SIGNIFICANCE OF LOW IMMUNOGLOBULINS

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What to do about lowered immunoglobulins?

- **Most frequent reason for referral to our adult Clinical Immunology/ Immunodeficiency clinic at U of U.**
- **Critical additional information required, however, that is seldom supplied initially and must be solicited.**
- **Referral form often returned to referring physician's office requesting such data; which may, or may not be returned.**

Critically Needed Clinical Data in Immunodeficiencies

- **Has the patient suffered from serious and recurrent infections?**
- **Pneumonia, usually lobar and requiring hospitalization and IV treatment. #??**
- **Chronic persisting diarrhea with weight loss.**
- **Sinusitis recurrent or chronic, draining otitis, bronchitis, conjunctivitis.**

Additional Clinical Data

- **Autoimmune disease of any type 10-20% in CVID – Get Igs first not later!!**
- **? Treatment with prednisone, IV steroids, seizure medications, retuximab which can all significantly lower Ig concentrations and vaccine responses & effect T,B and NK cells. Even low doses of 10-20 mg prednisone but certainly with 20+ mg per day. Takes 2-6 months to resolve!! Retuximab years to resolve! PainMeds?**

Secondary Antibody Deficiency in Steroid Treated Patients

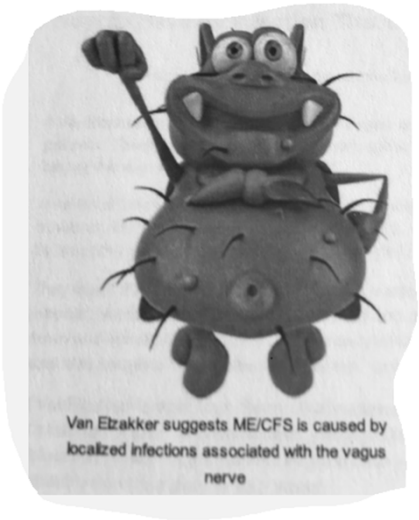
21 of 36 (60%) of Giant Cell Arteritis and Polymyalgia Rheumatica pts. treated with prednisone (5-50 mg/da.) developed AB deficiency

19/21 (90%) had low IgG; in 13 (62%) IgG only isotype involved; in 2/21 (10%) IgA was low also and in 4/21 (20%) IgM was low; six month decrease was seen in 8/21= 40%; low transitional and naïve B cells but normal IgM, IgA and IgM B memory cells. J Clin Immunol. 3/15/16

Fibromyalgia and CFS

- **Severe fatigue, inability to sleep.**
- **Muscle aches and pains, fibromyalgia, made much worse by any exercise!!!**
- **Clinical depression in 98+%!!**
- **20% have lowered immunoglobulins but most have normal antibody responses to vaccines: no clinical response to IVIG!!!**
- **HRH remedy: a gradual return to 30-40 min of regular exercise per day, anti- depressive meds. Endorphins!!**
- **Physical tiredness=Sleep.**

THE CAUSE OF CFS



Van Elzakker suggests ME/CFS is caused by localized infections associated with the vagus nerve

Exercise in Fibromyalgia and Chronic Fatigue Syndrome

White, P.D. et al. Comparison of adaptive pacing therapy, graded exercise therapy, and specialized medical care for chronic fatigue; a randomized trial. Lancet 377:823-6, 2011.

Wang, C., et al. A randomized trial of Tai Chi for fibromyalgia. New Eng. J. Med. 363:743-753, 2010.

Wallman, K.E. et al. Randomised controlled trial of graded exercise in chronic fatigue syndrome. Med. J. Australia 180: 444-448, 2004

Laboratory Data Required to Dx Hypogammaglobulinemia

- **<u>Repeat</u> IgG, IgA, IgM, IgG subclasses!! Different labs have different normal ranges! IgM 35 vs 60-70 – tons of referrals**
- **IFE in any >15 yo to rule out MGUS / Myeloma which can significantly lower Igs**
- **Pre and one month post S. pneumonia 23 valent vaccine, DT, Flu A&B vaccines, 2-4 fold or majority of serotypes (50-70%) > 1 ug ml (1.0 ug vs 1.3 ug makes no difference!!!!;)** Daly, T.M., Hill, H.R.: Clin. Vaccine Immunol. 22:148-152, 2015..

Additional PRIOR/POST Referral Labs Needed

- **T, B, and NK Cell determination – T EXTENDED, LYMP PANEL 6, Memory B cell panel, LAM or Flow LAM.**
- **HIV Molecular Screen – Usually high immunoglobulins but Reimer HIV patient had hypogammaglobulinemia**
- **In immunodeficiency or in infants must use molecular HIV tests not serology!!!! Can't make good antibody!**

Reference Ranges

- **Ogden Clinic IgG 700-1600, IgA 70-400, IgM 40-230**
- **LabCorp IgG 700-1600, IgA 91-414, IgM 40-230**
- **ARUP IgG 768-1632, IgA 68-378, IgM 60-263 Now 35!!!**
- **IHC Lab IgG 700-1600, IgA 44-441, IgM 50-300**

IgG Subclass Ranges

- **ARUP IgG 1 (240-1118), IgG2 (124-549), IgG3 (21-134), IgG4 (7-89)**
- **LabCore IgG1 (422-1292), IgG2 (117-747),IgG3(41-129),IgG4(0-100)**

