L’emofilia acquisita

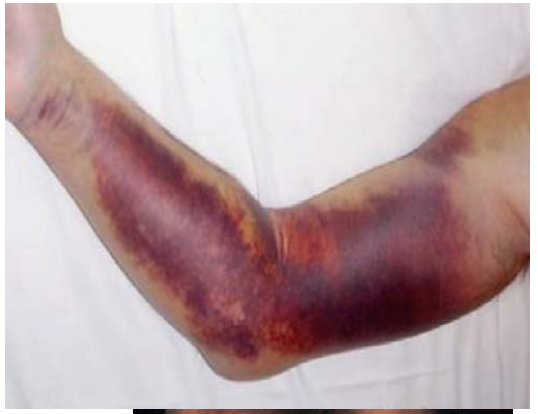
Massimo Franchini
ASST Mantova

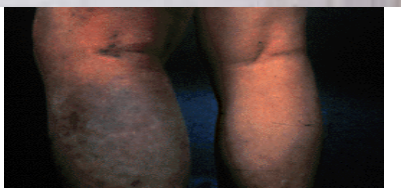
Dichiarazione sul conflitto di interessi

- Partecipazione come membro o speaker a tavole rotonde e convegni sponsorizzati da:
- Novo Nordisk
- Bayer Healthcare
- Daiichi-Sankyo

un venerdì pomeriggio (04/16) al Centro Emofilia…

‘ Pronto Soccorso, abbiamo un signore di 80 anni con imponenti ematomi spontanei da alcuni giorni agli arti. Ha 6,7 g/dL di emoglobina, GB e piastrine nella norma, APTT 2.58 con PT normale….‘

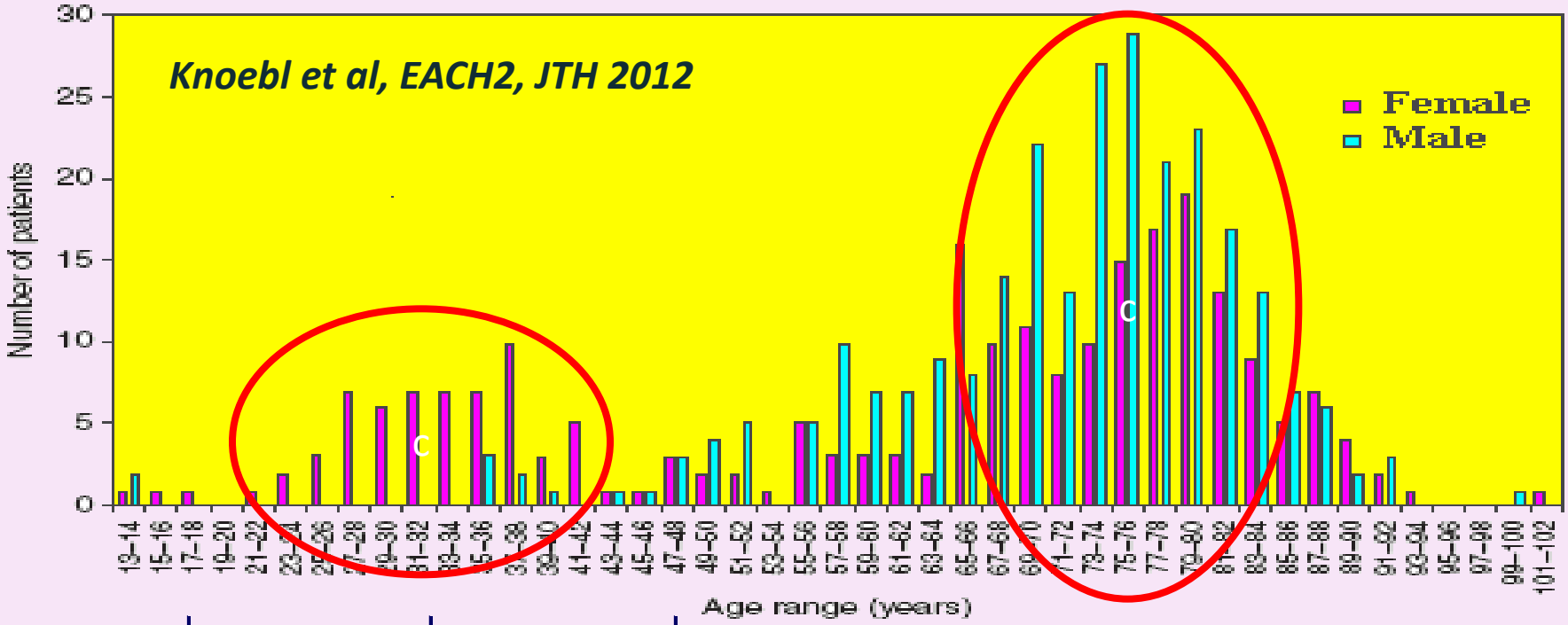




Acquired hemophilia

- **Rare bleeding disorder (~ 1.5 in $1x10^6$ year) occurring in subjects with negative personal and family history of bleeding.**
- **caused by circulating auto-antibodies, that partially or completely neutralize function and/or accelerate clearance of a specific coagulation factor (inhibitors).**
- **Factor VIII (FVIII) inhibitors are the most commonly reported autoantibodies, therefore AH is in the majority of cases an acquired Factor VIII deficiency (acquired hemophilia A, AHA).**

Epidemiologia of AHA - *Age and gender*



Registri	Età anni	Sesso M/F %	Pz ≥ 60 anni %
Knoebl 2012	74 (6-102)	58 / 42	79.5
Collins 2007	78 (2-98)	57 / 43	88.2

Incidence (in $1x10^6$ yr)

< 65 yrs	0.28
65-85 yrs	5.97
> 85 yrs	16.6

Cosa fare – I ?

