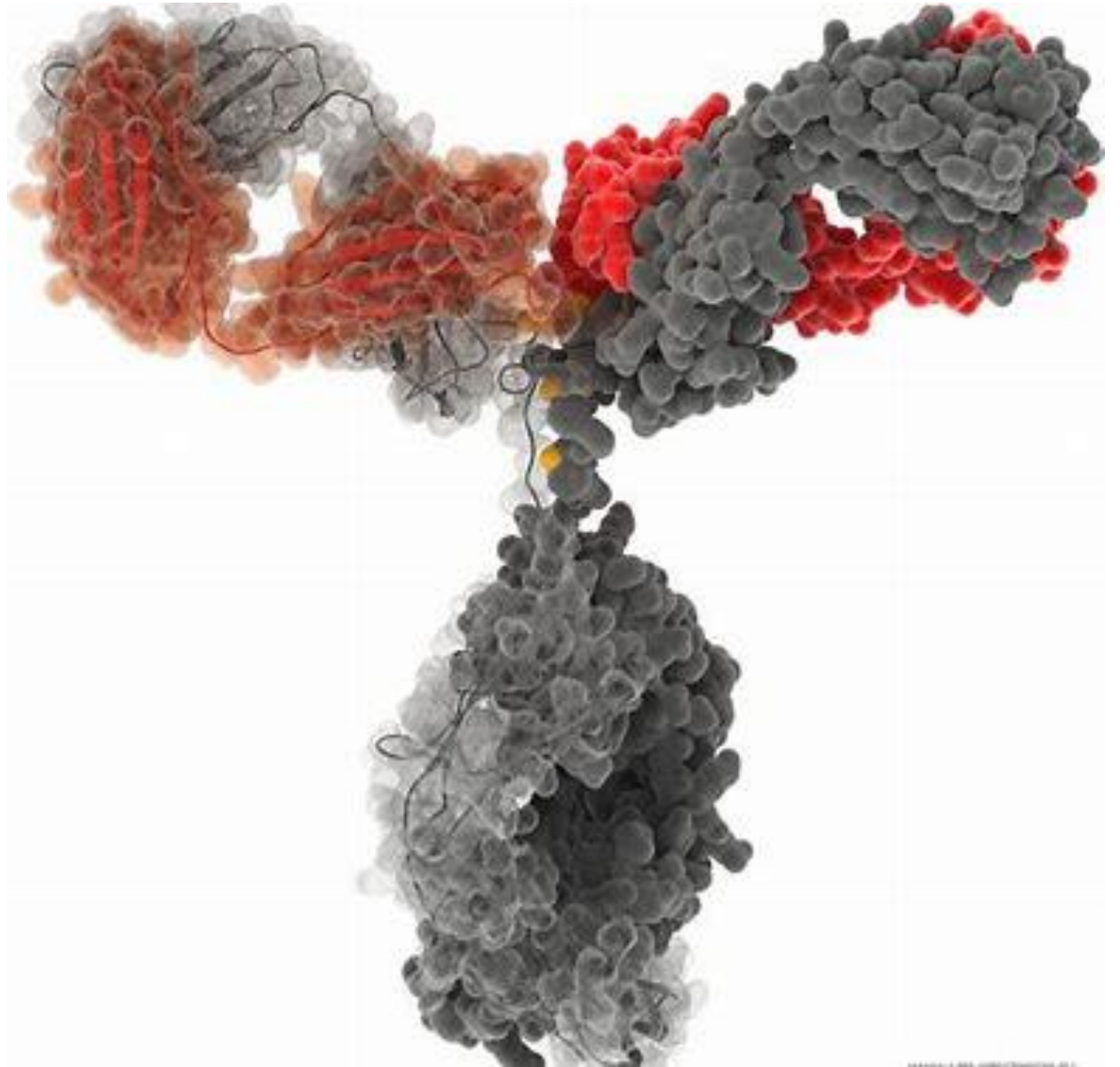


Individualizing Immune Globulin Therapy

James L. Sheets, Pharm.D.