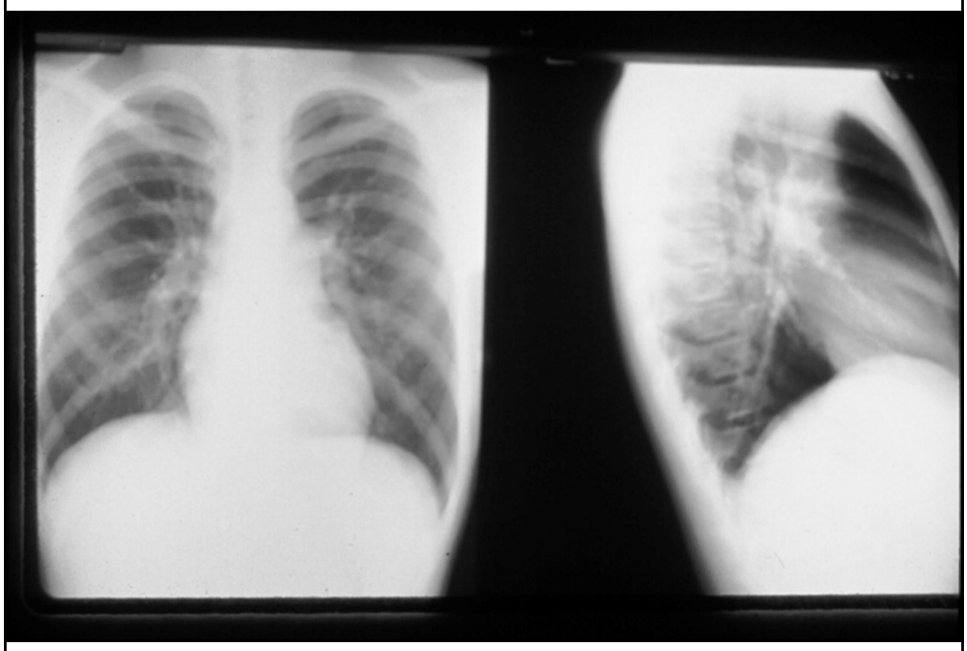
IgG Subclass Vaccine Responses

- **IgG 1 – Diphtheria, Tetanus, Conjugated H. flu b, Prevnar 7 and 13, Conj N. menin**
- **IgG 2 – Pure polysaccharide Pneumovax, not Prevnar! N. meningititis nonconj**
- **IgG 3 – Influenza A & B, Measles, Mumps, Rubella – No live vaccines!!!!!!! VZV ??**
- **IgG 4 – Cell sensitizing allergic antibody (IgA, Foods, Pollens?) Blocking IgG4 antibodies from desensitization! <u>LOW OK!</u>**

CASE HISTORY

<u>16 Year Old Male</u>

6 mo – 8 yrs	**Recurrent Otitis**
8 yr – 16 yrs	**Recurrent Sinusitis**
12 -14 yrs	**2-3 Episodes of Pneumonia**



LABORATORY DATA

- **IgG - 190 mg% (750-2000)**
- **IgA - 98 mg% (82-462)**
- **IgM - 32 mg% (63-250)**
- **Isohemagglutinins – Negative**
- **AOS - Negative; Schick - Positive**
- **Skin Tests - Positive**
- **T Cells - 40% (40-75)**
- **B Cells - 41% (10-25)**

