A New Twist to an Old Therapy

- Home infusion options for patients with immunodeficiency and hereditary angioedema -

Stephen D. Betschel, MD, FRCPC
St. Michael’s Hospital
University of Toronto
Putting Patients at the Centre — the Right Care, Right Place, Right Time

• “Continuing to expand home and community care to ensure that people receive care as close to home as possible.”
A Older Twist to a Newer Therapy

- Home infusion options for patients with immunodeficiency and hereditary angioedema -

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Objectives

• List the indication for the use of blood products in the treatment of antibody immunodeficiency and hereditary angioedema

• Describe the product preparation and infusion requirements of Berinert ® and Cinryze ®
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• Describe the product preparation and infusion requirements of Berinert ® and Cinryze ®

• **Transfusion Medicine plays a critical role in care**
Overview

• **Antibody Deficiency**
  - Primary and Secondary Antibody Deficiency
  - Treatment options

• **Hereditary Angioedema (HAE)**
  - What is Hereditary Angioedema
    - pathophysiology
    - clinical manifestations
  - Treatment Options
  - Not all is swell
    - What are the current recommendations internationally and nationally
    - Why are we not meeting those recommendations
Declaration of Funding Sources

• Advisory Boards and Consultancy
  ➢ Altana, Baxter, Canadian Blood Services, CSL Behring, Green Cross, Shire, Talecris, Viropharma, WSIB

• Speaker’s Honoraria
  ➢ GSK, Schering, CSL Behring

• Research Funding
  ➢ CSL Behring, GSK, Pharming, Talecris, WSIB
Classification of Immunodeficiencies

- Immune deficiency
  - Primary Immune deficiency
  - Secondary Immune deficiency
Classification of Immunodeficiencies

Immune deficiency

Primary Immune deficiency
- Infections
- Medications
- Hematologic malignancies

Secondary Immune deficiency
- Burns
- Transplantation
Classification of Immunodeficiencies

Immune deficiency

- Primary Immune deficiency
- Secondary Immune deficiency
Classification of Immune Deficiency

Primary Immune deficiency

- Innate Immunity
- Humoral
  - IgA deficiency
  - Ig subclass deficiency
  - CVID
  - XLA
  - Specific Ab deficiency
- Cellular
- Combined (cellular + humoral)
Antibody deficiency is the most common Primary Immunodeficiency
Primary Immunodeficiency in Adults
Why Replace Immunoglobulins?

Why Replace Immunoglobulins?

- Immunoglobulin replacement is effective
  - Reduces the number of overall infections
  - Reduces the number of serious recurrent bacterial infections
  - Reduces the number of pneumonias
- Dosages usually range from 400-600 mg/kg every 3-4 wks

Cunningham-Rundles Ann Int Med (1984); Roifman Ann Int Med (1985); Busse JACI(2002); Bonilla AAAI (2005); Eijkhout Ann Int Med (2001)
How do We Replace Immunoglobulins?
Intravenous Immunoglobulin Therapy

Advantages

• Ability to give large volumes per infusion allows intermittent dosing (q3-4 weeks)
• Convenient and well tolerated by most patients

Adapted from Ballow M. JACI 2008
Intravenous Immunoglobulin Therapy

**Advantages**
- Ability to give large volumes per infusion allows intermittent dosing (q3-4 weeks)
- Convenient and well tolerated by most patients

**Disadvantages**
- Requires venous access and trained personnel in most situations
- Large shift in IgG levels during dosing may cause adverse effects at or just after peak, and during low troughs
- Infrequent dosing may result in low troughs and could increase the infection rate
- Interruption of patients schedule

Adapted from Ballow M. JACI 2008
Subcutaneous Immunoglobulin Therapy

• Initially done in the 1980’s in noncompliant patients due to pain of IM injections.

• Increased usage in Europe due to large amounts of IM preparation available combined with the hepatitis contamination in IVIG products.

• Has been available in Quebec for many years and in January 2009 was available through CBS without need for SAA.
How do patients infuse SCIlg?

- **Methods described for administering SCIlg:**
  - **PUSH Method:** pushing the product using small doses regularly
    - Frequency: every day, every 2-3 days, 5 days/wk, etc
    - Daily Dose: weekly dose divided in vial sizes or number of treatment days required
How do patients infuse SCIg?

