Blood Products

Albumin, IVIG, and Factor

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Objectives

- Appreciate the progression of blood product development and the advances made to decrease the risks associated with them
- Understand the function and clinical applications of albumin
- Understand the importance of proper dosing, product selection, and proper preparation of IVIG products
- Understand what factor products are, why they are used, and the general difference between products

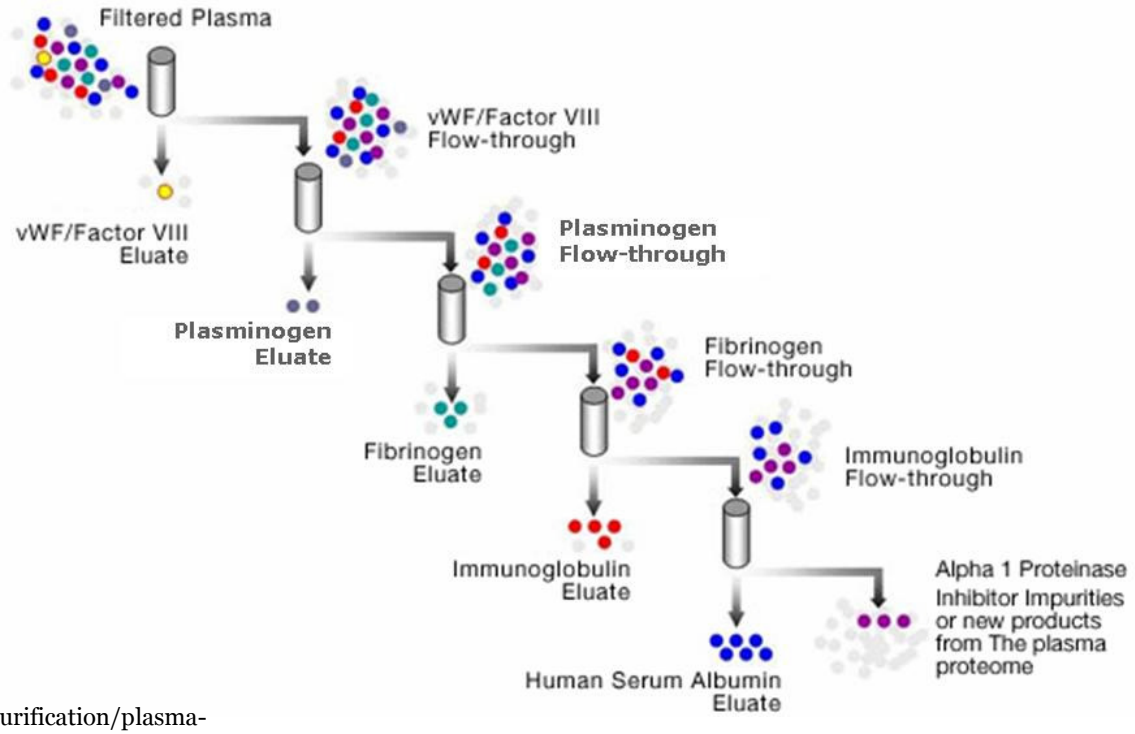
History of Blood Products

- WWII era - Albumin and dried plasma were vital elements to treat wounded soldiers
  - Around the same time, the Cohn process was developed to separate products in plasma
- 1952 - Treatment of immune deficiency using immune globulin
- 1960s - Preparations of clotting factors VIII and IX developed
- 1980s - Transmission of viruses by plasma products discovered

Franklin D. Roosevelt Library Public Domain Photographs, compiled 1882 - 1962 (ARC identifier: 195301

Why are they so special

- Production
  - Plasma derived products made from pooled plasma from 2,000-30,000 donors
  - Plasma has to be fractionated into its different protein components.



http://www.prometicbiosciences.com/applications/protein-purification/plasma-

Safety and Tracking

- Blood exposure to >2000 people!
  - Initial screening of donors
  - Inactivation processes
    - Wet and dry heat
    - Filtration
    - Solvents/detergents
    - Psoralens + UVA light
- Track product/lot # so if anything happens, can report to manufacturer and MedWatch

Albumin

Overview

- What is Albumin?
  - Normal blood protein, produced by the liver
    - Colloid (rather than Crystalloid)
  - Makes up ~50% of the plasma protein in blood
  - "Plasma Volume Expander"
    - Increase plasma volume 3.5x the volume infused
  - Transport Protein
    - Binds and transports various blood components, drugs, and toxins

History

- First documented clinical use on December 8, 1941
- Approved by FDA in 1942
- Originally was derived from bovine serum
- Although no conclusive evidence was ever discovered, bovine albumin was abandoned in 1943 due to concerns of serum sickness

Preparations

Albumin 5%

- Oncotic pressure similar to that of normal plasma
- Use in patients that need additional volume
- REPLACE VOLUME

Albumin 25%

- Oncotic pressure much higher than normal plasma
- Use in patients that can't handle additional volume
- REDISTRIBUTE VOLUME

Some Indications

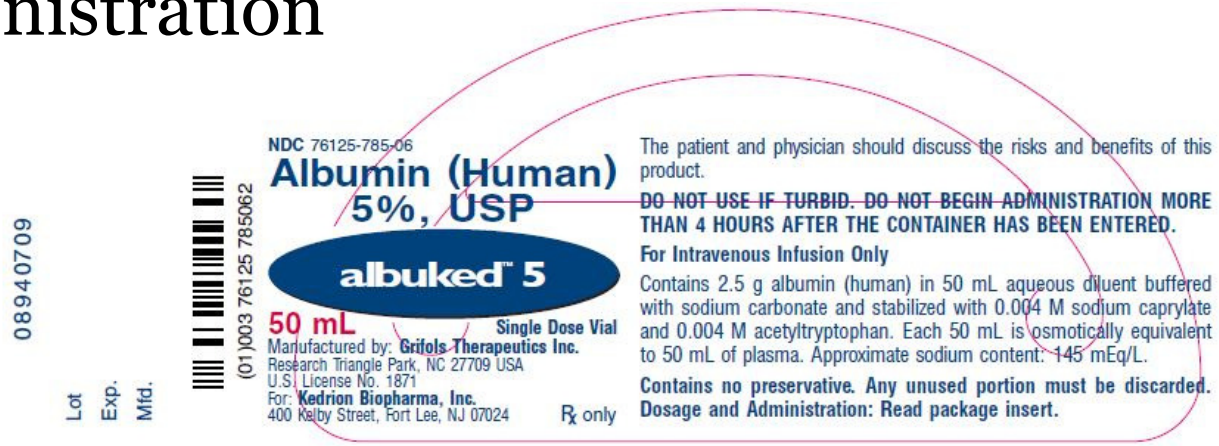
- Shock*:
  - Hemorrhagic: Usually use 5% albumin
  - Non-hemorrhagic: Usually use 25% albumin
- Burns*:
  - Given after 24 hours, with >30% surface burns
- Plasmapheresis:
  - Large volume plasma exchange only (>20 mL/kg)
- Nutritional Support: NO!

