Acquired Inhibitors in Cancer

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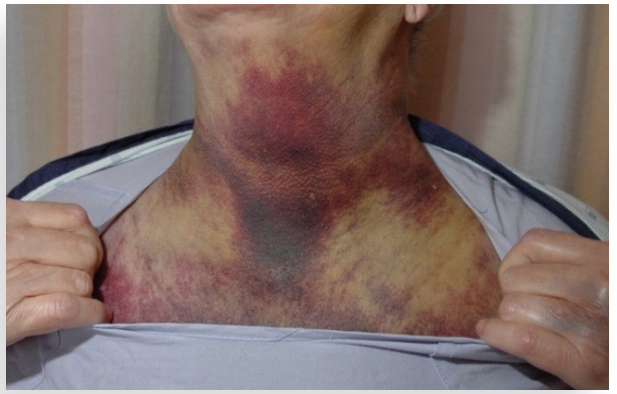
Clinical Case

- 74 yo man
  - DM
  - HTN
  - No previous bleeding hx
  - No recent medication changes
  - Not on anticoagulants or anti-platelets



- Noticed some swelling in his jaw after chipping a tooth – the next morning had bruising in his jaw, neck and into his trunk

Clinical Case

- CBC: Hgb 9.0, MCV 83, PLTS 400,000, WBC nl
- PT 12 sec (INR 1.0)
- PTT 80 sec
- Mixing study of PTT: no correction after 2 hr incubation @ 37°C

Clinical Case

- CBC: Hgb 7.5, MCV 83, PLTS 400,000, WBC nl
- PT 12 sec (INR 1.0)
- PTT 80 sec
- Mixing study of PTT: no correction after 2 hr incubation @ 37°C
- FVIII 1%
- FVIII inhibitor 50 BU

Acquired Hemophilia A

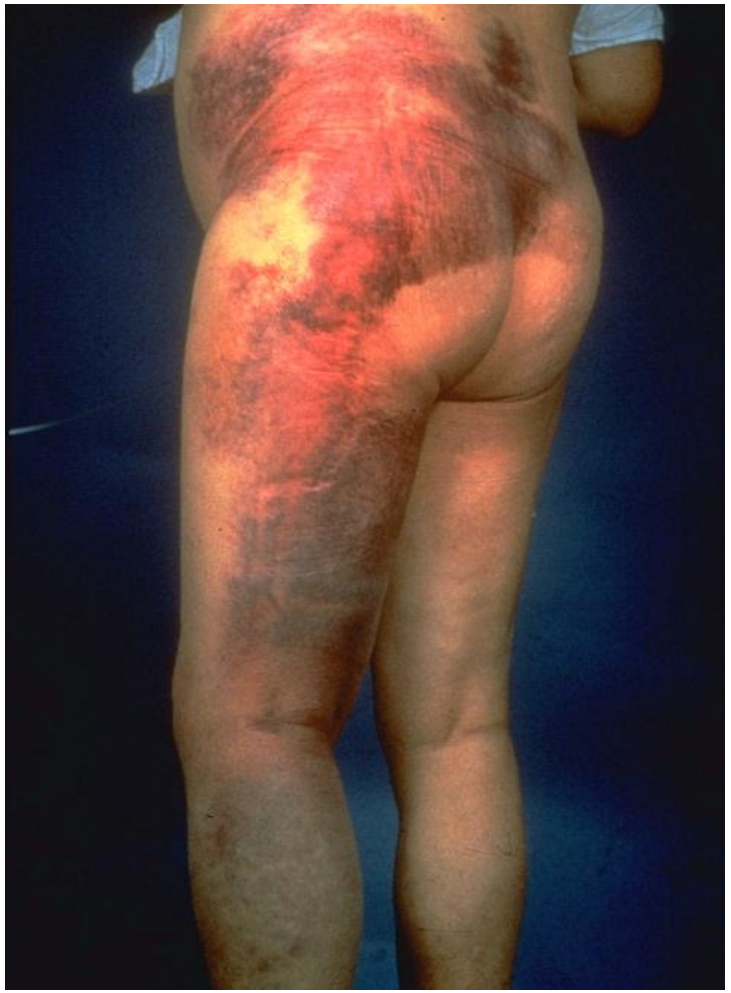
- Symptomatic bleeding
- Isolated prolonged PTT
- Very high mortality rates (~25%)

- *Mortality related to delay in diagnosis and proper treatment*

Definition of Acquired Hemophilia A

- Bleeding caused by autoantibody (IgG) directed against factor VIII (FVIII)
- Presents in patients without personal or family history of bleeding
- Bleeds are often life- or limb-threatening

