Immunoglobulin Replacement for PIDD: Indications for Initiating and Continuing Treatment

Eastern Allergy Conference 2021

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Disclosures

- **Investigator** – CSL Behring, Grifols, Kedrion, Korean Green Cross, Takeda, TherapureBio
- **Consultant** – ADMA Biologicals, Grifols, Korean Green Cross, Takeda, TherapureBio
- **Speaker** – CSL Behring, Grifols, Takeda

Learning Objectives

- Explain the criteria to be considered for initiating IGRT
- Describe the data elements informing the decision to continue IGRT
- Characterize the IGRT products currently available in the US

Choosing Wisely – AAAAI, 2012

- **Don't recommend replacement immunoglobulin therapy for recurrent infections unless impaired antibody responses to vaccines are demonstrated.**
- Immunoglobulin (gammaglobulin) replacement is expensive and does not improve outcomes unless there is impairment of antigen-specific IgG antibody responses to vaccine immunizations or natural infections.
- Low levels of immunoglobulins (isotypes or subclasses), without impaired antigen-specific IgG antibody responses, do not indicate a need for immunoglobulin replacement therapy.
- Exceptions include IgG levels <150mg/dl and genetically defined/suspected disorders.
  - Measurement of IgG subclasses is not routinely useful in determining the need for immunoglobulin therapy.
  - Selective IgA deficiency is not an indication for administration of immunoglobulin.

https://www.choosingwisely.org/clinician-lists/american-academy-allergy-asthma-immunology-replacement-immunoglobulin-therapy-for-recurrent-infections/ Accessed April 26, 2021

Diagnoses Appropriate for IGRT

- Genetically defined immunodeficiency
  - Humoral immunodeficiency
  - Severe Combined Immunodeficiency
- CVID/CID without known mutation
- Hypogammaglobulinemia
  - How hypo?
- Dysgammaglobulinemia
  - How dys?
- Specific antibody deficiency
  - How deficient?

Perez EE, Orange JS, Bonilla F, Javier Chinen J, Ivan K, Chinn IK, et al. Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol. 2017 Mar;139(3S):S1–S46.

Clinical Criteria for IGRT in Presumed Immunodeficiency

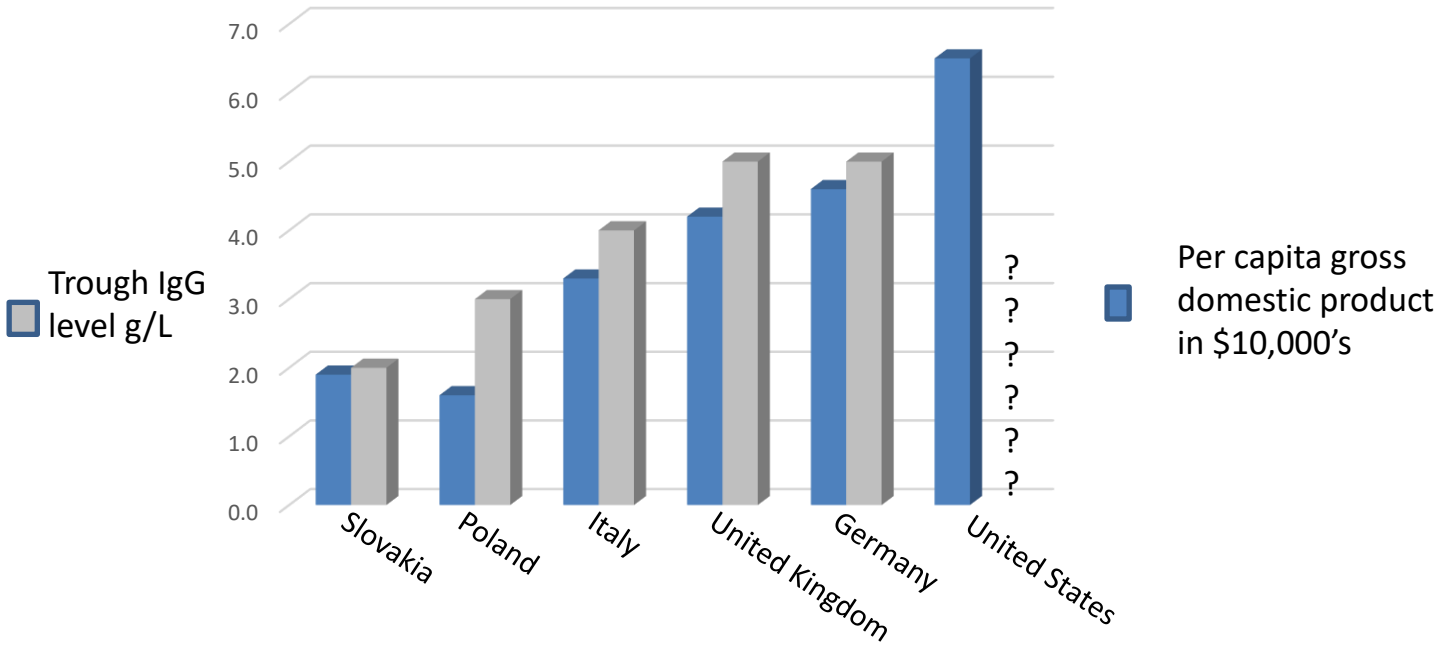
Weak/Negative	Moderate	Strong
Recurrent Group A strep	Recurrent sinusitis/surgery	Osteomyelitis
Urinary tract infection	Repeated need for IV Abx	Septic arthritis
Wheezy bronchitis	>4 courses of Abx/year	Bacteremia
Purulent rhinitis <2yo	Bronchitis in a non-smoker	Visceral abscess
Recurrent otitis <2yo	Cutaneous abscesses	Bacterial meningitis
Chronic Fatigue Syndrome	Bacterial conjunctivitis	
	Infection despite prophylaxis	
	Cytopenias	
	Inflammatory bowel disease	
	Rheumatologic disease	
	Growth retardation	