• Methods for administering SCIg:

  – **PUMP Method**: an ambulatory infusion pump or syringe driver is used to infuse the dose as described in the product monograph
    • Frequency: Weekly dose
    • Weekly Dose: $\approx \frac{1}{4}$ monthly IVIg dose
    • Patient can be ambulatory during administration
Subcutaneous Immunoglobulin Therapy

Advantages

• No venous access required
• Slow administration and gradual absorption reduces severe headaches and other adverse events
• Maintains more consistent IgG levels; eliminates low troughs

Adapted from Ballow M. JACI 2008
Timing for starting SCIG

Serum IgG Level

-3 -2 -1 0 1 2 3 4 5 6 7 16

Months

IVlg once a month

SClg once a week

Start weekly SCIG

Individualized SCIG Dose Adjustment

USA/Cdn 1:1.37 = 255 mg/dl
EU Brazil 1:1 = 86 mg/dl

PK Substudy 3001 NA CSL
Subcutaneous Immunoglobulin Therapy

**Advantages**

- No venous access required
- Slow administration and gradual absorption reduces severe headaches and other adverse events
- Maintains more consistent IgG levels; eliminates low troughs
- Facilitates self or home infusion, increasing patient autonomy – may improve patient’s self-image and sense of control

Adapted from Ballow M. JACI 2008
Immunoglobulin Replacement

• Home therapy
  ➢ Reduced number of infections on home IVIg (1)
  ➢ Improved quality of life (2)
  ➢ Questionnaire based study in Sweden
    • Better functional status, improved general health, higher trough levels, fewer breakthrough infections, and more patient independence (3)

(1) Ochs H. J Infect. Dis. 1987
(2) Sorensen R. JACI 1987
Evidence-based practice guidelines in Canada for Ig therapy in PID patients recommended that patient preferences should be taken into account when deciding on route of Ig administration (1)

1) Shehata, N. Transfusion Medicine Reviews 2010
Home Infusion Toolkit
Intended for use by Transfusion Medicine services that issue products for home infusion

ORBCoN
Ontario Regional Blood Coordinating Network
Inspiring and facilitating best transfusion practices in Ontario.
Subcutaneous Immunoglobulin Therapy

Advantages
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Disadvantages
- Relatively small volume per infusion and requires frequent dosing – at least once a week in most cases
- Ability to self-infuse requires reliable and adherent patient
- Requires commitment for product storage and recording

Adapted from Ballow M. JACI 2008
Who Are Candidates for SCIG?

PID Patients with:

- IV access problems
- Tolerability / adverse events with IVIg
- A desire for:
  - another less invasive mode of administration
  - independence from IV infusion units in Hospitals/Clinics
  - greater convenience and freedom

Implications to payers of switch from hospital-based intravenous immunoglobulin to home-based subcutaneous immunoglobulin therapy in patients with primary and secondary immunodeficiencies in Canada

William C Gerth¹*, Stephen D Betschel² and Arthur S Zbrozek³
Methods

- **Net economic benefit**: was estimated by multiplying the number of nursing hours and related labor costs in year 1 and in subsequent years for each route of administration.

- **Number needed to switch (NNS)**: The number of PID/SID patients needed to switch to reduce one nurse FTE was estimated by dividing the hours worked in a year (1,813) by the 49.2 hours in average annual savings in nurse time over three years.

- **The population-wide savings potential**: The prevalence of treated PID/SID in Canada was calculated using provincial IgG audit data to extrapolate the potential population-wide savings of switching patients to SC1g therapy.
# National impact to Canada of Nursing Savings

## Estimated 3-Year Savings (Hours, FTEs, Costs) From Switching 50% to 75% of Treated Patients With PID/SID From Hospital IVIg to Home SCIg in Canada by Province

