Treat the Patient, Not the Number:
Immunoglobulin Replacement for IgG Deficiency

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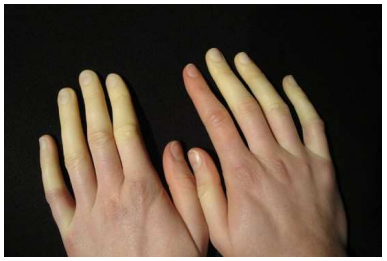
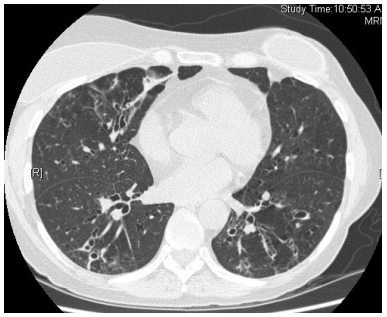
Case

- 57 year old F with history of autoimmune disease referred to your office for progressive bronchiectasis



PMHx: Sjogren's, Raynaud's, Chilblains



Infectious history: mild pneumonia x4 (only one recently), bronchitis "every few years", no recurrent OM/sinusitis, skin, GI, or bloodstream infections

  - Rare use of antibiotics, no hospitalizations

Based on AAAAI.org "Ask the Expert," 10/25/13

Case

Immune workup

IgG 1457	(700-1600 mg/dL)
IgG1 1240	(341-894 mg/dL)
IgG2 102	(171-632 mg/dL)
IgG3 99.5	(18.4-106 mg/dL)
IgG4 <0.3	(2.4-121 mg/dL)
IgA 443	(70-400 mg/dL)
IgM 139	(40-230 mg/dL)
Tetanus titers	Protective
Diphtheria titers	Protective
Pneumococcal titers	15/23 serotypes, s/p PPSV23

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IgG2 and IgG4 Subclass Deficiency

Based on AAAAI.org "Ask the Expert," 10/25/13

The Questions

- Your eager fellow asks, “Would you treat this patient with IgG replacement therapy?”

- Is her IgG subclass deficiency clinically relevant?
- What are indications for starting Ig?
- Are there other treatment options?
- Is there evidence for Ig replacement?

Figure 1. Confused Allergy Fellow

Our current guidelines **do not** advocate for Ig replacement:

IgGSD can be indicative, but not causative...

Isolated IgG subclass deficiency (IgGSD) is **not** an indication for treatment, and may not be clinically relevant.

Ig replacement *could* be considered for IgGSD **if** there is evidence of severe infection **and** impaired antibody response.

There *are* other less risky and less expensive treatment options.

There is a lack of data to support Ig prophylaxis in IgGSD.

Outline

- IgG subclass deficiency (IgGSD): a brief review
- Diagnosis of IgGSD
- Expectant Management of IgGSD
- Treatment of IgGSD
- The Data for Ig therapy in IgGSD…or Lack Thereof
- Concluding Arguments

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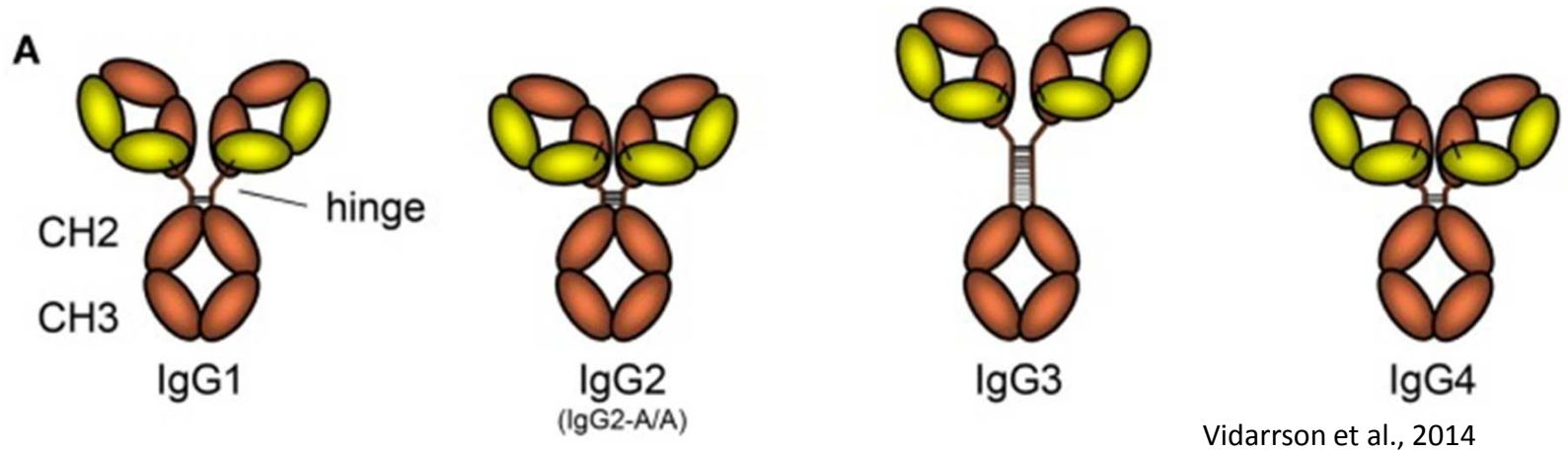
IgG Subclasses: Similar, but Different



