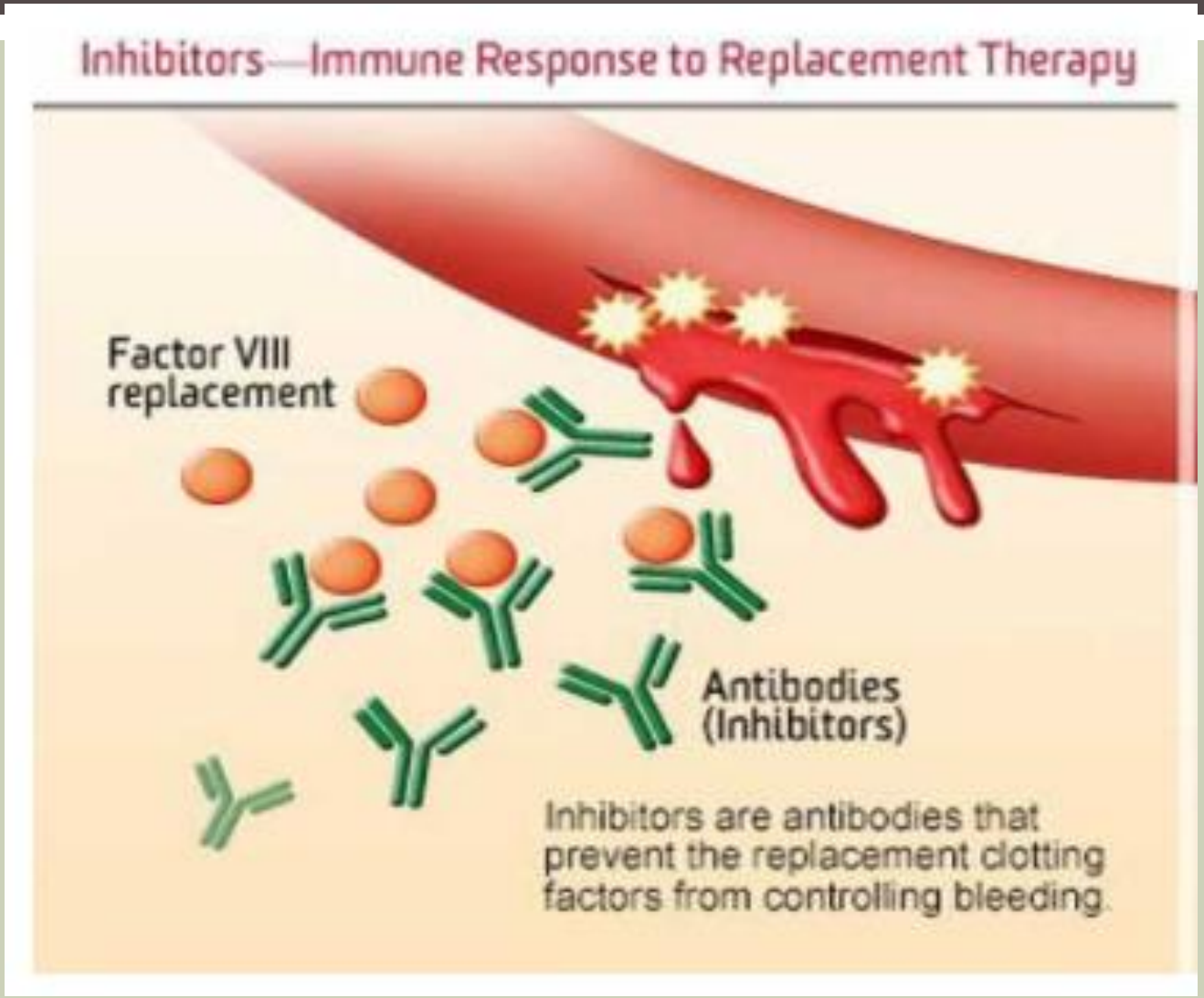
KOMPLIKASI HEMOFILIA: INHIBITOR DAN INFEKSI TERKAIT TRANSFUSI

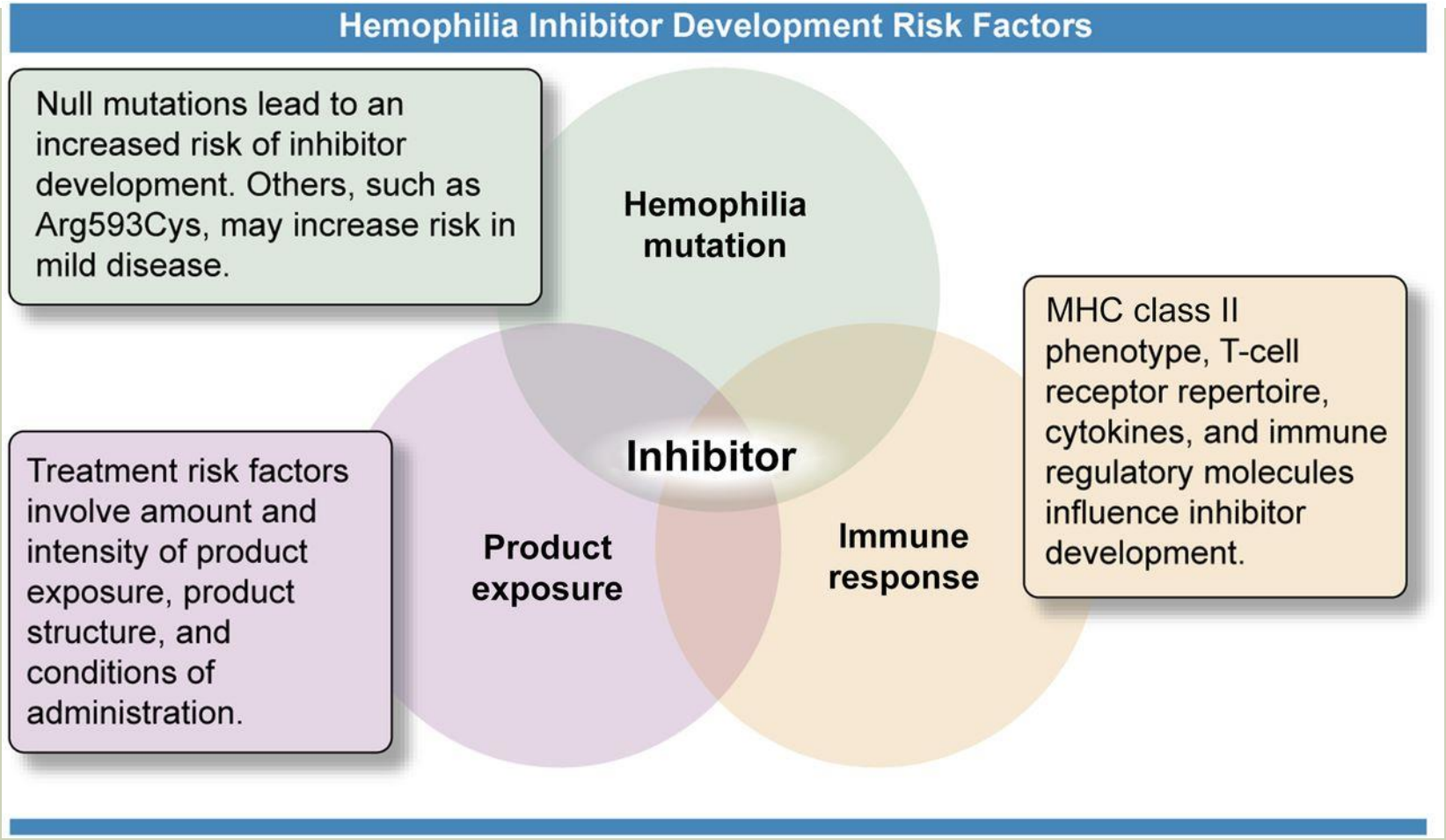
BANJARMASIN

Findy Prasetyawaty

INHIBITOR


Inhibitors—Immune Response to Replacement Therapy
Factor VIII replacement
Antibodies (Inhibitors)
Inhibitors are antibodies that prevent the replacement clotting factors from controlling bleeding.