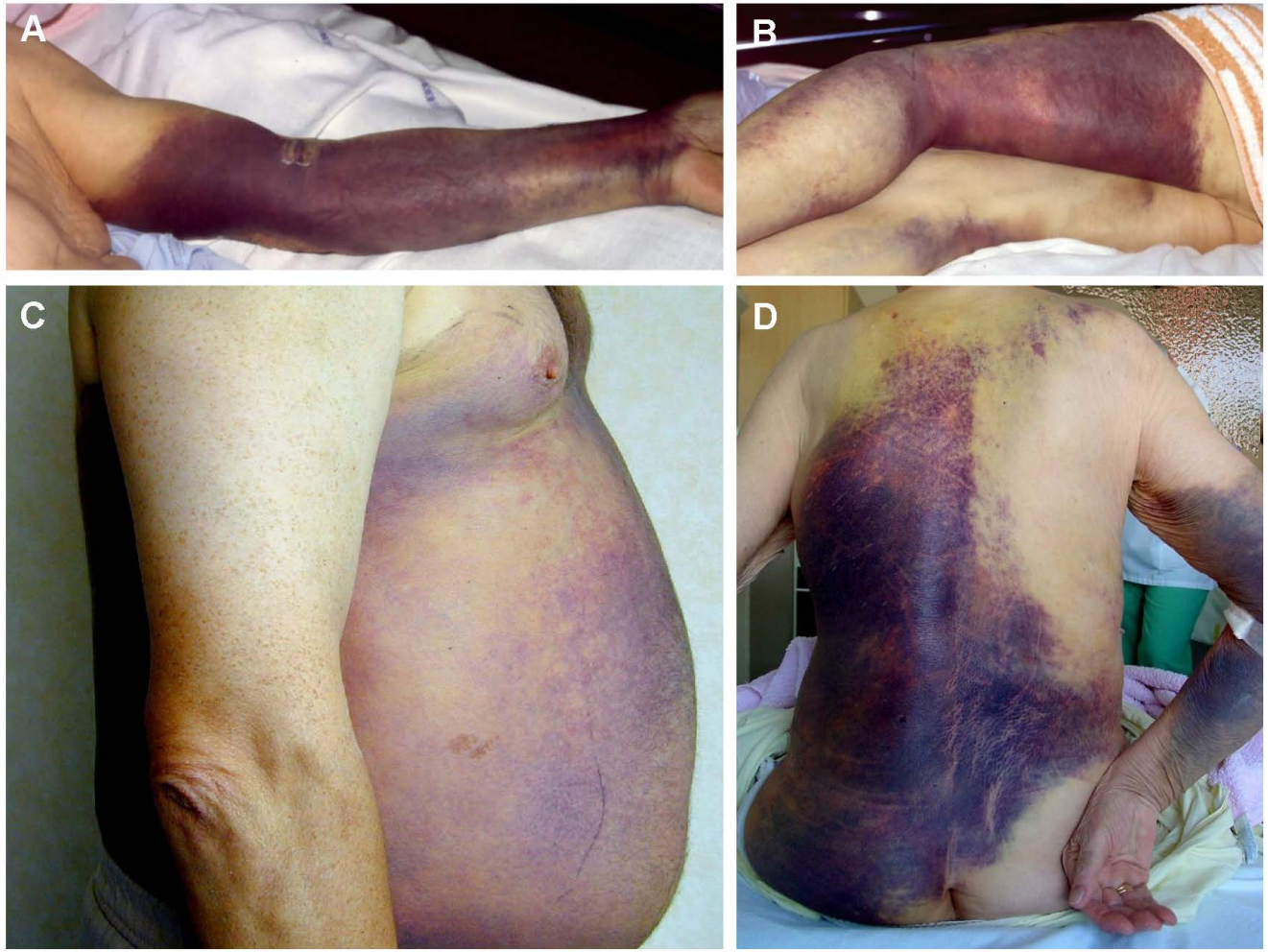
Characteristic Bleeding



- Soft tissue (subcutaneous) most common
- GI bleeding
- GU bleeding
- Post-procedure/post-partum bleeding
- ICH

