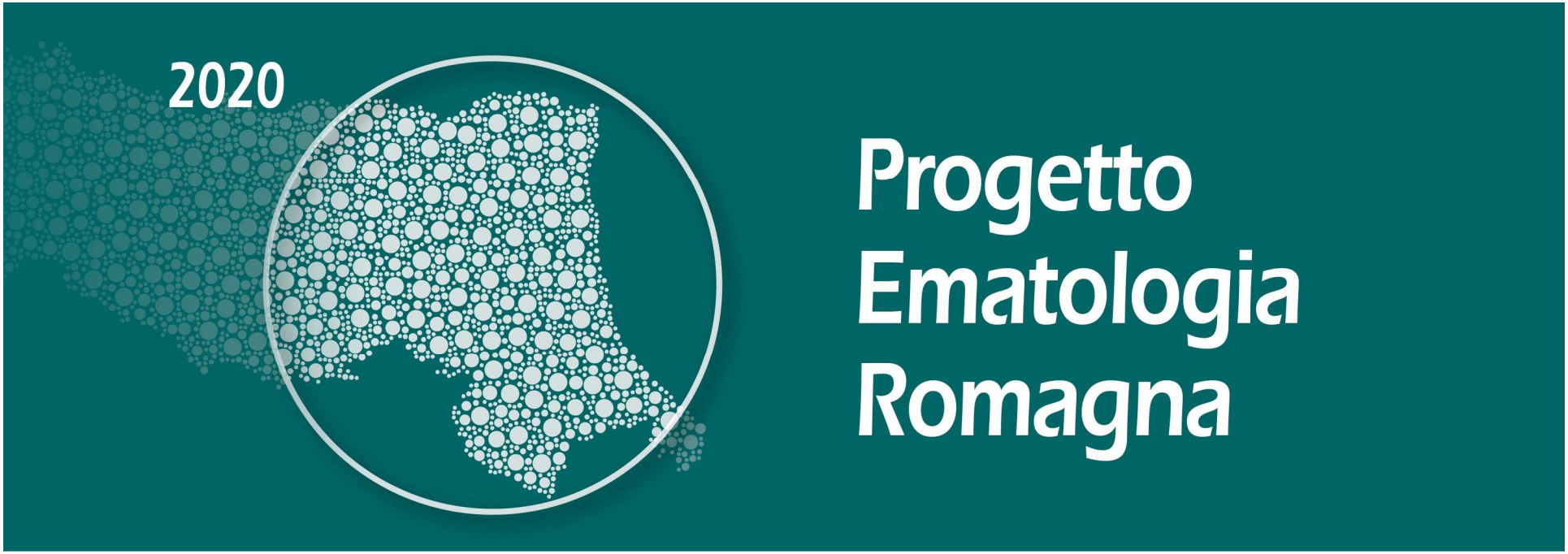


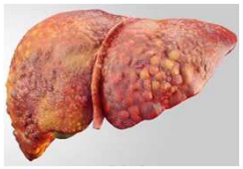
L'emofilia acquisita

Giovanni Poletti

EMOFILIE

ACQUISITE
storia familiare e personale assenti

NON IMMUNI



In ampia prevalenza multi-fattoriali

IMMUNI
Autoanticorpi (inibitori)

Fattore normalmente prodotto
(tutti i f[illegible]o essere coinvolti)

FVIII

CONGENITE
storia personale e familiare (*X-Linked)

Carenza di un singolo Fattore
vWF FVIII* FIX* …
(rarissimi difetti multifattoriali)

FVIII

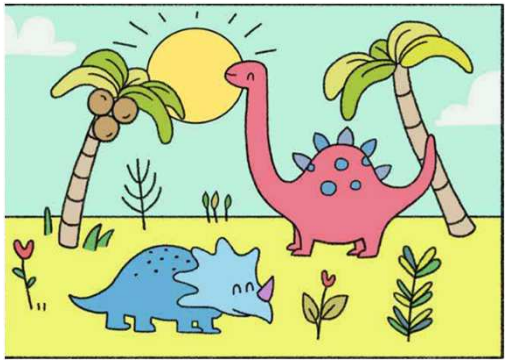
Fattore trasfuso

Alloanticorpi (inibitori)

EMOFILIA A ACQUISITA (AHA)
(FVIII)

malattia autoimmune rara
con elevato rischio di morbidità e mortalità
spesso incontrata in ambiente non specialistico

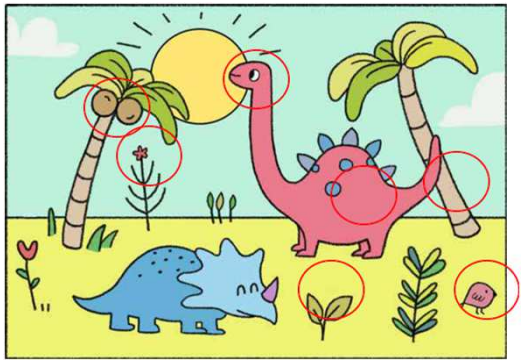
CONGENITA



EMOFILIA A

…non sono proprio uguali!