Laboratory Evaluation of Antibody Deficiency

- IgA, IgG, IgM
- Specific antibodies
  - Isohemagglutinins
  - Diphtheria and tetanus toxoid titers
  - Antibody to *Streptococcus* Pneumoniae
  - Antibody to *Salmonella* Typhi
  - Antibody to rabies
  - Antibody to bacteriophage phi-x 173
- Memory B-cell enumeration

Bonilla FA, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015;136:1186–1205.e78.

IG Replacement Level versus National Wealth



Personal observation, 2015. RL Wasserman

Limitations of Antibody Deficiency Testing

- Isohemagglutinins – don't assess memory
- DT titers – often preserved unless IgG is very low
- Pneumococcal antibodies
  - Poor precision from assay to assay in a single lab
  - Inconsistent results from different labs
  - What is a normal response?
- Phi X-173 – difficult to access
- *Salmonella typhi* – limited clinical correlation
- Memory B-cells – limited clinical correlation

Orange JS, Ballow M, Stiehm ER, Ballas ZK, Chinen J, De La Morena M, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: A working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2012;130:S1-24.

Laboratory Criteria That Don’t Support IGRT

- Recurrent infection in the absence of an abnormality of antibody production
- IgG subclass deficiency
- Selective IgA deficiency
- Isolated hypogammaglobulinemia with normal vaccine responsiveness

Case 1 – 6 Year Old Male

- Frequent otitis media before age 2, now 1-2 episodes per year
- Chronic, antibiotic responsive purulent rhinorrhea
- Height at the 3rd %ile, weight < 3rd %ile
- Two x-ray documented lobar pneumonias in the past 3 years
- Immunoglobulins
    - IgA 15 mg/dL (66-120mg/dL)
    - IgG 255mg/dL (701-1147mg/dL)
    - IgM 25mg/dL (38-74mg/dL)
- *Streptococcus pneumoniae* titers to 2/23 serotypes

Case 2 – 36 Year Old Female

- Chronic sinusitis for more than 15 years
- Six to ten antibiotic courses per year
- Negative allergy testing this year and 10 years ago
- No pneumonias or other invasive infections
- Three sinus surgeries
- Immunoglobulins
    - IgA 105 mg/dL (66-120mg/dL)
    - IgG 795 mg/dL (701-1147mg/dL)
    - IgM 65 mg/dL (38-74mg/dL)
- *Streptococcus pneumoniae* titers to 5/23 serotypes
- Repeated infection despite antibiotic prophylaxis

Case 3 – 15yo male treated for 12 years with IVIG

- History of recurrent otitis and purulent rhinitis, no x-ray documented pneumonias
  - Initial evaluation
    - IgA 50mg/dL (66-120mg/dL)
    - IgG 595mg/dL (701-1147mg/dL)
    - IgM 25mg/dL (38-74mg/dL)
  - DT response low positive
  - Pneumococcal antibody response 3/14 serotypes tested
  - Diagnosis: CVID
  - Treated with 500mg/kg/mo
  - Studies since starting IVIG: Semi annual IgG level
- Antibiotics <1 course/year
- Stop IGRT and reevaluate