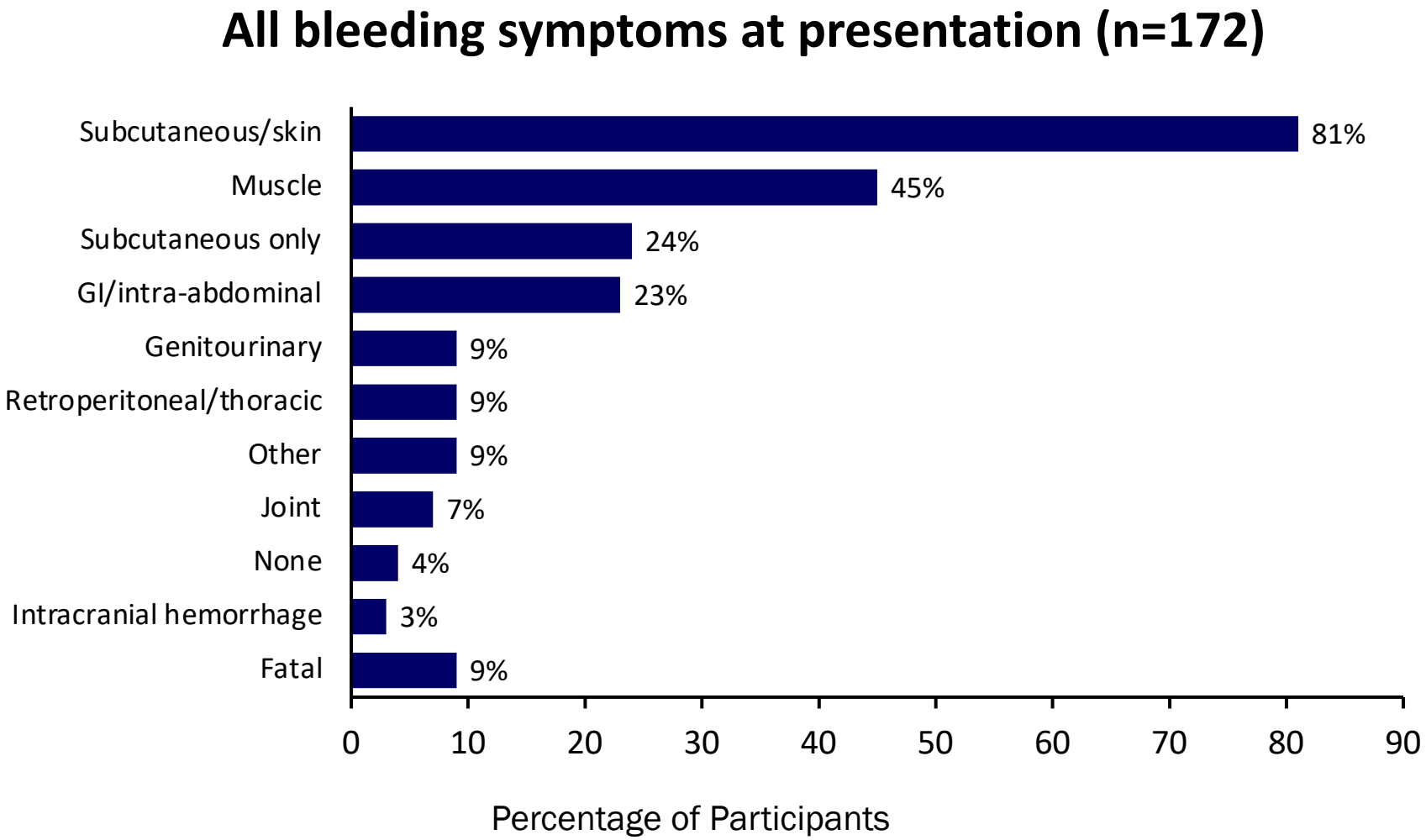
- Hemearthroses ***rare***

Subcutaneous Ecchymoses



Collins P, et al. *BMC Res Notes.* 2010;3:161.

Bleeding Patterns at Presentation



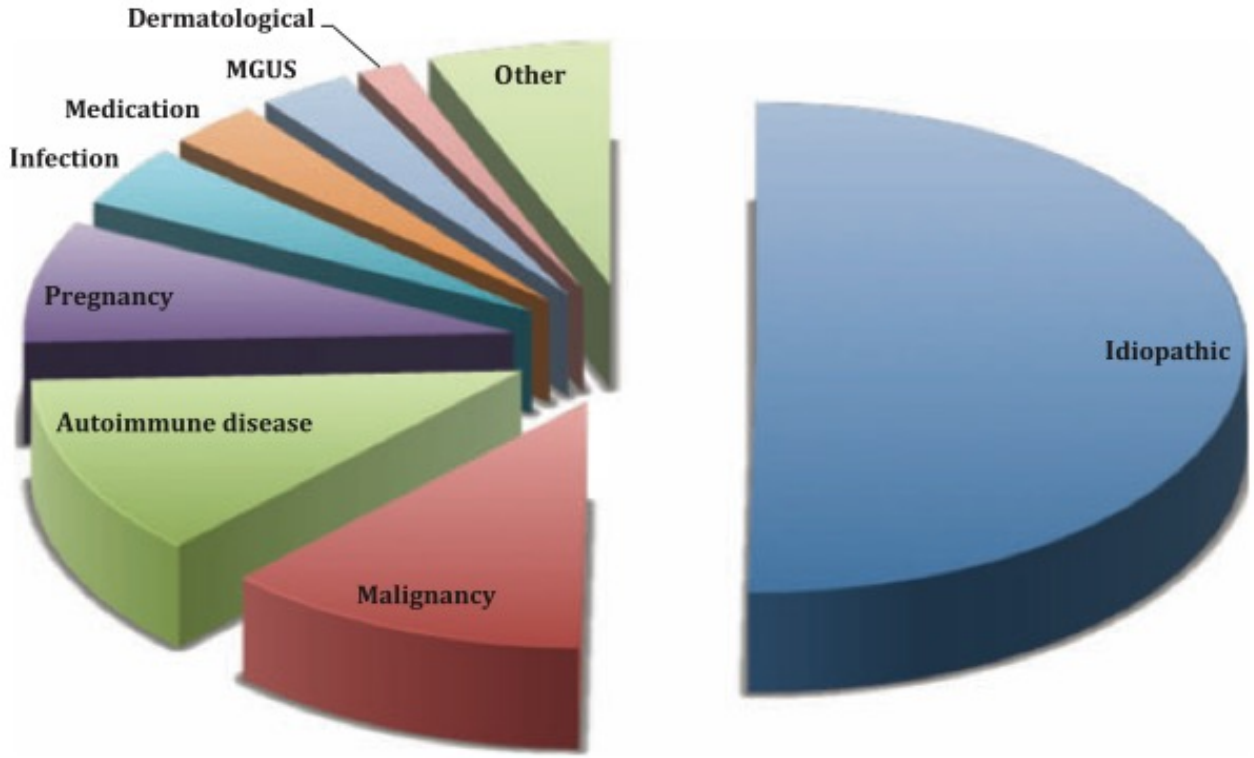
Collins PW, et al. *Blood*. 2007;109(5):1870-1877.

Affected Populations

- Most common in the elderly
- Underlying cancer diagnosis in ~12-15% of cases
  - Lymphoproliferative disorders
  - Myeloproliferative disorders
  - Solid tumors: prostate, lung, breast, colon, bladder