ACQUISITA



FAMILIARITA'
SESSO
CARATTERISTICHE DELL'INIBITORE
SETTING CLINICO
CARATTERISTICHE DEL SANGUINAMENTO

bjh review

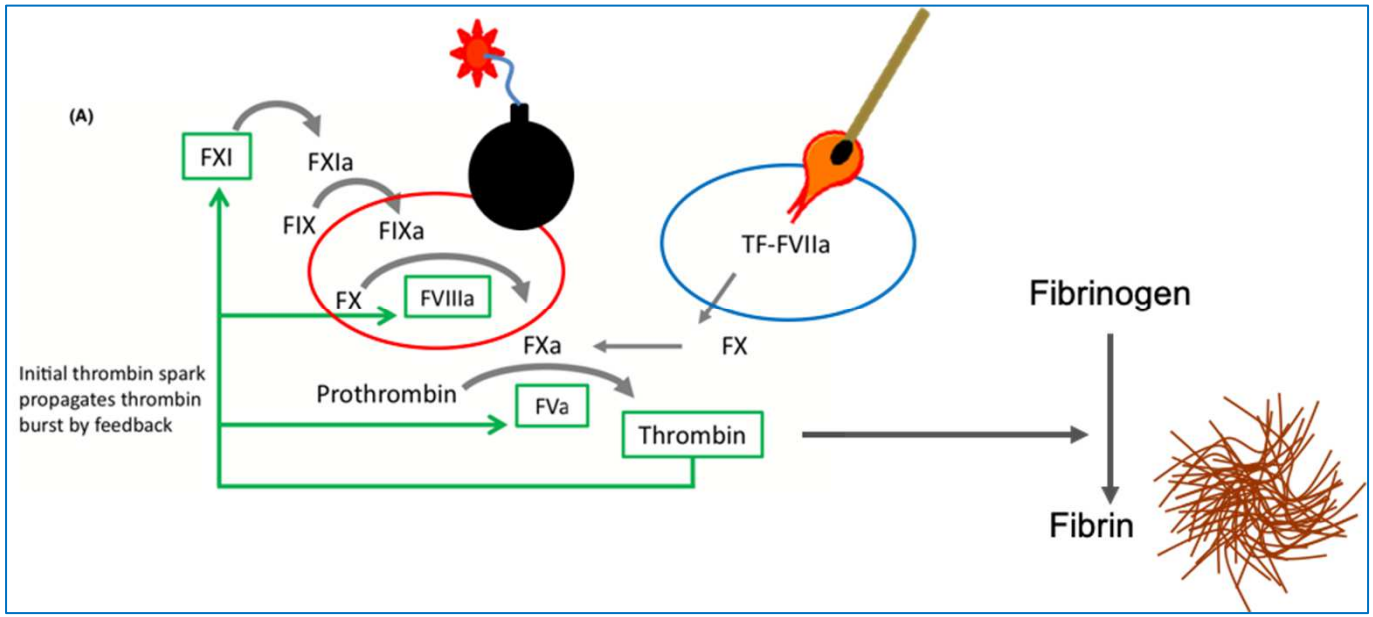
Advances in understanding the molecular mechanisms that maintain normal haemostasis

James S. O'Donnell, Jamie M. O'Sullivan and Roger J. S. Preston

Haemostasis Research Group, Department of Molecular and Cellular Therapeutics, Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, Ireland

British Journal of Haematology, 2019, **186,** 24–36

Il FVIIIa è il cofattore del complesso intrinseco



AUTOANTICORPI anti-FVIII

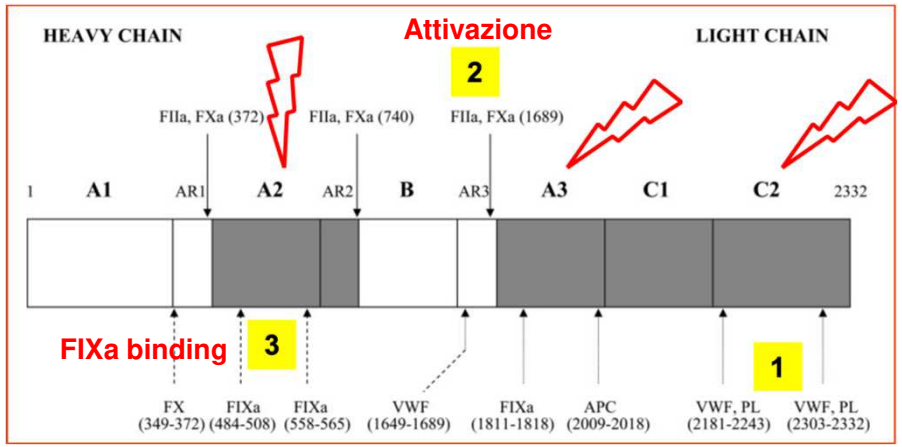


Table 2 Autoantibody subclass pattern in patients with acquired hemophilia A [8]

Isotype or subclass	Positive screening	Titer in positive patients
IgG1	71 (88)	1:640 (1:320–1:2560)
IgG2	62 (77)	1:80 (1:40–1:320)
IgG3	33 (41)	1:80 (1:40–1:320)
IgG4	79 (98)	1:5120 (1:1280–1:20,480)
IgA	37 (46)	1:80 (1:40–1:160)
IgM	7 (9)	1:80 (1:40–1:80)

Data are presented as *n* (%) or median (interquartile range) unless otherwise indicated
Ig immunoglobulin, *ND* not determined

American Journal of Hematology 80:55–63 (2005)

Acquired Hemophilia A: A Concise Review

Massimo Franchini,[1*] Giorgio Gandini,[1] Tiziana Di Paolantonio,[2] and Guglielmo Mariani[3]
[1] Servizio di Immunoematologia e Trasfusione—Centro Emofilia, Azienda Ospedaliera di Verona, Verona, Italy
[2] Novo Nordisk Italia, Rome, Italy
[3] Divisione di Ematologia con Trapianto, Azienda Policlinico Universitario, Palermo, Italy

Prevention and Management of Bleeding Episodes in Patients with Acquired Hemophilia A

Paul Knöbl[1]

Drugs (2018) 78:1861–1872

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 CONTRIBUTORS[1]

J Thromb Haemost 2012; **10**: 622–31.

AHA

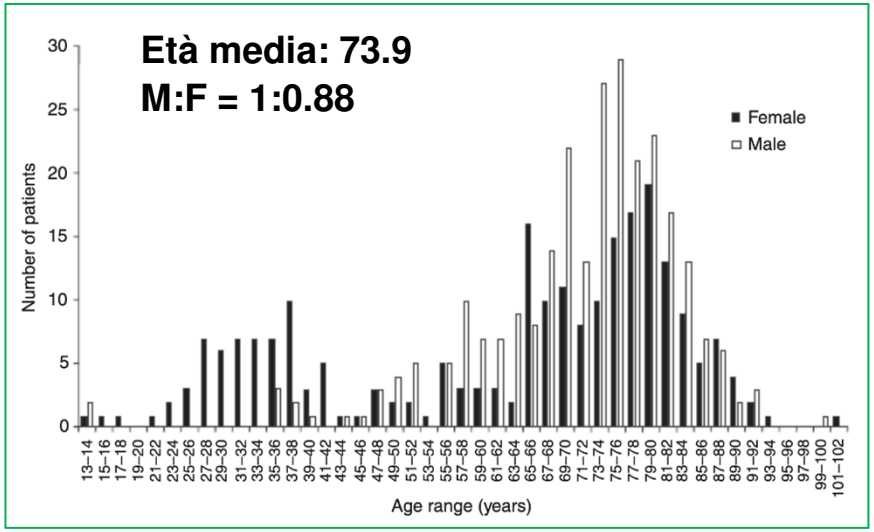
incidenza

1.5/1.000.000/y

1: 350.000 gravidanze

(Thrombosis Research 181S1 (2019)S60-S61)