Case 4

- 47 yo female treated for 20 years with IVIG, 500mg/dL for CVID
- Pre-treatment studies
  - IgA <7mg/dL (66-120mg/dL)
  - IgG 165mg/dL (701-1147mg/dL)
  - IgM 18mg/dL (38-74mg/dL)
- Annual IgG levels for the past 5 years >900mg/dL
- Antibiotics 1-2 courses per year for sinusitis or bronchitis, no pneumonias since starting IVIG
- Antibody deficiency in adults rarely improves over time
- Measure IgA and IgM
- Continue IGRT

Case 5 – 47 YO Female IVIG for 20 Years

- Chronic sinusitis prior to treatment with 500mg/kg/mo for CVID
- Pre-treatment studies – not available
- Annual IgG levels for the past 5 years >900mg/dL
- Antibiotics 1-2 courses per year for sinusitis or bronchitis, no pneumonias since starting IVIG
- Continue IGRT or stop and reevaluate?
  - Pre-treatment history of invasive infection
  - Lab while receiving IGRT
    - IgA, IgM, memory B-cell enumeration
    - Antibody titers – trough or serial

Re-evaluating Patients Receiving IGRT

- IgA and IgM
- *Streptococcus pneumoniae* titers without vaccination
- *Streptococcus pneumoniae* titers with vaccination
- *Salmonella typhi* vaccine response
- Rabies vaccine response
- Phi X-174 response
- Memory B-cell enumeration

Orange JS, Ballow M, Stiehm ER, Ballas ZK, Chinen J, De La Morena M, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: A working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2012;130:S1-24.

Immunoglobulin Products

Product Characteristics

- Stabilizers
  - Carbohydrate
  - Amphophilic amino acids
    - Glycine, proline
  - Saline
- Physical form
  - Lyophilized
  - Liquid
- IgA concentration
  - Irrelevant to most patients
- Storage
  - Refrigerated
  - Room temperature

Products Available in the US

- 5% IV – several
  - Lyophilized or liquid
  - Mostly carbohydrate stabilized
  - Some with saline
- 10% IV – many
  - Liquid
  - Amino acid stabilized
  - Mostly carbohydrate, saline free
- 10% SC – two
  - Liquid, glycine stabilized
- 16% SC – one
  - Liquid, carbohydrate stabilized
- 20% SC – three
  - Liquid, amino acid stabilized
- 10% facilitated SC – one
  - Liquid, amino acid stabilized

Efficacy

- The primary efficacy outcome of all IgG pivotal (licensing) trials is the rate of acute Serious Bacterial Infections (aSBI); pneumonia, bacteremia, septic arthritis, osteomyelitis, abscess
  - ALL products exceed the standard of <1 aSBI/patient year
- Secondary efficacy outcomes
  - Rate of all infections
  - Days of antibiotic therapy
  - Acute visits
  - Days missed from work or school
  - Relative efficacy comparisons between products is NOT possible

CFR - Code of Federal Regulations Title 21. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=640&showFR=1&subpartNode=21:7.0.1.1.7.10 Accessed April 26, 2021

Safety – Serious, Life-Threatening Events

- Rare among PIDD patients, more common in patients treated with high dose IG
- Renal failure
  - Carbohydrate contain products, particularly sucrose
  - Risks – age, renal compromise, diabetes
- Thrombosis
  - Activated factor 11a contamination
  - Risks – age, previous thrombotic event, thrombophilia, hyperviscosity
- Hemolysis – anti-A and anti-B titers
- Aseptic meningitis – history of migraine
- TRALI – rare, no known risk factors
- Product related differences decreasing

Tolerability – "Rate Related" AEs

- Causes - unproved
  - High IgG peaks
  - Chronic bacterial colonization
  - More common with IVIG than with SCIG or fSCIG
- Most common – migraine headache, myalgias, malaise, fatigue
- Less common – fever, diarrhea, rash, cough, chest tightness, sinus tenderness
- Reactions are more frequent on the first or second infusion or after a hiatus in treatment
- It is not possible to predict the best product for a given patient
- Note product/patient pairs