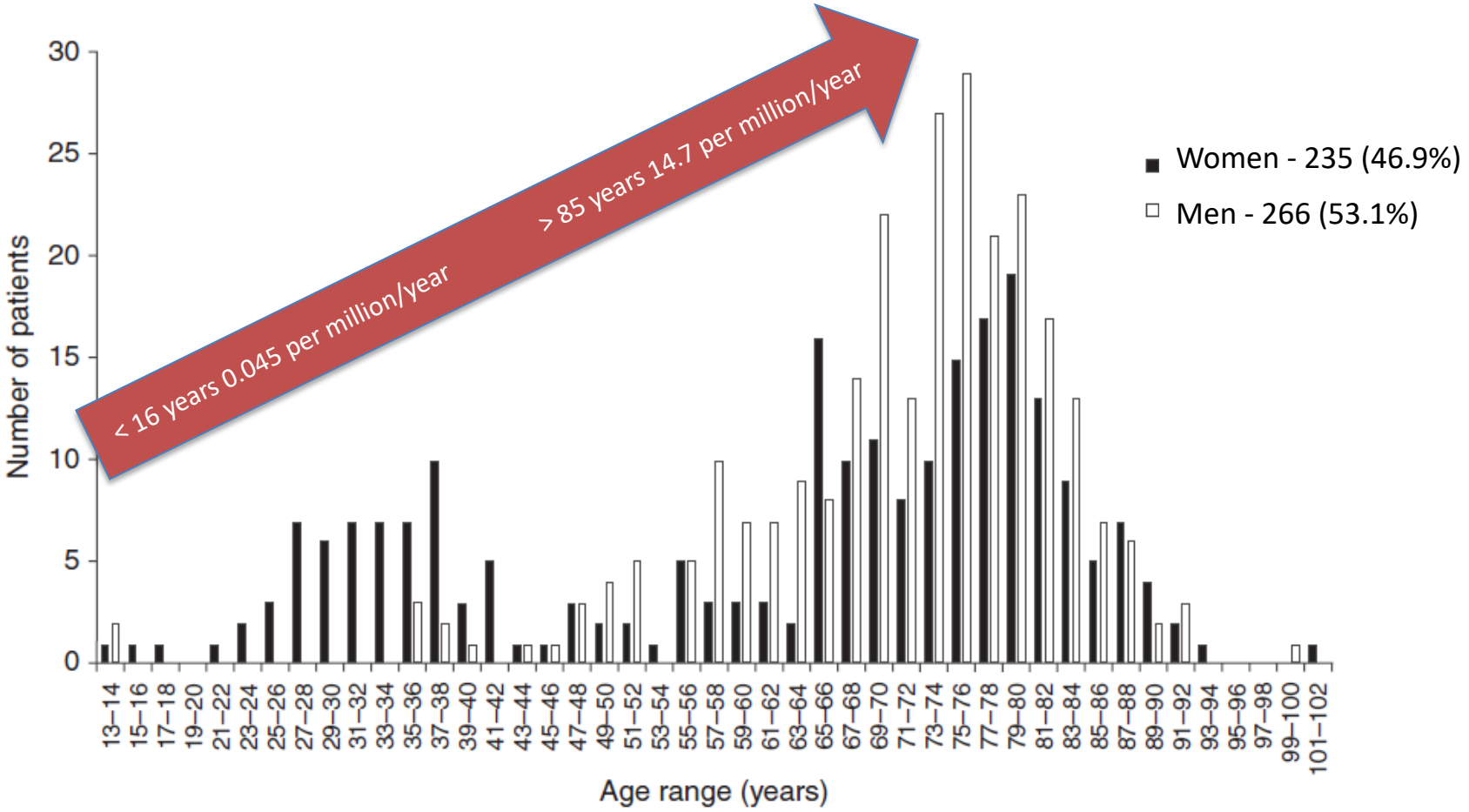
FVIII Inhibitor may be first manifestation of malignancy or autoimmune disorder

Associated Conditions



Adapted from: Knoebl P, et al. *J Thromb Haemost*. 2012;10:622-631.

AH Median Age at Diagnosis: 73.9 Years



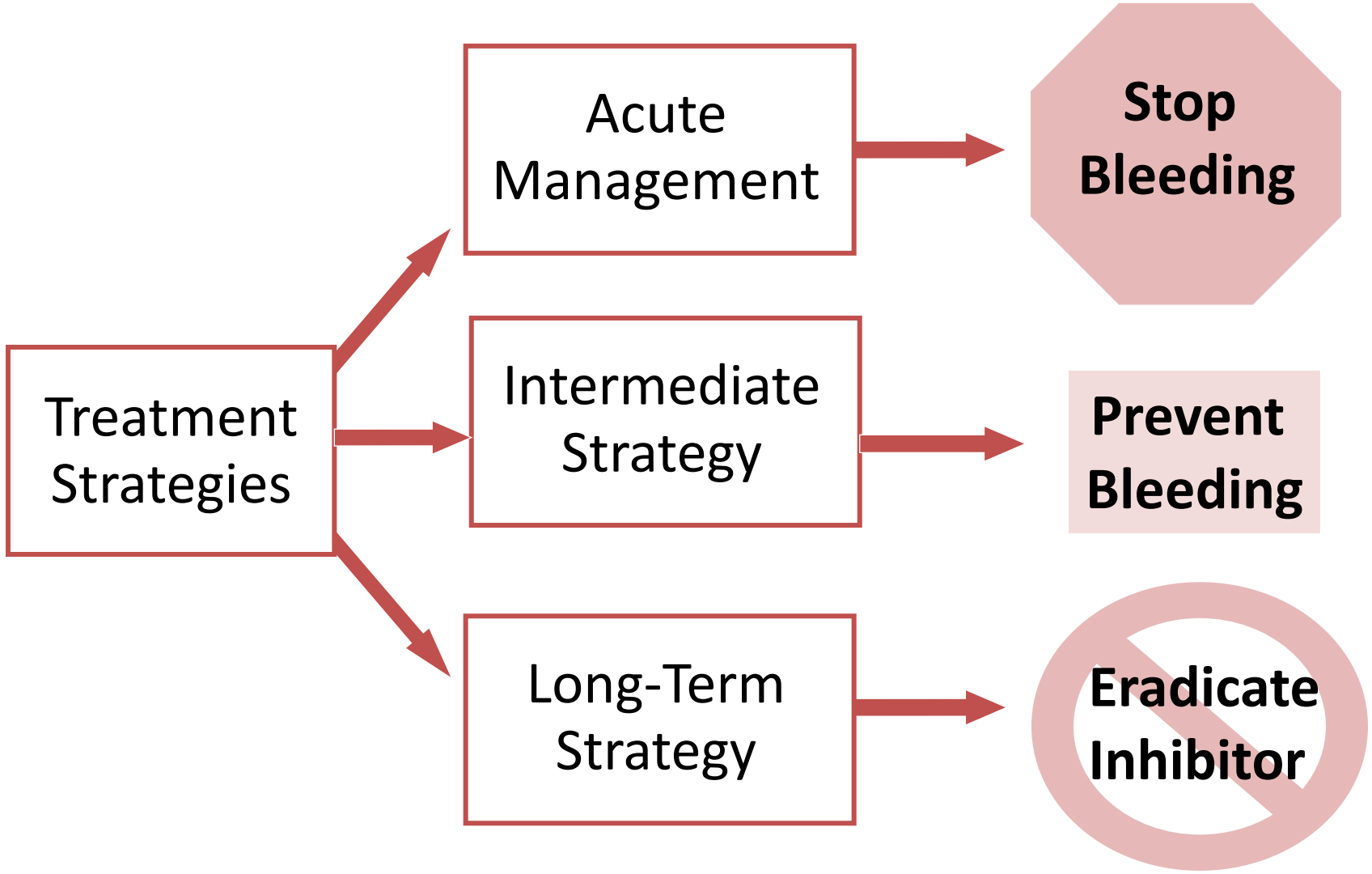
Knoebl P, et al. *J Thromb Haemost.* 2012;10:622-631.