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About Me

- **18 Years of Experience in Home Infusion**
- **Co-Founder & CEO for CSI Pharmacy**
- **IgNS Committee Member**
- **Therapure Biopharma Advisory board member**
- **BoD for MG Hope Foundation**



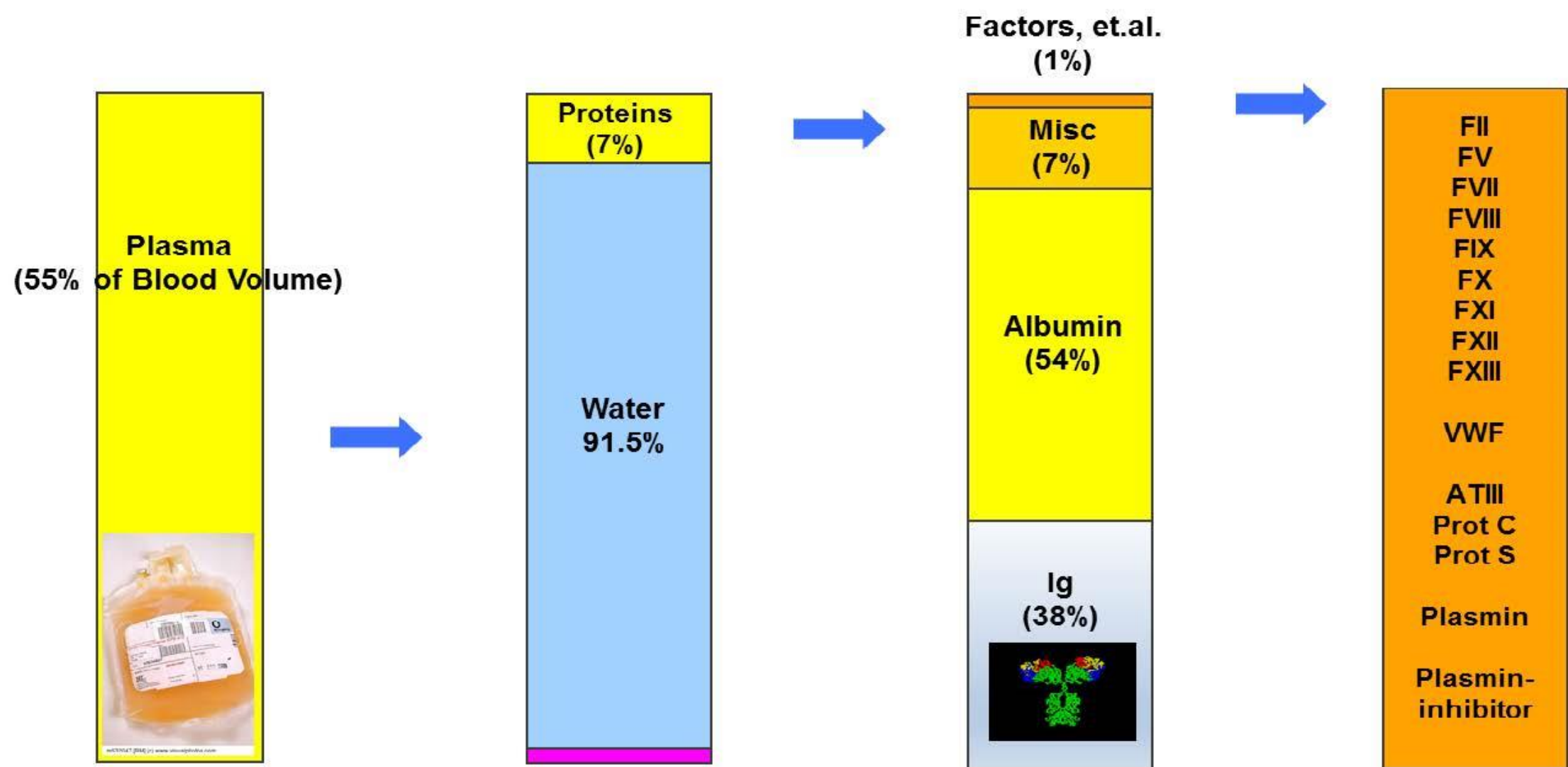
Objectives / Goals

- What is Immune Globulin Therapy? IVIG versus SCIG
- How can IG Therapy be individualized?
 - Brand Selection
 - Hydration & Infusion Rate
 - Adverse Reactions (Prevention versus Treatment).
- Complaints we have heard about home infusion.