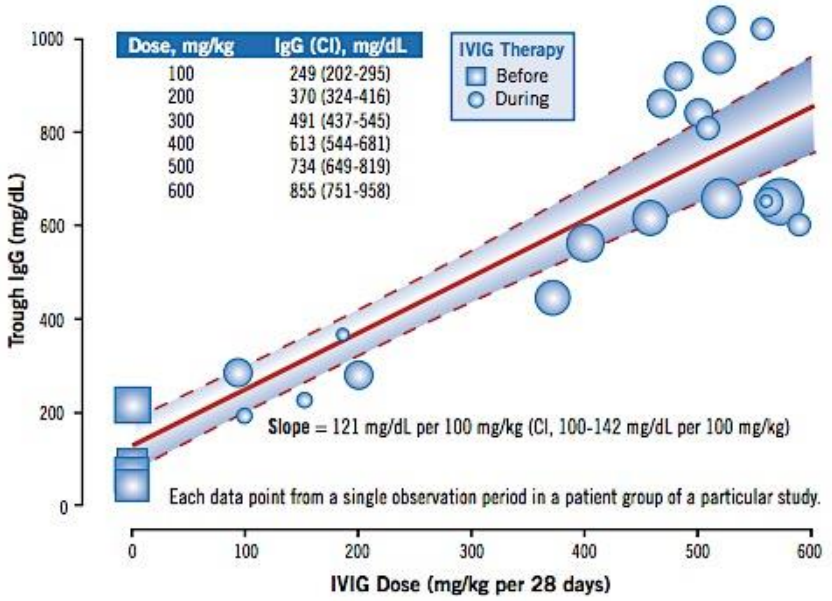
Wasserman RL. J Clin Immunol. 32:1153-64. 2012.

Optimizing Immunoglobulin Replacement Therapy

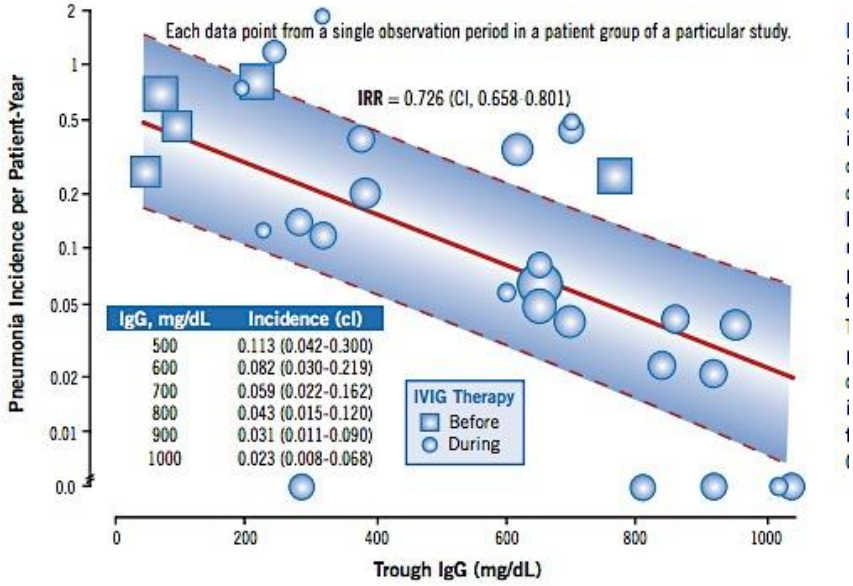
- Prevent infections by raising the trough IgG level
  - Increase the dose
  - Decrease the interval between infusions
- Improve tolerability and minimize adverse events
  - Limit the dose per infusion
  - Limit the infusion rate
- Manage end of cycle deterioration
  - Increase the dose
  - Decrease the interval between infusions
  - Switch to SCIG

Wassserman, RL. Personalized therapy: Immunoglobulin replacement for antibody deficiency. Immunol Allergy Clin North Am. 2019. 39:95-111.

IGIV Dose Related IgG Level



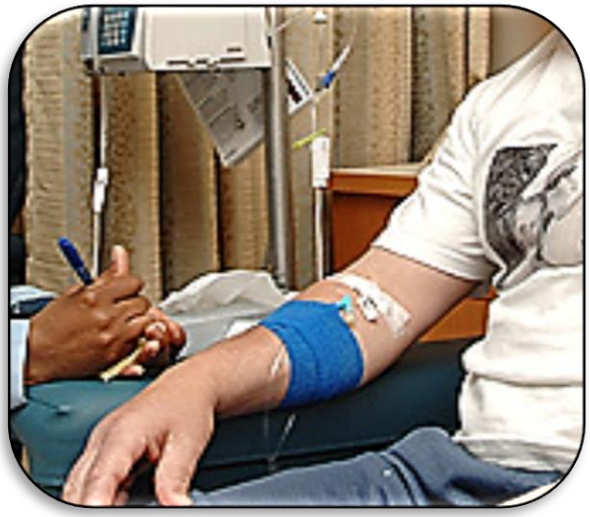
IgG Level and Pneumonia



Orange JS, Grossman WJ, Navickis RJ, Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency:a meta-analysis of clinical studies. Clin Immunol. 2010;137:21–30.