Vidarrson et al., 2014

- IgG has four subclasses
- Highly conserved, but with structural differences at hinge region
- Structural differences = varying immunological properties
  - Antibodies to polysaccharide antigen: mostly IgG2
  - Antibodies to protein and viral antigen: mostly IgG1 and IgG3

Deficiency does not always mean disorder

- IgG subclass deficiency (IgGSD): deficiency in one or more of the IgG subclasses for age with a **normal total IgG.**
- IgGSD is well-described in otherwise healthy children and adults.
- Most individuals are asymptomatic.
- Despite total IgGSD due to heavy-chain gene deletions, affected individuals can still produce normal antibodies (Buckley, 2002).

Deficiency does not always mean disorder

Sample population	Total number (n)	Percent (%)			
		IgG1	IgG2	IgG3	IgG4
Healthy children	3854	4.9	19.4	6.3	0.8
Healthy adults	162	8	3	1	1
Adults with suspected antibody defects	1175	28	17	13	9

Adapted from Meulenbroek et al, 2000

IgGSD can be a common finding in patients with frequent infection

IgGSD	Cohort	Number of cases/frequency	Ref
Any	Recurrent infections	21% (101/483)	Aucouturier et al. 1991
Any	Recurrent infections (pediatric only)	13% (7/55)	Visitsunthorn et al., 2011
IgG1	Recurrent infections	4% (119/3005)	Lacombe et al. 1997
IgG2	PID patients	17.6% (16/91) More frequently described in children	Javier et al. 2000
IgG2	Recurrent infections (adult only)	17% (199/1175)	Meulenbroek et al, 2000
IgG3	Recurrent infections (pediatric only)	0-25% (multiple studies)	Meyts et al. 2006
IgG3	Recurrent infections (adults only)	13% (152/1175) More frequently described in adults?	Meulenbroek et al, 2000
IgG4	Recurrent infections (adults only)	15.3% (9/59)	Kim et al. 2016
IgG4	Recurrent infections (pediatric only)	17% (21/127)	Moss et al. 1992

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Clinical IgG Subclass Deficiency

- **Defined as IgGSD for age with:**
  - ❑Clinical history of recurrent or severe infections
  - ❑Laboratory evidence of poor specific antibody responses (preferably to both protein and polysaccharide antigens)

- **Diagnostic challenges:**
  - ❑No consensus on when to check IgG subclasses
  - ❑Normal ranges of IgG subclasses vary by age and cohort
  - ❑ Normal ranges of IgG subclasses vary by lab
  - ❑ Low antibody titers can be over-interpreted (Buckley , 2012)

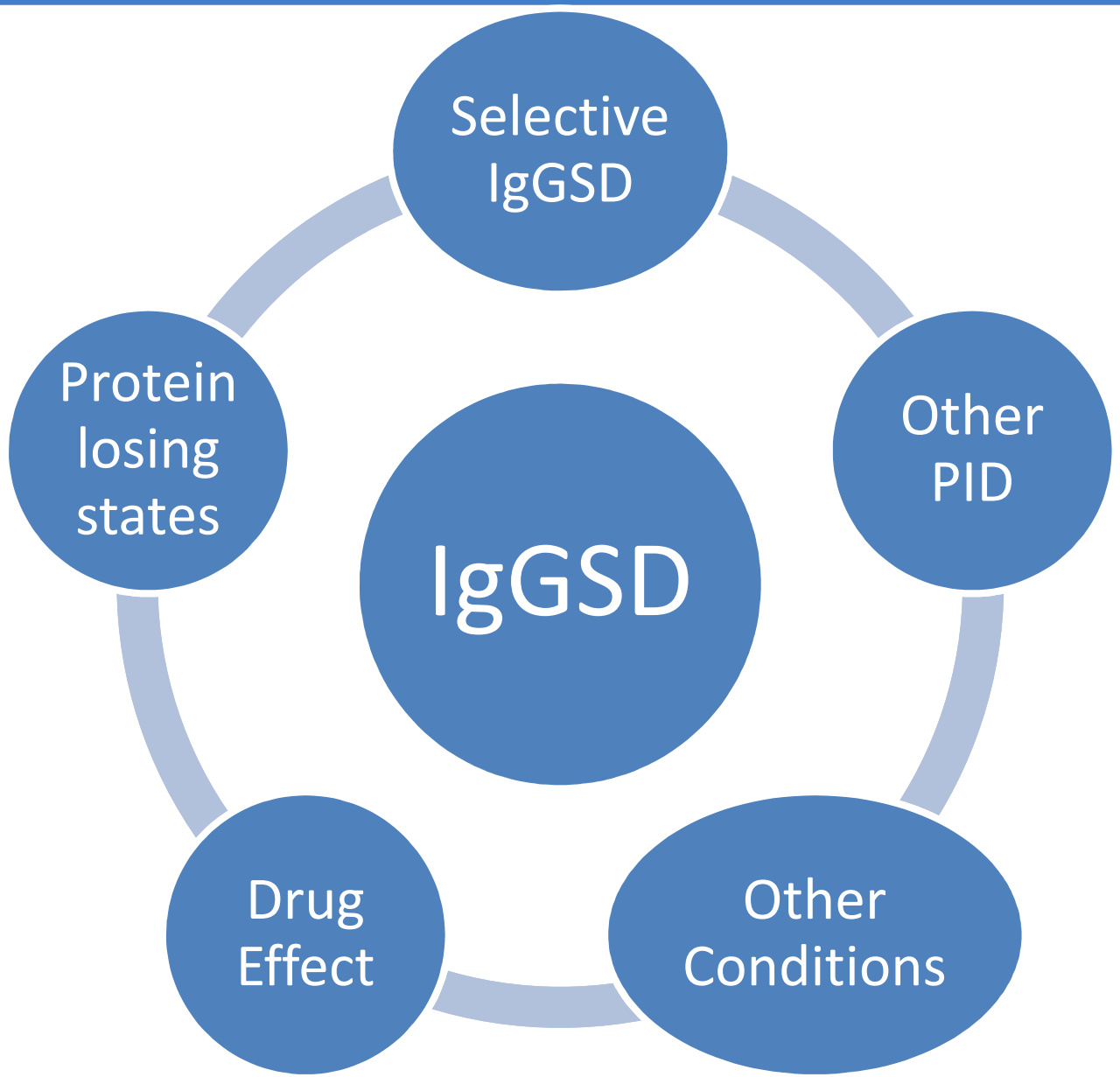
Sinopulmonary infections, asthma, and autoimmunity are frequently reported in symptomatic IgGSD

