IVIg Medication Safety: Facts and Fantasies associated with Use.

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Disclosure

I have financial relationships with the following manufacturers of IVIG:
CSL Behring: Research
Shire: Advisory Board; Speakers Bureau
**Goals and Objectives**

- **Objectives**
  - Differentiate the patient risk factors and how they may influence IVIG product selection
  - Compare and contrast the main IVIG product features that may affect tolerability
  - Define and compare the importance and differences of IVIG stabilizers
  - Describe the impact of rate of IVIG administration as it pertains to adverse events
  - List FDA-approved indications and the primary off-label uses of IVIG

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**What is IVIG or IGIV?**

- Intravenous immunoglobulin
- (IVIg) : (IGIV) is a sterile, highly purified immunoglobulin (IgG) preparation made from pooled human plasma
Introduction

- Since 1979, IVIG has been used for the treatment of primary immune deficiency disorders and numerous autoimmune diseases.
- During this time, the manufacturers of these products have worked to improve the safety profile through improvements in purification and stabilization.
- Clinicians through observation have improved the tolerability of IVIG for their patients.
- By appropriate product selection and utilization the rate of adverse events can certainly be reduced.
- By following the IVIG safety algorithm every attempt is made to maximize the safe use of IVIG and reduce the adverse reactions commonly associated with the infusion of these products.

FACTS AND FANTASIES

- Since the introduction of the first IVig in 1979 there have been “mythological” practices that have evolved.
- Some of these practices have been based on “fantasy” from observation and assumption of fact.
- It is best to practice medicine based on literature support and fact rather than “fantasy”.
- Today we will try to explore some of these related to the utilization of IVig.
### Chronology of IGIV Developments

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1944–1979</td>
<td>Only lmIgG* (aggregates caused severe reactions when given IV)</td>
</tr>
<tr>
<td>1979</td>
<td>1st IGIV was Fc cleaved and only for PID</td>
</tr>
<tr>
<td>1981</td>
<td>1st intact IGIV also indicated for ITP</td>
</tr>
<tr>
<td>mid-1980s</td>
<td>Low-IgA products developed</td>
</tr>
<tr>
<td>1990</td>
<td>NIH consensus conference</td>
</tr>
<tr>
<td></td>
<td>• all IVIG products clinically comparable</td>
</tr>
</tbody>
</table>

### Chronology of IVIG Developments

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>mid-1990s</td>
<td>HCV transmitted: new anti-viral steps added (S/D; pasteurization; antibody screening)</td>
</tr>
<tr>
<td>Late 1990s</td>
<td>Sucrose nephropathy warnings</td>
</tr>
<tr>
<td>2002</td>
<td>• ADE/thrombosis warnings</td>
</tr>
<tr>
<td></td>
<td>• Off-label uses predominate the market</td>
</tr>
<tr>
<td>2003</td>
<td>New Advances in IVIG safety (nanofiltration)</td>
</tr>
<tr>
<td>2006</td>
<td>• First SCIG marketed in US (Vivaglobin)</td>
</tr>
<tr>
<td></td>
<td>• Maltose warnings</td>
</tr>
<tr>
<td>2008</td>
<td>New Indications (CIDP)</td>
</tr>
<tr>
<td>2010</td>
<td>Octagam recall</td>
</tr>
<tr>
<td>2012</td>
<td>Widest selection of IV and SC IgG products available</td>
</tr>
<tr>
<td></td>
<td>New FDA approved indication for MMN</td>
</tr>
<tr>
<td>2014</td>
<td>HyQVIA comes to the Market</td>
</tr>
</tbody>
</table>
The Perfect match of the right IVIG to the right Patient

Are all Patients the Same?

**PATIENT and IVIG RISK FACTORS**

<table>
<thead>
<tr>
<th>Patient Risk Factors</th>
<th>Volume Load</th>
<th>Sugar</th>
<th>Sodium</th>
<th>Osmolality</th>
<th>pH</th>
<th>IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Impairment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-IgA Abs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Thrombotic risk</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(pre) Diabetic risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Elderly</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal/pediatric</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Are all IVIG products the Same?

