Optimizing Immunoglobulin Therapy in the Treatment of Primary Immunodeficiency Disease

Tuesday, April 5
7:00-8:45 a.m.
Hilton Orlando—Florida Ballroom 4

Supported by an unrestricted educational grant from Talecris Biotherapeutics, Center for Science and Education

A Symposium Held in Conjunction with the 2011 NHIA Annual Conference & Exposition

NHIA 20th Annual Conference & Exposition

Shaping Our Horizon
Optimizing Immunoglobulin Therapy in the Treatment of Primary Immunodeficiency Disease

Tuesday, April 5, 7:00 to 8:45 a.m.

Education Overview:
As our understanding of the human immune system continues to evolve, so, too, does research into treatment options that will be most efficacious for a wide variety of immune-related disorders. Home infusion clinicians on the front line of patient care, and consequently in the best position to observe patient response to treatment, can take what they learn in this educational program and apply it directly to their clinical practice. Armed with new knowledge about the impact of serum IgG trough levels on rates of pneumonia in primary immunodeficiency disease (PIDD), clinicians can collaborate with prescribing physicians to ensure each patient is receiving the drug, dose and administration method that results in their best clinical outcome. Dr. Jordan Orange will present a comprehensive update on the state of current treatment options for PIDD, addressing recent changes in immunoglobulin therapy options, evolving administration methods, and future treatments under study.

Faculty: Jordan S. Orange, MD, PhD, University of Pennsylvania School of Medicine, Children's Hospital of Philadelphia, Division of Immunology, Philadelphia, PA

Dr. Jordan S. Orange is an Associate Professor in the Department of Pediatrics at the University of Pennsylvania School of Medicine and an attending physician in the Divisions of Immunology, Allergy, and Rheumatology in the Children's Hospital of Philadelphia. He received his MD and a PhD in immunology Brown University and served as a resident in pediatrics at The Children's Hospital of Philadelphia. He received subspecialty training in Allergy, Immunology and Rheumatology at Boston Children's Hospital. He is currently the holder of the Jeffrey Modell Endowed Chair in Immunology at The Children's Hospital of Philadelphia.

Dr. Orange is actively involved in basic and clinical research. From a clinical standpoint he has focused entirely on Primary Immunodeficiency diseases and has focused on defects of innate immunity. He has received funding from the National Institutes of Allergy and Immunology and the US Immunodeficiency Network to support his laboratory work. Dr. Orange has also participated in several relevant clinical scholarship projects. These include the 2005 Practice Parameter for the Diagnosis and Management of Primary Immunodeficiency Diseases published in the Annals of Asthma Allergy and Immunology, and is the lead author on the 2006 supplement to the Journal of Allergy and Clinical Immunology entitled “Use of IGIV in Human Disease”. In 2010, Dr. Orange and colleagues published the first meta-analysis examining the correlation of IVIG trough level to incidence of pneumonia.

In addition to his work in immunodeficiency research, Dr. Orange has become involved in advocacy efforts on behalf of patients affected by primary immunodeficiency diseases and is the recipient of the Immune Deficiency Foundation 2007 Advocacy Award. In 2009, Dr. Orange received the American Philosophical Society’s Judson Daland Prize for his contributions to research and treatment of inherited immune deficiency diseases and in 2010 was elected to the American Society for Clinical Investigation.

Dr. Orange is a Fellow of the American Academy of Allergy Asthma and Immunology and is currently serving as chair of the committee on primary immunodeficiency, as well as the secretary of the Basic and Clinical Immunology interest section. He also serves as a member of the US Immunodeficiency Network’s Education and Advisory Committees and has participated on several projects with the Clinical Immunology Society including the Summer School for Primary Immunodeficiency and the Primary Immunodeficiency Diseases Consortium. Dr. Orange is also a member of the Medical Advisory Council of the Immune Deficiency Foundation and is director of the Jeffrey Modell Diagnostic Center at The Children’s Hospital of Philadelphia.

Pharmacist and Nurse Education Objectives:
1. Describe changes in the landscape of immunoglobulin G (IgG) products in recent years.
2. List emerging treatment options with IgG therapy.
3. Explain impact of current research in optimization of IgG therapy for patients with primary immune deficiencies.
4. Describe ongoing research and future implications for IgG therapy.

