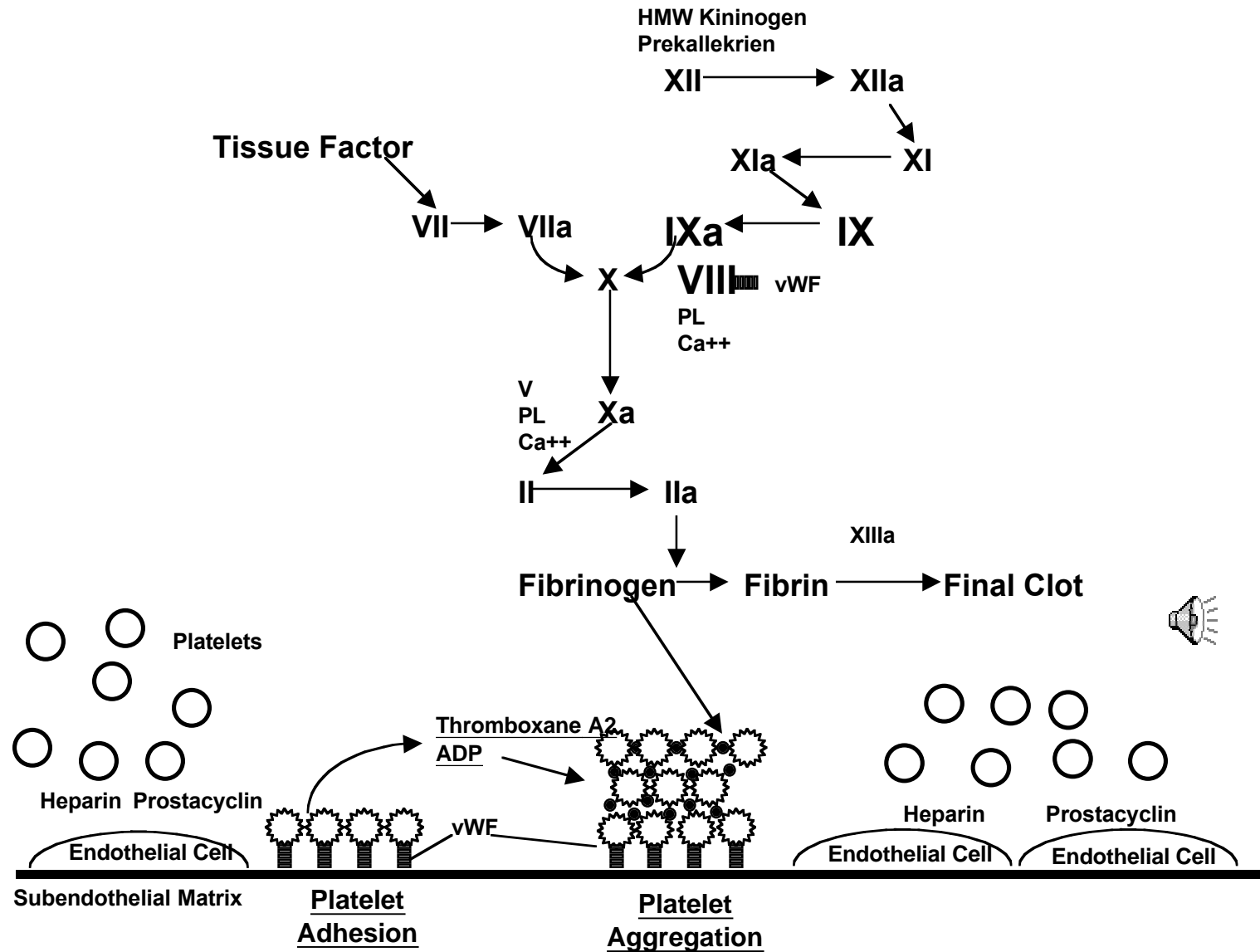


Inhibitors in Hemophilia

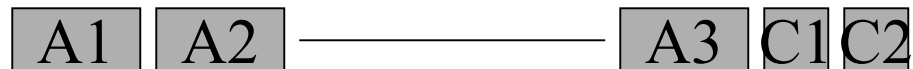
- What?
- Who?
- When?
- What to do?