IgGSD	Clinical Presentations	
	Infections	Other Co-Morbidities
IgG1	Recurrent sinopulmonary infections Gastrointestinal infections	Asthma, atopic disease, autoimmunity
IgG2	Recurrent sinopulmonary infections ⇧**risk of encapsulated organisms (*S. pneumoniae*)**	Asthma, bronchiectasis, autoimmunity (juvenile DM, SLE, Sjogren's)
IgG3	Recurrent sinopulmonary infections ⇧**risk of Moraxella/Strep pyogenes** recurrent erysipelas, HSV	Asthma, chronic bronchitis, autoimmunity
IgG4	Recurrent sinopulmonary infections	Asthma, atopic disease (allergic colitis), bronchiectasis

IgGSD can be a sign of other PID or chronic illness

IgGSD	Associated Conditions	
	Primary immunodeficiencies	Other Conditions
All	- CVID	- Congenital cardiac disease - DiGeorge Syndrome
IgG1	- Consider THI in infant	
IgG2	- Described with IgA deficiency - Complement C2 deficiency - STAT3 deficiency	- Growth hormone deficiency - Febrile seizures
IgG3	- Chronic neutropenia	- Henoch schonlein purpura
IgG4	- STAT3 deficiency	- Down Syndrome - Growth hormone deficiency

Differential diagnosis of IgG Subclass Deficiency



Differential diagnosis of IgG Subclass Deficiency

Selective IgGSD

- Selective IgG1 deficiency is rare
- Combined IgGSD:
  - IgG1 and IgG3 deficiency
  - IgG2 and IgG4 deficiency
  - IgA and IgG2 +/- IgG4
  - IgA and any IgGSD
  - IgM and any IgGSD

Differential diagnosis of IgG Subclass Deficiency

- Common variable immunodeficiency
- Specific antibody deficiency
- Transient hypogam of infancy (IgG1)
- IgA deficiency (IgG2)
- Complement C2 deficiency (IgG2)
- Ataxia-telangiectasis (IgG2, IgG4)
- Chronic mucocutaneous candidiasis (IgG2, IgG4)
- IFN-Gamma deficiency disorders (IgG2)
- STAT3 deficiency (IgG2, IgG4)
- Mannose-binding lectin deficiency (IgG2)
- Chronic neutropenia (IgG3)

Other PID

Differential diagnosis of IgG Subclass Deficiency

- Malignancy (leukemia, lymphoma)
- Viral infection/bone marrow suppression
- DiGeorge Syndrome
- Congenital cardiac disease
- Failure to thrive/cystic fibrosis
- Febrile seizures (IgG2)
- Growth hormone deficiency (IgG2, IgG4)
- Henoch-Schonlein purpura (IgG3)
- Friedrich's Ataxia (IgG3)
- Trisomy 21 (IgG4)

Other Conditions

Differential diagnosis of IgG Subclass Deficiency

Drug Effect

- Anti-epileptics
  - Carbemazepine
  - Phenytoin
  - Zonisamide
- Steroids
- Sulfasalazine
- Rituximab, imatinib

