Hypogammaglobulinemia and Secondary Immunodeficiency

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Updates in Primary Immunodeficiency
Cleveland Clinic - April 4-5, 2025

Learning Objectives

1. Understand the definition and significance of secondary immunodeficiency

2. Identify common etiologies of secondary hypogammaglobulinemia

3. Outline the treatment approach to secondary hypogammaglobulinemia

Which of the following is most associated with prolonged and/or or severe hypogammaglobulinemia?

A. Dermatomyositis
B. Rheumatoid arthritis
C. Guillain-Barre syndrome
D. ANCA-associated vasculitis

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A. Dermatomyositis
B. Rheumatoid arthritis
C. Guillain-Barre syndrome
D. ANCA-associated vasculitis

65 yo female with GPA

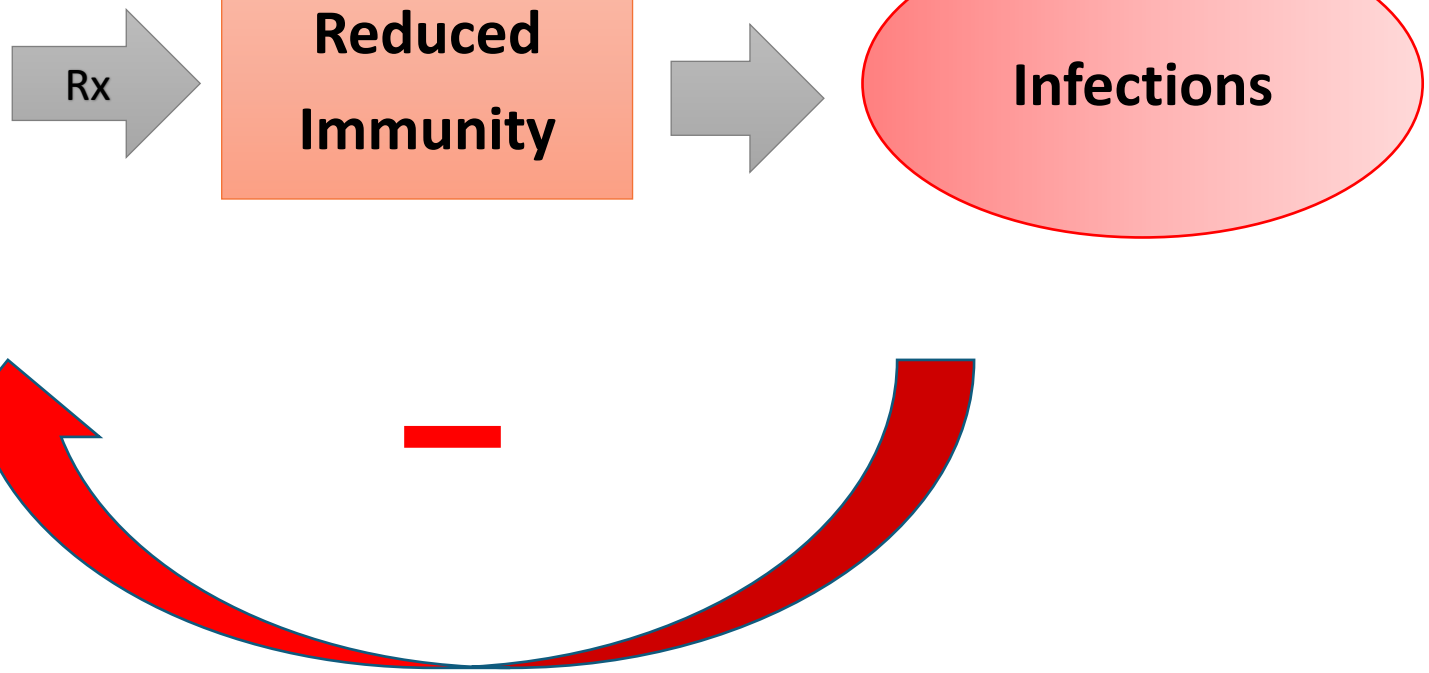
- Diagnosed with GPA maintained on IV Rituximab every 6 months for the past 3 years
- Recently hospitalized with pneumonia, and developed recurrent sinus infections
- Rituximab was held due to recurrent infections

Lab results

- IgG = 260 (600-1500 mg/dL)
- IgA = 35 (80-450 mg/dL)
- IgM = 10 (40-230 mg/dL)

- Absent IgG response to vaccines
- Flow cytometry: absent B cells; normal T, NK cells


treatment
degenerative
health
rheumatism
physical
lupus
patient
pain
skeleton
joint pain
paralyzed
skeletal
symptoms
therapy
disability
rheumatoid
illness
sickness
crippled
problem
mature
infection
deformed
rheumatic
chronic
osteoarthritis
injury
inflammation
inflammatory
osteoporosis
stiffness
elderly
orthopedic
anatomy
cure
trembling
elder
diagnosis
muscle
arthritis
gout
joint
adult
aged
ache
disorder
help
doctor
bone
surgery
trauma
old
arthritic
medical
disease
painful
sick
medicine
disabled
shaking
healthcare
septic
age
autoimmune
body
joints
aging
fibromyalgia
senior


Rx
Reduced Immunity
Infections
-

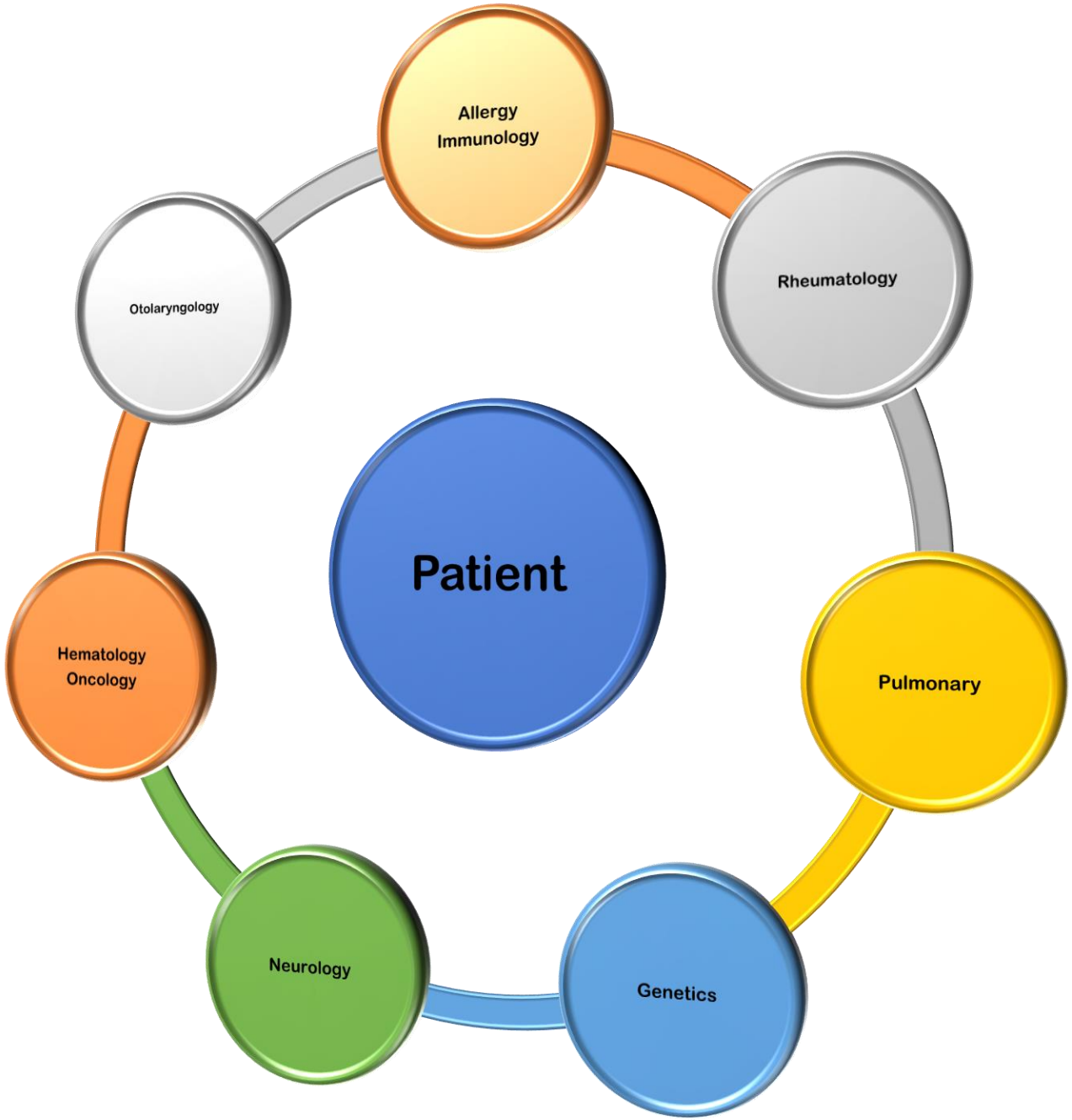
Secondary Immunodeficiency: Why so Important?