età/sesso



Setting

Disordini associati	**%**
Idiopatiche	**51.9**
Malattie autoimmuni	**13.4**
Neoplasie	**11.8**
Gravidanza	**8.4**
Infezioni	**3.8**
Farmaci	**3.4**
Malattie dermatologiche	**1.4**
Altro	**11.6**

LE EMORRAGIE

frequenza

94.6%

gravità

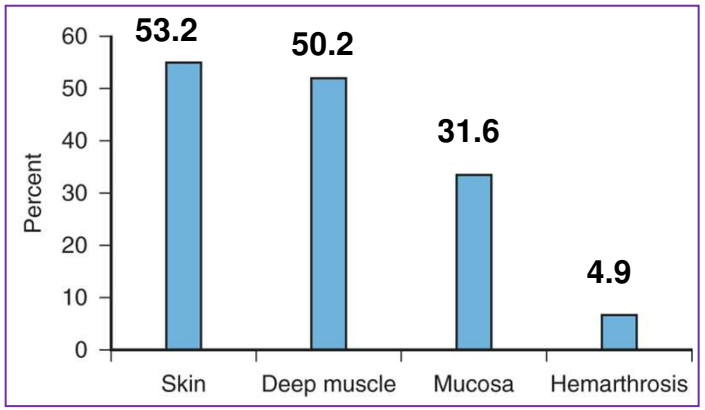
- Rischio per la vita
- HB < 8 g/dl o riduzione > 2 g/dl
- Trasfusioni: 2 UGRC
- Coinvolgimento d'organo
- Sindrome compartimentale

70.3%

cause

Spontanee	77.4 %
Trauma	8.4%
Chirurgiche	8.2%
Peripartum	3.6%
Altre	2.7%

sedi



J Thromb Haemost 2012; **10**: 622–31.

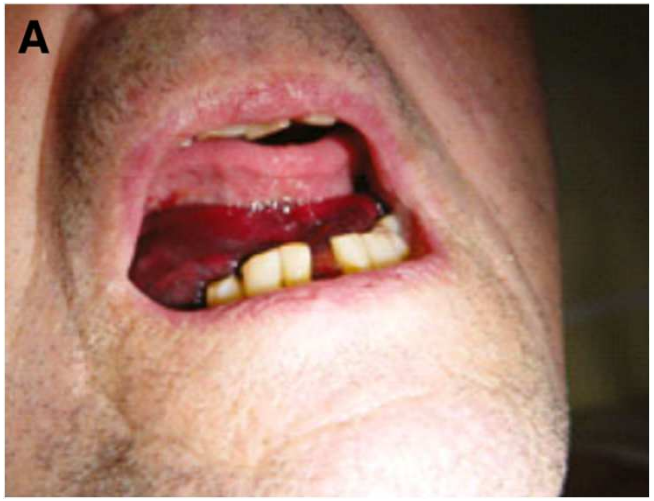
REVIEW ARTICLE

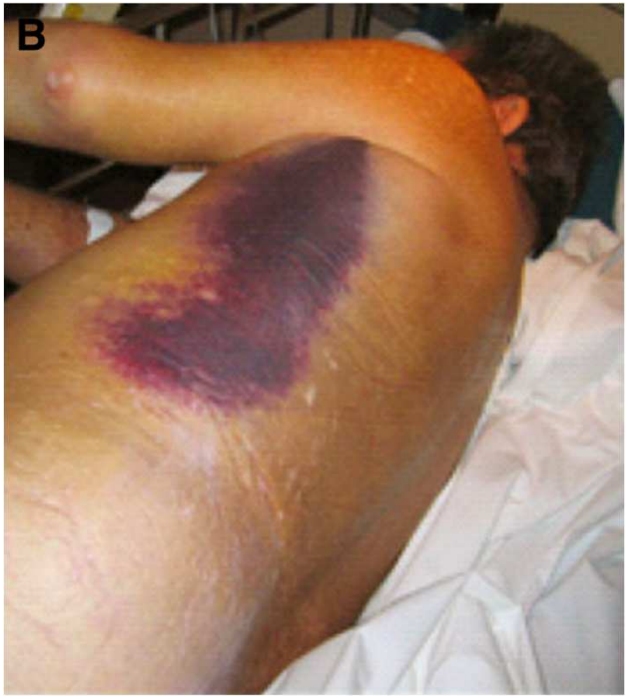
Acquired haemophilia: an overview for clinical practice

Craig M. Kessler[1], Paul Knöbl[2]

[1]Division of Hematology-Oncology, Georgetown University Medical Center, Washington, DC, USA; [2]Division of Hematology and Hemostasis, Department of Medicine 1, Medical University of Vienna, Vienna, Austria

European Journal of Haematology 95 Suppl. 81 (36–44)