- All buying groups would like you to believe they are all the same so that they can be bid head to head and the lowest bid wins?
- The products are all generic equivalents (fantasy)
- All IVIG products have the same FDA indications. (fantasy)
- All IVIG products can be given both IV and SC (fantasy)
- All IVIG products can be dosed by lean body weight (fantasy)
- Only IVIG products with the lowest IgA can be given to patients with low IgA levels (fantasy)

So you are Considering Using IVIG…now What?

- How much does he weigh?
- Are there any side-effects?
- IVIG 2gm/kg!
- Pre-Meds?
Challenging Patient:
Which of these comorbidities are important to IVIG considerations?

- 67 yo Male patient
- Comorbidity: Diabetes mellitus
- PIDD
- Paraproteinemia
- Mild renal impairment
- Thyroidectomy
- Cholecystectomy
- Volume depleted
- Any concerns about IVIG choice or administration restrictions?

IVIG “Black” Box Warning

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients with immune globulin intravenous (IGIV) products.

Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose.
IVIG “Black” Box Warning

RISK OF THROMBOSIS

Thrombosis may occur with immune globulin products
Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors.
Thrombosis might occur in absence of known risk factors.

IVIG Safety Algorithm
All Patients are the Same!

- Fantasy!
- Some Clinics will give all patients a flat dose regardless of their weight
- They will give all patients pre-medications no matter if they ever had any adverse reactions
- All patients are given IVIG at the same rate
- All patients tolerate IVIG the same! Fantasy!
- All of these are NOT best practice

Patients are not all the SAME
Intravenous Immune Globulin Safety Algorithm

IVIG Ordered By Prescriber

- FDA approved Indications: PID, ITP, Kawasaki’s, CLL, CIDP, MMN
- Order Reviewed by Nurse/Pharmacist
- Institutional approval
- Off-Label Indications: P&T committee Approved: Evidence Based support

IVIG is Good for Everything!

- FANTASY!
- On the television series “House MD” IVIG was used as the miracle cure in “virtually” every other episode!
- Despite case reports of its use in well over 100 indications in the literature. The body of evidence supports its use in 3 main categories of use
FDA approved indications:

- Primary immunodeficiencies
- Idiopathic thrombocytopenic purpura (ITP)
- Chronic lymphocytic leukemia (CLL)
- Kawasaki syndrome
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (2008)
- Multifocal Motor Neuropathy (2012)
- Bone marrow transplantation (BMT)
- Pediatric HIV

Off Label Indications

- 1st line: IVIG is recommended.
  - literature based evidence controlled trials or significant case based evidence
- 2nd line: IVIG should be considered
  - Limited literature based evidence in open label trials and case series
- 3rd line: IVIG may be considered
  - Small trials or case reports when all other standard therapies have failed
- 4th line: IVIG is not recommended
  - Literature does not support it’s use
Examples of Off label indications

**Primary**
- Guillain-Barre Syndrome
- Panautonomic Polyneuropathy
- Miller Fisher Syndrome
- Cross Match Positive Solid Organ Transplantation
- Multiple Myeloma
- Hemolytic disease of the newborn

**Secondary**
- Mucocutaneous Blistering Diseases
  - Pemphigus Vulgaris
  - Pemphigus Foliaceus
  - Mucous Membrane Pemphigoid (Linear Pemphigoid)
  - Epidermolysis Bulla Acquisita
- Myasthenia Gravis Syndrome
- Lambert Eaton Syndrome
- Multiple Sclerosis
- Inflammatory Myopathies
  - Dermatomyositis
  - Polymyositis
- Idiopathic Progressive Polyneuropathy
- Intractable Epilepsy
- Acute Cardiomyopathy
- Pure Red Cell Aplasia
- Hemolytic Anemia
- Refractory Platelet Transfusions
- FAIT (Fetal Autoimmune Thrombocytopenia)
- Stiff Person Syndrome
- HIV associated Thrombocytopenia

