The Emperor of All Bleeding Disorders: HEMOPHILIA

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Speaker Disclosure

I have no relevant financial relationships with manufacturers of any commercial products and/or providers of commercial services discussed in this CME activity.

I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

I have not used artificial intelligence in the development of this presentation.

Objectives

- At the conclusion of this activity, learners will be able to:
  - Recall the Coagulation Cascade
  - Identify a patient with Hemophilia
  - Learn the existing and novel therapies for Hemophilia

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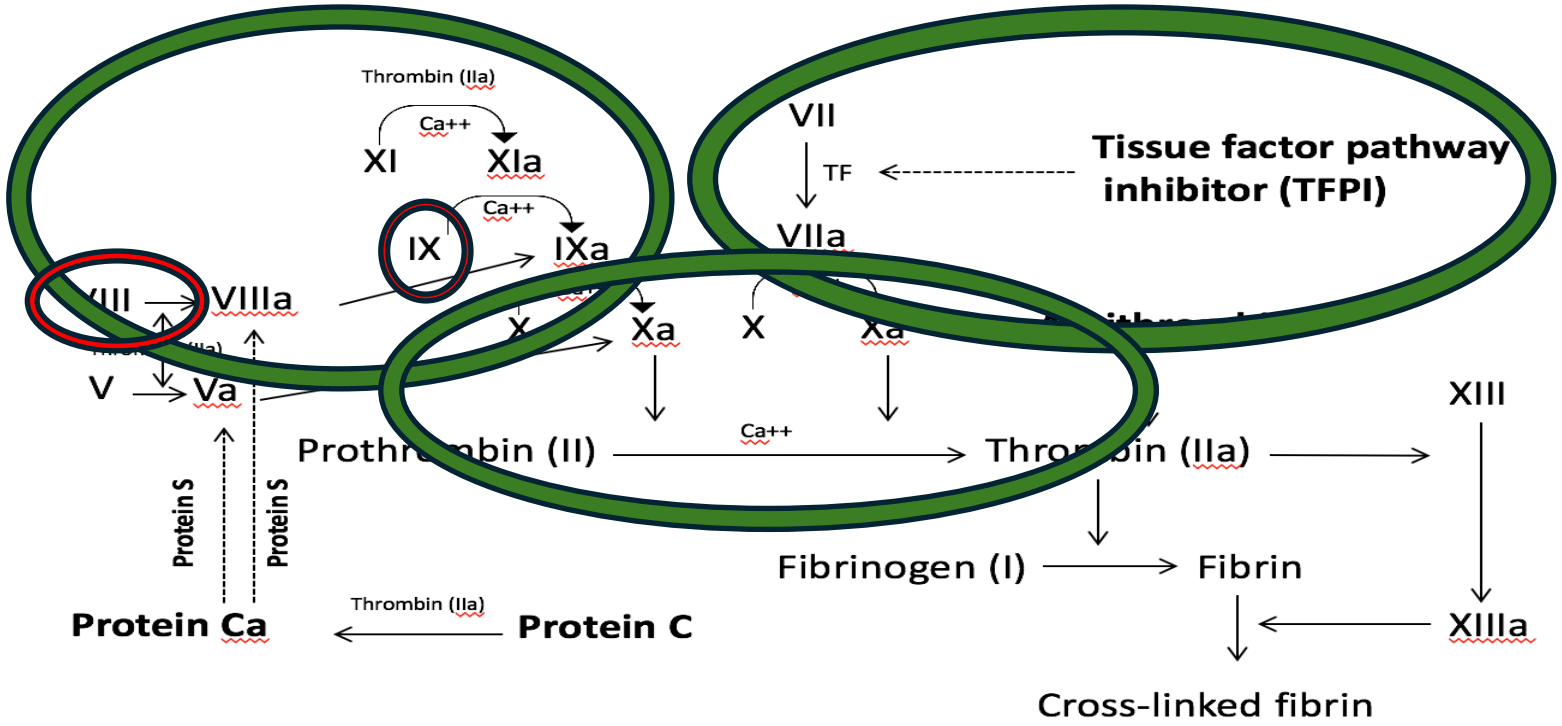
Background



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Background

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RECOMMENDATIONS AND GUIDELINES

A new hemophilia carrier nomenclature to define hemophilia in women and girls: Communication from the SSC of the ISTH