Laboratory Differential Diagnosis of Prolonged PTT/Normal PT

	Congenital FVIII Deficiency	Inhibitor in Congenital Hemophilia	Acquired FVIII Inhibitor	Lupus Inhibitor	Heparin
PTT	Prolonged	Prolonged	Prolonged	Prolonged	Prolonged
PTT correction with mixing study?	Correction	No correction After incubation	No correction After incubation	No correction Immediate	No correction
FVIII activity	Low	Low	Low	Normal	May be low
PTT correction with addition of phospholipid?	No	No	No	Yes	No

Clinical Management

Treatment Strategy: 3 Objectives



AH: Treatment

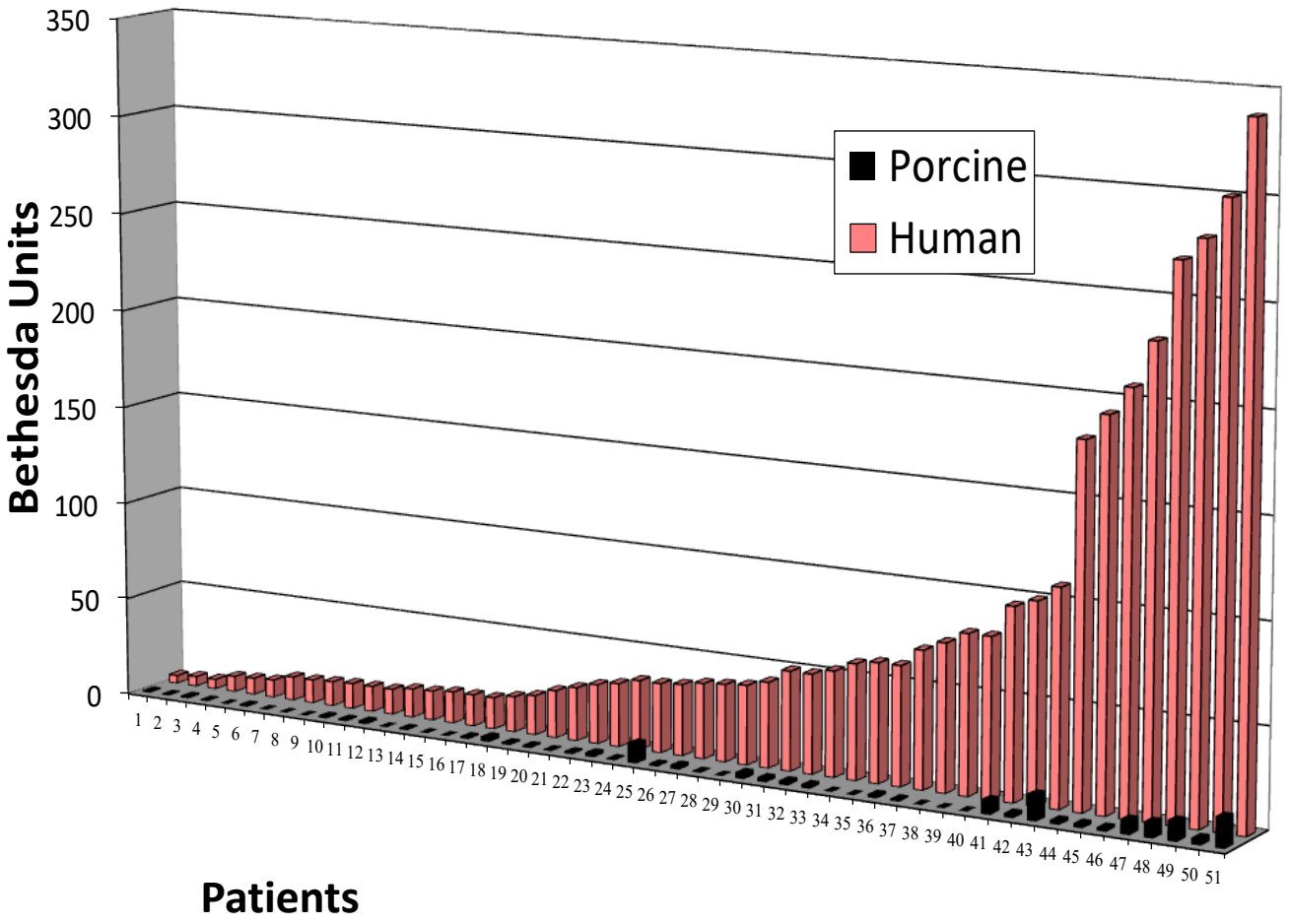
- **First priority is to *stop the bleeding***
  - Raise FVIII levels (FVIII therapy), or
  - Bypass the need for FVIII (Bypassing agents)
- **Consider emicizumab to prevent bleeding**
- Begin immunosuppressive therapy to eradicate the inhibitor
- Evaluate and treat for underlying, associated disease