What is IVIG

- **Immune Globulins = Antibodies (IgA, IgD, IgE, IgG, & IgM)**
- **Intravenous Immune Globulins (IVIG)**
 - 10 brands of IVIG, 3 brands of SCIG in the U.S.
 - manufactured from plasma pools (1,000 to 60,000 donors)
 - primary component is IgG
 - brands generally considered equally effective, however have different tolerability profiles.

Plasma Products

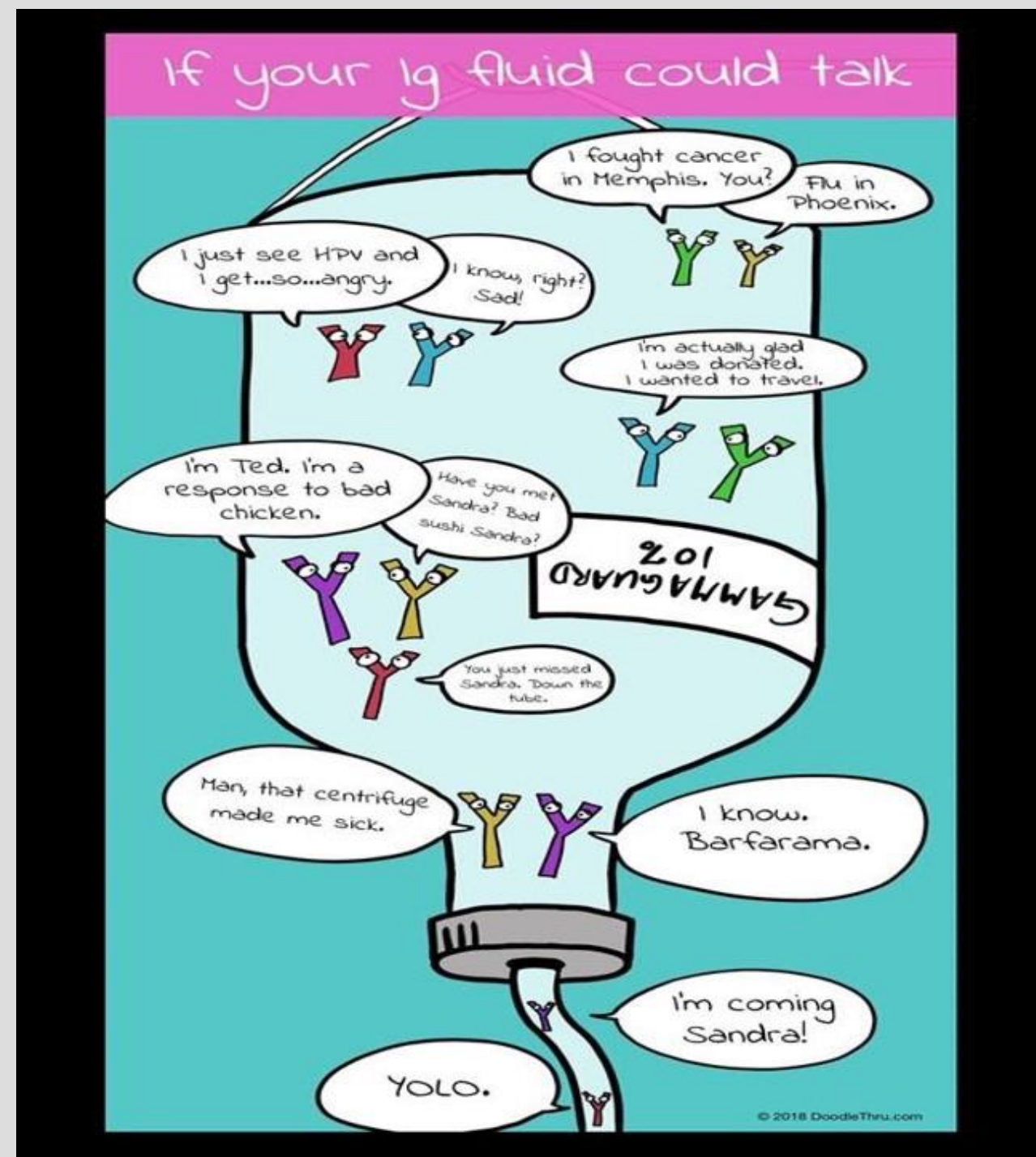


Antibody Function

Fight off harmful substances in the body.

