Support for Immune Globulin Replacement Therapy in IgG Subclass Deficiency

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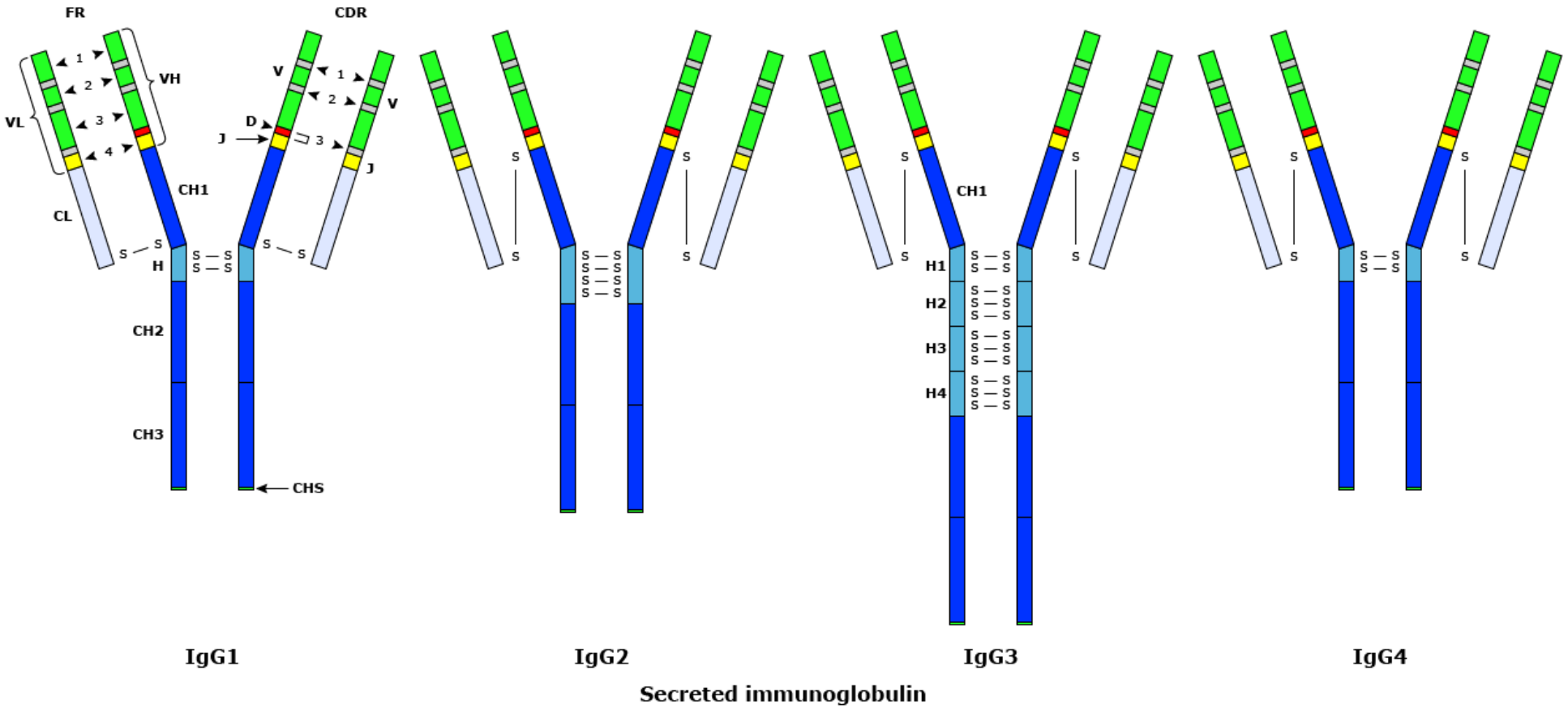
Disclosures

- I have nothing to disclose

What is an IgG subclass?