Urgenza

- Test di miscela: non corregge
- Dosaggio FVIII: <0.4% (diagnosi lab: probabile emofilia acquisita)

Poi…

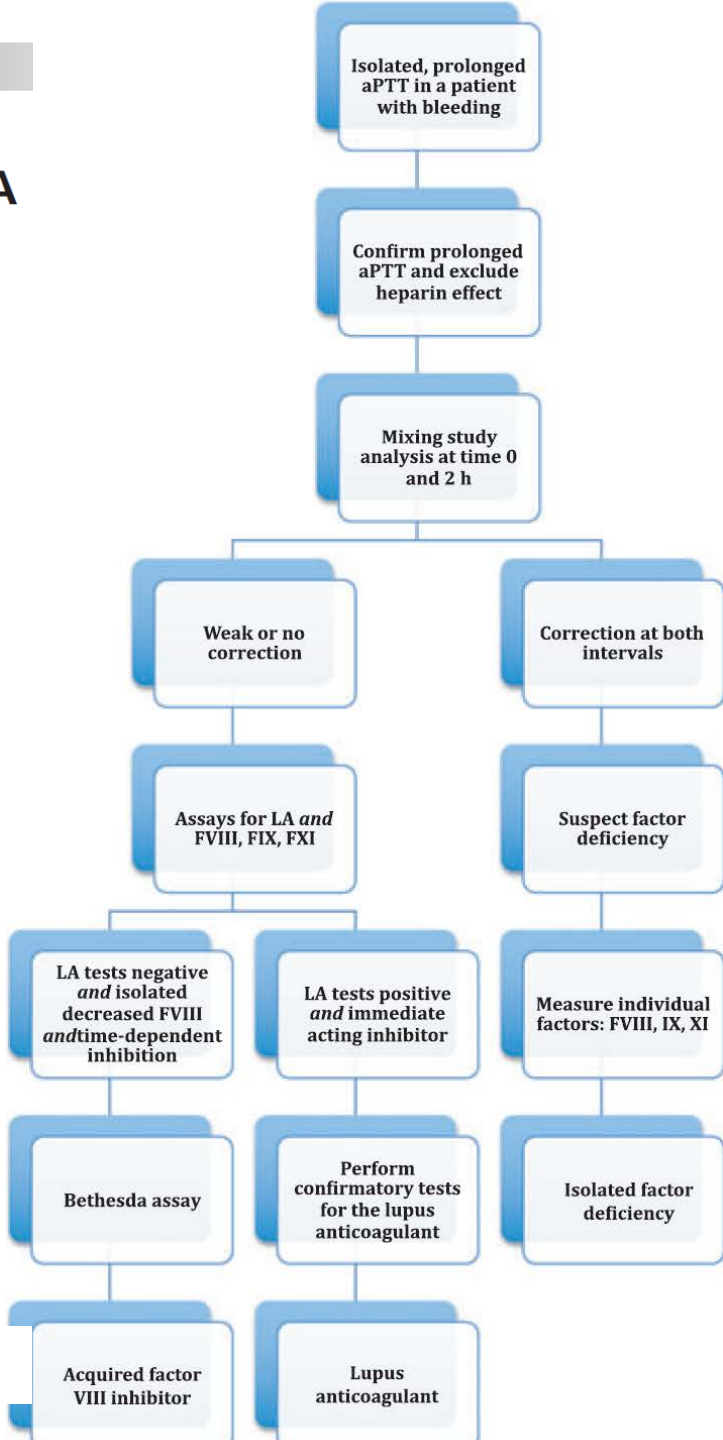
- Titolazione inibitore FVIII (Nijmegen): 26 BU

bjh review

How I manage patients with acquired haemophilia A

Douglas W. Sborov[1] and George M. Rodgers[2,3]

Attenzione alle cantonate…



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

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Semin Thromb Hemost 2014;40:803–811.