**Third line indication**
- Parvovirus Associated Disease
- rMAS (Reactive Macrophage Activation Syndromes)
- Haemophagocytic Lymphohistiocytosis
- Acute Hemolytic Rejection with Solid Organ Transplantation
- Wegener's Vasculitis
- Still's Disease
- Severe Asthma
- Cystic Fibrosis
- Nephrotic Nephritic Syndrome
- Von Willebrand Disease
- Spontaneous Abortion with Antiphospholipid Antibodies
- SLE (Systemic Lupus Erythematosus)
- Evan's Syndrome
- Blackfan Diamond Anemia
- Asymptomatic Factor VIII inhibitors
- Rheumatoid Arthritis
- Inclusion body Myositis
- Shy-Drager Syndrome
- Invasive Group A streptococcal facinate and septicemic
- Infectious disease prophylaxis in high risk neonate patient
- Infectious disease prophylaxis in solid organ transplant patient
- Infectious disease prophylaxis in high risk HIV patient
- Sjogren’s Syndrome
- Landau-Kleffner Syndrome
- Cystic Periphlebitis
- Birdshot Retinochoroidopathy
- TEN (Toxic Epidermal Necrolysis)
- Lyell’s Syndrome
- Stevens-Johnson Syndrome

**Fourth line Indications**
- West Nile Virus
- Infectious disease treatment
  - Trauma patient
  - High Risk Neonate
  - Burn Patient
- Chronic Fatigue (Unknown Cause)
- Congenital heart block
- Cystic Fibrosis
- Spontaneous Abortion (Unknown Cause)
- Congestive Heart Failure
- Thrombotic Thrombocytopenic Purpura
- Diabetes Mellitus
- Acute Cerebellar Ataxia
IGIV Product Features Potentially Affecting Tolerability

Finding the “right match” for the patient is a critical clinical concern

- Volume load (rate of infusion)
- Osmolality
- Sodium content
- Sugar content
- IgA content
- pH

ALL IVIG PRODUCTS ARE NOT THE SAME
**IVIG Dosing**

**Dose Selection:**
- 400mg/kg/5 days
- Most Indications: 2000mg/kg Per Course of therapy
- 1000mg/kg/2 days
- 500mg/kg/4 days

**Weight based dosing**

**Fat Cells**
**IVIG Weight Selection**
All PI use actual bodyweight for dosing!

- In most cases
  - Use Actual Body Weight

- If >100kg
  - Or
  - BMI >30

- Calculate Ideal Body Weight

\[(\text{ABW} - \text{IDW}) \times 0.5 + \text{IDW} = \text{Dosing Weight}\]

**IVIG Dosing Parameters**

- IVIG Dosing Calculation=Adjusted Body Weight=IBW + 0.5 (actual body weight–IBW)
- BMI=703 x (weight in pounds/height in inches^2)
- IBW (kg) for males=50 + [2.3 x (height in inches–60)]
- IBW (kg) for females=45.5 + [2.3 x (height in inches–60)]
- Adjusted Body Weight=IBW + 0.5 (actual body weight–IBW) *IVIG specific method
### Ideal Weight, Actual Weight or Adjusted Weight?
#### For Replacement Therapy (PIDD)

<table>
<thead>
<tr>
<th>Weight</th>
<th>Pediatrics</th>
<th>Adult –non-obese</th>
<th>Adult obese &gt;100kg &gt; 30 BMI</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideal</td>
<td>X (ck IgG level)</td>
<td>X</td>
<td></td>
<td>Level may be too low</td>
</tr>
<tr>
<td>Adjusted</td>
<td>X</td>
<td></td>
<td></td>
<td>ck IgG level</td>
</tr>
<tr>
<td>Actual</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Infusion rate may increase ADR</td>
</tr>
</tbody>
</table>

### Ideal Weight, Actual Weight or Adjusted Weight?
#### For Immunotherapy (ITP,CIDP)

<table>
<thead>
<tr>
<th>Weight</th>
<th>Pediatrics</th>
<th>Adult –non-obese</th>
<th>Adult obese &gt;100kg &gt; 30 BMI</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideal</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Check for clinical result or delay in therapeutic effect</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td></td>
<td>X</td>
<td>Check therapeutic effect</td>
</tr>
<tr>
<td>Actual</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Infusion rate may increase ADR</td>
</tr>
</tbody>
</table>
# IVIG Rate Determination

