

Emofilia A acquisita: il trattamento della malattia e delle complicanze emorragiche.

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Novita' in Coagulazione

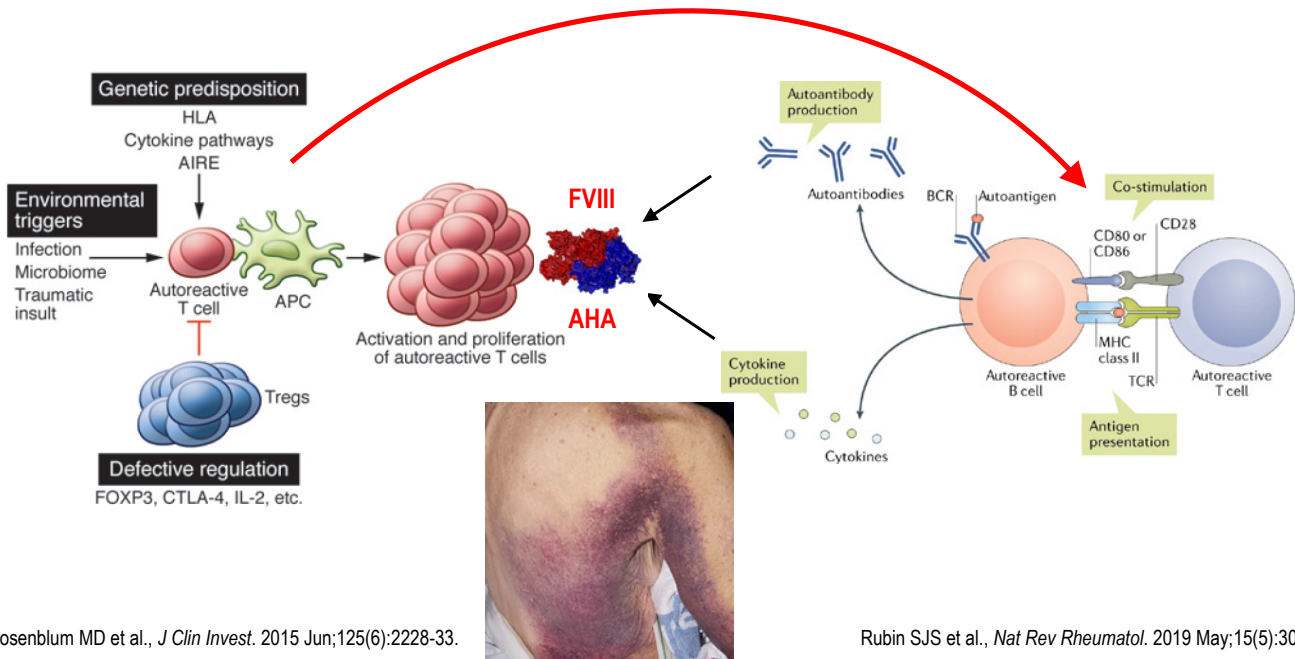
Torino, 12-13 Novembre 2021



AO S. Croce e Carle
Cuneo



Mechanisms of autoimmunity



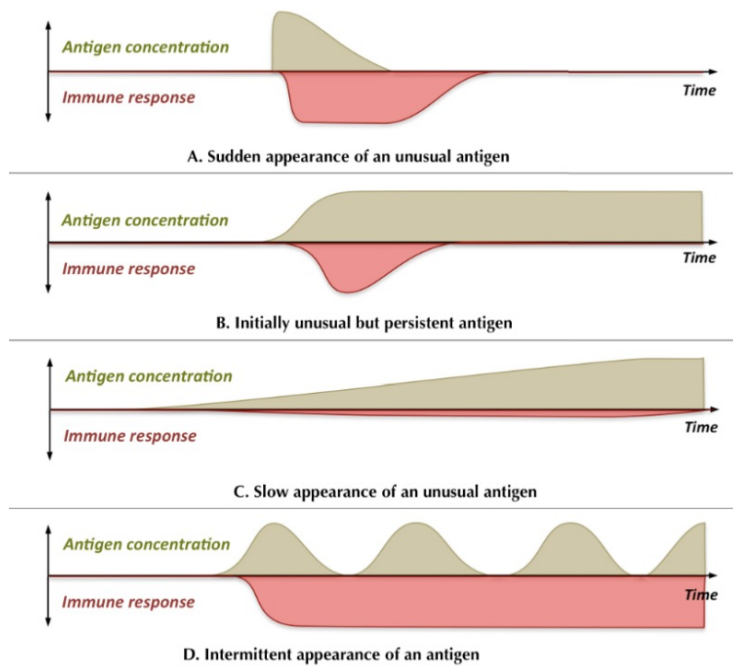
Rosenblum MD et al., *J Clin Invest.* 2015 Jun;125(6):2228-33.

Rubin SJS et al., *Nat Rev Rheumatol.* 2019 May;15(5):303-315.

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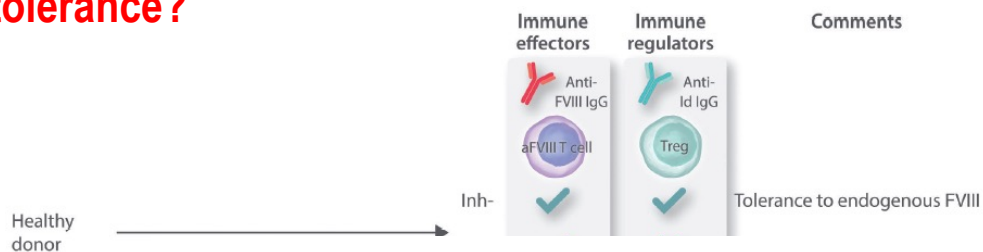
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The discontinuity theory of immunity



Pradeu T et al., *Nat Rev Immunol.* 2013 Oct;13(10):764-9.