Pharmacy Technician Education Objectives:
1. Describe changes in the landscape of immunoglobulin G (IgG) products in recent years.
2. List emerging treatment options with IgG therapy.
3. Explain impact of current research in optimization of IgG therapy for patients with primary immune deficiencies.
4. Describe ongoing research and future implications for IgG therapy.
Learning Assessment Questions:

1. List the three current FDA-approved indications for IVIG.

2. IVIG is proposed to work in Alzheimer’s disease by promoting neuronal synapses.
   a. True
   b. False

3. Recent meta-analysis defines an increasing impact of IgG trough levels in primary immunodeficiency up to what value?
   a. 400mg/dl
   b. 500mg/dl
   c. 800mg/dl
   d. 1,000mg/dl

4. Subcutaneous Ig administration is associated with which combination of adverse events compared to IVIG?
   a. Higher local, Higher systemic
   b. Higher local, lower systemic
   c. Lower local, higher systemic
   d. Lower local, lower systemic

5. Hyaluronidase being researched for use with subcutaneous immunoglobulin would allow for what types of infusions?
   a. Higher volume, lower frequency
   b. Lower volume, lower frequency
   c. Higher volume, higher frequency
   d. Lower volume, lower frequency

Answers can be found on the last page of this booklet.
Optimizing Immunoglobulin Therapy in the Treatment of Primary Immunodeficiency Disease

Jordan Orange MD/PhD
Associate Professor of Pediatrics
Division of Allergy and Immunology
University of Pennsylvania School of Medicine
Children's Hospital of Philadelphia

Top 5 Things to Know for CE:

- Make sure your BADGE IS SCANNED each time you enter a session, to record your attendance.
- Carry the Evaluation Packet you received on registration with you to EVERY session. If you're not applying for CE, we still want to hear from you! Your opinions about our conference are very valuable.
- Pharmacists, Pharmacy Technicians and Nurses need to track their hours on the Statement of Continuing Education Certificate form as they go.
- FOR CE: At your last session, total the hours and sign both pages of your Statement of Continuing Education Certificate form.
- Keep the PINK copies for your records.
- Place the YELLOW and WHITE copies in your Evaluation packet.
- Make sure an evaluation form from each session you attended is completed and in your Evaluation packet (forgot to pick up an evaluation form at a session? Extras are available in an accordion file near the registration desk.)
- Put your name and unique member ID number (six digit number on the bottom of your badge) on the outside of the packet, seal it, and drop it in the drop boxes in the NHIA registration area at the convention center.

Disclosures

Employment
- Children's Hospital of Philadelphia

Financial Interests
- Consultant to Baxter, CSL, Takeda, Genentech, IBT

Research Interests
- NIH-NIAID, Baxter Bioscience

Organizational Interests
- AAAAI, ACAAI, AAI, C.S., IDF

Gifts
- Nothing to Disclose

Other Interests
- Research grants review committee - Opephere USA

Clinical trials and off-label uses will be discussed but in a fair and unbiased manner.
Objectives

- Introduction to Ig therapy
- Ig products and changes in the landscape
- Emerging treatment options with Ig therapy
- Primary immunodeficiency disease (PIDD) and the optimization of Ig therapy
  - Opportunities for the home infusion professional
- Ongoing research and future implications in Ig therapy

Therapeutic polyclonal IgG:
What it is:

- Highly purified human IgG
- Major antibody in human blood
- A billion, billion specificities
- 4 major constant regions
  - IgG1, IgG2, IgG3, IgG4
- Produced by B lymphocytes

Therapeutic polyclonal IgG:
how it works

- Specifically binds harmful substances (bacteria, viruses, toxins, etc.)
  - Neutralizes
  - Interfaces with immune cells
- Binds to receptors on immune cells
  - Accesses immune function
  - Regulates immune function
Therapeutic polyclonal IgG: how it works – ingestion of a pathogen

Therapeutic Polyclonal Immunoglobulin: How its made
- From pooled plasma from 1000s of donors
  - Ensures broad specificity
  - US FDA recommends >15,000, but <60,000 pooled donors
- Sourced from commercial plasma collection centers
- US IGIV products must be manufactured from plasma donated in the US

Polyclonal immunoglobulin preparations
- IGIV - immunoglobulin (IG), intravenous (IV)
  - (IVIG)
- IGIM - immunoglobulin (IG), intramuscular (IM)
  - (IMIG)
- IGSC - immunoglobulin (IG), subcutaneous (SC)
  - (SCIG)
- Hyperimmune immunoglobulins
  - IM (tetanus) and IV (CMV)
Optimizing Immunoglobulin Therapy in the Treatment of Primary Immunodeficiency Disease

