HEMOPHILIE ACQUISE DU POST-PARTUM

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EQUIPE D'HÉMOSTASE BIO-CLINIQUE CRC-MHC CHU MONTPELLIER

ANTICORPS ANTI-FVIII DANS L'HÉMOPHILIE HÉRÉDITAIRE ET ANTICORPS ANTI-FVIII ACQUIS

Table 1. Inhibitory antibodies to FVIII in severe HA and AHA: clinical, laboratory, and treatment assessment

FVIII deficiency	X-linked	Acquired
Antibody	Alloantibodies	Autoantibodies
Sex	Mostly male	Male and female
Family history	Usually present	Absent
Risk factors	Genetic and environmental	Malignancy, autoimmune disease, postpartum period, drug-induced, ~50% idiopathic
Age onset	First 2 decades (20 exposure days)	Biphasic Female*: 20-30 y Male: >60 y
Bleeding phenotype	Recurrent hemarthrosis and hematomas not responsive to FVIII replacement therapy	Sudden onset of bleeding, >80% major hemorrhages mucocutaneous, extensive bruises, hematomas, and rarely hemarthrosis
Immunoglobulin type	IgG1 and 4	IgG1 and 4, IgA
Inhibitor type: inhibition of FVIII activity	Type I, linear-kinetics inhibition correlated with inhibitor titers	Type II, rapid initial inactivation phase followed by a slower equilibrium phase with some residual FVIII activity
Bypass agents for hemostasis†	Formal indication	Risk and benefit ratio: risk of bleeding and underlying cardiovascular risk
FVIII concentrate protein infusion (ITI)	Commonly indicated	No standard but used occasionally
Immunosuppression	Occasionally	Commonly indicated
Mortality risk in patients with current inhibitors	Threefold higher than noninhibitor due to bleeding (US data)	~15-20% due to severe infection, bleeding, and cardiovascular complications
Spontaneous remission	Rarely, low titers (transient inhibitors)	20-30% usually in postpartum inhibitors

*Postpartum women.

†Recombinant activated FVII, activated prothrombin complex concentrate for allo- and autoantibodies. Emicizumab is approved for allo- and autoantibodies, but the overall experience for autoantibodies is limited.

ETUDES ET REGISTRES RÉCENTS

GUIDELINE

International recommendations on the diagnosis and treatment of acquired hemophilia A

Ferrata Storti

Study name	Study type	Design	Collection period	Total n. of patients	Treatment/outcome data available information: Hemostatic therapy (n. of pts)*	Bleeding resolved (n. of pts or episodes)	IST (n. of pts)**	Remission (n. of pts)	Survival information (pts)	Reference	
UK surveillance study	Registry	Prospective, consecutive	2001–2003	172	97	-	151	105	113	(2)	n=3 (2%) n=42 (8,4%) Collins, Blood 2007
EACH2	Registry	Retrospective (3 years); prospective (3 years)	2003–2009	501	307	288 patients (1st episodes)	331	331	331	(3, 5, 7, 8)	Knoebl, JTH 2012 Tengborn, BJOG 2012
SACHA	Re									(9)	n= 6 (7,3%) Borg, Haemophilia 2013
GTH-AH 01/2010	Re									(10-12, 37)	n=5 (4,9%) Tiede, Blood 2015
HTRS	Re									(14)	n= 5 (3,4%) MA, BCF 2016
OBI-1	Clin									(15)	n= 0 Kruse-Jarres, Haemophilia 2015

Acquired factor VIII inhibitors in pregnancy: data from the Italian Haemophilia Register relevant to clinical practice

Italian Association of Haemophilia Centres (AICE): Register of acquired factor VIII inhibitors (RIIA)*

*Number of patients re /or recombinant porcine factor VIII (rpFV). Differences in the numbers reported vs. the total number of patients may be due to no treatment or lack of reporting. Number of patients reported to have received immunosuppressive therapy. N: number; IST: immunosuppressive therapy; UK: United Kingdom; EACH2: European ACquired Haemophilia; SACHA: *Surveillance des Auto-antiCorps au cours de l'Hémophilie Acquise*; GTH: *Gesellschaft für Thrombose- und Hämostaseforschung*; HTRS: Hemostasis and Thrombosis Research Society; OBI-1: susoctocog alfa.