FAKTOR RISIKO

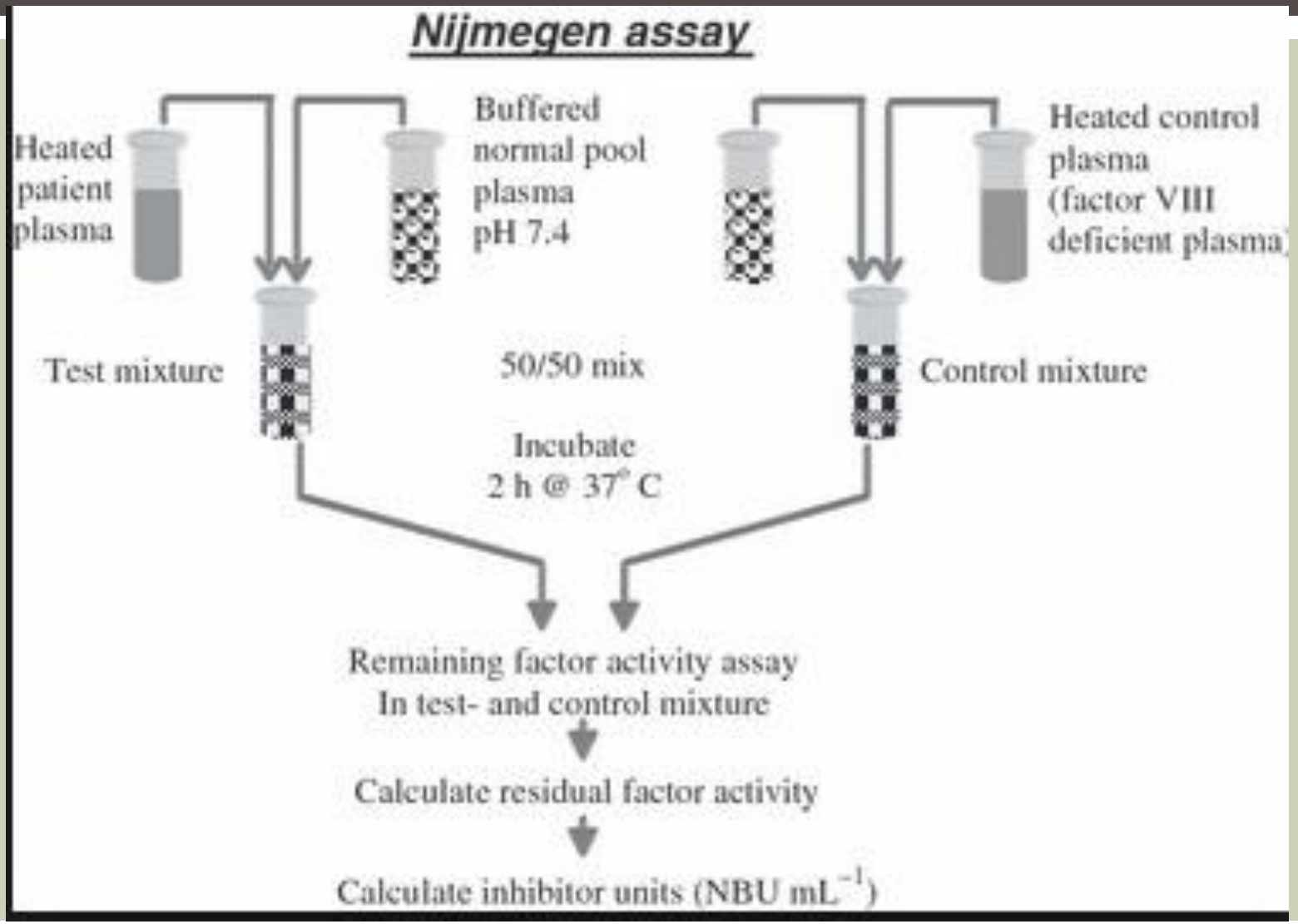


Connie H. Miller Blood 2015;126:829-830

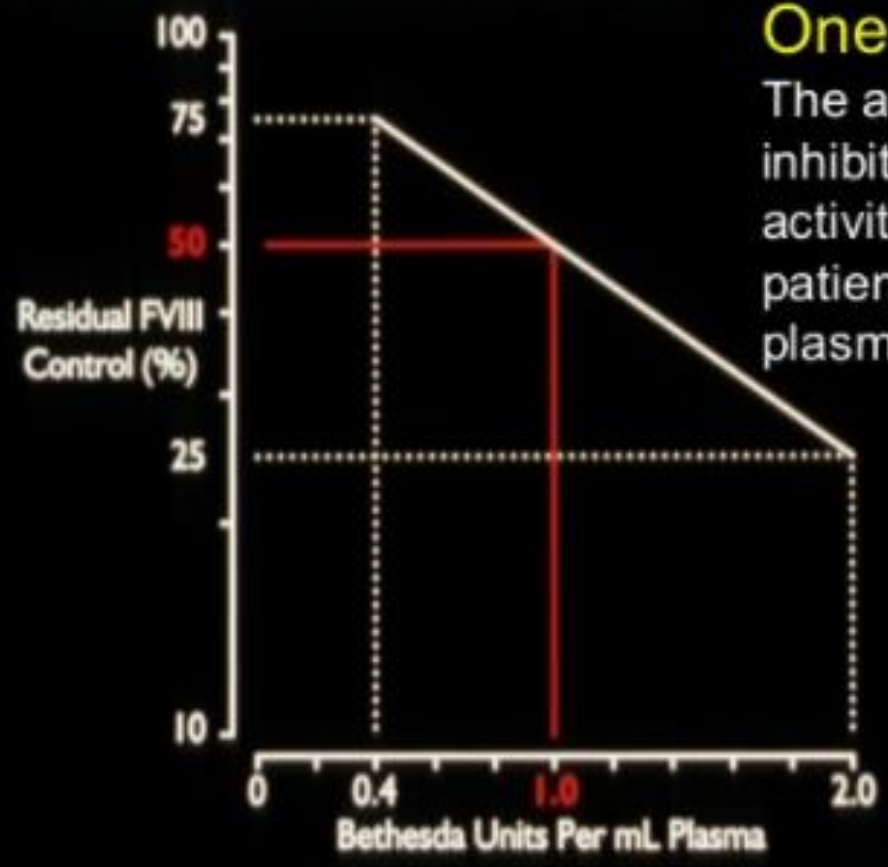
INSIDENS

- Hemofilia A: 20-33%
- Hemofilia B: 1-6%
- Mayoritas pembentukan inhibitor terjadi dalam 50 hari setelah pajanan