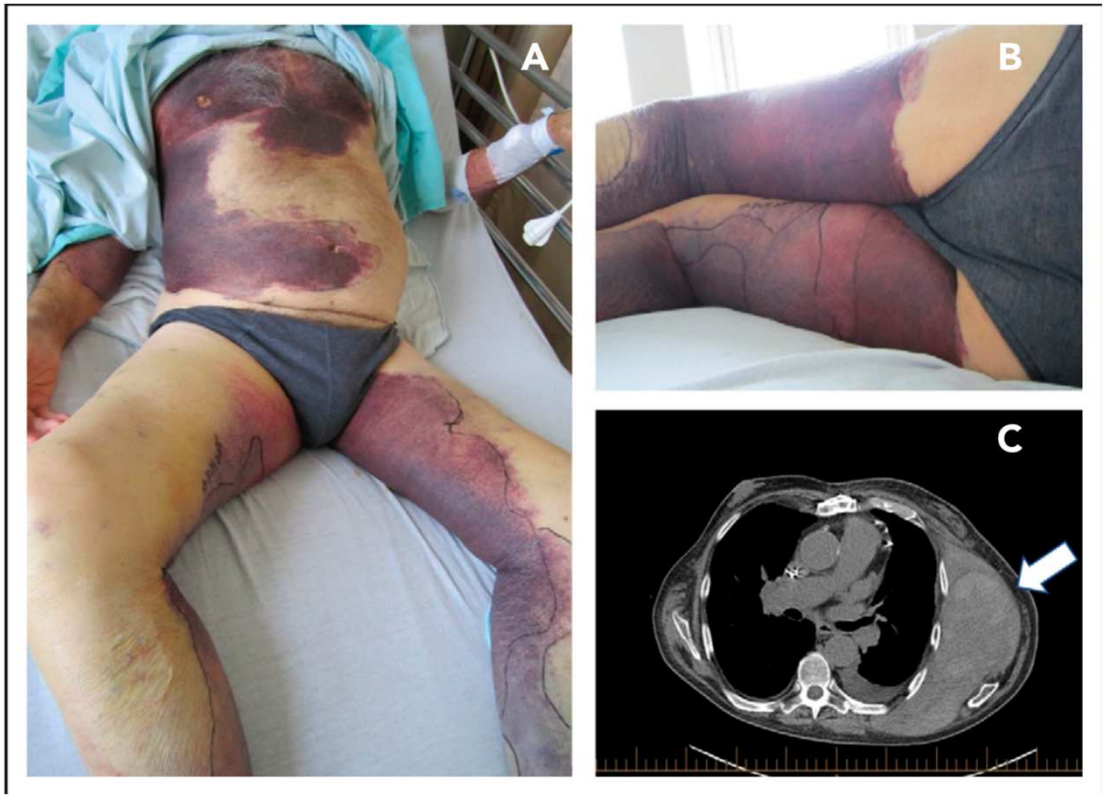




Bleeding in acquired hemophilia: have we figured it out?

Jean St-Louis | Université de Montréal

blood® 16 JULY 2020 | VOLUME 136, NUMBER 3



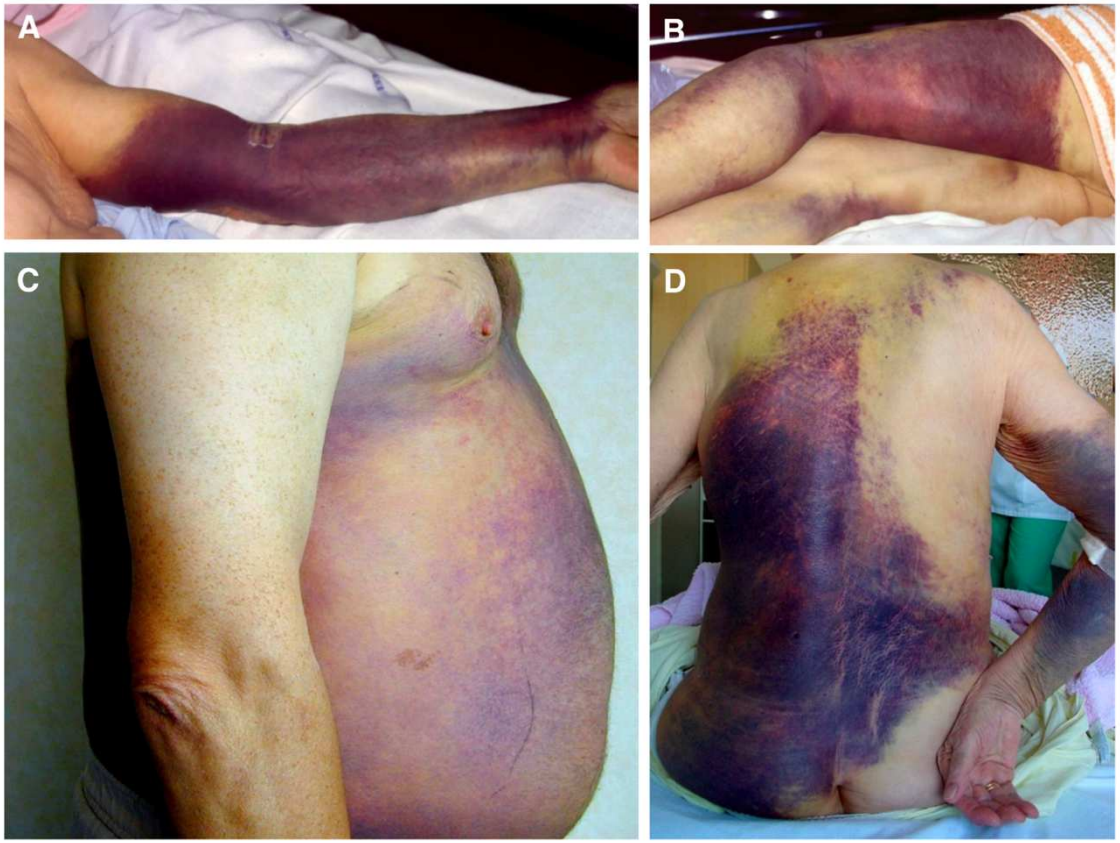
Collins et al. BMC Research Notes 2010, 3:161
http://www.biomedcentral.com/1756-0500/3/161

BMC Research Notes

RESEARCH ARTICLE Open Access

Consensus recommendations for the diagnosis and treatment of acquired hemophilia A

Peter Collins*, Francesco Baudo2, Angela Huth-Kühne3, Jørgen Ingerslev4, Craig M. Kessler5, Maria F. Mingot Castellano6, Midori Shima7, Jean St-Louis8 and Hervé Lévesque9