ETUDES ET REGISTRES RÉCENTS

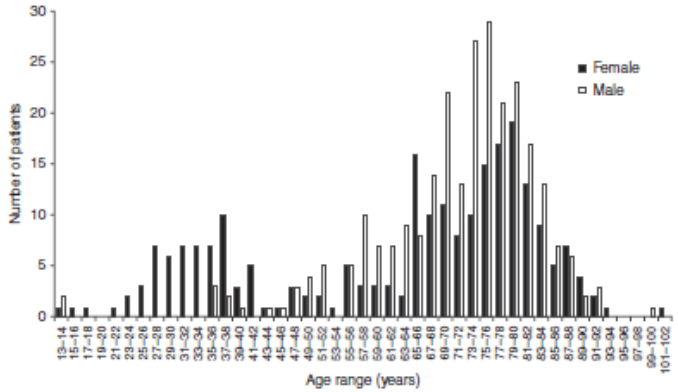
Acquired factor VIII inhibitors in pregnancy: data from the Italian Haemophilia Register relevant to clinical practice

Italian Association of Haemophilia Centres (AICE): Register of acquired factor VIII inhibitors (RIIA)*

BJOG, 2003

EPIDÉMIOLOGIE – HÉMOPHILIE ACQUISE

- Déficit acquis et isolé en FVIII
- Du à un auto-anticorps anti-FVIII (anti-FIX rare)
- 1ère description 1941, 176 cas rapportés (Dewart, 2021)
- 1 à 4 cas par million d'habitants et par an
  - augmentant avec l'âge, pic sujet âgé
  - pic 30-40 ans MAI, grossesse/pp
- 1/350 000 grossesses (registre UK)
- 4,6 et 12,5 % des séries ou registres récents:
  - 6 /82 cas - 7,3% - dans le registre prospectif français SACHA
  - 42/501 - 8,4%- dans le registre rétro/prospectif du registre européen EACH2



PRINCIPALES CARACTÉRISTIQUES

- Post-partum le plus souvent
  - délai moyen 89 jours (1-150), toujours avant 6 mois (1 an)
- Ante-partum 2-15%
- Première grossesse 75%
- *Titre inhibiteur faible (20 UB)*
- *Pronostic favorable*

Circonstances de diagnostic

- Rarement fortuit

- Allongement du TCA
  - Registre italien: 100%

- Manifestations hémorragiques +/- importantes
  - Ecchymoses sous-cutanées spontanées (50 % des cas),
  - Hémorragies des muqueuses (40 % des cas) ou musculaires (30 % des cas)
  - Sévères dans 2/3 des cas
  - Souvent spontanées ½ des cas
  - Parfois provoquées au cours de l'accouchement ou pp immédiat.
    - EACH2 n=42, 8
    - Registre italien n=20, 4 hystérectomies d'hémostase

CASE-REPORTS

Case report (2012)

- 19 ans
- J1 pp hématome paroi vaginale avec évacuation chirurgicale
- Complications hémorragiques+++
- TCA 2,9 (87/30), FVIII 7%, anti-FVIII 64 UB
- Novoseven, FEIBA
- Prednisolone + cyclophosphamide
- J8 choc hémorragique, décès

Case report (2020)

- 26 ans
- Césarienne en urgence sur non progression à terme
- J2 douleurs abdo, hémoperitoine
- TCA 90/32 sec, FVIII 1%, anti-FVIII +
- PFC, GR
- Prednisolone
- TCA normal à J8, retour domicile