- Increased incidence
  - ~ 30x more common than PID*
  - Immunomodulatory therapies in autoimmune, rheumatologic, neurologic, hem/onc conditions
  - Most notable is B-cell targeted therapy (BCTT)

- Primary Immunodeficiency literature & guidelines referenced and used

- Allergist/Immunologist role in patient care teams

*Patel SY, Carbone J, Jolles S. Front Immunol. 2019;10:33


Allergy
Immunology
Rheumatology
Otolaryngology
Patient
Hematology
Oncology
Pulmonary
Neurology
Genetics

Causes of Secondary Immunodeficiency

- Malnutrition
- HIV
- Malignancy
- Splenectomy
- Immunosenescence
- Immunosuppressive drugs
- Immunomodulatory agents, Biologics

- Protein loss
  - Nephrotic syndrome
  - Protein-losing enteropathy
  - Chylothorax
- Metabolic disease
  - Diabetes mellitus
  - Severe liver disease
  - Uremia
- Impaired barriers
  - Severe burns
  - Cystic fibrosis
  - Immotile cilia syndromes

American Academy of Allergy Asthma & Immunology

Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: A Work Group Report of the AAAAI Primary Immunodeficiency and Altered Immune Response Committees

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J Allergy Clin Immunol. 2022 May;149(5):1525-1560

Hypogammaglobulinemia (HG)

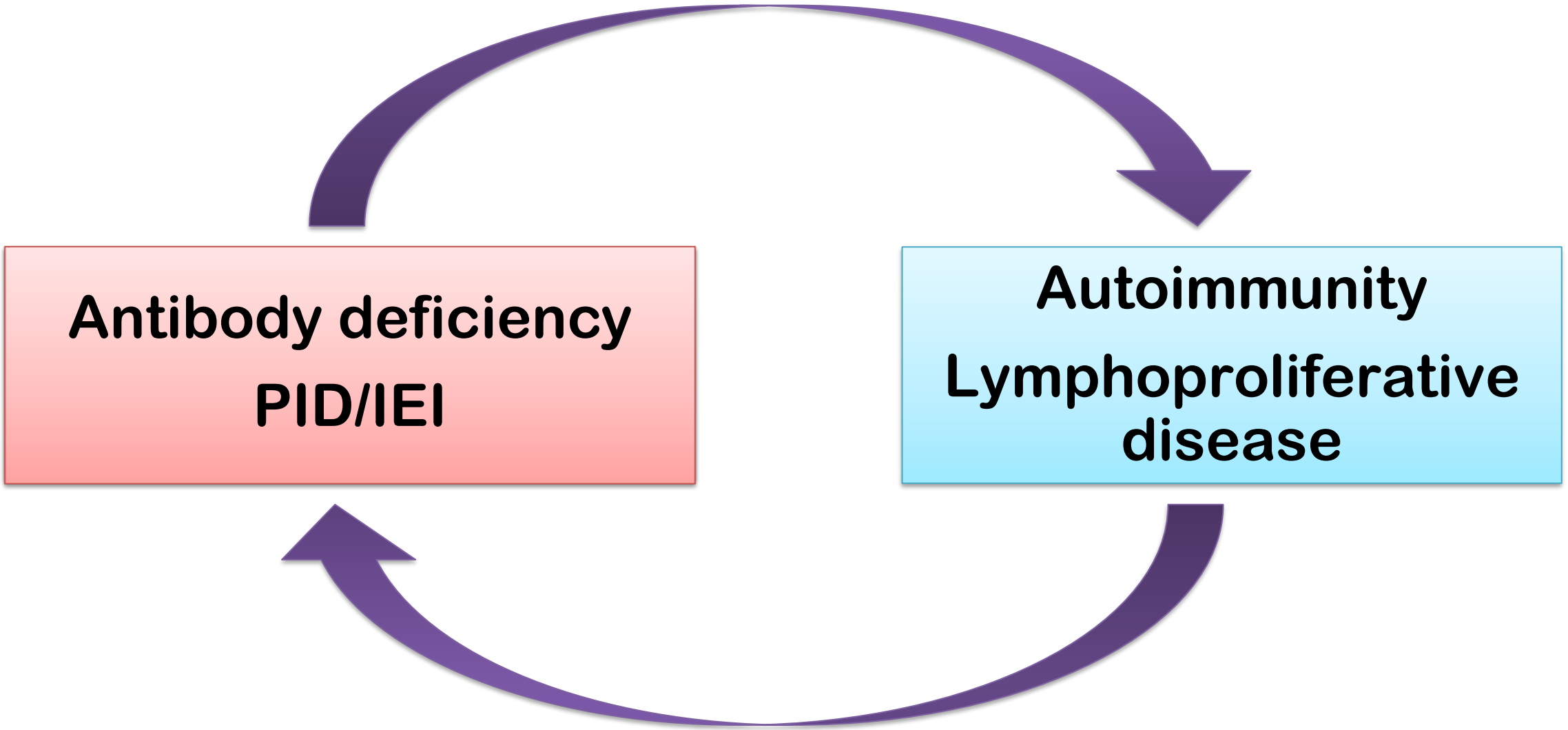
- By itself is a lab finding, and does not necessarily indicate a clinically symptomatic syndrome
- IgG levels alone do not measure B cell function
- Vaccine responses are essential for the evaluation of antibody function

Primary vs Secondary

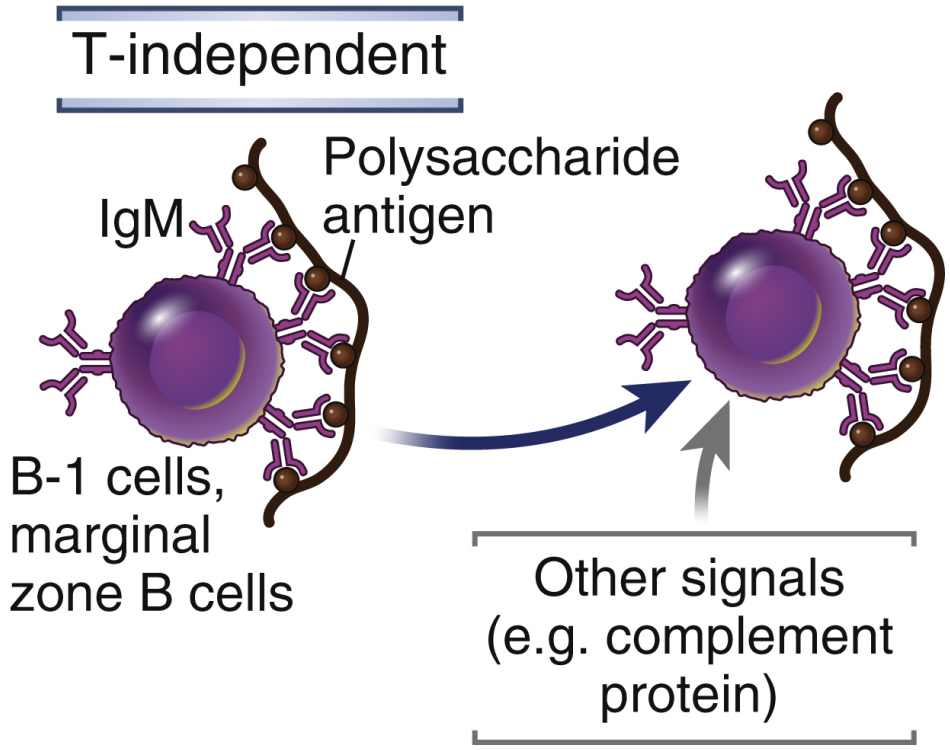
- PID (or IEI) are a heterogeneous group of disorders comprising ~500 inherited disorders of immunity

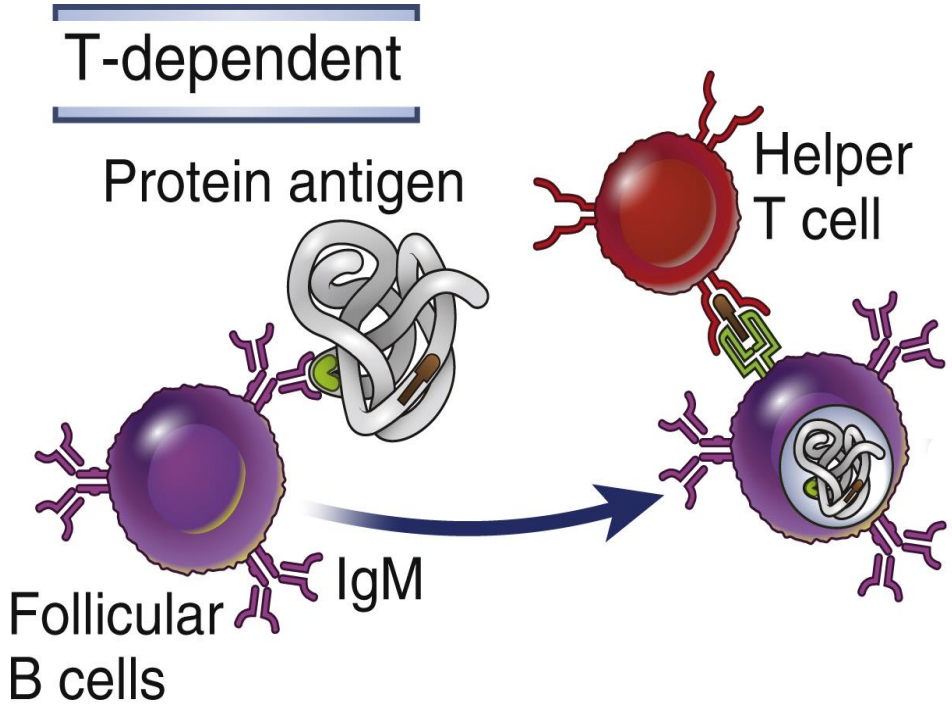
- HG: is the main abnormality in the Predominantly Antibody Deficiency Syndromes; also occurs in combined immunodeficiency disorders