Recognize antigens on the surface of pathogens and toxins.

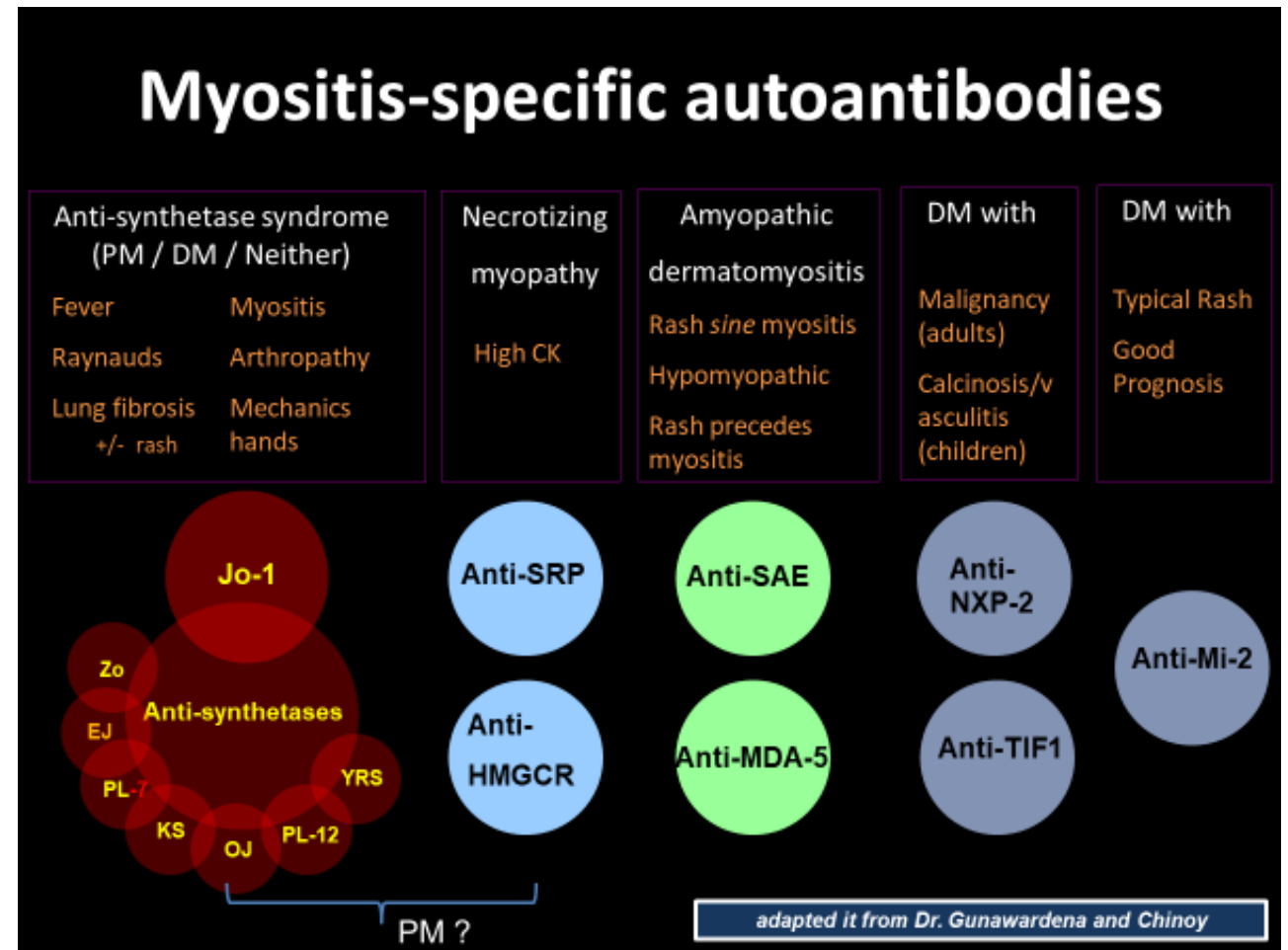
Facilitate the neutralization, destruction, and elimination of pathogens and toxins.