CARA PEMERIKSAAN



THE BETHESDA UNIT

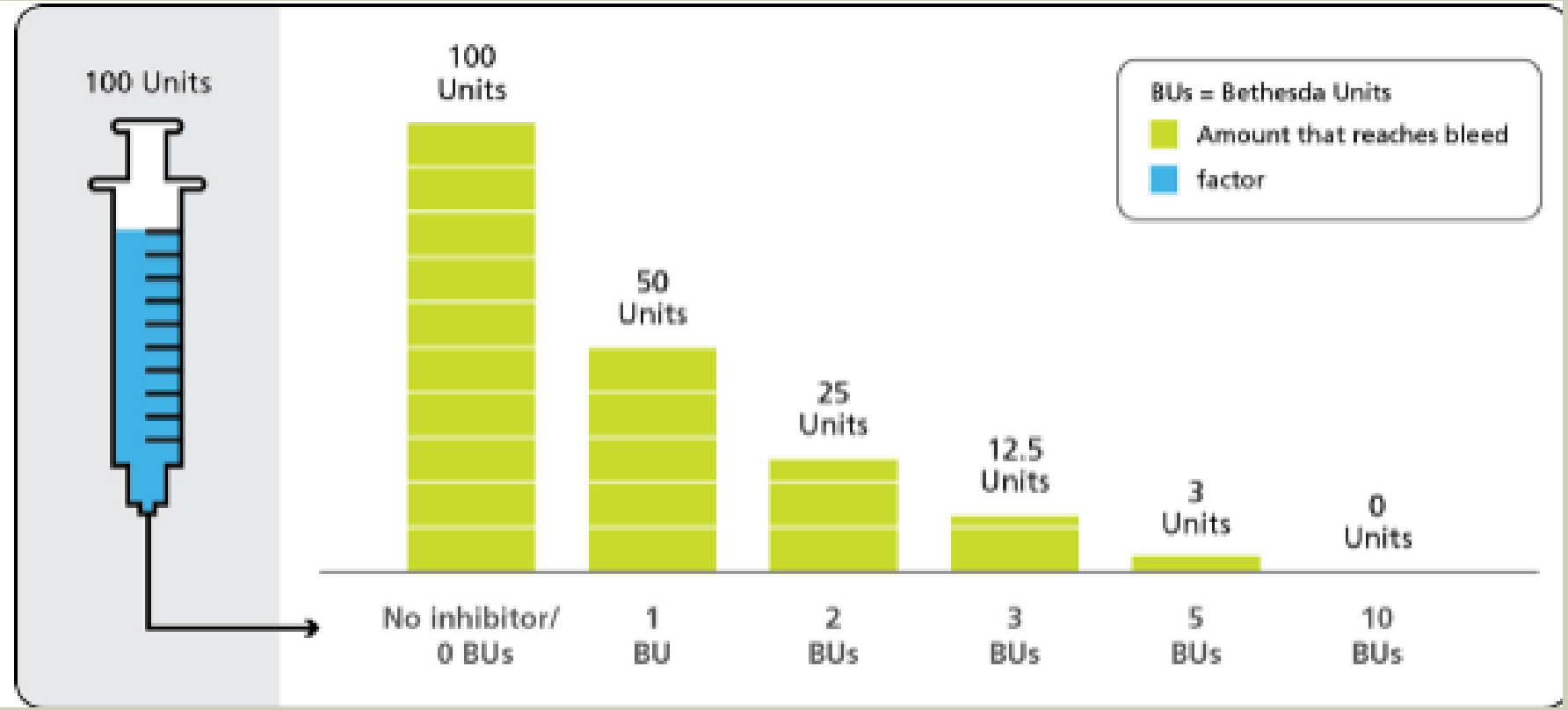


One Bethesda Unit:

The amount of antibody that inhibits half of the factor VIII activity in a 1 to 1 mixture of patient plasma and normal plasma incubated at 37°C for 2 hours