DIAGNOSTIC BIOLOGIQUE – ALLONGEMENT ISOLÉ DU TCA

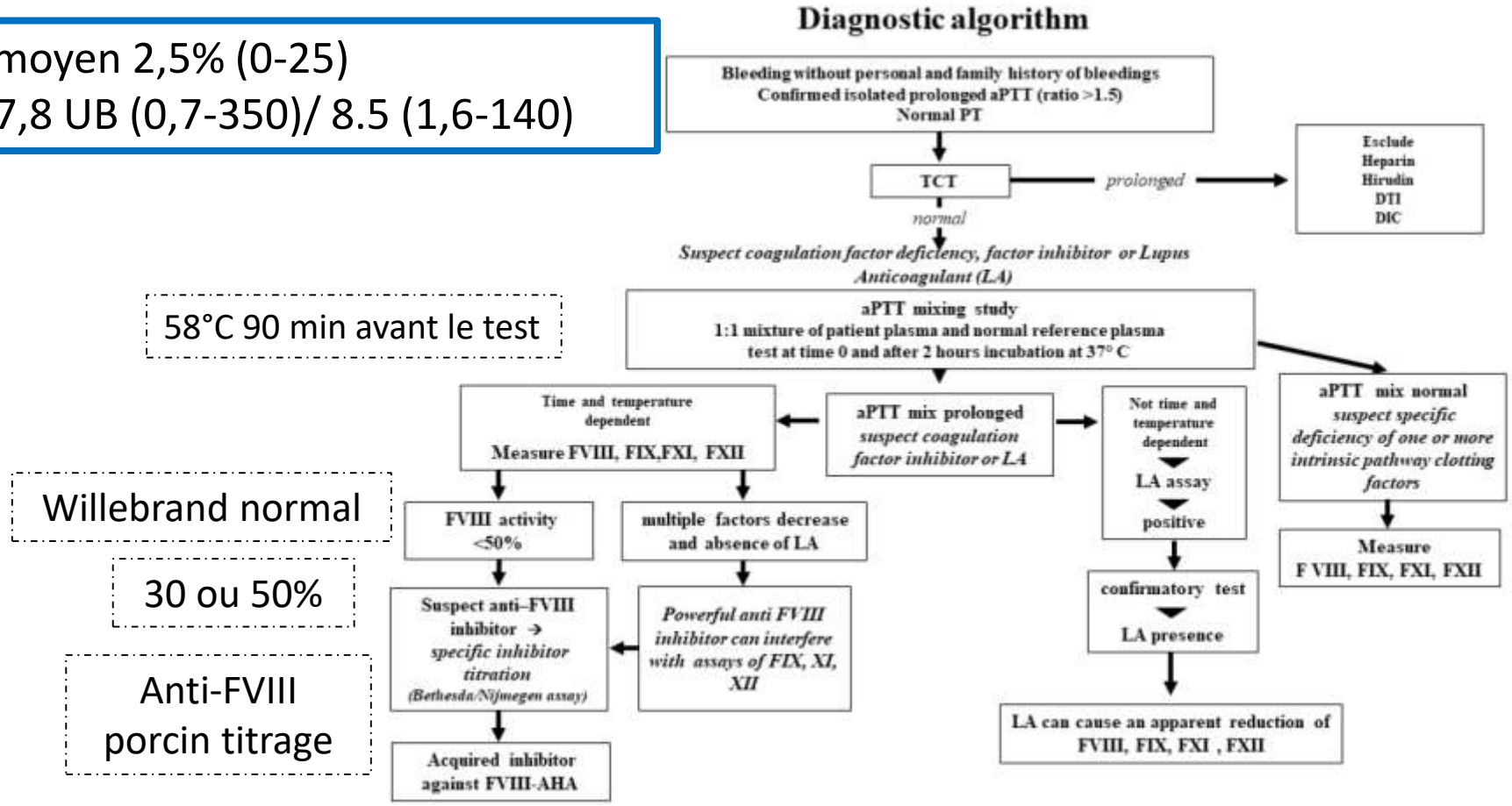
Taux moyen 2,5% (0-25)
Titre 7,8 UB (0,7-350)/ 8.5 (1,6-140)