Autoimmune Disorders

- Autoantibodies incorrectly label a healthy normal part of the body as harmful.

- IG Therapy (IVIg or SCIG) decreases the production of these autoantibodies.



IVIg and SCIG Preparations Approved For Use In The United States

Product	Route	Manufacturer	Indications
Carimune NF 3%, 6%, 9%, 12% (once reconstituted)	IV	CSL Behring	<ul style="list-style-type: none"> • Primary humoral immunodeficiency • Immune thrombocytopenic purpura
Cuvitru 20%	SC	Shire	<ul style="list-style-type: none"> • Primary humoral immunodeficiency
Flebogamma DIF 5%, 10%	IV	Instituto Grifols, SA	<ul style="list-style-type: none"> • Primary humoral immunodeficiency
Gammagard Liquid 10%	IV/SC	Shire	<ul style="list-style-type: none"> • Primary humoral immunodeficiency (IV/SC) • Multifocal motor neuropathy (IV)
Gammagard S/D 5%, 10% (once reconstituted)	IV	Shire	<ul style="list-style-type: none"> • Primary humoral immunodeficiency • B-cell chronic lymphocytic leukemia • Immune thrombocytopenic purpura • Kawasaki syndrome
Gammaked 10%	IV/SC	Kedrion Biopharma	<ul style="list-style-type: none"> • Primary humoral immunodeficiency (IV/SC) • Immune thrombocytopenic purpura (IV) • Chronic inflammatory demyelinating polyneuropathy (IV)
Gammaplex 5%, 10%	IV	Bio Products Laboratory	<ul style="list-style-type: none"> • Primary humoral immunodeficiency • Immune thrombocytopenic purpura
Gamunex-C 10%	IV/SC	Instituto Grifols, SA.	<ul style="list-style-type: none"> • Primary humoral immunodeficiency (IV/SC) • Immune thrombocytopenic purpura (IV) • Chronic inflammatory demyelinating polyneuropathy (IV)
Hizentra 20%	SC	CSL Behring	<ul style="list-style-type: none"> • Primary humoral immunodeficiency
HyQvia 10%	SC	Shire	<ul style="list-style-type: none"> • Primary humoral immunodeficiency
Octagam 5%, 10%	IV	Octapharma Pharmazeutika Octapharma USA	<ul style="list-style-type: none"> • Primary humoral immunodeficiency (5%) • Chronic immune thrombocytopenic purpura (10%)
Privigen 10%	IV	CSL Behring	<ul style="list-style-type: none"> • Primary humoral immunodeficiency • Immune thrombocytopenic purpura • Chronic immune thrombocytopenic purpura

July 2017 - Octapharma granted orphan drug status for the use of Octagam 10% in dermatomyositis

Aug 2018 – FDA approves Octapharma’s new IVIG product ... Panzyga 10%

PHASE III Trial – proDERM Study in DM by Octapharma.

2gm/kg IVIG Q 4 weeks in refractory DM.

Individualized Therapy

- Prevention of adverse effects
 - Product Selection.
 - Hydration & Pre-medications
 - Taper up rate slowly.
- Treatment of adverse effects
- Customize future Infusions

General Statements on Product Differences

- IG Manufacturers have tweaked their formulations over the past decades in an effort to improve their product's safety
- The primary component of Ig products is immunoglobulin G (IgG). Brands of Ig can differ in IgG monomer, dimer, and aggregate concentrations, IgA and IgM content, stabilizers, additives, and levels of impurities.
- These differences result in different side-effect profiles
- By appropriate product-selection & utilization, the rate of adverse drug reactions and adverse events can be reduced!