- SHG = reduced immunoglobulin levels, not due to a PIDD/IEI. Caused by decreased antibody production or increased antibody loss


Antibody deficiency
PID/IEI
Autoimmunity
Lymphoproliferative disease

Assess IgG Response to Polysaccharide and Peptide Antigens





Pneumo serotype	Pre	Post	Pre	Post
1	**0.3**	**<0.3**	**0.7**	**>13.1**
2	**1.0**	**1.0**	**0.5**	**2.7**
3	**0.4**	**0.4**	**2.8**	**14.2**
4	**<0.3**	**<0.3**	**0.2**	**>19.0**
5	**0.7**	**<0.3**	**0.3**	**11.5**
6B (26)	**<0.3**	**<0.3**	**0.1**	**>57.6**
7F (51)	**0.3**	**<0.3**	**0.2**	**2.5**
8	**0.6**	**<0.3**	**0.2**	**7.3**
9N	**0.7**	**<0.3**	**0.2**	**3.4**
9V	**<0.3**	**<0.3**	**<0.1**	**3.1**
10A	**0.6**	**<0.3**	**<0.1**	**3.2**
11A	**0.6**	**<0.3**	**0.7**	**>12.9**
12F	**<0.3**	**<0.3**	**0.2**	**1.1**
14	**0.9**	**0.8**	**0.3**	**3.5**
15B	**<0.3**	**<0.3**	**0.2**	**1.5**
17F	**0.9**	**0.4**	**1.0**	**11.9**
18C (56)	**0.6**	**<0.3**	**0.3**	**>16.7**
19A	**<0.3**	**<0.3**	**4.8**	**7.1**
19F	**0.6**	**0.7**	**2.2**	**14.0**
20	**0.7**	**0.3**	**6.8**	**>51.3**
22F	**2.3**	**2.1**	**0.2**	**1.9**
23F	**<0.3**	**<0.3**	**0.1**	**>22.5**
33F	**0.4**	**<0.3**	**0.6**	**>14.4**
Titers >1.3	**1/23**	**1/23**	**4/23**	**22/23**
Tetanus	**2.85**		**0.37**	
Diphtheria	**0.63**		**0.12**	

Secondary Hypogammaglobulinemia: Causes

Hematologic malignancy	▪ Chronic Lymphocytic Leukemia (CLL) ▪ Multiple Myeloma ▪ Lymphoma
Transplant	▪ Stem Cell Transplant ▪ Solid Organ Transplant
Protein loss	▪ Nephrotic Syndrome ▪ Protein-losing Enteropathy
Protein removal	▪ Plasma exchange ▪ Immunoadsorption

Secondary Hypogammaglobulinemia: Associated Conditions

Rheumatology	▪ ANCA-associated vasculitis (AAV) ▪ Eosinophilic granulomatosis with polyangiitis (EGPA) ▪ Granulomatosis with polyangiitis (GPA) ▪ Juvenile idiopathic arthritis ▪ Rheumatoid arthritis ▪ Systemic lupus erythematosus
Neurology	▪ Multiple sclerosis ▪ Neuromyelitis optica spectrum disorders

Medications

Corticosteroids	**Antipsychotics:** Clozapine, chlorpromazine **Anti-epileptics:** Phenytoin, carbamazepine, valproate, lamotrigine
Methotrexate	
Mycophenolate	
Sulfasalazine	
Cyclophosphamide	
Azathioprine	

Corticosteroids

- **Oral corticosteroids:**
  - **Short courses associated with transient drop in IgG; can last for weeks**
  - **Long-term use associated with more significant drop in IgG**
- **Inhaled corticosteroids do not affect IgG**
- **Specific antibody responses are likely preserved**
- **Infections primarily due to steroid effect on T cells rather than steroid-induced SHG**

Pediatric Asthma, Allergy & Immunology. 1988;2:309–16.
Ann Allergy. 1992;68:472–81.
J Pediatr. 1996;129:898–903.

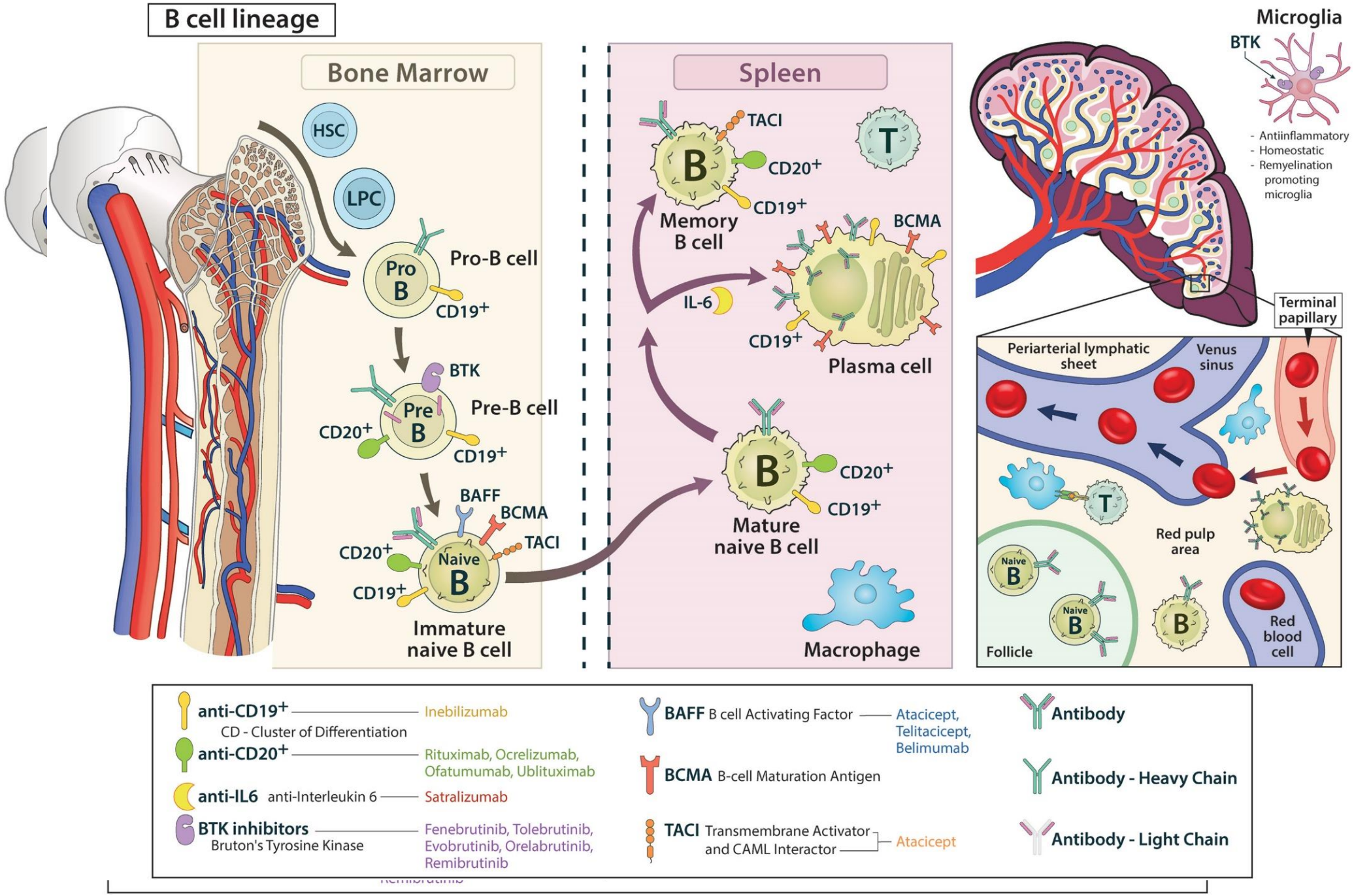
Vaccine Responses Maintained

Summary of Studies Evaluating Vaccine Responses While on OCS

Population	Vaccine	Humoral response in OCS-treated individuals	References
Children with OCS-dependent asthma	Bacteriophage ϕX174 Tetanus Diphtheria Haemophilus influenza type B Pneumococcal polysaccharide	Adequate antibody responses to both peptide and polysaccharide vaccines	Lack et al,[16] 1996
Adults with OCS-dependent asthma	Tetanus Influenza Pneumococcal polysaccharide	Adequate antibody responses to both peptide and polysaccharide vaccines	Katz et al,[17] 1988
Adults with OCS-dependent asthma	Pneumococcal polysaccharide	Adequate antibody response	Lahood et al,[18] 1993
Children with OCS-dependent nephrotic syndrome	Pneumococcal polysaccharide	Decreased antibody response	Spika et al,[19] 1982
Adults with rheumatologic illness	Influenza	Adequate rates of seroconversion, but decreased magnitude of antibody response	Herron et al,[20] 1979
Adults with OCS-dependent pulmonary disease	Influenza	Adequate antibody response	Kubiet et al,[21] 1996
Children and adults with asthma	Influenza	Possibly decreased magnitude of antibody response	Hanania et al,[22] 2004
Adults with chronic inflammatory conditions	mRNA COVID-19	Significantly decreased antibody response	Deepak et al,[23] 2021