58°C 90 min avant le test

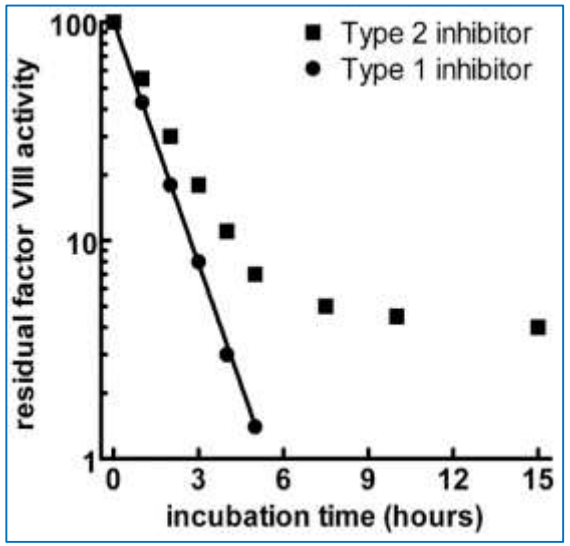
Willebrand normal

30 ou 50%

Anti-FVIII porcin titrage



Legend. aPTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; DTI = direct thrombin inhibitor; FVIII = factor VIII; FIX = factor IX; FXI = factor XI; FXII = factor XII; PT = prothrombin time; ratio = test plasma time/normal reference plasma time; TCT=thrombin clotting time.



American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Kinetics of type 1 and type 2 inhibitors against factor VIII.
Type 1 inhibitors develop in patients with congenital hemophilia A and are generally alloantibodies that show complete neutralization of FVIII activity. Acquired inhibitors to FVIII show type 2 kinetics, with a rapid neutralization phase, followed by an equilibrium in which residual FVIII activity can be detected *in vitro*.

PRISE EN CHARGE THÉRAPEUTIQUE

- Traiter le syndrome hémorragique si sévère ou le prévenir dans les situations à risque (VVC, ponction veineuse, évacuation hématome, chir…)
  - Pronostic : délai entre le diagnostic et le traitement

- Éradiquer l'inhibiteur
  - Contexte grossesse ou pp
  - Données biologiques: taux de FVIII résiduel et titre de l'inhibiteur

- Recommandations internationales hémophilie acquise (Tiede et al, Haematologica, 2020)

  = consensus à partir des registres et experts

  Particularités pour hémophilie acquise du pp?

TRAITEMENT ANTI-HÉMORRAGIQUE

International recommendations on the diagnosis and treatment of acquired hemophilia A

Hemostatic treatment

• We recommend that hemostatic treatment be initiated in patients with AHA and clinically relevant bleeding irrespective of inhibitor titer and residual FVIII activity.	1B
• We recommend the use of rFVIIa, APCC or rpFVIII instead of human FVIII concentrates or desmopressin for the treatment of clinically relevant bleeding in patients with AHA.	1B
• We recommend that alternative treatment strategies from among the first-line agents be used if appropriate initial treatment fails.	1C
• For initial treatment with rFVIIa, we recommend bolus injection of 90 μg/kg every 2–3 h until hemostasis is achieved.	1B
• For initial treatment with APCC, we recommend bolus injections of between 50–100 U/kg every 8–12 h, up to a maximum of 200 U/kg/day.	1B
• For initial treatment with rpFVIII, we recommend the approved dose of 200 U/kg, followed by further doses to maintain trough levels >50%.	1B
• We recommend close monitoring of FVIII activity during therapy with rpFVIII.	1B
• We suggest the use of recombinant or plasma-derived human FVIII concentrates only if bypassing agents or rpFVIII are unavailable or ineffective and the inhibitor titer is low. We recommend against the use of desmopressin.	1B
• We recommend the prophylactic use of bypassing agents or rpFVIII to cover minor or major invasive procedures.	1B