What Are Factor Inhibitors

- IgG antibody
- Specificity
 - A2 Domain
 - C2 Domain
 - Multiple domains
- Immunology
 - T Cell driven
 - IgG 4 antibody
- Proteolytic activity

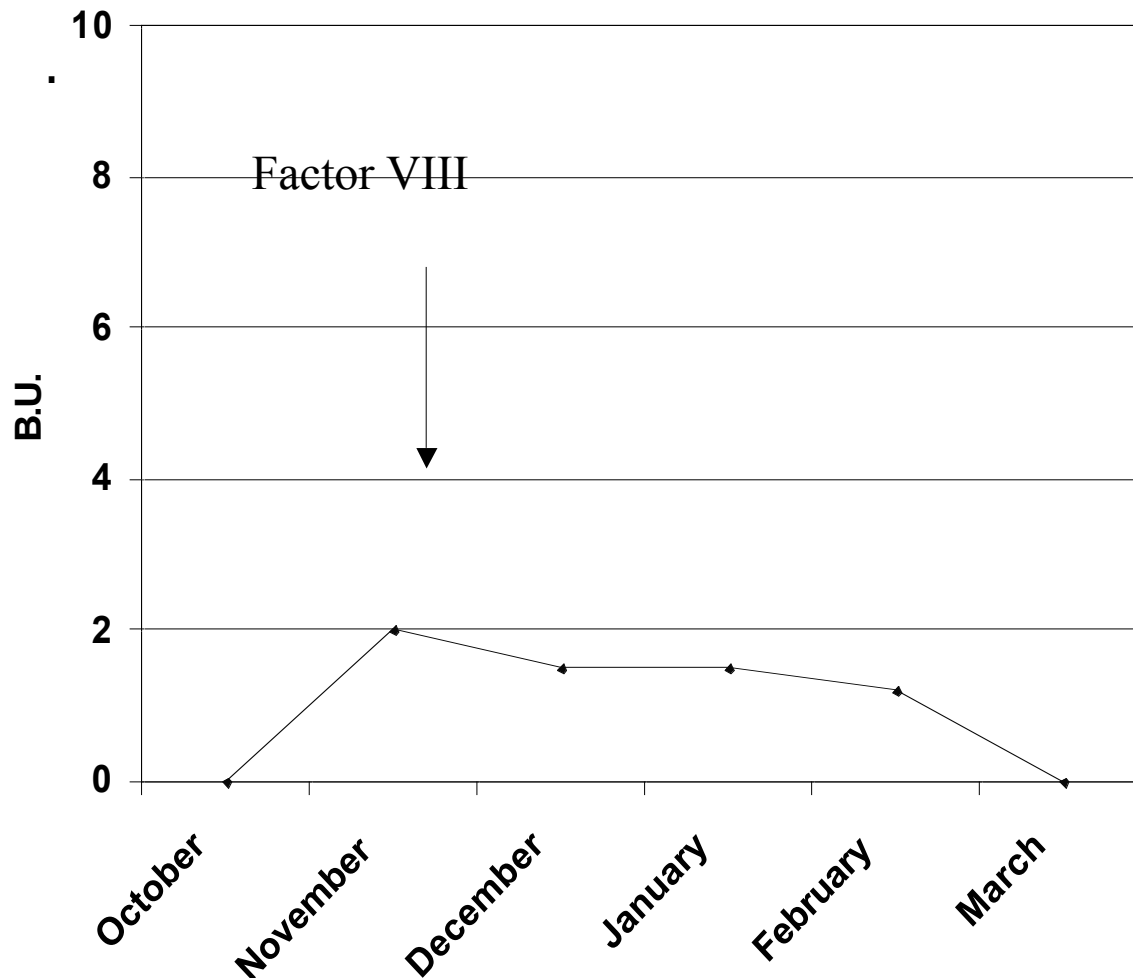


Diagnosis of Factor Inhibitors

- Decreased recovery and/or shortened half-life
- Plasma mixing studies
- Bethesda unit assay
 - 1 BU inactivates 50% of 1 unit of added FVIII in 2 hours
- Nijmegen assay
- Oxford assay



3 year old with moderate factor VIII deficiency (baseline factor VIII of 2 u/dL) develops an increased frequency of bleeding. Factor VIII level now <1 u/dL. Factor VIII 50 u/kg initiated with resolution of bleeding symptoms

