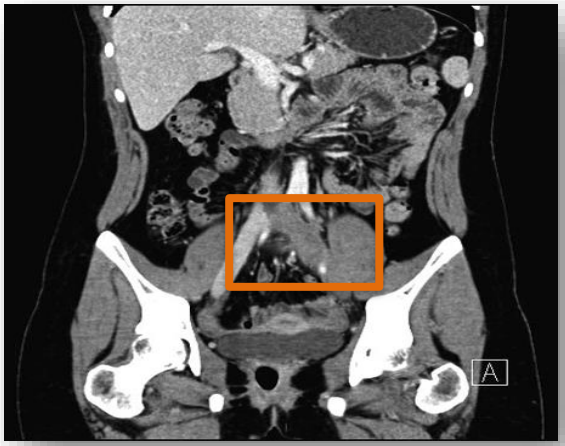
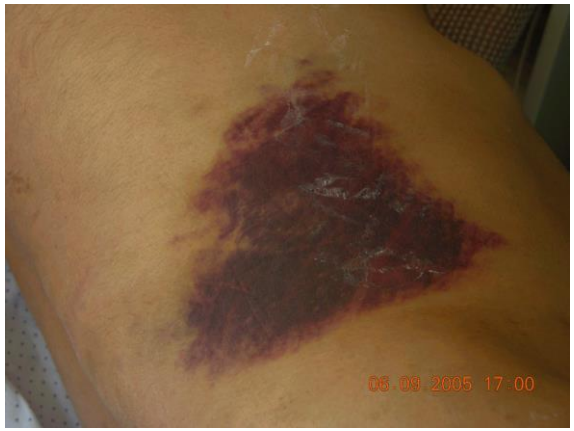




Manejo de la Hemofilia Adquirida

María Eva Mingot Castellano, PhD, MD
Profesor asociado Facultad de Medicina de Málaga
UGCi Hematología
HRU de Málaga

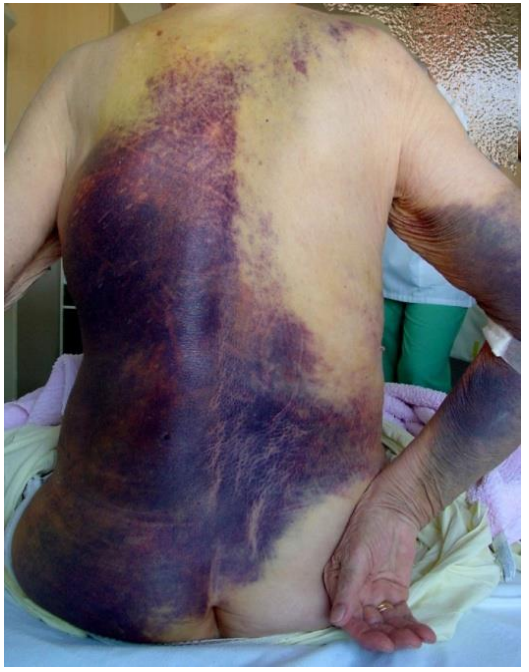
Disclosures:
María Eva Mingot Castellano

Shareholder	
Grant / Research Support	Shire, Bayer, Novo Nordisk, Amgen, Pfizer, Novartis
Advisory board member	Shire, Bayer, Novo Nordisk, Amgen, Novartis, Pfizer, Roche
Consultant	Member of Scientific Committee of SETH (Sociedad Española de Trombosis y Hemostasia, Spain), Head of the Scientific Committeee of Fundación Victoria Eugenia (Instituto Carlos III, Spain), Member of the Director Committee of the GEPTI (Grupo Español de trombopenia inmune primaria), Scientific Committeee of GACC (Grupo Andaluz de Coagulopatías), Scientific Committee for the securty of the patients, laboratory area, SSPA (Sistema Sanitario Público Andaluz)
Employee	
Paid Instructor	
Speaker bureau	
Other	

Definición y Epidemiología

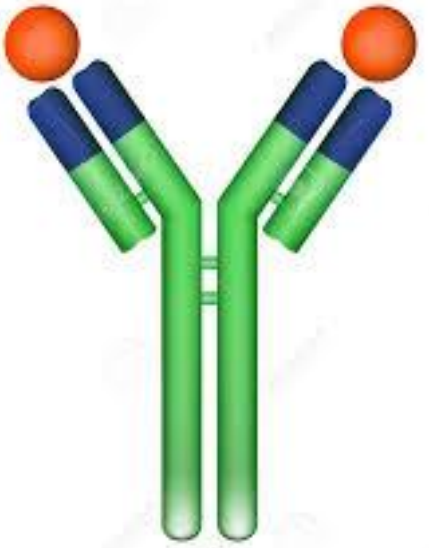
Coagulopatía Autoinmune:

Anticuerpos frente a proteínas de la coagulación



20 : 80

Qué son los inhibidores

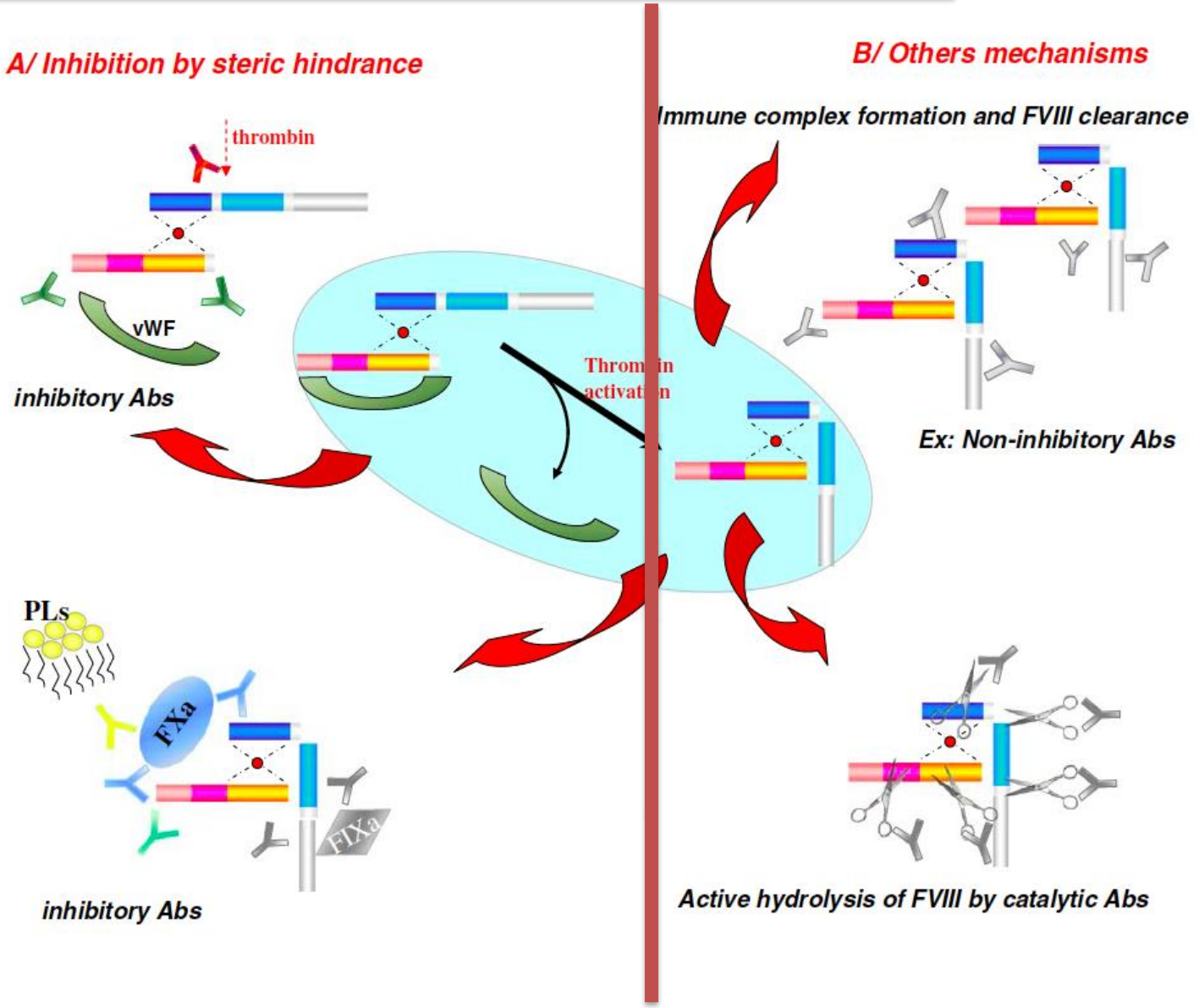


- Inmunoglobulinas del subtipo IgG policlonales.
- Las más frecuentes IgG1 e **IgG4**.
- Pueden dirigirse contra cualquiera de los dominios del Factor:

  Dominio A2 (IgG1), Dominio C2 (IgG4).
- Se han descrito IgM e IgA en hemofilia adquirida.
- Pueden presentar un **cinética tipo I** o tipo II (¿vW?).