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

Coagulation assays and anticoagulant monitoring

Dorothy M. (Adcock) Funk[1]

[1]*Colorado Coagulation, a business unit of Esoterix Inc, Englewood, CO*

Table 1. Effect of various anticoagulants on routine and select specialty coagulation assays

Assay	UFH	LMWH fondaparinux	VKA	Dabigatran (thrombin inhibitor)	Rivaroxaban or apixaban (Xa inhibitors)
APTT	Prolonged ↑ ↑	No effect or prolonged ↑	Prolonged ↑	Prolonged ↑ ↑	Prolonged ↑
PT/INR*	Little or no effect	No effect	Prolonged ↑ ↑	Prolonged ↑	Prolonged ↑ ↑
TCT	Prolonged ↑ ↑ ↑	Prolonged ↑	No effect	Prolonged ↑ ↑ ↑	No effect
Clauss fibrinogen	May be factitiously low	No effect	No effect	No effect or factitiously low†	No effect
AT activity					
a. FXa based b. FIIa based	a. & b. may be decreased‡	a. & b. No effect	a. & b. No effect	a. No effect b. Factitiously overestimated	a. Factitiously overestimated b. No effect
PC activity					
a. Clot based b. Chromogenic	a. Factitiously overestimated b. No effect	a. & b. No effect	a. & b. Decreased‡	a. Factitiously overestimated b. No effect	a. Factitiously overestimated b. No effect
PS activity					
a. Clot based b. Free PS Ag	a. Factitiously overestimated b. No effect	a. & b. No effect	a. & b. Decreased‡	a. Factitiously overestimated b. No effect	a. Factitiously overestimated b. No effect
APTT-based APCR with added FV deficient plasma	Factitiously elevated ratio	No effect	Factitiously elevated or decreased ratio possible	Factitiously elevated ratio	Factitiously elevated ratio
APTT-based factor assays, one stage	Factitiously low FVIII, IX, XI	Factitiously low FVIII, IX, XI§	Decreased FIX‡	Factitiously low FVIII, IX, XI	Factitiously low FVIII, IX, XI§¶
PT- based factor assays, one stage*	No effect	No effect	Decreased FVII, X, II‡	Factitiously low FII, V, VII, X§	Factitiously low FVII, X, V, II¶
Chromogenic FVIII activity	No effect	No effect	No effect	No effect	Factitiously low
APTT mixing study	Incomplete correction	Incomplete correction	Correction into normal range	Incomplete correction	Incomplete correction¶
PT mixing study*	Not indicated with normal PT	Not indicated with normal PT	Incomplete correction	Incomplete correction	Incomplete correction¶
LA tests	Possible to misclassify as LA	Effect unlikely	Possible to misclassify as LA	Possible to misclassify as LA	Possible to misclassify as LA¶

↑ indicates a slight increase in clotting time; ↑ ↑, moderate increase in clotting time; ↑ ↑ ↑, marked increase in clotting time; PC, protein C; and PS, protein S.

Management

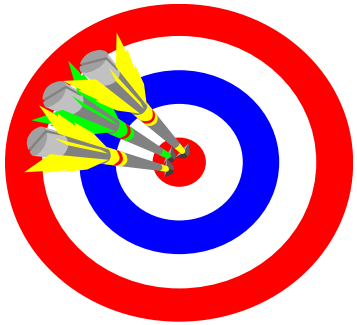
Diagnosis of AHA

Bleeding

Hemostatic Treatment

Inhibitor eradication (IST)

No bleeding



Identification and treatment of underlying conditions

Cosa fare – II ?

Ricovero in Medicina (18 giorni)

- Trasfusione di GRC (12 unità): target emoglobina 9-10 g/dL
- Iniziata terapia già al PS con rFVIIa (NovoSeven):

  Bolo iniziale: 90 mcg/kg + 90 mcg/kg ogni 3 ore per 24 ore;

  90 mcg/kg ogni 6 ore per 3 giorni e 90 mcg/kg ogni 12 ore per altri 10 giorni. Risposta: eccellente.

Domanda I – Perché rFVIIa?

Le mie ragioni….

Raccomandazioni per il trattamento delle emorragie

Sintesi della raccomandazione	Grado
'Wait and watch' nei pazienti senza manifestazioni emorragiche di rileivo	2C
Rimozione ove possibile della verosimile condizione scatenante approccio prioritario	2C
Acido tranexamico per emorragie mucose non gravi	2B
Agenti bypassanti trattamento di prima linea in pazienti con emofilia A acquisita ed emorragie clinicamente significative	**1B**
FVIII e DDAVP da riservare in paziento con FVIII misurabile e bassi titoli anticorpali. Monitoraggio assiduo livelli FVIII raggiunti e risposta anamnestica	2C
Switch precoce ad agente bypassante alternativo in caso di insuccesso	2C
Plasmaferesi e immunoadsorbimento da considerare in pazienti con emorragie gravi, non responsive ai bypassanti o per procedure invasive urgenti	2B