FVIII Replacement Therapy

- Avoid Human FVIII concentrates

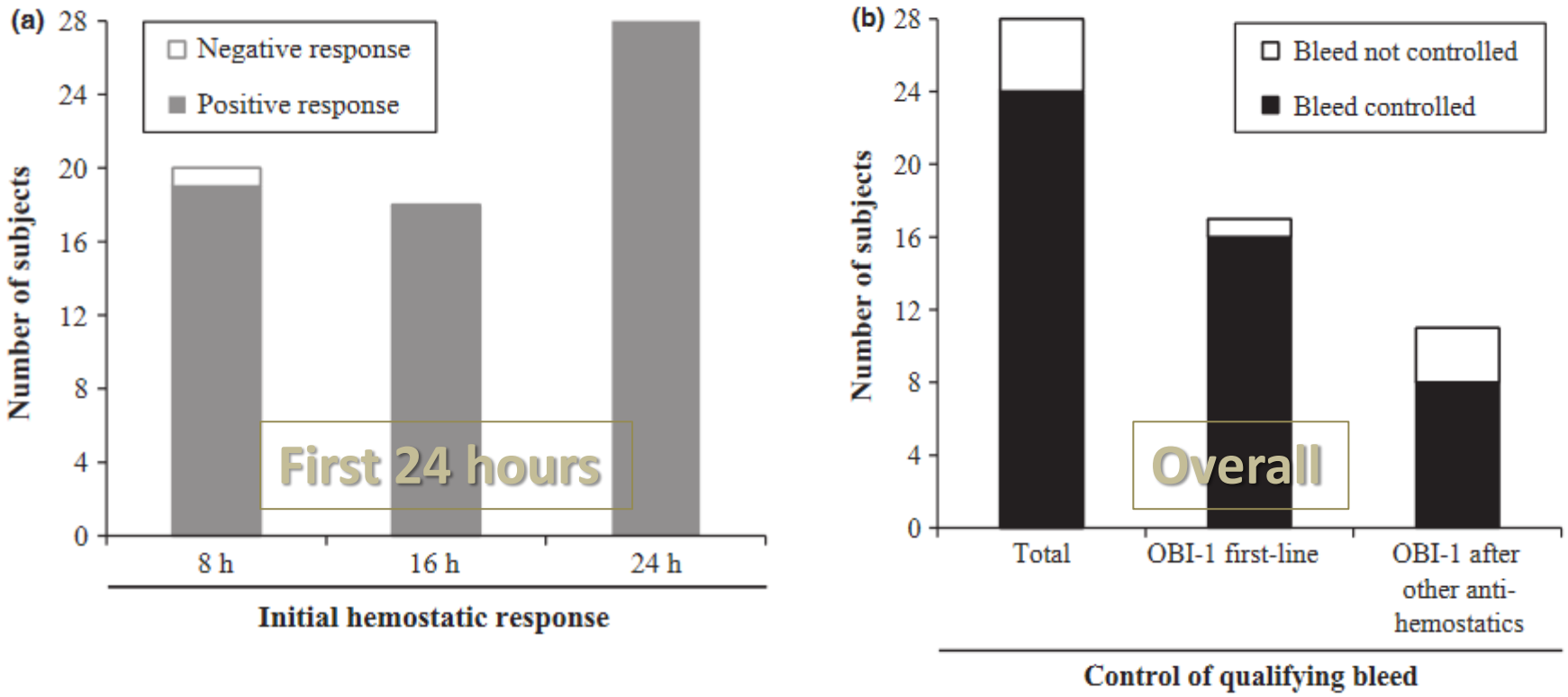
- Porcine FVIII (Obizur)
  - Usually effective even with high titer inhibitor
  - Can monitor by standard FVIII assays

Cross-reactivity with Porcine FVIII



Giangrande P. Haemophilia 2012; 18:305–309

Obizur Efficacy Results



- 100% of treated subjects showed a positive response at 24 hours
  - 25 effective / 4 partially effective (ITT)
- Control of initial serious bleeding episodes successful in: 25/29 subjects (86%, ITT)

Kruse-Jarres et al. Haemophilia 2015.

Bypass Therapy

- aPCC (FEIBA)
  - Response rates ~75% with 1-2 doses
  - Plasma-derived product
  - Longer duration of effect (~6 hours)

- rFVIIa (Novoseven)
  - Response rates ~80% with 2-3 doses
  - Recombinant product
  - Short duration of effect (~2-4 hours)

- Risk of thrombosis/DIC with large or frequent doses

Monitoring Bypassing Agents

- No validated laboratory monitoring technique
  - FVIII assay not helpful in patients treated with bypassing agents
- Therapy guided by clinical symptoms

Hoffman M, Dargaud Y. *J Thromb Haemost*. 2012;10(8):1478-1485.