Pathogenic anti-FVIII immune response: exacerbated response or failed tolerance?

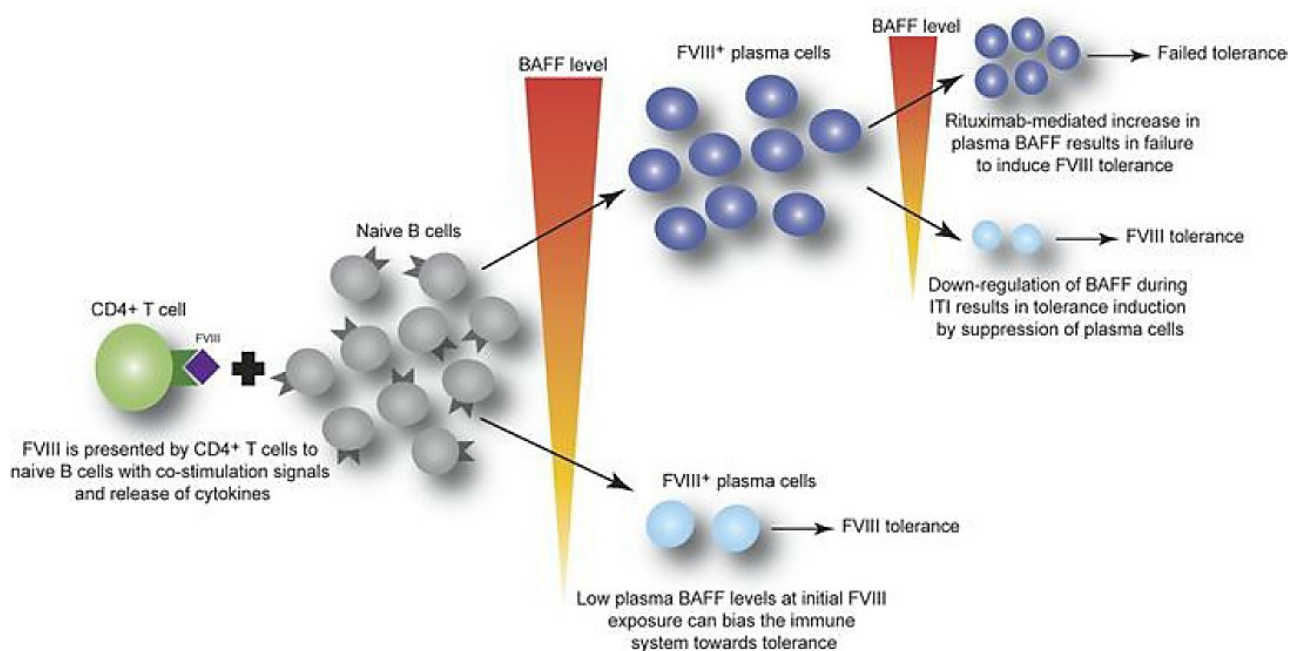


Varthaman A et al., *Haematologica.* 2019 Feb;104(2):236-244.

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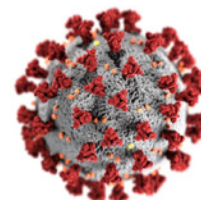
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BAFF modulates anti-FVIII immune responses in hemophilia A



Doshi BS et al., *J Clin Invest.* 2021 Apr 15;131(8):e142906

Case report: AHA after SARS-CoV-2 infection



November 2020: asymptomatic /mild COVID-19;

March 2021:

- large and deep bruises; fatigue;
- prolonged aPTT (1st NV; 2nd 78 sec; prolonged mixing test);
- hospital admission; (March 20, 2021)

FVIII %		Anti FVIII umano UB/ml	Anti FVIII porcino UB/ml
Synthasil silice	Synthafax ac.ellagico		
0,2	/	29	/



