

Treatment of Factor VIII Inhibitors In and Outside of Hemophilia

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Definition of FVIII Inhibitor

An antibody that neutralizes the function clotting factor VIII

In hemophilia, the development of an inhibitor reduces the response to factor concentrates

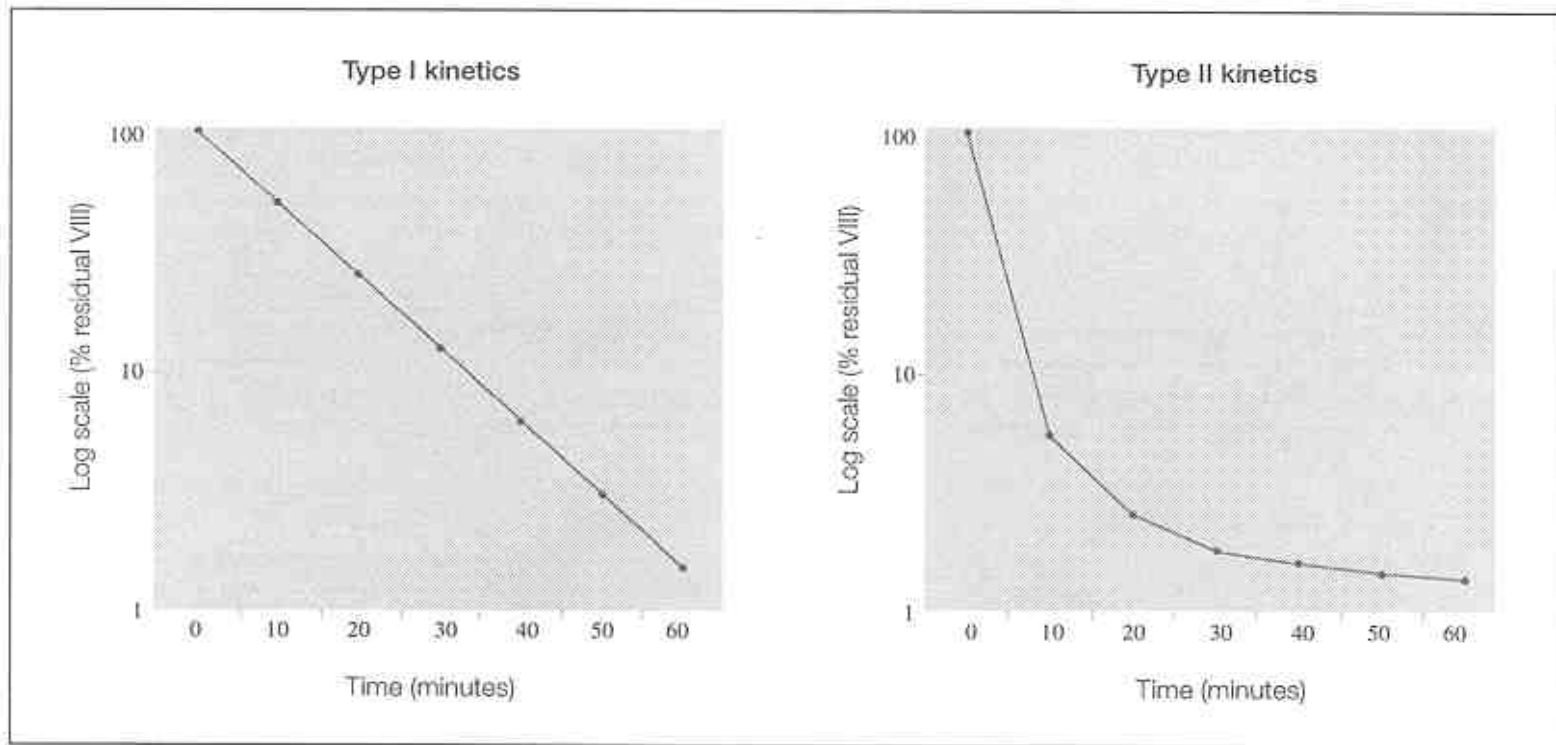
- Frequency of bleeds does not increase
- Response to therapy is dramatically reduced

In spontaneous inhibitor patients, the development is associated with unprovoked hemorrhage

- Skin, muscle, soft tissue bleeds

FVIII Inhibitors Inactivate FVIII

Figure 2: Kinetics of antibody inactivation of factor VIII.



