Update in the Diagnosis and Treatment of CVID

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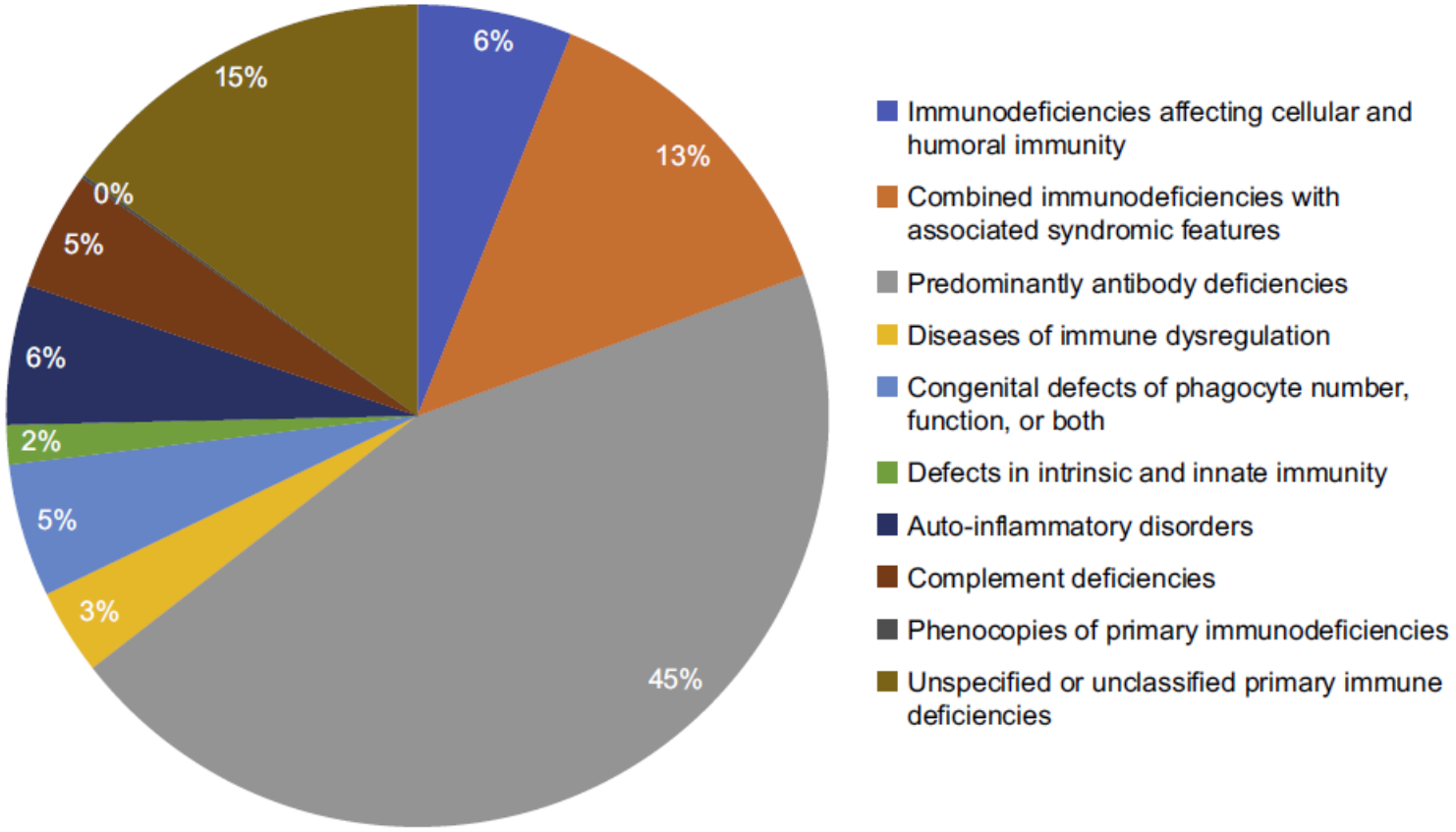
Upon completion of this learning activity, participants should be able to…

- Utilize CVID Clinical and Laboratory Diagnostic criteria to identify patients with the CVID umbrella diagnosis
- Recognize the importance of genetic testing to guide management of patients with CVID
- Choose the appropriate immunoglobulin replacement therapy for patients with CVID
- Plan for the use of immunomodulatory and definitive therapies for patients with CVID

Primary Immunodeficiency= PID
Inborn Errors of Immunity= IEI



Sullivan & Steim 2020

Immunodeficiency Algorithm

- Recurrent sinopulmonary infections with encapsulated organisms
- Chronic enteroviral meningioma encephalitis
- Unexplained Bronchiectasis
- Chronic/recurrent gastroenteritis

→ Assess for B cell deficiency with
CBC w/differential
Total IgG, IgA, IgM, IgE
Vaccine specific titers
B cell count
Genetic Testing

- Pneumocystis pneumonia
- fungal infections including mucocutaneous Candidiasis
- chronic viral infections (EBV, CMV, HPV , etc)
- Severe manifestations of common viral infections
- Failure to thrive
- Erythematous rash

→ Assess for T cell deficiency
CBC w/differtial
T cell count and assessment of naive T cells
T cell proliferation to mitogens
Genetic Testing

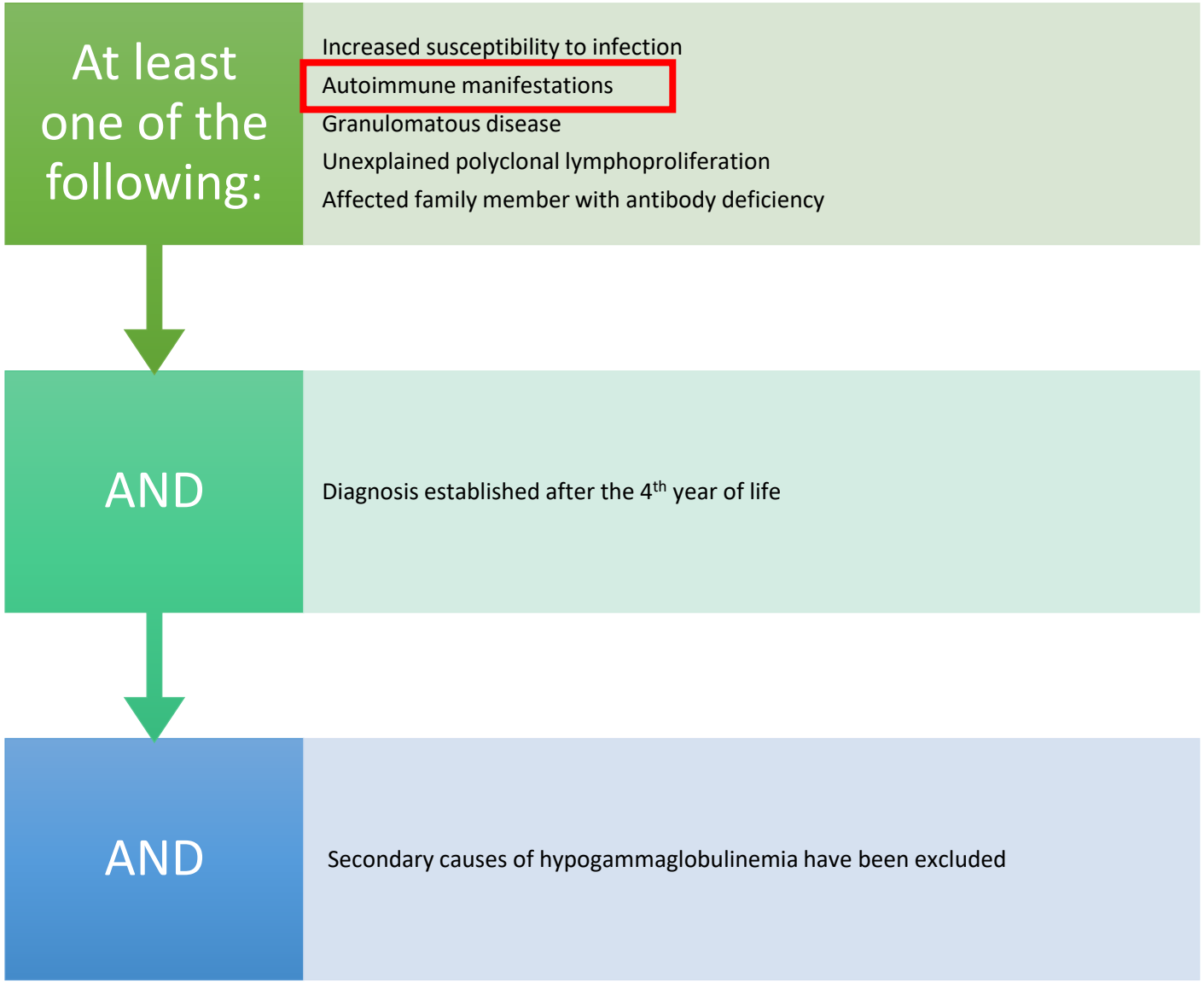
Consider combined immunodeficiency if mixed features

