Immune Globulin

Clinical Overview Program

Objectives

- Discuss Autoimmune disorders
- Describe IG structure, properties and clinical implications
- Discuss IG product usage, storage and mixing guidelines
- Discuss medication administration guidelines
- Describe side effects and monitoring parameters

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Overview

- Autoimmune disease is any of a large group of diseases characterized by abnormal functioning of the immune system which causes the immune system to produce antibodies against ones own tissue

- According to the American Autoimmune Related Diseases Association, autoimmune disease affects approximately 50 million Americans with 75%-85% of the cases affecting women

- There are more than 150 chronic conditions are considered autoimmune disorders (Zack, 2014)

Overview (cont.)

- Autoimmune diseases are categorized according to the organ system that they affect the most

- According to the National Institute of Heath. Health care costs for autoimmune disorders is estimated to be in excess of **$100 billion dollars**

History

Year	History
1952	Burton first uses IM (IG), IV not yet safe
1960's	Investigational IVIG outside US
1970's	Investigational IVIG in US
1980's	First commercial IVIG
1990's	SCIG infusion in Europe; 1st IVIG shortages

Year	History
1994	Hepatitis C transmission reported
1995	Concern over Creutzfeld-Jakob Disease transmission
1998	Additional antiviral steps added
2004	Medicare approves IVIG for PID administration under part B SCIG is released in Europe
2006	SCIG released in the US

Immune System

- The immune system is a network of cells, tissues and organs that work together to protect the body against "foreign" invaders such as bacteria, parasites, viruses and fungi
- The role of the immune system is to prevent these "invaders" in the prevention of infection
- A malfunction of the immune system can lead to illness and infection

Components of the Immune System

- White blood cells (leukocytes)
  - Phagocytes (neutrophils)
  - Lymphocytes (B and T)
- Antigens
- Antibodies
- Complement

The Immune System

- 3 Types of immunity
  - Innate
  - Adaptive
  - Passive
- Problems of Immune system
  - Immunodeficiency
  - Autoimmune disorders
  - Allergic disorders
  - Cancers

What is Immune Globulin

- Derived from human blood
- Serves as the body's defense system against infection
- Also referred to as IVIG, IG, SCIG, gamma globulin, immunoglobulin

Understanding Immune Globulin

- Immune globulins
  - are produced by B cells and are also known as antibodies
  - naturally occurring in the blood plasma serum of healthy individuals

Immune Globulin Structure/Properties

- The purpose of immune globulins is to neutralize pathogens:

IgG	most common major Ig in serum which crosses placenta , purpose is to fight bacteria and some viruses
IgA	found in secretions such as blood, tears, and saliva
IgM	found in blood
IgD	function is poorly understood
IgE	found in trace amounts and is responsible for allergic reactions

IgG

- IgG is the most prevalent immunoglobulin (80%) found in the bloodstream
- IgG is formed in large quantities, and easily travels from the bloodstream to tissues
- Lasts for approximately 1 month.

IgG (cont.)

- IgG is produced upon second exposure to an antigen at which time it binds to the antigen
- IgG is the only immunoglobulin that crosses the placenta and passes immunity from the mother to the newborn
- IgG is broken into four subclasses:
  - IgG1
  - IgG2
  - IgG3
  - IgG4