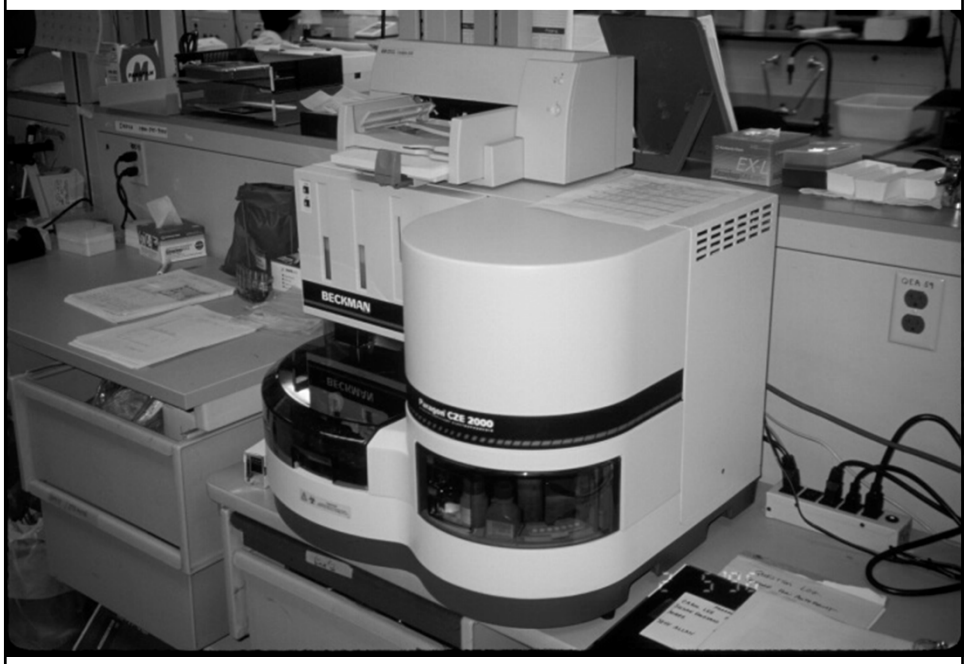
Chronic Persisting Giardiasis

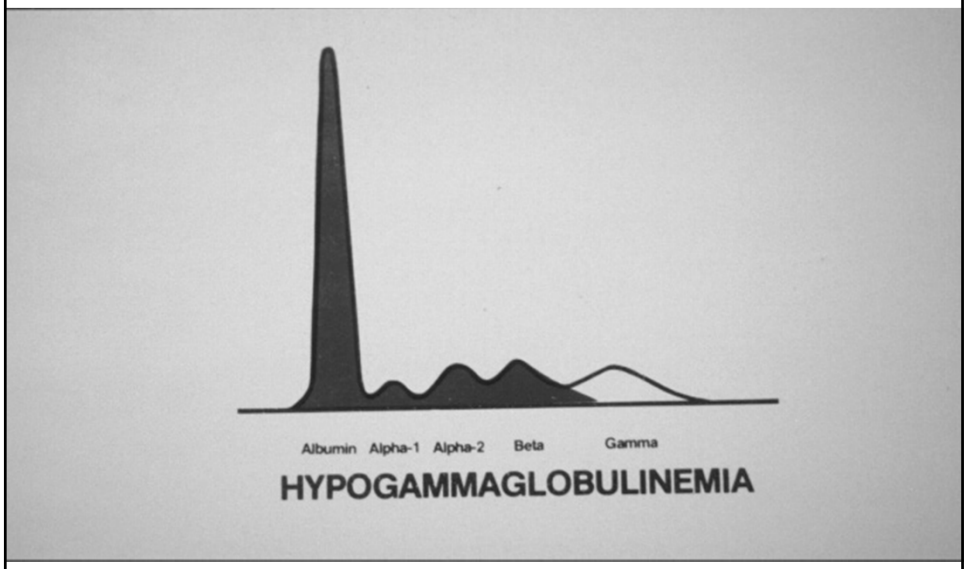
56 yr male diagnosed with CVID at 14

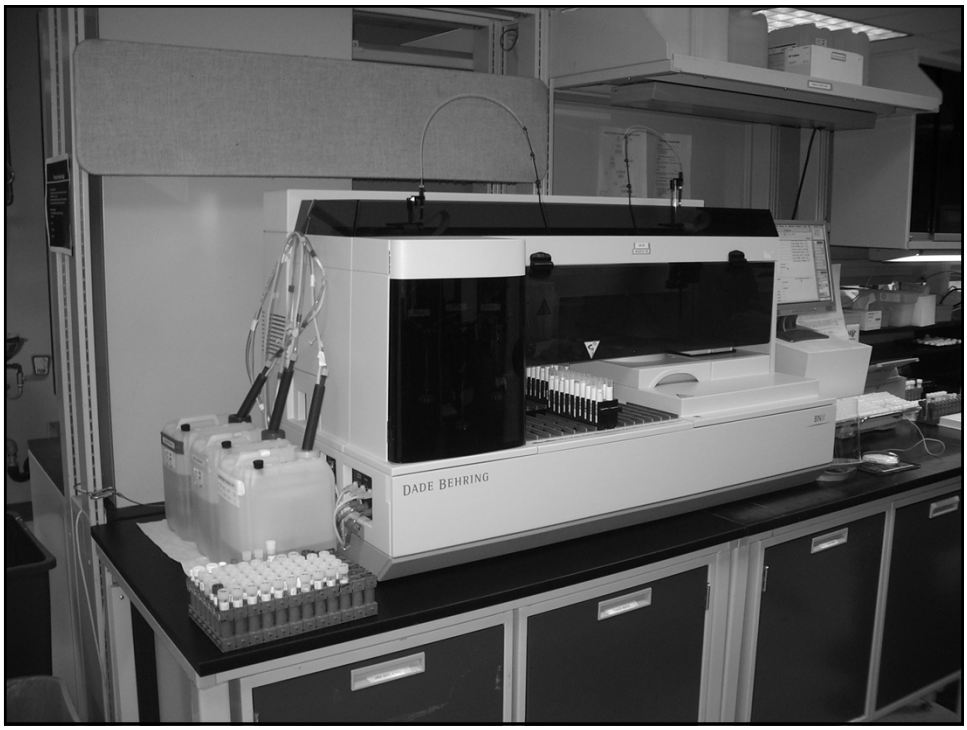
On 15 gm SQ IgG q week so well but

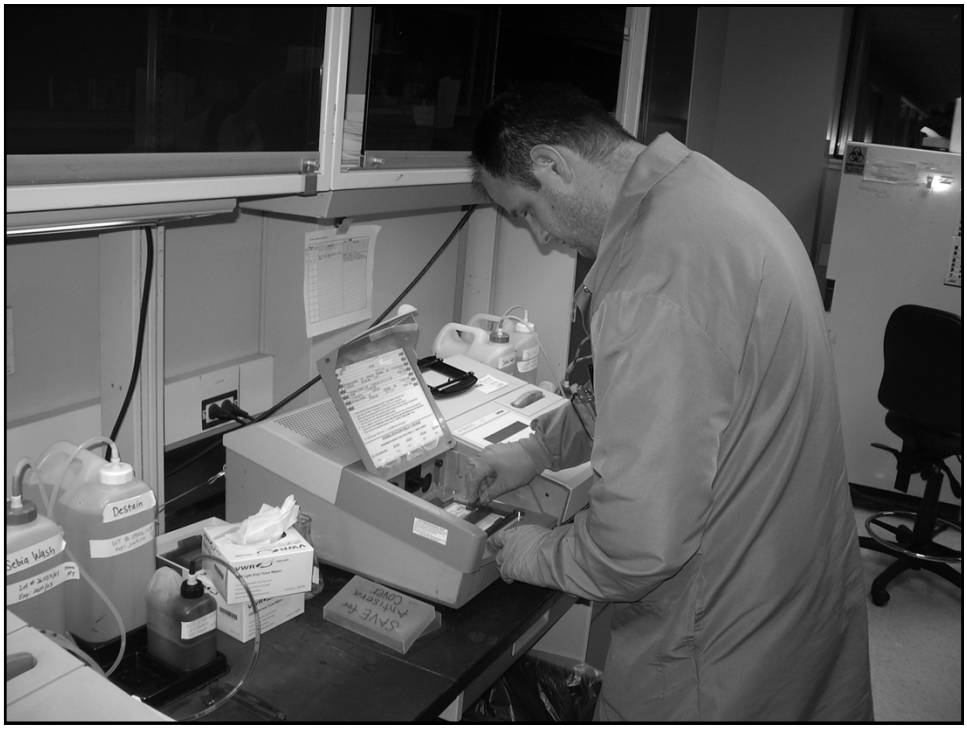
Chronic persisting diarrhea Dec-13Treated 25+ X metronidazole 1-4 wks, nitazoxanide 500mg BID x 3 weeks, tinidazole 500mg BID x 3weeks, quinacrine and alina (nitazoxanide) no response!!