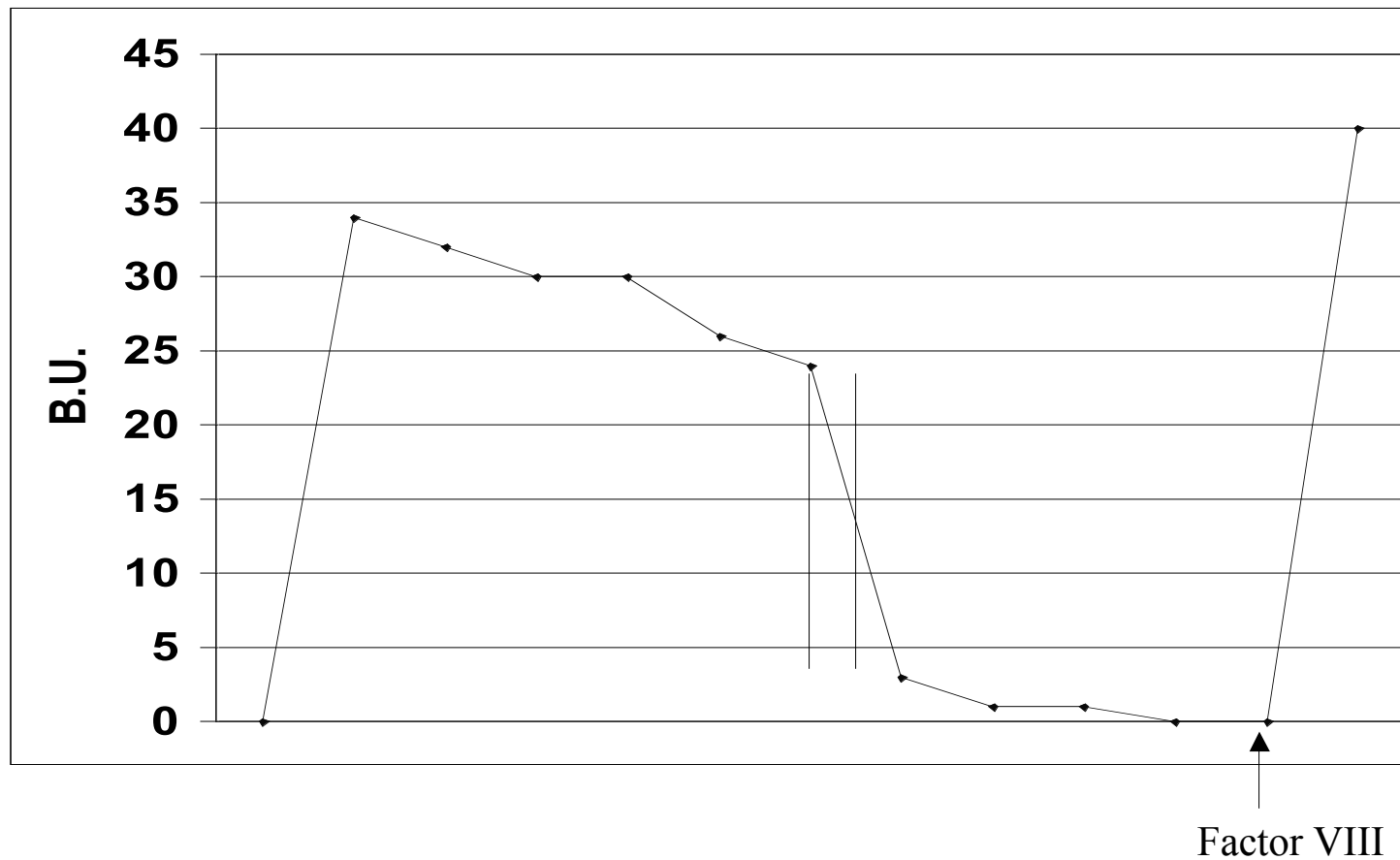


Low Titre/Responder Inhibitors

- < 5-10 Bethesda units
- Can be overcome with increased factor infusion
- Often transient
- Do not increase in response to factor infusions



2 y.o. with post-traumatic intracranial hemorrhage.
Found to have severe factor VIII deficiency. Treated
with 14 days continuous infusion recombinant factor
VIII.