Differential diagnosis of IgG Subclass Deficiency

Protein losing states

- Protein losing enteropathy
- Nephrotic syndrome
- Burns

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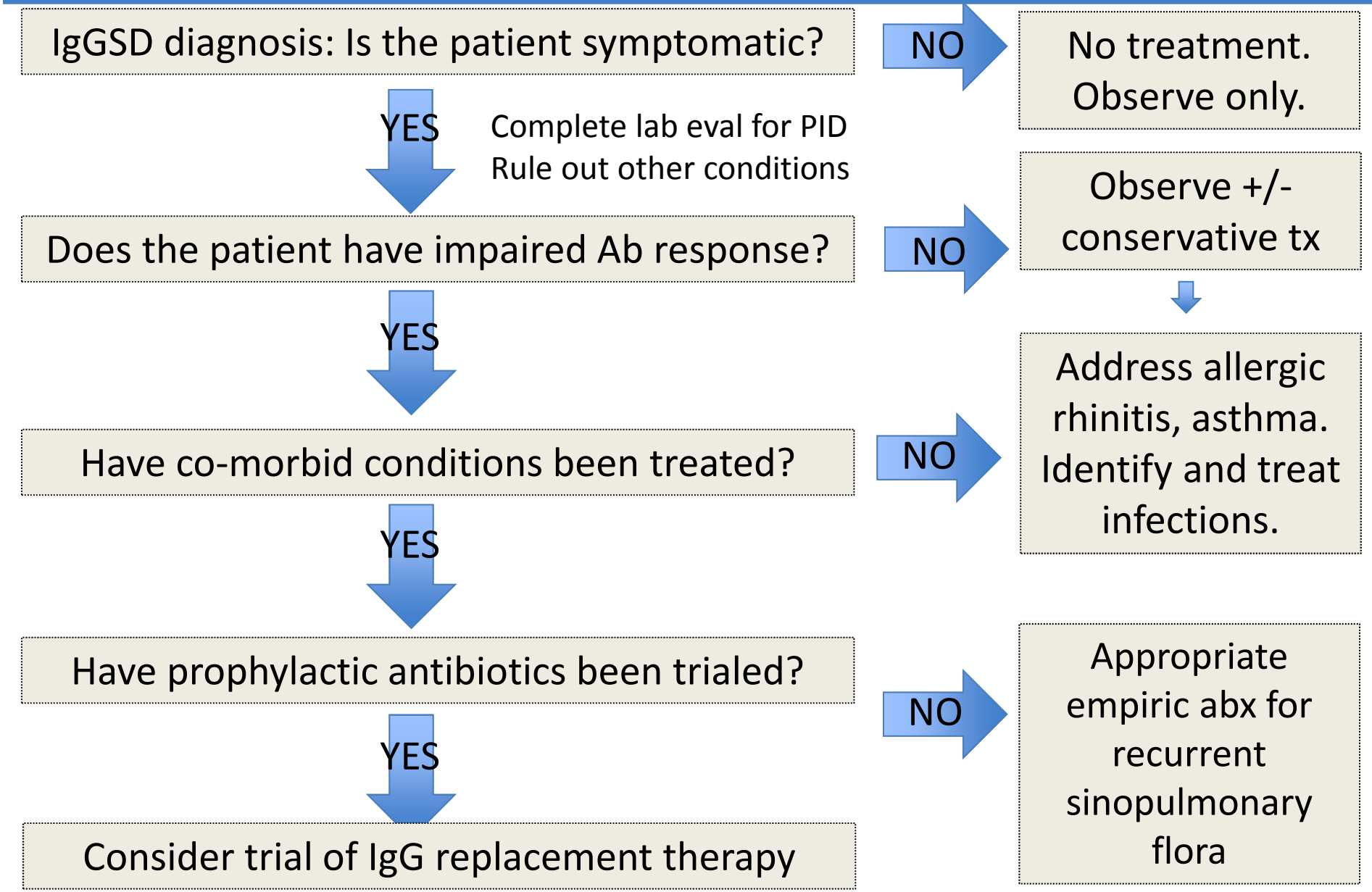
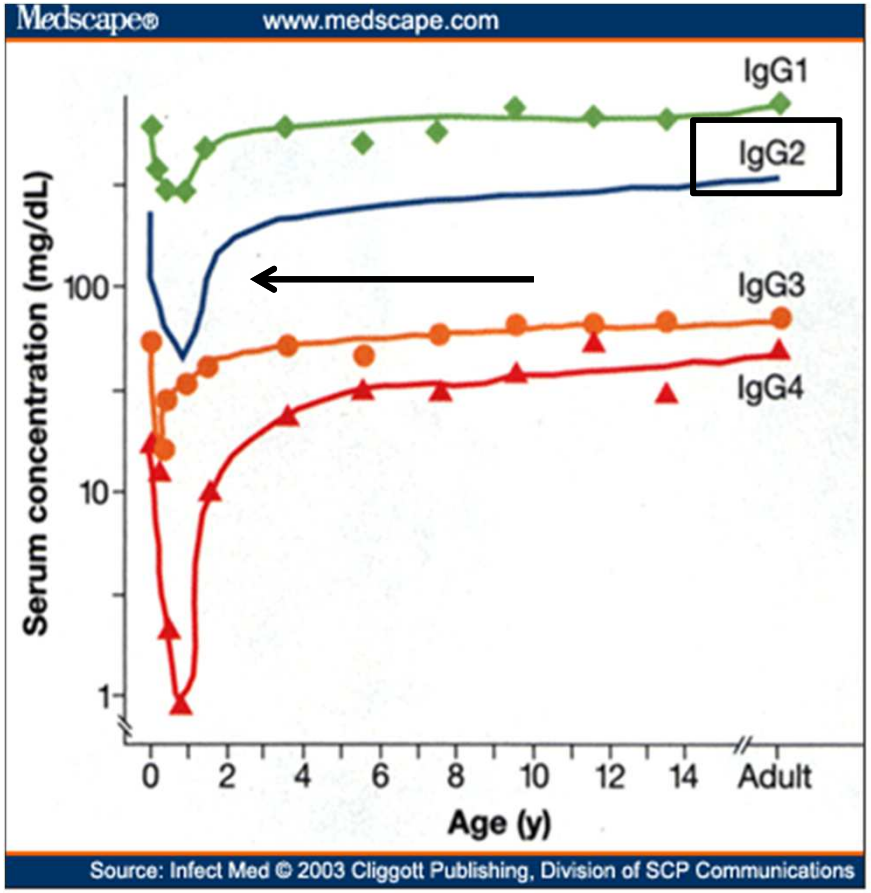
Most patients with IgGSD do not need Ig