US IVIG preparations (9)

<table>
<thead>
<tr>
<th>Product</th>
<th>Form</th>
<th>Stabilizer/sugar</th>
<th>IgA (g/L)</th>
<th>Osm (mosm/L)</th>
<th>Sodium (mEq/L)</th>
<th>Storage</th>
<th>Manufacturer</th>
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</thead>
<tbody>
<tr>
<td>Carmune®</td>
<td>lyophil.</td>
<td>Sorbitol</td>
<td>trace</td>
<td>768 (12%)</td>
<td>&lt;2.4</td>
<td>RT (24m)</td>
<td>CSL</td>
</tr>
<tr>
<td>Flebogamma®</td>
<td>5% liq</td>
<td>Sorbitol</td>
<td>&lt;50</td>
<td>240-370</td>
<td>7</td>
<td>RT (24m)</td>
<td>Griffins</td>
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<tr>
<td></td>
<td>10% liq</td>
<td>Sorbitol</td>
<td>&gt;50</td>
<td>240-300</td>
<td>7</td>
<td>RT (24m)</td>
<td></td>
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<tr>
<td>Gammagard Liquid®</td>
<td>30% liq</td>
<td>Glycine</td>
<td>3.7</td>
<td>1250 (10%)</td>
<td>8.5</td>
<td>RT (6m)</td>
<td>Baxter</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>625 (5%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gammagard SD®</td>
<td>lyophil.</td>
<td>Glucose</td>
<td>&lt;2.2</td>
<td>1250 (10%)</td>
<td>8.5</td>
<td>RT (24m)</td>
<td>Baxter</td>
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<tr>
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<td></td>
<td>625 (5%)</td>
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<tr>
<td>Gammunex®</td>
<td>10% liq</td>
<td>Glycine</td>
<td>46</td>
<td>trace</td>
<td>trace</td>
<td>RT (8m)</td>
<td>Talecris</td>
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<tr>
<td>Octagam®</td>
<td>5% liq</td>
<td>Maltose</td>
<td>&lt;200</td>
<td>310-380</td>
<td>&lt;0.7</td>
<td>RT (24m)</td>
<td>Octaph</td>
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<tr>
<td>Pariex®</td>
<td>10% liq</td>
<td>Proline</td>
<td>&lt;25</td>
<td>240-440</td>
<td>trace</td>
<td>RT (24m)</td>
<td>CSL</td>
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<tr>
<td>Gammaplex®</td>
<td>5% liq</td>
<td>Sorbitol</td>
<td>&lt;10</td>
<td>420-500</td>
<td>3</td>
<td>RT (24m)</td>
<td>BPL</td>
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US SCIG and IMIG preparations

<table>
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<tr>
<th>Product</th>
<th>Approved Route</th>
<th>Form</th>
<th>Stabilizer/sugar</th>
<th>IgA (g/L)</th>
<th>Osm (mosm/L)</th>
<th>Sodium (mEq/L)</th>
<th>Storage</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>Gammastan</td>
<td>IM</td>
<td>~16% liquid</td>
<td>Glycine</td>
<td>3.0</td>
<td>4°</td>
<td></td>
<td></td>
<td>Talecris</td>
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<tr>
<td>Vivaglobin</td>
<td>SC</td>
<td>16% liquid</td>
<td>Glycine</td>
<td>1.7/0</td>
<td>&lt;3.2</td>
<td>4°</td>
<td></td>
<td>CSL</td>
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<tr>
<td>Hizanta</td>
<td>SC</td>
<td>20% liquid</td>
<td>Proline</td>
<td>&lt;50</td>
<td>&quot;trace&quot;</td>
<td>Room Temp</td>
<td></td>
<td>CSL</td>
</tr>
</tbody>
</table>

IVIG product selection

- **Sucrose** (Caramune®)
  - avoid in renal risks
- **Glucose** (Gammagard SD®)
  - avoid in diabetes
- **Sodium** (Gammagard SD® - 0.85%, Caramune®)
  - avoid in infants and cardiovascular risks
- **High Osm** (Gammagard SD®)
  - avoid in infants and cardiovascular risks
- **Fluid load** (5% preparations – Flebogamma®, Octagam®)
  - avoid in water restriction, caution in infants.
- **Amino acids** (Glycine – Gammunex®, Gammagard Liquid®)
  - (Privigen®-Phosphate)
  - avoid in specific reactivity or certain metabolic disorders
- **IgA** (all except Gammagard SD®)
  - avoid in patients with history of reaction