Lavigne-Lissalde G et al. Clinic Rev Allerg Immunol (2009) 37:67–79

¿ Cómo actúa el inhibidor?



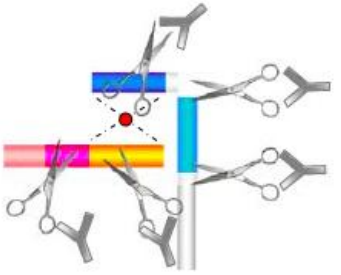
Lavigne-Lissalde G et al. Clinic Rev Allerg Immunol (2009) 37:67–79

¿ Cómo se produce el inhibidor?

- Propio de **autoAc, espontáneos**.
- Individuos sanos y otras patologías.
- IgG, pero también en resto de subclases.
- Misión: **Favorecer la endocitosis y eliminación de antígenos no necesarios.**
- Respecto al FVIII:

  -**Positivo**: Inmunes e infecciones.

  -**Negativo**: Si altera funcionalidad.



Active hydrolysis of FVIII by catalytic Abs

Lavigne-Lissalde G et al. Clinic Rev Allerg Immunol (2009) 37:67–79. Wootla B et al. Clinic Rev Allerg Immunol (2009) 37:97–104

Perfil sospecha diagnóstica

International recommendations on the diagnosis and treatment of patients with acquired hemophilia A

Diagnosis

We recommend that the diagnosis of AHA be considered whenever an acute or recent onset of bleeding symptoms is accompanied by an unexplained prolonged aPTT.

Haematologica 2009; 94:566-575. doi:10.3324/haematol.2008.001743

Sangrado Agudo Anormal

TTPa alargado no justificado

La sospecha… es básica

Retraso Dx = Morbimortalidad

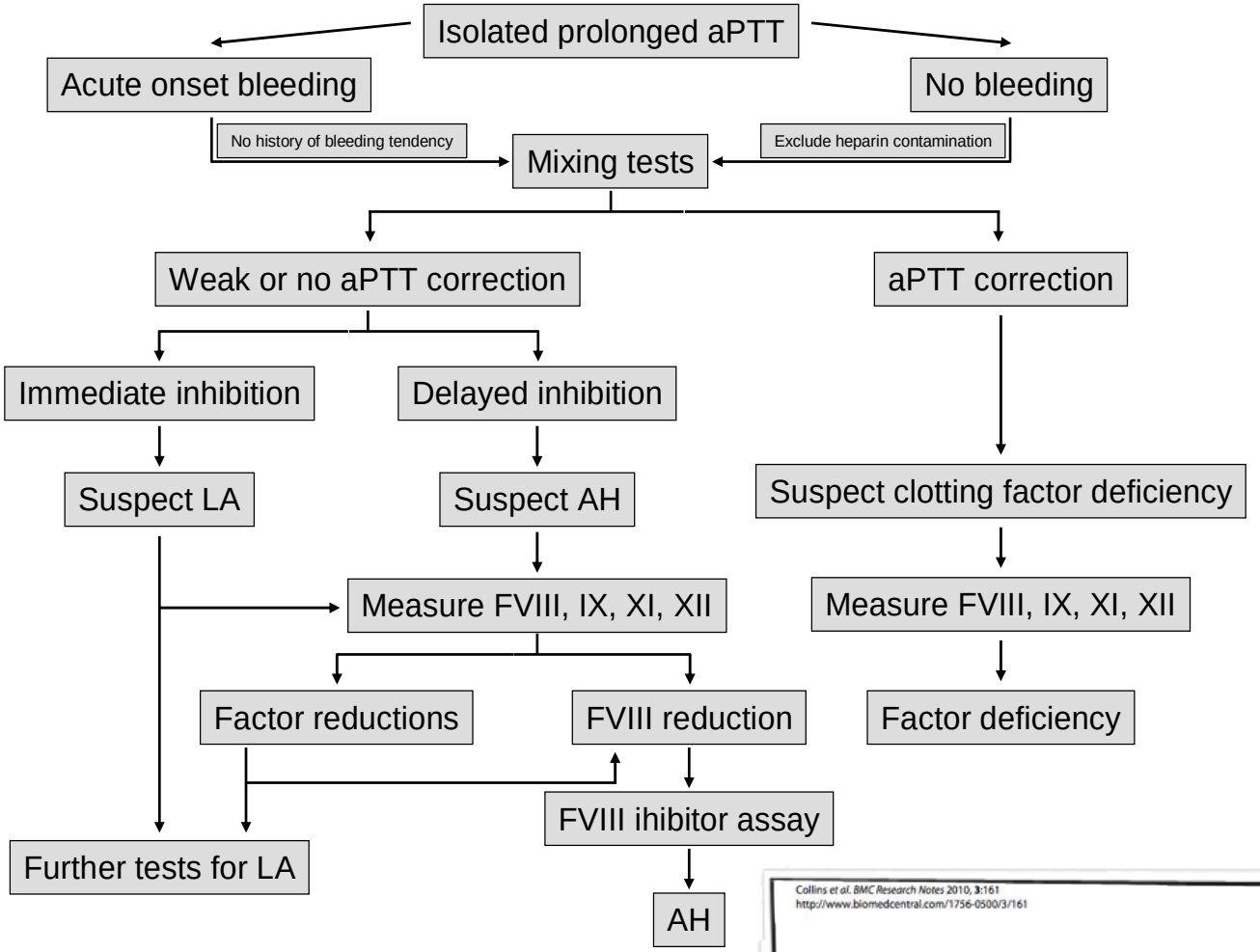
TABLE 2 Impact of diagnostic delay in our cohort of patients with acquired haemophilia

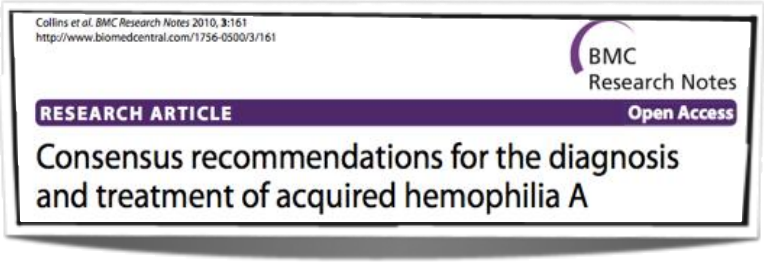
Variables	Diagnostic delay from 1st bleeding <1 mo	>1 mo	*P*
Patients (n, %)	17 (60.8)	11 (39.2)	
FVIII (activity %)	1.9 (2.9)	1.5 (1.2)	NS
Inhibitor title (BU)	46 (66)	36 (61)	NS
Hb (g/dL)	6.8 (1.6)	7.3 (2.4)	NS
Major bleeding (n,%)[a]	15 (88)	9 (81)	NS
Blood concentrates (n)	7.3 (6.5)	7.5 (6.8)	NS
Days to resolve bleedings[b]	20 (20)	49 (52)	.05
Days of haemostatic treatment	7.6 (5.7)	23.8 (13)	.003
Total dosage of Novoseven^{R} (mg)	62 (53)	190 (166)	.02
Total dosage of FEIBA^{R} (UI)	38000 (2800)	60000 (73539)	NS
Total dosage of FVIIIr (UI)	29000 (26000)	31000 (16750)	NS
Remission (n, %)[c]	15 (88)	10 (90.9)	NS
Recurrence (n, %)	3 (17.6)	3 (27.3)	NS

- **Antivitamina-K**
- **ACOD**

Pardos Gea et al. Haemophilia. 2018 May 6. doi: 10.1111/hae.13499.