Journal of Thrombosis and Haemostasis, **9** (Suppl. 1): 226–235

INVITED REVIEW

Management of acquired haemophilia A

P. W. COLLINS
Arthur Bloom Haemophilia Centre, School of Medicine, Cardiff University, Heath Park, Cardiff, UK

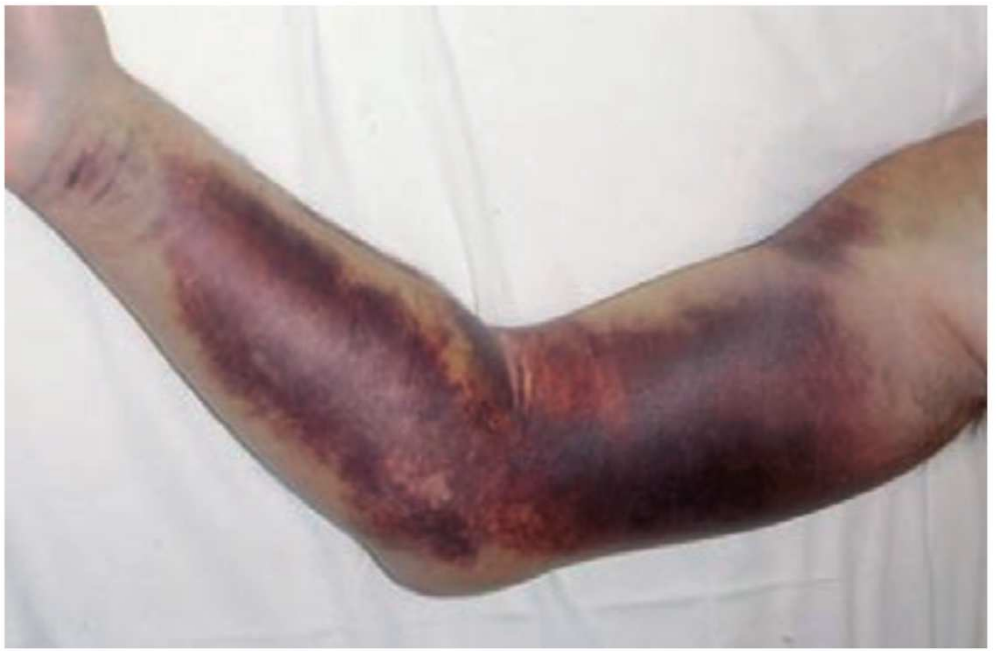


Fig. 2. Bleeding in acquired haemophilia. Typical bleeding in acquired haemophilia. The disorder in this patient was associated with Castlemann's disease and treatment with alpha interferon. The bleed was caused by venepuncture.

haematologica
Journal of The Ferrata Storti Foundation

International recommendations on the diagnosis and treatment of acquired hemophilia A

by Andreas Tiede, Peter Collins, Paul Knoebl, Jerome Teitel, Craig Kessler, Midori Shima, Giovanni Di Minno, Roseline d'Oiron, Peter Salaj, Victor Jiménez-Yuste, Angela Huth-Kühne, and Paul Giangrande

Haematologica 2020 [Epub ahead of print]

DIAGNOSI

Fondamentale è il sospetto:

emorragia e/o isolato aPTT allungato

1. **senza causa**

oppure

2. **causa non proporzionata**

screening coagulativo con PT aPTT Fibrinogeno!

Laboratory Diagnosis of Acquired Hemophilia A: Limitations, Consequences, and Challenges

Andreas Tiede, MD, PhD[1] Sonja Werwitzke, MD, PhD[1] Rüdiger E. Scharf, MD, PhD[2]

[1]Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany
[2]Department of Clinical and Experimental Hemostasis, Hemotherapy and Transfusion Medicine, Heinrich Heine University Medical Center, Düsseldorf, Germany

Semin Thromb Hemost 2014;40:803–811.

aPTT allungato: è fondamentale un contatto clinico-laboratorio

Table 2 Causes of aPTT prolongation

Cause	Note
Factor VIII deficiency	Congenital or acquired hemophilia A, some forms of von Willebrand disease or acquired von Willebrand syndrome
Factor IX deficiency	Hemophilia B
Factor XI deficiency	Less severe bleeding disorder
Factor XII, prekallikrein, and HWMK deficiency	Do not cause bleeding
Other coagulation factor deficiencies • Factor X • Factor V • Prothrombin • Fibrinogen (incl. dysfibrinogenemia)	Also cause prolongation of prothrombin time
Lupus anticoagulant	Increased risk of thromboembolism
Pharmacological anticoagulants	
• Unfractionated heparin	
• Indirect factor Xa inhibitors (low–molecular-weight heparin and fondaparinux)	• Only with higher (therapeutic) doses
• Direct factor Xa inhibitors (rivaroxaban and apixaban)	• Effect on prothrombin time often stronger than on aPTT
• Direct thrombin inhibitors (dabigatran, argatroban, and lepirudin)	• Effect on aPTT often stronger than on prothrombin time