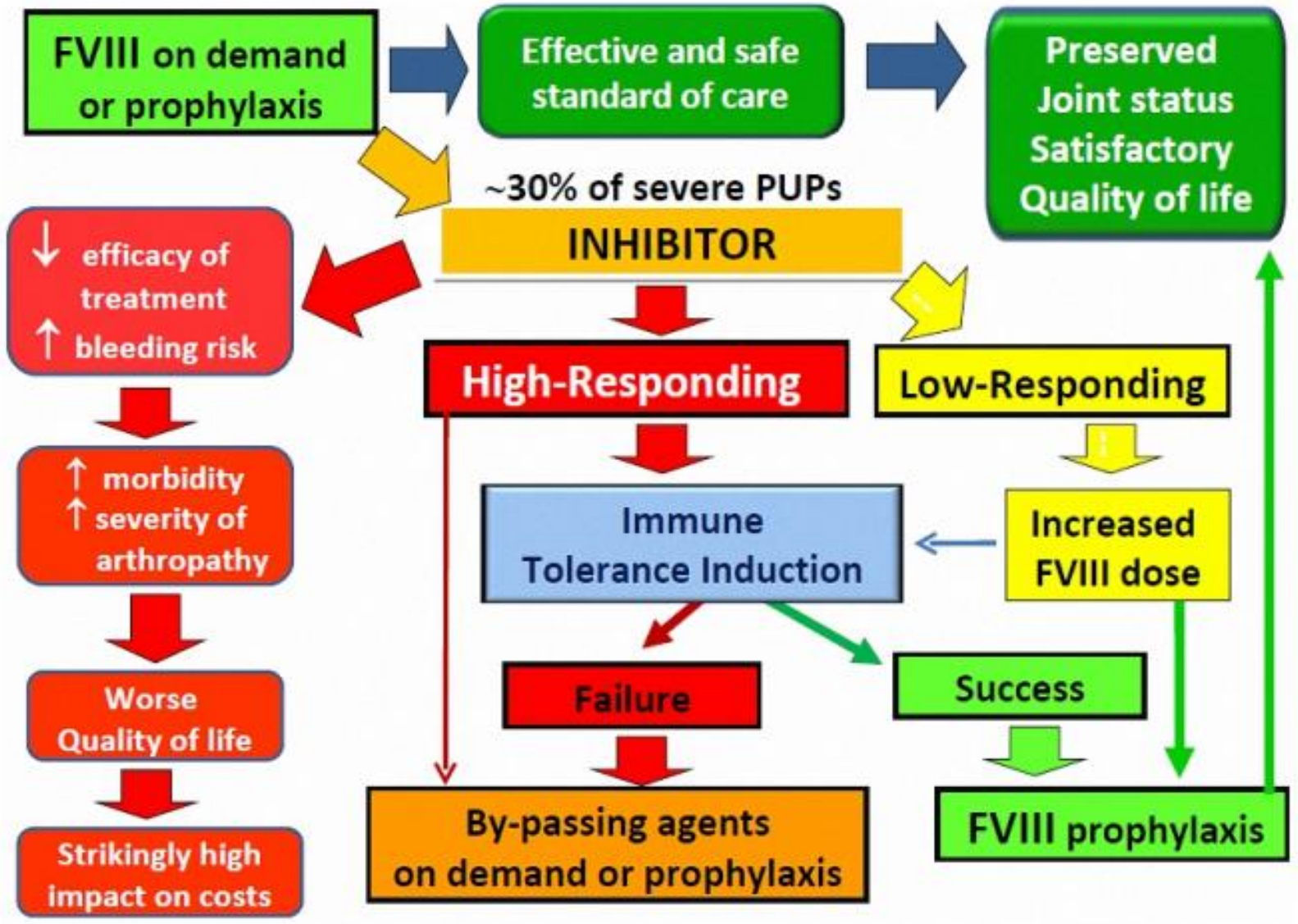
Kasper, 1975

EFEK INHIBITOR



INHIBITOR

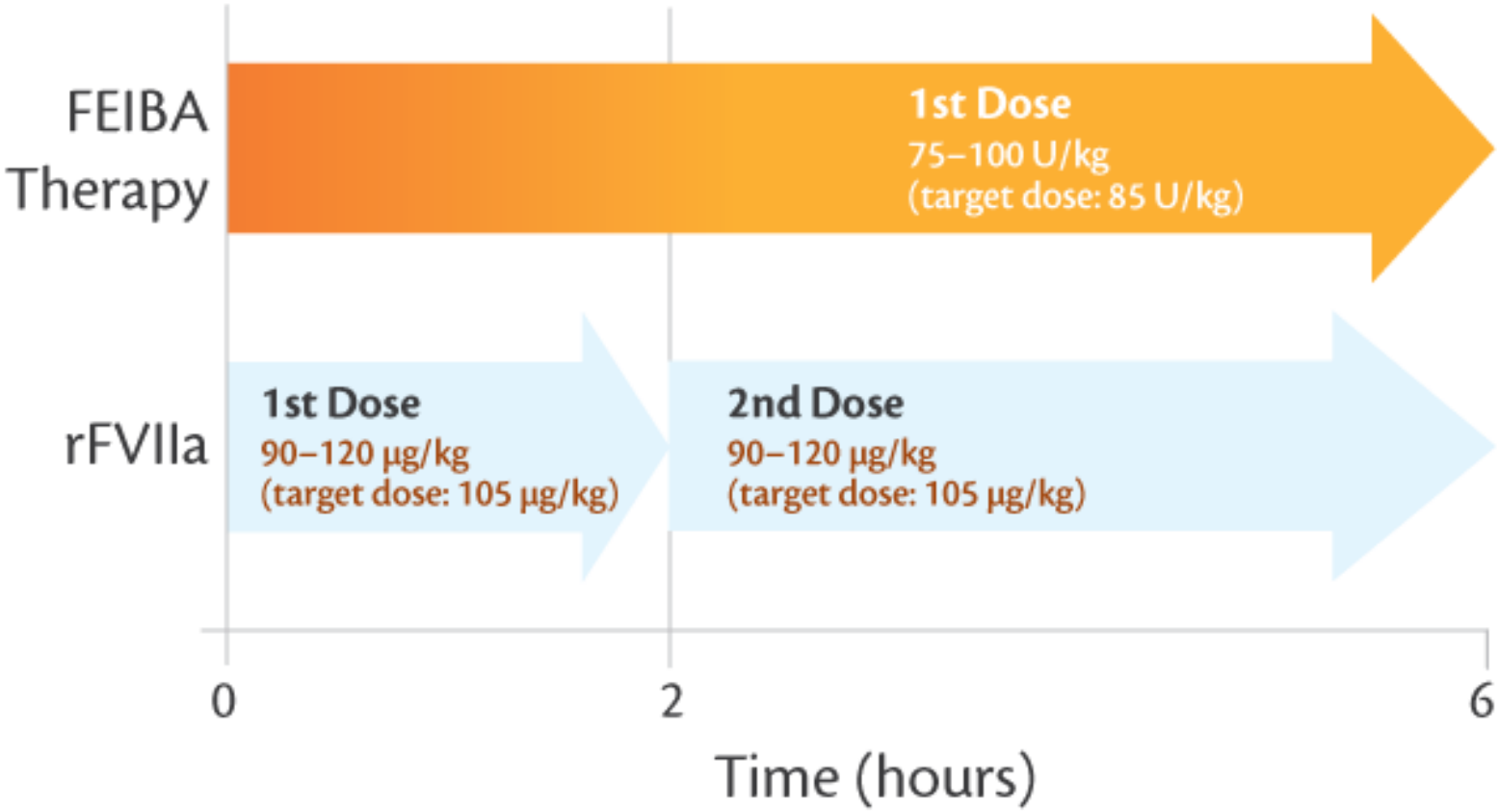
- Low responding: inhibitor < 5 BU, biasanya transien
- High responding: inhibitor ≥ 5 BU, cenderung persisten
  - Jika tidak diterapi, titer dapat turun namun terjadi respons anamnestik rekuren dalam 3-5 hari setelah pemberian konsentrat