High Titre/Responder Inhibitors

- Exceeds 5-10 Bethesda units
- Usually cannot be overcome by increased factor dosing.
- Often decrease over time without factor VIII exposure
- Anamnesis



Acquired Inhibitors

Factor VIII inhibitors in people with normal baseline factor VIII levels

No disorder	46%
Auto-immune disease	18%
Postpartum state	7%
Malignancy	7%
Drug reactions	5%
Dermatologic disorders	5%
Other	12%



Hultin, Am J Med, 1991



Epidemiology of Inhibitors

- Incidence affected by study design
 - Retrospective
 - Prospective
- Occur early
- Much more prevalent in factor VIII deficiency



Factor VIII Inhibitor Prevalence

	Total patients	Total Inhibitor	<10 BU	>10 BU
Ehrenkrantz	46	15	20%	80%
Bray	75	17	71%	29%
Lusher	81	16	56%	44%
Rothschild	28	14	71%	29%
Addiego	89	25	16%	84%
Lusher	39	7	14%	86%



Factor VIII Inhibitors by Severity

	Mild	Moderate	Severe
Lusher	0% (0/17)	13% (2/15)	29% (14/49)
Ehrenkrantz		5% (1/15)	52% (14/27)



Epidemiology of Factor VIII Inhibitors

Other Reported Risk Factors

Race

Family history

Gene deletion

Factor product utilized



Epidemiology of Factor IX Inhibitors

- 3-4% of all patients
- 1/3 low titre



Timing of Factor VIII Inhibitor *Exposure Days*

	Median	Range
Lusher	9	3-18
Bray		3-45
Addiego	9	<30
Ehrenkrantz	11	4-195
Rothschild	17	3-69



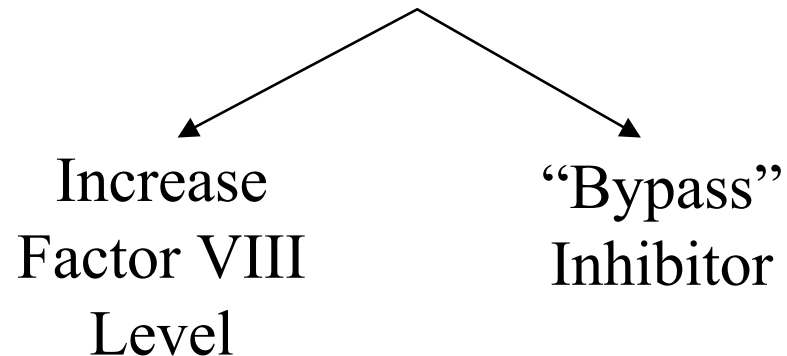
Complications of Inhibitors

- Lack of response to standard factor treatments
- Frequency of bleeding
- Increased morbidity and mortality from bleeding
- Increased medical interventions
- Increased cost of care
- Factor IX inhibitors
 - Anaphylaxis
 - Nephrotic syndrome