Subclass	IgG1	IgG2	IgG3	IgG4
% of total IgG	60-70%	20-30%	5-8%	1-4%
Half-life (days)	21-24	21-24	7-8	21-24
Ability to activate classical complement pathway	++	+	+++	-
Antibody response to proteins	++	+/-	++	++
Antibody response to polysaccharides	-	+++	+/-	+/-
Allergens	-	-	-	++, chronic parasitic disease?
Fc-gamma-receptor	I, II, III	II	I, II, III	I, II. Low affinity.
Normal level	540 (280 to 1020) by age 5	210 (60 to 790) by adolescence	58 (14 to 240) by adolescence	60 (11 to 330) by adolescence

Clinical Manifestations of Subclass Deficiency

- Subclass deficiency as a biomarker
  - Most with subclass deficiency are asymptomatic, but some have recurrent and serious sinopulmonary infections
  - Just like a positive ANA, subclass deficiency alone is meaningless without clinical context
  - There is no genetic test at this point for who will have clinically significant disease
- Infectious manifestations:
  - Recurrent sinopulmonary infections, vary between individuals in frequency and severity
  - Other serious infections: osteomyelitis, meningitis, septicemia, diarrhea, and various skin infections
- Associated disorders:
  - PI: IgA deficiency, ataxia-telangiectasia, IgM deficiency
    - 15 percent of IgA-deficient patients also have IgG subclass deficiency (N Engl J Med. 1981;304(24):1476)
  - Atopic dermatitis
  - Chronic lung disease, including asthma and COPD, bronchiectasis
  - Autoimmune disease, including vasculitis and autoimmune cytopenias

Infections in Subclass Deficiency

TABLE 3. Infectious Episodes per Individual per Lifetime Among 197 Adult Patients With IgG Subclass Deficiency and 40 Proportionally Age-Matched and Sex-Matched Healthy Blood Donors

	No. of episodes per individual per lifetime				
Disease or symptom	No deficiency (blood donors) (n = 40)	IgG1SD (n = 36)	IgG2SD (n = 20)	IgG3SD (n = 87)	Combined SD (n = 54)
Pneumonia	0.4	1.4	2.9	2.6	2.6
Bronchitis	2.1	44.5	63.7	62.3	76.6
Otitis	2.4	5.0	10.4	9.5	8.7
Sinusitis	1.5	10.8	12.5	10.9	19.6
Urinary tract infection	1.8	9.6	18.2	8.9	12.2
Skin infection	1.0	6.4	6.6	6.8	12.2
Eye infection	1.0	11.2	6.9	4.2	5.6
Asthma	0.1	113.3	51.6	112.7	151.7
Total	26.5	202.8	166.4	282.6	282.6

IgG: immunoglobulin G; SD: subclass deficiency.

Söderström, T., Söderström, R. and Enskog, A. (1991), Immunoglobulin subclasses and prophylactic use of immunoglobulin in immunoglobulin g subclass deficiency. Cancer, 68: 1426–1429.

Subclass Deficiency	IgG1	IgG2	IgG3	IgG4
Epidemiology	Most have hypogam 4% in study of adults with recurrent infections[1]	Children>Adults[2]	Adults>Children	Most asymptomatic, Seen in concert with IgG2 deficiency, and with IgA-IgG2 deficiencies
Infections	80% with recurrent sinopulmonary infections	Sinopulmonary infections, encapsulated organisms, meningitis, sepsis	Recurrent sinopulmonary infections, *Moraxella catarrhalis* and *S. pyogenes*	Symptomatic patients have recurrent sinopulmonary infections
Associated Conditions	20% asthma, chronic lung disease, autoimmunity, other PI[7]	COPD[6], autoimmunity, AT, IFNg def, CMC, MBL, HIV, CF, H1N1, GH deficiency, febrile seizures, Hodgkin lymphoma, allergic colitis, and others.[7]	Asthma, COPD[6], gastrointestinal infections, and recurrent lymphocytic meningitis. [7]	Ataxia-telangiectasia, chronic mucocutaneous candidiasis, growth hormone deficiency, allergic colitis, and Down syndrome. [7]
Special Notes		Poor polysaccharide vaccine response	34% had poor polysaccharide antibody response[3] Large subset (30-40%) with impaired mitogen and antigen responses[4,5]	Normal to be low in children, so do not diagnose before age 10 years