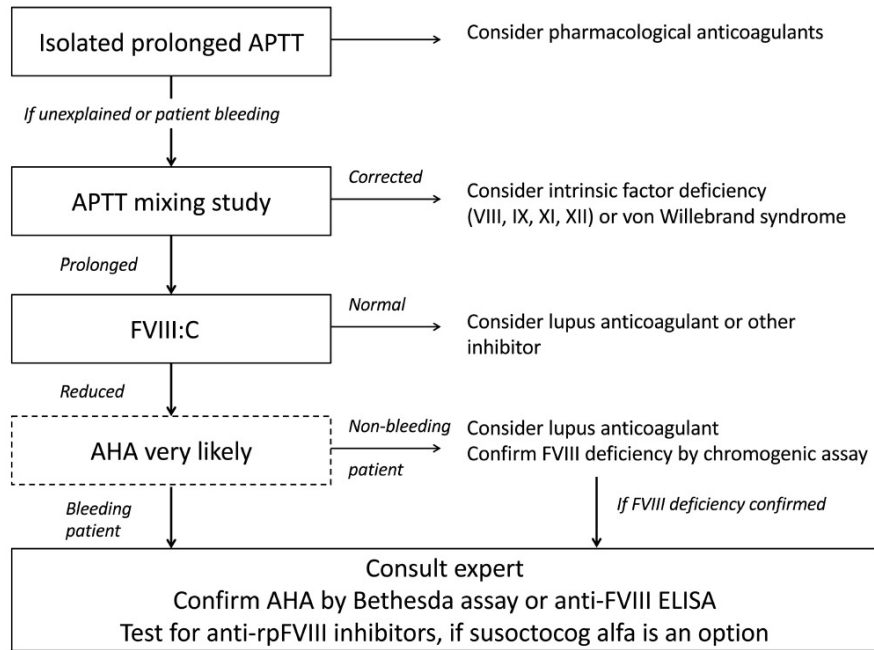
diagnosis of AHA

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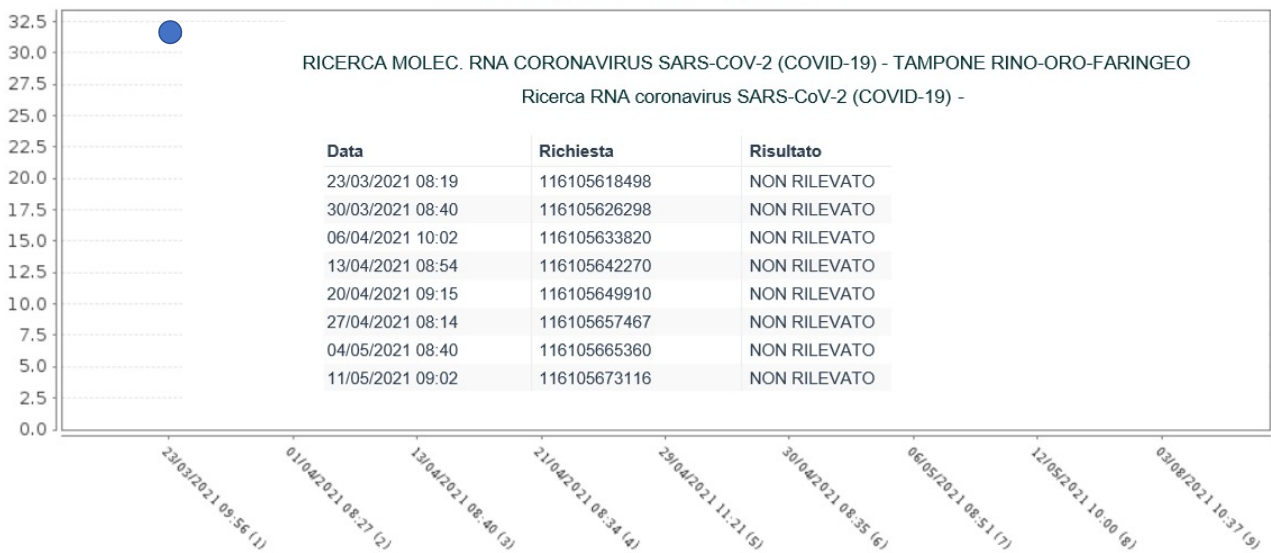
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Diagnostic pathway for AHA



Tiede A et al., *Haematologica*. 2020 Jul;105(7):1791-1801.

SARS-CoV-2 IgG Neutralizzante - (S) - Risultato



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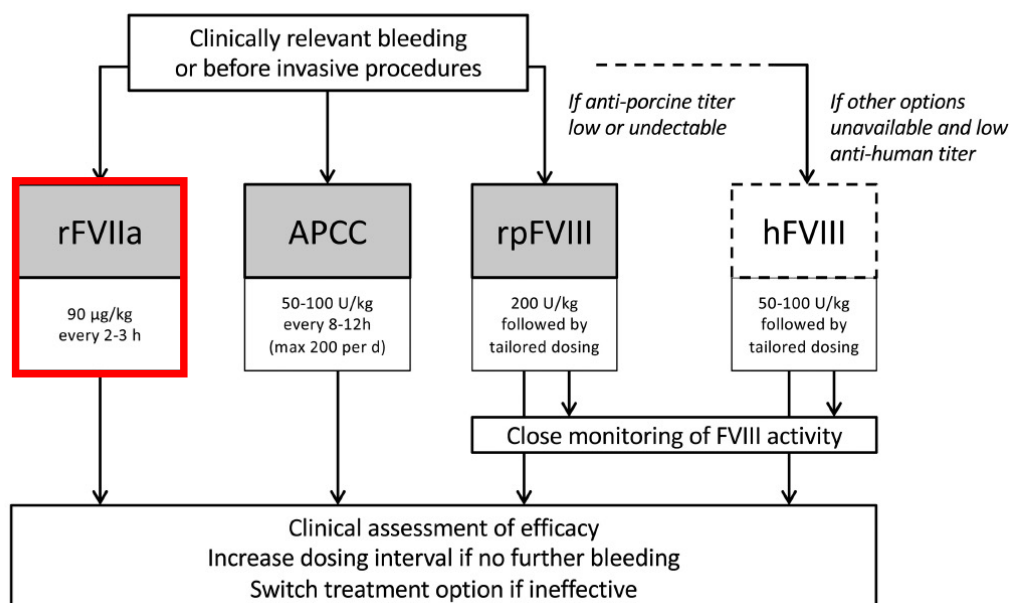
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Table 1: SARS-CoV-2 shares some characteristic features with other viruses that trigger autoimmunity.