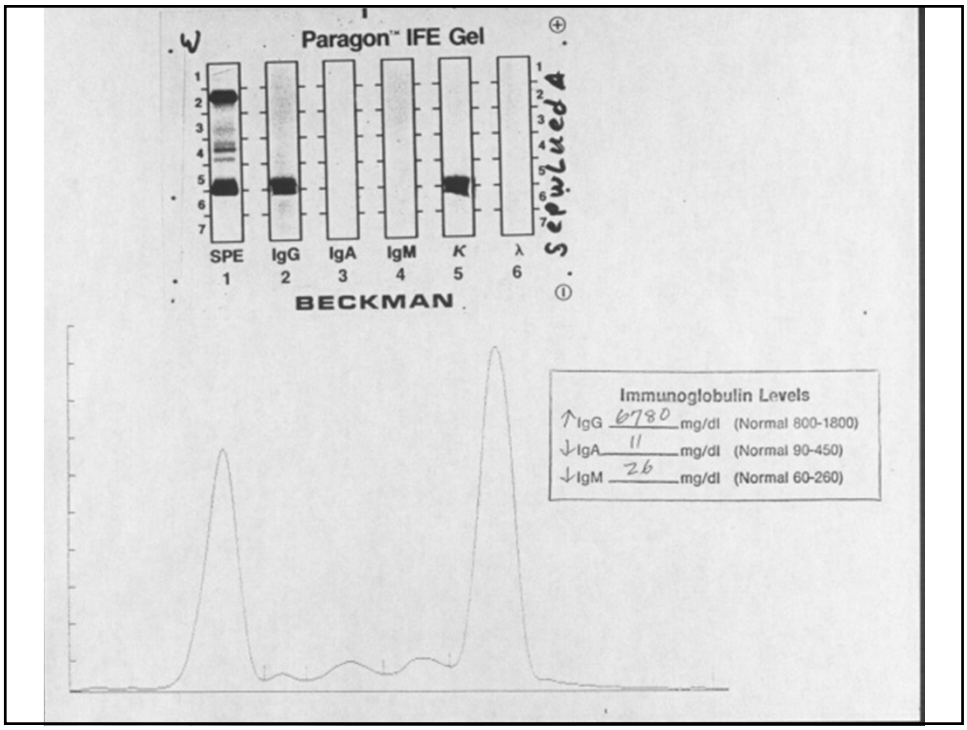
Finally after 3 years he got 3 WK of albendazole & alina he got better!!!???




Albumin Alpha-1 Alpha-2 Beta Gamma
HYPOGAMMAGLOBULINEMIA


DADE BEHRING


Destain
Sebia Wash


Paragon™ IFE Gel
SPE
IgG
IgA
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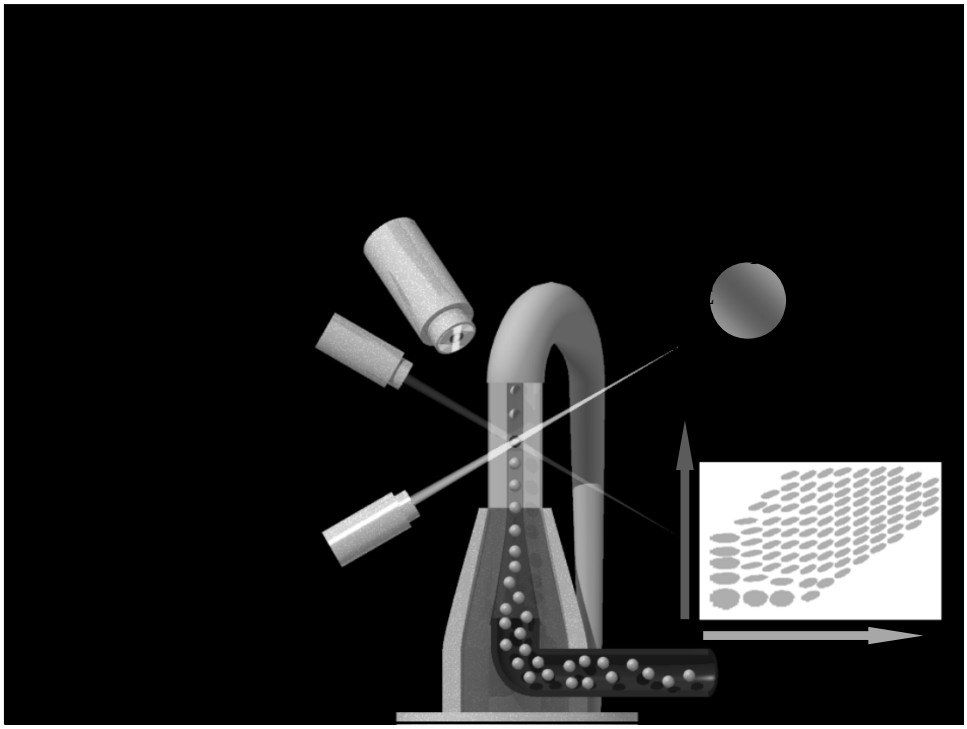
6
BECKMAN
Immunoglobulin Levels
↑IgG 6780 mg/dl (Normal 800-1800)
↓IgA 11 mg/dl (Normal 90-450)
↓IgM 26 mg/dl (Normal 60-260)