Laboratorio





Prolonged Activated Partial Thromboplastin Time: Difficulties in Discriminating Coexistent Factor VIII Inhibitor and Lupus Anticoagulant

Clinical and Applied Thrombosis/Hemostasis
2015, Vol. 21(2) 149-154

DOI: 10.1177/1076029614541516
cat.sagepub.com
SAGE

Paul R. J. Ames, MD, MSc, PhD[1,2], Maria Graf, MD[3], Jeremy Archer, BSc[2], Nicola Scarpato, MD[3], and Luigi Iannaccone, BSc[4]

						FVIII, IU		FVIII Inhibitor	
Age/Sex	Clinical Presentation	Associated Conditions	LA	aCL IgG/IgM	aB2GPI	Clotting	Chromogenic	Clotting (BU)	ELISA
37/F	DVT → hematoma	Postpartum	DRVVT + PL	ND	ND	2	ND	35	ND
64/F	DVT → hematoma		DRVVT + PL	ND	ND	<1	ND	64	ND
64/F	Multiple DVT + PE	NHL	Staclot LA/PNP (known LA)	33	ND	12	ND	9	ND
38/F	DVT + ecchymoses	Postpartum							
62/F	DVT → PE	CLL	KCT + inosithin	ND	ND	<1	ND	16	ND
29/F	Ischemic stroke	IDDM	DRVVT + PL	80/6000	ND	0	ND	48	ND
60/F	Ecchymosis	SLE/RA	DRVVT + PL	22/12	ND	IX 28	ND		ND
59/M	Hematoma		DRVVT (HP)	ND	ND	<1	ND	1	ND
30/M	Hematoma	MG	DRVVT + PL	-ve	-ve	<1		70.4	
68/M	Hematoma		DRVVT + PL	ND	ND	20.5	ND	52	ND
60/F	Hematomas		KCT + inosithin	ND	ND	<1	ND	320	ND
92/F	Ecchymoses	Pemphygoid	KCT + inosithin	ND	ND	<1	ND	80	ND
70/M	Bleed postliver biopsy	RA	Staclot LA/PNP	ND	ND	2	ND	32	ND
63/F	Bleeding mouth	EBV	DRVVT	ND	ND	<1	ND	500	ND
30/F	Hematoma	Postabortion	KCT	-ve	-ve	6	ND	123	+ve
			Staclot LA/PNP	ND	ND	ND	ND	56	ND

Abbreviations: LA, lupus anticoagulant; inh, inhibitor; DVT, deep vein thrombosis; PE, pulmonary embolism; CLL, chronic lymphoid leukemia; NHL, non-Hodgkin lymphoma; IDDM, insulin dependent diabetes mellitus; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; MG, monoclonal gammopathy; FEIBA, factor VIII by-passing activity; PF, plasmapheresis; CRY, cryoprecipitate; CYC, cyclophosphamide; PDN, prednisolone; V, vincristine; RTX, rituximab; EBV, Epstein Barr virus reactivation; IA, immunoabsorption; IVIG, intravenous immunoglobulins; ND, not done; C, cleared; NC, not cleared; IMP, improved; rVII, recombinant factor VII; PL, phospholipid; M, male; F, female.

Definición y Epidemiología

Idiopathic
Pregnancy
Autoimmune diseases
- SLE
- Rheumatoid arthritis
- Multiple sclerosis
- Giant cell arteritis
- Sjogren's syndrome
- Autoimmune haemolytic anaemia
- Good-Pasture Syndrome
- Myasthenia gravis
- Graves' disease
- Autoimmune hypothyroidism
- inflammatory bowel disease
- Ulcerative colitis

Allergic reaction to drugs
- Penicillin and derivatives
- Sulphonamides and quinolones
- Griseofulvin
- Phenytoin
- Chloramphenicol
- Methyldopa
- Levodopa
- Interferon alfa
- Peginterferon
- Fludarabine
- BCG vaccine
- Clopidogrel
- Antidepressants[a]
- Hydralazine
- Acetaminophen

Skin diseases
- Psoriasis
- Pemphigus

Respiratory diseases
- Asthma
- COPD

Diabetes

Acute HBV or HCV infection
Solid tumours
- Prostate
- Lung
- Colon
- Pancreas
- Stomach
- Bile duct
- Head
- Neck
- Cervix
- Breast
- Melanoma
- Kidney

Haematological diseases
- Chronic lymphocytic leukaemia
- Non-Hodgkin lymphoma
- Multiple myeloma
- Waldenstrom's disease
- Myelodysplastic syndrome
- Myelofibrosis
- Erythroleukemia

Idiopática

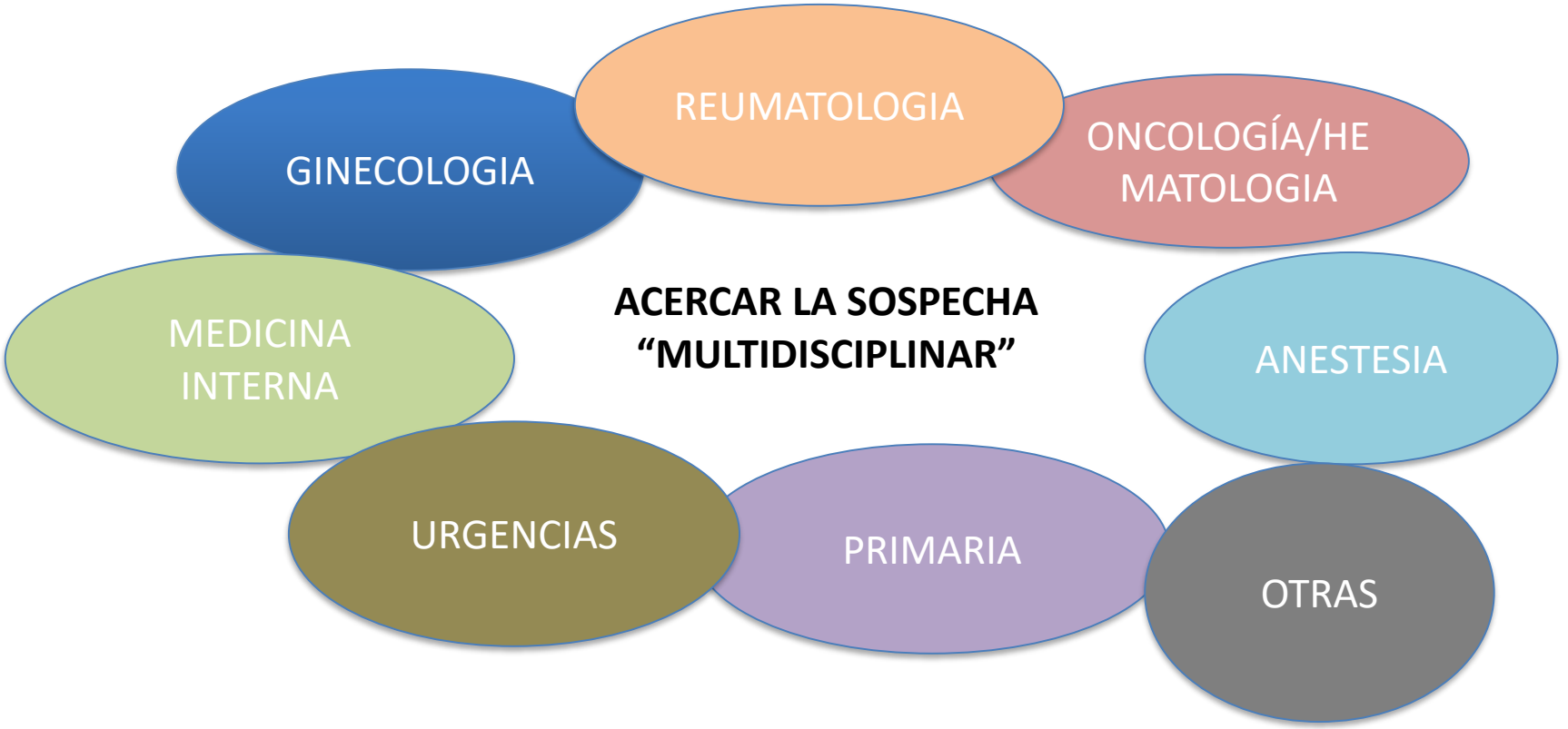
50%

Mingot-Castellano ME et al. Med Clin (Barc). 2017;148(7):314-322.

Hemofilia adquirida: Base

50% adquirida.

El otro 50%: Autoinmune, postparto, Neoplasias, Dermatología, otras.



Mingot-Castellano ME et al. Med Clin (Barc). 2017;148(7):314-322.