Preparation

- Reconstitution:
  - May dilute 25% human albumin with NS or D5W to obtain 5% human albumin in time of shortage
- Do NOT use sterile water as diluent
  - Potential for fatal hemolysis & ARF

Administration

- For IV administration only
- Use within 4 hr after opening vial; discard unused portion
- Record product and lot number with each administration



Storage

- Store at <30°C (86°F); do not freeze
- Do not use solution if turbid or contains a deposit
- Use within 4 hr of opening vial; discard unused portion

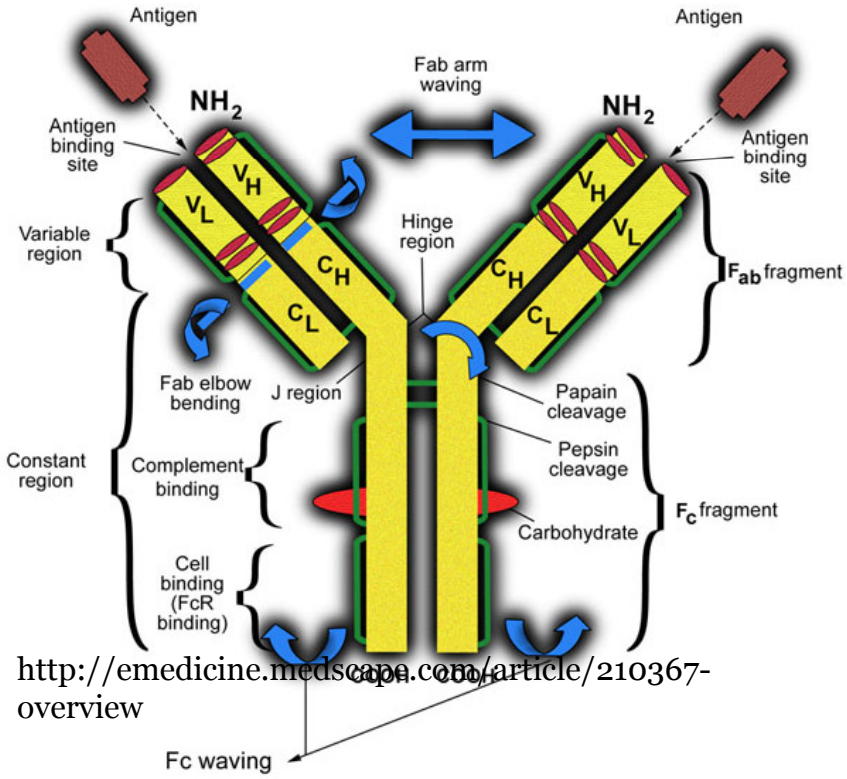
Intravenous Immune Globulins (Immunoglobulins, IVIG)

Overview

- What are immune globulins? ANTIBODIES
  - Y-shaped proteins produced by B-cells as part of the adaptive immune system that aid in ***antigen recognition*** and immune system ***modulation***.

Type	Description
IgA	Found in mucosal areas; Protect against outside foreign substances (10%)
IgG	**In all body fluids, smallest Ig, cross placenta; fight bacteria/viruses (75%)**
IgM	In blood and lymph; first response to infection (5%)
IgE	Found in lungs, skin, mucous membranes; allergic reactions
IgD	Unknown function

Overview



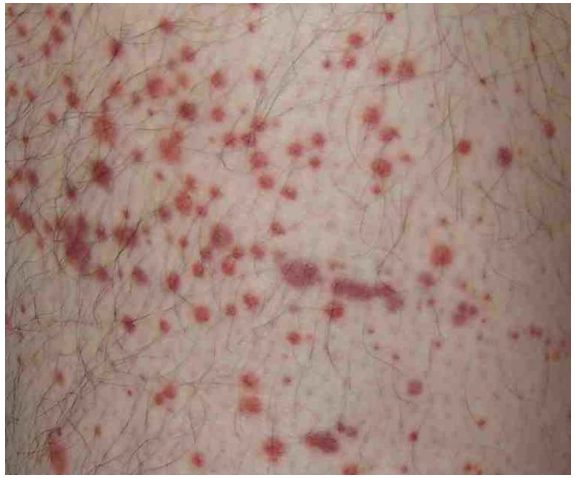
http://emedicine.medscape.com/article/210367-overview

IVIG = IgG (mostly)

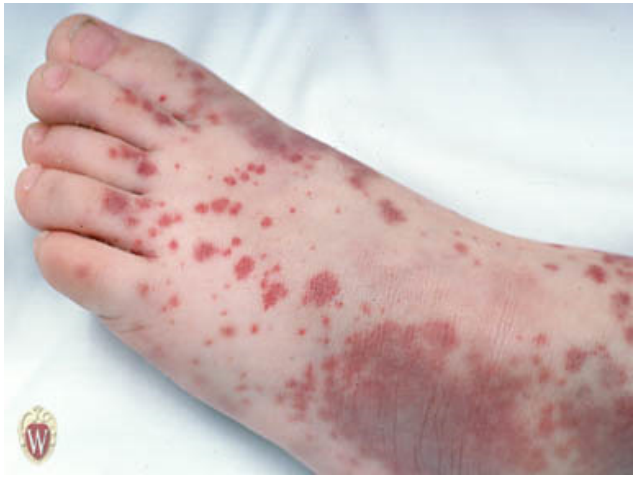
- Pooled from the plasma of thousands of donors
- Also may be trace amount of IgA and IgM in IVIG preparations
- IgG has intact Fc region that allows for interaction with B cells, phagocytes, and plasma proteins

Overview

- **1952**: First used to treat immune deficiency
  - "***Replacement Dose***": 200-400 mg/kg q 3-4 wks
- **1981**: Effective in autoimmune idiopathic thrombocytopenic purpura (ITP)
  - "***High Dose (Immunomodulatory)***": 2 g/kg/month