Management of Factor VIII Inhibitors

- Acute bleeding events



- Specific inhibitor management



Acute Bleeding Events in Low Titre Patients

Increase Factor VIII

Increased dosage

Increased frequency

Continuous infusion

Porcine



Acute Bleeding Events in High Titre Patients

Bypassing agents

Prothrombin complex concentrates

Konyne, Profilnine

Activated prothrombin complex concentrates

FEIBA, Autoplex

Recombinant VIIa

Novo-seven



Prothrombin Complex Concentrates

Effectiveness

PCC's better than placebo

Activated PCC's possibly better than PCC's



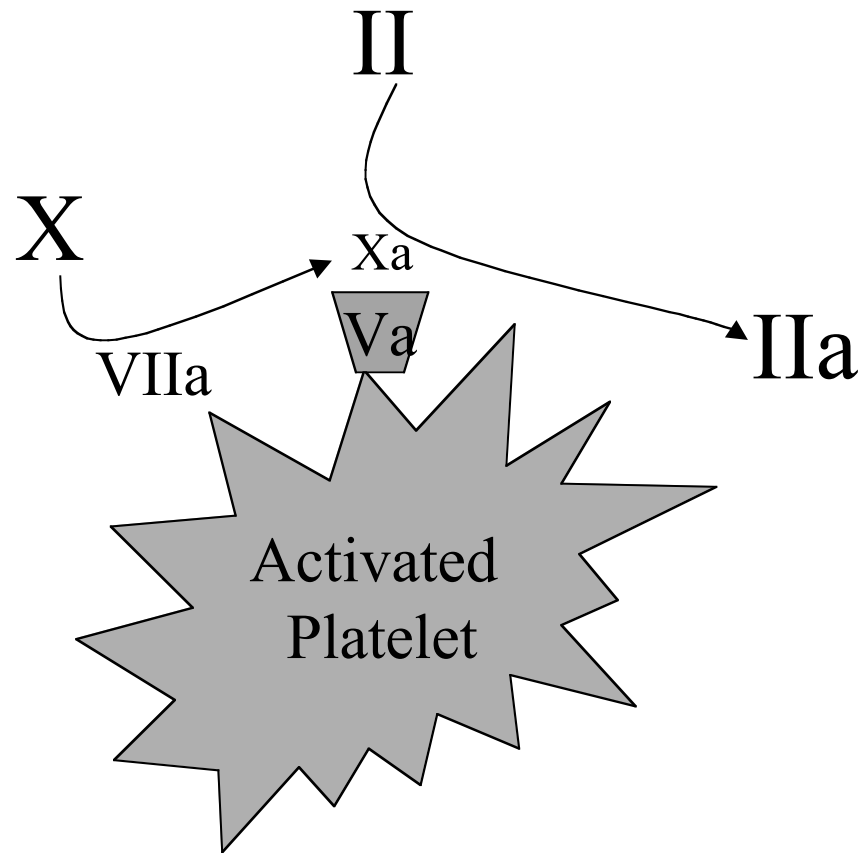
Prothrombin Complex Concentrates

Issues

- Thrombosis
 - Factor IX deficiency
 - High dosage
 - Repetitive infusions
- Inability to document laboratory response
- Plasma derived blood product
- Cost
- Anamnesis



Recombinant VIIa



Recombinant Factor VIIa

Effectiveness

Response

Intracranial Hemorrhage

89%

Surgery

Low dose (35 ug/kg)

80%

High dose (90 ug/kg)

100%

Home

72%-92%



Recombinant Factor VIIa

Potential Advantages

- Recombinant product
- Possibly less thrombogenic than APCCs
- No anamnesis



Recombinant Factor VIIa

Issues

- No objective laboratory monitor of effectiveness
- Cost
- Thrombosis
- Short half-life
- Uncertain optimal dosage



Porcine factor VIII

- Highly purified porcine factor VIII-vWF
- Human factor VIII inhibitors not all cross reactive
- Porcine inhibitor titres available



Porcine Factor VIII

Advantages

- More physiologic mechanism of action
- Measurable factor VIII response
- Documented clinical efficacy
- Lack of transmitted infection



Porcine Factor VIII

Issues

- Reactions

 - Development of anti-porcine antibody

 - Allergic reactions

 - Thrombocytopenia

 - Phlebitis

- Cost

- Availability



Treatment Recommendations

Low Responding Inhibitors

- Aim to increase factor VIII levels in low responding patients
 - Factor VIII
 - Porcine
 - Desmopressin