1. Clin Immunol Immunopathol. 1997;84(2):194
2. *Ann Allergy Asthma Immunol*. 2000;84(1):25
3. *Cell Immunol*. 2016 Jan;299:50-7.
4. *Clin Exp Imm*, 2009: 159: 344-350
5. *Int Arch Allergy Appl Immunolog* 1987; 82: 476-80
6. ERJ 1991; 4: 932-36.
7. UpToDate

Diagnosis of Subclass Deficiency

- Practice Parameter, JACI, 2015
- “A diagnosis of IGGSD should be considered for a patient with recurrent infections, 1 or more IgG subclass levels less than the fifth percentile, and normal total concentrations of IgG, IgM, and IgA.”
  - Measure all 4 subclasses at the same time and on more than one occasion at least 1 month apart
  - *If poor vaccine response, consider measuring subclasses because a diagnosis of IGGSD might be more appropriate*
- Consider associated immune deficiencies in the right clinical context

Management of Clinically Significant Subclass Deficiency

- Manage co-existing atopy
- Prophylactic antibiotics
- **Immune globulin replacement therapy may be indicated**
- Pneumococcal vaccination
- Monitoring for evolution (into CVID, for example) or resolution of subclass deficiency
- Monitoring for associated conditions
  - Autoimmunity
  - Malignancy not commonly associated with subclass deficiency alone

Work Group Report of the American Academy of Allergy, Asthma & Immunology

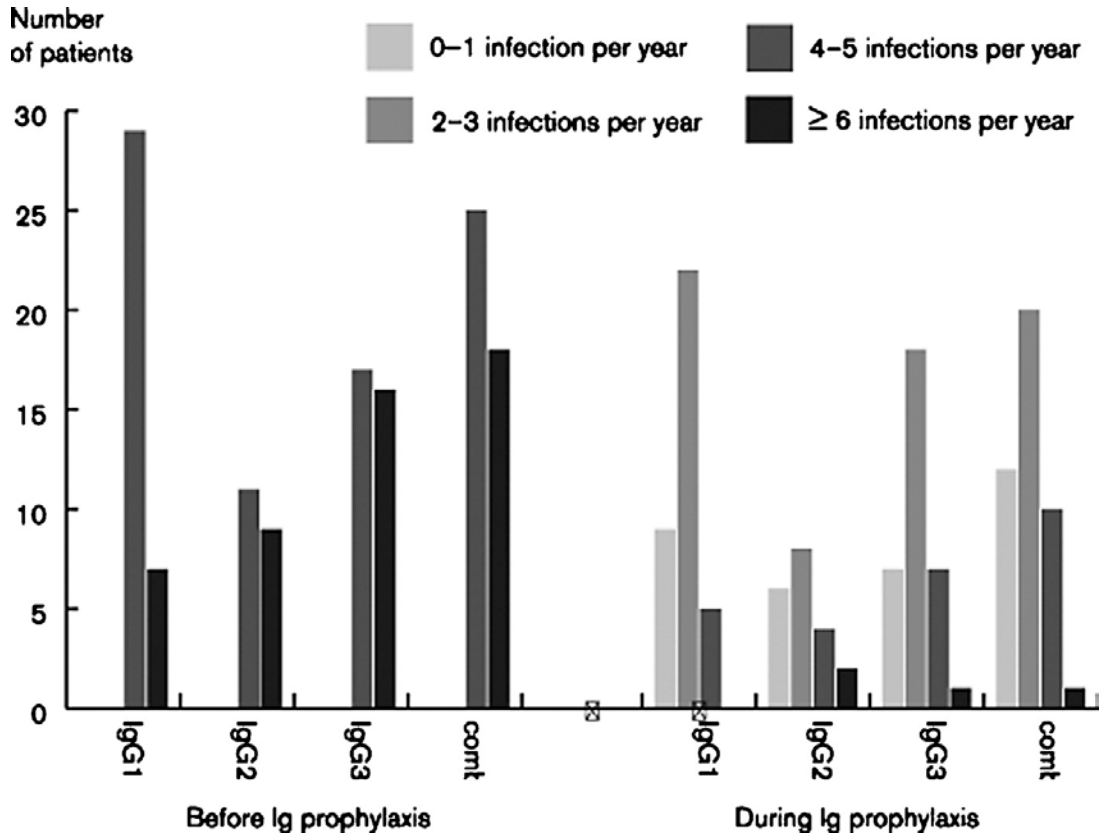
Update on the use of immunoglobulin in human disease: A review of evidence