Inhibition Kinetics According to Type of Antibody

Alloantibodies (ie. in hemophilia) exhibit Type I kinetics

Can be overwhelmed if at low titer

Autoantibodies (ie. spontaneous) exhibit Type II kinetics

Are not easily overwhelmed by factor concentrates

Laboratory Hallmark is Non-correction the Incubated 1:1 Mix

Table 1
APTT at 37°C with various incubation mixtures

Incubation mixture	15 minutes	30 minutes	1 hour	2 hours
Normal plasma alone	32	32	36	40
Normal plasma plus				
Factor VIII-deficient plasma	37	37	41	45
<i>Weak inhibitor (1 BU)</i>	37	38	45	53
<i>Moderate inhibitor (5 BU)</i>	43	47	55	64
<i>Strong inhibitor (20 BU)</i>	54	61	77	92

Adapted from Kasper (25)

Inhibitor Strength

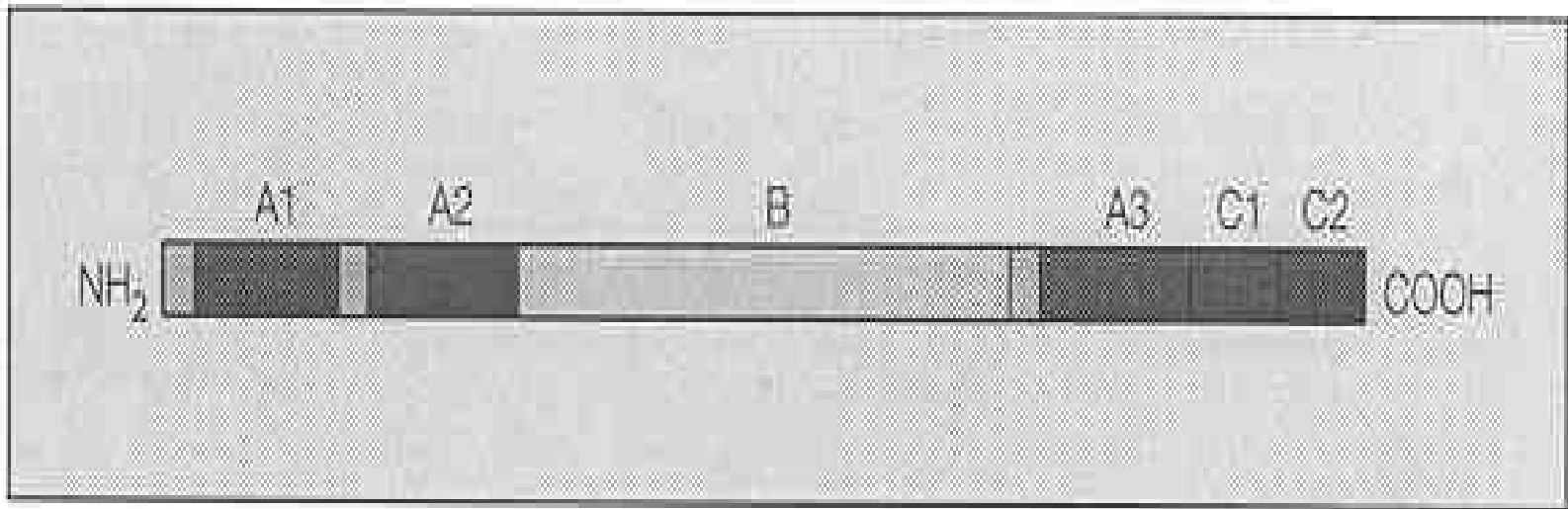
The Bethesda Unit

Factor VIII assays are done on 2-hour incubation mixtures of various dilutions of the patient's plasma with normal pooled plasma.