ONLY 2 STUDIES DOCUMENT HEAD-TO-HEAD COMPARISONS
- Gammunex® vs Gammimune® N in PIDD, Gammunex® vs Iveeegam® in KD
- Subcutaneous therapy- Characteristics may be less relevant
FDA Approved indications for IVIG
1. treatment of primary immunodeficiencies
2. prevention of bacterial infection in patients with hypogammaglobulinemia due to B cell chronic lymphocytic leukemia
3. prevention of coronary artery aneurysms in Kawasaki disease
4. prevention of infections and graft versus host disease after bone marrow transplantation
5. reduction of serious bacterial infection in HIV-infected children
6. increasing platelet count in idiopathic thrombocytopenic purpura to prevent bleeding.
7. To improve neuromuscular disability in Chronic Inflammatory Demyelinating Polyneuropathy

Classification algorithm

<table>
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<tr>
<th></th>
<th>Immune deficient</th>
<th>Auto-immune</th>
<th>Neuro</th>
<th>Infectious</th>
<th>Misc</th>
<th>Total</th>
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<tr>
<td>Definitely Beneficial</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Probably Beneficial</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Maybe beneficial</td>
<td>1</td>
<td>10</td>
<td>12</td>
<td>4</td>
<td>10</td>
<td>37</td>
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<tr>
<td>Unlikely beneficial</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>16</td>
<td>24</td>
<td>14</td>
<td>18</td>
<td>80</td>
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</table>

Optimizing Immunoglobulin Therapy in the Treatment of Primary Immunodeficiency Disease

**IVIG Prioritization algorithm**

Efficacy of other treatments

- poor
- excellent

Disease Severity

- fatal
- mild

**IVIG Prioritization algorithm**

<table>
<thead>
<tr>
<th>Efficacy of alternatives</th>
<th>None</th>
<th>Low</th>
<th>Med</th>
<th>High</th>
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<tbody>
<tr>
<td>Disease Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediately Life-Threatening</td>
<td>A</td>
<td>A1</td>
<td>A2</td>
<td>A3</td>
</tr>
<tr>
<td>Life-Threatening</td>
<td>B</td>
<td>B1</td>
<td>B2</td>
<td>B3</td>
</tr>
<tr>
<td>Life-Modifying (physical morbidity)</td>
<td>C</td>
<td>C1</td>
<td>C2</td>
<td>C3</td>
</tr>
<tr>
<td>Other</td>
<td>D</td>
<td>D1</td>
<td>D2</td>
<td>D3</td>
</tr>
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</table>

**Appropriate use within indications**

- Accurate definition of individual indications.
- Individual guidelines for usage within given indications.
- Collaboration with government and payors to generate rational and effective criteria.
- Advocacy on behalf of patients with indications for whom Ig is essential.
Optimizing Immunoglobulin Therapy in the Treatment of Primary Immunodeficiency Disease

**Short Report**

**Intravenous immunoglobulins containing antibodies against b-amyloid for the treatment of Alzheimer's disease**


400mg/kg every 4 weeks

**18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease**


Neurobiology of Aging ePUB 2008

**Anti-Aβ antibody titer with V/Vg base**

Study was conducted to determine the effectiveness of specific antibodies in the treatment of Alzheimer's disease. The results indicate a significant increase in antibody titer with increased V/Vg base.
Optimizing Immunoglobulin Therapy in the Treatment of Primary Immunodeficiency Disease

Risk for Alzheimer’s for patients on IVIG

- Filt, et. al. Neurology 2009 72:180

Primary Immunodeficiency

inherent inability of the immune system to provide an advantage over the environment
Primary Immunodeficiency

When the immune system inherently does not work

The immune system keeps most people healthy most of the time.