Test Name	Result (5y/o)
WBC	3.1
ANC (Normal >1500)	93
Hgb (Normal for age 10.9-15 g/dL)	9.5
Plt	307
CD3 (Normal for age 1400-3700)	1930
CD4 (Normal for age 700-2200)	694
CD8 (Normal for age 490-1300)	1153
NK (Normal for age 130-720)	157
CD19 (Normal for age 390-1400)	235
CD19+/CD27+/IgD- (Ideal percentage 5%)	1.1%
IgG (normal for age 490-1610)	450
IgA (normal for age 35-250)	30
IgM (normal for age 40-190)	137
# pneumococcal titers >=1.3	1/14
Tetanus titer	0.36

An Illustrative (Historical) Case

- 3y/o Caucasian male previously well and fully vaccinated, initially presented with persistent cervical adenopathy. Excisional biopsy demonstrated reactive hyperplasia.
- Failure to thrive developed
- 5y/o hospitalized with skin MSSA and Pseudomonas infection and Evans Syndrome.

CVID Umbrella CLINICAL Diagnostic criteria



CVID Umbrella LABORATORY DIAGNOSTIC CRITERIA

Marked decrease of IgG and marked decrease of IgA with or without low IgM levels

AND at least one of the following:

- poor antibody response to vaccines and/or absent isohemagglutinins
- low switched memory B cells

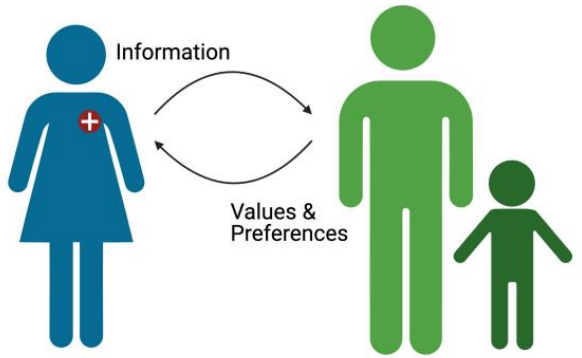
AND no evidence of profound T-cell deficiency

TABLE XIII. Currently available immunoglobulin products and their properties

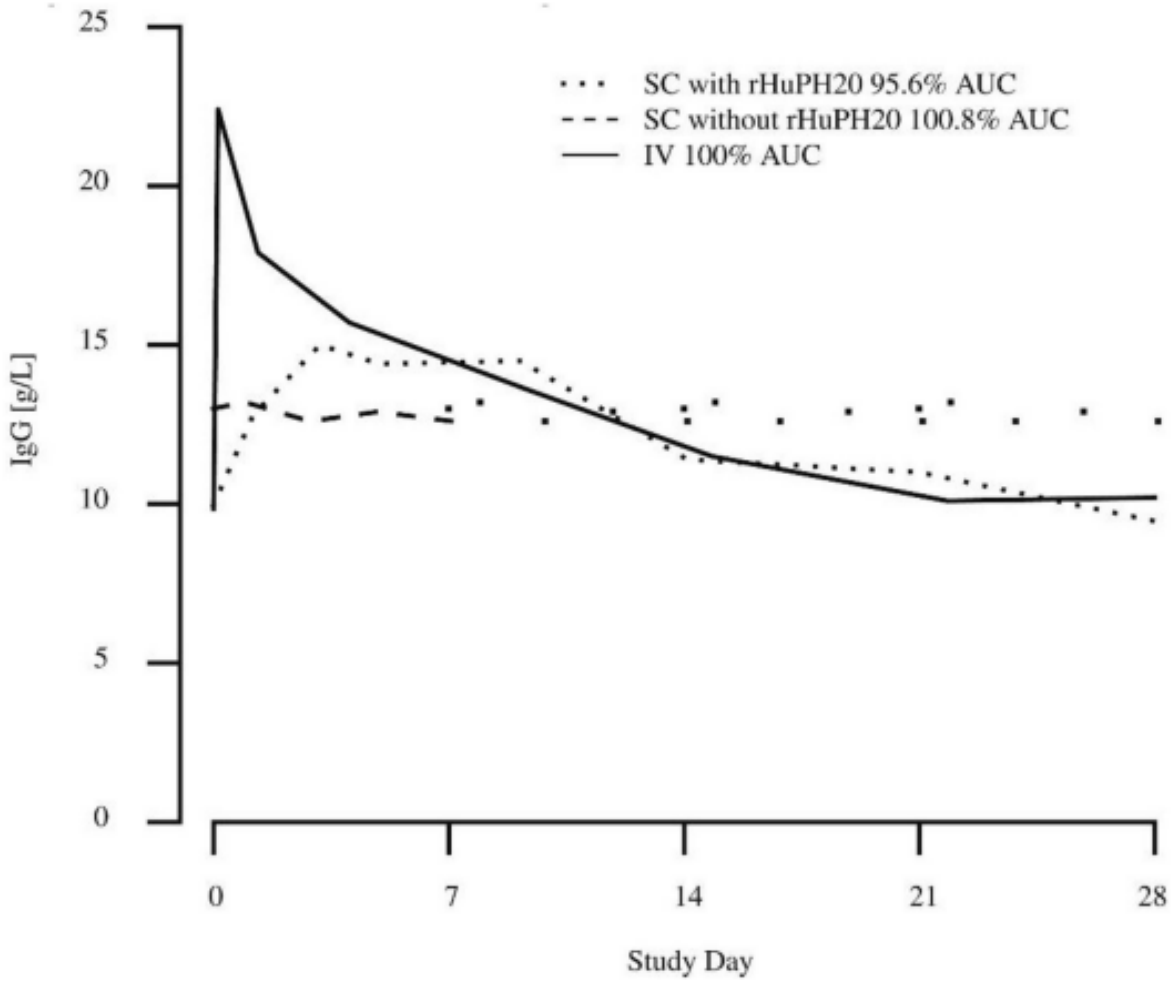
Route/product	Dosage formulation	Diluent	Refrigeration required?	Filtration required?	Osmolality (mOsm/L)	Sodium	pH	IgA (μg/mL)	Stabilizer or regulator	Pathogen inactivation/removal*
IV										
Bivigam	10% Liquid	NA	Yes	No	Not Available	0.100-0.140 mol/L	4.0-4.6	≤200	Glycine	FP, S/D, NF
Carimune NF	Lyophilized	0.9% sodium chloride, sterile water, 5% dextrose	No	No	498 (3%), 690 (6%), 882 (9%), 1074 (12%)	0.01 mEq/mL (3%), 0.02 (6%), 0.03 (9%), 0.041 (12%)	6.6	720	Sucrose	DF, pH 4, pH 4/pepsin, NF
					192 (3%), 384 (6%), 576 (9%), 768 (12%)	None				
					444 (3%), 636 (6%), 828 (9%), 1020 (12%)	None				
Flebogamma DIF 5%	5% Liquid	NA	No†	Optional	240-370	Trace	5-6	<50	D-sorbitol	Past, S/D, NF, FP, PEG, pH 4
Flebogamma DIF 10%	10% Liquid	NA	No†	—	240-370	Trace	—	<100	D-sorbitol	—
Gammagard 5% S/D	Lyophilized	Sterile water	No	Yes	636	8.5 mg/mL NaCl	6.8	<1	2% Glucose and glycine	CEF, pH 4.2, DF, CAP, CHROM
Gammaplex	5% Liquid	NA	No	15-20 micron filter preferred	420-500	30-50 mmol/L	4.8-5	<10	Sorbitol and glycine and polysorbate 80	S/D, VF, low pH
Octagam 5%	5% Liquid	NA	No†	No	310-380	0.03 mEq/ml	5.1-6.0	<100	Maltose	
Octagam 10%	10% Liquid	NA	No†	No	310-380	<30mmol/L	4.5-5.0	106 μg/mL	Maltose	
Privigen	10% Liquid	NA	No	No	240-440	Trace	4.6-5	<25	L-proline	
IV or SC										
Gammagard liquid	10% Liquid	NA	No	No	240-300	None added	4.6-5.1	37	Glycine	S/D, low pH, NF
Gammaked	10% Liquid	NA, incompatible with saline	No‡	No	258	None added	4-4.5	46	Glycine	CEF, pH 4.2, DF, CAP, CHROM
Gamunex-C	10% Liquid	NA, incompatible with saline	No‡	No	258	None added	4-4.5	46	Glycine	CEF, pH 4.2, DF, CAP, CHROM
SC										
Cuvitru	20% Solution	NA	No§	No	208-290	None	4.6-5.1	80	Glycine	CEF, CHROM, NF, SD
Hizentra	20% Liquid	NA	No	No	380	Trace, <10 mmol/L	4.6-5.2	≤50	Proline	pH 4, DF, VF, OAF
Hyqvia	10% Liquid + hyaluronidase	NA	No	No	240-300	None added	4.6-5.1	37	Glycine	S/D, low pH, NF