A test sample producing a residual Factor VIII activity of 50% of normal is considered to contain 1 Bethesda unit of inhibitor per milliliter.

The inhibitor titer equals the reciprocal of the dilution of inhibitor plasma that neutralizes 50% of normal Factor VIII.

Pathophysiology - It Starts with the Factor VIII Molecule



Activated Factor VIII Lacks the B-Domain

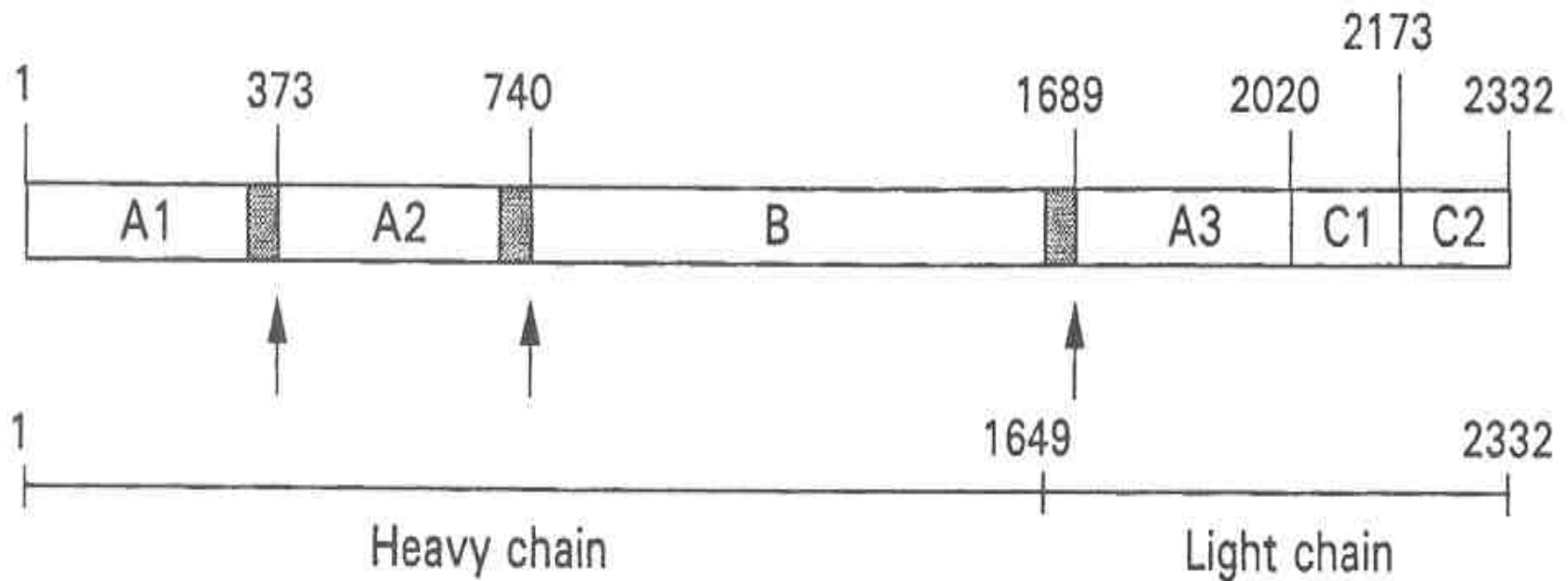
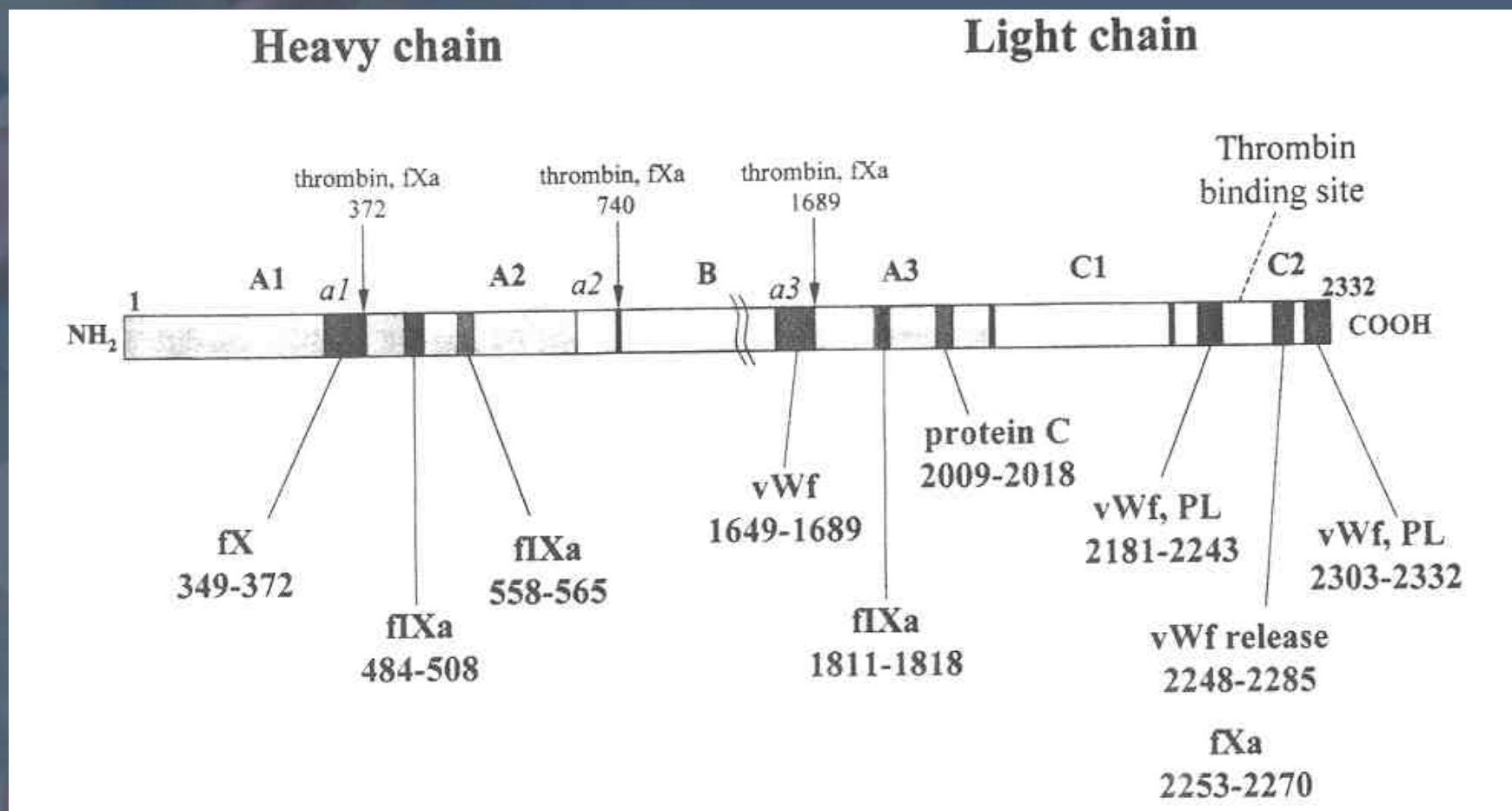