Follow Manufacturer's guidelines*

Always escalate Rate through 3 phases

Reduce rate if adverse events are noted
Use pre-medications if adverse events are noted

Stop infusion if reactions don't subside

Determine patients' maximum tolerated rate

## IVIG Rate Determination Table

<table>
<thead>
<tr>
<th>IVIG</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate</th>
<th>Maximum Infusion Rate</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carimune NF 6%</td>
<td>0.5 mg/kg/min (0.5 mL/kg/hr)</td>
<td>1 mg/kg/min - 2 mg/kg/min* (1.0 mL/kg/hr - 4.0 mL/kg/hr )</td>
<td>3 mg/kg/min (3.0 mL/kg/hr)*</td>
<td>Increased risk of renal and thrombotic adverse effects</td>
</tr>
<tr>
<td>Prisivgen 10%</td>
<td>0.5 mg/kg/min (0.3 mL/kg/hr)</td>
<td>Increase to 4 mg/kg/min (8.0 mL/kg/hr)</td>
<td>Increase to 8 mg/kg/min (16.0 mL/kg/hr) (for ITP)</td>
<td>For patients at risk of renal dysfunction or thrombotic events, administer Prisivgen at the minimum infusion rate practicable</td>
</tr>
<tr>
<td>Gammagard SD 5%</td>
<td>0.5 mL/kg/hr For 30 minutes</td>
<td>1– 2.0 mL/kg/hr Increase rate every 15 min as tolerated</td>
<td>4.0 mL/kg/hr for 5% 8.0 mL/kg/hr for 10%</td>
<td>15 micron filter required and supplied with administration set</td>
</tr>
<tr>
<td>Gammagard Liquid 10%</td>
<td>2.5 mL/kg/hr For 30 minutes (0.8 mg/kg/hr)</td>
<td>4.0 mL/kg/hr Increased gradually every 30 minutes as tolerated</td>
<td>5.0 mL/kg/hr (8.0 mg/kg/min)</td>
<td>Patients who are judged to be at risk of renal dysfunction or thrombotic complications be gradually titrated up to a maximum conservative maximal rate of less than 3.3 mg/kg/min (&lt; 20 mL/kg/hr)</td>
</tr>
<tr>
<td>Gamunex-C 10%</td>
<td>1 mg/kg/min (1.8 mL/kg/hr) 2 mg/kg/min (1.2 mL/kg/hr) for CIDP</td>
<td>3 mg/kg/min (4.8 mL/kg/hr) 6 mg/kg/min* (4.4 mL/kg/hr)</td>
<td></td>
<td>For patients at risk of renal dysfunction or thrombotic risk, infuse a minimum rate practicable</td>
</tr>
<tr>
<td>Flebogamma DIF 5% 10%</td>
<td>0.5 mg/kg/min (0.6 mL/kg/hr)</td>
<td>Increase gradually every 30 minutes as tolerated</td>
<td>5% 5 mg/kg/min* (8.0 mL/kg/hr) 10% (4.0 mL/kg/hr)</td>
<td>*Subjects over 65 are at increased risk of renal failure with IVIG treatment. For these subjects, and all others at risk of renal failure, the infusion rate of Flebogamma® DIF should be limited to 0.06 mL/kg/min (3 mg/kg/min)</td>
</tr>
<tr>
<td>Gammaplex 5%</td>
<td>0.5 mg/kg/min (0.6 mL/kg/hr)</td>
<td>4 mg/kg/min (6.0 mL/kg/hr)</td>
<td></td>
<td>For patients at risk of renal dysfunction or failure, administer Gammaplex at the minimum infusion rate practicable</td>
</tr>
<tr>
<td>Octagam 5%</td>
<td>0.6 mL/kg/hr for 30 minutes</td>
<td>1.2 mL/kg/hr for 30 minutes then 1.4 mL/kg/hr</td>
<td>4.0 mL/kg/hr</td>
<td>OCTAGAM is not supplied with an infusion set. If an in-line filter is used, the pore size should be 0.2 – 200 microns</td>
</tr>
</tbody>
</table>
Age Considerations