<table>
<thead>
<tr>
<th>Province</th>
<th>Savings With 50% Switch Rate</th>
<th>Savings With 75% Switch Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hours</td>
<td>FTEs</td>
</tr>
<tr>
<td>Alberta</td>
<td>44,969</td>
<td>24.8</td>
</tr>
<tr>
<td>British Columbia</td>
<td>53,662</td>
<td>29.6</td>
</tr>
<tr>
<td>Quebec</td>
<td>93,506</td>
<td>51.6</td>
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<tr>
<td>Manitoba</td>
<td>14,708</td>
<td>8.1</td>
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<tr>
<td>New Brunswick</td>
<td>8,776</td>
<td>4.8</td>
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<tr>
<td>Newfoundland &amp; Labrador</td>
<td>5,952</td>
<td>3.3</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>11,013</td>
<td>6.1</td>
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<tr>
<td><strong>Ontario</strong></td>
<td><strong>156,786</strong></td>
<td><strong>86.5</strong></td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td>1,696</td>
<td>0.9</td>
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<tr>
<td>Saskatchewan</td>
<td>12,537</td>
<td>6.9</td>
</tr>
<tr>
<td>Territories</td>
<td>1,313</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>404,918</strong></td>
<td><strong>223.3</strong></td>
</tr>
</tbody>
</table>

*Based on PID estimate populations determined from B.C. data extrapolations and SID Ig usage by indication ratios from provincial utilization audits*
Conclusions

• It is estimated on a non-cumulative basis that for every 37 patients switched to SCIg, one nurse FTE is recouped.

• With the 5,486 estimated number of PID/SID patients in Canada, between 223 to 335 FTE’s could be redeployed to other service needed over a 3-year timeframe if 50% - 75% of IVIg patients were switched
Angioedema is the rapid swelling of the dermis, subcutaneous tissue, mucosa, and sub-mucosal tissues most often around the lips and eyes.

The difference to hives is that in angioedema the swelling is beneath the skin rather than on the surface.
ANGIOEDEMA

Histamine

Non-Histamine
ANGIOEDEMA

- Histamine
- Non-Histamine
  - ACEi induced
  - Acquired Angioedema
  - Hereditary Angioedema
ANGIOEDEMA

Histamine

- ACEi induced

Non-Histamine

- Acquired Angioedema
- Hereditary Angioedema
Hereditary Angioedema
HAE is Not a New Disease

- Clinically described by Quinke in 1882

- William Osler described familial angioedema 1888
Hereditary Angioedema

- Prevalence 1:50,000
- Autosomal dominant
- Manifests with painful, non-pruritic, non-pitting swelling
- Disorder of complement - C1 inhibitor (C1-INH)
Importance of C1-Inhibitor

• Controls bradykinin formation

• Bradykinin causes blood vessels to dilate and become permeable, i.e., leak fluid into the soft tissues, thus, swelling

• If bradykinin is allowed to produce repeatedly, if it does not get broken down and destroyed, and if its receptor is not blocked,...there will be increased chances of swelling
C1-inhibitor [C1 INH] effects on coagulation, complement, contact and fibrinolytic pathways (Xu, Clin Exp Allergy 2013)
Effect of C1-inhibitor (C1 INH) on Bradykinin and Bradykinin effect on the B-2 Bradykinin receptor

(Xu et al, Clin Exp Allergy 2013)
Clinical Picture of C1-Inhibitor Deficiency

- Clinical symptoms are recurrent, non-inflammatory, non-pitting, self-limiting angioedema located to:
  - subcutaneous tissue,
  - gastrointestinal mucosa
  - oro-pharyngo-laryngeal mucosa

- Duration of each angioedema attack ranges between 1 and 5 days

- Frequency of recurrences varies among patients and also within the same patient:
  - From life-long asymptomatic to 3 attacks/week

- Mortality for HAE is >25% in undiagnosed patients
Cutaneous Angioedema
Cutaneous Angioedema

Myrtle during a Hereditary Angioedema attack (HAEA.org)
Angioedema of the Bowel

Normal bowel mucosa

Edematous bowel mucosa

Longhurst & Cicardi Lancet 2012
Angioedema

Oral  pharyngeal  laryngeal
Common trigger for HAE attacks

- Trauma
- Menstruation
- Infection
- Medications
- Stress

Angioedema attack
HAE Burden of Illness

- Web-based survey of 457 HAE patients found:
  - 100% felt disease prevented them from advancing in school
  - 69% felt unable to consider certain jobs
  - 58% affected career advancement

- Impact of last HAE attack:
  - 51% missed ≥1 work day
  - 44% missed ≥1 school day
  - 59% missed ≥1 leisure day

- Attacks result in 20-100 days of incapacitation annually
  - Approximately 15,000 to 30,000 ER visits/yr