Figure 1 Domain structure of FVIII. The amino acid number at the beginning and end of each domain is the bar with black dots. The arrows show sites at which FVIII is cleaved by thrombin. The structure of the unactivated FVIII is shown in the bottom line. The single cleavage site is produced intracellularly prior to FVIII secretion.

Factor VIII Must Bind to Multiple Enzymes, Proteins and Surfaces



Mechanism of FVIII Inhibition Varies By Antibody Epitope Specificity

Table 1 Epitopes of Inhibitor Antibodies and Mechanisms of Antibody Inhibition

Inhibitor Epitope Domain	Amino Acid Composition of Epitope	Antibody Inhibition of FVIII Binding to These Ligands
Acidic Region A1	329–379	Factor X
C2	2253–2270	Factor X
A2	484–508	Factor IX
A3	1804–1819	Factor IX
C2	2303–2332	Phospholipid
C2	2181–2243	Phospholipid, vWF
C2	2248–2312	Phospholipid, vWF
C2	2170–2327	Phospholipid, vWF
C2	2218–2307	Slowed vWF Release



Inhibitors in Hemophilia

Inhibitors in Hemophilia A

Alloantibodies stimulated by exposure to exogenous factor concentrate

Incidence of in severe Hemophilia A reported as high as 20-25%

Inhibitors much less common (1.5-3%) in Hemophilia B

FVIII Inhibitors in Hemophilia

Low Titer Inhibitors (LTI) $\equiv \leq 5$ BU/ml

High Titer Inhibitors (HTI) $\equiv > 5$ BU/ml

Low-Responder - demonstrate minimal or no increase in inhibitor titer following factor concentrate administration

High-Responder - exhibit high levels of inhibitors (> 5 BU/ml) following factor usage

Treatment of FVIII Inhibitors

Short Term - Temporary measures to Stop Bleeding

High level VIII replacement

Porcine Factor VIII

Bypassing Agents - FEIBA, AUTOPLEX, rFVIIa

Plasmapheresis

Long Term - Eradication of the Inhibitor

Immune tolerance induction therapy (in Hemophilia)

Immune suppression - steroids, CTX, IVIG

Plasmapheresis and Extracorporeal columns

Treatment of Bleeding in Hemophilia A with Inhibitor

Treatment *depends on inhibitor strength* and type of bleeding

Non-Life-Threatening Hemorrhage

Low titer - high dose human FVIII (100 - 200 U/kg)

or - porcine VIII (100 to 400 U/kg)

High titer - Activated prothrombin complex concentrate

FEIBA, Autoplex (70-75 U/kg q 8 to 12 hrs)

or - recombinant FVIIa (70-100 $\mu\text{g}/\text{kg}$ q 2 hrs)

Other - High dose IVIG plus FVIII, plasmapheresis,
immunoabsorption of FVIII inhibitors

Treatment of Bleeding in Hemophilia A with Inhibitor

Life-threatening CNS hemorrhage in plasma-naïve patients - treat with recombinant FVIIa

Home Therapy - aPCCs because of longer half-life unless patient is plasma-naïve

Prophylaxis with aPCCs has not been proven to be of benefit

Combined use of aPCCs and antifibrinolytics is not recommended due to increased thrombotic risk

Plasma Clearance of rFVIIa Is Twice as Fast in Children

Table 1. Pharmacokinetics of NovoSeven in Six Hemophilic Children Compared to Previously Measured Adult Values

	Mean Clearance (mL/h/kg)	Mean Residence Time (h)	Plasma Half-Life (h)
Children (mean age, 8 yr; range, 5-12)	67.0	1.94	1.32
Adults	32.8	3.33	2.72

Based on data from Hedner et al.⁹

Although Numbers Are Small, There Is Increasing Evidence That High Dose rFVIIa Maybe Be Better

Table 2. Response to Various NovoSeven Treatment Protocols in Hemophilia Patients Undergoing Surgical Intervention or Treatment for Bleeding Events

Type of Case	Protocol*	N	Median Dose NovoSeven ($\mu\text{g}/\text{kg}$)	Response (%)
Surgical	II	10	1074	100
	I	2	2940	100
Major bleeds	I	8	1746	65
Hemarthrosis	I	57	270	70
	II	72	360	72
	III	29	300	82

* Protocol I (standard-dose CI): 90 $\mu\text{g}/\text{kg}$ bolus followed by 14-16 $\mu\text{g}/\text{kg}$ CI for 2 days, and a clearance-adjusted rate thereafter to maintain FVII:C trough levels > 10 IU/mL; protocol II (high-dose CI): 180 $\mu\text{g}/\text{kg}$ bolus followed by 30 $\mu\text{g}/\text{kg}$ CI to maintain FVII:C trough levels > 20 IU/mL; protocol III: single high-dose (300 $\mu\text{g}/\text{kg}$) bolus.