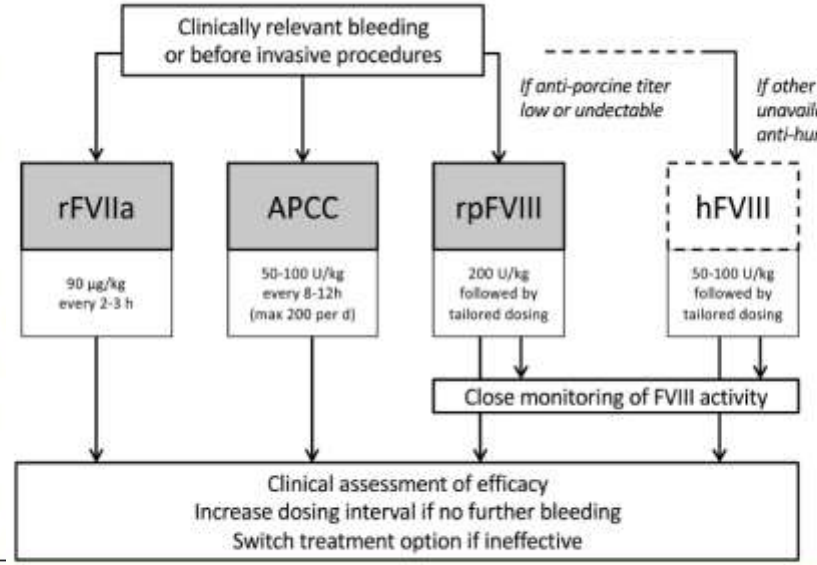


Figure 2. Choice and monitoring of hemostatic therapy in acquired hemophilia A. rFVIIa, recombinant activated factor VII (eptacog alfa); APCC, activate bin complex concentrate; rpFVIII: recombinant porcine factor VIII (susoctocog alfa), hFVIII, human (plasma-derived or recombinant) factor VIII; h: hour; d

EACH2 grossesse et pp (n=42)
Ttt chez 56% (symptomatiques), délai médian 3j (0-57), 41% J0
1ère ligne efficace à 87%, résolution 94%: rFVIIa (92%) > CCPa (100%)
(FVIII 1, desmopressine 1), AT, durée rFVIIa 1-16j , CCPa 2-90j
Transfusion 24%

Registre italien (n=20)
Ttt chez 55%
FVIII h ou p, rFVIIa, CPPa
Transfusion 50%

EACH2
Efficacité bypassants 93% vs FVIII et desmopressine 68%

GTH
3 décès avec le rFVIIa dont 2 + AT Attention!

TRAITEMENT ANTI-HÉMORRAGIQUE ET THROMBOSE

- Pas de thrombose EACH2 grossesse pp
  - rFVIIa 0-5% dans revue systématique (Tiede, 2018)
  - CCPa 4,8% dans EACH2
    - CIVD si posologie > 200 UI/kg

TRAITEMENT IMMUNOSUPPRESSEUR

Inhibitor eradication

• We recommend IST in all patients with AHA. However, particular caution should be exercised in frail patients.	1B
• We suggest using prognostic markers (FVIII activity, inhibitor titer, if available) to individualize IST.	2B
• We suggest that patients with FVIII ≥1 IU/dL and inhibitor titer ≤20 BU at baseline receive first-line treatment with corticosteroids alone for 3–4 weeks.	2B
• We suggest combining corticosteroids with rituximab or a cytotoxic agent for first-line therapy in patients with FVIII <1 IU/dL or inhibitor titer >20 BU.	2B
• We suggest extending observation in patients who do not achieve remission with first-line IST but have continued improvement of FVIII activity and inhibitor titer.	2B
• We suggest second-line therapy with rituximab or a cytotoxic agent, whichever was not used during first-line therapy.	1B
• For corticosteroid therapy, we suggest prednisolone or prednisone at a dose of 1 mg/kg/day PO for a maximum of 4–6 weeks (followed by a tapered withdrawal).	2B
• We suggest rituximab at a dose of 375 mg/m² weekly for a maximum of 4 cycles.	2B
• As cytotoxic therapy, we suggest cyclophosphamide at a dose of 1.5–2 mg/kg/day PO for a maximum of 6 weeks, or MMF at a dose of 1 g/day for 1 week, followed by 2 g/day.	2B
• We do not recommend the use of high-dose human FVIII for immune tolerance induction in AHA.	2C
• We do not recommend the use of high-dose intravenous immunoglobulins for inhibitor eradication in patients with AHA.	1B
• We recommend follow-up after complete remission, using FVIII:C monitoring monthly during the first 6 months, every 2–3 months up to 12 months, and every 6 months during the second year and beyond, if possible.	1B
• In women with pregnancy-associated AHA, we suggest the same approach for IST as in other patients, but with a more careful consideration regarding the use of cytotoxic agents.	2C
• We recommend thromboprophylaxis according to ASH guidelines if FVIII:C has returned to normal levels. If indicated, therapy with anti-platelet drugs or oral anticoagulants should be initiated after normal FVIII:C levels have been achieved.	1C