Features of other viruses	Evidence for SARS-CoV-2
Precedes autoimmunity	Case reports of patients developing classifiable autoimmune diseases following SARS-CoV-2 infection (56–64)
Induces type I interferons	SARS-CoV-2 induces robust type I interferon responses in a subset of patients (23–26)
Breaks tolerance	SARS-CoV-2 induces autoantibody production in patients with severe COVID-19 (42, 77)
Superantigen activity	SARS-CoV-2 spike protein contains a superantigen motif and patients with severe COVID-19 exhibit TCR skewing consistent with superantigen activation (109)
Inhibits apoptosis of infected cells	No evidence to date
Interferes with its own destruction	No evidence to date

Knight JS, et al., *J Clin Invest.* 2021 Oct 28:e154886.

Choice and monitoring of hemostatic therapy in AHA



Tiede A et al., *Haematologica.* 2020 Jul;105(7):1791-1801.

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Hemostatic Tx only

Immunosuppressive Tx only

Hemostatic & Immunosuppressive Tx

Immunosuppressive Tx

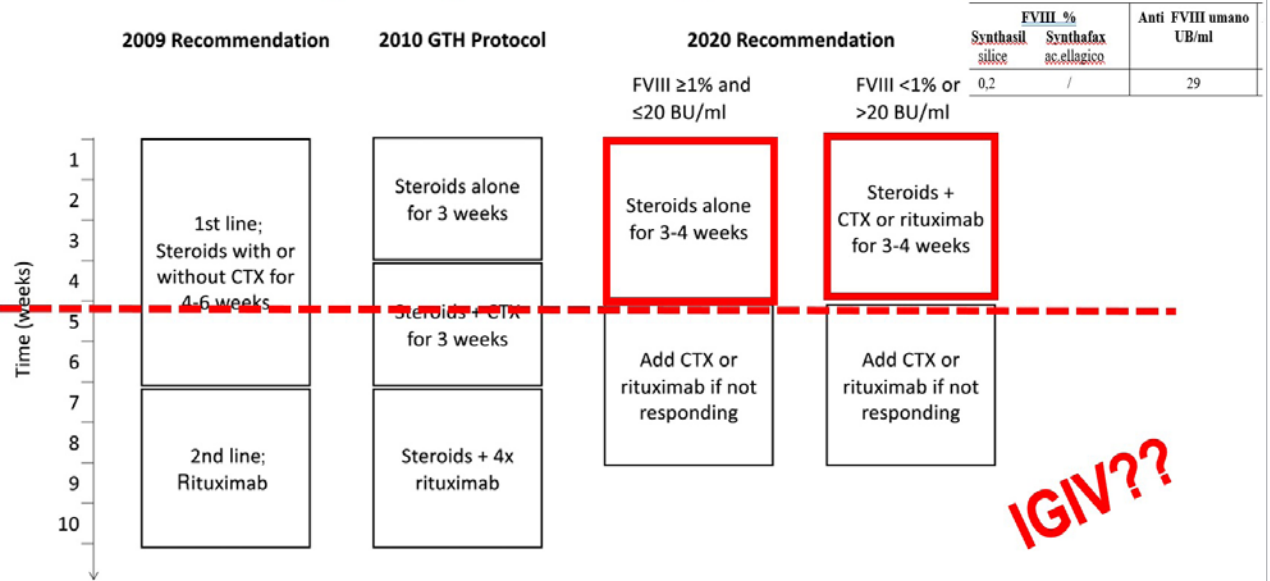
- **Steroids only**
- **CTX only**
- **Rituximab only**
- **Combination of steroids and rituximab or CTX**
- **Combination of rituximab and CTX**
- **Triplet (steroids/rituximab/CTX)**

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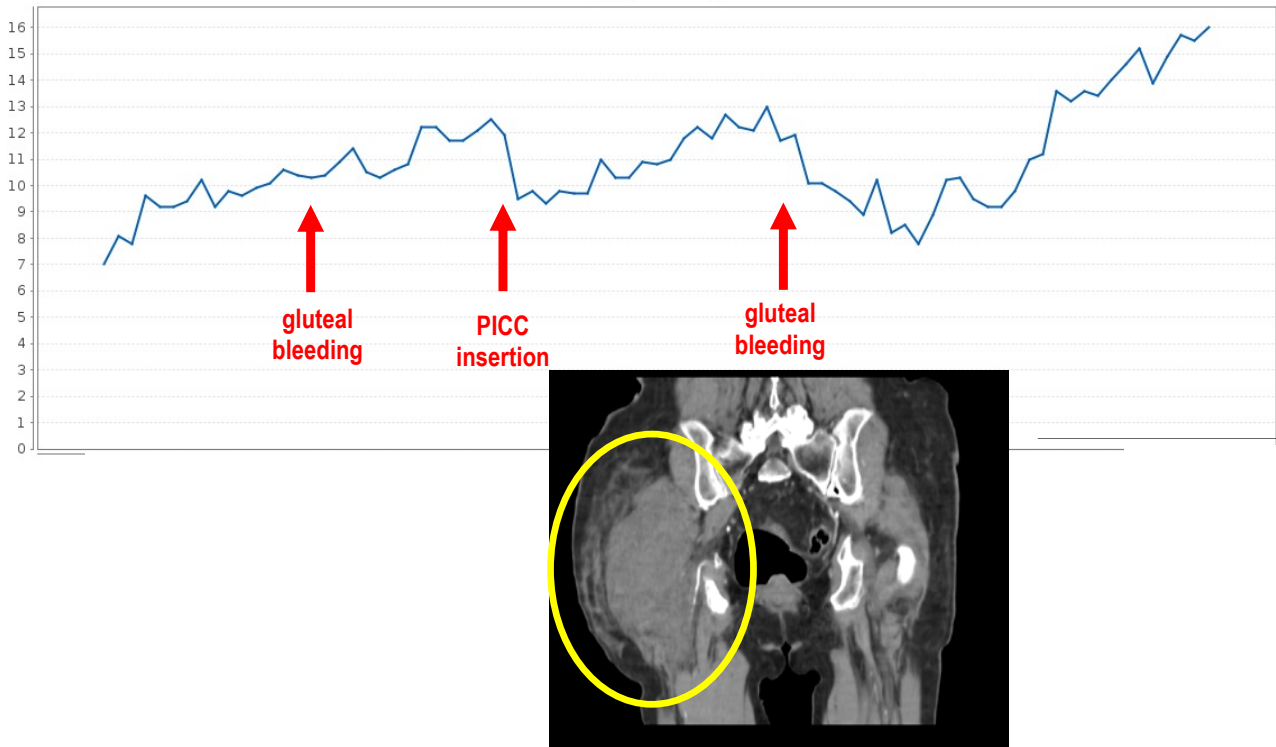
Recommendations regarding immunosuppressive therapy in AHA