Elena E. Perez, MD, PhD,[a] Jordan S. Orange, MD, PhD,[b] Francisco Bonilla, MD, PhD,[c] Javier Chinen, MD, PhD,[b] Ivan K. Chinn, MD,[b] Morna Dorsey, MD, MMSc,[d] Yehia El-Gamal, MD, PhD,[e] Terry O. Harville, MD, PhD,[f] Elham Hossny, MD, PhD,[e] Bruce Mazer, MD,[g] Robert Nelson, MD,[h] Elizabeth Secord, MD, PhD,[i] Stanley C. Jordan, MD,[j] E. Richard Stiehm, MD,[k] Ashley A. Vo, PharmD,[l] and Mark Ballow, MD[m] *North Palm Beach and St Petersburg, Fla; Houston, Tex; Boston, Mass; San Francisco and Los Angeles, Calif; Cairo, Egypt; Little Rock, Ark; Montreal, Quebec, Canada; Indianapolis, Ind; and Detroit, Mich*

"Immunoglobulin replacement for this use [subclass deficiency] has been controversial. However, at least 3 recently published studies… demonstrated decreased infections, a need for antibiotics, and improved quality of life…immunoglobulin replacement should remain a therapeutic option in patients in whom other ameliorative interventions have failed."

Evidence Supporting the Use of Immune Globulin Replacement Therapy in Subclass Deficiency

- Olinder-Nielsen et al 2007
- Retrospective study of 350 patients with subclass deficiency and recurrent RTIs
  - 43-52% had chronic lung disease
  - 17 had bronchiectasis
- 132 with 4 or more antibiotic-demanding RTIs per year and subsequently treated with immune globulin replacement therapy
  - Distribution of lung disease equal between groups, 11 with bronchiectasis
- Did not identify those with selective antibody deficiency



Ann-Margreth Olinder-Nielsen; Carl Granert; Pia Forsberg; Vanda Friman; Auli Vietorisz; Janne Björkander; *Scandinavian Journal of Infectious Diseases* **2007,** 39, 44-50.

Evidence Supporting the Use of Immune Globulin Replacement Therapy in Subclass Deficiency

Table II. Efficacy of immunoglobulin prophylaxis.

		Objective improvement**			Subjective improvement***	
Type of deficiency	No. of patients*	≥50%	<50%	None	Improvement	None
IgG1	36	23	10	3	26	10
IgG2	20	16	2	2	18	2
IgG3	33	23	6	4	28	5
Combined	43	30	10	3	37	6
Total	132	92 (70%)	28	12	109 (83%)	23

*Patients with ≥4 antibiotic-demanding RTIs per y and Ig dose of 100 mg/kg/week ($n = 132$).
**Objective improvement = decreased number of antibiotic treated RTIs. ***Subjective improvement = patient's judgement.

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Evidence Supporting the Use of Immune Globulin Replacement Therapy in Subclass Deficiency

- Abdou et al 2009: Prospective, open-label, 10 adult patients with recurrent respiratory infections and subclass deficiency and/or specific antibody deficiency received monthly IVIG.