(Continued)

Lots of Products to Consider- How do you decide which one is right for the patient ???



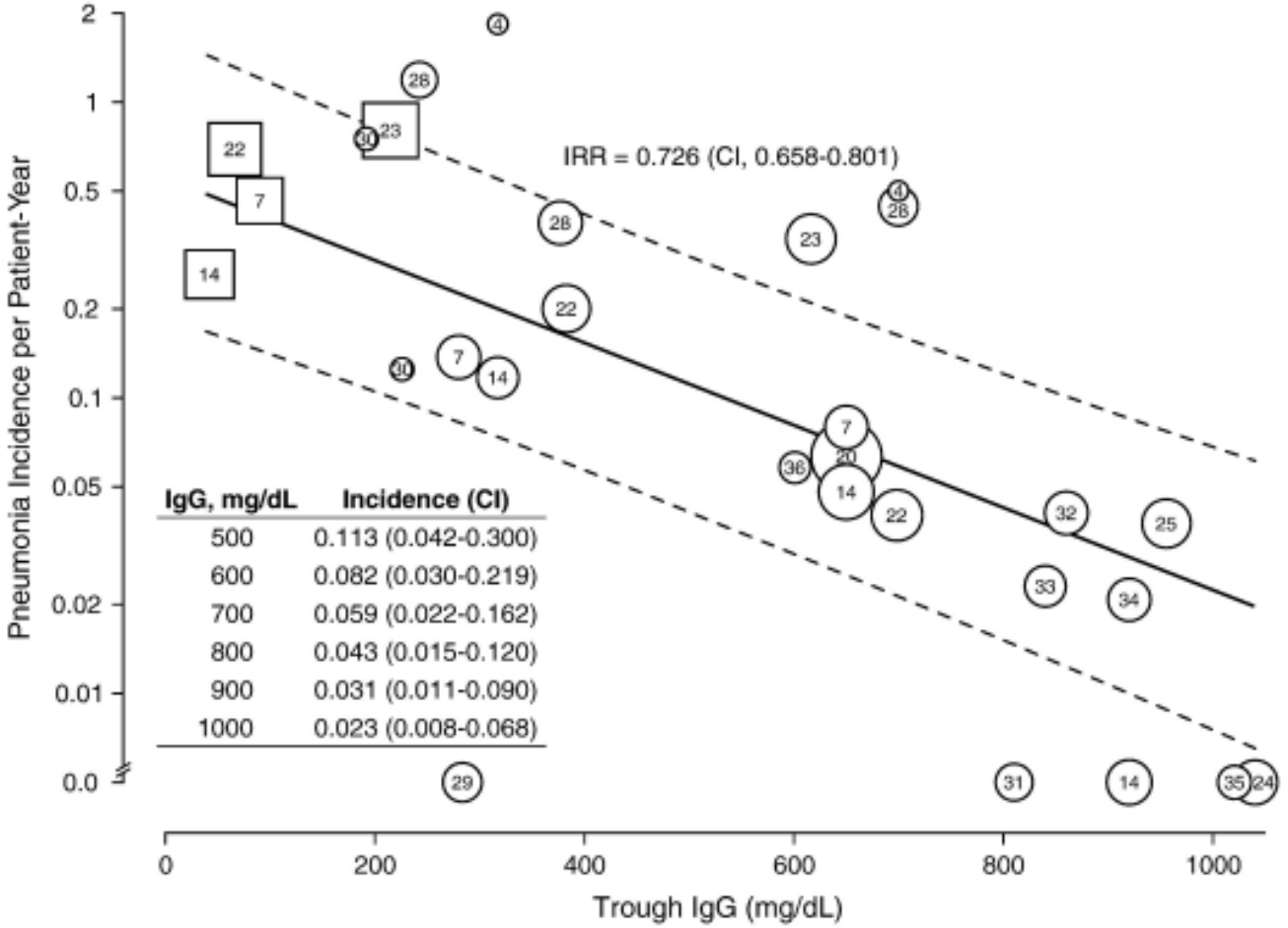
Difference in IgG Levels IV vs. SC



- Berger M Cl 2004

Target levels

Pneumonia decreases with increasing IgG trough level



- Orange J CI 2010

Ig Replacement Strategies

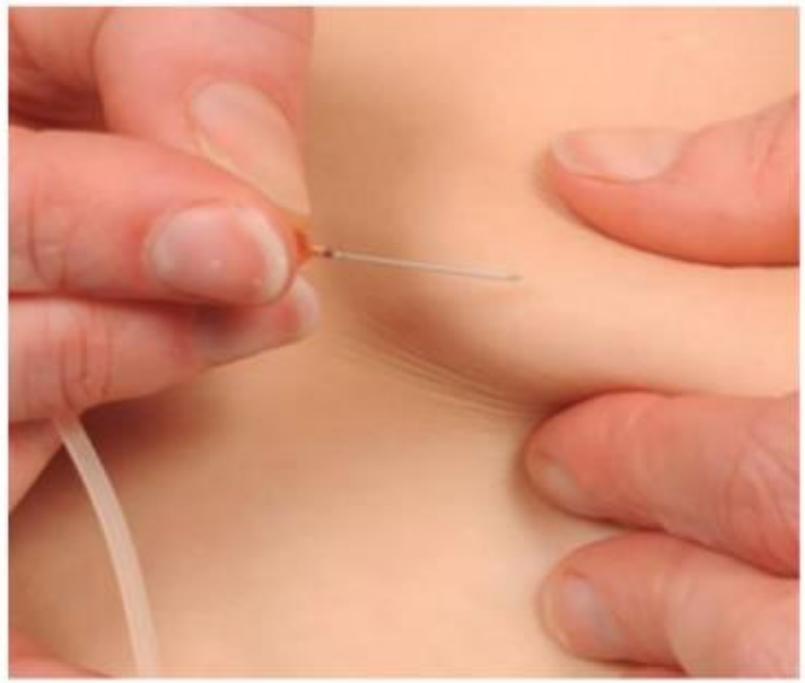
IVIG

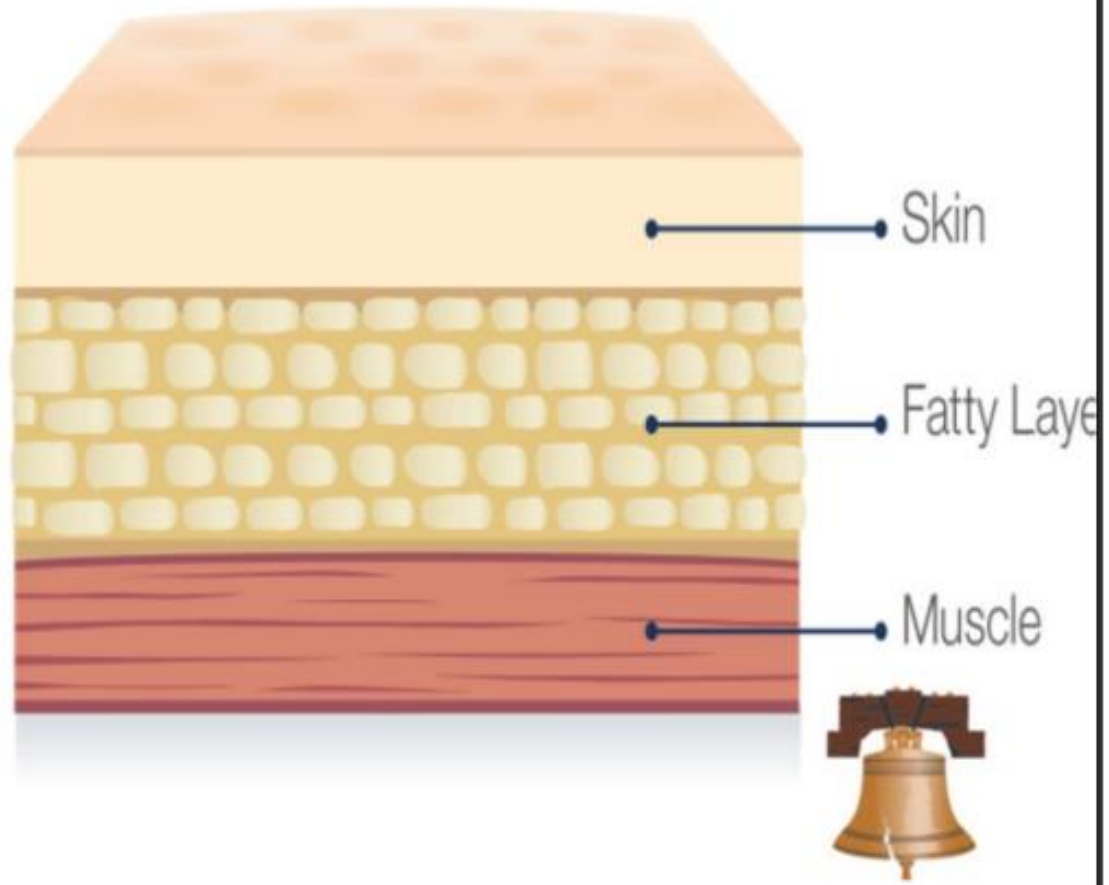
- Needs nursing support, given at home or infusion center
- 400-600mg/kg
- Usually every 3-4 weeks
- Typically target trough 800mg/dl
- For every 100 mg/kg dose increase in IVIG, IgG trough increases by ~120 mg/dl

SCIG

- Self administered
- 100-150mg/kg week
- Usually every 1-2 weeks
- Number of infusion sites is directed by volume of infusion
- Facilitated SC can be given every 4 weeks
- Typically Target Level 1000mg/dl

“ANYWHERE WHERE YOU CAN PINCH AN INCH”