- 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

Tiede A et al., *Haematologica*. 2020 Jul;105(7):1791-1801.

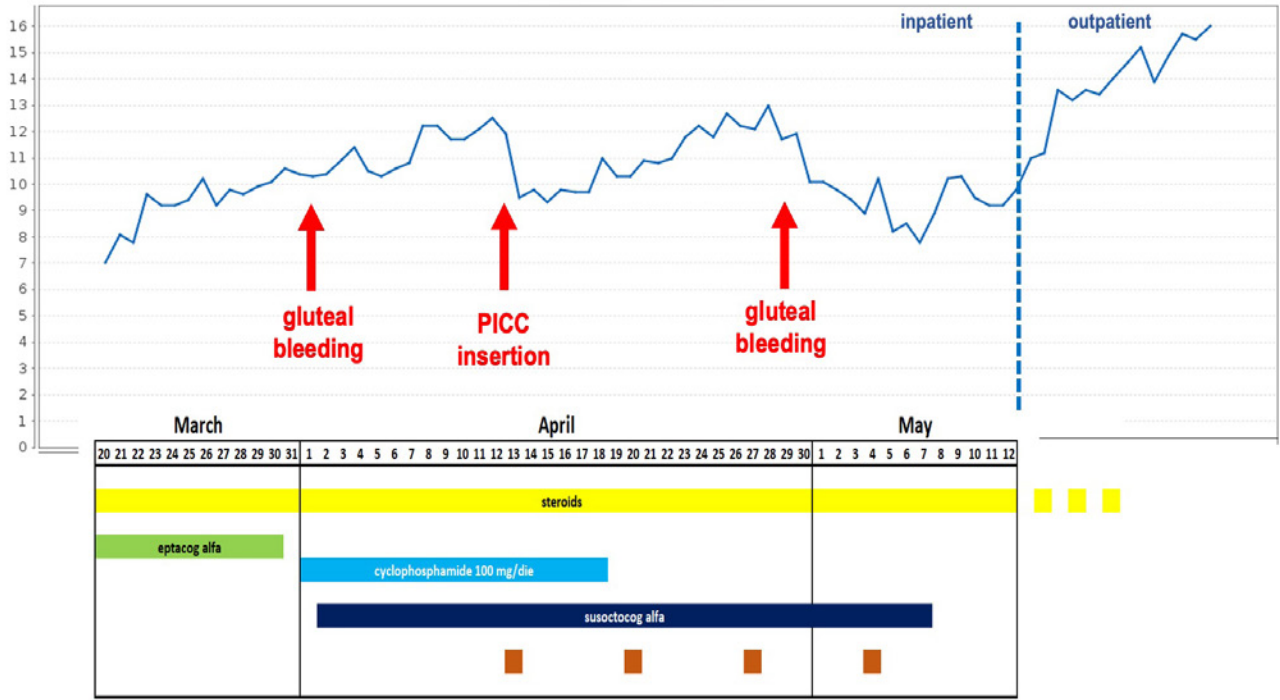
Emocromo (Sg) - HGB-Emoglobina