Understanding Subclasses

- Functions of the IgG Subclasses

  – IgG1 and IgG3

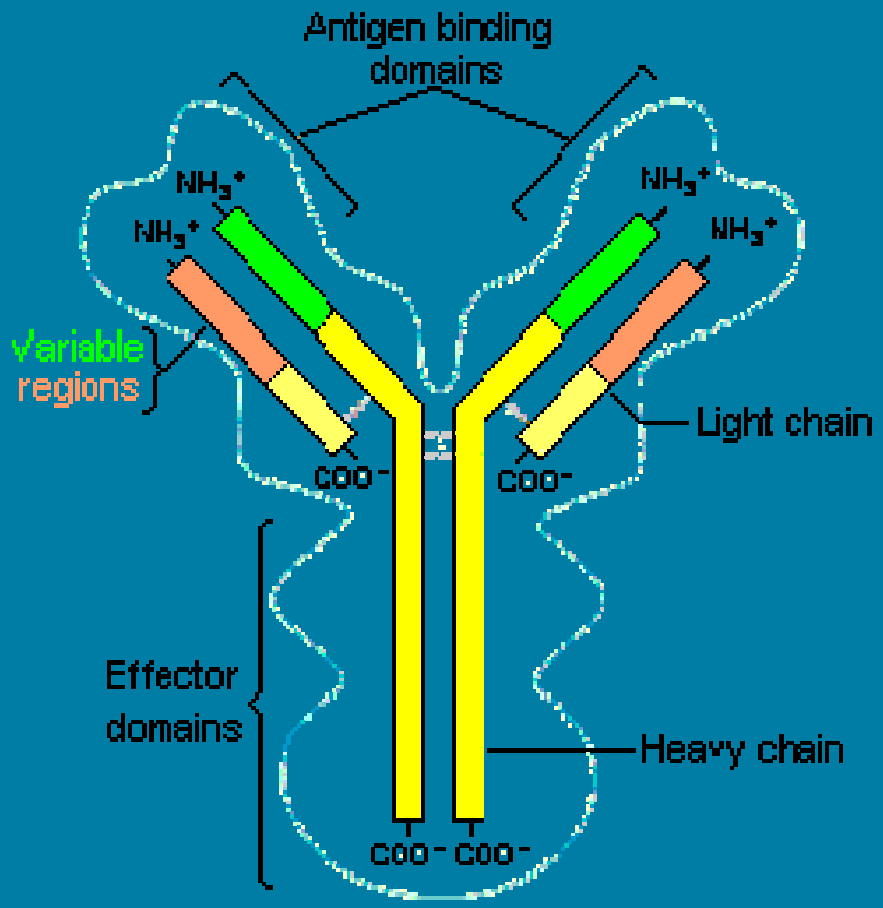
    rich in antibodies against proteins

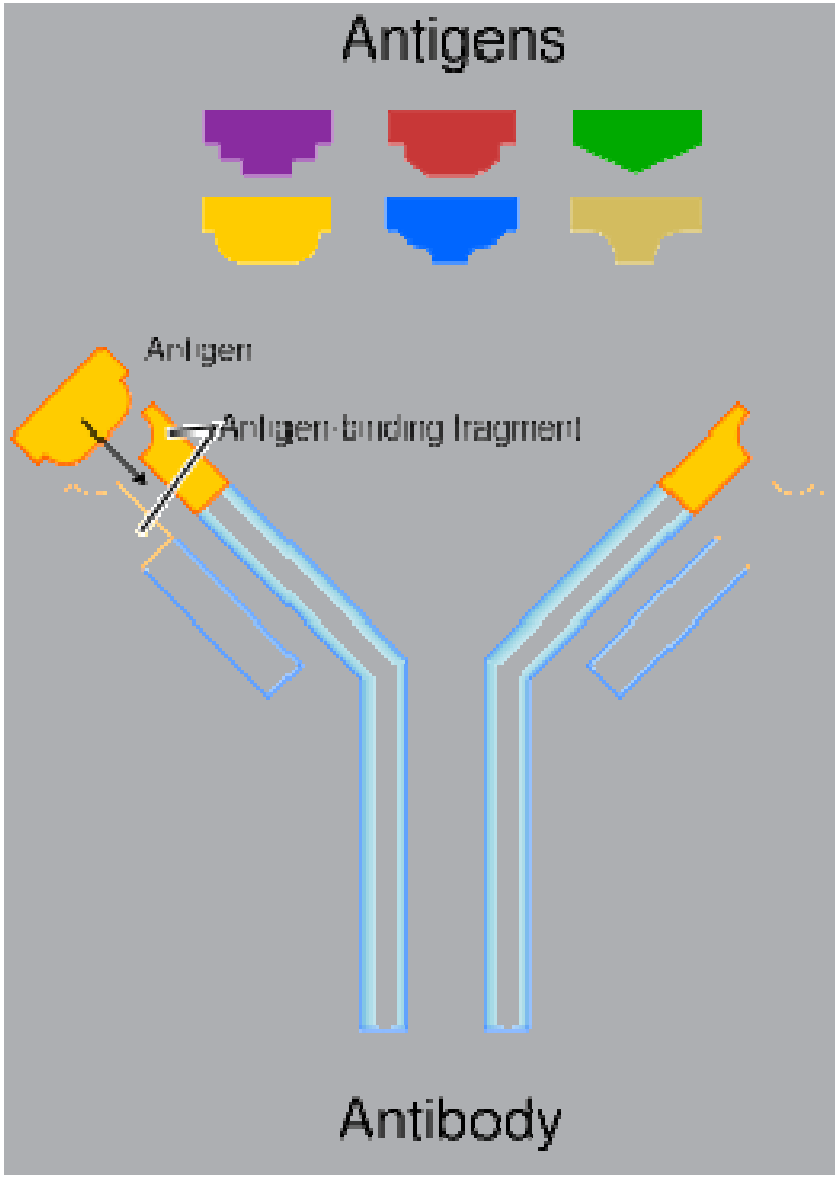
  – IgG2

    predominantly antibodies against the polysaccharide (complex sugar/carbohydrate) coating or capsule of certain disease producing bacteria