FVIII on demand or prophylaxis
Effective and safe standard of care
Preserved Joint status Satisfactory Quality of life
~30% of severe PUPs
INHIBITOR
↓ efficacy of treatment
↑ bleeding risk
High-Responding
Low-Responding
↑ morbidity
↑ severity of arthropathy
Immune Tolerance Induction
Increased FVIII dose
Worse Quality of life
Failure
Success
Strikingly high impact on costs
By-passing agents on demand or prophylaxis
FVIII prophylaxis

IMMUNE TOLERANCE INDUCTION

ITI protocol	FVIII dose and associated treatment	Success rate (%)	Median time to success, months	Comments
Bonn protocol (high-dose regimen)*	FVIII 100–150 iu/kg every 12 h until inhibitor <1 BU, then FVIII 150 iu/kg until normalization of FVIII recovery and half-life.	92–100	14	Very demanding for patients. High cost
Malmö protocol (high-dose regimen + immune modulation)†	FVIII continuous infusion targeting plasma levels >30 iu/dl until negative inhibitor titre, then 60–90 iu/kg weekly + cyclophosphamide (i.v. 12–15 mg/kg days 1–2, 2–3 mg/kg orally days 3–10) + i.v. immunoglobulins 2·5–5 g/kg day 1, 0·4 g/kg days 4–8. Preliminary protein A sepharose immunoadsorption if initial inhibitor titre >10 BU.	59–82	1	Rapid response and cost-saving but need for hospitalization and concerns regarding the use of cyclophosphamide in children
Dutch protocol (low-dose regimen)‡	Neutralizing dose (25–50 iu/kg twice daily, 1–2 weeks), then tolerizing dose (50–75 iu/kg weekly)	61–88	1–12§	Less demanding for patients and cost-saving
Other low or intermediate dose protocols	Ewing *et al*, 1988: 50 iu/kg/d	67	2¶	Developed for improving cost-effectiveness of treatment
	Kucharski *et al*, 1996: 50 iu/kg/week	45	10	
	Unuvar *et al*, 2000: 50–100 iu/kg/d	57	6	
	Rocino *et al*, 2001: 100 iu/kg/d	75	8	