Karin P. M. van Galen[1] | Roseline d'Oiron[2] | Paula James[3] | Rezan Abdul-Kadir[4] | Peter A. Kouides[5,6] | Roshni Kulkarni[7] | Johnny N. Mahlangu[8] | Maha Othman[9] | Flora Peyvandi[10,11] | Dawn Rotellini[12] | Rochelle Winikoff[13] | Robert F. Sidonio[14]

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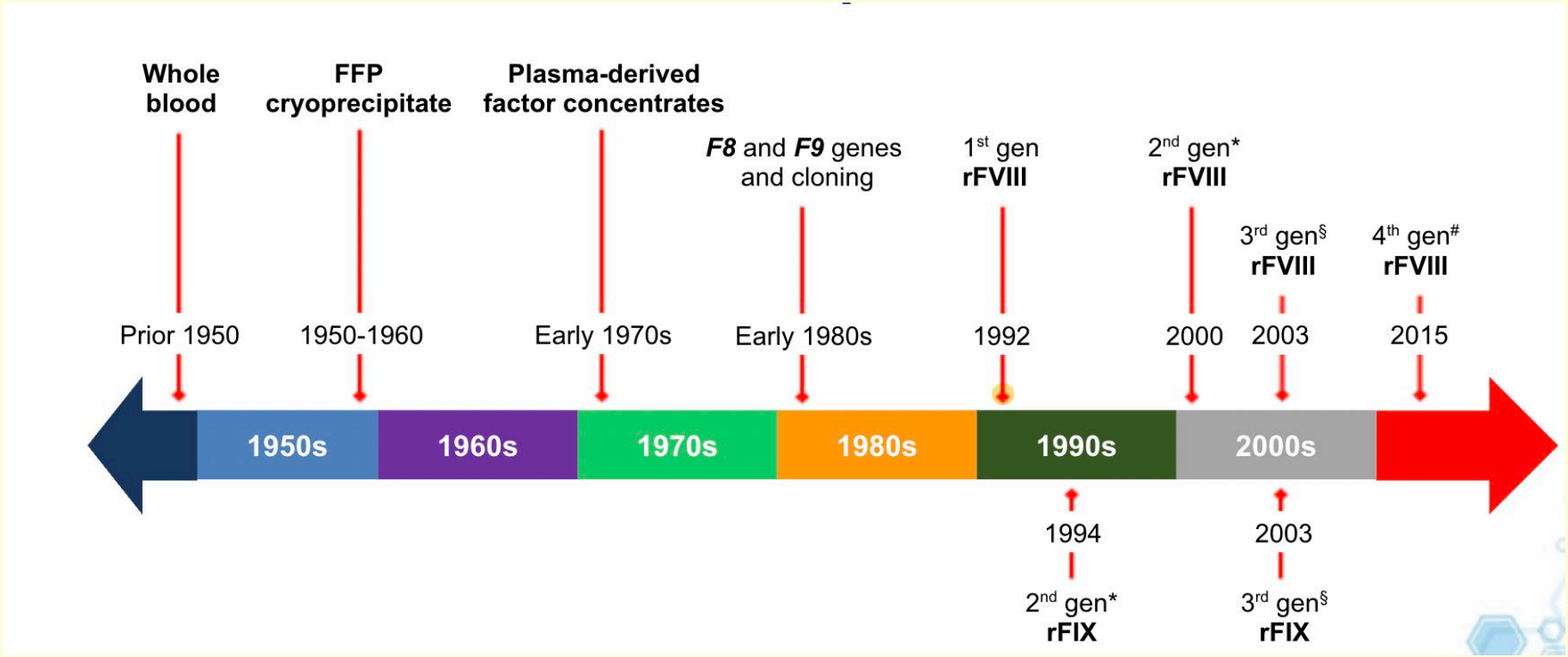

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Background

20-30% of patients develop ***inhibitors***

Table 1. Standard half life recombinant factor VIII products.