APTT allungato

valutare sempre la proporzionalità fra causa e difetto

Nessuna terapia

PT INR: 1.0
APTT ratio: 2.8

Rivaroxaban

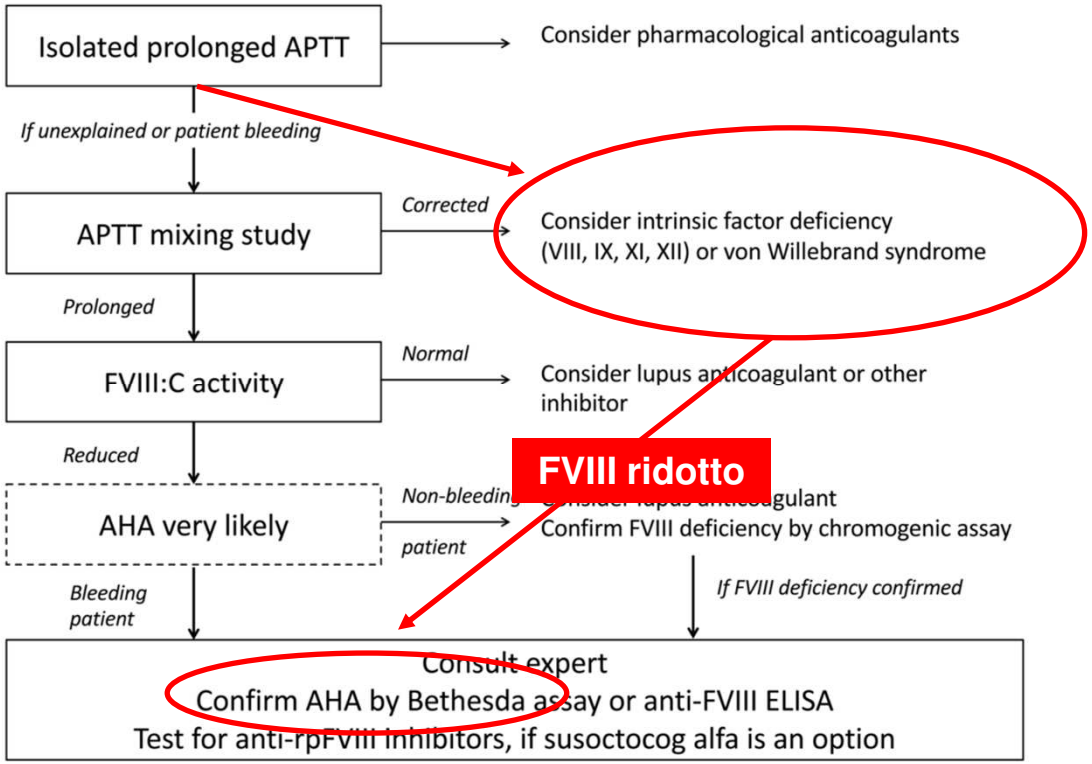
PT INR: 1.3
APTT ratio: 3.0

Coumadin

PT INR: 2.5
APTT ratio: 3.5

Dabigatran

PT INR: 1.3
APTT ratio: 4.0



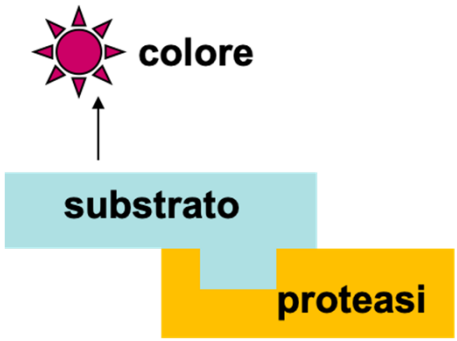
haematologica
2020

DOSAGGIO FVIII

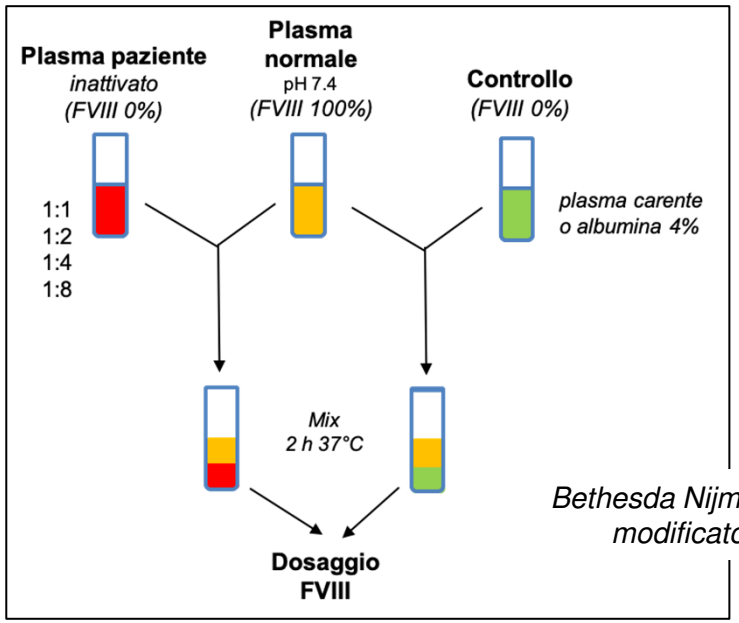
- **One-stage coagulation assay (FVIII FIX FXI FXII)**
  - *capacità di un plasma test di normalizzare l'aPTT di un plasma carente*
  - *Utilizzo di una curva di calibrazione di riferimento*

coagulo

- **Two-stage chromogenic assay (FVIII)**
  - *capacità di un plasma test di generare FXa con un reagente in cui l'unico fattore limitante è il FVIII*
  - *Rilevare con un substrato cromogeno specifco la quantità di FXa generata*
  - *Utilizzo di una curva di calibrazione di riferimento*

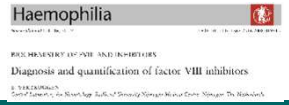


RICERCA DELL'INIBITORE

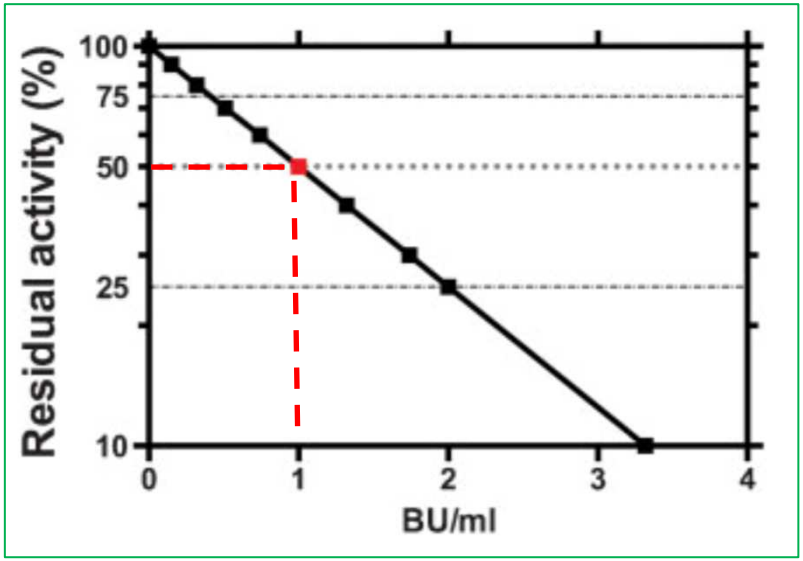


Bethesda Nijmegen modificato

FVIII residuo (RA) = FVIII paziente/FVIII controllo x 100

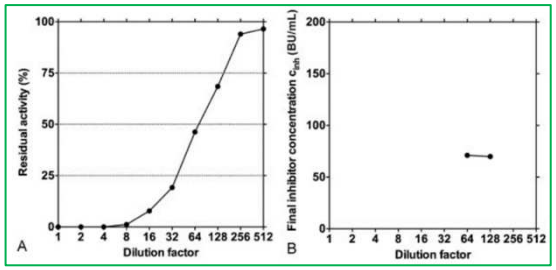

Haemophilia

Diagnosis and quantification of factor VIII inhibitors



Un residuo (RA) del 50% corrisponde a 1 Unità Bethesda (BU). Scegliere la diluizione con il residuo più vicino al 50% e moltiplicare per la diluizione.