Las bases del tratamiento de la HA

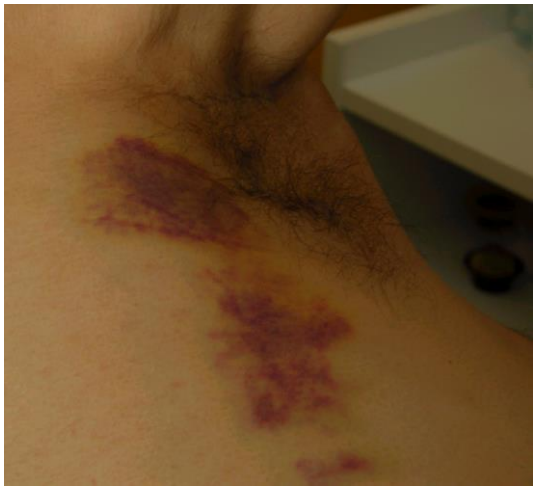
Las bases…Sentido Común, Prevenir

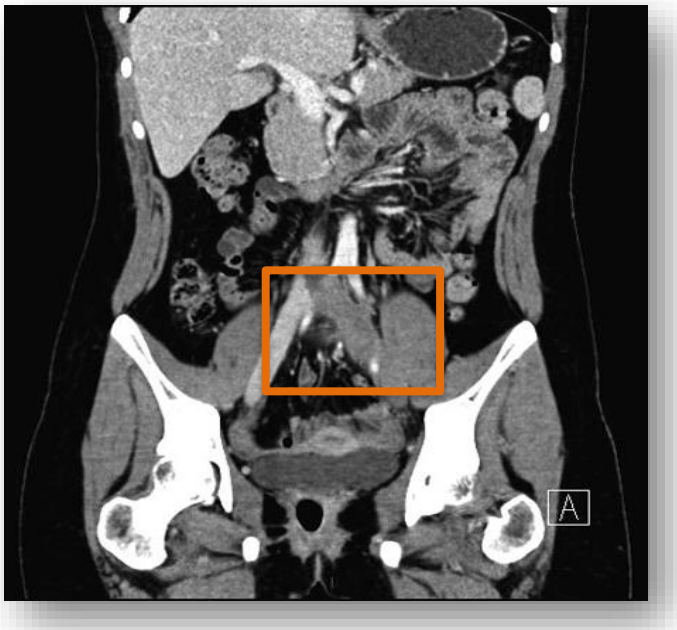
- **Tratamiento** en un **centros con experiencia**.
- **Evitar cualquier procedimiento invasivo** que no sea estrictamente necesario.
- **Una punción venosa, la colocación de una vía, la toma de la tensión** arterial pueden causar hemorragia grave: **restringirse al mínimo.**
- **Inyecciones intramusculares están contraindicadas**.
- **Vía central, punción lumbar o arterial** solamente deben realizarse bajo cobertura con un **agente hemostático.**
- **Suspender antiagregantes, anticoagulantes, antinflamatorios**.
- **Entrenar al paciente en reconocimiento de sintomatología** hemorrágica.

1. Huth-Kühne A, et al. Haematologica 2009; 94: 566-575. 2. Mingot-Castellano ME et al. Med Clin (Barc). 2017;148(7):314-322.

¿Qué sangrado necesita tratamiento hemostático?

- Sangrados graves.
- Sangrados con disminución de Hemoglobina.
- Cobertura procedimientos cruentos.





1. Huth-Kühne A, et al. Haematologica 2009; 94: 566-575. 2. Mingot-Castellano ME et al. Med Clin (Barc). 2017;148(7):314-322. 3. Kruse-Jarre R, et al. Am J Hematol. 2017 Jul;92(7):695-705. 2.

Perfil hemorrágico

FVIII

≠

Titulo inhibidor

≠

Severidad Sangrado

EACH2 Registry
European Acquired Haemophilia Registry

	severe	non-severe	P (Wilcoxon, single sided)
N	329	135	
Body weight (kg)	70 (60/78)	67.5 (59.8/77.3)	ns.
Time to diagnosis (days)	3 (0/11)	2 (0/25.3)	ns.
F VIII (U/dL)	2 (1/5)	2 (0/5)	ns.
Inhibitor (BU/ml)	13 (4.9/40.8)	10 (1.9/32.5)	ns.

Knoelb P et al. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J Thromb Haemost 2012;10:622-31.

¿Cuál es el agente hemostático de elección?

Agent	Recommended dose	Comments
Replacement therapy		
Recombinant porcine FVIII (rpFVIII)	*If no anti-porcine FVIII inhibitor*[a]: 50–100 U/kg initially then monitor every 2–3 h with FVIII activity and redose as needed *If detectable anti-porcine FVIII inhibitor*[a]: 200 U/kg initially for severe bleeding 50–100 U/kg for less severe bleeding Monitor and redose as above	ADVANTAGE Can be monitored with one stage FVIII clotting assay Replaces missing component Proven efficacy DISADVANTAGE Less effective in case of cross-reactive anti-porcine antibody May develop anti-porcine FVIII antibody during therapy = needs close monitoring CONSIDER First LINE Where drug readily available No underlying rpFVIII inhibitor FVIII activity measurement readily available Life-threatening/limb-threatening bleeding
Bypassing Therapy		
Activated prothrombin complex concentrate (aPCC)	50–100 U/kg every 8–12 h Do not exceed 200 U/kg/d	ADVANTAGE Proven efficacy for clinical bleeding DISADVANTAGE No laboratory to monitor underdosing or overdosing Potential arterial or venous thrombotic risk CONSIDER First LINE Where drug readily available If underlying high titer rpFVIII inhibitor (>10 BU) FVIII activity measurement not readily available Non-life-threatening/limb-threatening bleeding
Recombinant FVII activated (rFVIIa)	70–90 mcg/kg every 2–3 h until hemostasis achieved, then prolong dosing interval	ADVANTAGE Proven efficacy for clinical bleeding DISADVANTAGE No laboratory to monitor underdosing or overdosing Short half-life (2 h) Potential arterial or venous thrombotic risk CONSIDER First LINE Where drug readily available If underlying high titer rpFVIII inhibitor (>10 BU) FVIII activity measurement not readily available Non-life-threatening/limb-threatening bleeding

1

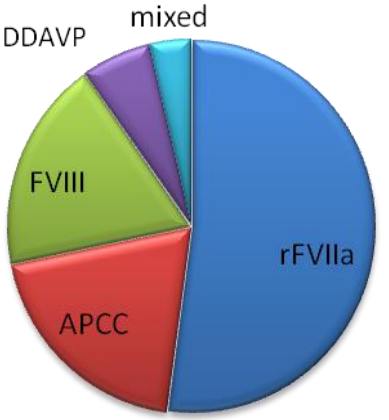
2

1. *Kruse-Jarre R, et al. Am J Hematol. 2017 Jul;92(7):695-705. 2. Mingot-Castellano ME et al. Med Clin (Barc). 2017;148(7):314-322.*

¿Cuál es el agente hemostático de elección?

TRATAMIENTO DE PRIMERA LÍNEA

334 pacientes (70.5 % presentaron sangrado)



	n
rFVIIa (Novoseven®)	170 (50.9%)
Activated Prothrombincomplex Concentrates (CCPa)	64 (19.2%)
FVIII concentrates	60 (18 %)
Desmopressin	20 (6 %)
Mixed rFVIIa + APCC: 1; rFVIIa+FVIII: 3; rFVIIa+DDAVP: 1; CCPa+FVIII: 1; APCC+DDAVP: 4; FVIII+DDAVP: 2	12 (3.6 %)

Baudo et al. Blood. 2012 120: 39-46

¿Cuál es el agente hemostático de elección?