http://www.bloodystoolcauses.com/wp-content/uploads/2011/07/Purpura.jpg



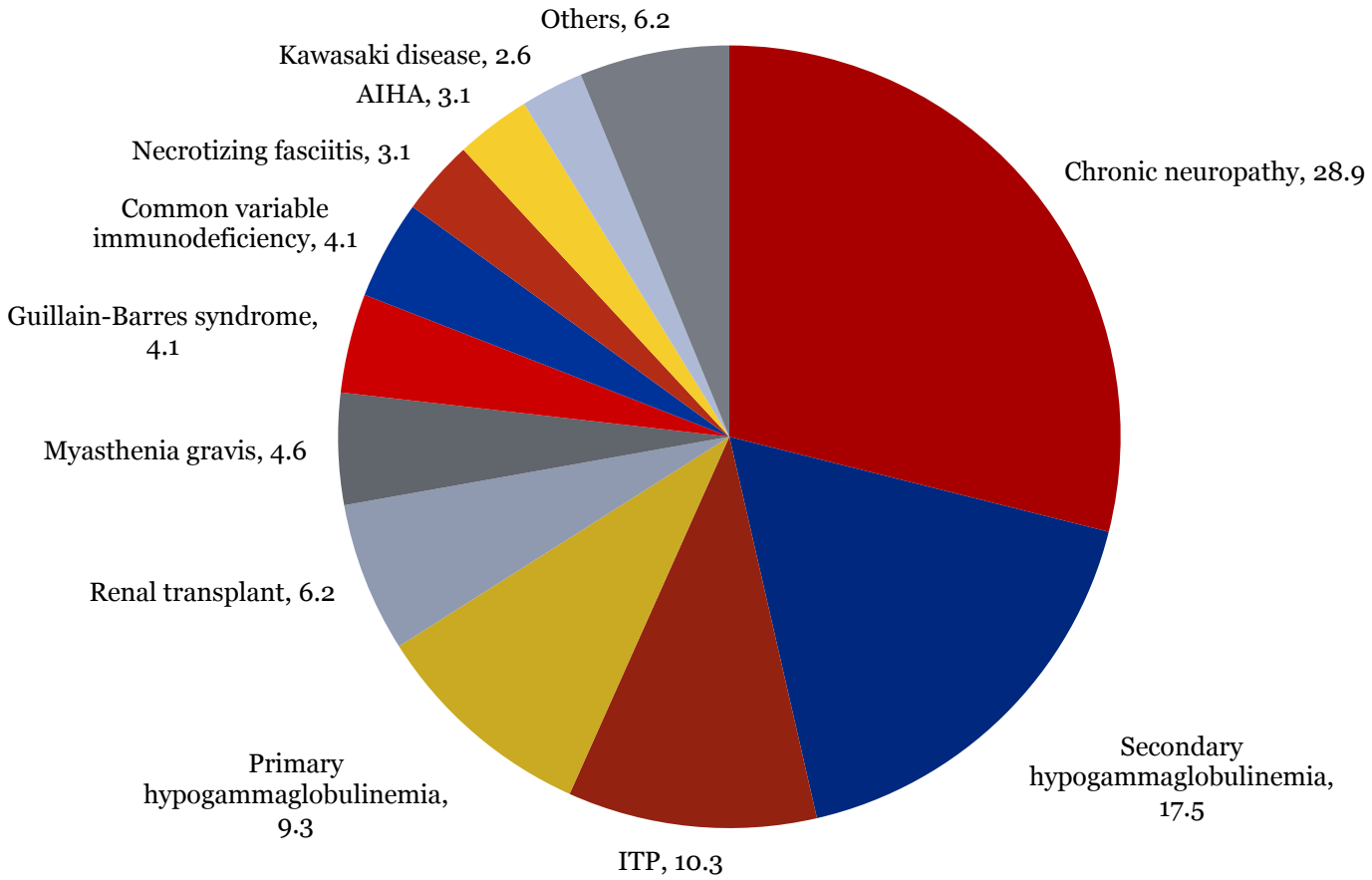
http://www.bitkiseltedavi.com/class/INNOVAEditor/assets/purpura.jpg

Overview

- **Uses**: "Multiple immune deficiency, autoimmune, infectious, and idiopathic diseases"
- **FDA Indications**: This does not include multiple guideline recommendations for off-label use in hematology, infectious disease, neurology, pulmonology, rheumatology, etc.

- Allogeneic bone marrow transplant
- Secondary immunodeficiency in chronic lymphocytic leukemia
- Common variable immunodeficiency (CVID)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Renal transplant with high-Ab-recipient, or ABO incompatible donor
- Primary immunodeficiency disorders
- Immune thrombocytopenia (ITP)
- Kawasaki disease
- Hematopoietic stem cell transplant in adults
- Pediatric HIV-1 infection

Darabi K, Abdel-Wahab O, Dzik WH. Current usage of intravenous immune globulin and the rationale behind it: the Massachusetts General Hospital data and a review of the literature. Transfusion 2006; 46:741.

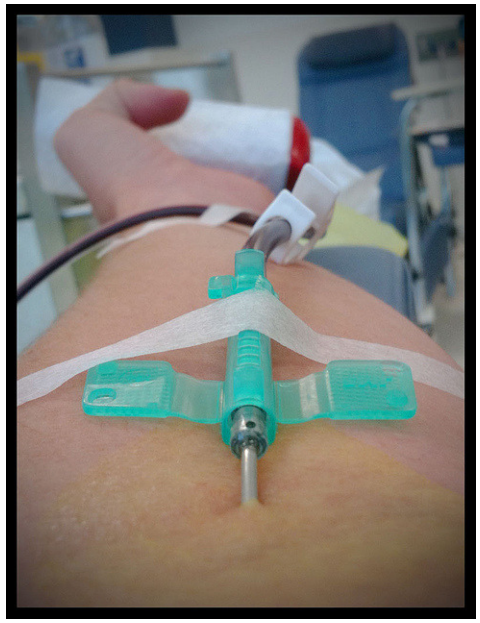


Cost

- Cost per gram (2006): $50 - $80
- MGH treated ~200 patients over the course of this study's data collection period for a cost of $4 million (US)
- Canadian study estimated cost of treating ONE chronic neuropathy patient to be ~$70,000 per year.

Darabi K, Abdel-Wahab O, Dzik WH. Current usage of intravenous immune globulin and the rationale behind it: the Massachusetts General Hospital data and a review of the literature. Transfusion 2006; 46:741.

Production



- Plasma Donation
- Isolation of Ig
- Purification of IgG
- Sterilization

Preparations:

Product	Indications
Carimune NF (lyophilized)	PID, ITP
Flebogamma 5% DIF (liquid 5%)	PID
Gammagard (liquid 10%)	PID, MMN
Gammagard S/D (lyophilized)	PID, ITP, CLL, KS
Gammaplex (liquid 5%)	PID
Gamunex-C (liquid 10%)	PID, ITP, CIDP
Octagam (liquid 5%)	PID
Privigen (liquid 10%)	PID, ITP

PID = Primary Immune Deficiency
ITP = Idiopathic Thrombocytopenic Purpura
CLL = Chronic Lymphocytic Leukemia
KS = Kawasaki Syndrome
MMN = Multifocal Motor Neuropathy
CIDP = Chronic Inflammatory Demyelinating Polyneuropathy

Preparations

For product-specific comparisons, visit:

- http://www.ashp.org/s_ashp/docs/files/DShort_IVIGsidebysideupdatedDec07.pdf

Excellent reference with indications, stability, administration rates, content/characteristics (IgA, albumin, sugar, sodium, pH, osmolarity)

May be slightly out of date (2007)

Dosing / Administration

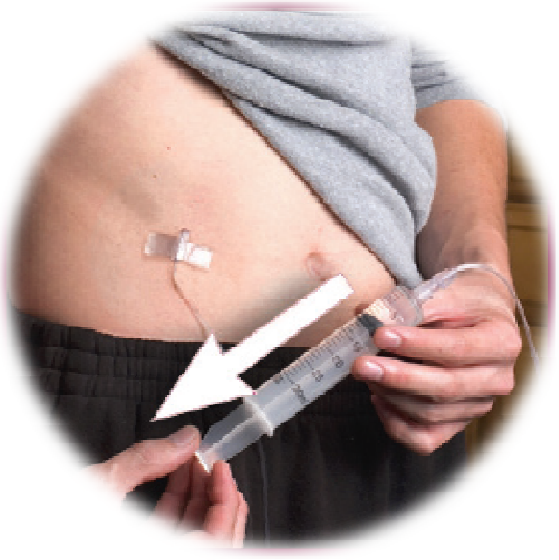
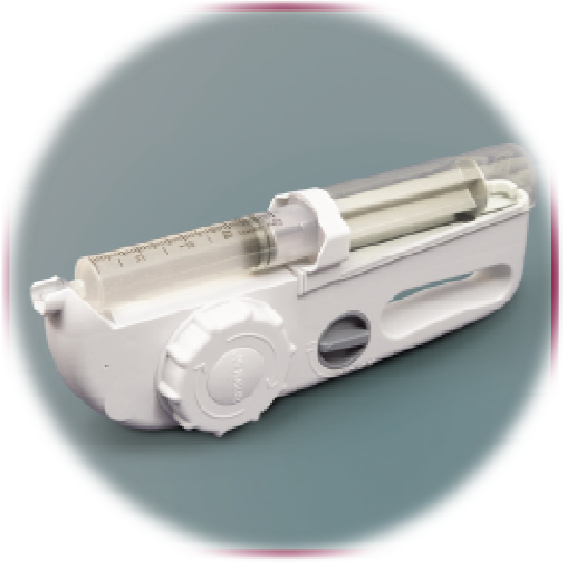
Low Dose (Deficiency)