Patient No.	Number of infections			Number of antibiotic courses			Number of hospitalizations		
	1 year prestudy	during study (1 year)	3 months poststudy	1 year prestudy	during study (1 year)	3 months poststudy	1 year prestudy	during study (1 year)	3 months poststudy
1	13	6	1	13	6	1	0	0	0
2	2	1	0	3	1	0	0	0	0
3	7	3	0	7	3	0	0	0	0
4	6	2	0	6	2	0	0	0	0
5	10	3	0	10	1	0	2	0	0
6	6	2	0	6	2	0	6	0	0
7	12	8	1	10	15	3	6	1	0
8	11	3	0	11	8	0	0	0	0
9	10	3	1	10	4	2	2	0	0
10	2	0	0	2	0	0	0	0	0
Total	79	31**	3***	78	42*	6***	16	1****	0

Abdou N, I, Greenwell C, A, Mehta R, Narra M, Hester J, D, Halsey J, F, Efficacy of Intravenous Gammaglobulin for Immunoglobulin G Subclass and/or Antibody Deficiency in Adults. Int Arch Allergy Immunol 2009;149:267-274

Evidence Supporting the Use of Immune Globulin Replacement Therapy in Subclass Deficiency

Patient No.	QOL scores		
	before the study	at 12 months (at end of study)	at 15 months (off IgIV for 3 months)
1	46.5	15	51
2	38.5	9	15
3	33	27	0
4	58.5	0	26
5	54	0	15
6	33	15	12
7	58.5	33	27
8	49.5	9	54
9	61.5	51	21
10	58.5	0	0
Mean ± SD	49.15 ± 10.96[a, c]	15.9 ± 15.82	22.1 ± 17.53[b]

Possible QOL scores range from 0 (best) to 99 (worst). See Materials and Methods section for further details.

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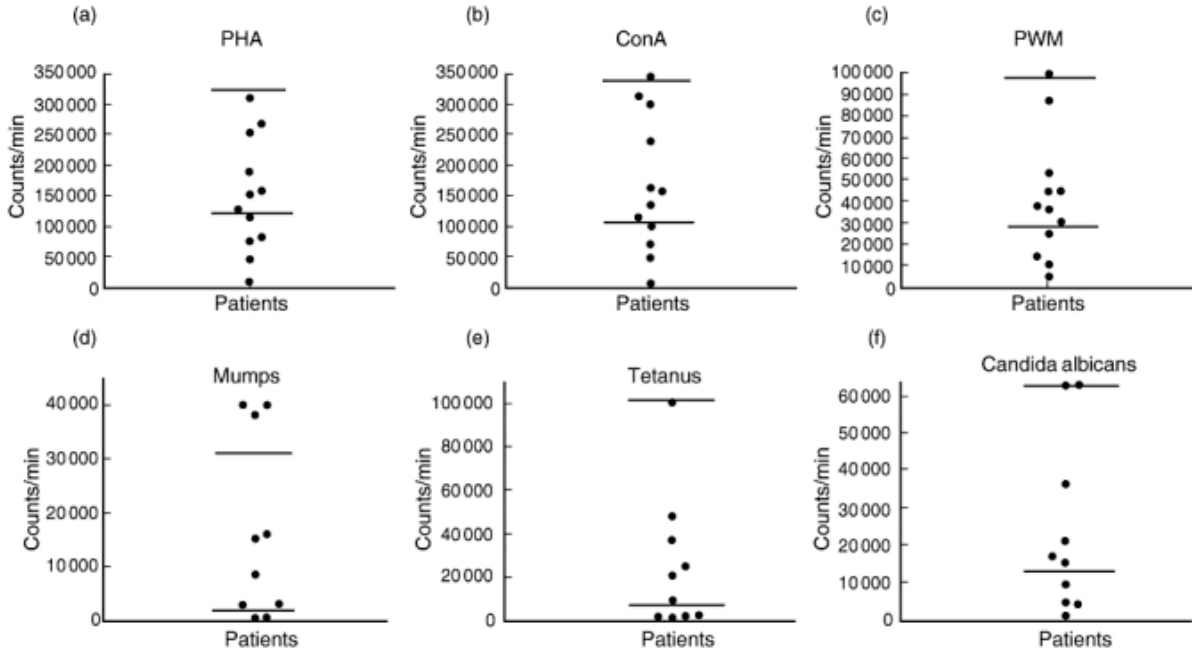
IVIG for IgG3 Subclass Deficiency