EACH2 Registry
European Acquired Haemophilia Registry

	Bypassing agents	FVIII elevation	P
N	254	69	
Bleeding did not resolve	21 (8.3%)	20 (29.0%)	<0.0001
Bleeding resolved	233 (91.7%)	49 (71.0%)	
Time to bleeding resolved (d)	1 (0/2)	1 (0/3)	0.62

Analysis	OR	95% CI	P
Univariate	0.22	0.11-0.44	<0.0001
Multivariate-adjusted	0.19	0.08-0.43	<0.0001
Propensity score quintiles-adjusted	0.25	0.12-0.53	0.0004

Adjustment for age, gender, FVIII level, inhibitor titer, hemoglobin level, site, severity and cause of bleeding

Baudo et al. Blood. 2012 120: 39-46

¿Cuál es el agente hemostático de elección?

	rFVIIa treatment information	Haemostatic treatment	Patients treated, n	Episodes treated, n	Haemostatic efficacy, n (%) bleeding episodes[a]		Overall bleeding control, %
					Effective	Partially effective	
Emergency and compassionate use programmes:							
Arkin et al., 2000 [17]	NR	rFVIIa	6	NR[b]	NR	NR	100
Hay et al., 1997 [12]	Median initial dose: 90.4 μg/kg (range 45–181)						
First-line		rFVIIa	6	14	14 (100)	0	100
Salvage		rFVIIa	29	60	45 (75)	10 (17)	92
Total		rFVIIa	35	74[c]	59 (80)	10 (14)	94
Registries:							
HTRS [21]	Median initial dose: 90 μg/kg (range 88–100)	rFVIIa	NR	139	117 (84)	15 (11)	95
EACH2 [6][d] (unmatched samples)	Median initial dose: 90 μg/kg (IQR 84.71–102.86)	rFVIIa	159	159	145 (91)	–	91
		pd-aPCC	60	60	56 (93)	–	93
EACH2 [6][d] (propensity score-matched samples)	NR	rFVIIa	57	57	53 (93)	–	93
		pd-aPCC	57	57	53 (93)	–	93
SACHA [22][e]	Total dose for initial bleeding episode: 0.8 mg/kg (SD 0.8; range 0.01–3.0)	rFVIIa	28	NR	13 (48)	9 (33)	81
		pd-aPCC	6	NR	2 (33)	4 (67)	100
Japanese PMS study:							
Seita et al., 2013 [24]	Median (mean) dose: 93.2 μg/kg (99.5)	rFVIIa	132	371	189 (51)	152 (41)	92

. *Tiede et al. Annals of Hematology 2018;* May 26. doi: 10.1007/s00277-018-3372-z. *Tiede A, et al. Blood Reviews. 2015;29 (Supp 1):S19–S25*

¿Cuál es el agente hemostático de elección?

1

Table 4. Odds ratios (OR) for the response rate (300 bleeding episodes).

		OR	95% CI	*P* value
Initial dose (μg kg^{-1})	≥90 <90	2.3	(1.4–3.9)	0.001
Dosing interval (h)	≤3 >3	1.5	(0.9–2.6)	0.136

Precocidad

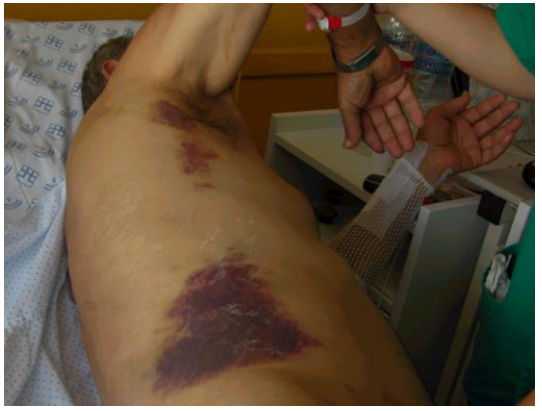
Dosis más altas ¿?

2

	Total	First-line rFVIIa	Second-line rFVIIa
Number of episodes	139	127	12
Initial dose (μg/kg)	90 (87.6–100.0)	90 (87.1–100.0)	90 (90.0–97.0)
Dose per infusion (μg/kg)	90 (87.8–98.7)	90 (87.6–98.7)	90 (90.0–97.0)
Total dose per episode (μg/kg)	333.5 (165.8–1382.9)	300 (118.7–1345.3)	576.9 (275.3–3430.0)
Number of injections (doses)	3 (2.0–14.0)	3 (1.0–13.5)	7 (3.5–25.0)
rFVIIa treatment duration (days)	1 (0–2.8)	1 (0–2.5)	1.5 (0.8–4.1)
Total treatment duration (days)	1 (0–4.42)	1 (0–4.0)	7.5 (0.8–13.5)

1. Amano K, et al. Haemophilia. 2017;23:50–58. 2. Ma A, et al. Blood Coagul Fibrinolysis. 2016; 27:753–760

PAUTA HEMOSTÁTICA



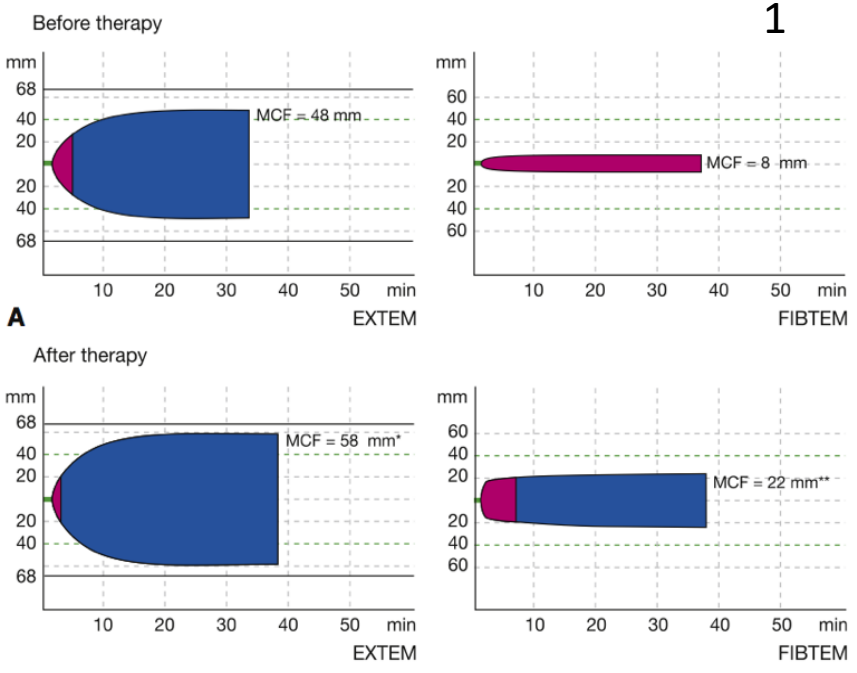
ADEVERS EVENTS
ACUTE RESPIRATORY FAILURE
19 DAYS

	CCPa	rFVIIa
1er fármaco hemostático recibido por el paciente	3	7
nº sangrados/1ª Línea (nº pacientes)	**11 (n=6)**	**7 (n=7)**
nº sangrados/2ª Línea (nº pacientes)	6 (n=6)	0
Dosis inicial (UF, µg)/kg media ± DE mediana (rango)	**54,4 ± 12,9** **50 (45-100)**	**91,4 ± 3,8** **90 (90-100)**
Dosis inicial (UF, µg)/kg - 1Línea media ± DE mediana (rango)	50,5 ± 3,5 50 (45 – 60)	91,4 ± 3,8 90 (90-100)
Intervalo de dosis inicial (h) media ± DE mediana (rango)	**12 ± 6,0** **8 (8-24)**	**5,4 ± 2,1** **4 (3-8)**
Intervalo de dosis inicial (h) - 1Línea media ± DE Mediana (rango)	**10,9 ± 4,8** **8 (8-24)**	5,4 ± 2,1 4 (3-8)
Duración tratamiento hemostático (días) media ± DE mediana (rango)	**8,6 ± 8,5** **5,5 (1-31)**	7,4 ± 4,9 7 (1-15)
Dosis total (UF, µg) media ± DE mediana (rango)	64 ± 65 $48x10^3$ (7-276)	137,9 ± 101,3 124 (14-259)
Nº dosis/paciente media ± DE mediana (rango)	**16,1 ± 12,3** **15 (2-50)**	**19,1 ± 15,8** **15 (2-48)**

Mingot-Castellano ME et al. Blood 2017;130:3688. ASH 2017

¿Cómo monitorizar la respuesta?

1



2, 3, 4

Hb

Parámetros Clínicos

DD

1. Tan S, et al. ISTH abstract 2017. 2. Kunth et al. Haematologica 2009;94:566-575. 3. Collins et al. Br J Haemtol 2013;162:578-773. 4. Qi et al. Blood coagul fibrinolysis 2014;25:754-60.

¿Qué hacer si no evolución adecuada?

Aumentar dosis y frecuencia

Cambiar de producto baipás

Aumentar dosis y frecuencia

No experiencia en terapia combinada

Kunth et al. Haematologica 2009;94:566-575. Collins et al. Br J Haemtol 2013;162:578-773.

¿Qué hacer si no evolución adecuada?

1

40% secuencial

2

Table 3. Comparison of haemostatic efficacy between the rFVIIa monotherapy and rFVIIa + aPCC/FVIII groups.