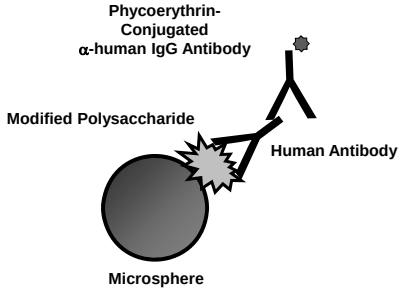
IMMUNOGLOBULIN G SUBCLASSES*

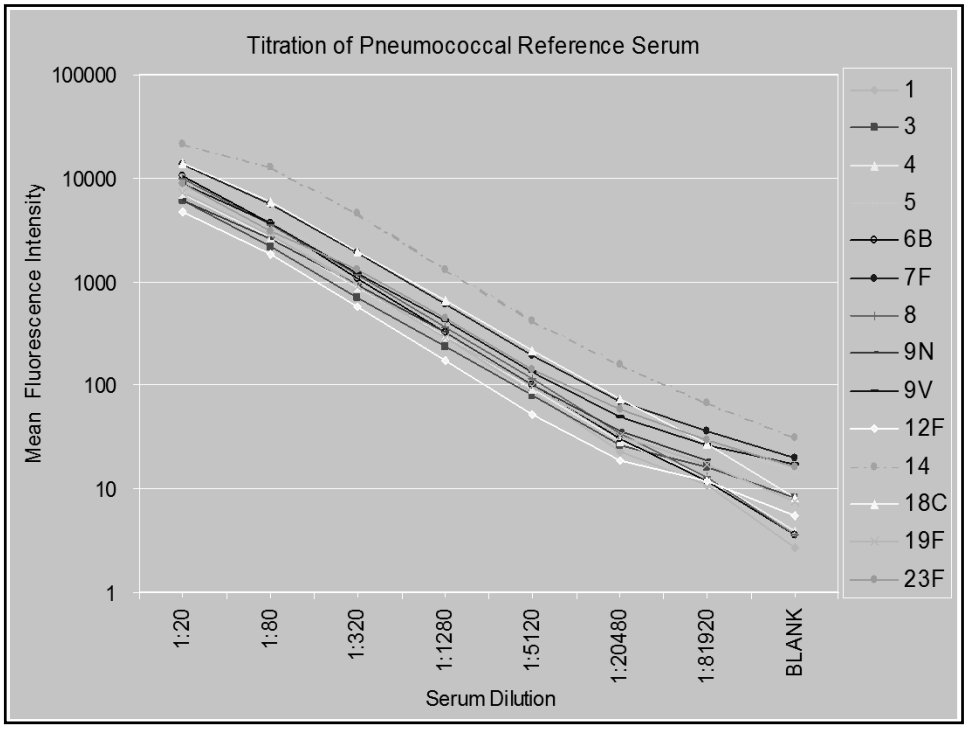
Characteristic	IgG1	IgG2	IgG3	IgG4
% in Serum	70	21	5	4
Half-Life Days	21	23	11	23
C1q Binding	++++	++	++++	-
Sensitize Cells	-	-	-	+
Polysaccharide AB	-	+++	-	-
Protein Ab (D,T)	++++	-	++	-
Viral Protein AB	++	-	++++	-

*Based on antigenic and structural differences of heavy chains.



Pneumococcal Serotype Assay



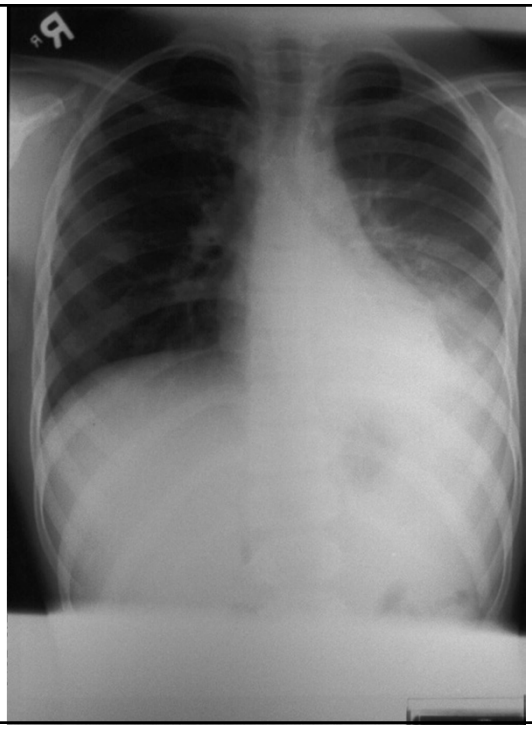


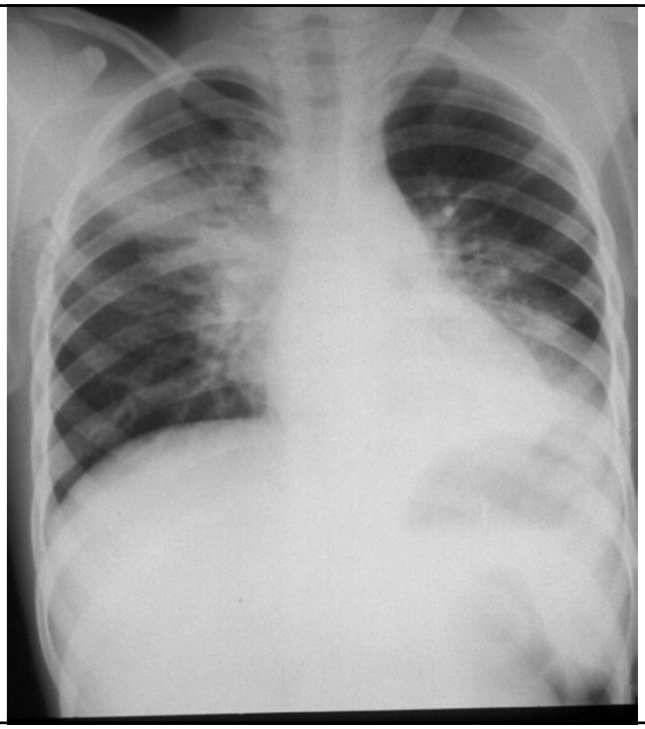
COMMON VARIABLE HYPOGAMMAGLOBULINEMIA

- **Starts several years after birth**
  - **Common**
  - **Variable immunodeficiency of B and T cells**
  - **One-quarter develop malignancies**
  - **Clinical manifestations:**
    - **Sinopulmonary infections 90-100%**
    - **Chronic diarrhea/giardia 50-60%**
    - **Sepsis, meningitis**
    - **Bronchiectasis**
    - **Autoimmune disease/arthritis**

PATIENT

- **11 year old male with otitis media since birth**
- **Sinusitis, URIs**
- **Admitted – Temperature 103^{o}**
- **LLL infiltrate**





LABORATORY VALUES

- **IgG – 80 IgA – 16 IgM – 44**
- **Rubella Titer – negative**
- **Anti-A and B antibodies – 1:1**
- **B Lymphocytes – 23%**
- **T Lymphocytes – 48%**
- **Blood Culture – *H. influenzae b***