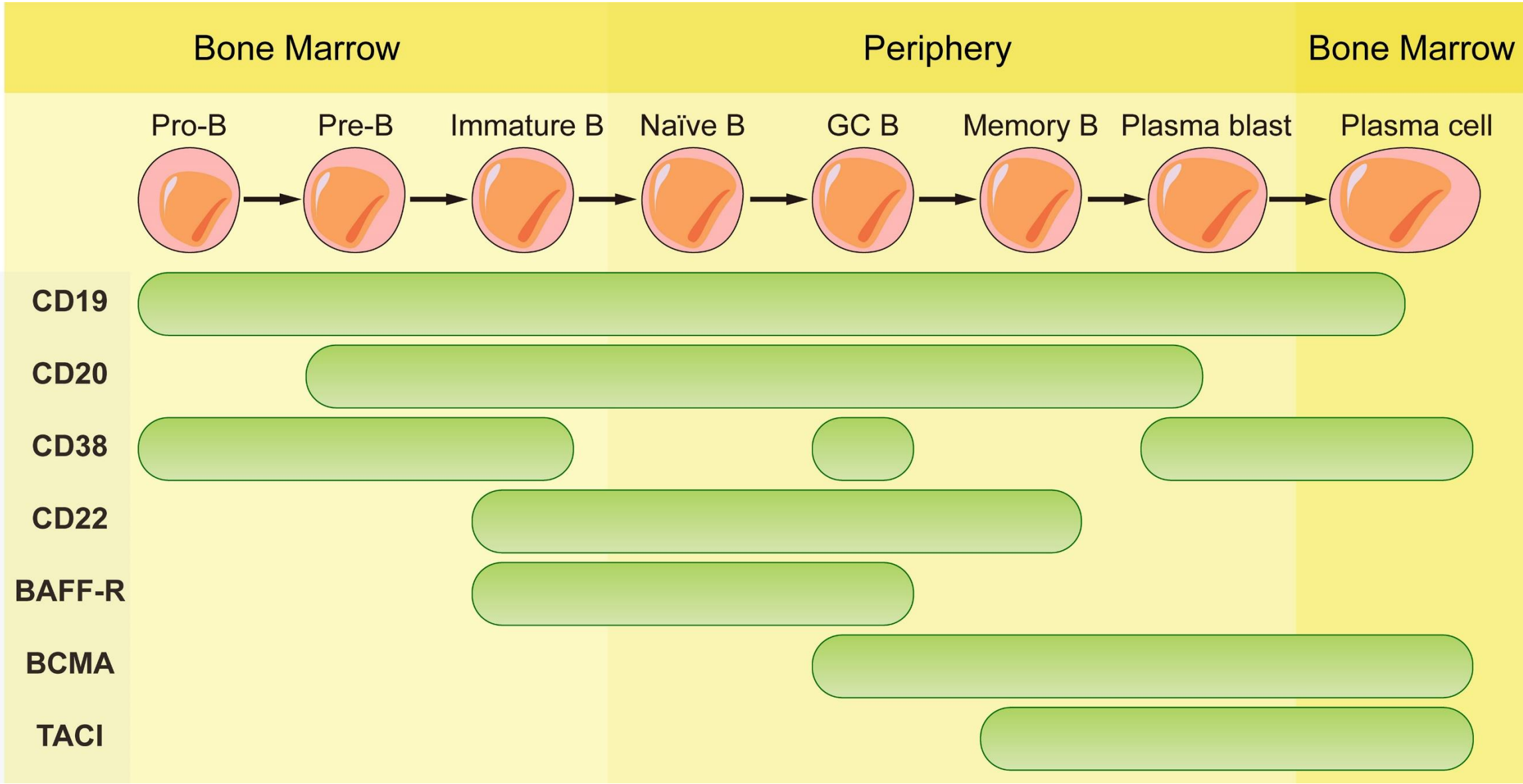
Abbreviations: COVID-19, coronavirus disease 2019; mRNA, messenger RNA; OCS, oral corticosteroid.

Mustafa. Ann All Asthma Immunol 2023; 130: 713.



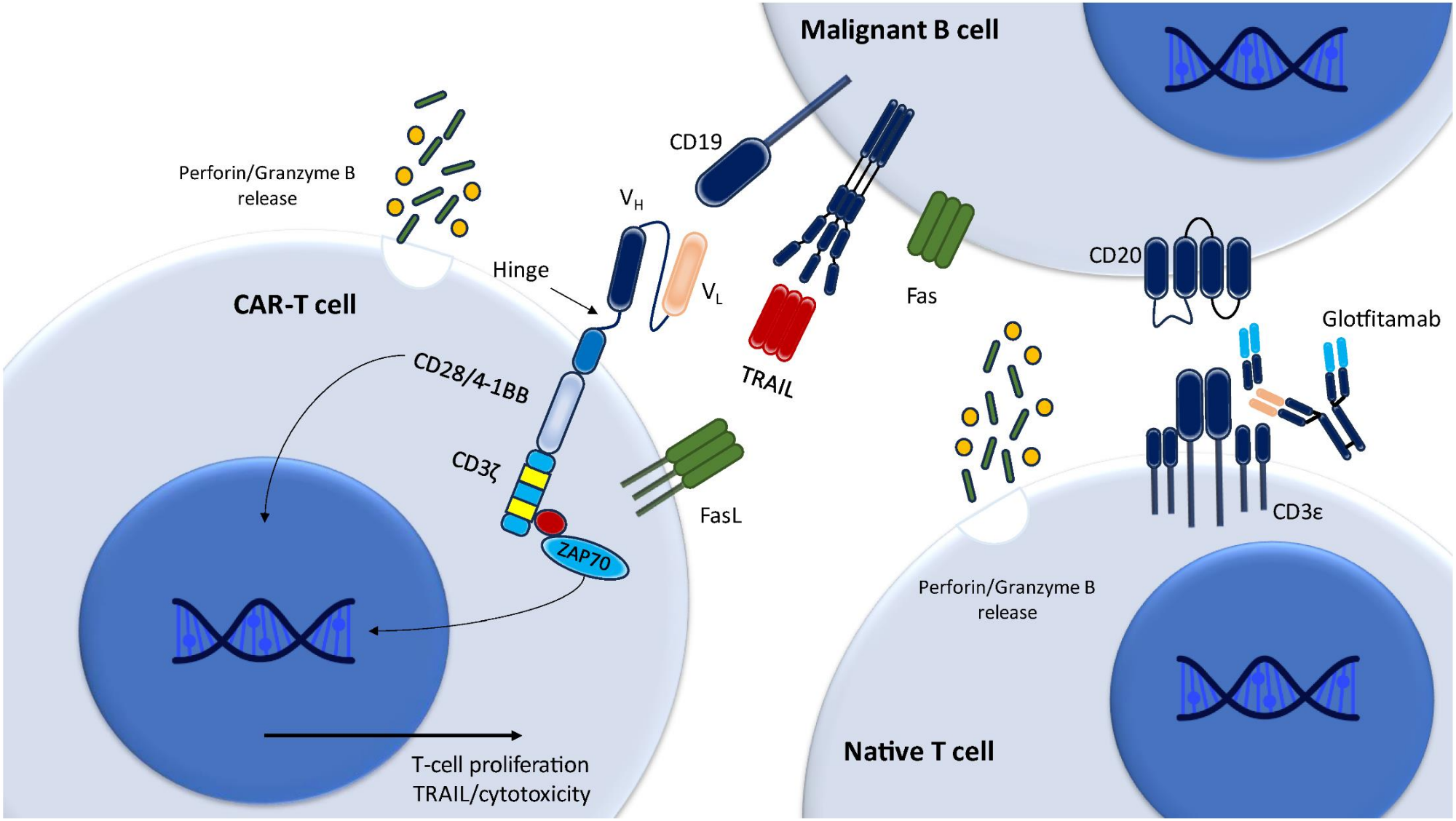
Moritz F et al. Front. Immunol. , 08 March 2023

B-cell Targeted Therapies (BCTT)