	Markedly effective <8 h	Effective 8–12 h	Moderate ≥12 h	Ineffective	Total	Response rate	*P* value chi-square
rFVIIa monotherapy, *n* (%)	129 (42.7)	26 (8.6)	120 (39.7)	27 (8.9)	302 (100.0)	155/302 (51.3)	0.8621
rFVIIa + aPCC/FVIII, *n* (%)	24 (34.8)	10 (14.5)	32 (46.4)	3 (4.3)	69 (100.0)	34/69 (49.3)	
Total, *n* (%)	153 (41.2)	36 (9.7)	152 (41.0)	30 (8.1)	371 (100.0)	189/371 (50.9)	

Response rate = (markedly effective + effective)/total.
aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.

1. Hay C, et al. Haemophilia. 2017;23:376–382. 2. Amano K, et al. Haemophilia. 2017;23:50–58

Eventos adversos, trombogenicidad

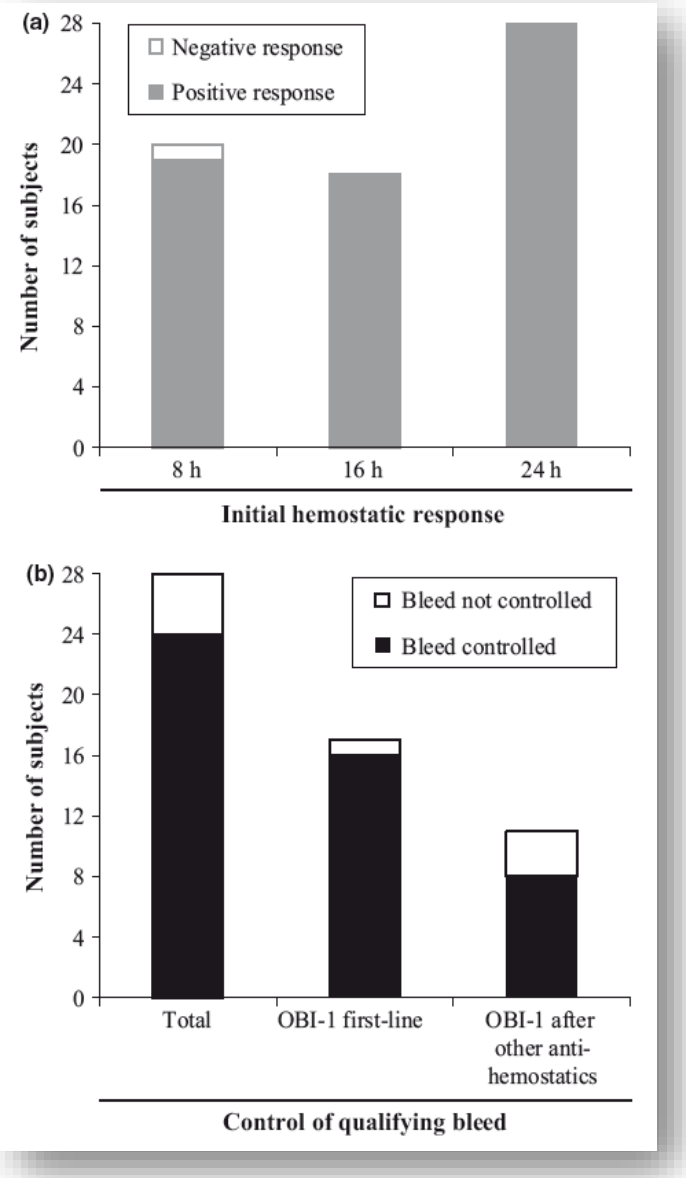
- **rFVIIa:**
  - >700,000 dosis estándar FVIIar, 25 eventos[1].
  - 80% sujetos con factores de riesgo vascular[1,2].
  - Mortalidad del 38%[3].
- **CCPa:**
  - 8,2x10[5] infusiones, 16 eventos[4].
- **Hemofilia adquirida:**
  - **CCPa**:
    - 1 caso de TVS en una serie de 10 sujetos tratados[5]. FRV
    - 6 eventos vasculares en 4 de los 34 pacientes de otra serie[6]. FRV
    - 46 eventos, 2,87 por cada 100.000 infusiones[7]:
      * 5,4 retrospectivos vs 1,09 prospectivos
      * 5,09 demanda vs 0 Profilaxis
      * 5 eventos (4 pacientes) en *cirugía.*
  - **rFVIIa**: 5 eventos, 3/132 pacientes[8]. FRV
  - **EACH2**: Eventos vasculares del 2.9% FVIIar (5/174) y 4.8% CCPa (3/63)[9].

1. *Abshire T, et al. J Thromb Haemost. 2004;2(6):899-909.*
2. *Abshire T. Semin Hematol. 2008;45(2 Suppl 1):S3-6*
3. *Neufeld E, et al. Blood Reviews 2015;29 (S1)S34–S44.*
4. *Aledort LM. Haemophilia. 2008;14(1):39-43.*
5. *Negrier C, et al. Blood Coagulation and Fibrinolysis 2016, 27:550-556.*
6. *Borg JY, et alHaemophilia 2015, 21, 330–337.*
7. *Rota et al.* Blood Adv. 2017;1(26):2637-2642.
8. *Amano K, et al. Haemophilia. 2017;23:50–58.*
9. *Baudo F, et al. Blood. 2012;120: 39-46.*

FVIIIr porcino, Obizur

- Eficaz.
- Monitorización.
- No trombocitopenia.
- No eventos trombóticos.
- 10 Ac con reactividad cruzada.
- 5 inhibidores de novo.
- 7 muertes/3 por sangrados (29 pacientes).

	Within first 24 h of treatment initiation*			
Statistic	Total dose (U kg^{-1})	Median dose per subject (U kg^{-1})	Dosing interval (h)	Number of infusions
N	24	24	20†	24
Mean	741.1	192.8	10.2	3.5
SD	616.4	82.9	6.6	2.0
Median	458.7	200.0	7.4	3.5
Min, Max	100, 2100	88, 400	3, 23	1, 7

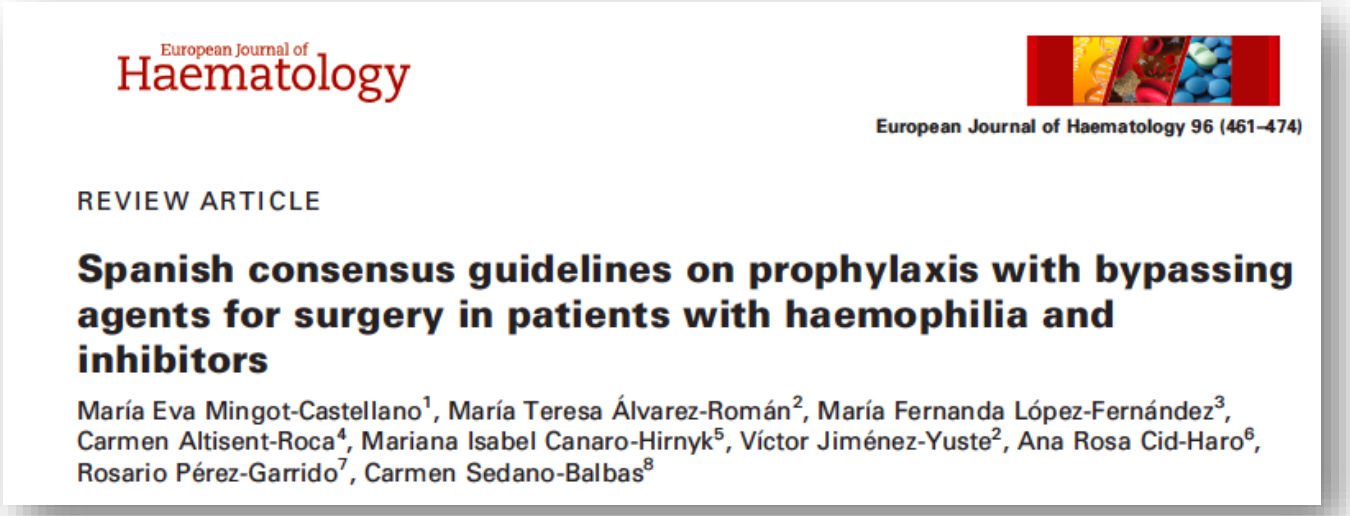


Kruse-Jarre R, et al. Haemophilia 2015;21:162-170.