**Neonatal**
- pH concerns: Local phlebitis at Site of infusion
- Metabolic acidosis if rapid high volume infusion
- Caution: Limit volume infused
- Caution: Sodium and Osmolar load causing hyper viscosity

**Geriatric**
- Caution: Cardiac, renal or pulmonary insufficiency
- Caution: Limit volume infused
- Caution: Sodium, sugar and osmolar load causing hyper viscosity
Product Selection Based on Co-morbid Conditions

Diabetes Mellitus

Caution: Avoid Products that can increase Insulin Requirement

Glucose Stabilizers: Increase Insulin Requirement. Avoid or accounted for.

Sucrose Stabilizers: Do not increase glucose level in the blood.

Maltose Stabilizers: Do not increase glucose level in the blood.

Amino Acid Stabilizers: Do not increase glucose level in the blood.

Avoiding Glucose Monitoring Errors in Patients Receiving Other Sugars (February 2006)

- FDA issued warning about glucose monitoring when patients receive oral xylose, parenteral maltose or galactose.
- Several patients died when falsely elevated glucose levels were aggressively treated with insulin. The patients had been receiving IVIG products containing maltose.
- This problem occurs only with the monitoring method that uses an enzyme called GDH-PQQ. This method is employed in some glucose monitoring devices used by diabetics at home and in point-of-care settings.
- Caution should be exercised when administering products containing maltose and galactose.
### Additional Stabilizer Considerations

- **Sorbitol:**
  - Does not increase glucose level in the blood
  - Sorbitol is metabolized to Fructose: caution with Hereditary Fructose Intolerance (HFI).

- **L-proline:**
  - Does not increase glucose level in the blood
  - Contraindicated in patients with hyperprolinemia

- **Glycine**
  - Does not increase glucose level in the blood

### Pharmaceutical Aspects of IGIV: Stabilizer

<table>
<thead>
<tr>
<th>Product</th>
<th>Stabilizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flebogamma DIF (liquid, 5%/10%)</td>
<td>D-sorbitol</td>
</tr>
<tr>
<td>Gammagard™ 5% S/D, (lyophilized)</td>
<td>2% Glucose</td>
</tr>
<tr>
<td>Gammagard™ Liquid (liquid, 10%)</td>
<td>No sugar (glycine-based)</td>
</tr>
<tr>
<td>Gamunex-C™ (liquid, 10%)</td>
<td>No sugar (glycine-based)</td>
</tr>
<tr>
<td>Gammaked 10% (liquid 10%)</td>
<td>No sugar (L-proline-based)</td>
</tr>
<tr>
<td>Privigen™ (liquid, 10%)</td>
<td>10% Sucrose (at 6% concentration)</td>
</tr>
<tr>
<td>Carimune® NF, (lyophilized)</td>
<td>Sorbitol /Glycine Glycine</td>
</tr>
<tr>
<td>Gammaplex 5%/Gammaplex 10%</td>
<td>Sorbitol /Glycine Glycine</td>
</tr>
<tr>
<td>Octagam® (liquid, 5%, Octagam (liquid 10%)</td>
<td>10% Maltose Maltose (90mg/ml)</td>
</tr>
</tbody>
</table>
Pharmaceutical Aspects of IGIV: Osmolality/Osmolarity