Adverse Reactions

- IVIG Generally Associated with higher rates of Systemic reaction than SC therapy

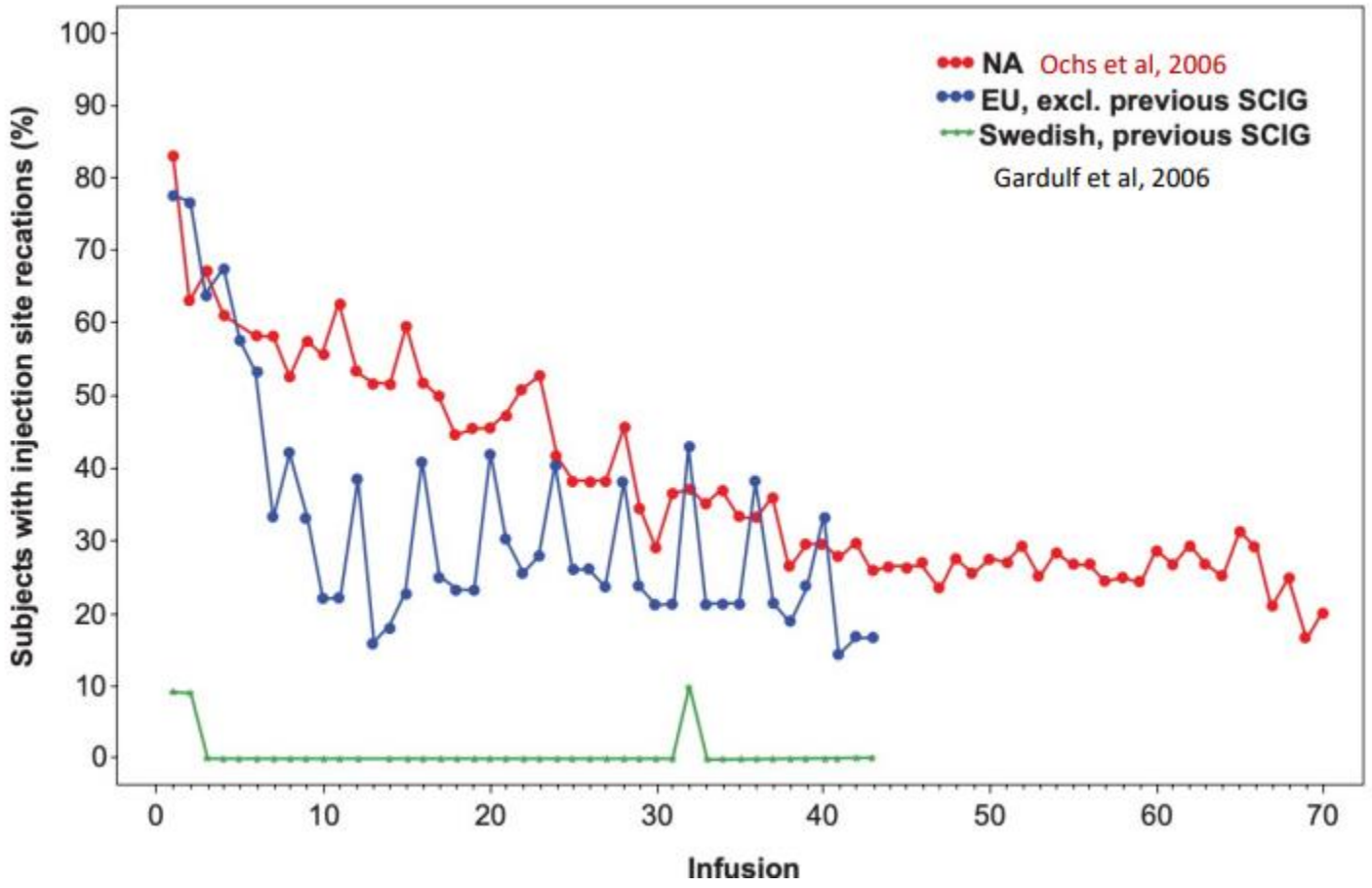
Table VI. Frequency and Types of Adverse Reactions (Number of Patients)[a]

Type of reaction	IVIg	SCIg
Mild: not requiring therapy		
Pain at application site	0	35 (9)
Erythema at site	0	71 (11)
Headache	15 (2)	2 (2)
Fatigue	13 (3)	2 (1)
Rigors, minor	7 (3)	24 (2)
Hot flushes	3 (1)	2 (2)
Urticaria–pruritis–eczema	3 (3)	7 (2)
Increase in pulse rate	2 (1)	1
Dizziness	1	2 (2)
Nausea	1	2 (1)
Others[b]	4 (3)	3 (3)
Moderate: hydrocortisone used for therapy		
Rigors, moderate	1	2 (1)
Headache, persistent	1	0
Tremor	0	1
Muscle stiffness	0	1
Myalgia	0	1
Arthralgia	0	1
Loin pain	0	1
Cold hands	0	1

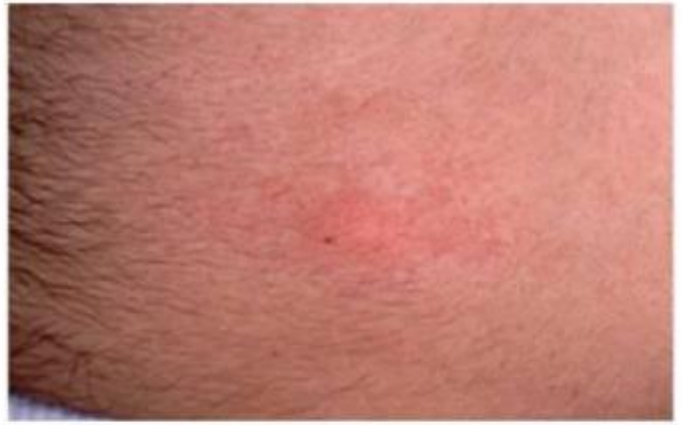
[a] Some patients had more than one type of adverse reaction in a given infusion.