Hemofilia adquirida y Cirugía

1, 2

Eficacia rFVIIa cirugía en HA: 77%
Eficacia FEIBA no series exclusivas en HA



European Journal of Haematology

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REVIEW ARTICLE

Spanish consensus guidelines on prophylaxis with bypassing agents for surgery in patients with haemophilia and inhibitors

María Eva Mingot-Castellano[1], María Teresa Álvarez-Román[2], María Fernanda López-Fernández[3], Carmen Altisent-Roca[4], Mariana Isabel Canaro-Hirnyk[5], Víctor Jiménez-Yuste[2], Ana Rosa Cid-Haro[6], Rosario Pérez-Garrido[7], Carmen Sedano-Balbas[8]

1. Ma A, et al. Haemophilia 2016;22:e18-e24. 2. Mingot-Castellano ME et al. Med Clin (Barc). 2017;148(7):314-322.

Hemofilia adquirida y profilaxis

	Acute phase-only *Group A* n = 11	Acute phase plus short-term prophylaxis *Group B* n = 7	P
Type of Bleeding			
Major (%)	6 (54.5)	3 (42.9)	0.4
Minor (%)	5 (45.5)	4 (57.1)	0.6
Cause of Bleeding			
Idiopathic (%)	6 (54.5)	6 (85.7)	
Post-traumatic	4 (36.4)	1 (14.3)	0.49
Post-partum	1 (9)	-	
aPCC loading dose (U kg-1 day)*			
Major bleeding	205.0 ± 7.1	162.2 ± 33.3	0.137
Minor bleeding	64.0 ± 40.4	85.0 ± 10.0	0.380
Treatment duration* (days)			
Major bleeding	4.2 ± 1.9	8.5 ± 0.7	0.004
Minor bleeding	2.0 ± 1.2	11.8 ± 11.2	0.178
*aPCC prophylaxis dose** (U kg-1 day)			
Major bleeding	-	77.3 ± 33.7	
Minor bleeding	-	28.5 ± 9.3	
Prophylaxis duration (days)*			
Major bleeding	-	12.7 ± 5.7	
Minor bleeding	-	12.25 ± 10.7	
*Total amount of aPCC** (U kg-1)	479.4 ± 335.1	1246.8 ± 952.1	0.05
Number of relapses	6	0	0.02

* expressed as median ± IQR.

50%

Más estudios…

Zanon E, et al. Thrombosis Research. 2015;136:1299–1302

Erradicar el inhibidor

Recommended first-line immunosuppression	Recommended dose	Comment
Corticosteroids alone	Prednisone 1 mg/kg PO daily (alternative dexamethasone 40 mg PO daily × 4–7 d)[a]	Unlikely to be effective in ≤3 wk in patients with FVIII <1 IU/dL or inhibitor >20 BU/mL at presentation Monitor for adverse events (elevated glucose, infection, psychiatric disorders)
Corticosteroid and cyclophosphamide	Corticosteroid same as above; cyclophosphamide 1–2 mg/kg PO daily (alternative ~5 mg/kg IV q 3–4 wk)[a]	May have faster response rated than steroids alone, but higher adverse event profile Associated with the highest CR rate Monitor for marrow suppression (WBC, platelets) and infection
Corticosteroids and rituximab	Corticosteroid same as above; rituximab 375 mg/m^2 IV weekly × 4 (alternative 100 mg weekly × 4)[a]	Rituximab is not recommended as initial monotherapy unless other IST is contraindicated
Comments		

Individualizar en base a[1,2]:

- Comorbilidades del paciente (introducir scores en la clínica).
- Enfermedad de base.
- FVIIIc <1%.
- Inhibidor >20UB.
- Presencia de Ac anti-IgA.

1. Huth-Kühne A, et al. Haematologica 2009; 94: 566-575. 2. Kruse-Jarre R, et al. Am J Hematol. 2017 Jul;92(7):695-705.

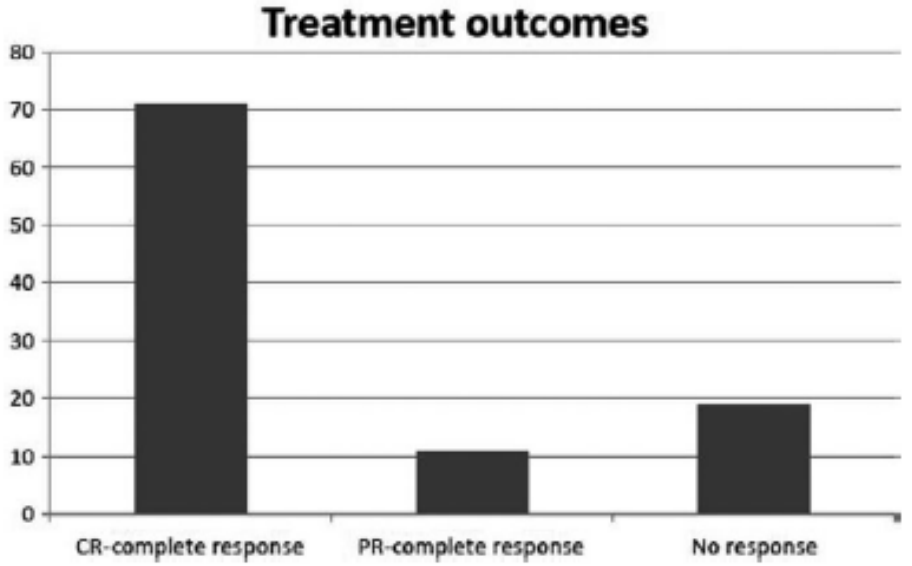
Erradicar el inhibidor

88%

Paciente con cancer:

Tratar de forma independiente a patología de base

- 105 pacientes, 90 tratados con inmunosupresión.
- 73% esteroides y ciclofosfamida, 20% rituximab.
- Mejores resultados: Erradicación y tratamiento (Qt o Cirugía) patología de base



Napolitano et al. Haemophilia. 2018 Jan;24(1):43-56

Erradicar el inhibidor

Steroids		Steroids Cyclophosphamide		Bibliography
RC/NR	RC%	RC/NR	RC%	
9/10	90%	14/16	88%	Bossi
3/4	75%	9/11	82%	Yee
8/9	89%	8/14	59%	Sallah
2/3	66%	10/12	83%	Collins
26/34	76%	35/45	78%	Collins
9/12	75%	15/19	79%	Lak
83/142	58%	68/88	77%	EACH2
	76%		**78%**	**TOTAL**

Tasa de recaida

4-20%

(7,5-12 meses)

EACH2 Registry
European Acquired Haemophilia Registry

Regimen	Age Years	FVIII at diagnosis (IU/dL)	Inhibitor titre at diagnosis (BU/mL)	CR after 1st line IS N (%)	Days from start of IS: Inhibitor -ve	Days from start of IS: FVIII >70 IU/dL	Days from start of IS: IS stopped	Relapse (%)	Stable CR after 1st line IS %	Alive and in CR at final FU %
Steroids alone n=142	75 (63–81)	3 (1–6)	13 (5–43)	83 (58)	34 (17–76)	32 (15–51)	108 (55–208)	19	48	60
	13–104	0–28	0.1–1020		5–321	3–551	11–1169			
Steroids and cytotoxics n=88	76 (63–80)	1 (1–4)	22 (8–67)	68 (77)	32 (12–77)	40 (18–81)	74 (52–151)	14	67	60
	16–101	0–34	0.4–2800		0–386	2–386	1–386			
All rituximab regimen n=51	74 (5–78)	2 (0–7)	16 (6–62)	31 (61)	65 (29–144)	64 (28–206)	43 (22–96)	4	59	67
	14–104	0–20	0.1–2176		10–436	10–569	17–257			
Rituximab plus another IS n=39	75 (57–78)	2 (0–7)	16 (9–62)	26 (67)	47 (28–96)	38 (28–141)	55 (26–96)	4	64	61
	14–104	0–20	0.1–2176		10–436	10–569	17–257			
Rituximab alone n=12	69 (65–77)	1 (0–8)	16 (3–71)	5 (42)	53, 145, 209, 334*	145, 209, 252, 334*	21, 21, 21, 21, 22*	0	42	70
	50–85	0–15	1–460							

Collins P et al. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). Blood 2012;120(1):47-55.
Collins P et al. Acquired Haemophilia A in the United Kingdom: a 2 year national surveillance study by the United Kingdom Haemophiia Centre Doctors Organization. Blood 2007;109(5):1870-77.