- 300-500 mg/kg every three to four weeks (IBW)
- Doses often rounded to accommodate vial size
- Patient may infuse at home after initial infusion
- **Route**: SC/IM/IV

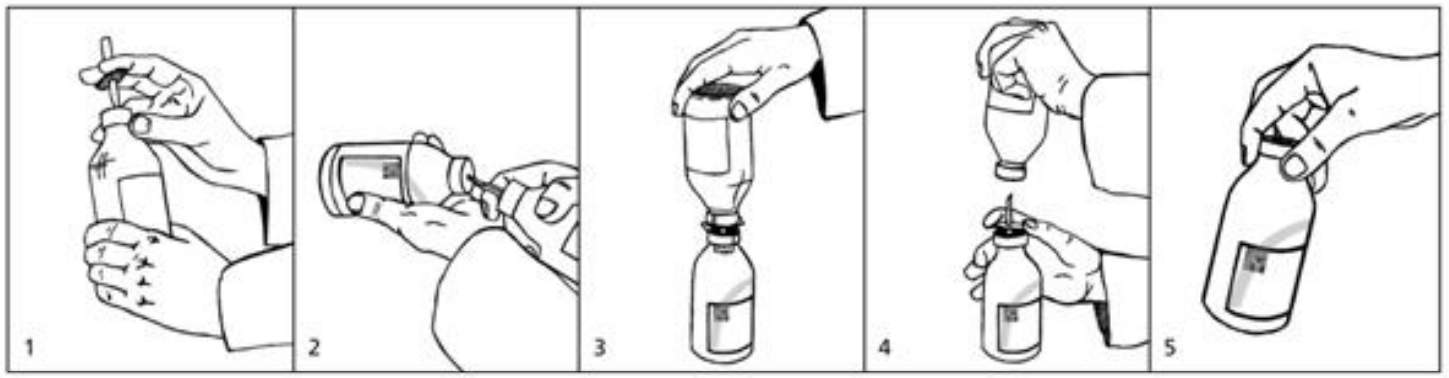
High Dose (Modulation)

- 2 g/kg per treatment, i.e. monthly (IBW)
- Doses often rounded to accommodate vial size
- Separate doses if patient unable to tolerate side effects
- **Route**: IV

Filtration: Required for Gammagard S/D & Octagam 5%, optional or recommended for others… Best practice to filter all IVIG?

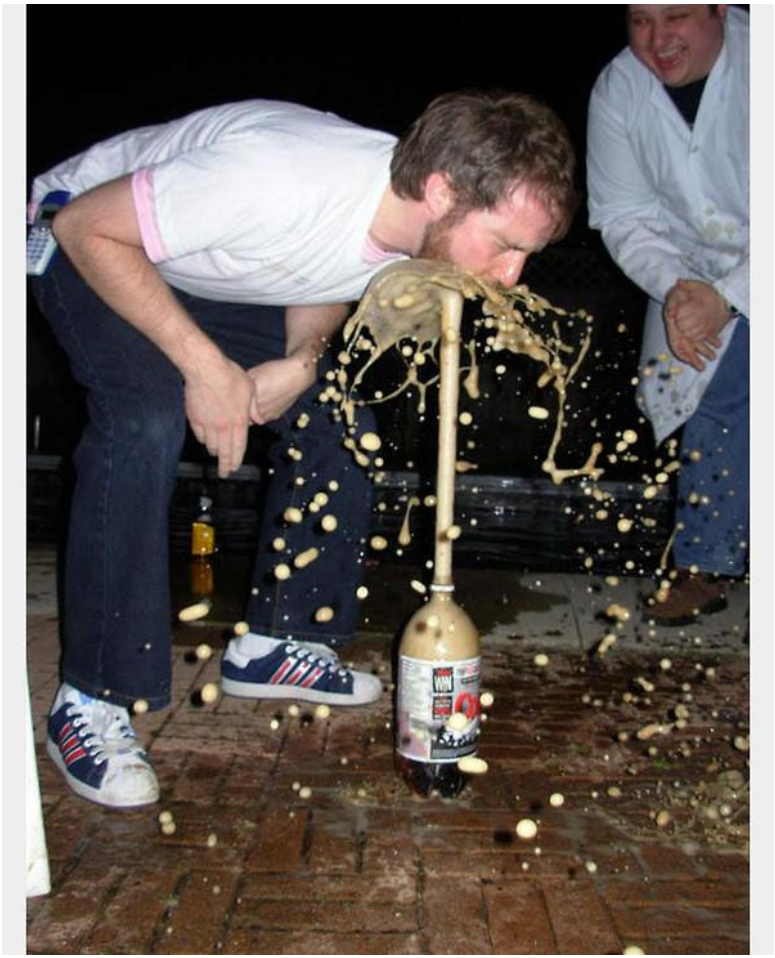




Reconstitution



- Use provided diluent and transfer sets if provided, unless otherwise indicated by physician/pharmacist
  - Patient factors may require alternate diluent (D5W vs NS) or diluent volume (higher concentration)
  - Check package insert before using diluent other than those provided!

Reconstitution



- Swirl gently, DO NOT SHAKE
  - May take up to 20 minutes to dissolve
  - Shaking will cause foaming and may inactivate the immune globulin in solution

Reconstitution

- Always observe for particulate matter or discoloration
- May combine multiple vials (not different products) in empty sterile glass/plastic IV container
- Do not mix liquid preparations with IV fluids
  - Note: Some liquid preparations may be diluted if necessary, usually with D5W, but you should first consult package insert

Storage

Product	Storage	Reconstituted
Carimune NF (lyophilized)	**Room Temp**	**Refrigerate (24 hours)**
Flebogamma 5% DIF (liquid 5%)	Room Temp	N/A
Gammagard (liquid 10%)	Room Temp	N/A
Gammagard S/D (lyophilized)	**Room Temp**	**Refrigerate (24 hours)**
Gammaplex (liquid 5%)	Room Temp	N/A
Gamunex-C (liquid 10%)	Refrigerate (36 months), Room Temp (6 months)	
Octagam (liquid 5%)	Refrigerate (24 months), Room Temp (18 months)	
Privigen (liquid 10%)	Room Temp	

DO NOT FREEZE ANY IVIG PREPARATIONS!