Thrombosis Risk with Bypassing Agents

- N=482 patients treated for bleeding
- Thrombotic events in 3.6% of treated patients
  - rFVIIa 2.9%
  - aPCC 4.8%
- Types of events:
  - 6 myocardial infarctions
  - 1 stroke
  - 4 venous thromboemboli

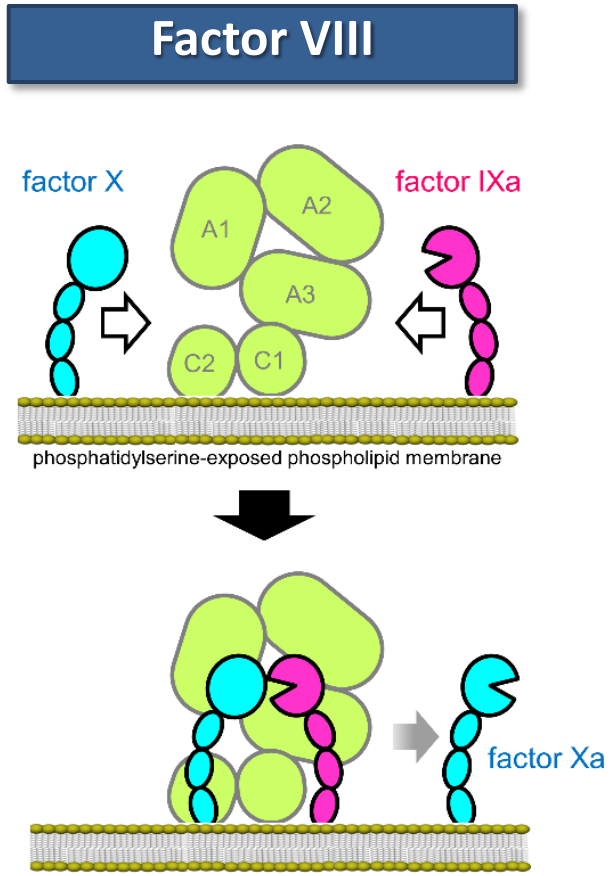
Baudo F, et al. *Blood*. 2012;120(1):39-46.

Therapy to Prevent Bleeding

- Preventing bleeds can be life-saving in patients with acquired hemophilia

- Emicizumab – FVIII mimetic not affected by the presence of FVIII inhibitors

How Factor VIII Works



Shima, et al. *NEJM* 2016;374(21):2044-2053.

Emicizumab: Factor VIII Mimetic

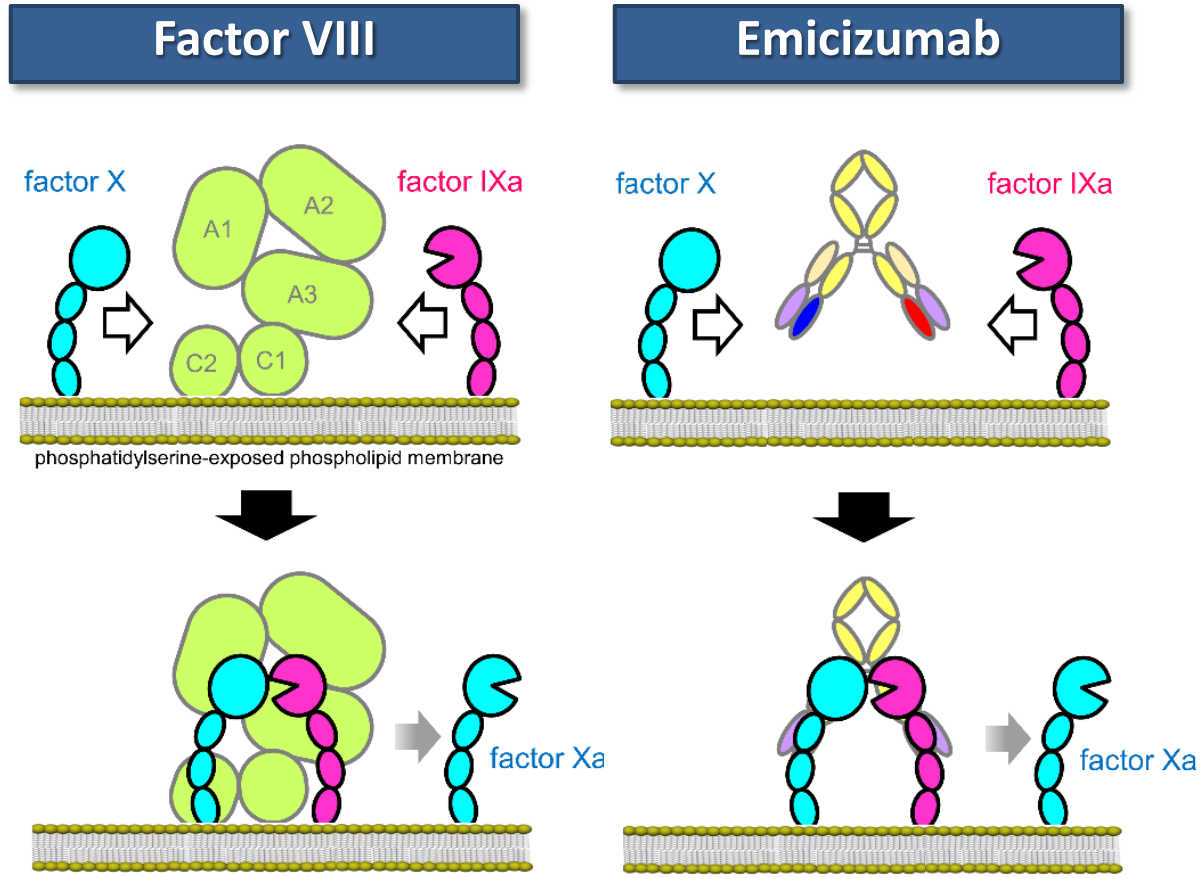
Humanized bispecific antibody

Exerts FVIII-mimetic activity

Not affected by FVIII inhibitors

Good subcutaneous absorption

Long half-life (4-5 weeks)



Shima, et al. *N Engl J Med* 2016;374(21):2044-2053.