Diagnosi e trattamento degli inibitori acquisiti dei fattori della coagulazione. Raccomandazioni AICE 2014

rFVIIa or aPCC ?*

Author, Year	Design	Agent	Patients, *n* (Bleeds)	Efficacy, %		Other Findings
				First-Line Therapy	Salvage Treatment	
Hay et al, 1997[69]	Retrospective	rFVIIa	38 (74)	100[b]	75[b]	Median 28 doses (range 1–541), initial dose 90 μg/kg (45–181), every 2–6 h over a median 3.9 d (0–43).
Baudo et al, 2004[5]	Retrospective	rFVIIa	15 (20)	87[b,c]		Median 10 doses (range 1–60), initial dose 90 μg/kg (46–118), every 2–6 h over a median 2.75 d (0–8); 7 patients were treated by continuous infusion.
Sallah, 2004[72]	Retrospective	APCC	34 (55)	85[b,d]		75 IU/kg in 29 patients and 100 IU/kg in 5 patients. Median number of infusions 6 and 10 and time to complete response 36 and 48 h in severe and moderate bleeds, respectively.
Goudemand, 2004[73]	Retrospective	APCC	17 (55)	89[e]		Median dose 68 IU/kg (range 35–80) every 8–24 h over median 3.5 d (1–17).
Sumner et al, 2007[70]	Registries and literature review[f]	rFVIIa	139 (182[g])	83[e]	66[e]	Partially effective in 14% of cases. Ranges of administered dose 60–160 μg/kg, number of bolus 1–33, duration 1–7 d; 10 patients with 12 thrombotic events.
Knoebl et al, 2010[71]	Prospective, EACH2 Registry	rFVIIa APCC	NR (170) NR (64)	91[e] 94[e]		No significant difference in efficacy or severe adverse events between the two bypassing agents (1.4% myocardial infarction, 0.2% stroke, 1.0% venous thromboembolic events).
Ma et al, 2011[6]	Retrospective, HTRS Registry	rFVIIa	87 (193)	95[e]		Partially effective in 12% of bleeds. Median 3 doses (range 1–240), initial dose 90 μg/kg (22–270), over a median 1 d (1–60); One thromboembolic event.
Borg et al, 2011[7]	Prospective, FEIBAHC study	APCC	23 (NR)	95[e]		Only 1 patient switched because of lack of efficacy. 75 IU/kg doses, 1–3 times daily. Treatment ≤ 7 d in 70% of patients. Two deep vein thromboses (in the same patient) and one DIC.

*studies reporting at least 15 treated patients; ***Coppola et al, Semin Thromb Hemost 2012***

Terapia eradicante

- **Prednisone 1.5 mg/kg (100 mg/die)**

Domanda II – Perché solo prednisone?

- **Le mie ragioni……..**

Immunosuppressive treatment
Steroids ± cyclophosphamide?

Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2)

Peter Collins,[1] Francesco Baudo,[2] Paul Knoebl,[3] Hervé Lévesque,[4] László Nemes,[5] Fabio Pellegrini,[6] Pascual Marco,[7] Lilian Tengborn,[8] and Angela Huth-Kühne,[9] on behalf of the EACH2 registry collaborators

Table 3. Response to first-line immunosuppression

Regimen	n	CR, n (%)	Days from start of immunosuppression, median (IQR)			Relapse, n (%)	Stable CR, n (%)
			Inhibitor negative	FVIII > 70 IU/dL	IS stopped		
Steroids alone	142	83 (58)	34 (17-76)	32 (15-51)	108 (55-208)	15 (18)	68 (48)
Steroids + cyclophosphamide	83	66 (80)	32 (12-77)	40 (18-81)	74 (52-151)	8 (12)	58 (70)
Steroids + rituximab	28	18 (64)	46 (28-109)	35 (26-189)	62 (31-113)	0 (0)	18 (64)
Cytotoxic + rituximab	3	2 (67)	ND	ND	ND	0 (0)	2 (67)
Steroids + cytotoxic + rituximab	8	6 (75)	50 (20-122)	67 (45-113)	67 (29-129)	1 (17)	5 (63)
Rituximab alone	12	5 (42)	53, 145, 209, 334*	145, 209, 252, 334*	21, 21, 21, 21, 22*	0 (0)	5 (42)
Rituximab + any other agent	39	26 (67)	49 (28-93)	42 (28-138)	67 (31-109)	1 (3)	25 (64)
All rituximab-based regimens	51	31 (61)	65 (29-144)	64 (28-206)	43 (22-96)	1 (3)	30 (59)

Table 5. Adverse events associated with first-line treatment

Regimen	n	Any	Infection	Neutropenia	Diabetes	Psychiatric disorder
Steroids alone	142	36 (25)	23 (16)	2 (1)	11 (8)	6 (4)
Steroids + cyclophosphamide	83	34* (41)	22 (27)	12 (14)	5 (6)	3 (4)
Rituximab-based regimens	51	19 (37)	6 (12)	9 (18)	11 (22)	1 (2)

Table 7. Final outcome of acquired hemophilia A by first-line immunosuppressive therapy

Regimen	n	Alive at final follow-up, n (%)	Alive and inhibitor-free at final follow-up, n (%)
Steroids alone	142	95/135 (70)	90/135 (67)
Steroids + cyclophosphamide	83	44/69 (64)	43/69 (62)
Rituximab-based regimens	51	38/49 (78)	35/49 (71)

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.