Administration

Product	Max Rate	Renal Rate	Filter
Carimune NF (lyophilized)	See insert	< 2 mg/kg/m	No
Flebogamma 5% DIF (liquid 5%)	0.1 mL/kg/m	< 0.06 mL/kg/m	Rec
Gammagard (liquid 10%)	5 mL/kg/h	< 2 mL/kg/h	Opt
Gammagard S/D (lyophilized)	*4-8 mL/kg/h	*< 2-4 mL/kg/h	Yes
Gammaplex (liquid 5%)			
Gamunex-C (liquid 10%)	0.08 mL/kg/m	< 0.08 mL/kg/m	No
Octagam (liquid 5%)	0.07 mL/kg/m	< 0.07 mL/kg/m	Yes
Privigen (liquid 10%)	^0.04-0.08 mL/kg/m	< 0.02 mL/kg/m	No

* = Dependent on 5% or 10% concentration (after reconstitution)
^ = Dependent on indication

Safety Concerns

- **Patient Factors**:
  - Contraindications, age, comorbidities, precautions
- **Product Factors**:
  - Volume, osmolarity, IgA content, sodium content, sugar content, stabilizer, pH
- **Indication**: Approved? Literature?
  - Find your hospital policy – i.e. case-by-case approval, P&T committee approval, etc.

Siegel, J. IVIG Medication Safety: A Stepwise Guide to Product Selection and Use. Pharmacy Practice News 2011: 77-84.

Safety Concerns

- **Contraindications**: IgA Deficiency
- **Age**: Neonatal vs. Geriatric
- **Comorbidities**: Diabetes, renal insufficiency, history of thrombotic disease
- **Obesity**: IBW for patients with BMI >30 or weight >100kg
- **Rate**: Consider 15-30 minute infusion for observation/monitoring

Siegel, J. IVIG Medication Safety: A Stepwise Guide to Product Selection and Use. Pharmacy Practice News 2011: 77-84.

Table 2. Pharmaceutical Aspects of IVIG: Osmolality/Osmolarity, Sodium Content, and Stabilizer

Product	Osmolality/Osmolarity	Sodium Content	Stabilizer
Carimune NF, CSL Behring (lyophilized)	*In water:* 3%, 192 mOsm/L; 6%, 384 mOsm/L *In saline:* 6%, 690 mOsm/L; 12%, 1,074 mOsm/L	0%-0.9%, depending on diluent	10% sucrose at 6% concentration
Flebogamma 5% DIF, Instituto Grifols (liquid 5%)	240-370 mOsm/L	<3.2 mmol/L	5% D-sorbitol
Gammagard, Baxter Healthcare (liquid 10%)	240-300 mOsm/kg	Trace	No sugar (glycine based)
Gammagard S/D, Baxter Healthcare (lyophilized)	5%, 636 mOsm/L; 10%, 1,250 mOsm/L	0.85% at 5% concentration	2% glucose
Gammaplex, Bio Products (liquid 5%)	480 mOsm/kg	Approximately 40 mmol/L	Sorbitol, glycine
Gamunex-C, Talecris (liquid 10%)	258 mOsm/kg	Trace	No sugar (glycine based)
Octagam, Octapharma (liquid 5%)	310-380 mOsm/kg	<30 mmol/L	10% maltose
Privigen, CSL Behring (liquid 10%)	240-440 mOsm/L	Trace	No sugar (L-proline based)

Siegel, J. IVIG Medication Safety: A Stepwise Guide to Product Selection and Use. Pharmacy Practice News 2011: 77-84.

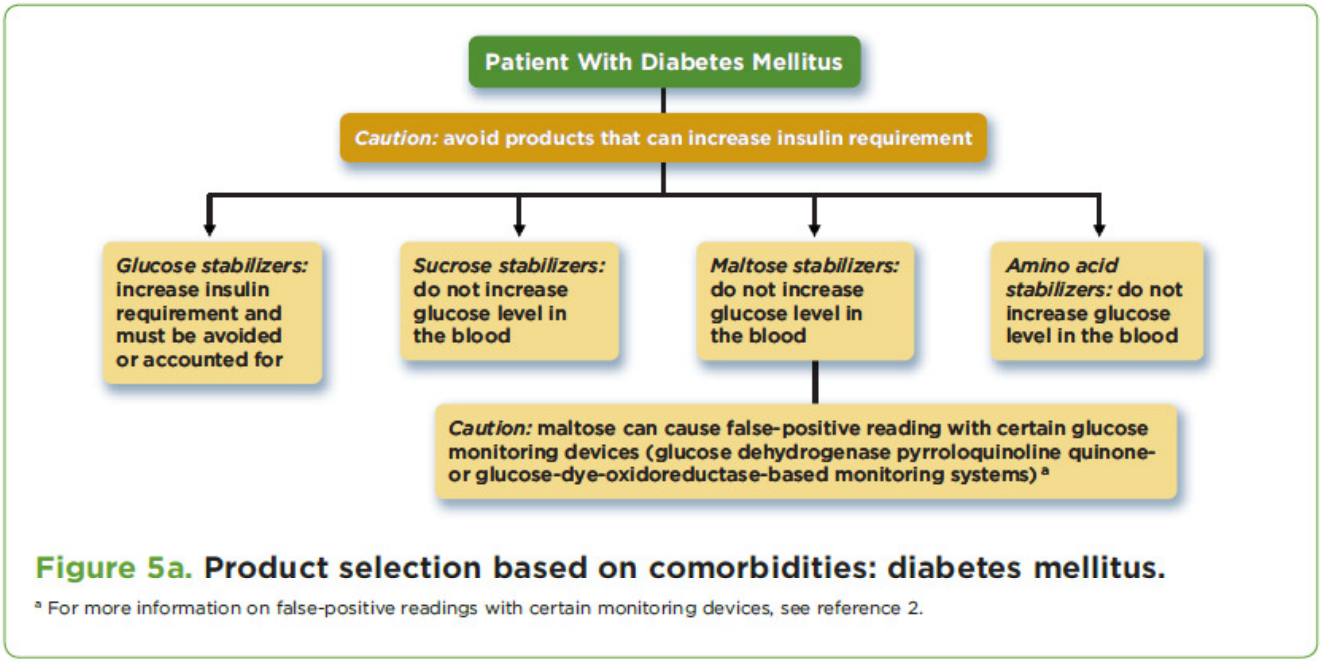


Figure 5a. Product selection based on comorbidities: diabetes mellitus.

[a] For more information on false-positive readings with certain monitoring devices, see reference 2.