Rémission spontanée ~ 30% mais 2-3 mois…..

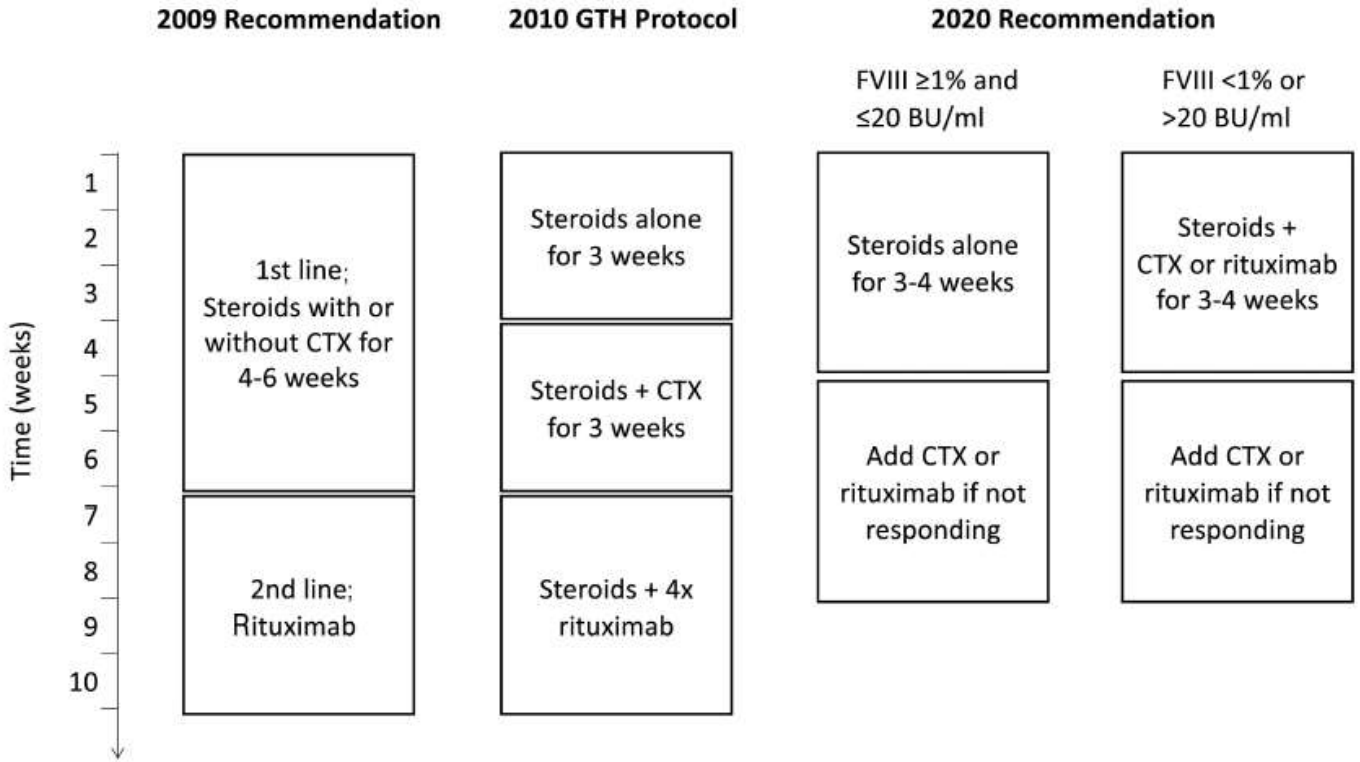
International recommendations on the diagnosis and treatment of acquired hemophilia A