Generation	Trade name	Manufacturer	Cell line	Protein length	Albumin use	Stabilizer
1	Recombinate	Baxalta/Shire	CHO	Full	Cell culture	Bovine albumin
2	Kogenate FS	Bayer	BHK	Full	Cell culture	Sucrose
	Refacto	Pfizer	CHO	B-domain deleted	N/A	Sucrose
3	Advate	Baxalta/Shire	CHO	Full	N/A	N/A
	Refacto AF	Pfizer	CHO	B-domain deleted	N/A	Sucrose
	Xyntha	Pfizer	CHO	B-domain deleted	N/A	N/A
	Kovaltry	Bayer	BHK-expressing HSP 70	Full	N/A	N/A
	Novoeight	Novo Nordisk	CHO	B-domain deleted	N/A	Sucrose
	Afstyla	CSL Behring	CHO	B-domain truncated single chain protein	N/A	Sucrose
4	Nuwiq	Octapharma	Hek-293	B-domain deleted	N/A	Sucrose

Table 2. Extended half-life factor VIII products.

Extended half-life FVIII product	Trade Name	Manufacturing techniques	Plasma half-life	Half-life prolongation	Manufacturer	Year of licensing
Efmoroctocog alfa	Elocta/Eloctate	Fc fusion	19	1.5–1.7	Biogen/Sobi	2014
Rurioctocog alfa pegol	Adynovate	PEGylation	14.3	1.3–1.5	Takeda	2015
Damoctocog alfa pegol	Jivi	PEGylation	19	1.6	Bayer	2018
Turoctocog alfa pegol	Esperoct	PEGylation	18.4	1.6	Novo Nordisk	2019

Kizilocak H, Young G. Emerging drugs for hemophilia A: insights into phase II and III clinical trials. Expert Opin Emerg Drugs. 2021 Oct 11:1-14. doi: 10.1080/14728214.2021.1988073. Epub ahead of print. PMID: 34601977.

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Background

Inhibitors to FVIII/ FIX

↑ ***Bleeding Episodes*** ↑ ***Morbidity*** ↓ ***Quality of Life***

Novel Agents

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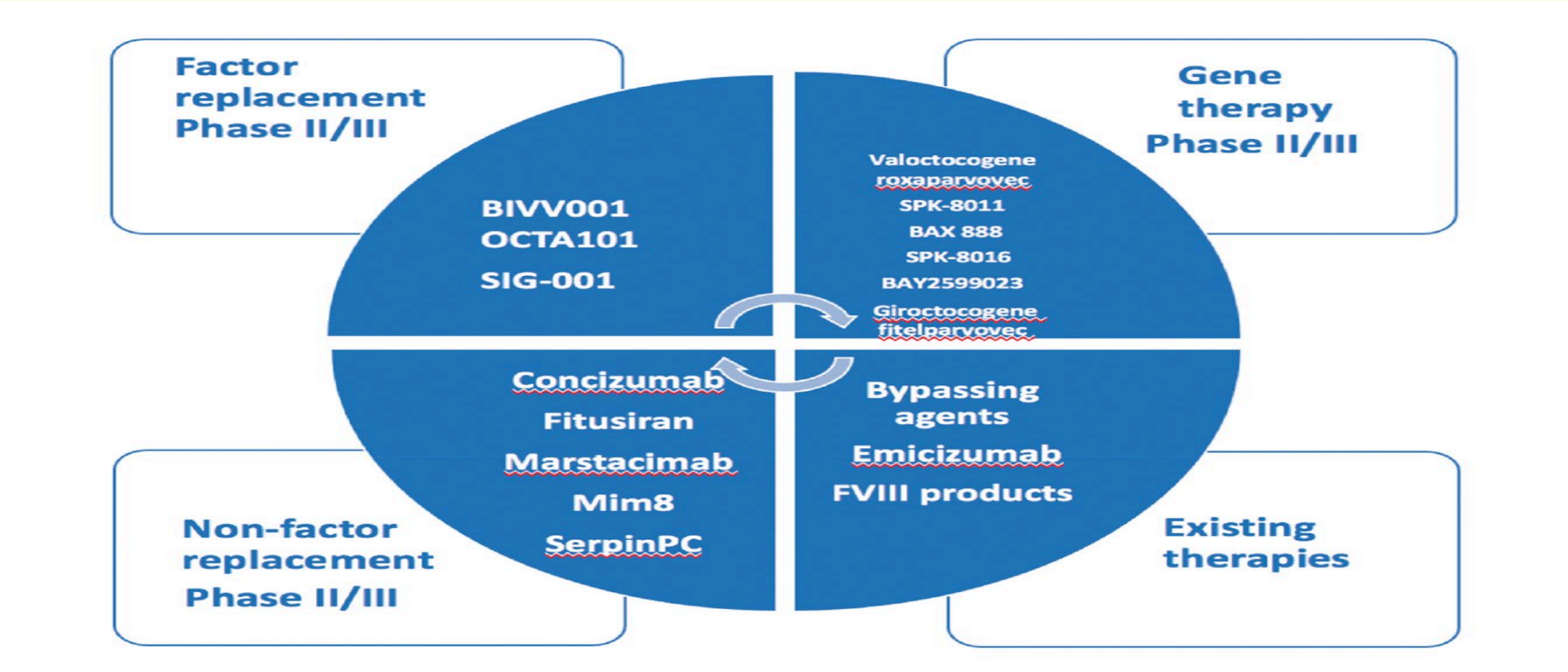
Background