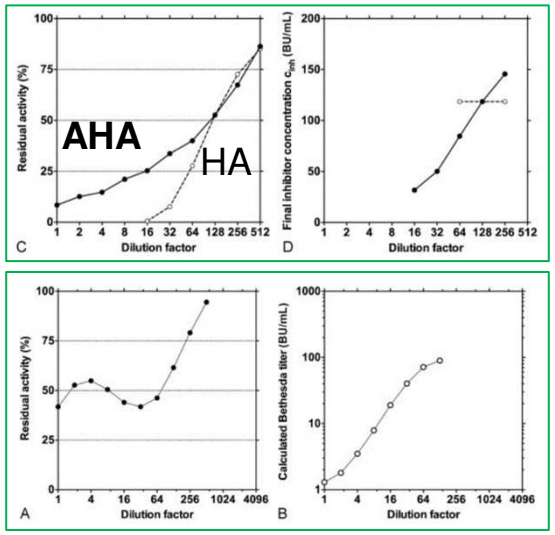
INIBITORI



Tipo 1 HA

- **Linearità fra diluizione e FVIII residuo**
- **A basse diluizioni il residuo di FVIII si azzera**
- **Il titolo di inibitore (e FVIII) hanno una correlazione clinica**

Tipico degli alloanticorpi dell'emofilia congenita (HA)



Tipo 2 AHA

- **Mancata linearità fra diluizione e FVIII residuo**
- **A basse diluizioni permane un residuo di FVIII**
- **Il titolo di inibitore (e FVIII) NON hanno correlazione clinica alla diagnosi**

Tipico della emofilia A acquisita (AHA)

Laboratory Diagnosis of Acquired Hemophilia A: Limitations, Consequences, and Challenges

Andreas Tiede, MD, PhD[1] Sonja Werwitzke, MD, PhD[1] Rüdiger E. Scharf, MD, PhD[2]

[1] Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany
[2] Department of Clinical and Experimental Hemostasis, Hemotherapy and Transfusion Medicine, Heinrich Heine University Medical Center, Düsseldorf, Germany

Address for correspondence Andreas Tiede, MD, PhD, Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Carl Neuberg Str. 1, 30625 Hannover, Germany (e-mail: tiede.andreas@mh-hannover.de).

Semin Thromb Hemost 2014;40:803–811.

Acquired haemophilia: an overview for clinical practice

Craig M. Kessler[1], Paul Knöbl[2]

[1]Division of Hematology-Oncology, Georgetown University Medical Center, Washington, DC, USA; [2]Division of Hematology and Hemostasis, Department of Medicine 1, Medical University of Vienna, Vienna, Austria

European Journal of Haematology 95 Suppl. 81 (36–44) 2015

Frequente ritardo nella diagnosi

ritardo	%
1 settimana	26
1 mese	22
1-6 mesi	10
> 6 mesi	1

Gravità della patologia

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 CONTRIBUTORS[1]

J Thromb Haemost 2012; **10**: 622–31.

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) (4.8% of patients receiving IST)	16 (16% of deaths) (3.2% of group) (3.3% of patients receiving IST)
Underlying disease	40 (46% of deaths) (12.1% of group) (25.2% of patients with underlying disease)	45 (45% of deaths) (9.0% of group) (18.8% of patients with underlying disease)
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.

TERAPIA: OBIETTIVI

- **Limitare una emorragia acuta**
- **Affrontare procedure invasive**
- **Ridurre il rischio emorragico anche nei soggetti che non sanguinano**
- **Riportare il FVIII a valori normali o almeno > 50%**
- **Eliminare l'inibitore**

- ***Con particolare attenzione ai rischi associati:***

Trombosi
Infezioni
Reazioni allergiche
Diabete
Disordini psichiatrici

TERAPIA

Terapia emostatica
- rFVIIa
- aPCC
- rpFVIII

- E' la gravità clinica dell'emorragia e la necessità di procedure invasive che fanno decidere il ricorso alla terapia emostatica e non FVIII né titolo dell'inibitore

- Ha ridotto la mortalità per emorragia
- dal 20% nel 1981 a meno del 5%

- Può prevenire gravi complicanze (s. compartimentale)

Immunosoppressione (IST)
- Cortisone
- Cortisone + Ciclofosfamide o Rituximab
- …

- Risposta: 77-89%
- Accelera il conseguimento della remissione
- Riduce il rischio di sanguinamento indipendentemente dal FVIII
- FVIII < 1%; Inibitore > 20 BU: risposta minore e in tempi più lunghi
- IgA: maggior probabilità di ricaduta

haematologica 2020

WHO performance status > 2: rischio di mortalità 4 volte maggiore

DOI: 10.1111/j.1471-0528.2012.03469.x
www.bjog.org

Intrapartum care

Pregnancy-associated acquired haemophilia A: results from the European Acquired Haemophilia (EACH2) registry

L Tengborn,[a] F Baudo,[b] A Huth-Kühne,[c] P Knoebl,[d] H Lévesque,[e] P Marco,[f] F Pellegrini,[g] L Nemes,[h,*] P Collins,[i,*] on behalf of the EACH2 registry contributors†