- Unpredictability of attacks causes significant psychological burden

• National and International Experts

• Evidence-Based guideline

• Criteria for determining the Levels of Evidence and Strength of Recommendations were based on GRADE methodology
Treatment of HAE

• Acute Attacks

• Prophylaxis
  • Short-term
  • Long-term

• Self-Administration

• Approach to Individualized Therapy

• Quality of Life

• Comprehensive Care
Treatment of HAE

• Acute Attacks

• Prophylaxis
  • Short-term
  • Long-term

• Self-Administration

• Approach to Individualized Therapy
Treatment of HAE

• Acute Attacks
  • Prophylaxis
    • Short-term
    • Long-term
  • Self-Administration
  • Approach to Individualized Therapy
  • Quality of Life
  • Comprehensive Care
Acute Treatment

Recommendation #1

Effective therapy should be used to treat acute attacks of angioedema to reduce duration and severity of attacks.

High/Strong
Acute Treatment

Recommendation #2

pdC1-INH is an effective therapy for the treatment of acute attacks

High/Strong
Treatment of HAE

Berinert ®

- Purified, pasteurized, lyophilized concentrate of C1-INH
- Licensed for treatment of acute abdominal, facial, or laryngeal attacks of moderate to severe intensity.
- Dosing 20 U/kg
- Administered by slow IV infusion of 4ml/ min or 20 cc (1000 U) in 5 minutes.
Factor XIIa

Bradykinin Receptor

(Xu, Clin Exp Allergy 2013)
Acute Treatment

Recommendation #8

Frozen plasma could be used for treatment of acute attacks if other recommended therapies are not available

Low/Strong
Recommendation #9

We recommend early treatment of attacks to reduce morbidity and mortality

Moderate-Expert Opinion/Strong
Acute Treatment

Recommendation #10

All attacks of angioedema involving the upper airway are medical emergencies and must be treated immediately.

Low-Expert Opinion/Strong
Treatment of HAE

- Acute Attacks
- Prophylaxis
  - Short-term
    - Long-term
- Self-Administration
- Approach to Individualized Therapy
Short-term Prophylaxis

Recommendation #12

Short-term prophylaxis should be considered prior to known patient-specific triggers and for medical, surgical or dental procedures

Low/Strong
Short-term Prophylaxis

Recommendation #13

HAE-specific acute treatment should be available during and after any procedure.

Low/Strong
Treatment of HAE

- Acute Attacks
- Prophylaxis
  - Short-term
  - Long-term
- Self-Administration
- Approach to Individualized Therapy
Prophylactic Treatment of HAE

Long-term Prophylaxis:

• Ongoing regular treatment to prevent attacks of HAE when on demand treatment does not sufficiently meet patient treatment requirements.

• Prophylactic therapy may be considered for patients with recurrent episodes of angioedema to reduce the frequency, duration and severity of attacks.
Long-term prophylaxis may be appropriate for some patients to reduce frequency, duration and severity of attacks.

Recommendation #14

High/Strong
Long-term Prophylaxis

Recommendation #15

Attenuated androgens are effective for long-term prophylaxis in some patients

Moderate/Strong
Prophylactic Treatment of HAE

- Androgens can affect serum lipid levels, can be hepatotoxic resulting in hepatitis and have been associated with hepatocellular adenoma and, in very rare cases, carcinoma.
- Virilising effects of androgen therapy can occur and include menstrual irregularities, masculinization, irreversible voice alteration, and hirsutism.
- Psychological side effects include emotional irritability and lability, aggressive behaviour and depression.
- Contraindicated in pregnancy and during lactation, before puberty, and in patients with androgen-dependent malignancy.
- Physicians should carefully consider the risks and benefits for the particular patient.
Plasma-derived C1-INH is effective for long-term prophylaxis in some patients

High/Strong
Prophylactic Treatment of HAE

• Cinryze™

  – Currently, Cinryze™ is the only approved pdC1INH product for HAE prophylaxis in Canada.

  – Routine prevention of angioedema attacks in adults and adolescents with hereditary angioedema (HAE)

  – 1000 IU of CINRYZE every 3 or 4 days for routine prevention against angioedema attacks.
Recommendation #18

It is not necessary to fail other long-term prophylaxis therapies before use of C1-INH for long-term prophylaxis is considered.