COMMON VARIABLE IMMUNODEFICIENCY

- **Incidence:** **1:50,000 – 1:200,000**
  - **Australia:** **0.77/1000,000**
- **Onset:** **3-90 years**
  - **Average:** **2-3 decade – 25 years**
- **Diagnosis:** **28 years**

CLINICAL FEATURES OF ACQUIRED HYPOGAMMAGLOBULINEMIA*

INFECTION	%	INFECTION	%
Sinopulmonary	100	Empyema	4
Sinusitis	66	Meningitis	4
Otitis	32	Bacteremia	5
Pneumonia	86	Giardiasis	34
1-10 episodes	68	UTI	4
10 or more	18		
Bronchiectasis	28		

H. flu, S. pneumoniae, S. pyogenes, S. aureus

ASSOCIATED FINDINGS IN ACQUIRED HYPOGAMMAGLOBULINEMIA*

FINDING	%	FINDING	%
Diarrhea	60	Arthritis	8
Malabsorption	60	Allergy	40
Achlorhydria	53	Malignancy	24
Giardia	64	Stomach CA	
X-ray NLH	28	Lymphoma	
Splenomegaly	28	Thymoma	
Conjunctivitis	6		

**Amer. J. Med. 61:221, 1976*

COMMON VARIABLE IMMUNODEFICIENCY WITH LOW IL-2

18 year old male

- **4-5 years recurrent otitis, sinusitis, bronchitis, pneumoniae, arthritis, diarrhea**
- **IgG – 150; IgM – 8, IgA - <6.6, IgE – 0**
- **B cell surface Ig – 10%, M – 4%, G – 1%, D – 5%, A – 0%**
- **Severe chronic lung disease 1994**
- **CD4/8 – 1.58 (normal)**

IL-2 PRODUCTION BY MMC OF CVI PATIENT (E.B.)

Stimulus	Thymidine Uptake	L-2 Production % of Control
PHA	49,188 N	2.7%
PWM	87,599 N	23.3%
Candida	105,581 N	3.5%
Tetanus	59,719 N	1.1%

COMMON VARIABLE IMMUNODEFICIENCY WITH LOW IL-2

- Now 36 yo who developed severe lung disease and was seen at USC for Lung Tx
- Fix immune system first, (low B and T cells) bone marrow transplant from matched brother in Spring 2014.
- Doing much better with better B cell, T cell, NK cell numbers, requires less IVIG
- Pulmonary status improving; ? Need for lung Tx?
- Evaluating spontaneous heterozygous mutation in CPG methylation pathway

Mongenic Models of CVID

- **Transmembrane activator and CAML interactor (TACI) +BAFF and APRIL induce IgA and antibody response to polysaccharides; 13 of 162 CVID patients - 15%**
- **Flow Cytometry & Sequencing**
- **Deficiency of Inducible Co-stimulator (ICOS) T-cell costimulator molecules on activated cells – induces IL-4,5,6,17, GM-CSF, TNFa, IFNg and superinduction of IL-10; AR in 4 families. Flow Cytometry – 2.5%**
- **CD 19 Deficiency - AR disorder with decrease in BCR stimulation, poor AB responses but no autoimmunity or lymphoproliferation. – 2.5%**
- **BAFFR, B cell Activating Factor Receptor**

Other Genetic Causes CVID 2016

CD 19, CD20, CD21, CD81, TACI, BAFF-R, ICOS, LRBA, PLCG2, PRKDC, NFKB2, PIK3CD, IKAROS

Variable Phenotypes of RAG1, JAK3, TFRC with late onset cause picture similar to CVID but CID

Family F in Utah

F2 – 70 year old female, IgG <7, IgA < 4, IgM < 2

- **29 yo recurrent pneumonias + sinusitis**
- **Started elsewhere on IgG (2ml/mo)**
- **Recurrent sinusitis, pneumonias**
- **52 yo sinus surgery**
- **IVIG recommended, insurance didn't pay**
- **57 yo seen at U of U - undetectable IgG, IgA, & IgM**
- **No antibody responses – started on IVIG**
- **70 yo – 2-3 sinusitis per year, one walking pneumonia, otherwise doing well; B cell 1.0**

Family of F1, Sister of F2

F1 – Sister, 57 years old

- **IgG 113, IgA <6, IgM 14**
- **2-3 sinusitis per year but doing well**
- **Refuses IgG, B cell 0.8**

F3 – Son of F1

- **Recurrent sinusitis, URIs**
- **21 yo started on IVIG**
- **40 yo on IVIG, IgA < 6, IgM 5**
- **1-2 sinusitis per year, B cell 0.6**

F4 – Son of F1, 24 yo

- **Immunoglobulins very low**
- **25 yo on IVIG, IgA < 6, IgM 7**
- **1-2 sinusitis per year, B cell 0.1**

F5 – Daughter of F1, 31 yo

- **1 walking pneumonia**
- **Immunoglobulins extremely low**
- **Refuses IgG, IgG 382, IgA 29, IgM 21, B cell 0.5**

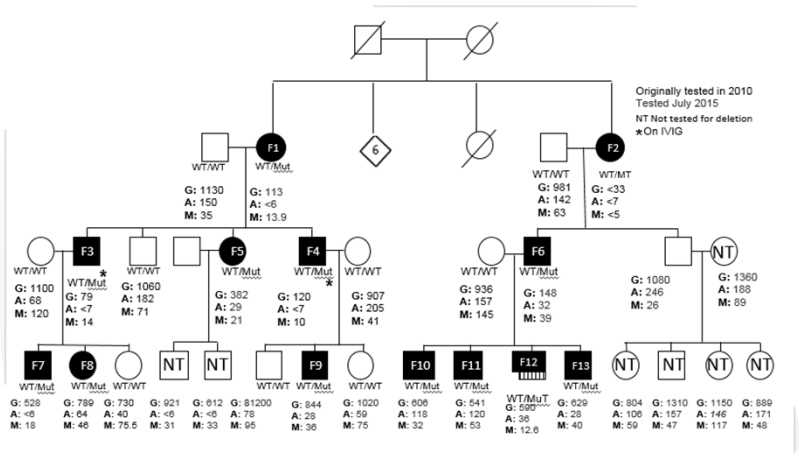
F6 – Son of F2 – 42 yo

- **Immunoglobulins very low**
- **Refuses IgG**
- **IgG 148, IgA 3, IgM 39, B cell 5.5**
- **3-5 sinusitis per year**