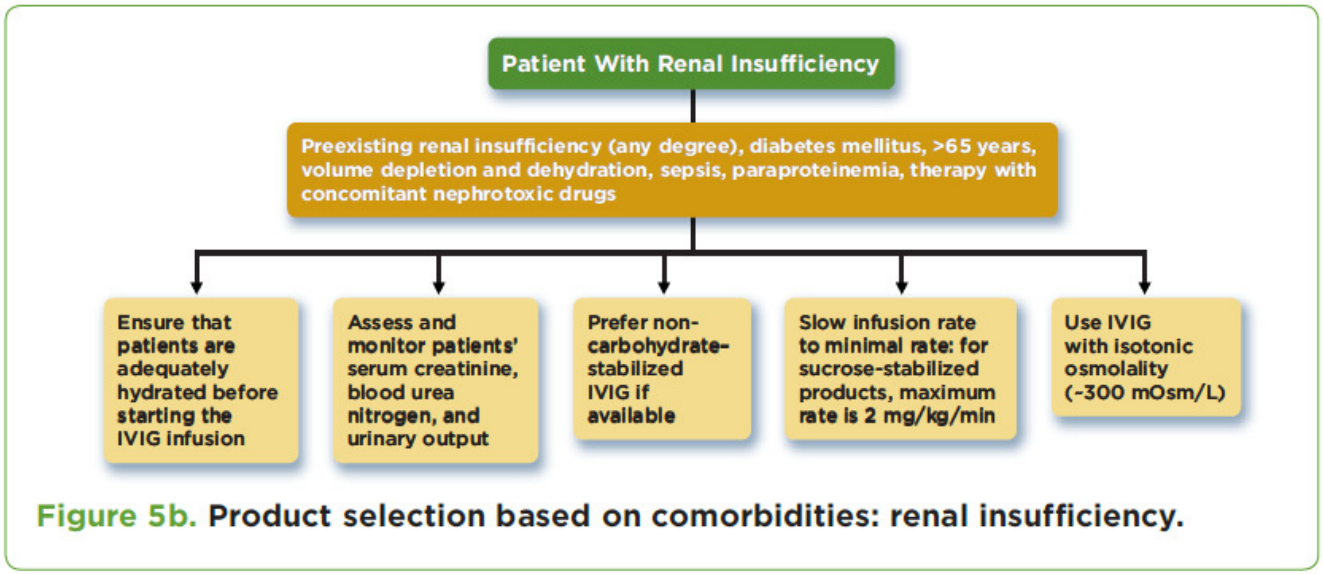


Figure 5b. Product selection based on comorbidities: renal insufficiency.

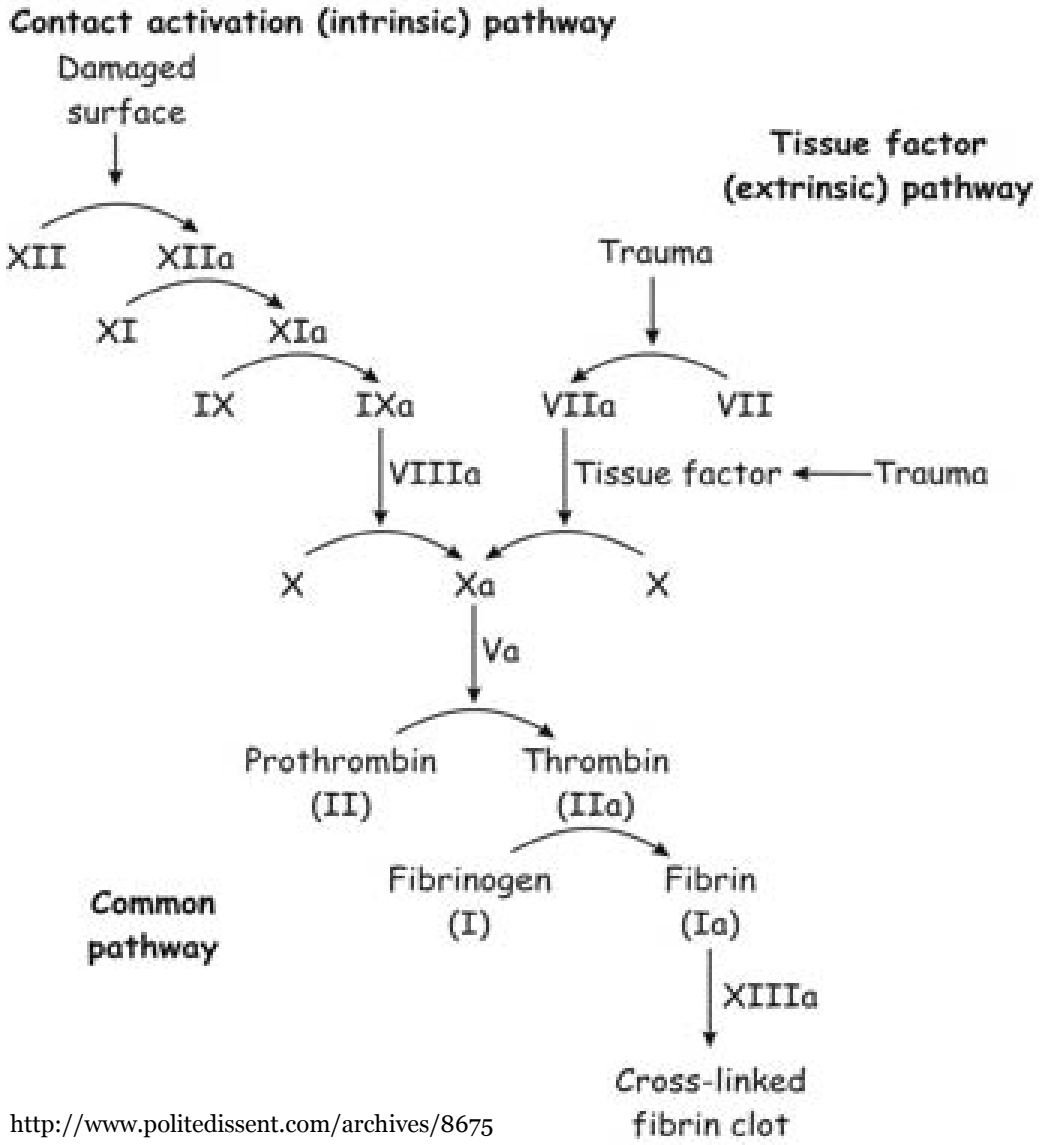
Siegel, J. IVIG Medication Safety: A Stepwise Guide to Product Selection and Use. Pharmacy Practice News 2011: 77-84.

Clotting Factor

Factor

- Specific one or combination of clotting factors isolated from human plasma or prepared by recombinant DNA technology
- Used for:
  - Hemophilia A, B, and acquired
  - Von Willebrand Disease
  - Reversal of anticoagulants
  - Other clotting factor deficiency diseases