Watchful waiting: it's not just for otitis media

- Consider first a diagnosis of THI in a child <5 yrs with IgGSD
- Adult concentrations of IgG2, IgG3, and IgG4 may not be reached until puberty:



Watchful waiting: pediatric IgGSD can improve

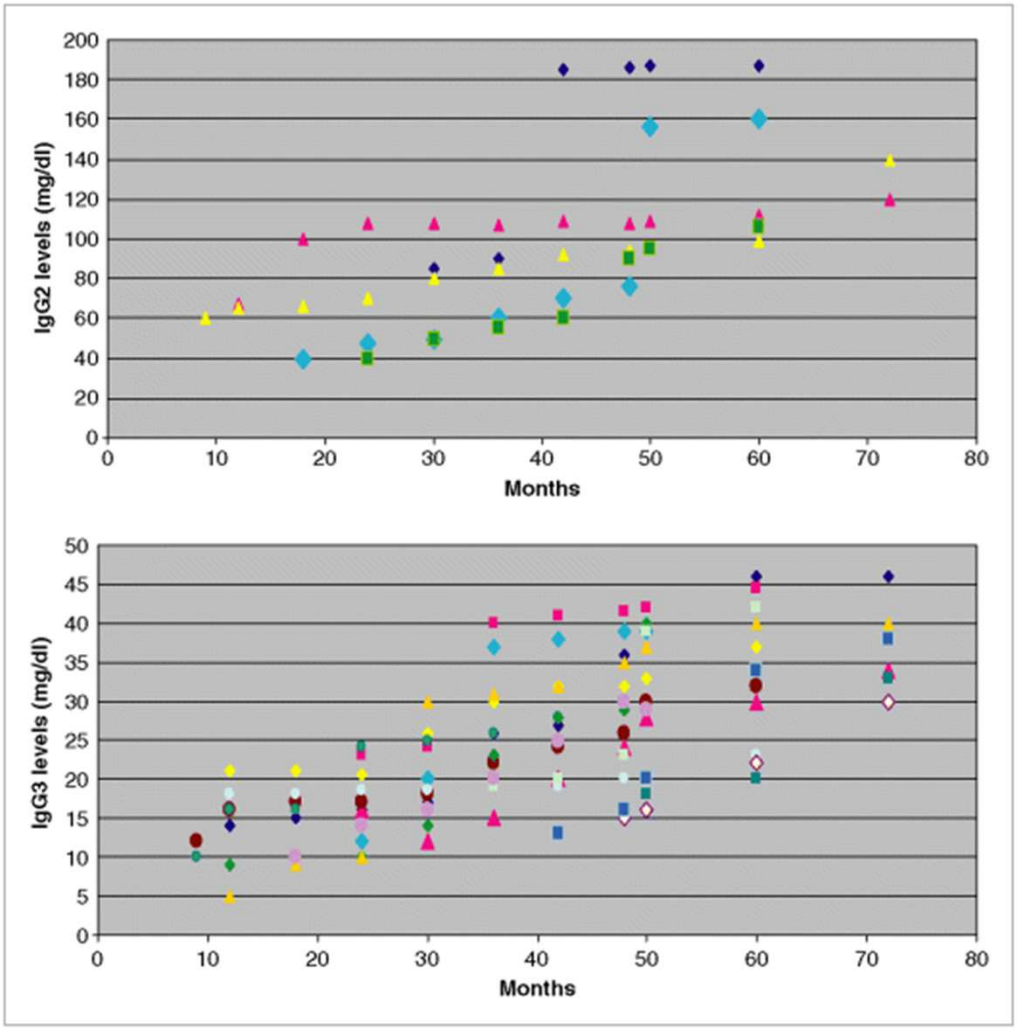
- Most children with symptomatic IgG2SD and initial poor antibody response will normalize IgG levels and antibody response (Wolpert et al., 1998)

- 25% of children (n = 24) with IgGSD and/or specific antibody deficiency demonstrated normalization (Schatorje et al., 2016)
  - Half of original n = 40 in study unreachable for follow up

- 30-40% of Turkish children (n=59) had normal Ig subclasses by age 6 (Karaca et al., 2009)

Watchful waiting: pediatric IgGSD can improve

- 30% of children with isolated IgGSD normalized IgG levels by 45-83 months of age (Kutuculer et al., 2007)



If it doesn't improve, it's probably not IgGSD:

- Persistent IgGSD in a child >6-8 years old will not likely improve with time.