Erradicar el inhibidor

Cochrane Library

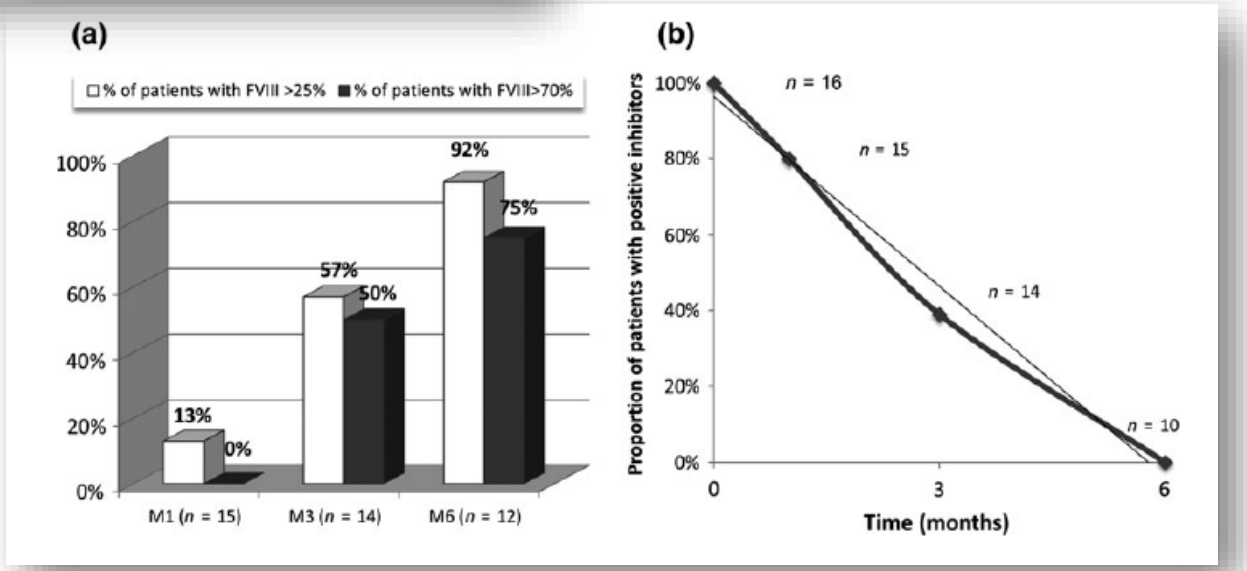
Cochrane Database of Systematic Reviews

Rituximab for eradicating inhibitors in people with acquired haemophilia A (Review)

Zeng Y, Zhou R, Duan X, Long D

Authors' conclusions

No randomised clinical trials of rituximab for acquired hemophilia A were found. Thus, based on the highest quality of evidence, we are not able to draw any conclusions or make any recommendations on rituximab for eradicating inhibitors in people with acquired haemophilia A. Given that undertaking randomised controlled trials in this field is a complex task, the authors suggest that, while planning such trials, clinicians treating the disease continue to base their choices on alternative, lower quality sources of evidence. The authors plan, for a future update of this review, to appraise and incorporate any randomised controlled trials, as well as other high-quality non-randomised studies.



Rossi B, et al. Haemophilia. 2016;22:e338-41.

Erradicar el inhibidor

Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study

Andreas Tiede,[1] Robert Klamroth,[2] Rüdiger E. Scharf,[3] Ralf U. Trappe,[4,5] Katharina Holstein,[6] Angela Huth-Kühne,[7] Saskia Gottstein,[2] Ulrich Geisen,[8] Joachim Schenk,[9] Ute Scholz,[10] Kristina Schilling,[11] Peter Neumeister,[12] Wolfgang Miesbach,[13] Daniela Manner,[14] Richard Greil,[15] Charis von Auer,[16] Manuela Krause,[17] Klaus Leimkühler,[18] Ulrich Kalus,[19] Jan-Malte Blumtritt,[1] Sonja Werwitzke,[1] Eva Budde,[20] Armin Koch,[20] and Paul Knöbl[21]

Blood. 2015;125(7):1091-1097

- **34 fallecimientos:**
- 16 infecciones.
- 6 patología cardiovascular.
- 3 patología de base.
- 3 por sangrados
- **16/37, 46% de los pacientes infectados fallecen.**
- **Eventos vasculares fatales 10% rFVIIa y tranexámico.**
- **Eventos vasculares fatales 5% rFVIIa monoterapia.**

Experiencia: Tratamiento erradicador

	1 Línea tratamiento inmunosupresor	2 Línea tratamiento inmunosupresor
Steroids plus Cyclophosphamide	7	0
Steroids+ Rituximab	2	1
Steroids	1	1

Response Rate:

- **80%.**
- 100% steroids plus cyclophosphamide.
- 50% steroids plus rituximab
- 0% steroids monotherapy.

Median time to response:

- Steroids plus cyclophosphamide, **56.5 days (40-108, IQR).**
- Rituximab plus other immunosuppressive drug, **56.5 days (50-56.5 days, IQR).**

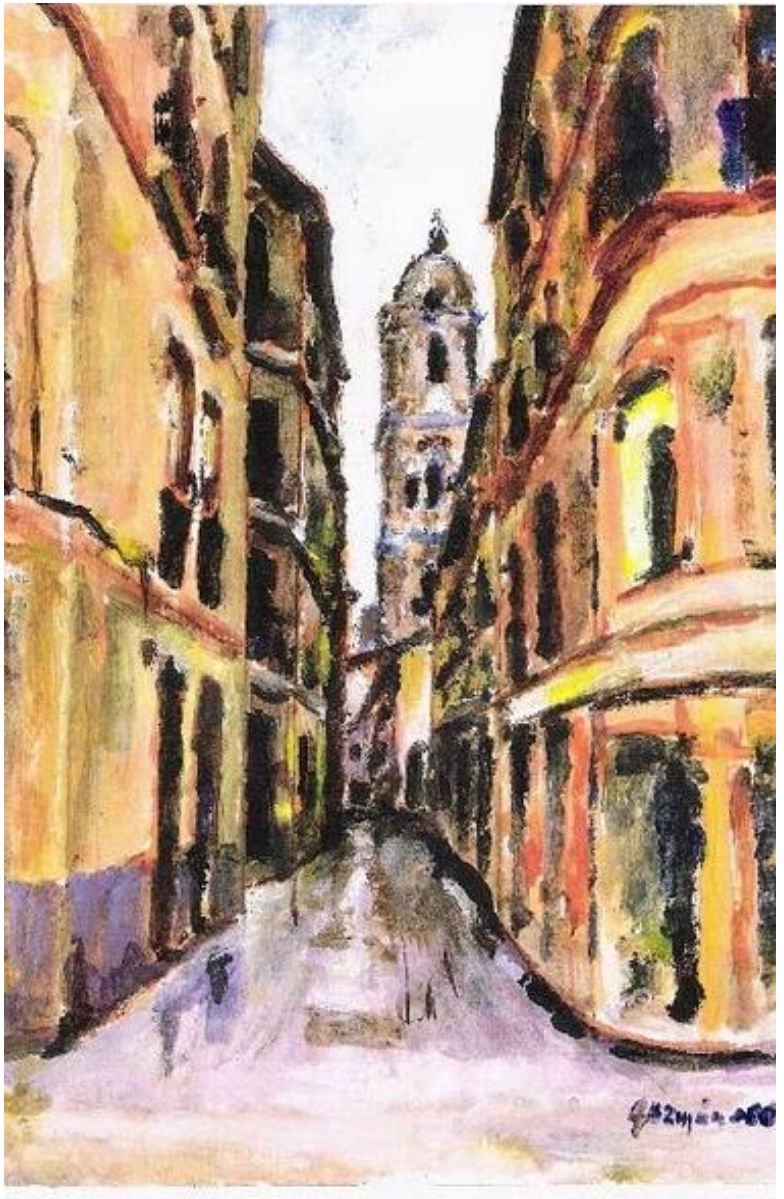
Mingot-Castellano ME et al. Blood 2017;130:3688. ASH 2017

Conclusiones

- **SENTIDO COMUN, lo primero.**

- **Erradicación del inhibidor:**
  - *Primera medida hemostática.*
  - *Individualizar según comorbilidades y pronóstico del paciente.*

- **Tratamiento hemostático:**
  - *La eficacia hemostática de ambos agentes baipás es similar.*
  - *La elección del agente hemostático:*
    - *Respuesta previa* a alguno de los dos agentes.
    - *Disponibilidad* en el hospital
    - *Comodidad* de la dosificación



Gracias