Intravenous IgG Administration

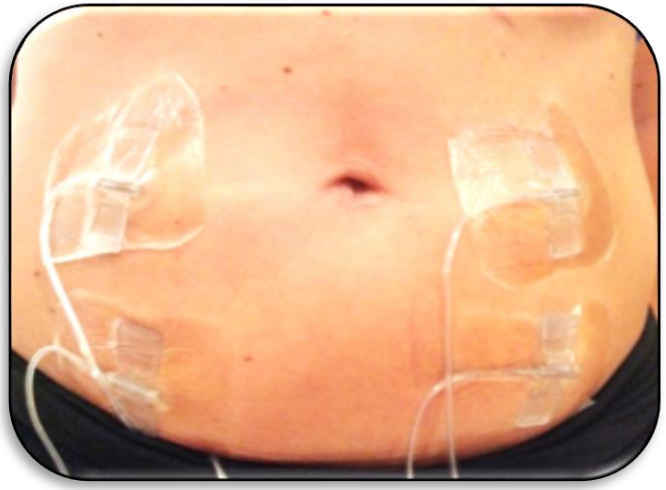
- Infusions are usually every 3-4 weeks
- Requires venous access
- Most patients require an IV start by an HCP
- Home infusion with an HCP, office or infusion center
- Bioavailability 100%
- One site per month (3 or 4 weeks)
- Systemic AEs are more frequent than with IGSC
- Local AEs are rare



Wassserman, RL. Personalized therapy: Immunoglobulin replacement for antibody deficiency. Immunol Allergy Clin North Am. 2019. 39:95-111.

Subcutaneous IgG Administration

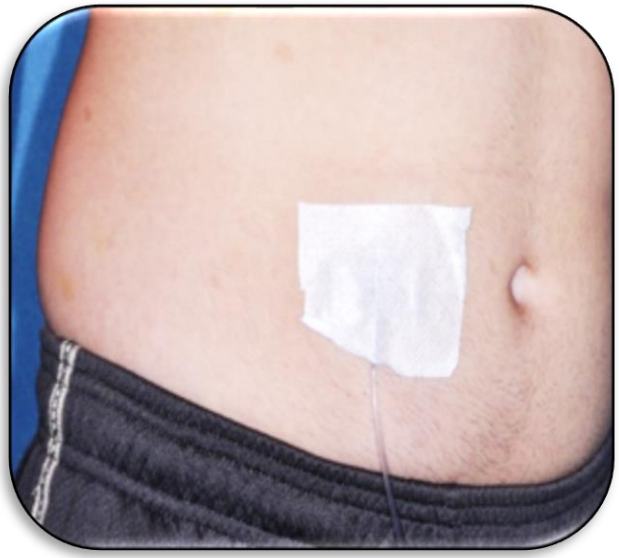
- Infusions are usually every week (daily to biweekly)
- No need for venous access
- Home self-administration
- HCP seldom needed
- Bioavailability 63%
  - Dose adjustment
- 2-30 sites per month
- Systemic AEs are less frequent than with IGIV
- Local AEs are common but decrease over time



Wassserman, RL. Personalized therapy: Immunoglobulin replacement for antibody deficiency. Immunol Allergy Clin North Am. 2019. 39:95-111.

Enzyme Facilitated IgG Administration

- Infusions are usually every 3-4 weeks (biweekly possible)
- No need for venous access
- HCP seldom needed
- Home self-administration, office or infusion center
- Bioavailability 92%
  - No dose adjustment
- 1-2 sites per month
- Systemic AEs are less frequent than with IGIV
- Local AE rate comparable to IGSC



Wassserman, RL. Personalized therapy: Immunoglobulin replacement for antibody deficiency. Immunol Allergy Clin North Am. 2019. 39:95-111.