Therapeutic options for the patient with a primary immunodeficiency

- Prophylaxis Immunoglobulin
- Antibiotic Prophylaxis
- Adjunct measures
- Stress reducing therapies
  - Exercise, acupuncture, massage, biofeedback, sleep hygiene
- Nutrition
  - Optimized, weight management, supplementation, xylitol
- Probiotics
- Hygiene-related
  - Daycare avoidance, hand washing, hand gels

Adjunct therapeutic measures

- Manage co-morbidities
- Therapeutic (not diagnostic) vaccination
- Stress reducing therapies
- Exercise, acupuncture, massage, biofeedback, sleep hygiene
- Nutrition
- Optimized, weight management, supplementation, xylitol
- Probiotics
- Hygiene-related
- Daycare avoidance, hand washing, hand gels
- Little data exist in PIDD
Optimizing Immunoglobulin Therapy in the Treatment of Primary Immunodeficiency Disease

Information for Families
Boosting Your Immune Health

The immune system is the body's defense against infections and other substances that can cause disease. Usually the immune system keeps the body healthy by making an immune response to fight off bacteria, viruses, and other disease-causing organisms. For people who have immunodeficiency, it is very important that the immune system works properly and is able to fight off disease. The goal is to help the immune system fight off disease. To do this, you can do simple things like eating a healthy diet and getting plenty of rest. A healthy diet can help your immune system fight off disease. Getting plenty of rest can help keep you healthy and strong.

Infection Frequency in PIDD Is Reduced by Immunoglobulin Replacement

Reduction of infection
- 20-year treatment period with IVIG
- Reduction of infection rate in general pediatric population after replacement

Before Diagnosis / Treatment
- 90%
- 70%
- 50%
- 30%
- 10%

After Treatment
- 10%
- 50%
- 70%
- 90%
- 100%

Case Presentation

12 month old with recurrent otitis/URI

First ear infection at 6mos
5 episodes since then
"always getting sick"

IgG = 72, IgM=12, IgA<10
Tetanus titer = 0.03, Diptherhia titer <0.01
Pneumoccal titer 0/14 are greater than 1.3μg/ml

Agammaglobulinemia
Optimizing Immunoglobulin Therapy in the Treatment of Primary Immunodeficiency Disease

Agammaglobulinemia

Bruton, G.C. Pediatrics 1952 9:727

Ig replacement therapy = PI patient survival

The Journal of Allergy and Clinical Immunology

Use of intravenous immunoglobulin in human disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology
Phenotypic categorization of antibody deficiency

- B cells
  - Present or absent
- IgG quantity
  - Absent, low, normal
- IgG quality
  - Absent, low, normal

As derived from: Orange, et. al., JACI 2006 S525
As proposed in Stiehm, Orange and Ballow, advances in pediatrics, in press

<table>
<thead>
<tr>
<th>Category</th>
<th>B cells</th>
<th>IgG quantity</th>
<th>IgG quality</th>
<th>Diagnostic examples</th>
<th>IG replacement therapy</th>
<th>Cessation of therapy for reassessment</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Diagnosis - Autoimmune, infection - severe infections - hypersensitivity</td>
<td>Evaluate immune status, start IG therapy</td>
<td>Cessation of therapy for reassessment</td>
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<tr>
<td>II</td>
<td>Present</td>
<td>Low</td>
<td>Low</td>
<td>Diagnosis - Autoimmune, infection - severe infections - hypersensitivity</td>
<td>Evaluate immune status, start IG therapy</td>
<td>Cessation of therapy for reassessment</td>
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<tr>
<td>III</td>
<td>Present</td>
<td>Normal</td>
<td>Low</td>
<td>Diagnosis - Autoimmune, infection - severe infections - hypersensitivity</td>
<td>Evaluate immune status, start IG therapy</td>
<td>Cessation of therapy for reassessment</td>
</tr>
<tr>
<td>IV</td>
<td>Present</td>
<td>Low</td>
<td>Normal</td>
<td>Diagnosis - Autoimmune, infection - severe infections - hypersensitivity</td>
<td>Evaluate immune status, start IG therapy</td>
<td>Cessation of therapy for reassessment</td>
</tr>
<tr>
<td>V</td>
<td>Present</td>
<td>Normal, but IgG subclass deficient</td>
<td>Normal</td>
<td>Diagnosis - Autoimmune, infection - severe infections - hypersensitivity</td>
<td>Evaluate immune status, start IG therapy</td>
<td>Cessation of therapy for reassessment</td>
</tr>
<tr>
<td>VI</td>
<td>Present</td>
<td>Normal</td>
<td>Normal</td>
<td>Diagnosis - Autoimmune, infection - severe infections - hypersensitivity</td>
<td>Evaluate immune status, start IG therapy</td>
<td>Cessation of therapy for reassessment</td>
</tr>
</tbody>
</table>