[b] Including systemic pain, increase in blood pressure, vertigo, diarrhea, anxiety, cold, and abdominal pain.

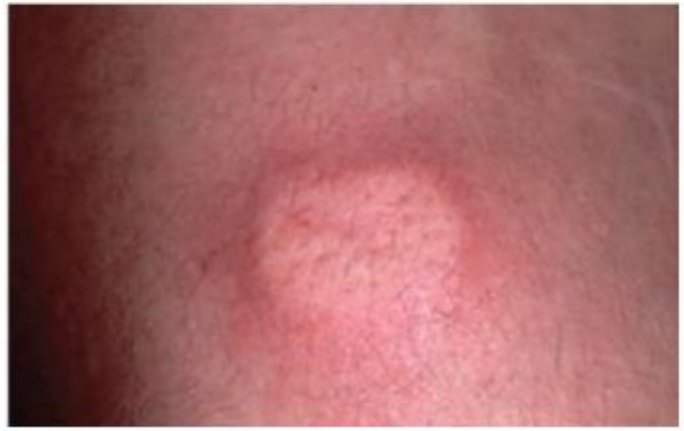
SQIG and Site Reactions



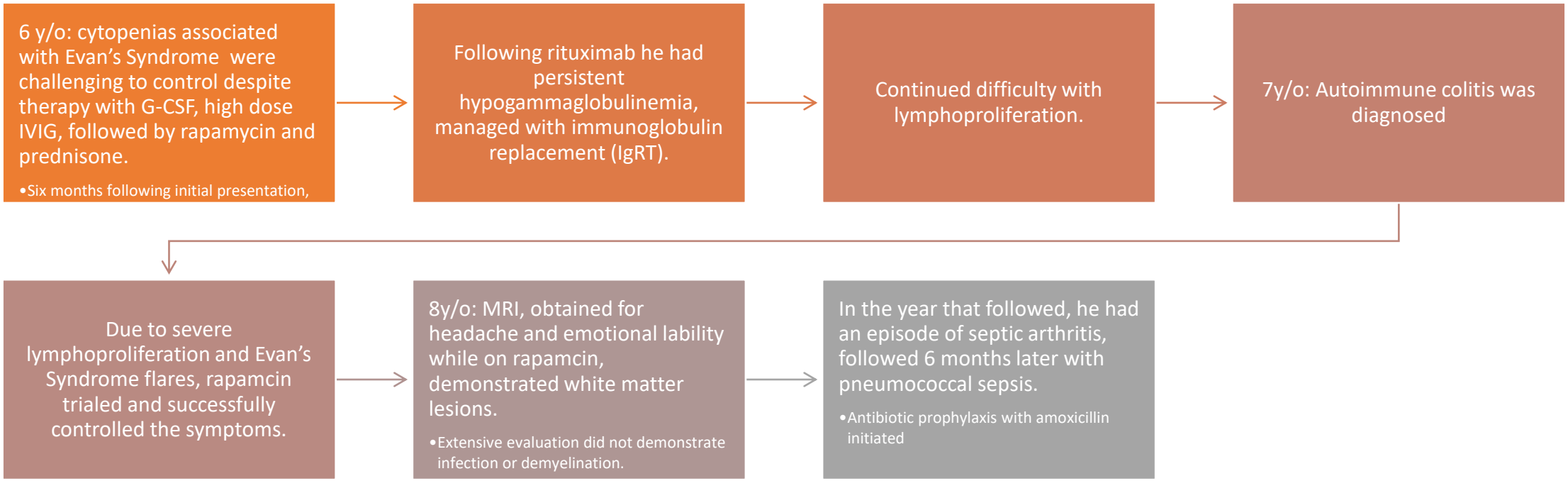
Mild



Moderate



Evolution of Clinical Presentation

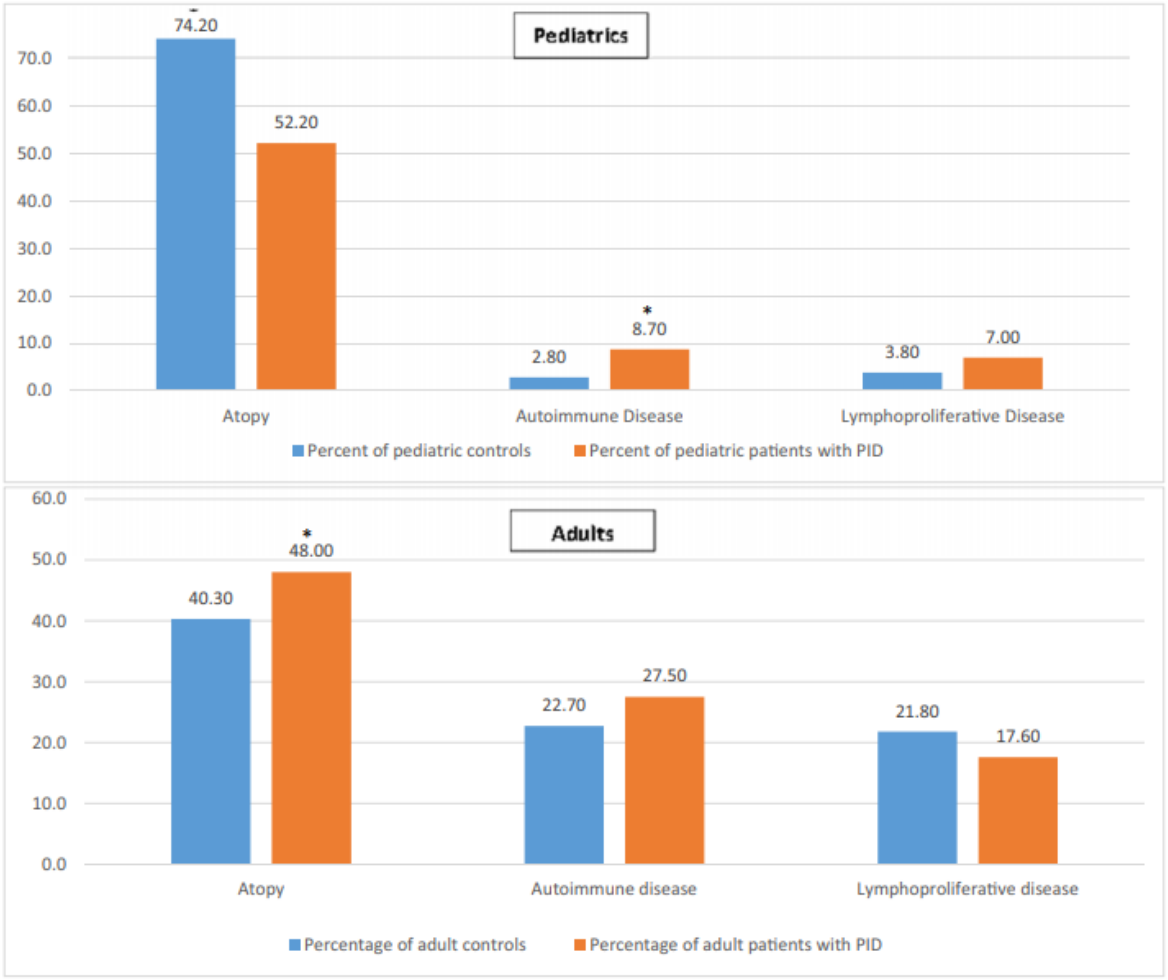


Updated Laboratory Findings

Test Name	Result (5y/o)	Result (8y/o)
WBC	3.1	8.9
ANC (Normal >1500)	93	6577
Hgb (Normal for age 10.9-15 g/dL)	9.5	12.7
Plt	307	205
CD3 (Normal for age 1400-3700)	1930	1075
CD4 (Normal for age 700-2200)	694	658
CD4/CD45RA	Not tested	29
CD4/CD45RO	Not tested	615
CD8 (Normal for age 490-1300)	1153	307
NK (Normal for age 130-720)	157	78
CD19 (Normal for age 390-1400)	235	441
CD19+/CD27+/IgD- (Ideal percentage 5%)	1.1%	0.2%
IgG (normal for age 490-1610)	450	821*
IgA (normal for age 35-250)	30	<6
IgM (normal for age 40-190)	137	102

Differing Non-Infectious Symptoms

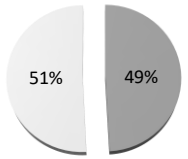
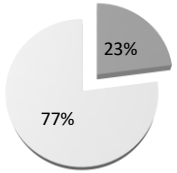