Treatment Attributes of IGRT Modalities[1–6]

	IVIG	SCIG	fSCIG
Infusions			
Frequency	Every 3 to 4 weeks	Weekly (typically)	Every 2 to 4 weeks
Injection sites per month	1	Multiple	1 or 2
Administration by	Trained medical profession	Self	Self or trained professional
Site of administration	Clinic (minority of cases at home)	Home	Home (majority of cases) or clinic
Venous access	Required (may be difficult in some)	Not required	Not required
PK/PD			
Dose adjustment	None	137% of IVIG	None
Volume	Larger	Limited	Larger
Bioavailability	100% of dose administered	65%–69% of dose administered	92% of dose administered
IgG peak level	Higher	Lower	Between IVIG and SCIG
Safety			
Local adverse reactions	Fewer	More	Comparable to SCIG
Systemic adverse reactions	More	Fewer	Between IVIG and SCIG

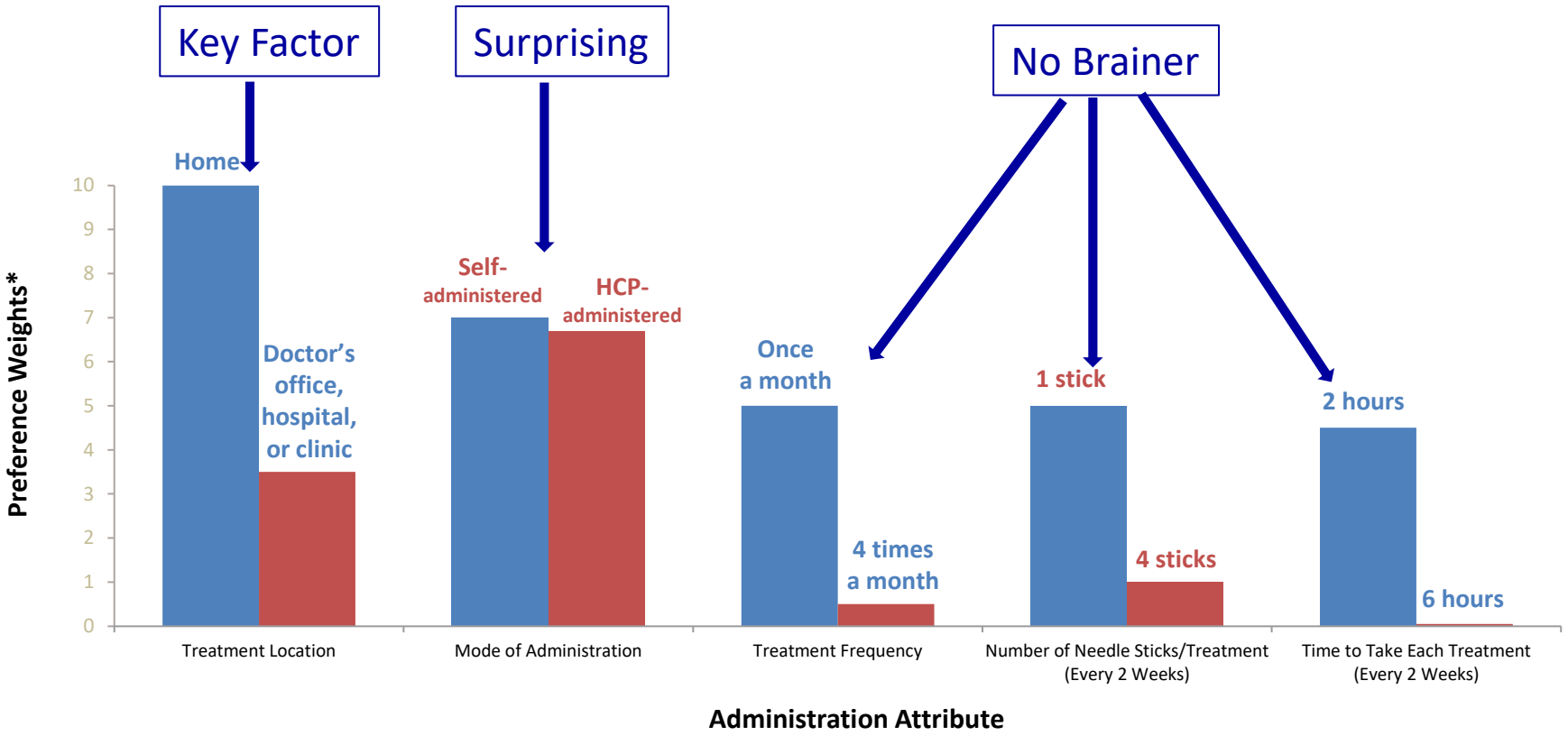
Ig, immunoglobulin; IVIG, intravenous immunoglobulin; PK/PD, pharmacokinetics/pharmacodynamics; SCIG, subcutaneous immunoglobulin; fSCIG enzyme facilitated subcutaneous immunoglobulin.

