Initiating IgG Replacement

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Historical note

• **Edwin Cohn**, during **World War II**, employed a cold-alcohol fractionation process to separate plasma proteins → focused on using the **albumin** fraction on the battlefield as a **blood substitute**

• Attention later turned to Cohn **fraction II** which contained **human antibody**

• **Immunoglobulin** fractionated from human plasma was available
1940s
Cohn: Plasma ptn fractionation – albumin

1952
Bruton SC 3.2g

50s – 60s – 70s IM
IM 100 mg/kg/wk

50s – 60s – 70s
IM
100 mg/kg/wk

80s – 90s
IV - monomeric
5% - 10%
Stabilizers
Viral inactivation

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SCIG
- Berger 1981: SC – low infusion
- Gardulf 1990: rapid infusion – pump
- FDA approval 2006: SC / US
- Shapiro 2010: SC - push

- Painful: poorly tolerated, particularly children – poor compliance
- Volume that could be given was limited
- serum IgG levels rarely approached physiologic concentrations
- If some of the IM-Ig would inadvertently enter a vein, resulting in a severe anaphylactic reaction

- Plasma transfusions
- 60s: IVIG attempts → Ig aggregates → activate complement → anaphylactic reactions
- Stabilizers (sugars – amino acids) → monomeric
- Donor selection & testing –
- NAT test: HAV – HBV – HCV – PV B19
- Depletion of potential viruses: separation of fraction I/III – ttt with octanoic acid - solvent/detergent ttt - nanofiltration

Pediatrics
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Indications for IgG replacement therapy: PID (primary immunodeficiency)

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
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<tbody>
<tr>
<td>• Agammaglobulinemia (XLA – AR)</td>
<td>• Specific Ab deficiency with normal IgG</td>
</tr>
<tr>
<td>• CVID</td>
<td>• HIES</td>
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<tr>
<td>• Hyper-IgM</td>
<td>• XLP</td>
</tr>
<tr>
<td>• SCID</td>
<td>• THI</td>
</tr>
<tr>
<td>• awaiting for HSCT</td>
<td>• DiGeorge syndrome</td>
</tr>
<tr>
<td>• Post-HSCT (B function not restored)</td>
<td>• IgG subclass deficiency</td>
</tr>
<tr>
<td>• WAS</td>
<td></td>
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<tr>
<td>• NEMO - IKKB</td>
<td></td>
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<tr>
<td>• WHIM</td>
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Indications for IgG replacement therapy: SID (Secondary Immunodeficiency)

• HIV
• Immunosuppressants: eg rituximab
• Multiple myeloma - lymphomas
• Intestinal lymphangiectasia
• Burns
25% to 30% of IgG replacement used in the US remains as replacement therapy for Primary immunodeficiency disease (PID)
Once the decision is made to initiate IgG replacement therapy

- Dose?
- Frequency?
- Route of administration?
- Rate of infusion?
- Brand?
Initiating IVIG replacement therapy

• Prior to initiating IVIG:
  • **Spirometry**: establish baseline pulmonary function
  • **High-resolution CT scan**: presence of lung pathology
  • **Hematologic** and **Biochemical** values.

• Following the patients on a regular basis (4-6m/as indicated):
  • monitoring lung function regularly: spirometry
  • IgG levels
  • hematology
  • biochemistry as indicated.
  • Follow-up lung CT scans (12 – 24 m)
## Place of IgG administration

<table>
<thead>
<tr>
<th>IVIG:</th>
<th>SCIG:</th>
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<tbody>
<tr>
<td>in the hospital</td>
<td>With a pump to deliver SCIG</td>
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<td>in office-based clinics/infusion centers</td>
<td>Push method</td>
</tr>
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<td>home-care setting: nursing supervision during the IV administration</td>
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<td></td>
<td>• Tolerate IgG well, without adverse events</td>
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<tr>
<td></td>
<td>• This does not obviate the need for regular physician follow-up</td>
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<td></td>
<td>• Some patients may even self-infuse?</td>
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</table>
Initiation of Ig replacement therapy: Dose?