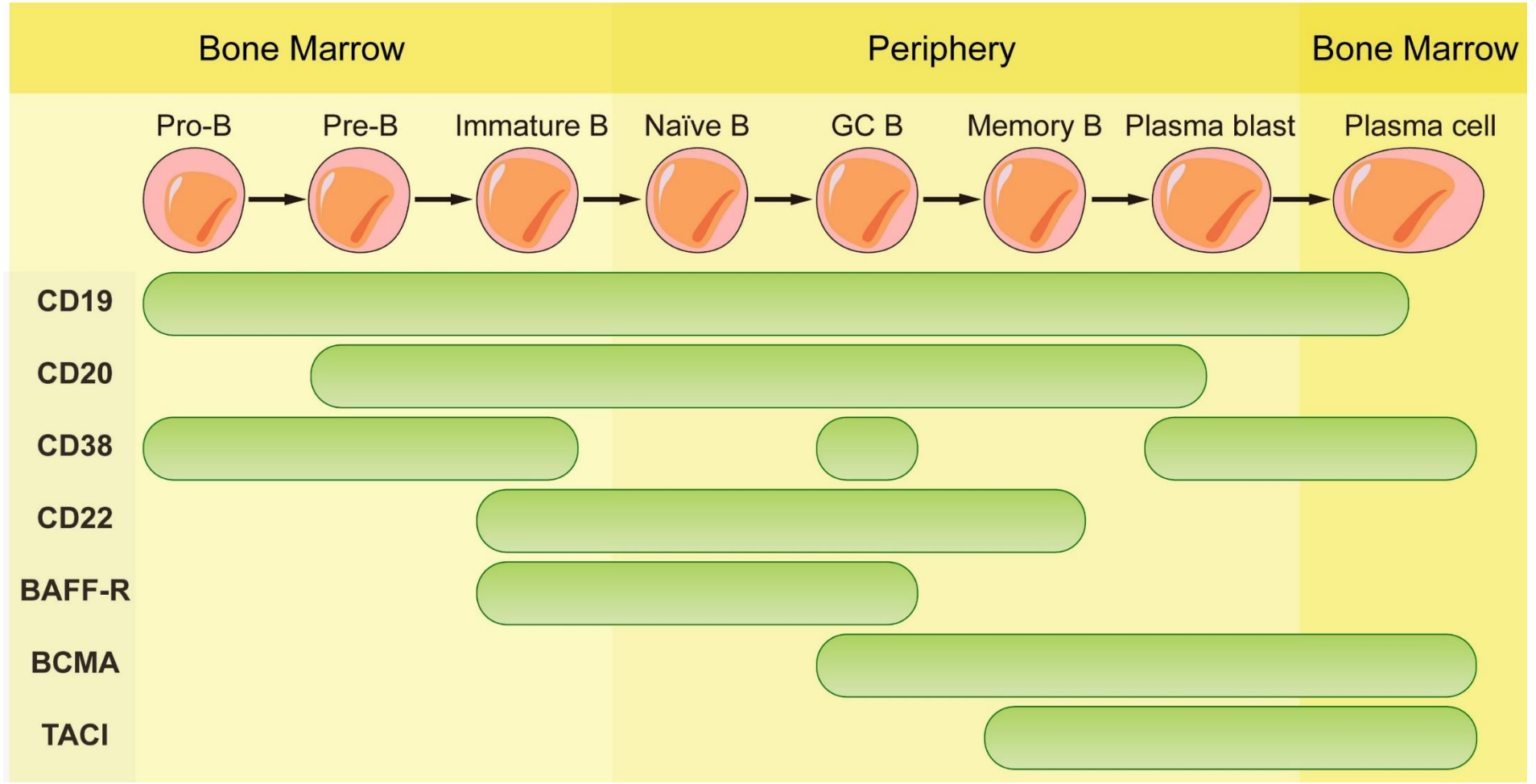
Zhang Z et al. Front. Immunol. , 08 March 2023

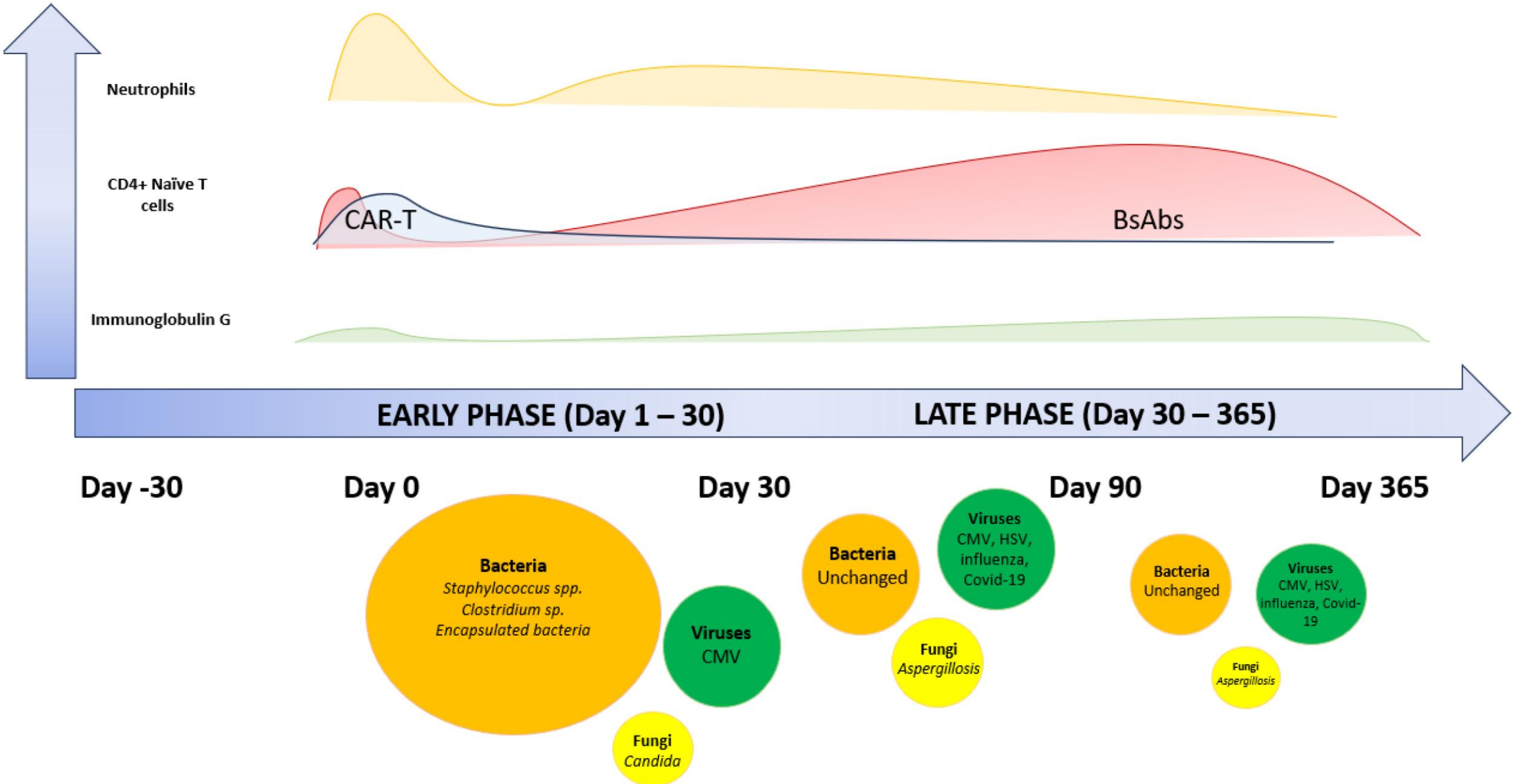
CAR-T and Bispecific T-cell Engagers



Day W.G. et al. Lymphatics 2024, 2, 244–259

CAR-T	BiTE
X	X
	X
X	X





Day W.G. et al. Lymphatics 2024, 2, 244–259

CAR-T for R/R B-NHL

Drug	Rates of Neutropenia	Rates of Hypogamma-globulinemia	Rates of Infections
Axicabtagene	-All Grade: 71% -Grade ≥3: 69% -Febrile Neutropenia All Grade: 31% -Febrile Neutropenia Grade ≥3: 31%	-All Grade: 14% -Grade ≥ 3: 3%	-All Grade: 45% -Grade ≥ 3: 17%
Brexucabtagene	-All Grade: 97% -Grade ≥ 3: 95 to 97% -Febrile Neutropenia All Grade: 6 to 35% -Febrile Neutropenia Grade ≥ 3: 35%	-All Grade: 16% -Grade ≥ 3: 1%	-All Grade: 44 to 56% -Grade ≥ 3: 30%
Lisocabtagene	-All Grade: 79 to 94% -Grade ≥ 3: 79 to 94% -Febrile Neutropenia All Grade: 1.6 to 12% -Febrile Neutropenia Grade ≥ 3: 12%	-All Grade: 10% -All Grade: Not Specified	-All Grade: 34% -Grade ≥ 3: 12%
Tisagenucleucel	-All Grade: 63 to 82% -Grade ≥ 3: 63% to 82% -Febrile Neutropenia All Grade: 13 to 34% -Febrile Neutropenia Grade ≥ 3: 13 to 34%	-All Grade: 17 to 53% -Grade ≥ 3: 1%	-All Grade: 52 to 72% -Grade ≥ 3: 21 to 48%

Day W et al. Lymphatics **2024**, 2, 244–259

Anti-CD20 BsAbs for R/R B-NHL

Drug	Rate of Neutropenia	Rate of Infections
Epcoritamab	-All Grade: 34% -Grade ≥ 3: 23% -Febrile Neutropenia All Grade: 2.5% -Febrile Neutropenia Grade ≥ 3: not specified -All Grade: 55% -Grade ≥ 3: 30% -Febrile Neutropenia All Grade: 3.1% -Febrile Neutropenia Grade ≥ 3: not specified	-All Grade: 15% -Grade ≥ 3: 14% -1.3% grade 5 -All Grade: not specified -Grade ≥ 3: 40% -6% Grade 5
Glofitamab	-All Grade: 37.7% -Grade ≥3: 26% -Febrile Neutropenia All Grade: 3.4% -Febrile Neutropenia Grade ≥3: not specified	-All Grade: 16% - Grade ≥ 3: 10%
Mosunetuzumab	-All Grade: 28% -Grade ≥ 3: 25% -Febrile Neutropenia All Grade: 3.6% -Febrile Neutropenia Grade ≥ 3: 3.6%	-All Grade: 17% -Grade ≥ 3: 14%

Day W et al. Lymphatics **2024**, 2, 244–259

Which of the following has the most profound effect on reducing serum IgG without affecting B cell numbers?