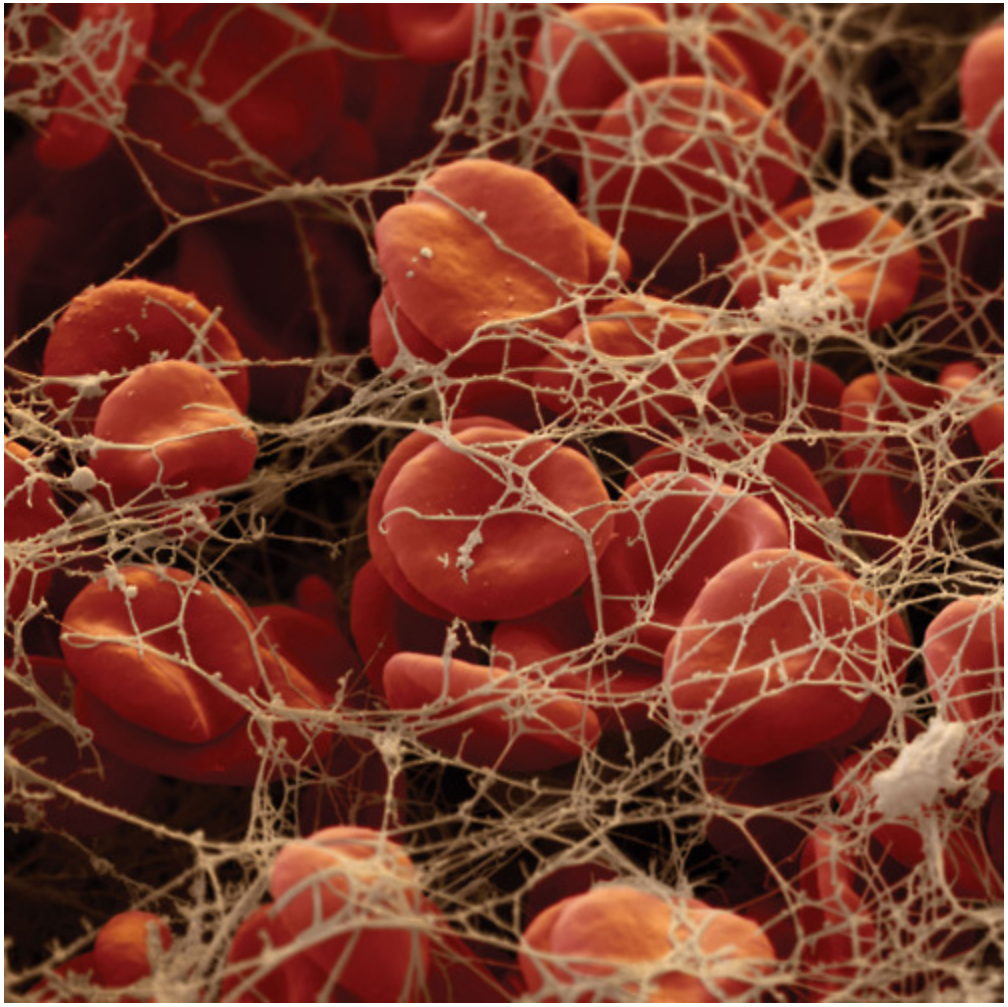
What are Clotting Factors



http://www.politedissent.com/archives/8675

- Substances in blood plasma involved in producing a blood clot
- Coagulation cascade depicts interactions between different clotting factors to form fibrin, part of a blood clot

Blood Clot



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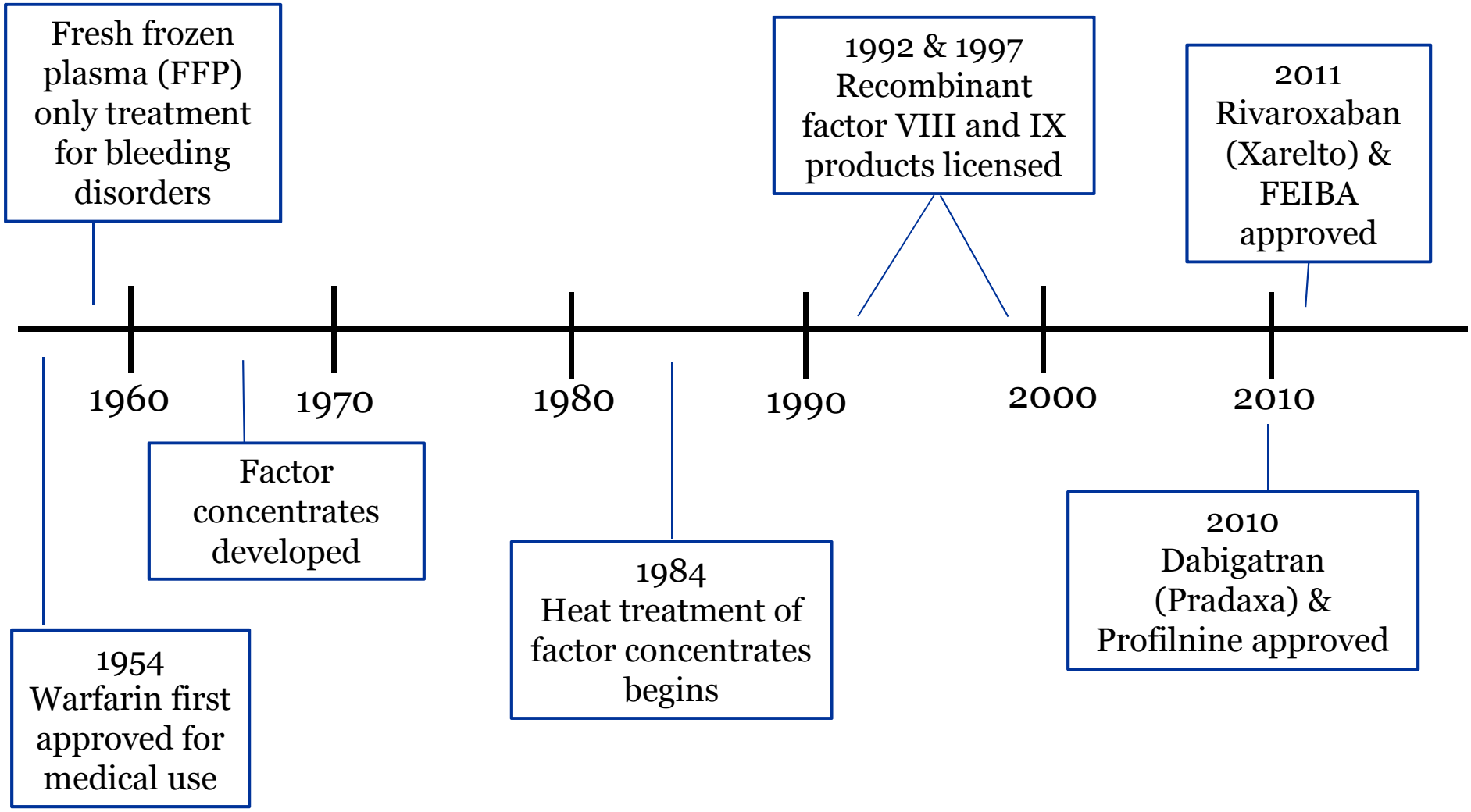
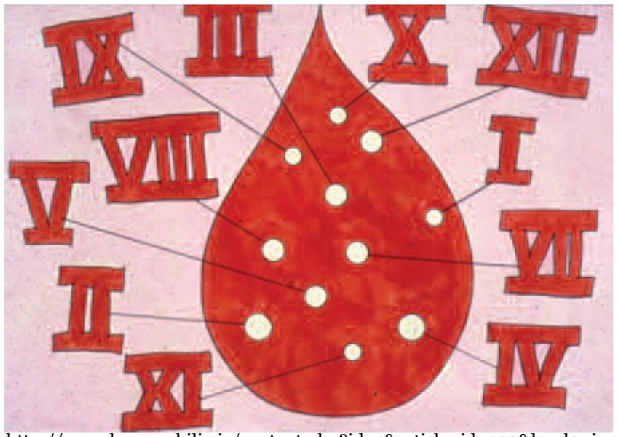
Factor Timeline