1. Wasserman R et al. *J Allergy Clin Immunol* 2012;130:951-957; 2. Misbah S et al. *Clin Exp Immunol* 2009;158:51-59; 3. Gardulf A. *BioDrugs* 2007;21:105-116; 4. Jolles S et al. *Clin Exp Immunol* 2015;179:146-160; 5. Berger M et al. *J Clin Immunol* 2013;33:984-990. 6. Wasserman RL, et al. J Allergy Clin Immunol. 2012;130:951-957.

Choosing A Route In A New Patient

- The patient is acutely ill
  - Hospitalized – 1g/kg administered IV over 12-24 hours
  - Acutely ill, not hospitalized 500-600mg/kg administered IV following the package insert
- Not acutely ill – **Shared Decision-Making**
  - Patient and clinician discuss the ideal treatment for the individual patient and the clinician makes a recommendation
  - Intravenous 5% or 10%
    - Patient requires frequent ongoing monitoring
    - Patient/family is unable to self-administer
  - Conventional subcutaneous 10%, 16% or 20%
    - Minimizes adverse events
  - Enzyme facilitated subcutaneous (IGHy) 10% plus hyaluronidase
    - Poor venous access
    - Administer by HCP or self-administer

Survey of Patients' IGRT Administration Preferences



N=252 US adult respondents. *The differences between adjacent preference weights indicate the relative importance of moving from one level of an attribute to an adjacent level of that attribute.

Mohamed AF, et al. *J Med Econ*. 2012;15(6):1183-1191.

Home versus Hospital

- 12 month prospective study of Canadian PIDD patients receiving SCIG at home versus IVIG in the hospital[1]
  - Non-drug costs
    - Hospital $4,187 versus home $1,836
    - Physician $744 versus home $84
- Home IVIG treatment is associated with fewer episode of bronchitis and pneumonia than hospital/clinic infusion[2]

1. Fu LW, et al. Ann Allergy Asthma Immunol (2018) 120:195–199
2. Wasserman RL, et al. J of Clin Immunol. (2017) 37:180-186

Trends In IgG Site of Care - Expert Immunologists

Survey of Jeffrey Modell Foundation "Expert Immunologists"

Modality/Site of Care	2013	2018	Percent Change
IVIG - Clinic	2572	3299	28
IVIG - Home	2423	2381	-2
SCIG	1631	2881	77

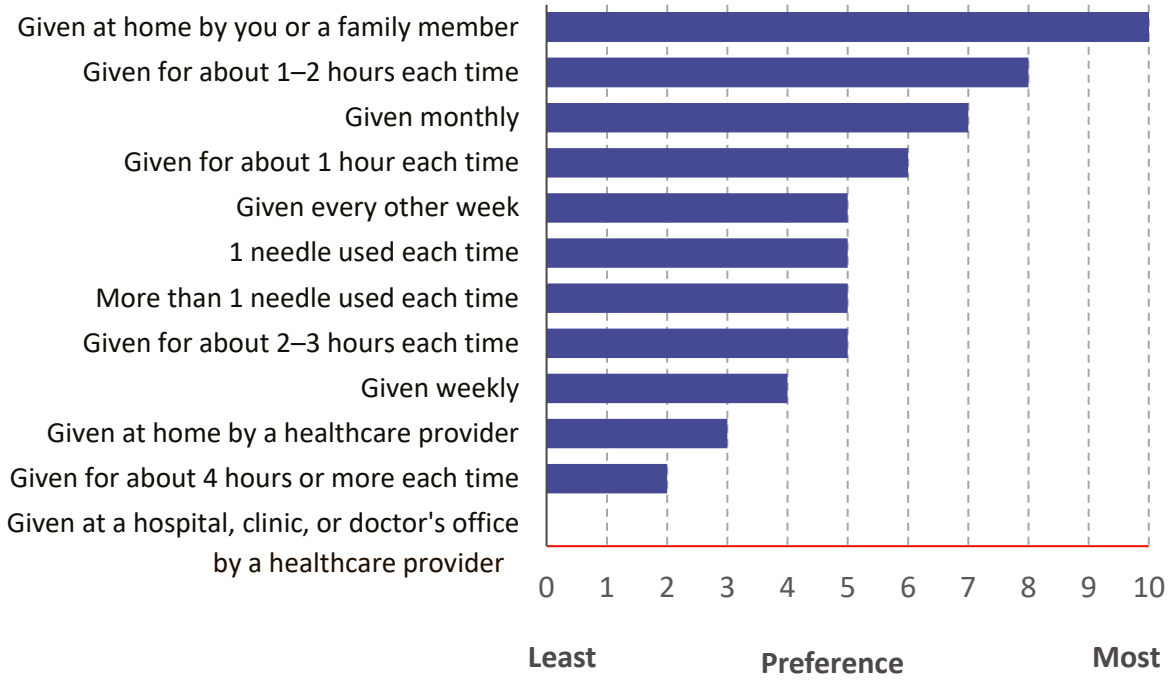
- SCIG increased from 25% to 34% of total patients
- Clinic infusions continue to account for 39% of total patients