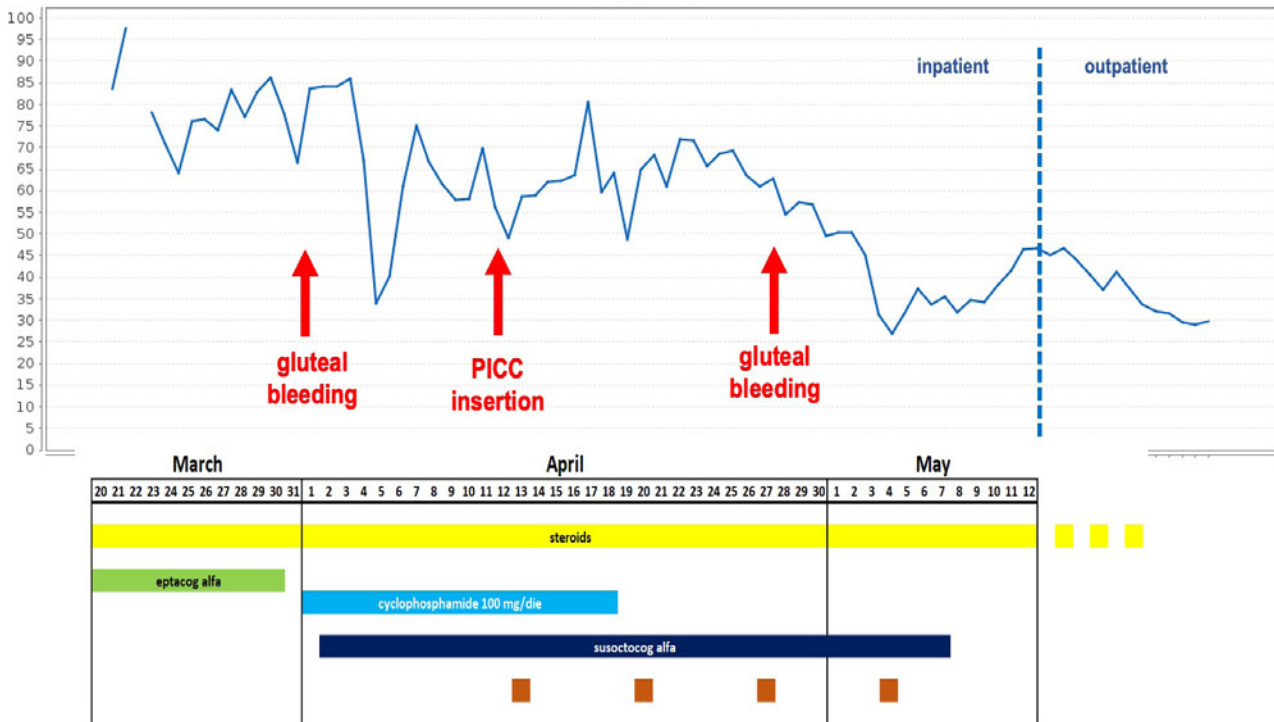
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Emocromo (Sg) - HGB-Emoglobina



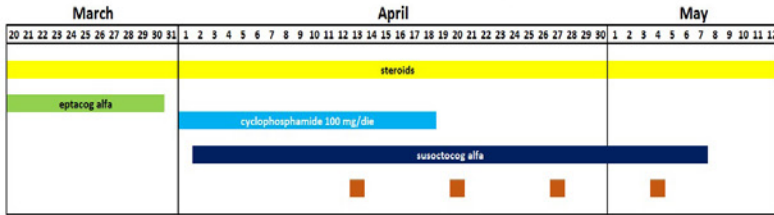
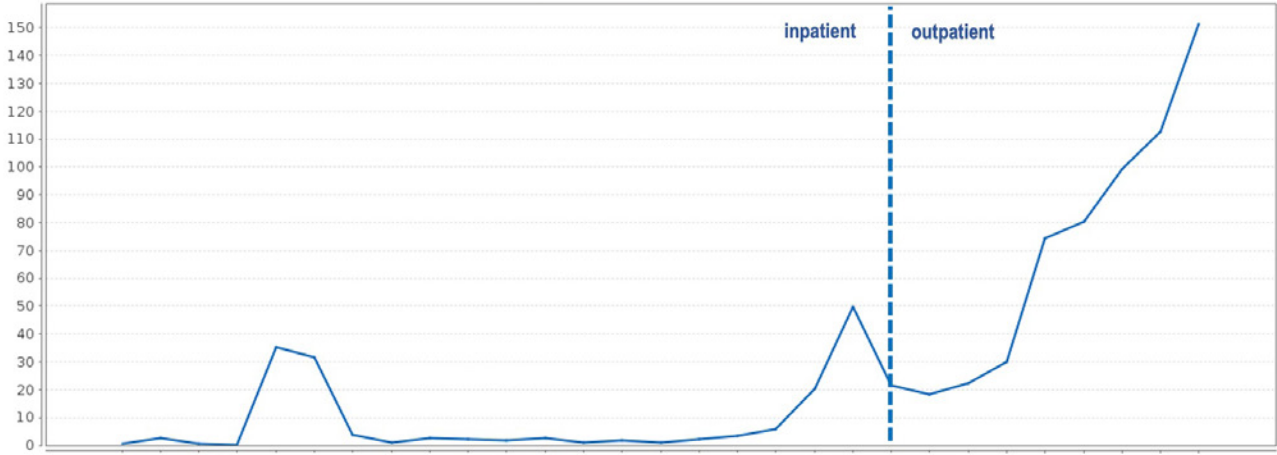
aPTT (P) - Tempo