Treatment Recommendations

High Responding Inhibitors

Non-life threatening
bleeds

Bypass agents

PCC or APCC

Recombinant

VIIa

Life threatening bleeds

Aim for factor VIII
level

High dose factor
VIII

Porcine factor VIII

Immunoabsorption

Recombinant VIIa

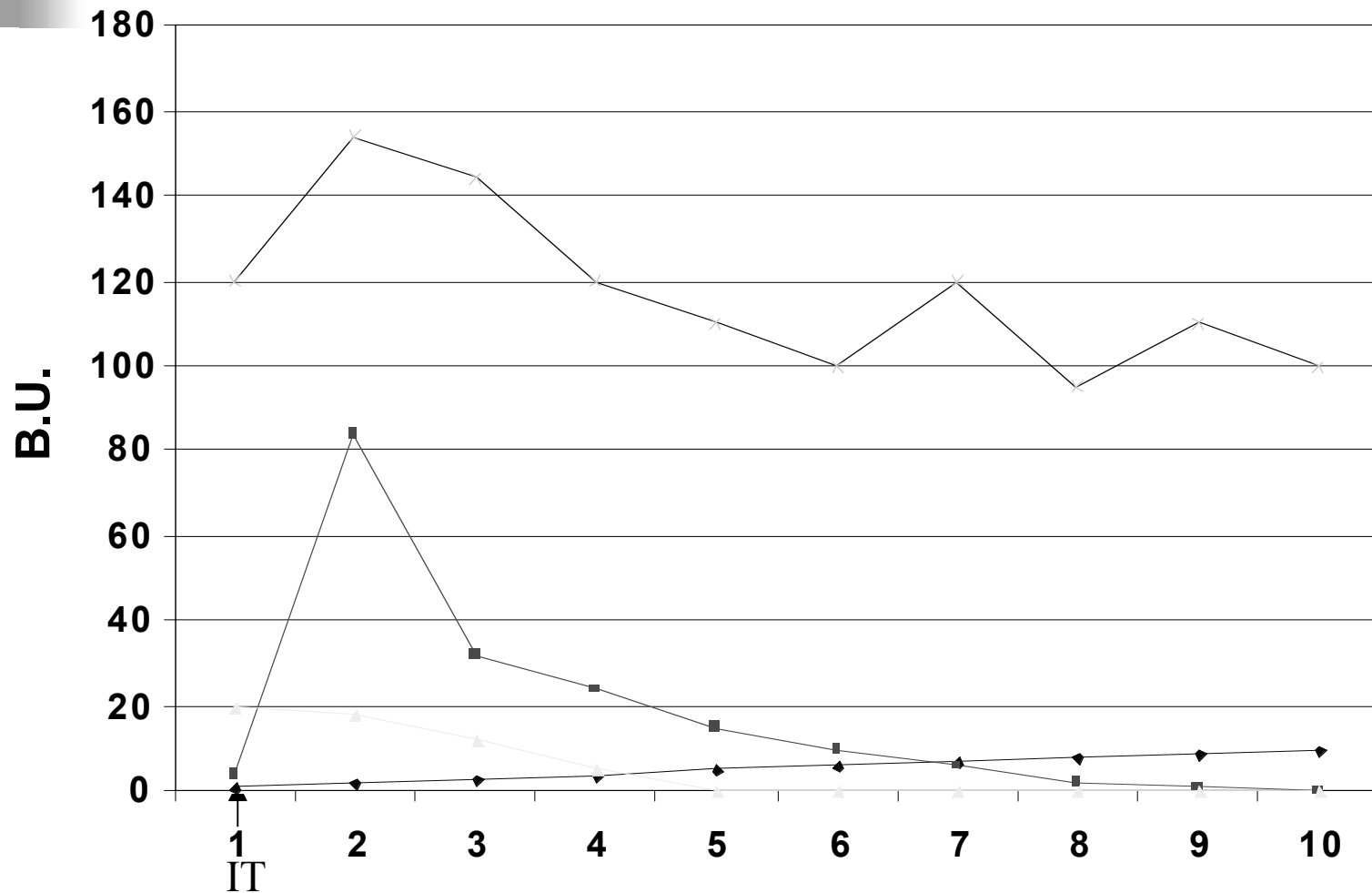


Immune Tolerance

- Repetitive infusions of factor VIII
- Definition of success varies
 - Absence of measurable factor VIII inhibitor
 - Normal factor VIII recovery
 - Normal factor VIII half-life



Immune Tolerance



Immune Tolerance Protocols

Protocol	Dosage (u/kg)	Frequency	Other	Results
Bonn	100-150	BID	FEIBA	76%
Malmo			Cyclophosphamide, IVIG, Immunodisorption, Factor VIII	82%
Ewing	50	daily		75%
Gruppo	50-100	weekly		63%
van Crevald	25	q.o.d.		88%



Immune Tolerance

Prognostic Factors

Peak inhibitor titre

Inhibitor titre at outset of IT

Other

Age

Dosage

Interruption of IT

Interval between onset of inhibitor and IT



Cost

IT

No IT

Factor

Complications

Central venous
catheter

Hospitalizations

High cost treatments

Lab monitoring

Morbidity

Clinical management

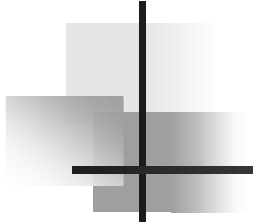
Nursing



Conclusion

- Inhibitors Happen!
- Multiple treatment options





Return to Main
Menu