[a] Clinical Coagulation Research Unit, Skåne University Hospital, Malmö, Sweden [b] Thrombosis Haemostasis Unit, Niguarda Hospital, Milan, Italy [c] SRH Kurpfalzkrankenhaus Heidelberg GmbH and Haemophilia Centre, Heidelberg, Germany [d] Department of Medicine 1, Division of Haematology and Haemostasis, Medical University of Vienna, Vienna, Austria [e] Department of Internal Medicine, Rouen University Hospital, Rouen, France [f] Unidad de Hemostasia y Trombosis. Servicio de Hematologia, Hospital General Universitario, Alicante, Spain [g] Unit of Biostatistics, Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Santa Maria Imbaro (Chieti), Italy [h] National Haemophilia Centre and Haemostasis Department, State Health Centre, Budapest, Hungary [i] Arthur Bloom Haemophilia Centre, University Hospital of Wales, School of Medicine, Cardiff University, Cardiff, UK

Correspondence: L Tengborn, Clinical Coagulation Research Unit, Skåne University Hospital, SE-20502 Malmö, Sweden.
Email lilian.tengborn@med.lu.se

* LN and PC contributed equally to the study and manuscript.

†A complete list of the EACH2 registry contributors appears as a data supplement (see Supplementary material, Appendix S1) to the online version of this article.

Accepted 4 July 2012. Published Online 20 August 2012.

AHA associata a gravidanza
42/501 (8.4%)

EACH2 Registry 2012

- ❑ Le donne con < 50 aa e AHA nel 64% dei casi sono gravide
- ❑ Nel 17% dei casi l'esordio è durante la gravidanza
- ❑ Età media: 34
- ❑ FVIII valore medio alla diagnosi: 2.5%
- ❑ Inibitore valore medio: 7.8 UB
- ❑ Nel 74% dei casi è la prima gravidanza
- ❑ Emorragia
  - presente in tutte e grave nel 59%
  - spontanee: 45%
  - peripartum/postpartum: 35%
  - post-chirurgiche: 9%
  - traumatiche: 2%
- ❑ Impiego di Terapia emostatica e IST nel 56% e 92% delle donne con buona risposta
- ❑ Passaggio transplacentare di inibitore 4%

EACH2 Registry 2012

Risposta a IST

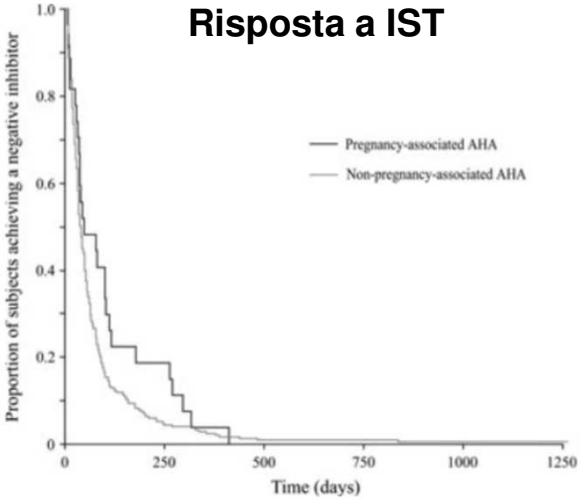


Figure 1. Time to negative inhibitor following first-line immunosuppression, comparing women with a pregnancy-associated acquired haemophilia (n = 42) and acquired haemophilia due to other causes (n = 459) among women for whom an outcome was recorded. There was no significant difference using a log rank test (P = 0.09).

Sopravvivenza

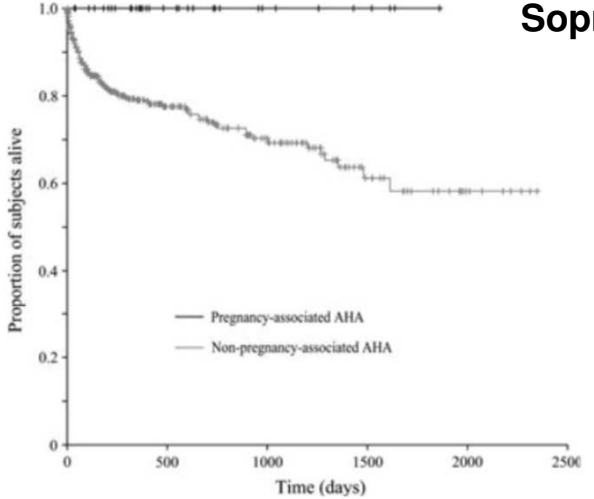
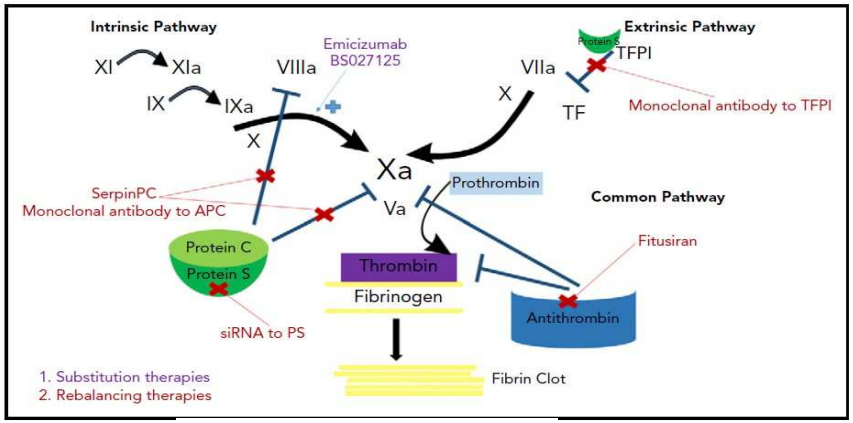


Figure 2. Survival of women with pregnancy-related AHA (n = 42) compared with the rest of the EACH2 cohort (n = 459) among women for whom survival at final follow up was recorded. The difference is highly significant using a log rank rest (P < 0.001). Vertical lines represent individual patient censorship points.



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Data Interpretation D
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Emicizumab in the Treatment of Acquired Haemophilia: A Case Report

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Emofilie congenite (15)

Fattore	sesso	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
“	M	2 giorni
FIX	M	1 giorno
“	M	16 mesi

Periodo 2011-2020
Romagna

Emofilie acquisite (27)

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
“	M	91
FV	M	39

GRAZIE