Use of Ig therapy in PIDD
AAAAI Working Group Report

- Web-based survey
- E-mail invitation to 3,000 AAAAI members
- 405 unduplicated respondents
- Data collection period of ~4mos
- 13.5% response rate
  

- Parallel survey was performed of ESID
  – Response rate 28.5%

AAAAAI Respondent Characteristics

<table>
<thead>
<tr>
<th>% of practice devoted to PID</th>
<th>General</th>
<th>Focused</th>
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<tbody>
<tr>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90%</td>
<td></td>
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</tr>
<tr>
<td>80%</td>
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<td>70%</td>
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<td>0%</td>
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Optimizing Immunoglobulin Therapy in the Treatment of Primary Immunodeficiency Disease

Survey of AAP pediatricians

Optimal use of Ig in PIDD
Payor-directed potential barriers to applying best practice in PIDD:
flags for the home infusion professional

- Excessive trough level monitoring
- Under-appreciation of antibody quality
- Recommending dosage reductions to achieve "target" trough (no data)
- Allowing dosing only after a particular IgG threshold is crossed (no data)
- Requiring proven infections before approving therapy (no data – dangerous in genetic PIDD)
- Variability in diagnostic criteria and requirements for initiation of therapy
- Excessive requests for cessation of therapy
Surveyed Effect of Medicare Reimbursement

- 51% have had patients change site of care because of reimbursement
- 36% of physicians have had to reduce frequency of infusion
- 26% of physicians have had to reduce IVIG dosage
- 36% have had patients who have experienced health problems because of reimbursement
- THERAPY NEED BE OPTIMAL TO PREVENT ADVERSE OUTCOMES

AAAAI Specialist Survey - Orange and Boyle J. Allergy Clin. Immunol. 2007 119:S71

Variables in IVIG therapy

- IVIG dose
- Frequency of administration
- IgG trough level
- "clinical effect"
- Adverse events

Access to Ig therapy does not ensure access to OPTIMAL therapy

Individualized therapy for PI:
“The biological trough”
What pre-infusion IgG level do AAAAI members target initially?


Agammaglobulinemia: the purest example

IGIV dosing in PI

Low Dose IVG
300mg/kg adult
400mg/kg pediatric

High Dose IVG
600mg/kg adult
900mg/kg pediatric

Optimizing Immunoglobulin Therapy in the Treatment of Primary Immunodeficiency Disease

**IVIG dosing in PIDD**

- **Initial Trough**
- **IgG Trough**

- Standard Dose
- High Dose

**Specific Titer (IU/mL)**

- Type 3
- Type 9
- Type 14

**Pneumococcal Serotype**

**IVIG dosing in PIDD**

- Treatment Antibiotics
- PC-related infections

**Ig dosing to prevent lung damage in PI**

- Serum IgG (mg/dL)
- Forced Vital Capacity (% below normal)
- CT score

**Post**

- Pre
- Post

Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency.
IgG trough levels: a meta analysis

impact of IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies


Study selection for meta-analysis

Studies included in meta-analysis

Abbreviations: C-RCT, crossover randomized controlled trial; IVIG, intravenous immunoglobulin; P, prospective; R, retrospective.

aMean (range) at baseline except as otherwise indicated
bMedian; assumed equal to mean for classification of mean age as < 18 years vs. ≥ 18 years
Summary of studies

- Mean patients per study = 34
- 49% CVID, 37% XLA
- Pneumonia diagnosed by CXR and hospitalization (1), unspecified (10), or specifically as “bacterial pneumonia” (6)


Relation of IgG dose to trough level

Trough IgG increases 1.21 mg/dl for every 100 mg/kg dose increase


Relation of IgG trough level to pneumonia incidence

Every 100 mg/kg trough level increase decreases pneumonia incidence by 27%

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Relation of IVIG dose to pneumonia incidence

![Graph showing the relation of IVIG dose to pneumonia incidence.](Image)


Meta-Analysis conclusion

- Trough IgG increases 121mg/dl for every 100mg/kg dose increase
- Every 100mg/kg trough level increase decreases pneumonia incidence by 27%
  - No threshold identified up to 1000mg/dl trough (where data end)
- Experience underscores the need to better define studies in PIDD patients
  - Standard definitions for infections and consistent application
  - Consistent reporting of endpoints relevant to therapy


Original article

**Infection outcomes in patients with common variable immunodeficiency disorders: Relationship to immunoglobulin therapy over 22 years**