- Abrahamian et al 2010: Retrospective chart review of 17 adults with recurrent sinopulmonary infections and IgG3 subclass deficiency
- Pneumococcal antibody response recorded in 11, 6 with low titers
- Large subset had diminished proliferative response to mitogens and antigens (33%, 40%)
- Majority had concurrent allergic rhinitis and/or asthma
- 15 of 17 patients had significant improvement in infection frequency with IVIG



IVIG for IgG3 Subclass Deficiency– it's not just IgG3

- Barlan et al JACI 1993: prospective study of 22 children with IgG3 subclass deficiency and recurrent sinusitis and/or otitis media.
- 15 had polysaccharide response to *H. influenzae* type B polysaccharide vaccine evaluated, and all normal.
- 12 continued to have recurrent sinopulmonary infections on prophylactic trimethoprim-sulfamethoxazole and were placed on IVIG
  - IVIG preparation contained no IgG3!
- Sinusitis decreased from 8.2 to 1.8 per year
- Otitis media decreased from 4.6 to 0.3 per year ($p < 0.01$).

Conclusion: improvement is not due to increasing IgG3 levels, but rather probably due to passive transfer of specific antibodies to multiple different pathogens

Isil B. Barlan, Raif S. Geha, Lynda C. Schneider, Therapy for patients with recurrent infections and low serum IgG3 levels, Journal of Allergy and Clinical Immunology, Volume 92, Issue 2, 1993, Pages 353-355.

Work Group Report of the American Academy of Allergy, Asthma & Immunology

Update on the use of immunoglobulin in human disease: A review of evidence

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Prognosis of Patients with Subclass Deficiency

- Dutch cohort of 45 children with recurrent infections and subclass deficiency, IgG2 was most common
  - 11 SAD, 14 more than 1 subclass deficiency, 5 IgA deficiency. None with IgM deficiency.
  - 10% already had bronchiectasis.
- Follow up at 12-65 months, half available for follow up
  - 29% had no clinical change
  - 46% (11) showed progressive immune deficiency
    - 4 developed CVID
  - 25% were no longer symptomatic
- 33% (8) received IVIG

Table 2 Clinical problems in the past year at baseline

	Yes	No	Unknown
≥4 ENT infections*	36 (73 %)	10 (20 %)	3 (7 %)
>1 lower airway infection	28 (57 %)	19 (39 %)	2 (4 %)
Bronchiectasis	5 (10 %)	26 (53 %)	18 (37 %)
Hearing loss	1 (2 %)	5 (10 %)	43 (88 %)
Severe infections**	9 (18 %)	25 (51 %)	15 (31 %)

J Clin Immunol. 2016 Feb;36(2):141-8. Epub 2016 Feb 4

Immune globulin replacement therapy: Give it a try when all else fails

- Subclass deficiency as a biomarker
  - Must be interpreted within clinical context
  - Some have real disease, with chronic lung disease and bronchiectasis
- Trial of immune globulin replacement therapy when prophylactic antibiotics have failed
  - Evidence to support
  - Consensus to support
  - No other good options
- Stop if it is not working

Rebuttal

Recap of Reasons to Support Immune Globulin Replacement Therapy

- Subclass deficiency as a biomarker
  - Some have real disease that merits treatment
  - Some even have bronchiectasis
- Trial of immune globulin replacement therapy in those that fail prophylactic antibiotics
  - Evidence and consensus to support it
  - Can always stop if no improvement