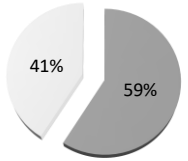
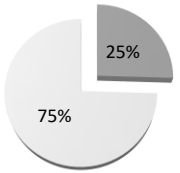
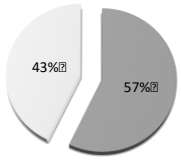
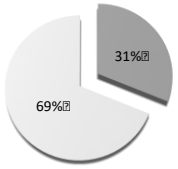
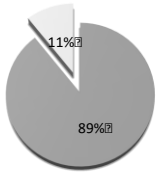
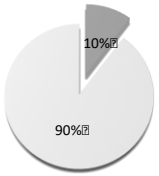
JOCI 2019



Impact of genetic testing on CVID Patient care

- Prognostic value
- Personalized medicine with use of biologics
- Consideration for HCT
  - Likely to work?
  - Is conditioning needed?
- Gene therapy
- Gene editing

Genetic Testing: Molecular Defects are Not Rare

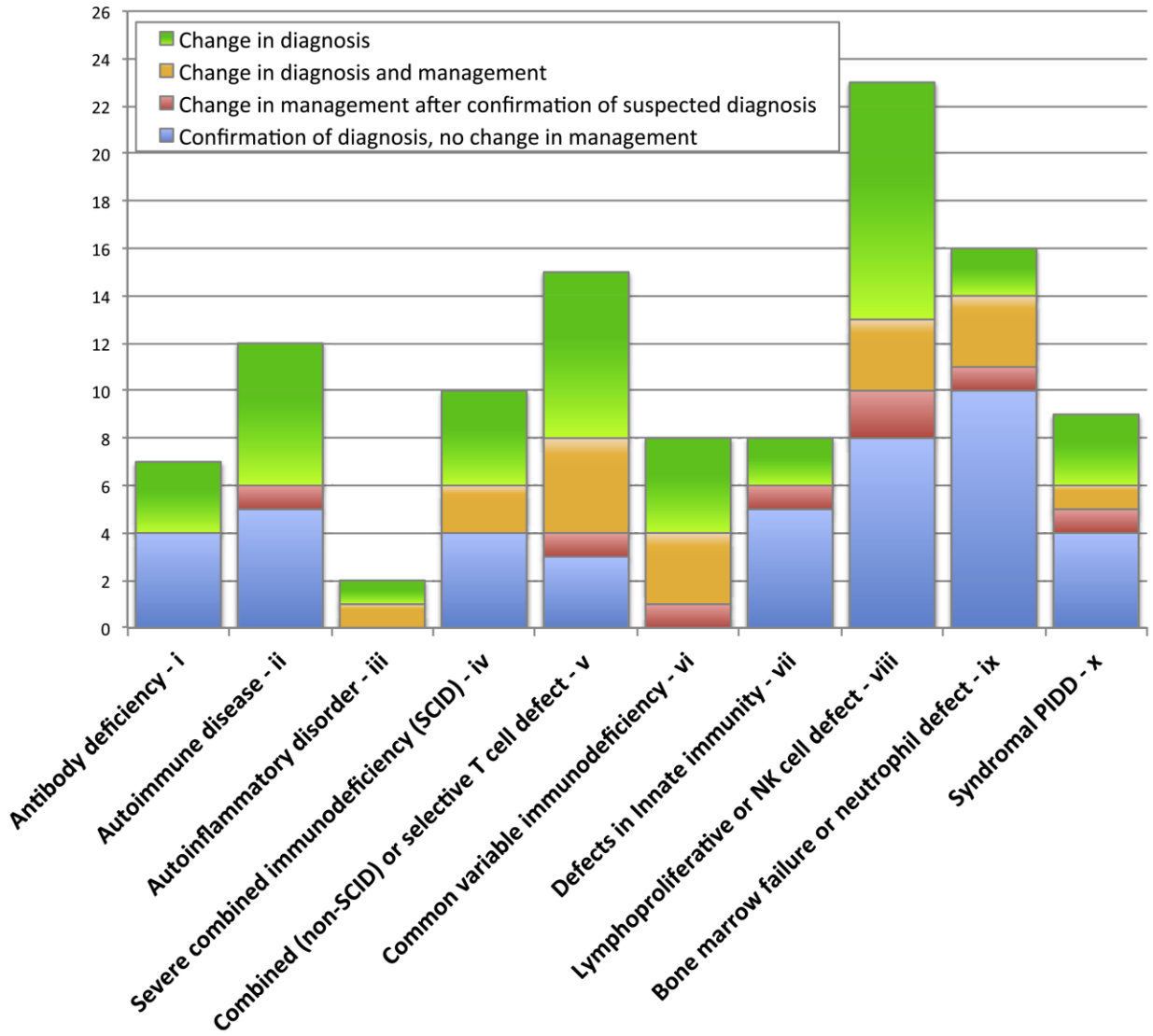
	High consanguinity		Low consanguinity	
Gene panels or focused exome sequencing		49% Total *n* = 1221 (5 studies)		23% Total *n* = 1484 (12 studies)
Exome sequencing (no CNV analysis)		59% Total *n* = 212 (3 studies)		25% Total *n* = 208 (3 studies)
Exome sequencing (with CNV analysis)		57% Total *n* = 84 (1 study)		31% Total *n* = 509 (3 studies)
Whole genome sequencing		89% Total *n* = 206 (1 study)		10% Total *n* = 886 (1 study)