Mortality - EACH2 Registry

Deaths* Cause of death	100 n (%)	20%
Fatal bleeding	16 (16)	3.2% of patients
Hemostatic therapy	0 (0)	
IST complications	**16 (16)**	3.2% of patients 3.3% of those receiving IST
Underlying disease	**45 (45)**	9% of patients 18.8% of patients with underlying disease
Other/unknown	39 (39)	

***n=501, median (range) follow-up: 318 (111-759) days**

Steroid-based or rituximab-based IST ?

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All rituximab-based regimens	51	31 (61)	65 (29-144)	64 (28-206)	43 (22-96)	1 (3)	30 (59)

56%

The outcome of first-line immunosuppressive therapy (IS) is shown. Complete remission (CR) was defined as inhibitor-negative, FVIII > 70 IU/dL, and immunosuppressive therapy stopped. Stable CR was defined as achieving CR with no relapse during follow-up. Because the groups are not matched, it is not appropriate to make statistical comparisons between the treatment arms.

BLOOD, 5 JULY 2012 • VOLUME 120, NUMBER 1

Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2)

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Raccomandazioni per la terapia eradicante: AHA

Sintesi della raccomandazione	Grado
La terapia immunosoppressiva deve essere iniziata non appena possibile, idealmente appena formulata la diagnosi di emofilia A acquisita	1B
Prednisone (1-2 mg/Kg os) in monoterapia o in combinazione con ciclofosfamide (1-2 mg/Kg os) trattamento di prima linea	1B
Rituximab in monoterapia o in combinazione con altri agenti terapia di seconda linea in caso di mancata risposta a ter. di I linea entro 8-12 settimane	2B
Rituximab può essere indicato come agente di prima linea in pazienti con controindicazioni all'uso di farmaci immunosoppressori	**2B**
Associazione di più farmaci immunosoppressori (inclusa ciclosporina) e regimi di immunotolleranza ulteriori alternative in caso di mancata risposta	2C
HDIg non indicate come trattamento eradicante	1B
Risposta completa: persistente riscontro di inibitore negativo e FVIII >70%	2B
Tromboprofilassi nei pazienti con fattori di rischio tromboembolico, specie in caso di livelli di FVIII elevato in corso/al termine di terapia eradicante	2C

Diagnosi e trattamento degli inibitori acquisiti dei fattori della coagulazione. Raccomandazioni AICE 2014

Anamnesi

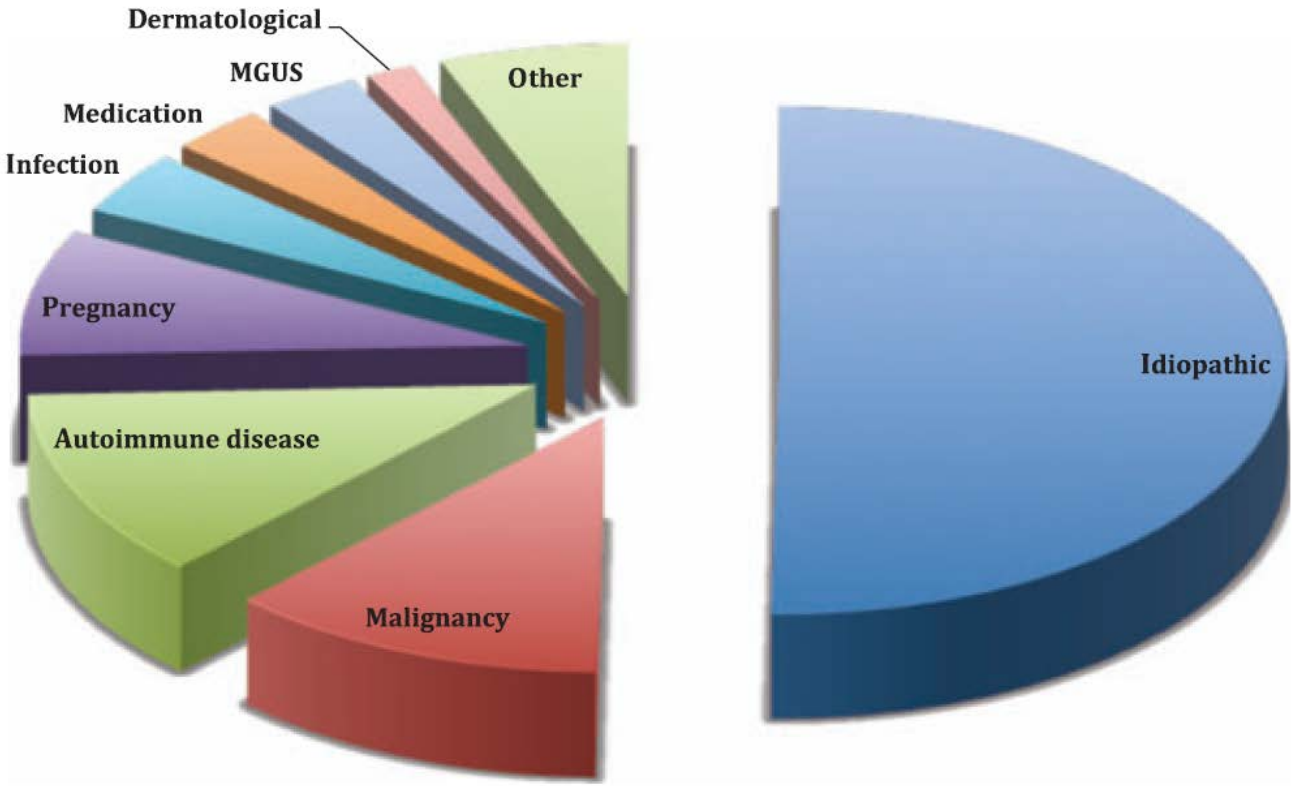
- **IMA (STEMI anteriore) nel 2014 trattato con PTCA + duplice stent DES in tp con ASA + clopidogrel**
- **Ecocardio recente: VS dilatato con necrosi anteriore e FE moderatamente ridotta (45%).**
- **AAA tratto sottorenale noto dal 2014**
- **Iperuricemia, dislipidemia.**