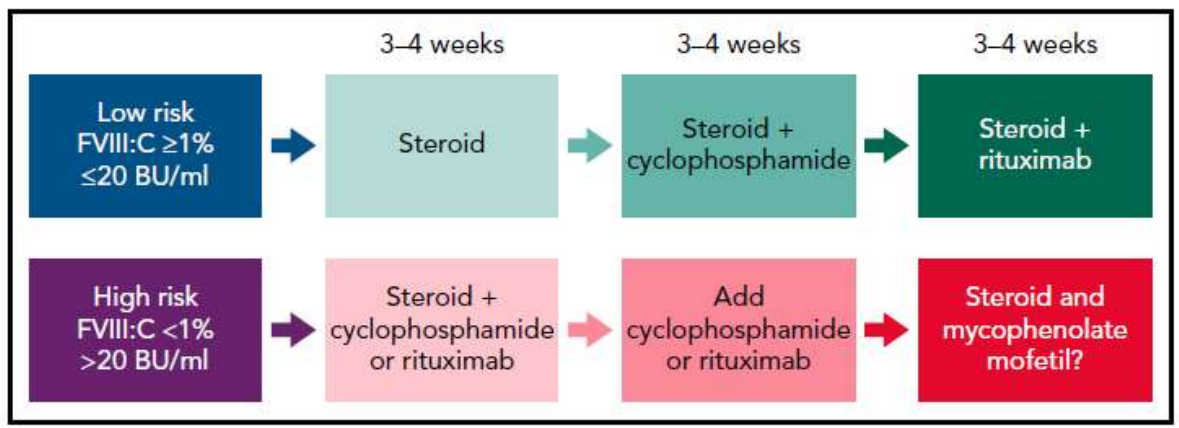
2020 Recommendation

FVIII ≥1% and ≤20 BU/ml	FVIII <1% or >20 BU/ml
Steroids alone for 3-4 weeks	Steroids + CTX or rituximab for 3-4 weeks
Add CTX or rituximab if not responding	Add CTX or rituximab if not responding

Each 2 grossesse pp
1ère ligne corticoides 70%, Rémission 74%
Ttt stoppé 96 j (moy), inhibiteur neg 47 j, FVIII>70% 26j

Registre italien
n=18/20 Corticoides seuls ou + cyclophosphamide azathioprine/IgIV
Rémission complète 78%
2,5 mois (0.5-36)
Pas de différence/ AHA non liée à la grossesse mais CI cyclophosphamide


2009 Recommendation
2010 GTH Protocol
2020 Recommendation
FVIII ≥1% and ≤20 BU/ml
FVIII <1% or >20 BU/ml
Time (weeks)
1
2
3
4
5
6
7
8
9
10
1st line; Steroids with or without CTX for 4-6 weeks
2nd line; Rituximab
Steroids alone for 3 weeks
Steroids + CTX for 3 weeks
Steroids + 4x rituximab
Steroids alone for 3-4 weeks
Add CTX or rituximab if not responding
Steroids + CTX or rituximab for 3-4 weeks
Add CTX or rituximab if not responding


3–4 weeks
3–4 weeks
3–4 weeks
Low risk FVIII:C ≥1% ≤20 BU/ml
Steroid
Steroid + cyclophosphamide
Steroid + rituximab
High risk FVIII:C <1% >20 BU/ml
Steroid + cyclophosphamide or rituximab
Add cyclophosphamide or rituximab
Steroid and mycophenolate mofetil?

HA CHEZ LE NOUVEAU NÉ?