  – IgG4

    function is largely unknown possibly due to it's limited prevalence in the total IgG serum





Usage of IG

- Multiple mechanisms of action:
  - Protection against infection:
    - In congenital (primary) hypogammaglobulinemia and other primary immune deficiencies
    - In secondary immunodeficiencies such as CLL, transplant/rejection, chronic parvovirus and HIV infections.
  - Suppression of inflammatory & immune mediated processes
    - In autoimmune disorders such as ITP
    - In allergic diseases including JRA, Asthma, and dermatomyositis

FDA approved Indications IVIG

- Primary Immune Deficiency (PID)
- Kawasaki's Disease
- Chronic B-cell lymphocytic leukemia (CLL)
- Idiopathic Thrombocytopenia Purpura (ITP)
- Pediatric HIV I infection
- Bone marrow transplant (adults over 20 yrs)
- Chronic inflammatory demyelinating polyneuropathies

Non-FDA Approved Indications or Off-Label Use of IVIG

- Autism
- Alzheimer's disease
- Autoimmune hemolytic anemia
- Autoimmune neutropenia
- Bone marrow transplant; Adjunct
- Cytomegalovirus infection; Treatment and Prophylaxis
- Dermatomyositis, Systemic
- Guillain-Barré syndrome
- HIV infection
- Kidney disease
- Myasthenia gravis
- Neonatal jaundice
- Pemphigus vulgaris
- Renal transplant rejection
- Respiratory syncytial virus infection
- Sepsis
- Toxic shock syndrome
- Pre-transplant desensitization of highly-sensitized patients
- Uveitis
- von Willebrand disorder
- Fertility / Prevention of spontaneous abortion

s2

Current Products

- **Gammagard S/D** (Baxter)
- **Gammagard Liquid 10% (IV or SC route)** (Baxter)
- **Gammaplex** (Bio Products Labs)
- **Carimune NF** (CSL Behring)
- **Hizentra (SC route only)** (CSL Behring)
- **Privigen** (CSL Behring)
- **Flebogamma DIF** (Grifols)
- **Gammaked (IV or SC route)** (Grifols-Talecris)
- **Octagam** (Octapharma USA)
- **Gamunex – C (IV or SC route)** (Grifols-Talecris)

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s2 add types of stabilizing agents in speaker notes
setup, 5/27/2014

IG products	Manuf.	Storage	Shelf-life (months)	Stability after reconstitution
Carimunne NF	CSL Behring	Room temp	24; (PF)	24 hrs refrig.
Flebogamma 5%	Grifols	2-25°C (protect from light)	24; (PF)	N/A (Use promptly)
Gamunex 10%	Talecris	RT/refrigerated Do not freeze	6-36 depending on storage; (PF)	N/A (Use promptly)
Gammagard SD	Baxter	≤25°C; do not freeze	24; (PF)	24hrs refrig. Or within 2 hrs
Gammagard liq	Baxter	RT/refrig.; Do not freeze	9-36 depending on storage; (PF)	N/A
Octagam 5%	Octapharma	RT/refrig.; Do not freeze	18-24 depending on storage; (PF)	N/A (Use promptly)
Privigen	CSL Behring	RT/refrig.; Do not freeze	24; (PF)	N/A (Use promptly)
Hizentra	CSL Behring	RT; Do not freeze protect from light	30; (PF)	14 days

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Primary Immunodeficiency Disease

- Disorders resulting from mostly inherited defects of the immune system
  - humoral immune deficiencies
  - severe combined immunodeficiencies
  - disorders resulting from phagocytic and complement defects.
  - Congenital agammaglobulinemia
  - Common Variable immunodeficiency (CVID)
  - Wiskott-Aldrich Syndrome
  - X-linked agammaglobulinemia