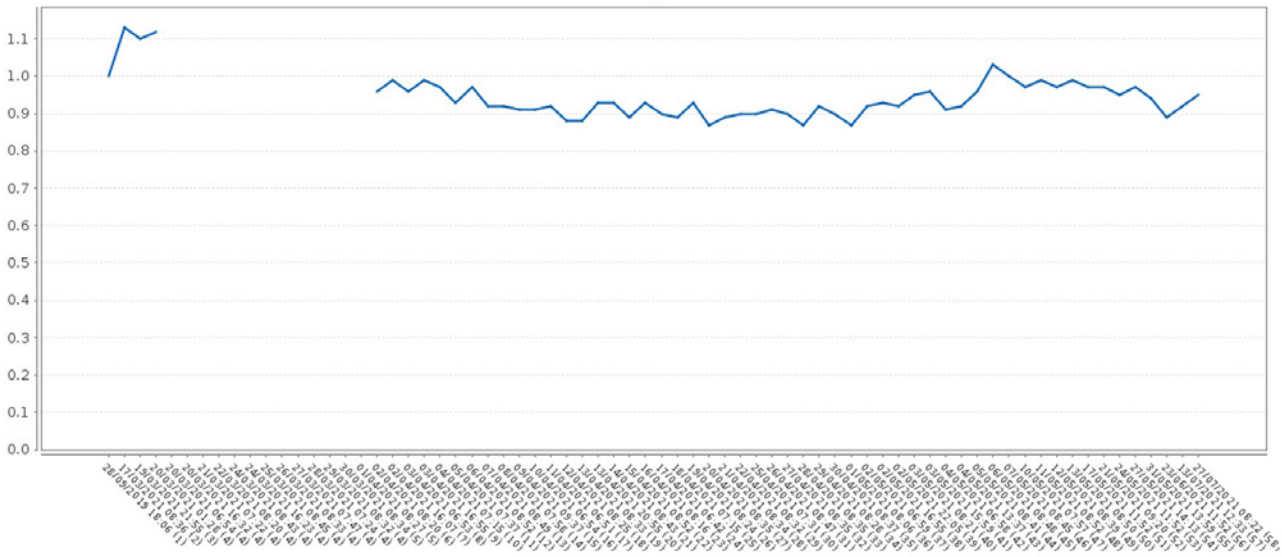
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Attività Fattore VIII (P) - Fattore VIII



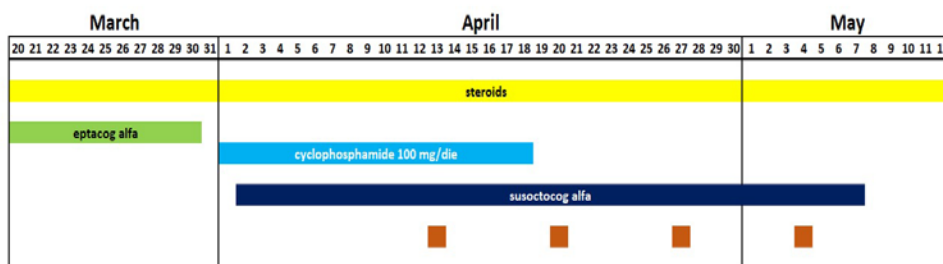
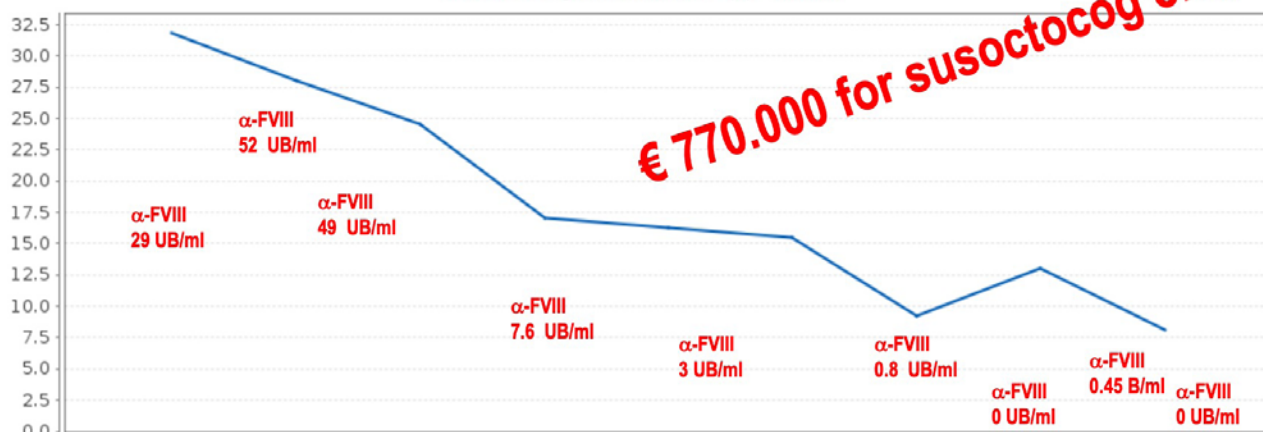
PROTROMBINA (P) - PLASMA
Protrombina (P) - INR



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SARS-CoV-2 IgG Neutralizzante - (S) - Risultato



Visita 2 Settembre 2021

Emocromo (Sg)

WBC-Globuli Bianchi	5,63	K/ μ l
RBC-Globuli Rossi	5,03	M/ μ l
HGB-Emoglobina	16,0	g/dL
HCT-Ematocrito	47,2 *	%
MCV-Volume Eritrocitario	94	fl
MCH-Contenuto Corpuscolare HGB	31,7	pg
MCHC-Concentrazione Corpuscolare Hgb	33,8	g/dL
RDW-Indice Anisocitosi Eritrocitaria	14,5	%
PLT-Piastrine	168	K/ μ l
MPV-Volume Piastrinico	8,66	fl

aPTT (P)

PLASMA		
Tempo	29,8	sec.
Ratio	0,99	Ratio

Attività Fattore VIII (P)

PLASMA	151,3 *	%
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Coagulazione

p-Inibitore Fattore VIII	ASSENTE
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Stop steroidi.