Sospensione del clopidogrel

bjh review

How I manage patients with acquired haemophilia A

Douglas W. Sborov[1] and George M. Rodgers[2,3]



Emofilia acquisita e clopidogrel

ORIGINAL ARTICLE

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

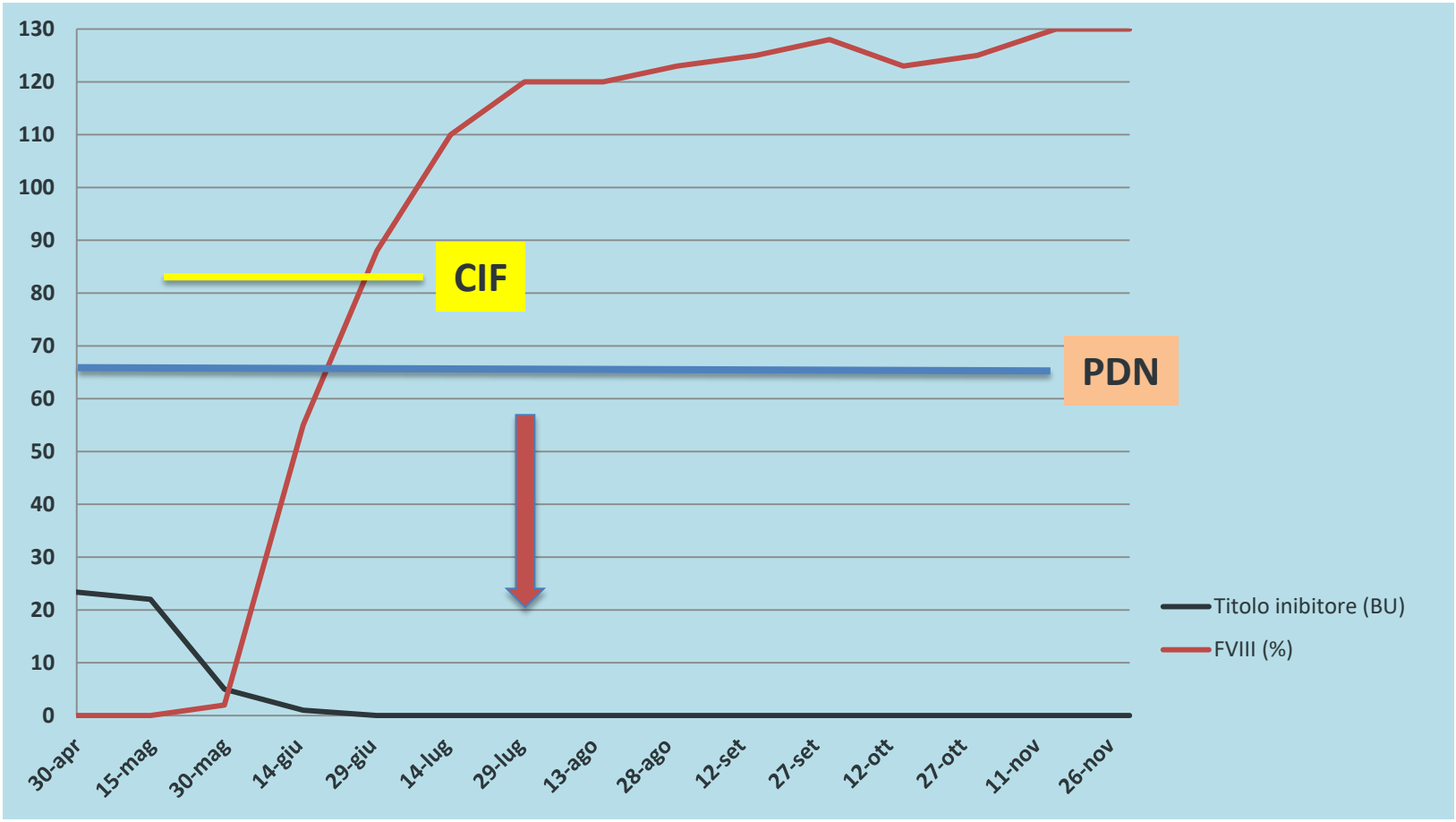
P. KNOEBL,* P. MARCO,† F. BAUDO,‡ P. COLLINS,§ A. HUTH-KÜHNE,¶ L. NEMES,**
F. PELLEGRINI,†† L. TENGBORN,‡‡ and H. LÉVESQUE,§§ ON BEHALF OF THE EACH2 REGISTRY CONTRIBUTORS[1]