Diagnostic yield shaded in gray

Chinn IK and Orange JS. *Expert Rev Clin Immunol* 2020;16(9):897-909

Genetic Testing Impact in Immunodeficiency

n=110 families

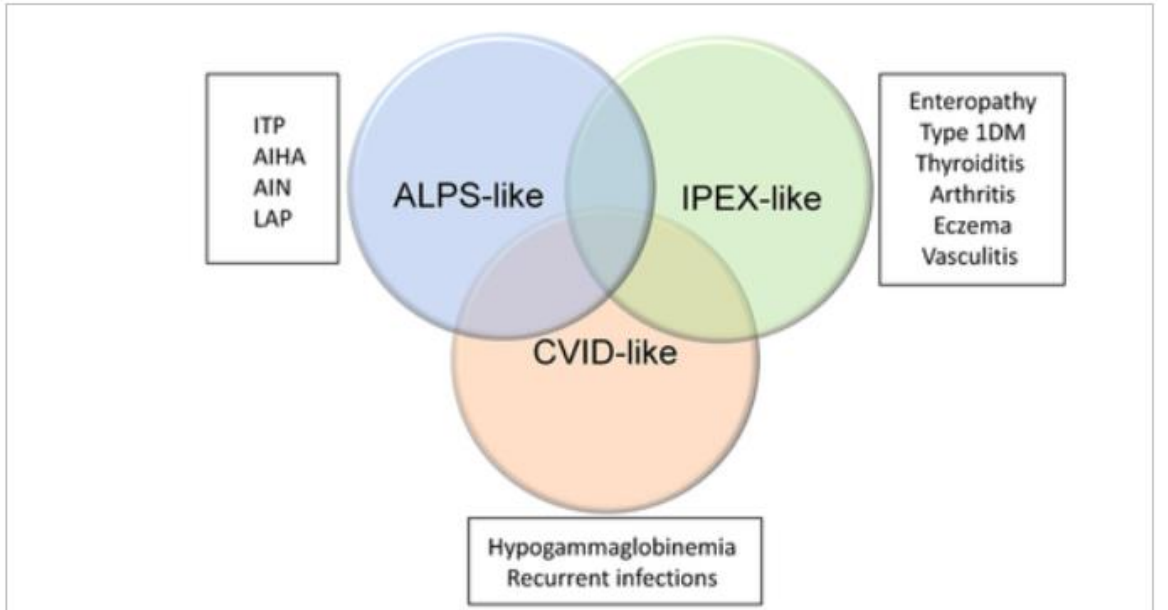


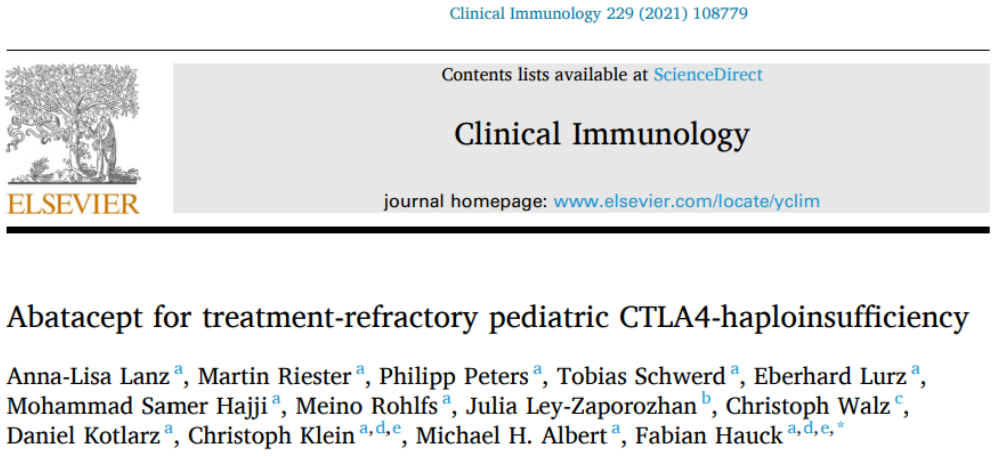
- 55% of 110 families with clinical diagnosis had diagnosis altered
- 25% of 110 families had change in management

Stray-Pedersen et al. *J Allergy Clin Immunol* 2017;139:232-45

Diagnosis- Finding the Spokes that lead to the CVID Umbrella Diagnosis

- Clinical syndromes of early onset marked lymphocyte driven autoimmune disease and/or lymphoproliferation in addition to infections
- Commonly affected organ systems include
  - Cytopenias
  - Enteropathy
  - Hepatosplenomegally
  - Endocrinopathy
- Type of infection varies by genotype
- Immune profile (lymphocyte subsets and immunoglobulin levels) vary by genotype
- Genetic testing typically necessary to make the diagnosis





Clinical Immunology 229 (2021) 108779

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Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Abatacept for treatment-refractory pediatric CTLA4-haploinsufficiency

Anna-Lisa Lanz [a], Martin Riester [a], Philipp Peters [a], Tobias Schwerd [a], Eberhard Lurz [a], Mohammad Samer Hajji [a], Meino Rohlfs [a], Julia Ley-Zaporozhan [b], Christoph Walz [c], Daniel Kotlarz [a], Christoph Klein [a,d,e], Michael H. Albert [a], Fabian Hauck [a,d,e,*]

Genetic testing Informs Application of Precision Medicine

- 9 y/o: panel-based sequencing was performed and demonstrated
  - Heterozygous frameshift mutation in CTLA-4, c.255_356delTG(p.A86fs)
- Abatacept initiated with initial clinical improvement
- Maintained on Ig RT

Clinical Case Presentation: Definitive Therapy (DT)

- 11y/o: severe flare of Evan's syndrome, with concomitant bacterial pneumonia
- HLA typing demonstrated sibling to be full match
- Received MSD BMT following conditioning with alemtuzumab, fludarabine and melphalan

J Allergy Clin Immunol. 2022 Feb;149(2):736-746. doi: 10.1016/j.jaci.2021.04.039. Epub 2021 Jun 7.

Therapeutic options for CTLA-4 insufficiency

David Egg [1], Ina Caroline Rump [1], Noriko Mitsuiki [1], Jessica Rojas-Restrepo [1], Maria-Elena Maccari [2], Charlotte Schwab [1], Annemarie Gabrysch [1], Klaus Warnatz [3], Sigune Goldacker [3], Virginia Patiño [4], Daniel Wolff [5], Satoshi Okada [6], Seiichi Hayakawa [6], Yoshiaki Shikama [7], Kenji Kanda [8], Kohsuke Imai [9], Manabu Sotomatsu [10], Makoto Kuwashima [11], Takahiro Kamiya [12], Tomohiro Morio [13], Kazuaki Matsumoto [13], Takeshi Mori [14], Yuri Yoshimoto [15], Ingunn Dybedal [16], Maria Kanariou [17], Zeynep Yesim Kucuk [18], Hugo Chapdelaine [19], Lenka Petruzelkova [20], Hanns-Martin Lorenz [21], Kathleen E Sullivan [22], Jennifer Heimall [22], Michel Moutschen [23], Jiri Litzman [24], Mike Recher [25], Michael H Albert [26], Fabian Hauck [26], Suranjith Seneviratne [27], Jana Pachlopnik Schmid [28], Antonios Kolios [29], Gary Unglik [30], Christian Klemann [2], Scott Snapper [31], Lisa Giulino-Roth [32], Michael Svaton [33], Craig D Platt [34], Sophie Hambleton [35], Olaf Neth [36], Geraldine Gosse [37], Steffen Reinsch [38], Dirk Holzinger [39], Yae-Jean Kim [40], Shahrzad Bakhtiar [41], Faranaz Atschekzei [42], Reinhold Schmidt [42], Georgios Sogkas [42], Shanmuganathan Chandrakasan [43], William Rae [44], Beata Derfalvi [45], Hanne Vibeke Marquart [46], Ahmet Ozen [47], Ayca Kiykim [47], Elif Karakoc-Aydiner [47], Pavlína Králíčková [48], Godelieve de Bree [49], Dimitra Kiritsi [50], Markus G Seidel [51], Robin Kobbe [52], Jennifer Dantzer [53], Laia Alsina [54], Thais Armangue [55], Vassilios Lougaris [56], Philipp Agyeman [57], Sofia Nyström [58], David Buchbinder [59], Peter D Arkwright [60], Bodo Grimbacher [61]