- Symptomatic IgGSD in an adult with antibody impairment will also not likely spontaneously improve.

IgG Subclass deficiency or CVID in evolution?

IgG Subclass deficiency or CVID in evolution?

- Children with symptomatic and persistent IgG2 subclass levels are likely to have other concurrent immune defects on evaluation (Shackelford et al., 1990)

- 11/24 children with IgGSD or SAD had progressive hypogammaglobulinemia in follow up (12-65 months); 4 met criteria for CVID (Schtorje et al, 2010)

- In 20 patients with selective IgA deficiency that progressed to CVID, 47% also had IgG2 and/or IgG4 deficiency (Aghammohammadi et al., 2008)

The big picture: Key Points

- IgGSD can be a transient condition, reflective of infection, inflammation, or even normal growth in children, so **it is worth it to WAIT on Ig prophylaxis if clinically feasible**.

- In persistent symptomatic pediatric IgGSD or adult IgGSD, this may signal evolution of CVID.

- **Early initiation of Ig replacement could mask evolving humoral defects and delay diagnosis of CVID.**

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Treatment of co-morbid conditions as infectious prophylaxis

- Current AAAAI Guidelines recommend **treatment of co-morbid allergic rhinitis and asthma** as infectious prophylaxis:
  - Maximize management of allergic rhinitis and asthma
  - Consider allergy immunotherapy: AIT resulted in complete resolution of chronic effusion/drainage in 85% of cases (n = 127 ears)
  - Consideration of surgical referral/intervention
  - Obtaining bacterial culture data when possible can direct tx

- **Treatment of comorbid conditions:**
  - Baseline low IgG3 levels improved after treatment of chronic sinusitis (n= 30, Armenaka et al., 1994).

Re-vaccination as infectious prophylaxis

- Lack of antibody response to both protein and polysaccharide antigens should be documented in all patients with IgGSD.
  - IgG2SD patients may have uniformly poor polysaccharide responses.

- Patients with specific antibody deficiency have **decreased sinopulmonary infections** following conjugated pneumococcal vaccine (Sorensen et al., 1998)

- Recommend protein conjugate vaccines for patients with impaired polysaccharide antibody response (i.e. IgG2): HiB, Pneumococcal, Meningococcal (Buckley, 2002)

And finally, antibiotic prophylaxis as infectious prophylaxis

- Patients with IgG3SD (n=22) were treated with prophylactic Bactrim +/- IVIG; **45% had fewer infections after 1 year of Bactrim only** (Barlan et al., 1991)
- **72% of children with IgGSD** (n=120) had fewer infections with appropriate prophylactic antibiotics only (Wolpert et al., 1998)
- Frequency of infection decreased (6-20/yr to 2-10/yr) in **85% of pediatric IgGSD patients on bacterial prophylaxis** (n=59) (Karaca et al., 2009).

Close Monitoring, Vaccination, and Antibiotic Prophylaxis are Effective: Key Points

- Preventing infection is a good treatment for infection.
  - Allergists (i.e. you) are key to management of atopy in IgGSD.
  - Suggest AIT when clinically appropriate.
- Conjugated vaccines prevent infection in SAD patients with impaired antibody response, so why not IgGSD?
- Antibiotic prophylaxis doesn't work for everyone, but it works in the majority, and worth a trial

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IgG Replacement in IgGSD

- **Lack of controlled, blinded clinical studies on Ig for IgGSD:**
  - Single-blinded crossover study (n=43) suggested fewer infections on 1 year Ig prophylaxis compared to placebo. (Sodorstrom T et al., 1991)
  - Double-blinded crossover study to evaluate IVIG ppx in IgG2SD or SAD was not completed (Herrod HG et al, 1993)

Improvement in some, but not all

- **Retrospective studies suggest improvement in some, but not all:**
  - In 132 patients with IgGSD on Ig prophylaxis with >4 respiratory tract infections/yr, infections were decreased in most patients. However:
    - 28 patients had **less than 50% reduction in infections**
    - 12 patients saw **no effect at all**
    - 5 patients ended Ig prophylaxis prematurely **due to adverse reactions**

Improvement in some, but not all

- Meyts et al. report a case series of 7 patients with isolated Ig3 deficiency and history of frequent infection; **2/7 were not treated with IVIG and remained well (observation only)**

- Abrahamian et al. report a case series of 13 IgGSD patients with isolated IgG3 deficiency and frequent infection; however enrolled patients **may have had other underlying immune defects**
  - Low CD8 T cells, low CD19 B cells, low TLR function, decreased NOI among defects reported.
  - 2/13 patients stopped IVIG due to no effect

Will potential benefit outweigh risks?