- revue de la littérature n=274 femmes, 45 nnés

Received: 10 June 2020 | Revised: 5 December 2020 | Accepted: 9 December 2020
DOI: 10.1111/hae.14233
REVIEW ARTICLE
Haemophilia WILEY

Acquired haemophilia A in the postpartum and risk of relapse in subsequent pregnancies: A systematic literature review

Natacha Dewarrat[1] | Mathilde Gavillet[1] | Anne Angelillo-Scherrer[2] | Olaia Naveiras[1] | Francesco Grandoni[1] | Dimitrios A. Tsakiris[3] | Lorenzo Alberio[1] | Sabine Blum[1]

Transplacental hemophilia A and prophylactic treatment with intravenous immunoglobulin and recombinant factor VIIa in the newborn period: a case report

Ilkin E. Gunel Karaburun[a], Gozdem Kayki[b], Sevkiye S. Aytac[c], Hasan T. Celik[b], Fatma Gumruk[c] and Sule Yigit[b]

Table 1 Cases of newborn acquired hemophilia a in the literature are shown in the table

No	Refs.	M/F	Term/ Preterm	Age (days)	Pregnancy	Treatment during pregnancy	Symptoms	Peak inhibitor titer (BU)	Treatment	Outcome (time to inhibitor disappearance)
1	Frick [11]	1M	Term	0	Second	None	None	NA	None	Resolution (3 months)
2	Broxson and Hathaway [12]	M	Term	0	Second	Unknown	None	2.0	None	Resolution (1 week)
3		M[a]	Term	0	Second	Unknown	None	2.0	None	Resolution (1 week)
4	Vicente *et al.* [13]	1M	Term	0	Second	Unknown	None	150	None	Resolution (3 months)
5	Ries *et al.* [8]	1M	Term	5	First	None	Intracranial hemorrhage	5.2 (may be masked by hFVIII replacement therapy)	IVIG, hFVIII	Resolution (5 weeks)
6	Lulla *et al.* [6]	1F	Term	12	First	None	Postsurgical epistaxis and hematemesis	34	hFVIII rFVIIa	Resolution (3 weeks)
7	Kotani *et al.* [14]	1F	Term	0	Second	None	Subcutaneous hemorrhage on the hand	199	None	Resolution (4 months)
8	Current patient	1M	Term	0	Second	hFVIII rFVIIa	Blood in the stool	320	IVIG, rFVIIa	Resolution (5 weeks)

There have been eight cases reported in the literature before. The characteristics of all cases are stated and it is seen that the highest inhibitory titer is in our patient. hFVIII, human coagulation factor VIII; IVIG, intravenous immunoglobulins; rFVIIa, recombinant factor VIIa. [a]Twin.

+ 2 décès néonataux dont 1 imputable à HA

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TOUTE HÉMOPHILIE ACQUISE ANTE-PARTUM NÉCESSITE:
SURVEILLANCE FŒTALE ++++
MANOEUVRES CI, MESURE DU PH CI
DOSAGE DU FVIII
DURÉE AC? 3 MOIS
TTT PRÉVENTIF?

EVOLUTION

- Rémission spontanée
  - 31 à 36%
  - Mais plusieurs mois…….
- Mortalité
  - 0-6% vs 3-9% pour l'ensemble des hémophilies (22-31% études anciennes)
- Récidive
  - lors de toute AH 5 à 12% durant la 1ère année
  - lors de la grossesse suivante:
    - EACH2: 2/42
    - Dewarrat N, 2021++++: 24 nouvelles grossesses chez 179 cas d'HA grossesse/pp (13,6%) 6 récidives soit 22%

EN CONCLUSION

- Rarissime …..
- Y penser si allongement du TCA, histoire hémorragique récente
- Traitement anti-hémorragique non systématique
- Prévention du saignement++++++++++++
- Traitement immunosuppresseur
  Corticothérapie
- Récidive très rare


teşekkür ederim
mulțumesc
ارگش
MERCI
grazas
thank you
dankeschön
dankie
ذوذمم
Благодарю вас
谢谢
gràcies
gracias
kiitos
Хвала
GRAZIE
OBRIGADO
gratias ago
dankon
ありがとう
tack