- **Initial doses**: 300 - 600 mg/kg body weight, given every 3-4 wks
- **Higher doses** [600 – 800 up to 1,200 mg/kg]:
  - Bronchiectasis – chronic Sinusitis
  - Infections /Autoimmunity/ Inflammatory comorbidities (↑IgG catabolism)
  - Genetic factors (↑ catabolism)
  - Enteropathy (↑IgG loss)
  - Splenomegaly (sequestration)
- Patients with **severe hypogammaglobulinemia** (<100 mg/dl):
  - “Loading” dose of 800 mg/kg given in 2 separate doses (few days apart)
  - followed by monthly 400-500 mg/kg
IVIG: Adverse reactions (2–25%)

**Frequent/mild – moderate:**
- Related to infusion rate:
  - Headache – Chills
  - Pruritis - Rashes
  - Fever – Fatigue – Flu-like
  - Hypotension – Hypertension – Tachycardia
  - Nausea – Vomiting
  - Back pain – Myalgia – Malaise
  - ↑ creatinine

**Rare/ severe:**
- CNS:
  - aseptic meningitis
  - severe headache

- Renal:
  - acute tubular necrosis (sucrose as stabilizer)

- Thrombo-embolic events:
  - cerebral infarction
  - pulmonary thromboembolism
  - myocardial infarction

**Very Rare/ severe:**
- Anaphylaxis
- Arrhythmia
- Coagulopathy
- Hemolysis (anti-A/B) – group AB
- Neutropenia
- Cryoglobulinemia
- Alopecia
- Uveitis
- Hepatitis (non-infectious)

Significant Adverse Reactions reported with IVIG

- Renal failure
- Aseptic meningitis
- Thrombosis
- Hemolysis

- Sucrose-containing IVIG products
- Product with high osmolality
  Patient hydration
- Higher IVIG doses
- Old age
- Pre-existing disease: cardiac – thromboembolic – renal
- Blood group AB (non-O)
Measures to Prevent Adverse Events with IVIG

• **Control of predisposing factors:**
  • treat infectious processes
  • slow down infusion: in the 1st infusions & in case of major infection/fever
  • avoid unnecessary product switching
  • avoid long periods between infusions

• **Pre-hydration** (30 minutes prior) with 0.9% saline solution:
  • 10 to 20mL/kg in children
  • 500mL in adults

• **Allow product to reach room temperature**

• **Properly reconstitute** lyophilized products

• **Monitor vital signs** every 20 to 30 minutes
Facing Common IVIG Adverse reactions

- Tend to subside in subsequent administrations
- **Pre-medicate** patients with:
  - Acetaminophen – Non-steroidal anti-inflammatory agents
  - Antihistamines – Corticosteroids
- Slowing the rate of infusion can abate the symptoms.
- If a patient reacts to one IVIG product:
  - He may tolerate the infusion when **switched to another brand**
  - He may need to **shift to SCIG**
IVIG

• Nowadays, most **reactions are related to the rate of infusion**
• Patients are more likely to experience reactions to IVIG:
  • during the 1st - 2nd infusion
    • advisable to initiate IG therapy in a hospital setting and under the supervision of a physician experienced in this type of treatment
    • adjustments in dosage, type of product and rate of infusion
  • **after** a significant **interruption** in therapy
  • if they have an **active infection** at the time of their infusion
Infusion Rate in IVIG

• Slow infusion rate, particularly in 1st infusions

• Using infusion pumps, whenever possible
  • Start at 0.01mL/kg/minute (0.5 to 1mg/kg/minute)
  • increasing gradually (every 15 to 30 minutes) to
    • 0.02mL/kg/min,
    • 0.04mL/kg/min,
    • 0.06mL/kg/min
    • up to 0.08mL/kg/min (4 to 8mg/kg/min, - for products at 5 and 10%), over 3 to 6 hours

• Regimen with shorter intervals can be used in subsequent infusions, or even continuous infusion, as tolerated by the patient

• Observe for 30 to 60 minutes after completion, before releasing the patient
Drawbacks of IVIG

• **Venous access:**
  • concern for chronically ill children
  • newly venous access on a monthly basis in children
  • tends to become more difficult over time
  • placing the patient and risk should resuscitation be required

• **Indwelling permanent central catheters → higher risk for:**
  • sepsis
  • thrombosis
  • arrhythmias
  • emboli
Use of plasma

Anaphylactoid reactions with IVIG (aggregates)

IVIG available
- popular
- Good control
- Higher serum levels

Adverse events: up to 27%
- Limitations of venous access
- Port-a-cath ???