- **44% report adverse reactions to IVIG unrelated to rate** (Perez et al., 2017)
- **Administration reactions**
  - SCIG – local pain, bruising, swelling, and erythema in 75% of patients
  - IVIG – systemic headache, aches, chills, fever in up to 15% of patients (up to 50% in all Ig patients)
  - Subset of patients will require premedication with Benadryl and steroids, also not without side effects
  - Phlebitis and line infection could be potential risks

Severe reactions in IVIG administration is a real risk

TABLE XIV. Adverse events with IVIG administration

Frequency	Adverse event
Common‡	Headache; myalgia, back pain, arthralgia; chills; malaise, fatigue, anxiety; fever; rash, flushing; nausea, vomiting; tingling, infusion site pain/swelling, erythema; hypo- or hypertension, tachycardia; fluid overload
Uncommon (multiple reports)	Chest pain or tightness; dyspnea; severe headaches; aseptic meningitis; pruritis. urticaria; thromboembolic*; (cerebral ischemia, strokes; myocardial infarction; deep vein thrombosis; pulmonary emboli; renal toxicity†); hemolytic reactions due to isoagglutinins to Rh or other blood groups; anaphylactic/anaphylactoid reactions
Rare (isolated reports)	Anaphylaxis due to IgE or IgG antibodies to IgA in the immunoglobulin product; progressive neurodegeneration; arthritis; cardiac rhythm abnormalities; transfusion-related acute lung injury (granulocyte antibody mediated); neutropenia; pseudohyponatremia; uveitis; noninfectious hepatitis; hypothermia; lymphocytic pleural effusion; skin (leukocytoclastic vasculitis of the skin, erythema multiforme, urticaria, dyshidrotic eczema, maculopapular or eczematoid rashes, alopecia)

*Related to the procoagulant activity in the IVIG, eg, Factor XIa as well as hyperosmolality.

†Majority due to sucrose containing IVIG products, osmotic nephrosis with injury to proximal renal tubules.

‡Infusion rate related and/or higher doses, eg, 2 g/kg.

Severe reactions in Ig replacement:

- There is risk of IgA mediated **anaphylaxis or anaphylactoid reaction:**
  - IgA deficient patients may have IgE anti-IgA antibodies
  - IgA deficient patients may have IgG anti-IgA antibodies

- Further prospective studies are needed to determine true risk/frequency of anaphylaxis in IgGSD

Severe reactions in Ig replacement:

- Thromboembolism can happen in patients even without risk factors (Perez et al.)
  - High dose therapy (1000 mg/kg)
  - Cardiovascular risk factors
  - Hypercoagulable states
  - Indwelling catheters
  - Autoimmunity
  - Older age

Will potential benefit outweigh cost?

- Monthly IVIG can be costly:
  - Expense to healthcare system and patients
  - Lost hours at school and work

- Ounce for ounce, IVIG is more expensive than gold
  - Highest expense pre-diagnosis in CVID: hospitalization ($25K/year)
  - Highest expense post-diagnosis in CVID: medication ($40.6K/year)

(Sadeghi et al., 2015)

Ig replacement should be a reserved as a last option: key points

- IVIG/SCIG is a costly drug compared with vaccinations and antimicrobial medications, **and it is not without risks.**

- IVIG treatment reduces overall costs in CVID, but there is no data in IgGSD to suggest the same.

- It shows promise in decreasing infection in small studies, but **needs large, controlled, blinded studies** to determine sustained efficacy, dosing guidelines and duration of therapy in IgGSD.

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IgGSD: treat the patient, not the number