Modell V, et al Immunol Res. 2018 May 9. doi: 10.1007/s12026-018-8996-5.

Key IGRT Features Selected for the SMD Tool

Key IG Treatment Features Categories	Treatment Features
Self-administration and Site of Care	• Given at home by you or a family member • Given at home by a healthcare provider • Given at a hospital, clinic, or doctor's office by a healthcare provider
Frequency	• Given weekly • Given every other week • Given monthly
Duration	• Given for about 1 hour each time • Given for about 1–2 hours each time • Given for about 2–3 hours each time • Given for about 4 hours or more each time
Needles	• 1 needle used each time • More than 1 needle used each time

MyIg Preferences Assessment Report



MyIg Preferences Assessment provides

- Patient's ranked preferences
- An explanation of the graph
- A reminder of the tool's purpose
- Next steps for starting a conversation
- Additional factors for patients to consider and discuss
- Space for patients to write in additional notes and questions they want answered

Graph is for illustrative purposes only.

https://www.myigsource.com/my-ig-preferences-assessment. Accessed March 15, 2021

Minimizing the Risks of Severe AEs[1]

- Age – no CHO containing products if >55 years old
- Comorbid condition risks
  - Diabetes or renal disease – no CHO containing products
  - Thrombosis history – limit dose per infusion, limit infusion rate
  - Cardiac disease – avoid sodium containing products
- General risk factors
  - Dose per infusion
  - Decrease infusion rate
  - Mitigate risk by decreasing dose and infusion interval
- IGSC – risks appear to be lower than with IVIG but not zero
- fSCIG – appear to be lower than IGIV

1. Wasserman RL. J Clin Immunol. 32:1153-64. 2012.

Immunoglobulin Choices for Special Populations

Problem	IGRT Choice
Compensated congestive heart failure	sodium free, 10% IVIG, 20% SCIG, fSCIG
Renal compromise, diabetes, elderly	carbohydrate free
Poorly controlled migraine	SCIG, fSCIG – if using IVIG, consider giving 50% on the first dose, pre-treat with NSAID, triptan
Hyperviscosity (e.g., MGUS)	SCIG, fSCIG – if using IVIG, use a 5% product or 10% product using a slow infusion rate
Hemodynamically unstable neonate	10% IVIG
Stable neonate, infant, toddler	20% SCIG

Managing IVIG Side Effects

- 1981 to mid-2000's
  - Slow the rate
  - Change the product
  - Pre-medicate with NSAIDs, antihistamine and steroids
- After 2005
  - Change to IGSC
- After 2013/2014
  - Change to SCIG or fSCIG

SCIG Problems

- Infusion site reactions
  - Needle length
  - Clean needle tip
  - Local heat
  - Change products

- Systemic adverse events
  - Change products
  - Hyper-fractionate the dose
- Infusions too slow
  - Use an electromechanical pump
  - Switch to fSCIG

- Adherence – too many needle sticks/infusions per month
  - Increase the concentration, decrease infusion frequency
  - Change to fSCIG

Immunoglobulin Replacement Therapy

- Ameliorates infections in PI patients
  - Decreases infection frequency
  - Enhances anti-microbial responsiveness
  - Decreases morbidity and premature mortality
  - The correct dose is the dose that keeps the patient well
- Carries the potential for serious adverse events
  - Diminish risk by optimizing infusion mode and parameters
- Is generally well tolerated
  - Improve tolerability by customizing infusion parameters
- Creates a significant burden of care for patients/families
  - Engage in Shared Decision-Making to improve quality of life

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