Kizilocak H, Young G. Emerging drugs for hemophilia A: insights into phase II and III clinical trials. Expert Opin Emerg Drugs. 2021 Oct 11:1-14. doi: 10.1080/14728214.2021.1988073. Epub ahead of print. PMID: 34601977.

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Background

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FDA NEWS RELEASE

FDA Approves First Gene Therapy for Adults with Severe Hemophilia A

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For Immediate Release: June 29, 2023

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Case Presentation - 1

- 23 yr old female with asymptomatic Hemophilia B G1P0 31GW
- C/S - r-PEG-FIX 30 U/kg + Tranexamic acid
- Daily FIX infusion post C/S
- STAT FIX activity and aPTT from the cord blood
  - Forceps & Vacuum extractions- AVOID!!!

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Case Presentation - 1

Newborn Nursery Precautions:

- IM Vit K should be held until the dx is confirmed
  - If Hemophilia– SC Vit K
  - If Hemophilia is ruled out– IM Vit K
- Avoid VP – no arterial access
- Hep B can be given SC
- Heel sticks should be done with caution- pressure for 5 mins and monitor
- Any sign of cephalohematoma or extra cranial hemorrhage - ***Treat!***
- No circumcision in the nursery!!

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Case Presentation - 1

- rFVIIa – 70 mcg/kg – ***preemptively***
  - US: intracranial bleeding with midline shift
  - FIX < 1%
  - aPTT 146 sec
  - rFIX – aPTT 48 sec
  - Decompressive craniotomy/ hematoma evacuation w/ cont FIX infusion

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Case Presentation - 2

- 22 yo female with asymptomatic Hemophilia B G2P0 39GW
- NVD- prior to delivery TXA & FIX
- Prolonged labor – shoulder dystocia
- Cord blood sent for aPTT - FIX activity

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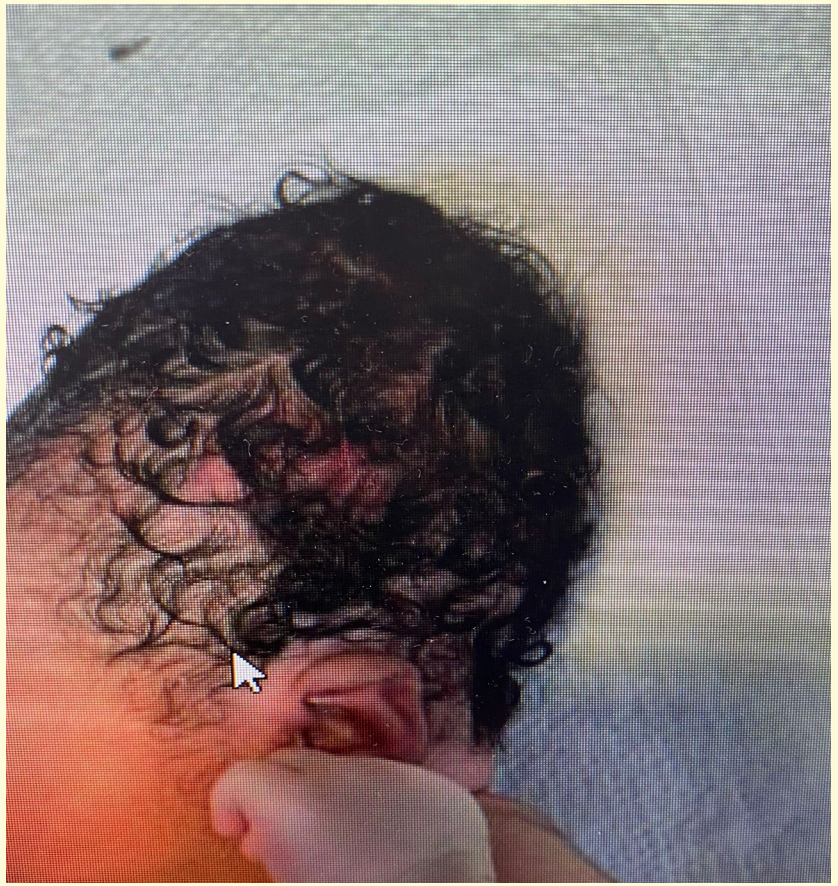
Case Presentation - 2