Slow SC infusion
1-2 ml/h
Several times/wk

16% IM prep.
Via pump: rapid SC infusion
Up to 20 ml/h
- No need for hospital
- Specially for those with AR to IVIG

As no IM Ig preparation in US
↓
Use of IVIG 10-12% prep for SC use

1st preparation specifically formulated for SC use 20%

Skoda Smith et al. Therapeutics & Clinical risk management; 2010:6
Calculation for converting from IVIG to SCIG

- **Calculation of weekly IVIG dose:**
  \[ \frac{gm/month}{4} = gm/wk \]

- **Calculation of weekly SCIG volume (16% preparation):**
  \[ \frac{gm/week}{0.16} = ml/wk \]

- **Infuse into 1 or more sites?**
  - \( \leq 25 \text{ mL/site in adults} \)
  - \( \leq 15 \text{ mL/site in children} \)
  - Infusion rate: \( \leq 1\text{mL/ mn} \)

- A 50 kg patient receives 20 gm/4 wk (400 mg/kg) of IVIG

  Weekly dose = \( \frac{20}{4} = 5 \text{ gm/wk} \)

  \[ \frac{5}{0.16} = 31.25 \text{ mL/wk (round up)} \]

- Infuse in 2 sites - once weekly

Therapeutics and Clinical Risk Management 2010:6
SCIG: FDA approved since 2006

- A more concentrated preparation of IG is delivered
  - Via a catheter and small volume infusion pump
  - Into the SC tissue of the abdomen, thigh or arm.
  - IG is gradually absorbed via lymphatics and is returned to the circulation via normal lymphatic pathways.
- Over the time → more stable levels of IgG
- Limits the fluid load
- Avoids the need for venous access

Advantages of SCIG

• SCIG is at least equivalent to IVIG in reduction of infections

• **Improved quality of life** for patients and **substantially reduced cost**

• **Slightly higher trough** levels of IgG, probably due to ↑ frequency of infusion

• **Higher steady-state** IgG levels

• **Limited fluid load** and no association with renal failure

• **Limited technical skill**
  • parents / children themselves can deliver the infusion without the need for nursing services or being logistically dependent on an infusion center.

• **No loss of working / school time**
Advantages of SCIG

• **Children** tolerate SCIG despite the increased exposure to needle sticks and seem to prefer it to IVIG

• SCIG appears to be **safe in pregnancy**

• **Cost:** considerable savings (family/society) with SCIG
  • product, infusion supplies and pump

• **Tolerated well by patients with:**
  • mild bleeding disorders
  • IgA-deficient patients
  • Adverse events with IVIG
Limitations of SCIG

• **Limited volume** of fluid that can be delivered subcutaneously
  • **Higher concentration** of the IG preparation is required
  • **Infusion in multiple sites** may be required
  • **Weekly** rather than monthly infusion
  • **Preparation with hyaluronidase included** to improve diffusion through SC tissue → allowing delivery of a greater volume → the **infusion can be delivered once /month**

• **Local site reactions:**
  • Redness – swelling – pain
  • ≈Universal at the start (91%)
  • With time become less problematic, usually do not require return to IV infusion

• **Increased number of needle sticks** is a concern
  • Anesthetic creams should be used for the 1st few infusions
### IVIG
- Peak reached within few hours – as soon as infusion is completed
- 100-200 mg/dL rise in serum IgG for every 100 mg/kg
- Rapid ↓ in serum level over the 1\textsuperscript{st} few days (tissue redistribution)
- Stable state is reached within 6m
- Interdose interval: 3-4 wk

### SCIG
- Peak reached within 2-4 d
  - IgG → Lymphatics → Thoracic duct → blood stream
- 84.4 mg/dL rise in serum IgG for every 100 mg/kg
- More stable level
- Stable state: within 6-10 wk
- Interdose interval: daily-up to 2 wk

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**Incidence of systemic adverse effects**

For both: superior results are noticed with higher doses
**IVIG**
- Effective in infection control
- Rarely, **systemic reactions**
  - Related to infusion rate / pre-existing co-morbidities
- Preferred by patients / caregivers who **do not wish to self-administer** / want less frequent applications
- **Preferable in patients with:**
  - poor adherence to the treatment
  - patients resistant to self-administration
  - low socioeconomic and education level
  - extensive or severe skin lesions
  - coagulation disorders

**SCIG**
- Effective in infection control
- Frequent **infusion site reactions**:  
  - Improve with time - > in lean individuals
- Improvement in the quality of life:
  - **Independence** - fewer trips to the hospital
  - Those who **had adverse events** with IVIG
- **Preferable in patients with:**
  - good treatment adherence, good hygiene conditions at home, and trained and motivated to perform administration
  - some comorbidities
  - difficult venous access, poor clinical control
  - significant adverse effects with IVIG
  - difficult access to the healthcare facility