<table>
<thead>
<tr>
<th>Product Description</th>
<th>Osmolality/Osmolarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flebogamma 5%/ 10% DIF</td>
<td>240-370 mOsm/L</td>
</tr>
<tr>
<td>Gammagard™ Liquid 10%</td>
<td>240-300 mOsm/kg</td>
</tr>
<tr>
<td>Gammagard™ S/D</td>
<td>5%: 636 mOsm/L; 10%: 1250 mOsm/L</td>
</tr>
<tr>
<td>Gamunex-C™ (liquid 10%); Gammaked 10%</td>
<td>258 mOsm/kg</td>
</tr>
<tr>
<td>Privigen™ (liquid, 10%)</td>
<td>240-440 mOsm/L</td>
</tr>
<tr>
<td>Carimune® NF (lyophilized)</td>
<td>In water: 3%: 192 mOsm/L; 6%: 384 mOsm/L; In saline: 6%: 690 mOsm/L; 12%: 1074 mOsm/L</td>
</tr>
<tr>
<td>Gammaplex 5%; Gammaplex 10%</td>
<td>420-500 mOsm/kg; 280-288 mOsm/kg</td>
</tr>
<tr>
<td>Octagam® (liquid, 5%,10%)</td>
<td>310-380 mOsm/kg</td>
</tr>
</tbody>
</table>

Product Selection Based on Co-morbid Conditions

Renal Insufficiency

- Assess and monitor patients’ serum creatinine, blood urea nitrogen, and urinary output.
- Ensure that patients are adequately hydrated before starting the IV Ig infusion.
- Prescriber renal insufficiency (any degree), diabetes mellitus, older than 65 years, volume depletion and dehydration, sepsis, paraproteinemia, therapy with concomitant nephrotoxic drugs.
- Slow infusion rate to maximal rate: For sucrose stabilized products maximum rate is 2mg/kg/min.
- Pick non-carbohydrate stabilized IV Ig if available.
- Use IV Ig with isotonic osmolality (~300mOsm/L).
Pharmaceutical Aspects of IGIV: Viral Inactivation Methods

<table>
<thead>
<tr>
<th>Product</th>
<th>Viral Inactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flebogamma DIF (liquid, 5%/10%)</td>
<td>Solvent detergent; nanofiltration (35 + 20 nm); pasteurization; low pH; PEG precipitation; Fraction II + III alcohol incubation; Fraction I precipitation</td>
</tr>
<tr>
<td>Gammagard™ S/D, (lyophilized)</td>
<td>Solvent detergent, ultrafiltration, anion exchange</td>
</tr>
<tr>
<td>Gammagard™ Liquid 10%</td>
<td>Solvent detergent; low pH nanofiltration 35 nm</td>
</tr>
<tr>
<td>Gamunex-C™ (liquid, 10%)</td>
<td>Caprylate precipitation / incubation; low pH</td>
</tr>
<tr>
<td>Privigen™ (liquid, 10%)</td>
<td>Depth filtration; nanofiltration 20 nm; low pH</td>
</tr>
<tr>
<td>Carimune® NF, (lyophilized)</td>
<td>Nanofiltration; low pH/ pepsin</td>
</tr>
<tr>
<td>Gammagard™ Liquid 5%,10%</td>
<td>Solvent Detergent, nanofiltration 20 nm low pH</td>
</tr>
<tr>
<td>Octagam® (liquid, 5%,10%)</td>
<td>Solvent detergent; low pH</td>
</tr>
</tbody>
</table>

Viral Log Reduction Comparison

<table>
<thead>
<tr>
<th>IVIG</th>
<th>Enveloped Viruses</th>
<th>NonE Virus</th>
<th>TSE (prion)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV</td>
<td>SV</td>
<td>BVDV</td>
</tr>
<tr>
<td>Flebogamma 5% DIF</td>
<td>&gt;20.3</td>
<td>&gt;6.49</td>
<td>&gt;11.92</td>
</tr>
<tr>
<td>Gamunex-C</td>
<td>&gt;14.0</td>
<td>16.3</td>
<td>12.2</td>
</tr>
<tr>
<td>Privigen 10%</td>
<td>&gt;16.0</td>
<td>&gt;9.4</td>
<td>&gt;12.2</td>
</tr>
<tr>
<td>Gammagard Liquid 10%</td>
<td>&gt;14.8</td>
<td>&gt;16.8</td>
<td>&gt;16.9</td>
</tr>
<tr>
<td>Octagam 5%</td>
<td>&gt;14.6</td>
<td>&gt;16.7</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Caprylate Treatment

- Caprylate is a saturated medium-chained (8) fatty acid
- Plant origin
- Non-toxic
- Caprylate precipitation/cloth filtration
- Caprylate incubation