F-12 – Son of F6

- **B cell acute leukemia at 6 yo**
- **Bone marrow transplant from F13 affected brother**
- **IgG 540, IgA 36, IgM 13**

Family F in Utah



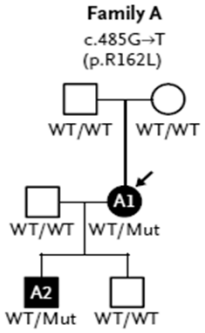
Family A

A1 – 24 yo with CVID

- **1 yo, recurrent otitis, bronchitis**
- **9 yo, 2 episodes of pneumonia**
- **10 yo – *S. pneumoniae* meningitis**
- **Started on IVIG**
- **IgG < 33, IgA < 7, IgM 21, B cells 0.5**

A2 – Son of A1

- **Recurrent sinusitis, otitis**
- **3 yo ITP, IgG 431**
- **6 yo, low IgG, IgA 7, IgM 5, IgG 727**
- **?Retuximab for ITP**
- **B cell – 0.3**



Family B

B5 – 23 yo with Swiss female

- 3 yo, otitis, cough, aphthous ulcers
- 15 yo, started on IVIG
- 23 yo, diarrhea, Giardia, blastocystis
- IgG 1430, IgA 21, IgM 22; B cells 2.0

B6 – Brother of B1

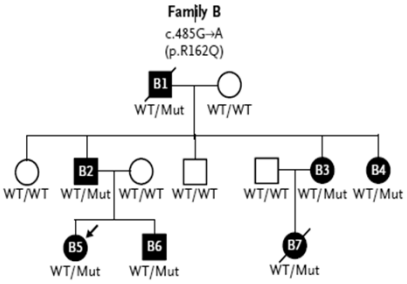
- Otitis, bronchitis, aphthous
- 9 yo pneumococcal sepsis, pneumonia
- IgG 1260, IgA 12, IgM 21; B cells 1.0

B1 – Father , 71 yo diagnosed CIVD

- History of recurrent respiratory tract infect
- IgG 386, IgA 30, IgM 60

B3 – B4 – B7

- Recurrent infections, low immunoglobulins
- B3: IgG 283, IgA 15, IgM 71; B cells 7.0
- B4: IgG 433, IgA 19, IgM 56; B cells 2.0
- B7: NA ALL



Family C

C1 – 32 yo female

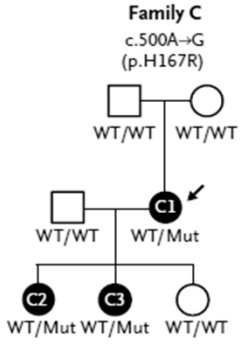
- 2 episodes pneumococcal sepsis – ICU
- 30 yo pneumococcal meningitis
- All immunoglobulins very low
- 32 yo, started IVIG
- IgG 887, IgA 73, IgM 11, B cells 1.0

C2 – Daughter of C1, 13 yo now

- 9 months investigated and started on IVIG
- Poor antibody responses
- IgG 1052, IgA 157, IgM 12, B cells 0.2

C3 – 2nd Daughter of C1, 11 yo now

- 18 months old, 4 episodes otitis media
- Low IgG and IgM
- 4 yo, pneumonia on IVIG
- IgG 1030, IgA 12, IgM 6, B cells 0.4



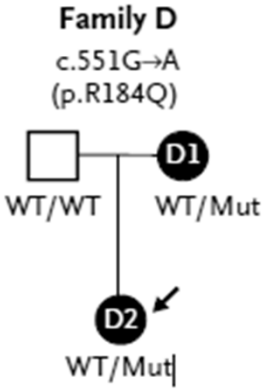
Family D

D2 – 25 yo female now

- **9 yo, pneumonia**
- **Severe hypogammaglobulinemia**
- **IgG 42, IgA < 1, IgM 7**
- **On-and-off of IVIG**
- **23 yo, pneumonia**
- **Back on IVIG; B cells 0.3**

D1 – 50 yo Mother of D1

- **Evaluated – mild hypogammaglobulinemia**
- **Normal B cells, 7.0**
- **IgG 637, IgA 5, IgM 45**



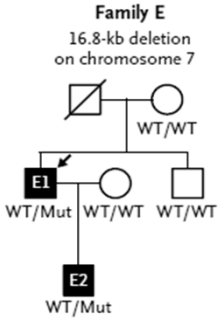
Family E

E1 – 57 yo Norwegian Male

- **IgG – 860, IgA - <1, IgM - 10**
- **2 yo, sepsis, *S. pneumoniae, H. influenzae***
- **3 yo, hip osteoarthritis, *S. pneumoniae***
- **4 yo, severe hypogammaglobulinemia**
- **Low B cells, 0.2**
- **On IVIG**

E2 – 6 yo Male

- **Healthy at present**
- **Normal immunoglobulins**



Loss of B Cells in Patients with Heterozygous Mutation in IKAROS

New England J. Med: 374:1032-1043, 2016

- **32 Authors from across the World: NIH, Rockefeller, Utah, Columbia, National Jewish, Paris, Zurich, Baylor, Georgia etc.**
- **Six different mutations/deletions in 29 individuals from six families**
- **Previously Described Genes in CVID (13)**

ICOS	**TWEAK**	**GATA2**
CD19	**CTLA4**	**CXCL12**
CD81	**LRBA**	**NFKB1**
CD20	**GATA 2**	**(IKAROS)**

THERAPY OF HYPOGAMMAGLOBULINEMIA

- Gammaglobulin IVIG or SQ IgG
- Intermittent antibiotics; prophylaxis TMX-s
- Pulmonary therapy
- Metronidazole etc
- Close follow-up – malignancies, autoimmunity

GAMMAGLOBULIN (IM)