Mary Loes, Bl.**1**, Winer-Lee, BA, PhD; Jenny Lutter, MD, PhD; Eduardo Lopez Granados MD, PhD;**1** Kay Metcalf, RNP,**1**, and New Haas, MD, PhD.**1** (United States and los Angeles, Calif)

90 CVID – 8891 patient months of data
15 XLA – 1152 patient months of data

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*Note: The page contains a graphical representation of data showing the relation of IVIG dose to pneumonia incidence.*
IgG Trough vs. IVIG dose


IgG trough required to be infection free

Blue XLA   Red CVID

Risks of IgG replacement

• Anaphylaxis
• Transmitted infection
• Aseptic meningitis
• Renal failure
• Neurodegeneration
• Thrombosis/stroke
• Mild events¹
  – Chills, fever, aches, Headache, vomiting, anxiety
  – Can occur in a high percentage of patients

¹Fahrendorn et al., J. All. 2008:10-16
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2002 IDF Patient Survey
IVIG Rates of AEs

- 1170 patients with primary immunodeficiency
- 61% report infusion rate related AEs
- 44% report “serious” AEs
- Rates are higher than product licensing studies but represent actual patient experience

Subcutaneous Immunoglobulin (SCIG)

IV vs. SC replacement

- Therapeutically equivalent to IV for PI
- Less systemic adverse events with SC
- More local effects for SC
- More stable serum IgG levels for SC
  - AUC issue
- More frequent infusion for SC
- Improved quality of life for SC

16%, 20% and soon to be 10% preparations available
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11/13 improved on SCIG

Will SCIG serve patients better than IVIG
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**IV vs SC replacement**

2 year crossover trial

- **Number of infections per year**
  - Sweden: p=0.76
  - UK: p=0.21 (2 tailed)


**IV vs SC replacement**

2 year crossover trial

- **Percentage of Infections**
  - Pain at site: 0%
  - Erythema at site: 0%
  - Headache: 0%
  - Fatigue: 0%


**Vivaglobin® local adverse events**

- **Graph showing local adverse events**
Comparative local tolerance study


Benefits for Pediatric Patients


Benefits for Parents

Health care utilization


Who Are Candidates for SCIG?

Patients with:
- Adverse Events with IVIG
- IV access problems
- A desire for independence from IV infusion
  - Either hospital or home based
- Difficulty in access to nursing care or medical facilities


Practical aspects of SCIG therapy
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SCIG dosing
- Patients on IVIG treatment can be switched to weekly administration of SCIG
- Treatment can be started one week after the patient has received a regularly scheduled IVIG infusion
- SCIG dose is determined by converting IVIG dose into weekly doses
  - The initial weekly SCIG dose = previous IVIG dose X 1.37 (16%) or 1.53 (20%)  
  - Then divide this dose into weekly doses based on the patient’s previous IVIG treatment interval
- Adjust slightly, if necessary, to match convenient vial sizes
- Initial recommended weekly dose of SCIG is 100 to 200 mg/kg body weight administered subcutaneously

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SCIG: Infusion sites and Time
- Consider patient tolerance, and lifestyle
- A typical infusion lasts 1 – 3 hours
- For a shorter time, use more sites
- for fewer sites, take more time
- US-FDA labeling recommends no more than 15ml/site
  - Many patients tolerate significantly more
- Encourage rotation of SCIG sites
- Evaluate sites over time
- 20% SCIG has better local tolerability than 16% SCIG*


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Administration of SCIG,  
(syringe driver)
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Administration of an SCIG Process steps

Options for Pumps and Syringes

Roller/Cassette Pump

Syringe Driver Pumps

Subcutaneous Needles

Potential for flexibility and innovation for patients with SCIG therapy

- Dosing regimens
  - Daily, push, bi-weekly
- Future innovation in devices
  - Packaged syringes?
  - Auto-infusers?
- IV-SC transition
  - Flexibility in meeting patient needs and lifestyle
  - Now possible with single products licensed for both routes
New directions in SCIG

SCIG Hyaluronidase Study

- Objective: more per site + less frequent infusion
- Hyaluronidase (Hy) digests fibrilar subcutaneous elements containing hyaluronan that prevents lateral diffusion
- 4 week Ig dose into single site + 50, 200u/g Hy
- 11 patients (1 withdrawal)
- Infusion Rates 120-300ml/hr
  - IV pumps alarm due to back pressure