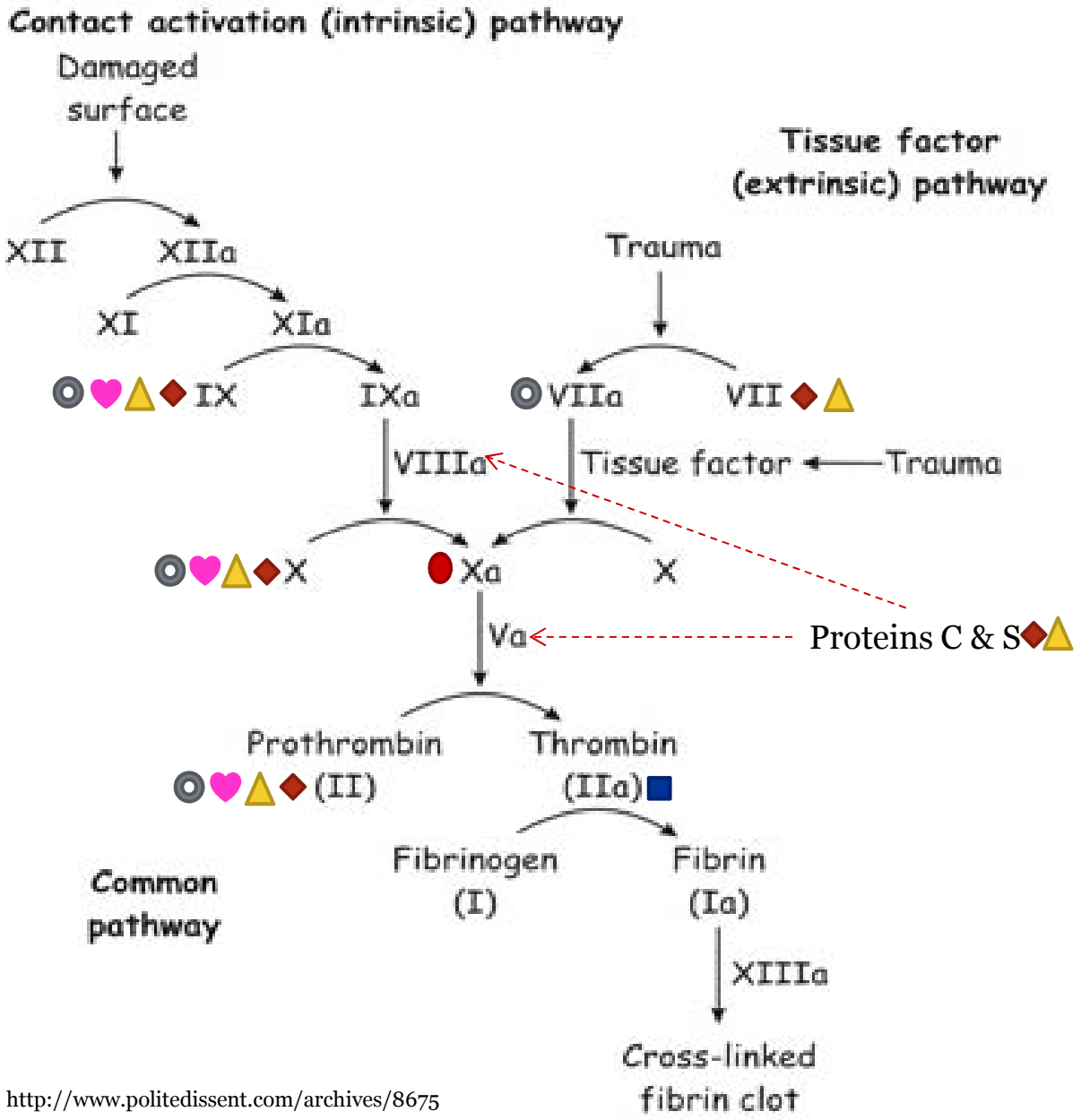
Factor Products

- Combinations
  - Kcentra (PCC: II, VII, IX, X, proteins C & S)
  - Profilnine (Factor IX complex: II, IX, and X)
  - Humate-P (VIII and von Willebrand)
  - FEIBA (II, IX, X, VIIa)
- Specific Factors/Proteins
  - Protein C (Ceprotin)
  - Factor XIII (Corifact)
  - Factor IX (Mononine)
  - Antithrombin (Thrombate III)
  - Factor VIII (Antihemophilic Factor)



http://www.haemophilia.ie/content.php?id=1&article_id=102&level3_id=415

- Rivaroxaban/Apixaban
- Dabigatran
- Warfarin
- Kcentra
- Profilnine
- FEIBA

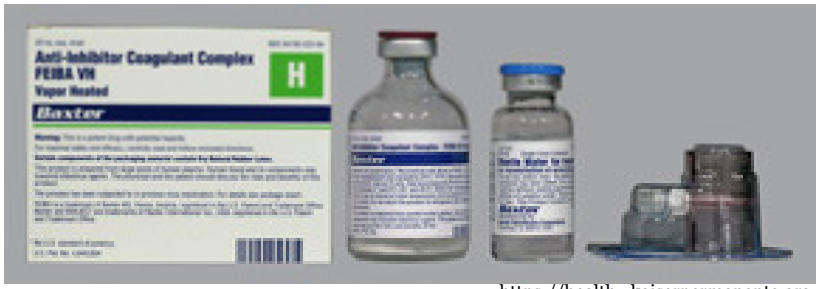


http://www.politedissent.com/archives/8675

Preparation & Administration

- Preparation is agent specific, but in general:
  - Use the provided diluent
  - Do not shake
  - Do not freeze
  - Do not tube
  - Do not drop
- Administration
  - Slow IV infusion completed within 3 hours of reconstitution

FEIBA



https://healthy.kaiserpermanente.org/

Kcentra

http://www.kcentra.com/docs/Kcentra_Reconstitution_Guide.pdf

Profilnine

Money, Money, Money!

Cost

- FEIBA
  - General dose: 50-100 units/kg Q12H
  - Price: $1.60/1 unit
- Profilnine
  - General dose: 25-70 units/kg OT
  - Price: $0.96/1 unit

Example: 80kg person

- FEIBA: $12,800/dose our cost
  - Patient cost $24,960/dose
- Profilnine: $3,840/dose our cost
  - Patient cost $11,160/dose

Conclusion

- Blood products are products of necessity that have been advanced significantly in the past decade
- Albumin, IVIG, and Factor products all serve unique roles of normal blood
- Each product has specific preparation, administration, and storage requirements

Questions

- What are blood products derived from (more specific than blood…)?

- Which of the following would be the least likely appropriate indication for albumin use?
  1. Malnutrition
  2. Volume replacement
  3. Severe burn
  4. Shock

Questions

- What should you know about shaking IVIG products in either the preparation or transport/delivery to the patient?
  1. This may cause them to 'explode' (like a soda bottle) upon administration to the patient.
  2. This will help the products dissolve faster, as they can sometimes take up to 20 minutes to do so.
  3. Liquid IVIG products may be shaken, but powder for reconstitution should be handled more delicately.
  4. All IVIG formulations should not be shaken as this can lead to foaming and potentially affect stability of the product.
- What was a major risk associated with clotting factor concentrates before heat treatments began to be used in their preparation in 1984?

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