3/17 (17.6%) drug-induced
(secondo solo ai beta-lattamici)

Altri 4 casi segnalati in letteratura dopo una ricerca sistematica elettronica su PubMed e manuale sulla bibliografia degli articoli recuperati

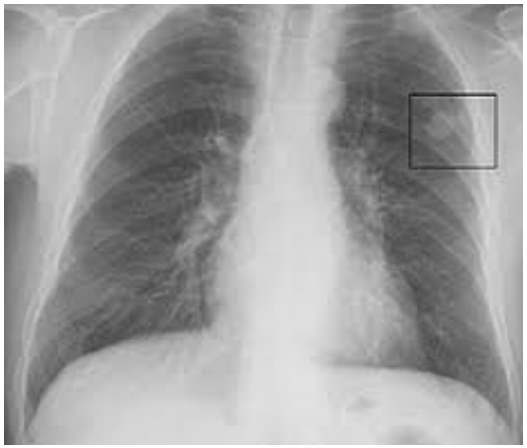
Tutti ad esito favorevole

Andamento del titolo dell'inibitore



Follow-up

- Diabete iatrogeno
- Peggioramento situazione cardiologica (FE35%)
- Monitoraggio parametri coagulativi
- Complicanza infettiva: nel luglio 2016 scadimento condizioni generali, calo ponderale, astenia ingravescente, difficoltà respiratorie, incremento di VES e PCR (82 e 129).
- RX Torace



un venerdì pomeriggio (02/17) al Centro Emofilia…

‘ Pronto Soccorso, abbiamo il Sig. ….., suo paziente emofilico, con ematomi spontanei arti superiori e inferiori.

Ha 9,6 g/dL di emoglobina, GB e piastrine

nella norma, APTT 3.24 con PT normale….‘

Ricovero in medicina (11 giorni). Esami eseguiti il giorno successivo: FVIII 2.1%, titolo inibitore FVIII: 6 UB

Terapia anti-emorragica ed immunosoppr.

- **rFVIIa (dosaggio standard per 6 giorni)**
- **Prednisone 75 mg/die + ciclofosfamide 100 mg/die**
- **Persistenza VES aumentata: diagnosi di polimialgia reumatica (il pz. aveva sofferto 20 anni prima!).**

Domanda III – perché ancora PDN + CIF?

Le mie ragioni….

Raccomandazioni per la terapia eradicante: AHA

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Rituximab in monoterapia o in combinazione con altri agenti terapia di seconda linea in caso di mancata risposta a ter. di I linea entro 8-12 settimane	**2B**
Rituximab può essere indicato come agente di prima linea in pazienti con controindicazioni all'uso di farmaci immunosoppressori	2B
Associazione di più farmaci immunosoppressori (inclusa ciclosporina) e regimi di immunotolleranza ulteriori alternative in caso di mancata risposta	2C
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Tromboprofilassi nei pazienti con fattori di rischio tromboembolico, specie in caso di livelli di FVIII elevato in corso/al termine di terapia eradicante	2C

Diagnosi e trattamento degli inibitori acquisiti dei fattori della coagulazione. Raccomandazioni AICE 2014

