse events [n (%)]		
Total	136 (41.1%)	171 (34.1%)
Stroke	1 (0.3%)	1 (0.2%)
Cardiac disorders (all)	10 (3.0%)	15 (3.0%)
Myocardial infarction	7 (2.1%)	9 (1.8%)
Venous thromboembolism	5 (1.5%)	5 (1.0%)
Infection/sepsis	53 (16.0%)	64 (12.8%)
Neutropenia	29 (8.8%)	33 (6.6%)
Thrombocytopenia	4 (1.2%)	6 (1.2%)
Decompensated diabetes	24 (7.3%)	35 (7.0%)
Psychiatric disorders	10 (3.0%)	12 (2.4%)

IST, immunosuppressive therapy. *Centers could enter all patients.

Frequente ritardo nella diagnosi

Table 4 Impact of diagnostic delay

Time bleeding to definite diagnosis	No. of patients (%)	Median FVIII activity [U dL ⁻¹ (IQR)]	Median inhibitor titer [BU mL ⁻¹ (IQR)]	Hb [g dL ⁻¹ (IQR)]	Severe bleeding [n (%)]	Median time to start of hemostatic therapy [days (IQR)]	Median time to bleeding resolved [days (IQR)]
0–1 day	174 (38.2)	2 (1–4)	14 (6–58)	9.4 (7.6–9.4)	121 (70.0)	1 (0–3)	4 (2–11)
2–7 days	121 (26.5)	2 (1–5)	15 (5–41)	8.5 (7.1–10.7)	95 (78.5)	4 (2–5)	4 (2–9)
> 7 days	161 (35.3)	2 (0–6)	7 (2–30)	8.9 (7–11.3)	108 (67.1)	20 (12–43)	5 (2–13)
<i>P</i> *	NA	NS	NS	NS	NS	< 0.0001	NS

IQR, interquartile range; BU, Bethesda Units; Hb, hemoglobin; NA, not applicable; NS, not significant. Data are reported as *n* (%) and median (IQR) for categorical and continuous variables, respectively. *Kruskal–Wallis test.

JTH 2012;10:622-631



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DIAGNOSI

- PT: normale
- APTT: allungato**
- Fibrinogeno: normale

- FVIII: ridotto**
- Inibitore: presente**





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AUSL ROMAGNA

Emergenza clinica emorragica o a rischio emorragico



- LRR (Ospedali):

Esami di 1 livello e Dosaggio DOAC, Eparina



- Problema clinico-laboratoristico non risolto



- Consulenza Clinica Specialista (SIT)



- Laboratorio Pievesestina:

(Esami di 2 livello: Fattori; Inibitori)





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Emofilie congenite (14)

Fattore	sezzo	Età
FVIII	M	14 mesi
“	M	4 mesi
“	M	11 mesi
“	M	1 mese
“	M	4 giorni
“	M	3 anni
“	M	7 mesi
“	M	1 giorno
“	M	2 anni
“	M	1 mese
“	M	1 giorno
“	M	1 giorno
FIX	M	1 giorno
“	M	16 mesi

Periodo 2011-2019 Romagna



Emofilie acquisite (26)

Inibitore	Sesso	Età
FVIII	F	66
“	F	37
“	M	77
“	M	83
“	M	93
“	M	86
“	M	77
“	F	98
“	M	82
“	M	74
“	F	77
“	M	84
“	M	79
“	F	76
“	M	76
“	F	34
“	M	84
“	M	80
“	F	77
“	M	77
“	M	80
“	M	83
“	M	74
“	F	85
“	F	85
vWF	M	81
FV	M	39
FXIII	M	81



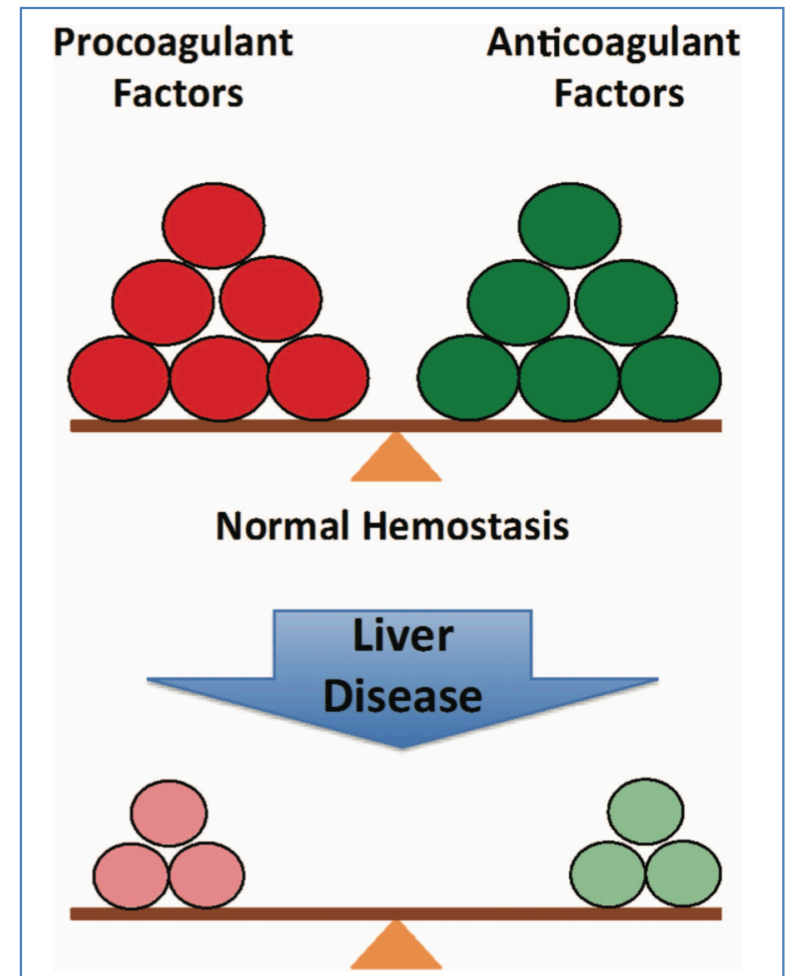
Coagulopathy in liver disease: a balancing act