Melamed, et. al. 2008 J. Allergy Clin. Immunol 121:583

PKiv vs PKsq for Subject 400002

Data provided by Dr. Richard Schiff – Baxter Biosciences
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Initial Hyaluronidase experience

- Permitted single site infusions of more than 600 ml
- Once a month or twice a month dosing possible
- Infusion rates of 300 ml/hr (= to IV)
- Local reactions mostly mild

Hyaluronidase + SCIG

Hyaluronidase + SCIG
## Preliminary Hyaluronidase conclusions

- Longer-term safety data are needed
- Will be amenable to home care provision
  - Should reduce IV-associated adverse events
  - May not be amenable to self-administration
- Different set of management considerations

## Future increases in “off label” SCIG usage

- We recently approved for all “replacement” indications
  - Oncology with IgG less than 500
  - Transplant instead of IV
- Other experiences accumulating…
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Equivalent effect of IVIG and SCIG in MNN

Dermatomyositis?

Used for poor venous access
1.7g/kg/mo divided over 2d per week
Follow-up at 1yr – stable CPK decreased from 2890 to 225

-2 adults already responded to IVIG
-Changed to chronic therapy with SCIG 6.4g/wk
-Stabilized nerve conduction velocities and global symptom scores
Synthesis and guidance for practice

Tenets of antibody replacement therapy for primary immunodeficiency “Eight Guiding Principles”

1) Indication - Ig therapy is indicated as replacement therapy for patients with primary immunodeficiency diseases characterized by absent or deficient antibody production.

2) Diagnoses - There are a large number of primary immunodeficiency diagnoses for which IVIG is indicated and recommended.

3) Frequency of Ig treatment - IVIG is indicated as continuous replacement therapy for primary immunodeficiency.

**4) Dose** - IVIG is indicated for patients with primary immunodeficiency at a starting dose of 400-600mg/kg every 3-4 weeks (100-200mg/kg/wk for SCIG).

**5) IgG trough levels** - IgG trough levels can be useful in some diagnoses to guide care but are NOT useful in many and should not be a consideration in access to Ig therapy.

**6) Site of care** – The decision to infuse IVIG in a hospital, hospital outpatient, community office, or home based setting must be based upon clinical characteristics.

**7) Route** – Route of immunoglobulin administration must be based upon patient characteristics.

**8) Product** - IVIG products are not interchangeable.

AAAAI - IVIG toolkit - http://www.aaaai.org/members/resources/initiatives/ivig.stm

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**Site of care guidelines**

Sites of Care - criteria supporting each in tool kit

- Hospital inpatient physician/nurse supervised infusion
- Hospital outpatient physician/nurse supervised infusion
- Physician office based physician/nurse supervised infusion
- Home based infusion with nurse supervision
- Home based infusion without nurse supervision

AAAAI - IVIG toolkit - http://www.aaaai.org/members/resources/initiatives/ivig.stm

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**Site of care guidelines**

The decision to infuse IGIV in a hospital inpatient, hospital outpatient, community office, or home-based setting must be based upon clinical considerations.

**Five key points**

1) Failure to base this decision upon patient experience and circumstance, and choose the appropriate site of care could place a patient at risk.

AAAAI - IVIG toolkit - http://www.aaaai.org/members/resources/initiatives/ivig.stm
2) **Changes of IGIV product** should be provided under physician supervision in a facility equipped to handle the most severe of acute medical complications.

3) Certain patients continue to require **higher levels** of monitoring and intervention during IGIV infusions.

4) Patients who have tolerated IGIV therapy without a history of adverse events **may be** considered for lower levels of supervision during infusions.

5) Given the options for providing IGIV therapy, specific patient experiences mandate or preclude specific sites of care.

### Conclusions: What is best practice in Ig therapy and how to support it

- Ig therapy represents life-saving or life-altering therapy in many diagnoses
- Optimization of Ig replacement regimens
  - New data for trough levels at 1000mg/dl
- SCIG equivalent with advantages for the right patient
  - New options in SCIG therapy for PIDD
- Future uses of and avenues for Ig therapy will require new approaches in the home administration setting
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Answers:
1. Primary Immunodeficiency; ITP (idiopathic thrombocytopenic purpura); and CIDP (Chronic inflammatory demyelinating polyneuropathy)
2. B
3. D
4. B
5. A
SHAPING OUR HORIZON

Maximizing 20 Years of Achievement to Craft a Future of Possibilities