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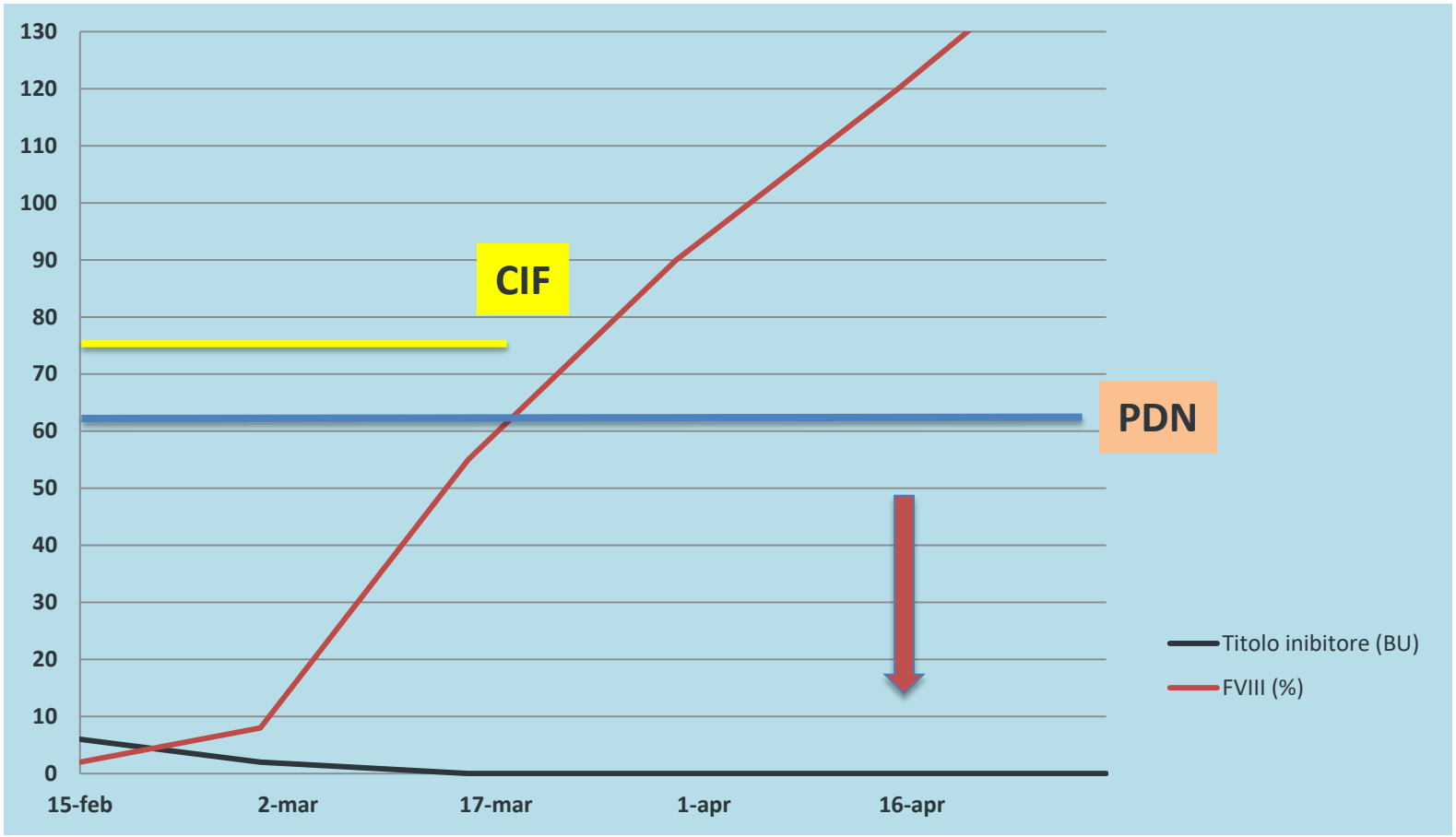
Table 6. Second-line immunosuppressive therapy after failure or relapse

	Steroids alone (n = 142)		Steroids + cyclophosphamide (n = 83)		Rituximab-based (n = 51)	
First-line treatment regimen	**Relapse (n = 15)**	**Nonresponse (n = 59)**	**Relapse (n = 8)**	**Nonresponse (n = 17)**	**Relapse (n = 1)**	**Nonresponse (n = 20)**
Second-line treatment regimen, n						
Steroids + cytotoxics	1	4	4	2	0	1
Steroids alone	5	8	1	0	0	6
Cytotoxics alone	0	17	0	0	0	5
Rituximab alone	1	25	0	5	0	1
Steroids + cytotoxics + rituximab	0	1	0	3	0	0
Cytotoxics + rituximab	0	0	0	0	0	1
Steroids + rituximab	0	1	2	3	0	3
No data available	8	3	1	4	ND	3
Second-line treatment outcome						
Complete response, n/total evaluable (%)	7/8(88)	28/44(64)	5/6(83)	8/11(73)	ND	7/14(50)
Relapse, n	2	2	1	1	ND	0
Stable complete response, n/total evaluable (%)	5/8(63)	26/44(59)	4/6(67)	7/11(64)	ND	7/14(50)

Second-line immunosuppressive therapy was reported as a proportion of cases and shown dependent on first-line treatment. In patients on whom data are available, 9 of 14 patients (64%) who relapsed had a stable CR, whereas 40 of 69 (58%) of those that did not achieve a first CR did so after second-line therapy.

Andamento del titolo dell'inibitore



Chiamata dal P.S. di Asola

- Dolori addominali, APTT nella norma
- Visita chirurgica (addome acuto) + TAC addome
- **PERFORAZIONE COLICA**
- Trasferimento in Chirurgia Osp. Cremona per addome acuto da perforazione intestinale con peritonite reattiva.
- Intervento di emicolectomia sinistra e resezione di tratto dell'ileo. Il ricovero è stato complicato da complicanze respiratorie (2 polmoniti). Ricovero in TI e successivo trasferimento in Pneumologia e successivamente in Riabilit. (APTT sempre normale e FVIII > 150%)
- Dimesso dopo 70 giorni di ricovero e trasferito in RSA

In conclusione….

- **Valutare attentamente l'eventuale malattia sottostante da cui dipende sicuramente la prognosi.**
- **Valutare attentamente la terapia immunosoppressiva**
- **Attenzione ai pazienti anziani con comorbidità.**
- **La gestione di questi pazienti fragili deve per forza essere….**

Medici d'urgenza

Specialisti
Geriatri, oncologi, ginecologi, reumatiologi, chirurghi…..

Radiologia

Centro emofilia

Laboratorio


GRAZIE