Brand Name	Carimune NF	Flebogamma DIF	Gammagard Liquid	Gammagard S/D IgA <1 µg/mL in a 5% solution	Gammaplex	Gamunex-C Gammaked	Octagam	Privigen
Form	Lyophilized	Liquid	Liquid	Lyophilized	Liquid	Liquid	Liquid	Liquid
Shelf-Life/Storage Requirement	24 months RT	24 months RT	36 months REF 24 months RT	24 months RT	36 months RT	36 months REF 6 months RT	24 months RT (5%) 24 months REF (10%)	36 Months RT
Concentration	3-12%	5%, 10%	10%	5%, 10%	5%, 10%	10%	5%,10%	10%
Stabilizer	Sucrose	Sorbitol	Glycine	Glucose, Glycine	Sorbitol, Glycine, Polysorbate 80 (5%) Glycine, Polysorbate 80 (10%)	Glycine	Maltose	Proline
Sodium Content mEq/L	20 mg/gm Ig 154 (NS as diluent)	<3.2	No added sodium	146 @5% 292 @10%	30-50 (5%) ≤5 (10%)	<7	≤30	Trace Amounts
Osmolality (mOsm/kg)	192-1074 (3-12%) 384 (6% SWFI)	240-370	240-300	636 (5%) 1250 (10%)	Not <240, typically 420-500 (5%) Not <240, typically 280 (10%)	258	310-380	320
pH	6.4-6.8	5.0-6.0	4.6-5.1	6.8±0.4	4.8-5.1 (5%) 4.9-5.2 (10%)	4.0-4.5	5.1-6.0 (5%) 4.5-5.0 (10%)	4.8
IgA Content (µg/ml)	1000-2000 (6%)	Average: <3 (Specification value: <50 [5%], <100 [10%])	37	≤1 @5% ≤2 @10%	<10 (5%) <20 (10%)	46	<100 (5%) Ave 106 (10%)	≤25
anti-A/anti-B titers	Very Low	Unknown	Moderate	Unknown	Unknown	High	Low	High* (*Will be lower)

Risk Factors Affecting Tolerability

Risk Factors	IVIG Factors					
	Volume Load	Sugar Content	Sodium Content	Osmolality	pH	IgA
Cardiac Impairment	●		●	●		
Renal Dysfunction	●	●	●	●		
Anti-IgA Antibodies						●
Thromboembolic Risk	●		●	●		
Diabetes		●				
Geriatrics	●	●	●	●		
Neonates/Pediatrics	●		●	●	●	

1. IVIG Medication Safety. Retrieved from Pharmacy Practice News on February 18, 2015, at http://pharmacypracticenews.com/download/IVIG_safety_ppr0910_WM.pdf