Product Selection Based on Co-morbid Conditions

Past history of DVT, MI, PE or any thromboembolic disorder

- Consider baseline assessment of blood viscosity for those at risk for hyper viscosity
- Use IVIG with isotonic osmolality (~300mOsm/L)
- Slow infusion rate
- Lower dose infused per infusion
Precaution

Volume Considerations

Cardiac Patient
Pulmonary Edema
Thromboembolic Risk
Geriatric Patients
Neonatal Patients

Precautions

Aseptic Meningitis

May occur 5-7 days post infusion
Educate patient about the relationship with symptoms and IVIG

Aseptic meningitis syndrome may occur, especially with high doses or rapid infusion

Changing IVIG products
May/may not prevent syndrome
* Use isotonic osmolality
* Lower dose and
* Slower infusion rate
Precaution

Hemolysis

Monitor patients for hemolysis and hemolytic anemia

Hemolysis can develop subsequent to IVIg treatments due to enhanced red blood cell sequestration.

Educate patient to signs of hemolysis. If at risk, increase post infusion monitoring

Hemolysis

• More likely to occur:
  – Patients with A,B or AB
  – Total IVIG dose \( \geq 2 \text{ gm/kg} \)
  – Within 10 days of IVIG administration
Patient Case

- 32 year old male CIDP patient received 400mg/kg of IVIG and reported brown discolored urine the following day.
- Is this IVIG induced hemolysis?
- What is the proper procedure for follow-up?
- Will you give IVIG next month and if so what will you do anything different for monitoring?

Risk Factors for Hemolysis in Patients Taking IVIG

**Patient Risk Factors**
- Non-O Blood type
- Underlying inflammatory condition
- Female gender

**IVIG Risk Factors**
- Total dose >2 g
- Liquid IVIG product
- IVIG with high titer IgG antibodies to isohemagglutinins A/B
Evidence Confirming IVIG-associated Hemolysis

- Positive direct antiglobin
- Signs of hemolysis within 10 days of IVIG infusion
- Decrease in hemoglobin >1 g/dL
- Any 2 of the following laboratory findings:
  - ↑ reticulocyte count
  - ↑ lactate dehydrogenase
  - ↓ haptoglobin
  - ↑ serum bilirubin
  - Hemoglobinemia
  - Hemoglobinuria
  - Significant spherocytosis

Considerations To Reduce Risk for IVIG-associated Hemolysis

Routinely screen patients for possible hemolysis risk factors
- Limit the total dose per course of therapy administered per patient to 2 g/kg
- Consider adjusted dose regimen for obese patients (>100 kg and BMI >30)
- Split dose over 4-5 days and avoid regimens of 1 g/kg per day, when possible
- Monitor hemoglobin 48-72 h after IVIG infusion
- Consider using a lyophilized IVIG product with low anti-A/B IgG antibodies
Current FDA-Approved SCIg Products

- Hizentra 20% Immune Globulin Subcutaneous (Human)
- Cuvitru 20% Immune Globulin Subcutaneous (Human)
- Gamunex-C 10% Immune Globulin for IV and Subcutaneous Use (Human)
- Gammaked 10% Immune Globulin for IV and Subcutaneous Use (Human)
- Gammagard 10% Liquid Immune Globulin for IV and Subcutaneous Use (Human)

Reasons to consider Subcutaneous IgG

- Limited intravenous access
- Provide patient control over administration schedule
- Potentially improve quality of life and patient preference
## SCIg and IVIg Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>SCIg</th>
<th>IVIg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>Stable serum trough IgG level</td>
<td>Variability in serum IgG level between peak and trough</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Clinical efficacy demonstrated in PIDD (non inferior when compared with IVIg)</td>
<td>Clinical efficacy demonstrated in PIDD</td>
</tr>
<tr>
<td>Systemic side effects</td>
<td>Infrequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Administration</td>
<td>Self-administration; patient autonomy</td>
<td>Infusion center/ home setting with nursing support for venous access</td>
</tr>
<tr>
<td>Average length of infusion</td>
<td>1 to 2 hours</td>
<td>2 to 4 hours</td>
</tr>
<tr>
<td>Dosing interval</td>
<td>Weekly to Biweekly</td>
<td>Variable – every 2 to 4 weeks</td>
</tr>
</tbody>
</table>