Primary Immunodeficiency Disease

- Humoral immune deficiency:
  - Refers to diseases resulting from impaired antibody production
  - Either a molecular defect intrinsic to B cells or a failure of interactions between B and T cells
  - Cellular immunity is largely intact, in contrast to diseases classified as combined immunodeficiencies, despite underlying T cell defects in some of these diseases

Idiopathic Thrombocytopenia Purpura (ITP)

- There is no "gold standard" test that can establish the diagnosis of ITP
  - An acquired bleeding disorder in which the immune system destroys platelets
  - Individuals with the disease have too few platelets in the blood. ITP is sometimes called immune thrombocytopenic purpura

Common Variable Immunodeficiency (CVID)

- low total serum concentrations of IgG,
- low IgA and/or IgM, and T-lymphocyte dysfunction.
- poor or absent response to immunization,
- characteristic clinical manifestations in the absence of any other detectable molecular defect (such as XLA, hyper-IgM syndrome).

Chronic Inflammatory Demyelinating Polyneuropathies CIDP

- A rare disorder of the peripheral nerves characterized by gradually increasing weakness of the legs, and arms to a lesser extent as compared to the legs

Nursing Procedures

- Standard infusion therapy policies are used for dose administration
- Nursing documentation must include tolerance of the administration and if improvements are noted over time.
- Be specific in your documentation

First Dosing in Home

- Patient specific based off co-morbidities
- No history of adverse reactions
- No significant allergies
- Close proximity to EMS (911)
- Anaphylaxis orders obtained and dispensed
- Whenever possible a caregiver is present
- Nurse needs to stay for entire infusion unless physician specifies otherwise

IG Administration

- IVIG
  - Anaphylaxis medications must be available
  - IV access required (central or peripheral)
  - Dose administered at varying intervals (3-4 weeks common intervals)
  - Nurse must administer each dose
  - pH of 5-9
  - Osmolality < 600 mOsm/L
  - No more than 2 attempts for PIV placement/nurse
- SCIG
  - Anaphylaxis medications must be available
  - More frequent administration
    - Weekly or bi-weekly if large dose
  - Patient can self-administer
  - Shorter infusions time with multiple administration sites

Administration Guidelines

- IVIG should be provided under physician orders and based on the titration rates recommended by the manufacturer. First doses in the home are individualized according to patient co-morbidities

- Important that **first dosing** in a facility (outpatient hospital infusion center) of an IG product is the **same** as home infusion pharmacy prescription

- Changes in IVIG products requires first dosing AGAIN

IG Administration –Vascular Access

- Peripheral Short Catheter
- Central access devices
  - PICC
  - Port
  - Hickman
  - Groshong

IVIG Administration

- **Prior to infusing, verify the following:**
  - IV access (Central or peripheral venous access required)
  - Expiration date/lot# and record in notes
  - Brand of IG has not changed
  - Rate has been tolerated by patient,
  - Assess time since last infusion if applicable (i.e. 4 wks/6 wks)
  - Availability of emergency medications
  - Check for signs/symptoms of infection
  - IV catheter (24-22 gauge) available for infusion or equipment for central line administration

IVIG Administration (cont.)

- Dose of Ig is determined by weight in Kg, and monitored by IgG levels and/or clinical response
- Rates vary based on concentration, dose, patient's wt, diagnosis, and length of interval between therapies
- **IVIG:**
  - 0.3-0.5 gm/kg every 3-4 weeks in antibody-deficient patients
  - Do not exceed an infusion rate of 4 mg/kg per minute

Mixing Considerations

- Do not mix with other medications or solutions
- Multiple bottles of IG can be pooled into one bag for an infusion
- Solution should be clear with no visible particles
- Filter product prior to infusion or use tubing with filter
  - Vented tubing used for administration from glass bottles (inspect glass bottles)

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Mixing Lyophilized IG

- Bring diluent and powder to room temperature
- Remove plastic flip-off caps
- Wipe vial top with sterile alcohol prep pads, let be wet for at least 10 seconds, then allow to air dry
- Spike the diluent with transfer spike
- Invert concentrate bottle and press firmly onto the transfer device
- Invert and allow diluent to flow into concentrate
- Gently rotate bottle until all concentrate is thoroughly wet

Pooling IG Solution in the Home

Sterile Technique and Standard Precautions must be followed!