IVIG & SCIG Dosing in DM & PM

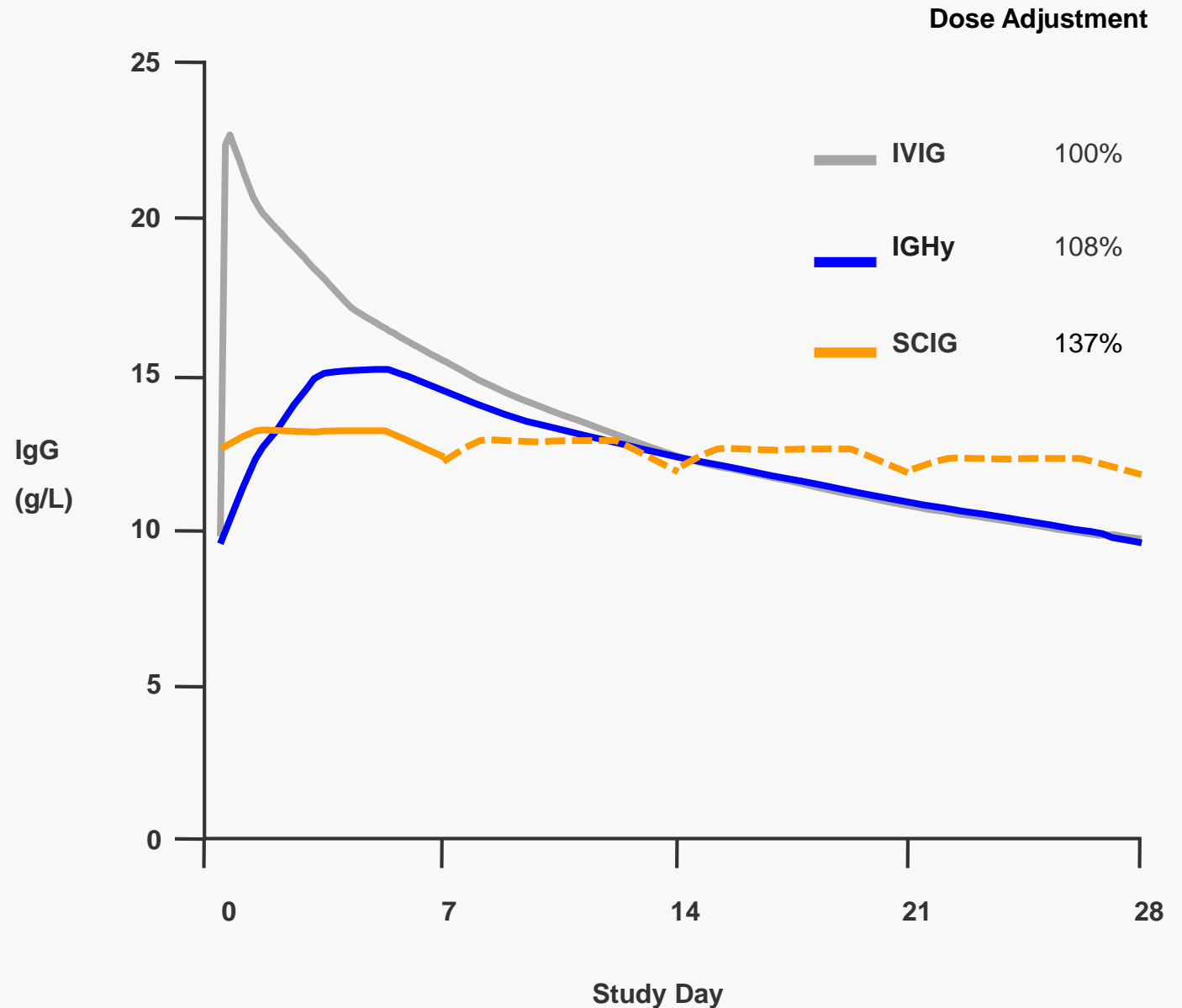
IVIG dose in dermatomyositis & polymyositis	2gm/Kg in divided doses over 2 to 5 days. Typically dosed once month and then according to patient response*
SCIG dose in Dermatomyositis & Polymyositis	Varies greatly, and not well defined in the literature. In our experience; 2gm/Kg per month divided into once weekly or twice weekly doses.

- **IgNS Immunoglobulin Therapy Standards of Practice AANEM Consensus, IVIG 2009**

Dosing Frequency

IVIG typically dosed every 2 to 4 weeks.

SCIG typically dose once or twice weekly.



Prevention of Adverse Reactions

- Product Selection based on risk factors
- Pre-medicate with Tylenol & Benadryl
- **Adequate Hydration**
- **Slow Infusion rate**

IVIIG Infusion Reactions

- 1) Aseptic Meningitis (Severe Post Infusion Headache)
- 2) Headaches during infusion or Hypertension/Hypotension
- 3) Flu-Like Symptoms
- 4) Dermatological
- 5) Anaphylactic reactions
- 6) Rigors
- 7) Severe Back and/or Leg pain
- 8) Thromboembolic events
- 9) Hemolytic Anemia

Anaphylactic Reaction

- True anaphylactic reactions to Ig therapy are extremely rare, but should be prepared for.
- Patient will experience severe hypotension and difficulty breathing.
- Stop Infusion, administer EPI & IV Benadryl, call emergency services
- IgA deficient patients may be at higher risk – choose low IgA product or switch to SCIG

Aseptic Meningitis (severe post-infusion headache)

- Severe HA after infusion, lasting for hours to days.
- Ig Induced inflammation of the spinal cord.
- Risk factors – high dose, rapid infusion, dehydration, history of migraine.
- Future infusions – Aggressive Hydration, slow infusion rate, Switch Brands, Ideal candidates for SCIG