Data from Kenet et al.¹³

Treatment to Produce Sustained Elimination of the Inhibitor

Immune tolerance therapy

Bonn protocol - High dose VIII plus aPCC

Induces immunotolerance in 87-91%

Malmo protocol - immunoadsorption of inhibitors prior to infusion of FVIII with IVIG and cytoxan

Induces immunotolerance in 62%

Main determinant of success - low titer inhibitor at start of treatment

PUP Study of Inhibitor Development with Concentrate Use

Table 1 Severity of Hemophilia and Type of Concentrate Used

	Number of Treated Patients	Number of Patients Treated with pd Concentrate	Number of Patients Treated with r Concentrate
FVIII residual activity <1%	46	35 (69%)	11 (52%)
FVIII residual activity 1-5%	26	16 (31%)	10 (48%)
Total	72	51 (100%)	21 (100%)

Incidence Greater in Severe Hemophilia (Both PD and r)

Table 2 Frequency of Inhibitor Development Dependent on Severity of Hemophilia and Type of Concentrate

	Patients Total/Inhibitors [n/n, %]	Patients pd/Inhibitors [n/n, %]	Patients r/Inhibitors [n/n, %]
FVIII residual activity < 1%	46/20 (43%)	35/16 (46%)	11/4 (36%)
FVIII residual activity 1–5%	26/2 (8%)	16/2 (13%)	10/0 (0%)
Total	72/22 (31%)	51/18 (35%)	21/4 (19%)

Inhibitors Develop with PD and R-Concentrates - Do Not Differ as to Responder Status

Table 3 Distribution of High and Low Responders in Patient Groups Treated with pd and rFVIII Concentrates

	LR/HR/Inhibitors Total [n/n, %]	LR/HR/ Inhibitors pd [n/n, %]	LR/HR/ Patient r [n/n, %]
Low responders (0.6–5 BU)	5/22 (23%)	5/18 (28%)	0/4
High responders (>5 BU)	17/22 (77%)	13/18 (72%)	4/4 (100%)
Inhibitors total	22	18	4

Most High Responder Inhibitors Occur in Severe Patients (Do not differ PD vs r)

Table 4 Frequency of Development of High Responding Inhibitors Dependent on Severity of Hemophilia and Type of Concentrate Used

	Patients Total/HR [n/n, %]	Patients Total/LR [n/n, %]	Patients pd/HR [n/n, %]	Patients r/HR [n/n, %]
FVIII RA < 1%	46/17 (37%)	46/3 (7%)	35/13 (37%)	11/4 (36%)
FVIII RA 1-5%	26/0 (0%)	26/2 (8%)	16/0 (0%)	10/0 (0%)
Total	72/17 (27%)	72/5 (7%)	51/13 (25%)	21/4 (19%)

Mutations Causing Large Changes in the VIII Molecule Are Associated with Higher Risk of Inhibitor Formation

Table 6 Mutation Type Profile of All Patients and Frequency of Inhibitor Development Dependent on Mutation Type

Type of Mutation	Mutation/ Patients Total [n/n]	Mutation Total/Inhibitor [n/n, %]
Large deletion	0/72	0/0
Stop mutation	3 out of 72	2/3 (67%)
Intron-22-inversion	35/72	14/35 (40%)
Missense mutation	18/72	3/18 (17%)
Small deletion	5/72	2/5 (40%)
Analysis ongoing	7/72	0/7
Not found	4 out of 72	1/4

PUP Study: Mutations in Each Arm (PD vs r) Were Similar

Table 7 Distribution of High and Lower Risk Mutation Types in Patients Treated with PD and Recombinant Concentrates