A. Oral prednisone
B. Anti-CD20 antibody (Rituximab)
C. Neonatal Fc receptor (FcRn) antagonist
D. Tumor necrosis factor (TNFα) antagonist

Which of the following has the most profound effect on reducing serum IgG without affecting B cell numbers?

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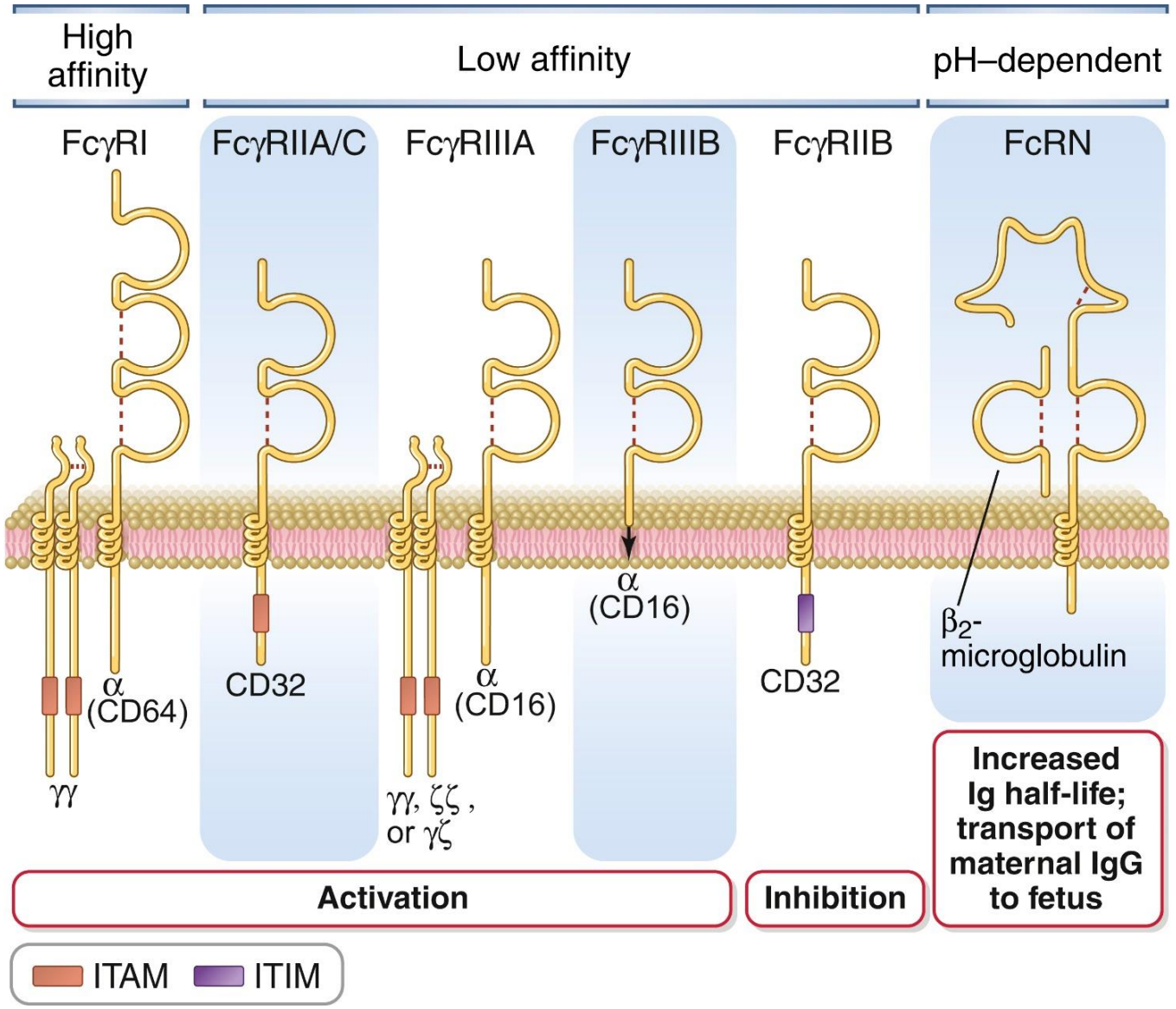
FcRn: Atypical FcγR