1. Wipe seal on each reconstituted Ig vial with alcohol.
2. Remove transfer tubing from package and aseptically attach a filter needle to one end.
3. Attach a vented vial access spike to the other end.
4. Wipe the rubber injection port of the empty IV bag with alcohol.
5. Insert the needle into the rubber injection port of the IV bag. Secure in place with tape.
6. Insert the spike into the center of the rubber seal.
7. Invert the vial and allow the solution to drain into the IV bag.
8. Remove the spike from empty vial and insert into new vial and repeat process until all vials are pooled.

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Compounding IG in the Home (if in powder form)

- *Sterile Technique and Standard Precautions must be followed!*

1. Remove lids from diluent and Ig powder
2. Access diluent vial first with 2 sided transfer needle, then insert into IG vial
3. After the diluent has been transferred, remove the empty vial and needle from the IG.
4. Gently swirl vials to help break up the Ig cake.
5. Repeat this procedure until all ordered vials are in solution

Nursing Assessment

- Full body assessment prior to infusion
- Patient assessment (during infusion)
  - Standard elements of patient evaluation
  - IV assessment (note complications i.e.)
    - Swelling at site
    - Phlebitis
    - Redness/Drainage
  - Allergic reaction / hypersensitivity
  - Vital Signs according to p/p and manufacturer recommendations
    - Decrease or stop infusion rate if required

IVIG Common Side Effects

- Infusion related side effects/ non anaphylactic reactions:
  - Headache
  - Fever
  - Chills
  - Nausea/vomiting
  - Muscle pain
  - Chest pain

Post Infusion Side Effect Management

- Flu-like symptoms
- Rash
- Headache/migraines (history of migraines)

- Management:
  - Acetaminophen, ASA, NSAIDS
  - Premed with propranolol (migraines)
  - Push fluids if appropriate

Rare/Serious Side Effects

- Hemolytic anemia
- Blood clots
- Pulmonary edema
- Aseptic meningitis syndrome
- Anaphylactic shock – greater in patients with IgA deficiency
- Renal dysfunction and failure – especially with preparations that are very concentrated/high sugar content

Factors that Increase Risk of Reaction

- IgA deficiency
- Renal insufficiency
- Diabetic
- > 65 years
- Dehydration
- Recent or current infection
- Delay since last treatment > 8 weeks

Patient education IVIG

- Instruct patient on proper storage and handling of IG
- Explain that IG provides passive immunity for immune compromised patients
- Instruct patient to drink plenty of water, day before, day of, and day after IG.

FDA approved Indications SCIG

- Primary humoral immunodeficiency (PI) which includes:
  - Humoral immune defect in congenital agammaglobulinemia
  - Common variable immunodeficiency
  - X-linked agammaglobulinemia
  - Wiskott-Aldrich syndrome
  - Severe combined immunodeficiencies

SCIG Administration s1

- Dose of Ig is determined by weight in kg, and monitored by IgG levels and/or clinical response
- Rates vary based on concentration, dose, patient's wt, diagnosis, and length of interval between therapies
- **SCIG:** 0.1-0.15 gm/kg per week

Slide 46

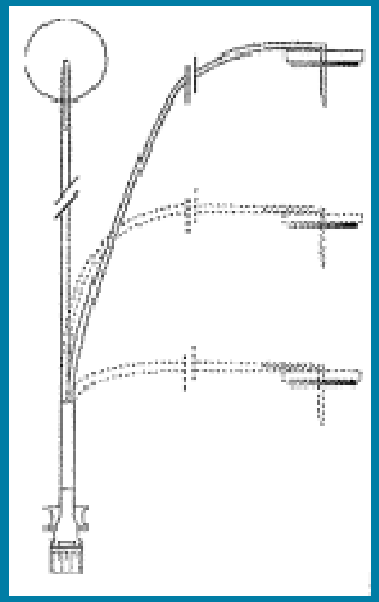
s1 check on new dosing for Hizentra dose and intervals