	Type of Mutation	Mutation/ Patients r [n/n, %]	Patients r/Group [n/n, %]	Mutation/ Patients pd [n/n, %]	Patients pd/Group [n/n, %]
High-risk mutation group	large deletion	0/21 (0)	n = 12/21 57%	0/51(0)	n = 27/51 53%
	stop mutation	0/21 (0)		3/51(6%)	
	intron-22-inversion	12/21(57%)		24/51(47%)	
Lower-risk mutations	missense mutation	3/21(14.5%)	n = 6/21 29%	15/51(29%)	n = 16/51 31%
	small deletion	3/21(14.5%)		1/51(2%)	
Analysis ongoing		3 out of 21	n = 3	5 out of 51	n = 8/51
Not found		0/21	14%	3 out of 51	16%

In All PUP Trials to Date, the Cumulative Incidence of Inhibitors Is About 30%

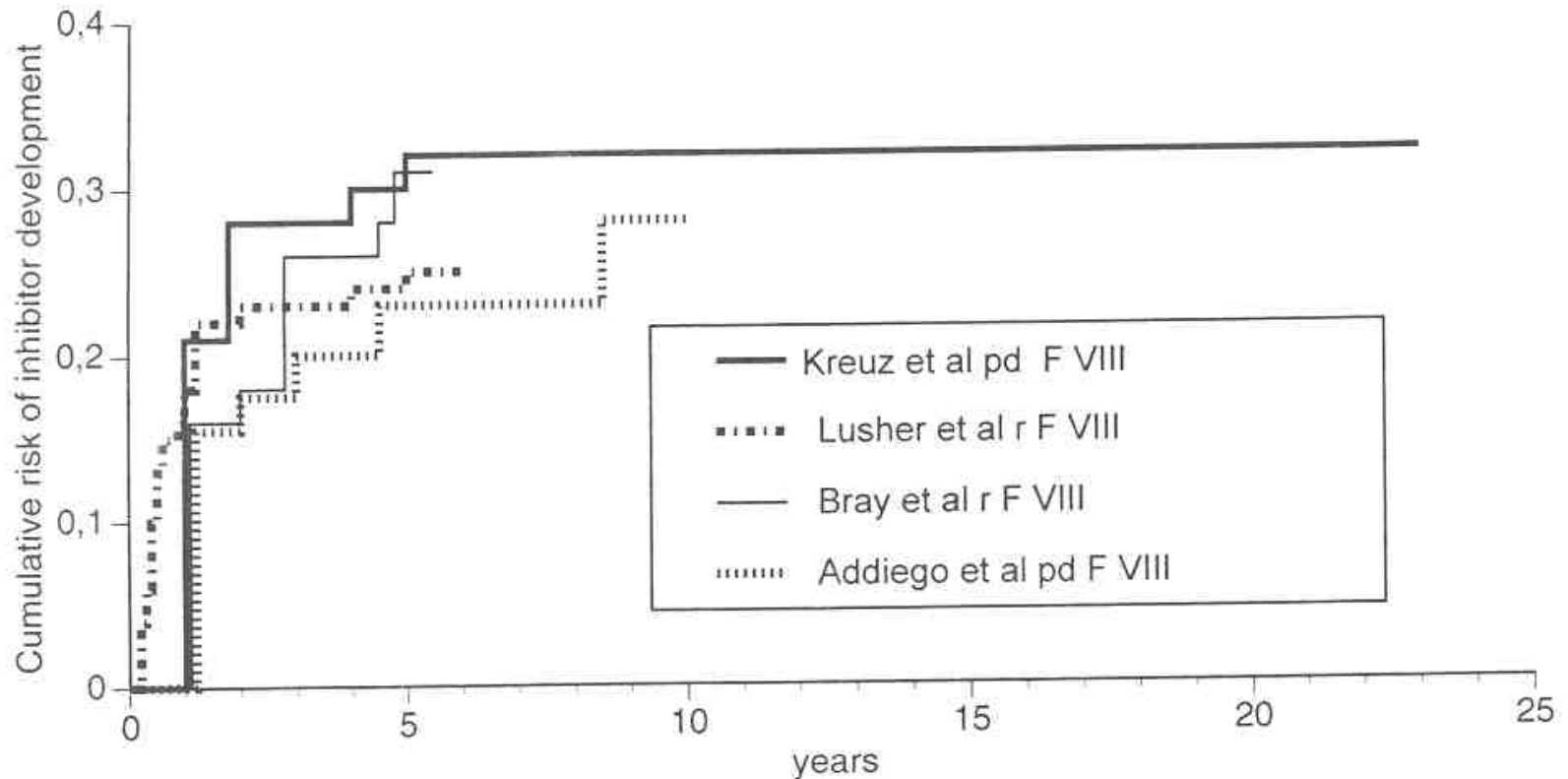


Figure 1 Cumulative risk of inhibitor development—comparison of different PUP studies.



Inhibitors Outside of Hemophilia

Acquired Hemophilia

Characteristics

Autoimmune Disease -----> Autoantibodies

Incidence 0.2-1.0 case per million per year

80-90% present with major hemorrhages

10-22% mortality attributed to inhibitor

Biphasic age distribution

Small peak in young postpartum women

Major peak in 60-80 years of age

Acquired Hemophilia

Characteristics

Most individuals are previously healthy

Some have defined or evolving autoimmune or lymphoproliferative disease

Systemic Lupus Erythematosus, Rheumatoid Arthritis

Multiple Sclerosis, Graft-vs.-Host after allogeneic BM transplant

Asthma, Inflammatory Bowel Disease, Pemphigus

Severe allergic reactions to:

antibiotics

interferon- α

BCG vaccine

FVIII Inhibitors in Postpartum Period

Rare

Usually in Primiparas

Occurs within 3 months of delivery

If low titer, generally spontaneously disappears

If >10 BU, may be resistant to all therapy

Etiology Unclear

precursor of autoimmune disease

factor produced by the placenta

FVIII Inhibitors in the Elderly

Associated with malignant lymphoproliferative disorders

Chronic Lymphocytic Leukemia