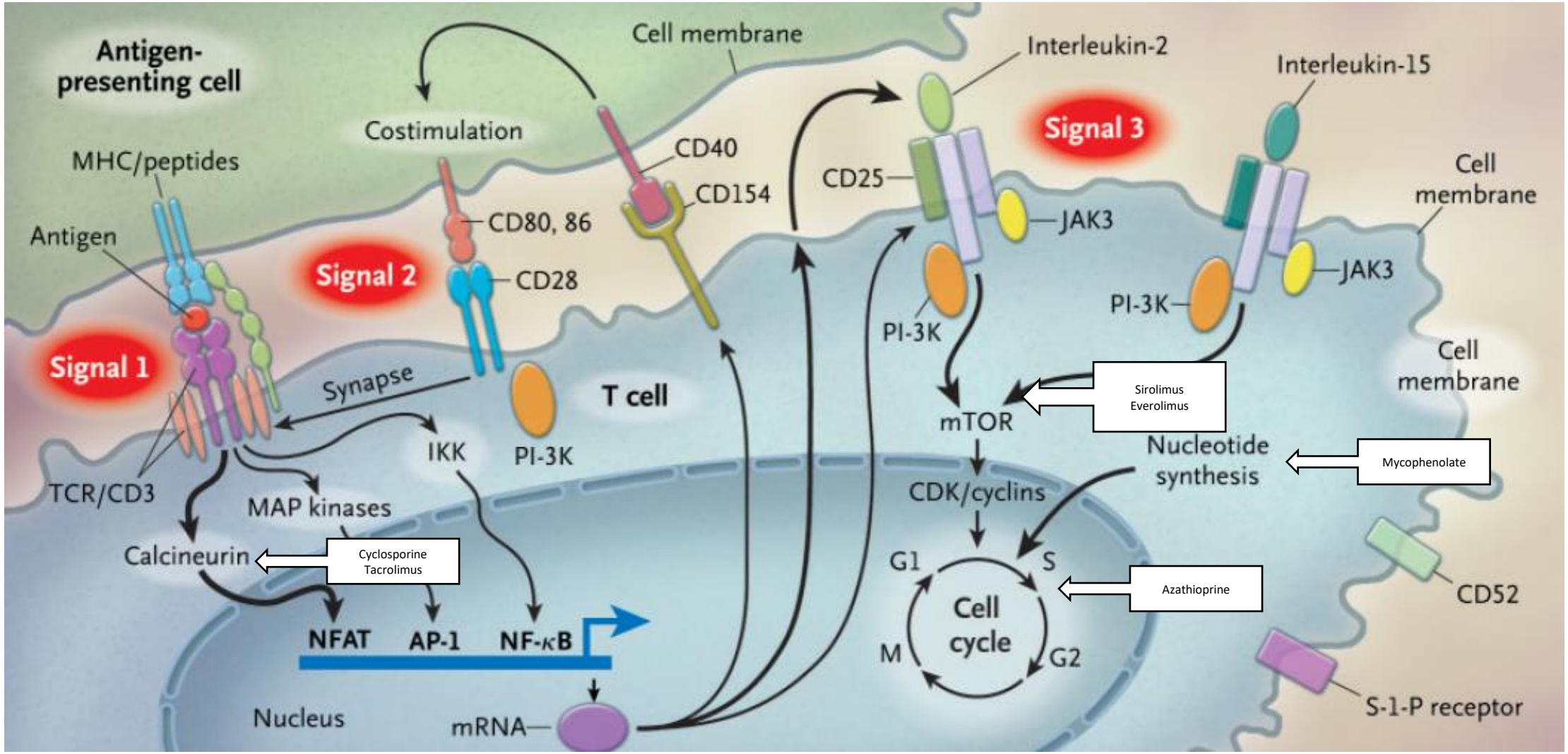
J Allergy Clin Immunol. 2018 Dec;142(6):1932-1946. doi: 10.1016/j.jaci.2018.02.055. Epub 2018 May 4.

Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects

Charlotte Schwab [1], Annemarie Gabrysch [1], Peter Olbrich [2], Virginia Patiño [3], Klaus Warnatz [1], Daniel Wolff [4], Akihiro Hoshino [5], Masao Kobayashi [6], Kohsuke Imai [7], Masatoshi Takagi [7], Ingunn Dybedal [8], Jamanda A Haddock [9], David M Sansom [10], Jose M Lucena [11], Maximilian Seidl [12], Annette Schmitt-Graeff [13], Veronika Reiser [14], Florian Emmerich [15], Natalie Frede [1], Alla Bulashevska [1], Ulrich Salzer [1], Desirée Schubert [16], Seiichi Hayakawa [6], Satoshi Okada [6], Maria Kanariou [17], Zeynep Yesim Kucuk [18], Hugo Chapdelaine [19], Lenka Petruzelkova [20], Zdenek Sumnik [20], Anna Sediva [21], Mary Slatter [22], Peter D Arkwright [23], Andrew Cant [22], Hanns-Martin Lorenz [24], Thomas Giese [25], Vassilios Lougaris [26], Alessandro Plebani [26], Christina Price [27], Kathleen E Sullivan [28], Michel Moutschen [29], Jiri Litzman [30], Tomas Freiberger [31], Frank L van de Veerdonk [32], Mike Recher [33], Michael H Albert [34], Fabian Hauck [34], Suranjith Seneviratne [35], Jana Pachlopnik Schmid [36], Antonios Kolios [37], Gary Unglik [38], Christian Klemann [39], Carsten Speckmann [40], Stephan Ehl [1], Alan Leichtner [41], Richard Blumberg [42], Andre Franke [43], Scott Snapper [44], Sebastian Zeissig [45], Charlotte Cunningham-Rundles [46], Lisa Giulino-Roth [47], Olivier Elemento [48], Gregor Dückers [49], Tim Niehues [49], Eva Fronkova [50], Veronika Kanderová [50], Craig D Platt [51], Janet Chou [51], Talal A Chatila [51], Raif Geha [51], Elizabeth McDermott [52], Su Bunn [53], Monika Kurzai [54], Ansgar Schulz [55], Laia Alsina [56], Ferran Casals [57], Angela Deyà-Martinez [56], Sophie Hambleton [22],

Hematopoietic stem cell transplantation for *CTLA4* deficiency

Three signal model of T cell immunosuppression



Halloran PF. N Engl J Med. 2004; 351: 2715-29.

Immune modulating therapy

Oral

- Tacrolimus → IPEX
- Cyclosporine → IPEX
- Sirolimus (mTOR inhibitor) → IPEX, STAT1 GOF, *LRBA, CTLA4, DEF6* defects
- Ruxolitinib (JAK1/2 Inhibition)→ STAT1 GOF, STAT3 GOF, others

Infusion

- Rituximab (anti-CD20)→ B cell mediated autoimmunity/immunedysregulation
- Abatacept (CTLA4 fusion protein)→ *LRBA, CTLA4, DEF6* defects
- Tocilizumab (anti-IL6R)→ STAT3 GOF
- Siltuximab (anti-IL6)→ STAT3 GOF

Toxicity of Oral T cell Immunosuppressants

	TAC	CSA	m-TOR Inhibitors	MMF
Potency	+++±	+++	++±	++
Nephrotoxicity	++	++	-	-
Neurotoxicity (PRES)	++	+	-	-
Diabetogenic	++	+	-	-
GI intolerance	-	-	+	++
Hepatotoxicity	±	±	+	-
Marrow suppression	-	-	+	+

TAC= tacrolimus
CSA= cyclosporine
M-TOR inhibitors = sirolimus & everolimus
MMF= Mycophenolate mofetil

Starting dose Guidance

Tacrolimus→ Standard starting dose: 0.05-0.1 mg/kg/DOSE q12h

Cyclosporine→ Standard starting dose: 2-3 mg/kg/DOSE q12h

Mycophenolate→ Standard starting dose: 300 mg/m2/dose q12h (MAX 500 mg)

Sirolimus → Standard starting dose:

- Children < 40 kg and pre-pubescent: consider loading dose: 3 mg/m^2 (day 1); followed by a maintenance dose of 1-5 mg/m^2/day divided every 12 hours
- Adolescents > 40 kg and adults: 2 mg PO once daily

Clinical Pearls

- CVID is an Umbrella Diagnosis that can be made based on Clinical and Laboratory Criteria
- There are a broad range of monogenic inborn errors of immunity that can present under the CVID clinical diagnostic umbrella
- Knowing the underlying genetic defect can aid in choosing the correct precision therapy and inform prognosis counseling to patients, thus genetic testing should be considered for all patients with CVID
- If patients are initiated on B cell depleting agents for autoimmune disease, it is critically important to evaluate for humoral IEI prior to starting these therapeutic agents because this can be a presenting symptom of CVID
- IgG levels >800mg/dl for patients on IVIG and >1000mg/dl for those on SC are associated with reduced frequency of severe sinopulmonary infection
- Autoimmune manifestations are common in patients with CVID, and use of immunomodulation in conjunction with Ig replacement is needed to manage these symptoms