## SCIg and IVIg Features (cont)

<table>
<thead>
<tr>
<th>Feature</th>
<th>SCIg</th>
<th>IVIg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common adverse events</td>
<td>Local reactions, headache, vomiting, and pain</td>
<td>Headache, chills, fever, myalgias, fatigue, nausea</td>
</tr>
<tr>
<td>Premedication</td>
<td>Typically not used</td>
<td>Acetaminophen, steroids, antihistamines (oral or intravenous) as needed</td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td>Flexibility of infusion frequency, site, patient autonomy, increased flexibility and independence</td>
<td>Need for venous access, desire for administration in an outpatient setting, need for nursing support staff</td>
</tr>
<tr>
<td>Associated costs</td>
<td>Cost of immunoglobulin, self-administration supply costs</td>
<td>Cost of immunoglobulin, nursing and facility costs, equipment costs, related infusion costs (ie, premedication, hydration)</td>
</tr>
</tbody>
</table>

Post Infusion SCIG

- The post-infusion “goose bump” will usually go down in a few hours
- Injection site swelling and mild inflammation is normal
- Rare but more serious site reactions have been reported

Future of SCIG

- Expectation is that use is to continue to increase
- Indications beyond PIDD
- Higher Volumes and Faster Rates being Explored
What is HyQVIA?

- **HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase]**
  - **Indication**
    - HYQVIA is an immune globulin with a recombinant human hyaluronidase indicated for the treatment of Primary Immunodeficiency (PI) in adults. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.
  - **Limitation of Use:**
    - Safety and efficacy of chronic use of recombinant human hyaluronidase in HYQVIA have not been established in conditions other than PI.

Adverse Events

- Hives, swelling in the mouth or throat, itching, trouble breathing, wheezing, fainting or dizziness.
- Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light.
- Reduced urination, sudden weight gain, or swelling in your legs. Swelling, warmth, redness, or a lump in your legs or arms, other than at the infusion site(s).
- Brown or red urine, fast heart rate, yellow skin or eyes. Chest pain or trouble breathing, blue lips or extremities.
Combination Packaging of Gammagard IG 10% + Hyaluronidase

Ramp up schedule: when getting started
Conversion from IVIG is 1:1 compared to SCIG

Patient Education and Documentation

- Patient Education and Documentation
- Documentation in the Medical Record: brand, rate, risks & tolerance
- Patient awareness of IVIG specific brand
- Patient has knowledge of IVIG rate escalation and tolerance
- Patient is aware of own risk factors
- Patient is aware of most recent IVIG dose
- Patient has knowledge of Pre-medication requirements
- Patient is aware of infusion related and delayed type of adverse events
Clinical Consideration: Matching the IGIV with the Patient Profile

Finding the “right match” for the patient

- IGIV patients are not all the same; nor are IGIV products
- The individual healthcare provider has to make a critical clinical decision as to the appropriate product selection

<table>
<thead>
<tr>
<th>Patient Risk Factors</th>
<th>IGIV Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume load</td>
</tr>
<tr>
<td>Cardiac Impairment</td>
<td>•</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>•</td>
</tr>
<tr>
<td>Anti-IgA Antibodies</td>
<td>•</td>
</tr>
<tr>
<td>Thromboembolic Risk</td>
<td>•</td>
</tr>
<tr>
<td>(Pre) Diabetic</td>
<td>•</td>
</tr>
<tr>
<td>Elderly Patients</td>
<td>•</td>
</tr>
<tr>
<td>Neonates/Pediatrics</td>
<td>•</td>
</tr>
</tbody>
</table>

Conclusions

- It is imperative to know the pharmaceutical differences of immune globulin products
- Clinical condition of the patient may dictate product selection or modification

- All Immune Globulin Products products are not the same!
- All Patients are not the Same!
Questions???