Per quanto riguarda la vaccinazione Covid, al momento si ritiene che sia controindicata perché vi è il sospetto che la patologia autoimmune sia insorta dopo l'infezione e non si può escludere che la vaccinazione determini una recidiva che sarebbe altamente pericolosa per la vita; inoltre, i nostri dati e quelli di letteratura dicono che per molti mesi dopo la terapia con Rituximab non vi è risposta alla vaccinazione. La paziente agli esami del 03/08 aveva peraltro ancora un discreto titolo anticorpale (8.7).

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Future perspectives:

- Hemostatic Tx
- Immunosuppressive Tx

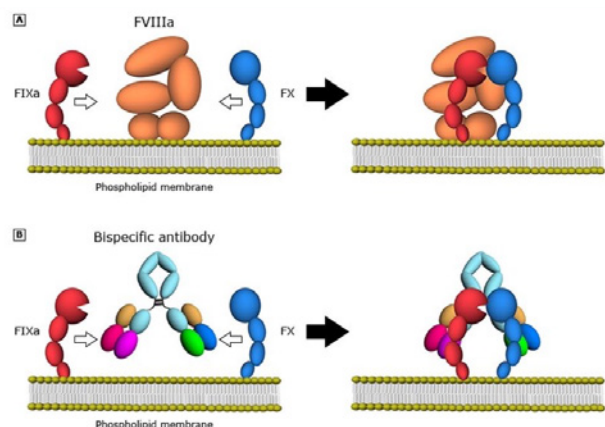
THROMBOSIS AND HEMOSTASIS

Emicizumab for the treatment of acquired hemophilia A

Paul Knoebl,¹ Johannes Thaler,¹ Petra Jilma,² Peter Quehenberger,² Karoline Gleixner,¹ and Wolfgang R. Sperr¹

¹Division for Hematology and Hemostasis, Department of Medicine 1, and ²Coagulation Laboratory, Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria

- Emicizumab has good hemostatic efficacy in AHA: within a few days after the first injection, less bypassing therapy is needed.
- Low emicizumab concentrations can prevent breakthrough bleeding: outpatient patient management with visits every 1 to 3 weeks is feasible.



Knoebl P et al., *Blood*. 2021;137(3):410-419

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Therapeutic approaches to target B cells in autoimmunity

Target	Molecule	Format	RA	SLE	Multiple sclerosis	Malignancy
B cell depletion						
CD20	Rituximab	Monoclonal antibody	Approved	Off-label use	Off-label use	Approved
CD20	Ocrelizumab	Monoclonal antibody	–	–	Approved	–
CD19	Inebilizumab	Monoclonal antibody	–	–	Investigational	Phase II
CD52	Alemtuzumab	Monoclonal antibody	–	–	Approved	Approved
CD38	Daratumumab	Monoclonal antibody	–	–	–	Approved
CD138	Indatuximab ravtansine	Chimeric monoclonal antibody	–	–	–	Approved
B cell activation or activity modulation						
CD19 and FcγRIIb	XmAb5871	Fc-engineered monoclonal antibody	Phase I and phase II	Phase II	–	–
Igβ and FcγRIIb	MGD010	DART	Phase I	–	–	–
CD40	CFZ533	Monoclonal antibody	Phase I	Phase II	–	–
CD40L	Dapirolizumab pegol	Pegylated Fab fragment	–	Phase II	–	–
ICOS	MEDI-570	Monoclonal antibody	–	Phase I	–	Phase I
ICOSL	AMG557	Monoclonal antibody	–	Phase I	–	–
CD22	Epratuzumab	Monoclonal antibody	–	Investigational	–	Phase III
PI3Kδ	Idelalisib	Small molecule	–	–	–	Approved
BTK	Ibrutinib	Small molecule	–	–	–	Approved
Inhibition of cytokines or cytokine signalling						
BAFF	Belimumab	Monoclonal antibody	Investigational	Approved	–	Investigational
BAFF and APRIL	Atacicept	TACI and human IgG-Fc fusion protein	Investigational	Phase III	Phase II	–
IL-6R	Tocilizumab	Monoclonal antibody	Approved	–	–	Phase II
IL-21	NNC114-0005	Monoclonal antibody	Phase I	–	–	–
JAK1 and JAK3	Tofacitinib	Small molecule	Approved	Phase I and phase II	–	–
JAK1 and JAK2	Baricitinib	Small molecule	Approved	Phase III	–	–
Trafficking blockade						
α4 Integrin	Natalizumab	Monoclonal antibody	Phase II	–	Approved	–

Rubin SJS et al., *Nat Rev Rheumatol.* 2019 May;15(5):303-315.

Biochemical and immunologic abnormalities in peripheral blood T lymphocytes of patients with hemophilia A.

Dianzani U, Pileri A, Bianchi A, Camponi A, Tamponi G, Massaia M.

Eur J Haematol. 1988 Oct;41(4):334-40. doi: 10.1111/j.1600-0609.1988.tb00206.x.

PMID: 3264249

Immunologic and virologic findings in hemophiliacs do not correlate with ecto-5'nucleotidase activity of peripheral blood lymphocytes. A difference with homosexual men.

Massaia M, Pioppo P, Dianzani U, Guerra MG, Peyretti F, Pileri A, Tamponi G.

Eur J Haematol. 1987 Apr;38(4):310-4. doi: 10.1111/j.1600-0609.1987.tb00003.x.

PMID: 3038600



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