BYPASSING AGENTS

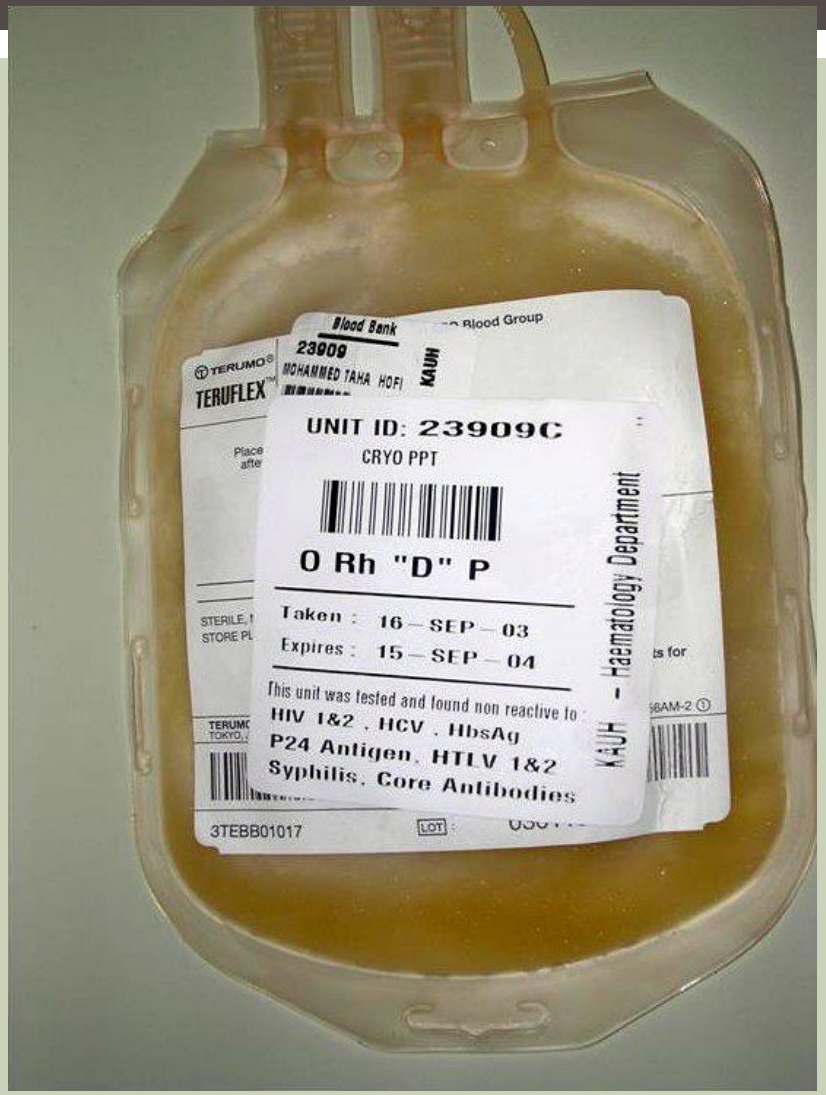


SKRINING

- Untuk anak-anak, inhibitor skrining setiap 3-12 bulan atau setiap 10-20 hari pajanan, dan untuk orang dewasa sesuai klinis
- Inhibitor diskrining sebelum operasi, dan ketika respons klinis terhadap terapi adekuat sub-optimal

INFEKSI TERKAIT PRODUK DARAH

PRODUK DARAH?



PRODUK DARAH?

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INFEKSI TERKAIT PRODUK DARAH

Pathogen	Year	Threat
Hepatitis B virus	1971	First reports of hemophiliacs treated with plasma-derived concentrates infected
HIV/AIDS	1982	First reports of hemophiliacs treated with plasma-derived concentrates infected
Avian influenza virus	1997	First evidence that virus can directly infect humans
Parvovirus B19	1998	Virus found present in 1st-generation FVIII concentrates and in majority of general population
Variant Creutzfeldt-Jakob disease (vCJD)	2000	Transmission of disease through blood transfusion demonstrated
	2009	Hemophilic patient with evidence of vCJD proteins received FVIII plasma product from a person who later developed vCJD.
Severe acute respiratory syndrome (SARS)	2003	First reports of outbreak in Asia
West Nile virus	2003	First reports of transfusion-related infections

Tapper ML. *Haemophilia*. 2006;12(Suppl 1):3-7.
Valentino LA, et al. *Pediatr Blood Cancer*. 2006;47(3):245-254.
Eaton L. *BMJ*. 2009;338:b705.

PREVALENSI PADA PASIEN HEMOFILIA

	% of patients (1984-1996)	% of patients (1998-2002)
Hepatitis B	54	0
Hepatitis C	87	27
Chronic hepatitis C	30	0
HIV	33	11

INFEKSI TERKAIT PRODUK DARAH

- Transmisi HIV, virus hepatitis B dan hepatitis C melalui produk faktor pembekuan mengakibatkan mortalitas tinggi pada orang dengan hemofilia di tahun 1980 dan awal tahun 1990an

- HIV → dengan teknik pemurnian konsentrat saat ini, risiko sangat kecil
- Hepatitis → risiko sangat menurun, namun tidak hilang sama sekali → 7 kasus terinfeksi hepatitis B dan C dengan penggunaan konsentrat

INFEKSI TERKAIT PRODUK DARAH

- Penggunaan produk rekombinan → sangat mengurangi risiko infeksi terkait transfusi
- Skrining hepatitis sebaiknya dilakukan secara periodik setiap tahun termasuk pemeriksaan fungsi hati dan serologi hepatitis (A, B, C)

PENCEGAHAN

- Vaksin hepatitis A dan B, subkutan
- Penyakit hati kronik: terapi sesuai standar terapi untuk hepatitis kronik
- Pasien dengan gangguan fungsi hati dapat terjadi defisiensi faktor pembekuan lain (cek PT, INR) atau hitung trombosit yang rendah

Terima Kasih