Art of Medicine: We don’t have randomized trials for much of what we do

- Subclass deficiency as a biomarker
  - Therefore, immune globulin replacement therapy is not one-size fits all
  - A minority of patients with subclass deficiency will need immune globulin replacement, but that does not mean it should not be a therapeutic option for these patients
- We give immune globulin replacement therapy in PI all the time without randomized studies:
  - WAS
  - AT
  - STAT-3
  - NEMO
  - STAT-1
  - Many others…

Immune Globulin Replacement Therapy in Subclass Deficiency is Low Risk

- Many available intravenous and subcutaneous options available
  - Subcutaneous form very well tolerated
  - IgA low products
- No documented transmission of infections since the mid-1990s
- Target a “biological trough”– dose of at least 400mg/kg every 4 weeks or 100mg/kg per week

IVIG is expensive, but being sick costs MORE!

- IVIG: average cost $29,406 for product administered in physician's office, assuming average dose of 32 grams of IVIG (adults)
- Reduced frequency of infections = SAVINGS
  - Fewer hospitalizations
    - Shorter hospitalizations (One day= $3,000)
    - Fewer ICU admissions (One night= $6,667)
  - Fewer surgeries (In-patient=$14,729, Out-patient=$2423)
  - Fewer sick visits ($100)
  - Fewer sick days (Average wage of $38,651, one sick-day is $148.66)
- Higher benefit if immune globulin replacement therapy started before permanent organ damage (bronchiectasis)
- Societal Impact and Responsibility
  - Fewer on disability (Disability costs US government an average of $22,600 per year per patient)
  - "If just 25% of the estimated 4,000 disabled patient with PIDD avoided long-term disability through early diagnosis and treatment, potential five year savings… would be over $110 million"

Boyle and Scalchunes. Pharmaceuticals Policy and Law 10 (2008) 133–146

Immune Globulin Replacement Reduces Need for Antibiotics

- Prophylactic antibiotics remain the first-step for clinically significant subclass deficiency
- Immune globulin replacement in subclass deficiency reduced the need for antibiotics!
- Antibiotics are not without risk
  - Adverse effects
  - C. difficile
  - Microbiome: immediate reduction in microbial diversity
    - 25% reduction in diversity with beta-lactams or fluoroquinolones with subsequent dominance of resistant species[1]
    - Impact lasts long after cessation of antibiotics[2,3]
- May contribute to antibiotic resistance if not using culture directed therapy[4]

1. PLoS One 2014; 9(4): e95476.
2. PLoS Biol 2008 6: e280.
3. PLoS One 2010 5: e9836
4. Arch Otolaryngol Head Neck Surg. 2004;130(10):1201-1204

Quality of Life Improves with Immune Globulin Replacement Therapy

- Patients with PIDD score lower on health-related quality of life (HRQOL) than patients with other chronic diseases
  - Contributing factors: delay in diagnosis leading to frequent infections and functional impairment
- Immune globulin replacement therapy improves HRQOL score, and further improved by SCIG

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Jiang F, Torgerson TR, Ayars AG. Health-related quality of life in patients with primary immunodeficiency disease. *Allergy, Asthma, and Clinical Immunology : Official Journal of the Canadian Society of Allergy and Clinical Immunology*. 2015;11:27.

Conclusions to Support Immune Globulin Replacement Therapy

- Subclass deficiency as a biomarker
  - Some have real disease that merits treatment
  - Some even have bronchiectasis
- Trial of immune globulin replacement therapy in those that fail prophylactic antibiotics
  - Evidence and consensus to support it
  - Can always stop if no improvement
- This is the ART OF MEDICINE!
- If it helps, you will be:
  - Saving the patient, the health care system, and society money
  - Reducing the need for antibiotics and decreasing associated complications
  - Improving your patient’s quality of life

Thank you!