Headache during the Infusion and/or Hypertension / Hypotension

- May be due to low levels of impurities or high concentration of Ig proteins.
- Slowing the infusion rate often rapidly reverses these side effects (establish max rate).
- Pretreatment with APAP, Benadryl, and Hydration
- Future infusions – If necessary, may switch brands or try SCIG

Flu-Like Symptoms

- Can be mild to moderate occurring hours to days after the infusion.
- Slowing the infusion rate and add pre and post-infusion hydration.
- Pretreatment with APAP & Solu-Medrol 1mg/Kg (max 125mg) IV push over at least 5 minutes.
- Switch Brands or try SCIG (very low incidence).

Dermatological (Rash or Hives)

- Likely allergic reaction to a component in the IVIG solution.
- Usually can be treated with single dose of antihistamine or glucocorticoid.
- Future Infusions – pre-medicate with antihistamine, switch IVIG brands, if necessary try SCIG.

Other Adverse Effects

Thromboembolism

- Increased plasma viscosity, Factor Xia

Acute Renal Failure

- Most associated with sucrose-containing Ig

Hemolytic Anemia

- Select Brand with low anti-ABO titers
- Separate Doses
- Switch to SCIG

Subcutaneous Immune Globulins (SCIG)

- Hizentra 20%
- HyQvia 10%
- Cuvitru 20%

- Gammagard Liquid, Gamunex-C & Gammaked may be administered IV or SC



Brand Name	Cuvitru	Gammagard Liquid	Gamunex-C / Gammaked	Hizentra	HyQvia
Form	Liquid	Liquid	Liquid	Liquid	Liquid
Shelf-Life/Storage Requirement	36 months REF 12 months RT	36 months REF 24 months RT	36 months REF 6 months RT	30 months RT	36 months REF 3 months RT
Concentrations	20%	10%	10%	20%	10%
Sugar Content (mg/ml)	None	None	None	None	None
Sodium Content (as Sodium Chloride) mEq/L	None	No added sodium	Trace Amounts	≤10	No added sodium
Osmolarity/ Osmolality (mOsm/kg)	280-292	240-300	258	380	240-300
pH	4.6-5.1	4.6-5.1	4.0-4.5	4.6-5.2	4.6-5.1
IgA Content (µg/mL)	(Ave) 80	37	46	≤50	37
anti-A/anti-B titers	Unknown	Moderate	High	Unknown	Moderate

SCIG Possible Advantages

- Subcutaneous weekly infusions keep IgG levels at a steady state – consistent
- No pre-meds required
- Side effects are mainly – localized*
- Autonomy and independence
- NO VENOUS ACCESS

Complaints with Home IVIG / Unacceptable Practices

- Pharmacy sent me a bill for my IVIG/SCIG because it wasn't covered by my insurance.
- I was told Medicare doesn't cover my IVIG unless I go to an infusion suite.
- Nurse starts infusion leaves patient and comes back at end of infusion.
- Nurse will only infuse IVIG but not saline/hydration.
- Nurse will stay for maximum of 4 hours because insurance will only cover that many hours.

Complaints with Home IVIG / Unacceptable Practices

- Nurse trains patient on how to infuse through port. Patients believe if they have serious adverse reaction they can administer an epi pen and call 911.
- Nurse tells patient that they have to infuse fast because they are required to see a certain number of patients a day.
- Patients having increased side effects...aseptic meningitis which can be due to fast rate of infusion.

Complaints with Home IVIG / Unacceptable Practices

- Lack of follow-up by nurse or home infusion company regarding reactions.
- Lack of training on administering IgG.
- Lack of hygiene (washing hands)



Q & A

james@csipharmacy.com

Toll Free: 1-844-680=2944

Treatment of Infusion reactions

- Slow Infusion Rate
- Administer IV Fluids
- Solu-Medrol 1mg/Kg (max 125mg) IV push over at least 5 minutes. May add as a premedication for future infusions.
- Consider a brand change
- Inability to tolerate IVIG, consider switching to SCIG