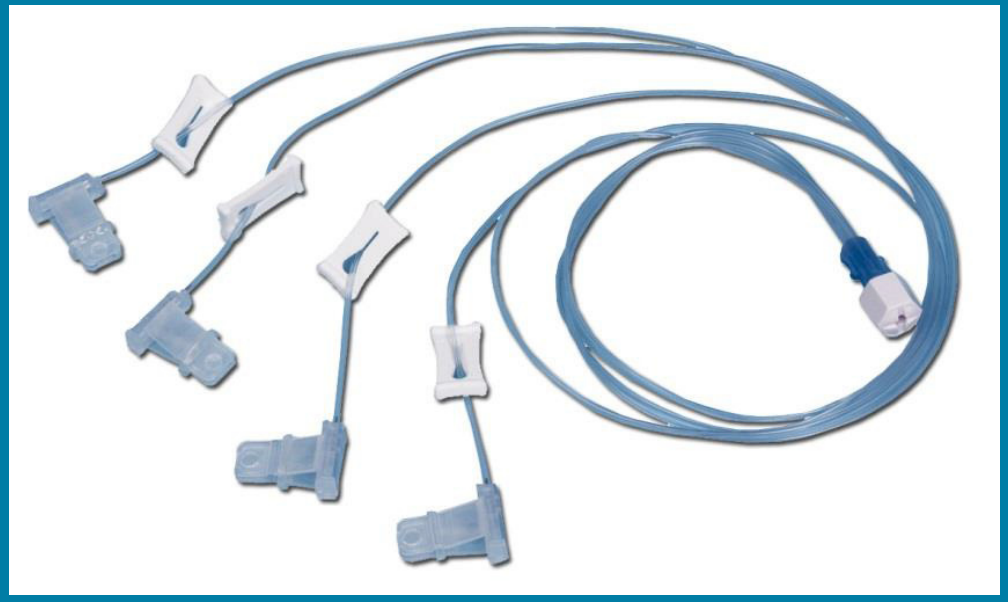
setup, 3/22/2014

SCIG Delivery Sets

- SCIG Delivery Sets are designed specifically for the administration of IgG (Immunoglobulin) where multiple infusion sites are needed
- The SCIG Infusion Set allows for multiple subcutaneous infusion sites connected to one common tube for connection to an infusion pump
- Most often syringe pumps are used to administer

SCIG Needles

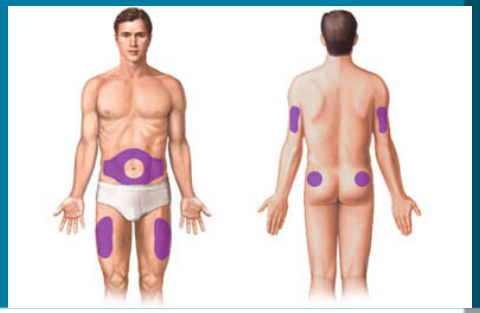




SCIG

- Sites for administration

  abdomen (avoid waist), upper arm, thigh, and buttock
- Use 2-6 , 23-25 gauge up tp 12 mm needles (longer the better)
- SC sets with multiple lumens frequently used
- Space sites at least 2 inches apart, and rotate with each infusion
- 10-25 ml total infusion per site in per patients
- 5 -7.5ml per site for very young patients.



RMS Freedom 60

Nursing Assessment

- Full body assessment prior to infusion
- Patients on SCIG can be trained to self administer within 1-2 visits
- Custom assessments will be performed by collaborative care team prior to medication refills

Side effects

- Less common than with IVIG

- Most common are site reactions:
  - Localized swelling
  - Erythema
  - Itching
  - Soreness/discomfort
  - Induration
  - Bruising and/or burning

Side effect management

- Infusion site reactions can be related to the skin preparation. Anti sting barrier products such as Cavilon (3M) can be applied to insertion site to minimize skin prep reations

- Discomfort associated with SCIG delivery: can be minimized by applying
  - Topical anesthetic cream (e.g. Emla)
  - Ice/heat therapy (may help reduce pain)

- Instruct patient to report continued swelling of infusion sites 3-4 days post therapy

Patient education SCIG

- To self administer SCIG, teach
  - patient and caregiver how to self administer
  - Mixing precautions as applicable
  - Access device care
  - Signs & symptoms of reactions and appropriate interventions
- Explain that for additional protection patient should
  - Practice good hand washing techniques
  - Practice infection control precautions

Ongoing Monitoring

- Ongoing laboratory monitoring:
  - IgA antibodies in patients with selective IgA deficiency or quantitative immunoglobulins (IgG, IgM, IgA, or IgE)
  - Annual IgG levels if in good control
  - Blood viscosity
  - Liver function and CBC prior to initiation and every 3-6 months thereafter.
  - Volume status
  - Renal function/urine output periodically
  - Neurologic symptoms

Summary

- IVIG/SCIG is generally well tolerated in the home
- Is more cost effective
- Improves patient quality of life
- Encourages normalcy of life

- *Thank you for attending this learning program*