Lymphoma

Associated with solid tumors - Prostate, Lung

Part of a paraneoplastic process?

Success treatment of underlying disorder leads to disappearance of inhibitor in about 20%.

Clinical Manifestations of Spontaneous FVIII Inhibitors

Anemia due to occult bleeding

Overt bleeding

most frequently - bruising, muscle hematomas

melena and hematuria

iatrogenic - IV lines, bladder catheterization

post surgical bleeding

Acute complications - compartment syndromes, airway

compression 2nd to subglottic bleeding

Treatment of Bleeding in Factor VIII Autoantibodies

Human Factor VIII Concentrates (if < 5 BU)

Porcine Factor VIII (90 U/kg q 12 hrs) (80% effective)

Bypassing agents

Recombinant FVIIa (90 μ g/kg q 2-6 hrs) (94% effective)

FEIBA (70 U/kg q 8-12 hrs) (81% effective)

Autoplex (\geq 50 U/kg) (75-80% effective)

Side Effects of Treatment of Bleeding in Autoantibodies

Porcine VIII - Antibody formation, Thrombocytopenia, Allergic Reactions

Recombinant FVIIa - Thrombosis ($\leq 2\%$)

FEIBA and Autoplex

Thrombosis

Allergic Reactions

Low risk for transmission of infectious agents

Management of Autoantibody to Factor VIII

Immunosuppressive Medications

Prednisone 60 mg/day x 3-6 wks

Work better in low titer, new inhibitors with no associated disease

Others

Combined Rx - prednisone plus cytoxan

Cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, rituximab, interferon α ,

Induction of immune tolerance does not work

Response to Corticosteroids Is About 50% in Spontaneous FVIII Inhibitors

Reference	Percentage responding (No./total)	Time to response (weeks)
Spero <i>et al.</i> , 1981 (44)	69 (11/16)	2.5
Green & Lechner, 1981 (4)	54 (22/41)	—
Green <i>et al.</i> , 1993 (45)	37 (13/35)	3 to 9
Green, 1998 (46)	60 (6/10)	3 to 9
<i>Total</i>	<i>51 (52/102)</i>	<i>2.5 to 9</i>

Reproduced from Hong JJ and Green D (47)