Expert Opinion/Strong
Treatment of HAE

- Acute Attacks
- Prophylaxis
  - Short-term
  - Long-term
- Self-Administration
- Approach to Individualized Therapy
Self-Administration

- Treatment of patients outside of a health care facility either by the patient’s themselves or by a trained caregiver.
Self-Administration

• Treatment of patients outside of a health care facility either by the patient’s themselves or by a trained caregiver.

• Shown to be a safe and convenient option for patients, allows for early treatment, and may reduce the overall treatment costs of this group when compared to hospital-based therapy.
Self-Administration

- Treatment of patients outside of a health care facility either by the patient’s themselves or by a trained caregiver.

- Shown to be a safe and convenient option for patients, allows for early treatment, and may reduce the overall treatment costs of this group when compared to hospital-based therapy.

- Despite the demonstrated benefits of self-administration in terms of efficacy and improved QoL, an online survey done in the USA revealed that only 8.1% of treating physicians had patients who self-treated and only 3.5% received home healthcare assisted administration.
Self-Administration

- Treatment is **more efficacious** when attacks are treated early.
Self-Administration

- Treatment is more efficacious when attacks are treated early.
- The earlier an attack is treated the sooner it resolves.

Patient consent obtained
Self-Administration

• The ability to treat an attack early depends on reducing the number of steps required between recognition of an attack that requires treatment and implementation of effective treatment.
Self-Administration

- Obligating patients to travel to a health care facility to receive a therapy which has been shown to be effective when administered at home, or outside of a healthcare facility, adds to the delay in receiving treatment, may result in many attacks not being treated.
Self-Administration

• Patients may also face difficulties in accessing treatment if local healthcare facilities are unfamiliar with this condition
All patients should be trained on self-administration of HAE-specific therapies if they are suitable candidates. If patients cannot self-administer therapy, provisions should be made to ensure timely access to all appropriate therapies.
Treatment of HAE

- Acute Attacks

- Prophylaxis
  - Short-term
  - Long-term

- Self-Administration

- Approach to Individualized Therapy
Approach to Individualized Treatment

• HAE is a dynamic chronic disease and attacks of angioedema can vary in frequency and severity over the patient’s lifetime.
Approach to Individualized Treatment

• HAE is a dynamic chronic disease and attacks of angioedema can vary in frequency and severity over the patient’s lifetime.

• This variability makes it important for patients to be evaluated regularly to ensure that therapy is appropriate and is being used correctly.
Approach to Individualized Treatment

• HAE is a dynamic chronic disease and attacks of angioedema can vary in frequency and severity over the patient’s lifetime.

• This variability makes it important for patients to be evaluated regularly to ensure that therapy is appropriate and is being used correctly.

• Side effects of therapies are being minimized.
The decision to start or stop long-term prophylaxis depends on multiple factors and should be made by the patient and an HAE expert.

Recommendation #21

Expert Opinion/Strong
Why Care and Be Aware?
Why Care and Be Aware?

- Patients, physicians (ER, GP, ENT), nurses, industry, blood banks and policy makers all are pieces of the puzzle.
Putting Patients at the Centre — the Right Care, Right Place, Right Time

• “Continuing to expand home and community care to ensure that people receive care as close to home as possible.”
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Intended for use by Transfusion Medicine services that issue products for home infusion

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ELEMENTS OF A HOME INFUSION PROGRAM

1. Home infusion programs must adhere to relevant standards for the administration of human blood products. These standards are reflected in this document.

2. Managing patients on home infusion should take place under a physician led program. Often portions of these programs are located at larger hospitals in major cities. Patients may prefer to pick up their product at their local community hospital. Hospitals that provide the product to the patient should establish policies and procedures to ensure the product is managed in compliance with the standards. Each hospital will have to determine the scope of their program in order to meet the needs of the patients they are serving.

3. The program should monitor patient safety elements as well as treatment efficacy.

4. **Approved patients should have access to home infusion products.**

5. These blood products are expensive and considered to be a limited resource. Patients are expected to use these products appropriately and to submit timely, accurate records of product use and document and report any adverse events. Failure to comply with these conditions is grounds for withdrawal from the home infusion program.

www.transfusionontario.org
Bridging the Gap
Thank You