Eradication of Inhibitor

- Inhibitors rarely remit spontaneously
  - Risk of fatal bleeding continues until FVIII antibody has been eradicated
- Need early early inhibitor eradication strategy
- Standard regimens:
  - Corticosteroids
  - Corticosteroids + cyclophosphamide
  - Rituximab

Collins P, et al. *BMC Res Notes*. 2010;3:161.

Immunosuppression: Steroid ± Cyclophosphamide

- Prednisone[1]
  - 1 mg/kg, effective in ~ 30% of patients

- Cyclophosphamide + prednisone[2,3]
  - Cyclophosphamide 50-100 mg/day po increases response rate to ~60%-70%
  - Most patients respond within 3-6 weeks, but some take longer (months) and may relapse with medication taper

1. Green D, et al. *Thromb Haemost*. 1993;70:753-757. 2. Hay RM, et al. *Br J Haematol*. 2006;133:591-605. 3. Ma AD, Carrizosa D. *Hematol Educ Program*. 2006:432-437.

Rituximab

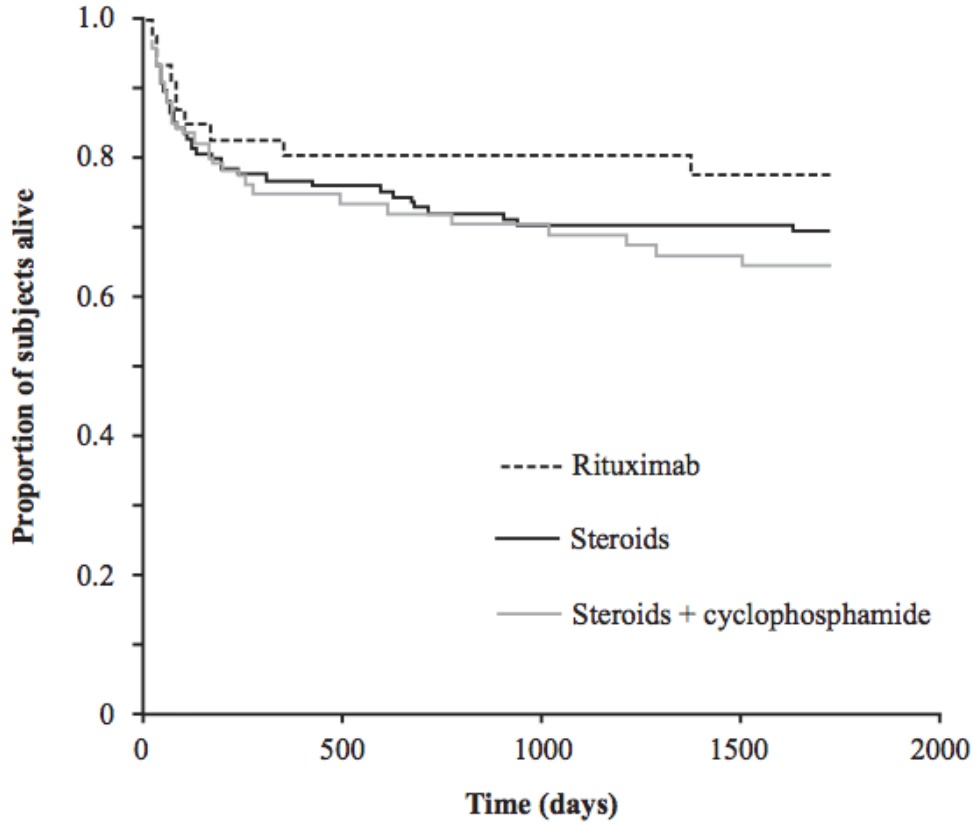
- EACH2 registry[1,2]
  - 59% of patients treated with first-line rituximab achieved sustained eradication
    - Rituximab monotherapy: 42% response rate
    - Rituximab + other agent: 64% response rate
  - Adverse event rate: 37%

- Consensus: rituximab should be used in patients intolerant of standard immunosuppression or resistant to first-line therapy

1. Franchini M, Mannucci PM. *Br J Haematol*. 2014;165(5):600-608. 1. Collins P, et al. *Blood*. 2012;120(1):47-55.

Immunosuppression Outcomes: EACH2 Registry

- Survival by first-line immunosuppression



Collins P, et al. *Blood*. 2012;120(1):47-55.

Other Acquired Clotting Factor Deficiencies

- Acquired VWD
  - Associated with essential thrombocythemia (platelet counts > 1 million)
  - Rarely associated with monoclonal gammopathy

- Acquired FX deficiency
  - Associated with amyloidosis – presumed due to adsorption

Summary

- Keys to survival
  - Immediate and appropriate lab testing
    - Mixing study
    - FVIII level
    - FVIII inhibitor level
  - Immediate and appropriate tx of bleeding
    - Pharmacy must be able to provide adequate supply of concentrates with minimum delay
    - If using porcine FVIII important to obtain immediate FVIII levels, and monitor frequently
- Acute management should be done at a specialized hemophilia treatment center
- Bleeding may be initially controlled by dose of porcine FVIII or bypassing agent (rVIIa) before transfer

Summary

- AH is a rare autoimmune disease with high morbidity and mortality
- Suspect the diagnosis in patient with bleeding, isolated prolonged aPTT
- rFVIIa and aPCC are effective
  - but are not replacing what is missing
  - can’t monitor levels
  - carry risk of thrombosis
- Porcine FVIII effective and safe; but need to monitor FVIII levels
- Emicizumab effective at preventing bleeds
- Steroids +/- cyclophosphamide good first-line IST
  - Rituximab (1L or 2L)
- Beware of thrombosis in a high-risk population
- Inhibitors can recur – patients need close monitoring