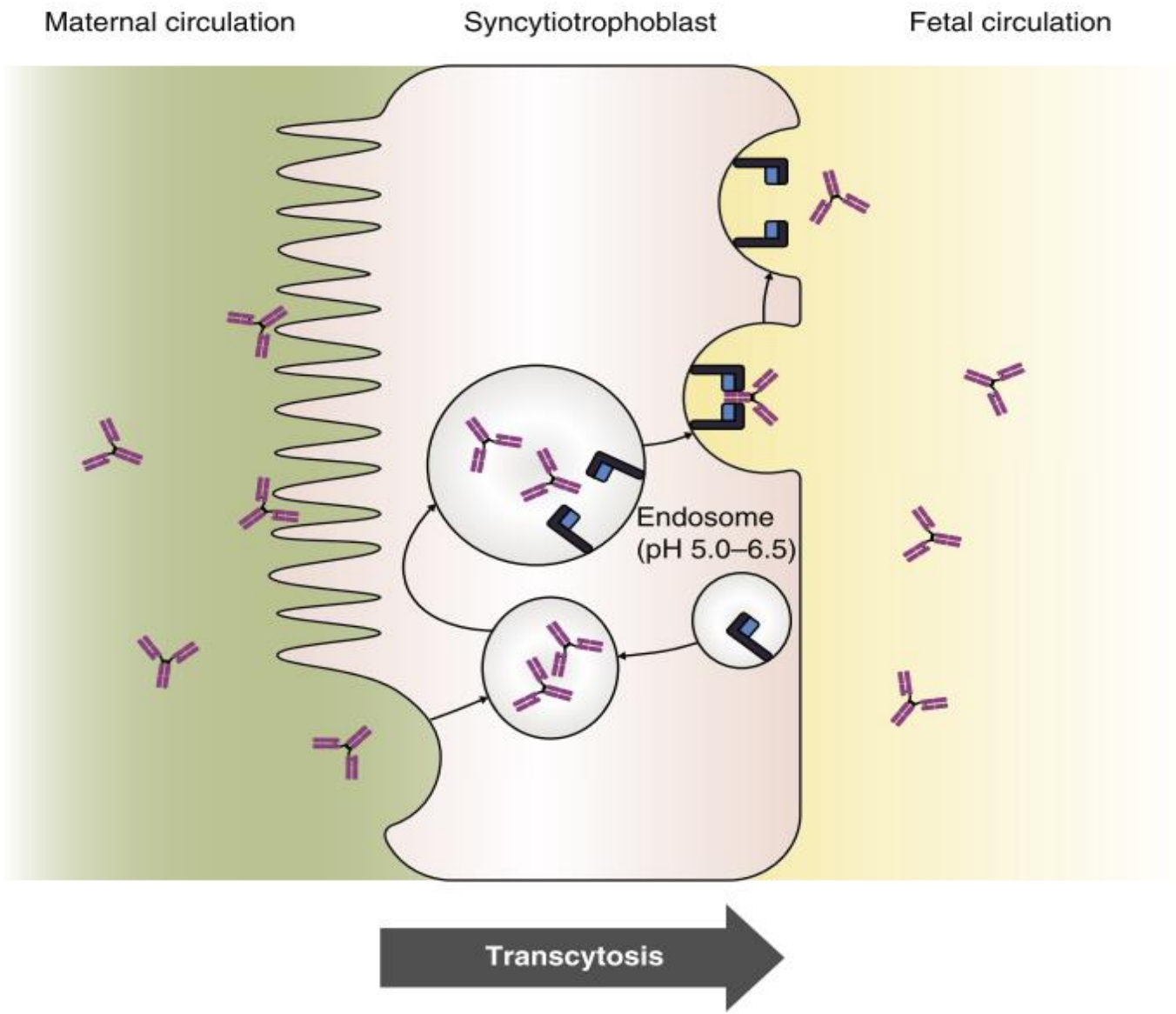


-Resembles MHC class I receptors

-No peptide binding cleft

Abbas/Lichtman. Cellular and Molecular Immunology. 2021

FcRn mode of action: Transcytosis of IgG across barriers



Patel D, Bussel J. J Allergy Clin Immunol 2020;146:467-78

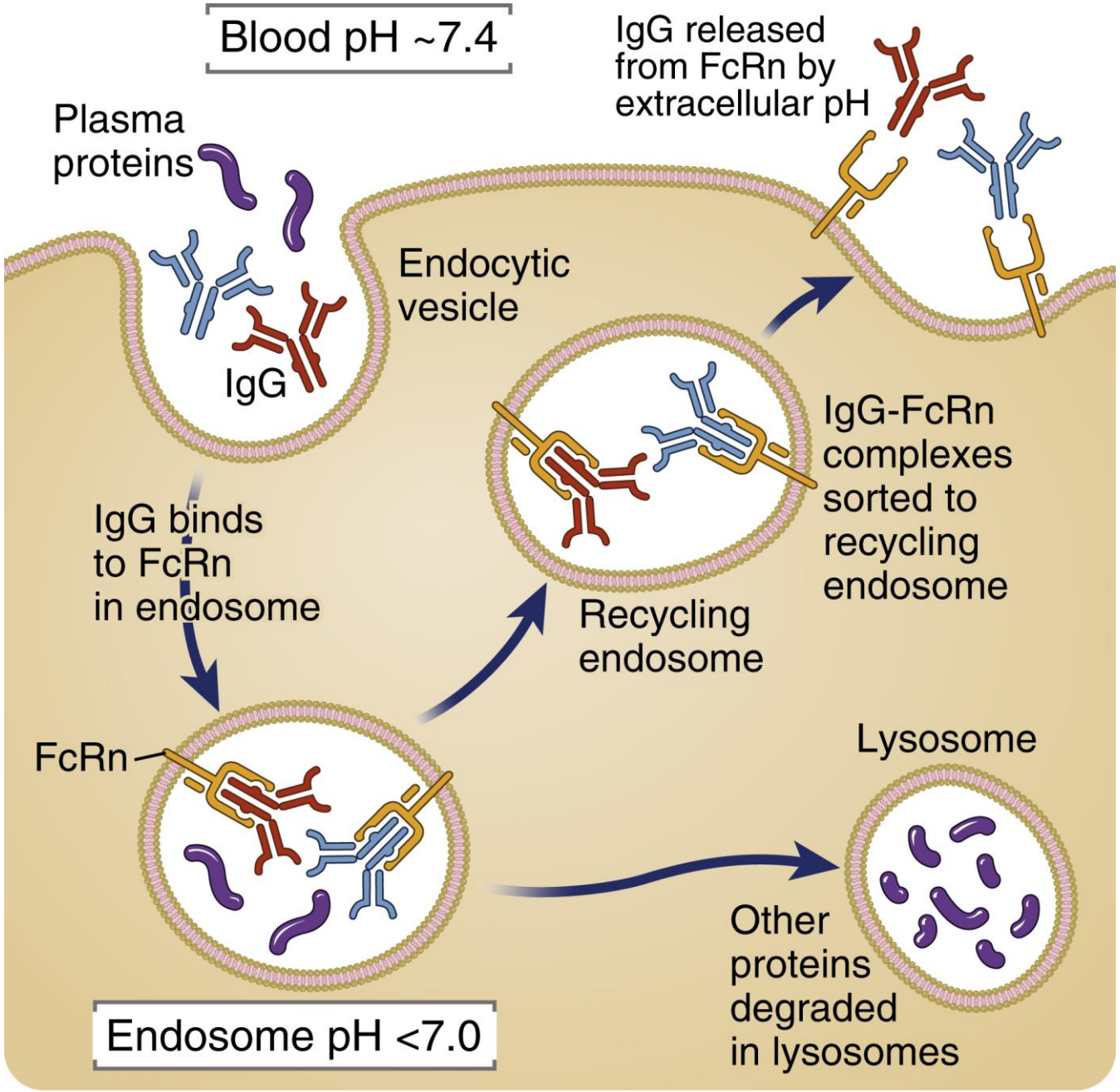
FcRn Function

- Specific for IgG; does not interact with other immunoglobulins
- Initially identified in IgG transport across placenta
- Important role protecting against degradation of **IgG + Albumin**
  - Most abundant proteins in circulation
  - Long half-lives >3 weeks

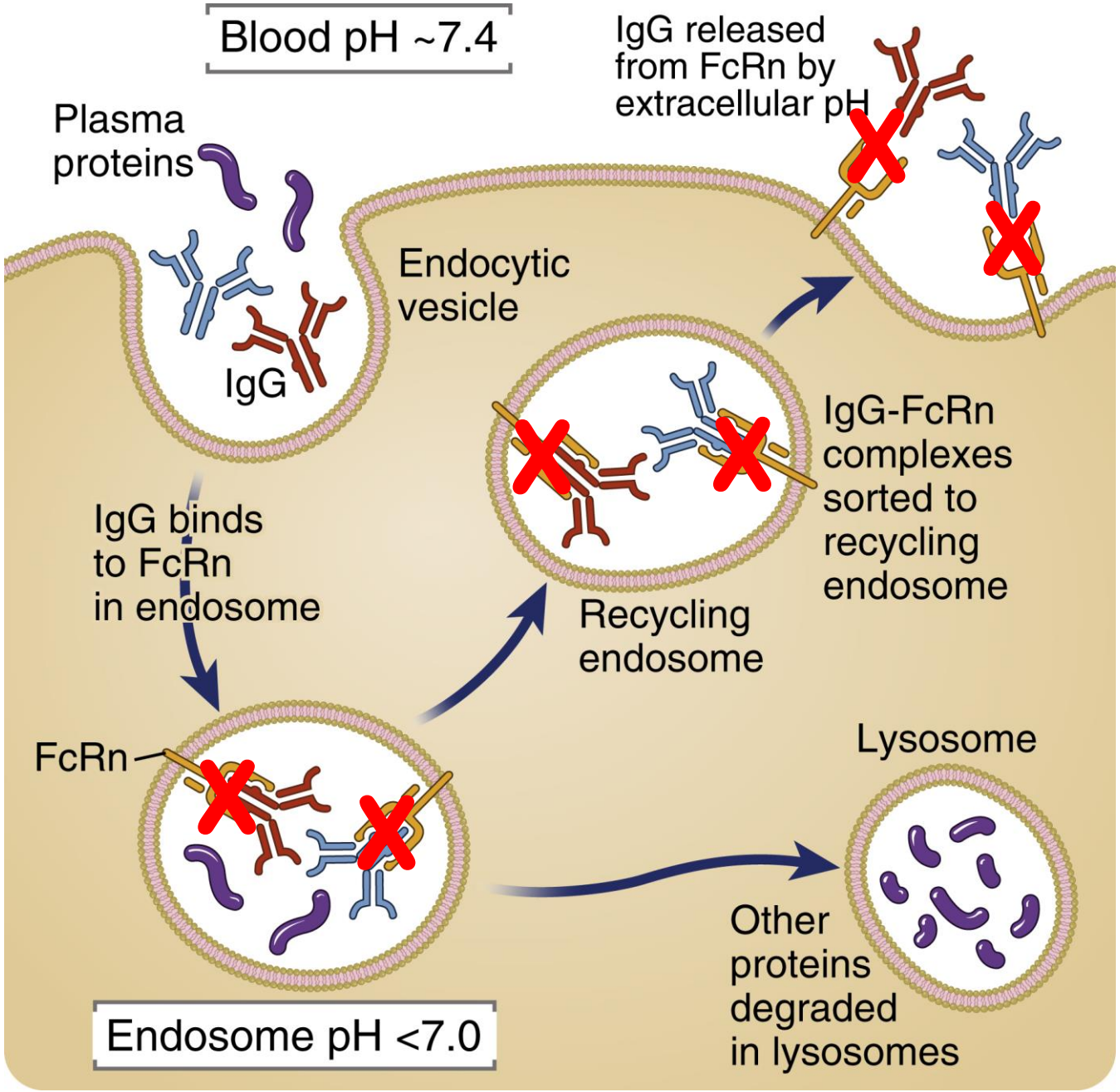
FcRn protects IgG (and albumin) from degradation

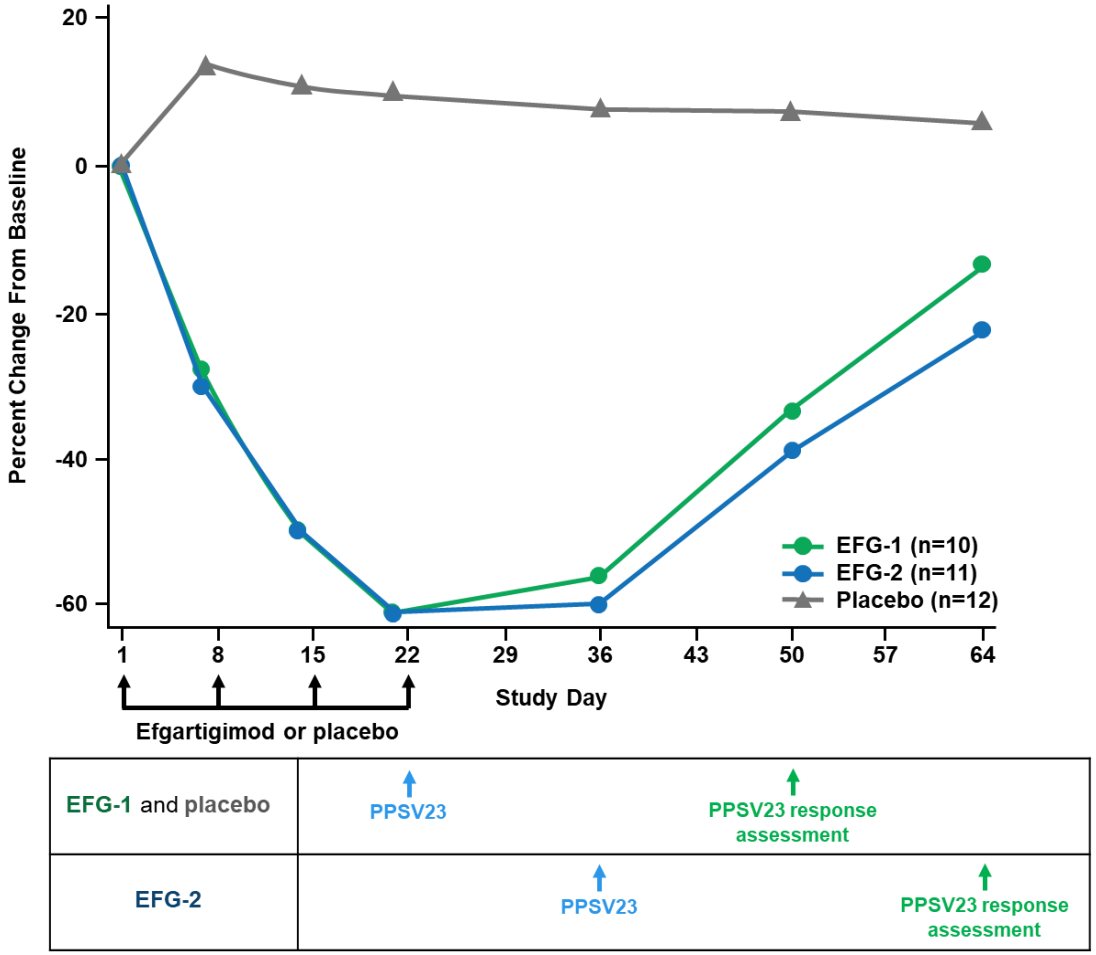
FcRn binds IgG only at mildly acidic pH 5.0-6.5, unlike conventional FcγRs and other Fc-binding proteins