Jody L. Kujovich¹

¹Oregon Health & Science University, Pediatric Hematology/Oncology, Oregon Hemophilia Center, Portland, OR

Hematology 2015

“rebalanced hemostasis”



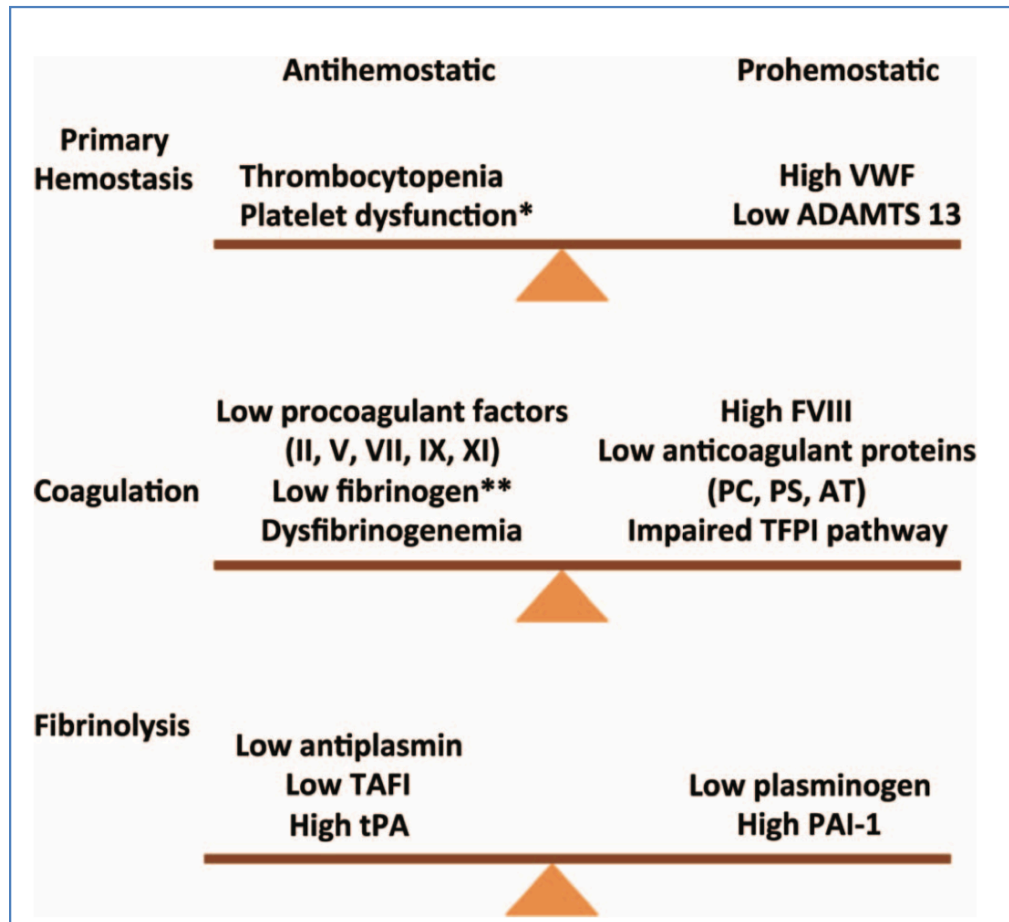


Coagulopathy in liver disease: a balancing act

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ASH 2015



PLT:

- ridotte ma con incremento di vWF

PT-INR:

- INR non appropriato
- non vede l'incremento di FVIII, la riduzione delle proteine anticoagulanti



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Emorragia in corso di terapia antitrombotica: i Test

Antiaggreganti

- PFA-100
- Test di aggregazione

VKA

- PT INR

UFH

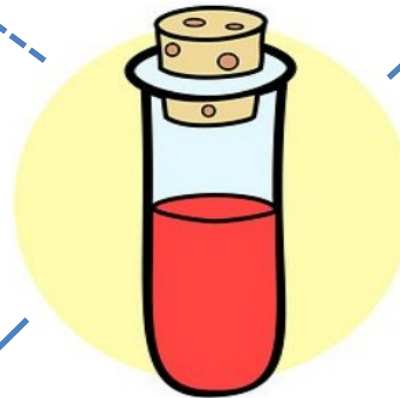
- APTT

- UFH
- LMWH
- Fondaparinux
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

- Dosaggio Farmaco

Fibrinolitici

- Fibrinogeno





UTILITA' DEI TEST



- 1. Identificazione di un difetto dell'emostasi in un soggetto ancora asintomatico**
- 2. Caratterizzazione di un difetto dell'emostasi in presenza di una clinica emorragica aspecifica**
- 3. Monitoraggio (emorragia grave, terapia, contesto clinico critico...)**
- 4. Gestione delle emorragie in corso di anticoagulanti**



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ATTENZIONE



LIMITI

- TAT: 40-60 minuti
- In molti contesti non esprimono un indice di rischio emorragico
- Le alterazioni dei test possono avere cause che non hanno implicazioni emorragiche
- I test sono la fotografia di un istante e non rappresentano la dinamica di una emorragia grave



OSTACOLI

- Difficile fare comprendere ai clinici la fondamentale importanza della “qualità” del campione
- Frequente difficoltà nella interpretazione clinica dei risultati



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Grazie