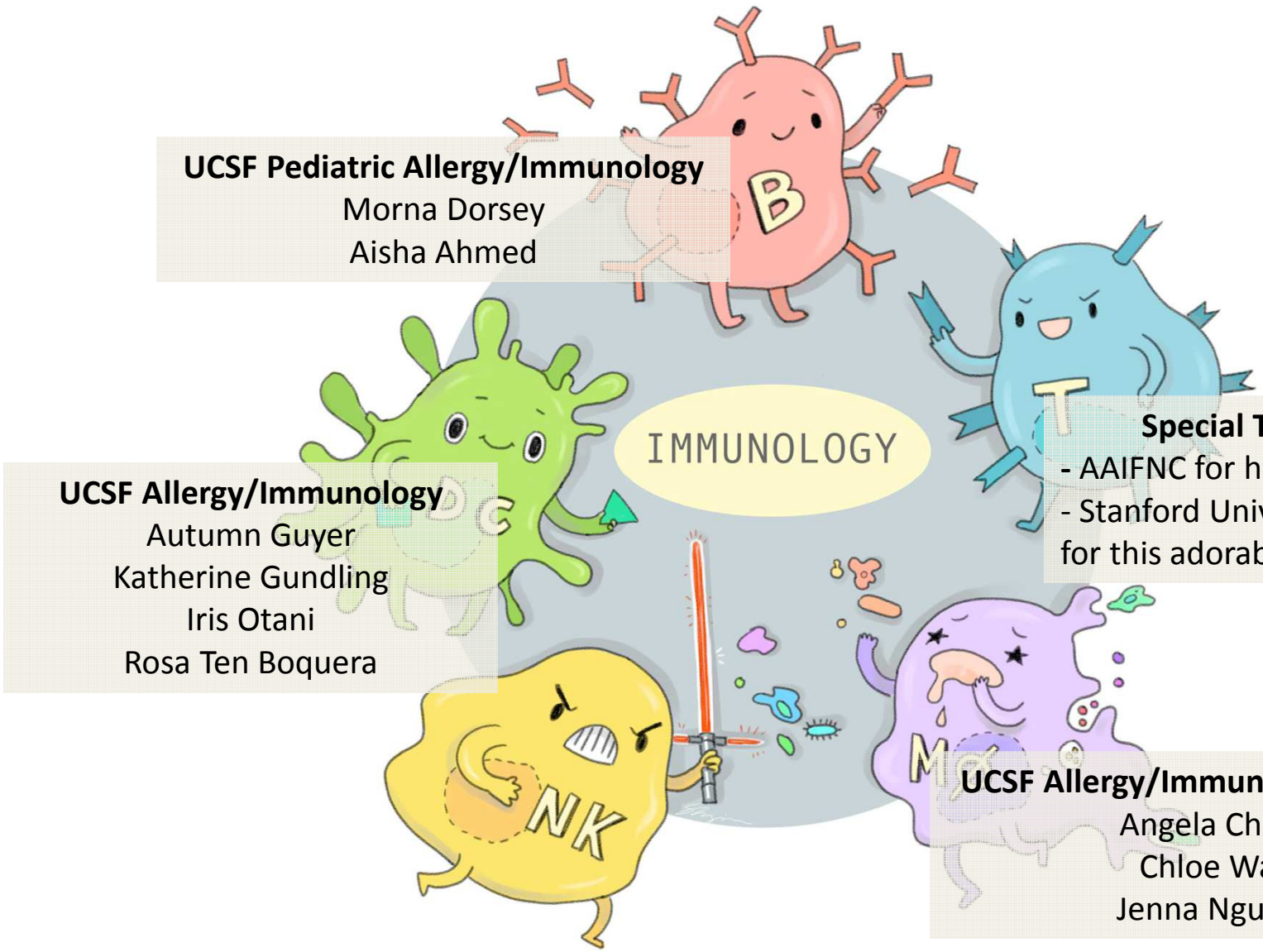
- IgGSD is nothing but a number. **Don't treat asymptomatic IgGSD**.

- Symptomatic IgGSD **can be transient or associated with other illness**; patients can be closely observed for severe, recurrent infections.

- Since sustained efficacy is still unclear, consider IVIG/SCIG **only** for IgGSD patients with significant history and impaired antibody responses.

- IVIG/SCIG is costly (!!!!), and not without its risks.

Thank you for your attention!



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Special Thank You to:
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REBUTTAL

REBUTTAL

- Argument: some symptomatic IgGSD patients who demonstrated improvement with Ig replacement have adequate response to pneumococcal (polysaccharide) vaccination (Abrahamian et al., 2009; Oxelius et al., 1986).
  - Consider antibodies are being produced but are not effective
  - Consider use of **opsonophagocytic activity** assay (OPA) in patients with high suspicion of antibody defect, but normal antibody titers
  - OPA assay **detects for functional antibodies to Strep pneumo** after complement mediated opsonization
  - May be more accurate for impaired antibody response rather than pre & post-vaccine titers

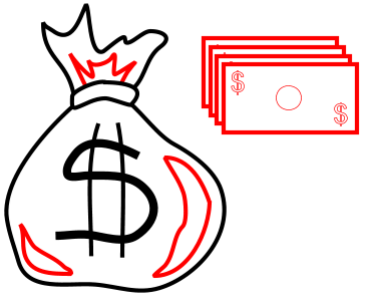
REBUTTAL

- Argument: Ig replacement therapy has been shown to reduce number of infections in IgGSD patients. Why not give everyone a trial on IVIG?
  - Is it a true diagnosis of IgSD? Have you treated infection? Have other immunodeficiencies been ruled out? A diagnosis of CVID or other PID makes your decision easier.
  - Who truly benefits? In a small study of 10 patients **with IgGSD or SAD** (7 with IgGSD), all had fewer infections and increased QoL scores on prophylactic IVIG but:
    - **4/10 had decreased MBL, 1 had MBL deficiency**
    - **5/10 had polymorphisms in TLR**

REBUTTAL

- Argument: Ig replacement therapy has been shown to reduce number of infections in IgGSD patients. Why not give everyone a trial on IVIG?
  - IVIG doesn't work for everybody. Antibiotic prophylaxis also doesn't work for everybody, but it is cheaper and logistically easier to try first.
  - IVIG is expensive, and we should be mindful of healthcare system costs and patient costs to finance and to quality of life





REBUTTAL

- Argument: the risks of serious side effects or anaphylaxis during IVIG administration are low; most patients will not have had IVIG before.
  - Anaphylaxis with first time administration of IVIG has been reported in a CVID patient (Rachid and Bonilla, 2001)
  - Theoretically increased risk in patients with IgA deficiency (production of IgE anti-IgA and/or IgG anti-IgA)