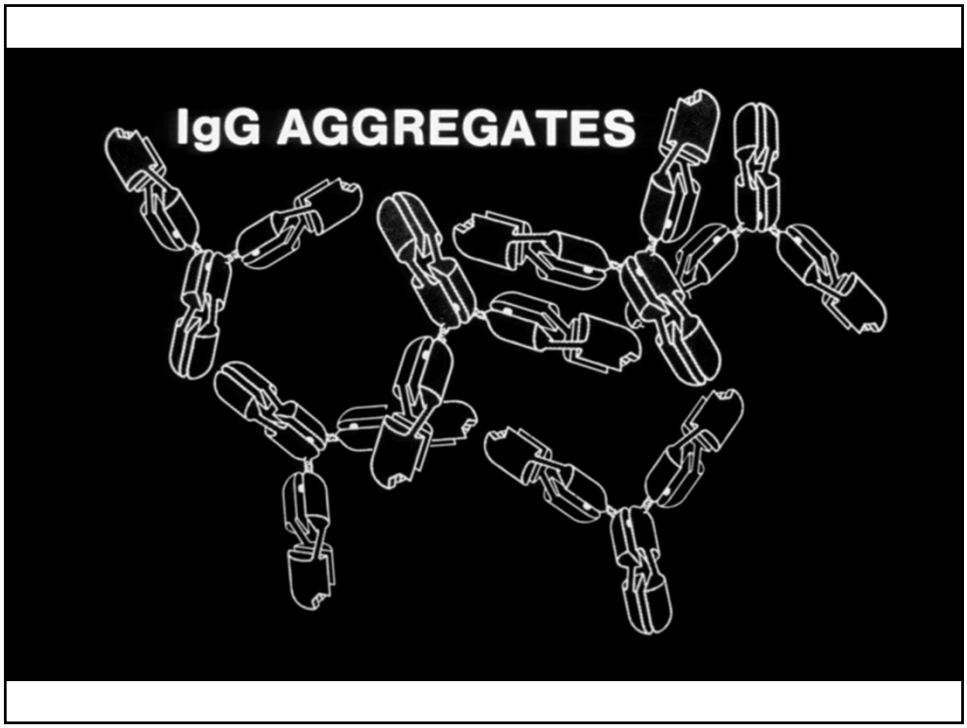
Cohn Fractionation – 1946

- Cold Ethanol Extraction
  - 25% Alcohol in the Cold
- Inactivates most Viruses
- 16.5 Gram Percent
- 95% IgG
- < 5% IgA

COMPLICATIONS OF IMIG

- **Pain at local site**
- **Aggregates into Vein**
- **Anaphylactic Reactions**
  - **Usually IgG4 or IgE to IgA**
- **Blocks Active Immunity**


SO CUT IT OUT!!
!
!



Available IgG Products

Brand Name	Available Concentrations	Manufacturer	Method of Administration	Osmolarity/ Osmolality	PH	IgA Content
Gammagard S/D	5% / 10%	Baxter	IVIg	636 m0sm/kg / 1250 m0sm/L	6.8 ± 0.4	1μg/mL N/A
Gammagard Liquid	10%	Baxter	IVIg / SCIg	240-300 m0sm/kg	4.6 – 5.1	37 μg/mL
HYQVIA	10%	Baxter	SCIg	240-300 m0sm/kg	4.6 – 5.1	37 μg/mL
Gammaplex	5%	Bio Products Lab	IVIg	460-500 m0sm/kg	4.6 – 5.1	<4 mcg/mL
Bivigam	10%	Biotest Pharm	IVIg	510 m0sm/kg	4.0 – 4.6	200 μg/mL
Carimmune NF	3% - 12%	CLS Behring	IVIg	192-1074 m0sm/kg	6.4 – 6.8	720 μg/mL
Hizentra	20% (200 mg/mL)	CLS Behring	SCIg	380 m0smol/kg	4.6 – 5.2	50 mcg/mL
Privigen	10%	CLS Behring	IVIg	isotonic (320 m0smol/kg)	4.8	≤ 25 mcg/mL
Flebogamma DIF	5% / 10%	Grifols	IVIg	240-370 m0sm/kg	5.0 – 6.0	<3 mcg/ml
Gamunex-C	10%	Grifols	IVIg / SCIg	258 m0sm/kg	4.0 – 4.5	46 μg/mL
Gammaked	10%	Kedrion	IVIg / SCIg	258 m0sm/kg	4.0 – 4.5	46 μg/mL
Octagam	5%	Octapharma	IVIg	310-380 m0sm/kg	5.1 – 6.0	<100 μg/mL

INDICATIONS FOR IgG THERAPY

- Recurrent bacterial infections
- IgG < 200 mg – 600 mg%; poor AB responses Pneumo, DPT, Flu
- IgG2 Def with Poor Pneumovax or Meningococcal Response, IgG3 and IgG4 seldom need IgG
- Specific AB Def with normal Igs and Subclasses but poor Pneumo & Polysaccharide AB!
- Severe immunosuppression with low IgG and Ab Retuximab, etc.

THERAPY FOR HYPOGAMMAGLOBULINEMIA

- IVIG 400-750 mg/kg q 3-4 weeks; SQ ¼ Monthly dose SQ q week, ½ q 2 wk, 1/1 q 4 wk; Keep trough IgG above 500-750 mg
- Treat acute infections promptly; ER: HRH-Card - Blood, Sputum C&S, CBC Diff, CRP, Chest X Ray, IV antibiotics and another dose IVIG immediately
- Occasional prophylactic antibiotics (HRH: TMX-S ONLY; no resistance in HIV prophylaxis; 98% MRSA still sens!)
- Pulmonary therapy
- Careful observations for malignancy

Common Variable Immunodeficiency

- **Heterogeneous Group of Disorders**
- **Late onset 2 years to 100 years**
- **Hypogammaglobulinemia (usually ≥ 2)**
- **Poor antibody responses to vaccination**
- **No exposures, immunosuppression, HIV**
- **Associated with autoimmunity, granuloma, malignancy, allergy**

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