- aPTT >100
- FIX < 1%
- Genetic testing sent



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Case Presentation - 2

- Received FIX 5 EDs
- No prophylaxis until the age of at least 1 yr – “WILL BE ADAPTED TO HIS NEEDS”
- Check ***Inhibitors*** prior to new doses in the future
- Immunization plan
  - Can receive SC
  - IM vaccines one at a time 1 week apart
  - 5 min pressure
  - Follow the leg for hematoma prior to the second vaccine

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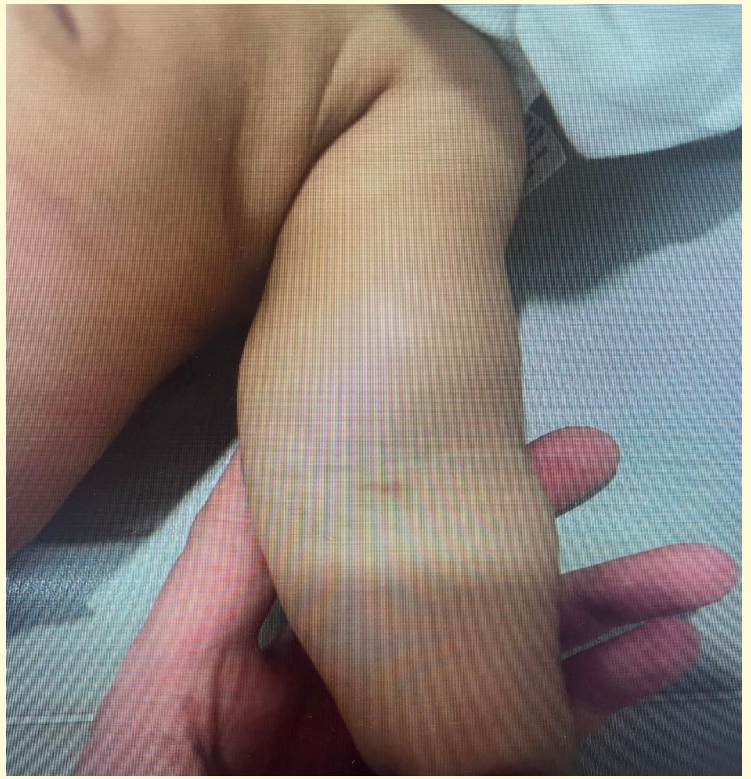
Case Presentation - 2

- 2 mo of age presented with acute LUE swelling after a VP
- Admitted for monitoring the signs of “Compartment Syndrome” and received on demand FIX infusion



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Case Presentation - 2

- 6 mo of age presented with left thigh swelling post vaccination
- Recommended US and FIX infusion at ED
- First joint bleed at 13 months- started prophylaxis

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Summary

- X-linked / de novo mutation
- Women with hemophilia
- Factor replacement/ Novel agents/ Gene therapy
- Inhibitors – Bypassing agents
- Vaccines – sc/ im

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Take home messages

- ***Treat first diagnose later*** in life threatening situations
- No response to Factor replacement- think **inhibitors**
- Give ***bypassing agents*** in case of ***inhibitors***
- Patients on Emicizumab prophylaxis ***still needs factor replacement for breakthrough bleeding***
- ***IM vaccinations*** once at a time and 1 week apart

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References and additional reading

- Kizilocak H, Young G. Diagnosis and treatment of hemophilia. Clin Adv Hematol Oncol. 2019 Jun;17(6):344-351. PMID: 31437138
- Kizilocak H, Young G. Emerging drugs for hemophilia A: insights into phase II and III clinical trials. Expert Opin Emerg Drugs. 2021 Dec;26(4):337-350. doi: 10.1080/14728214.2021.1988073. Epub 2021 Oct 11. PMID: 34601977
- World Federation of Hemophilia Guidelines

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