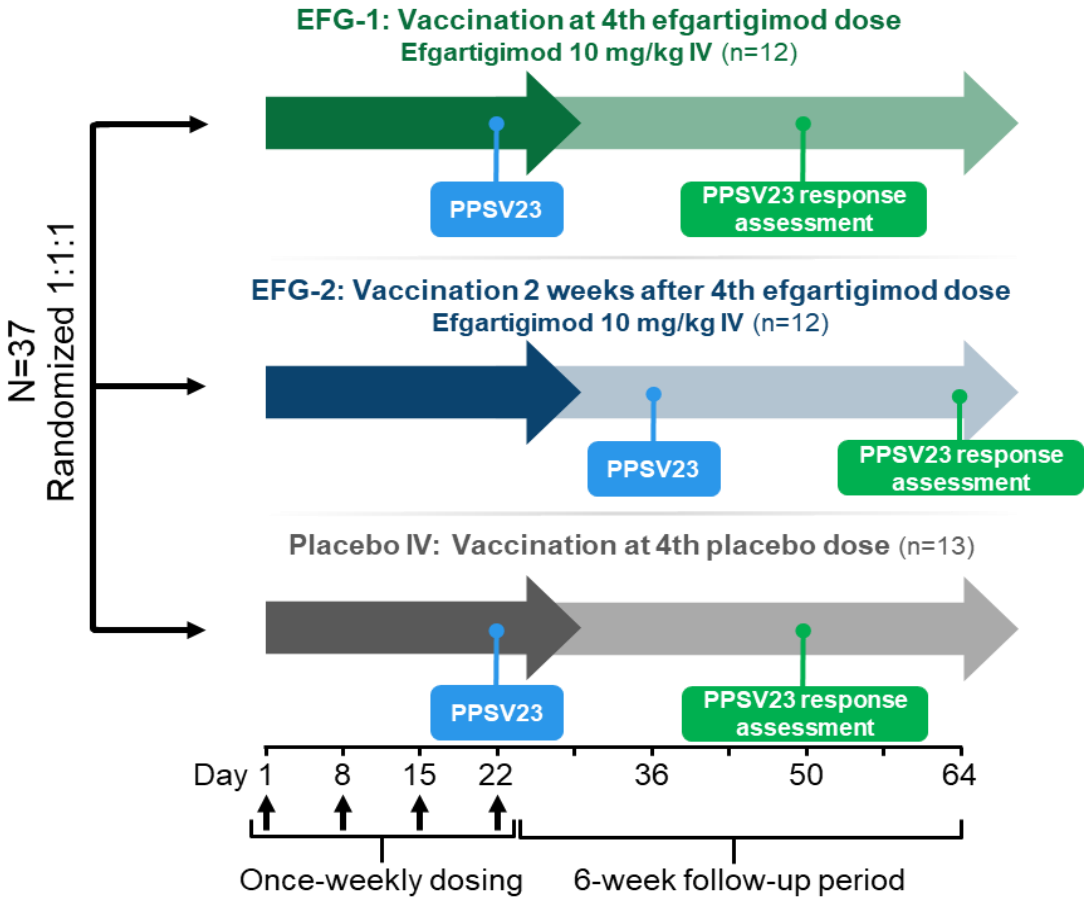
FcRn on endothelial surfaces does not bind IgG



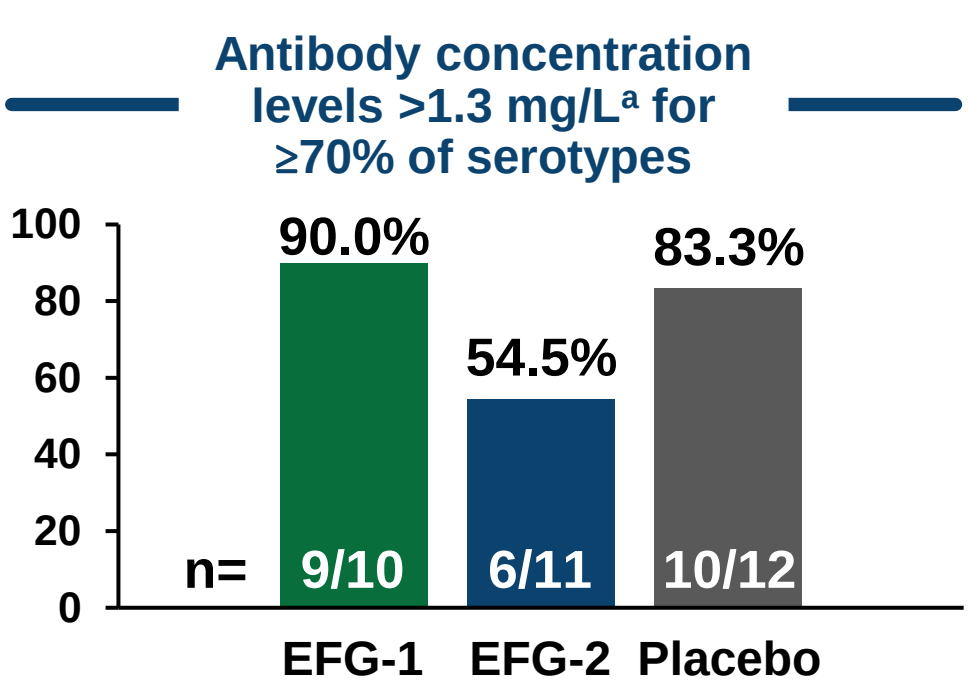
FcRn inhibition reduces both pathogenic and total IgG

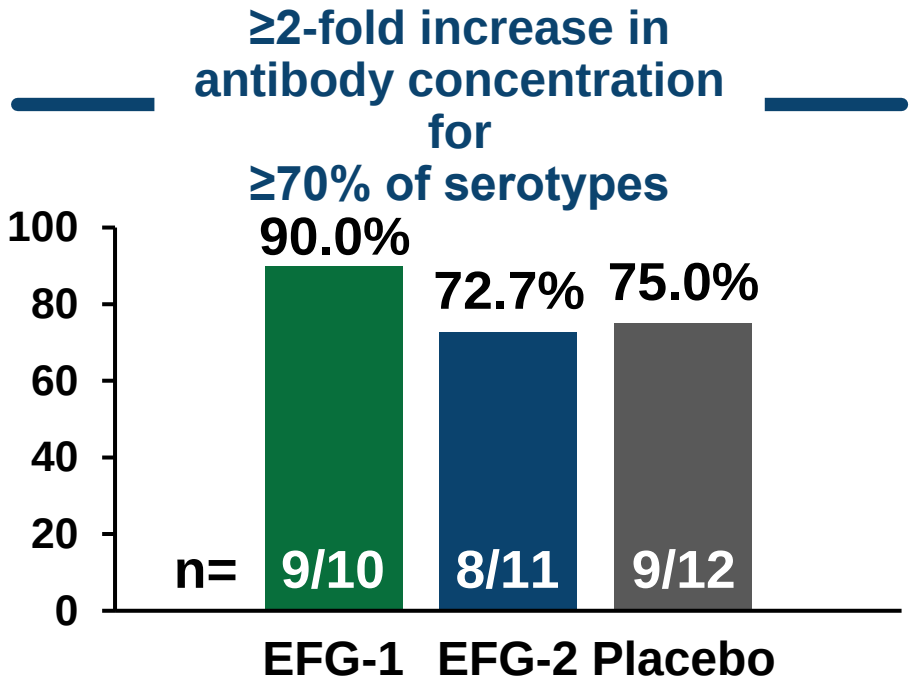




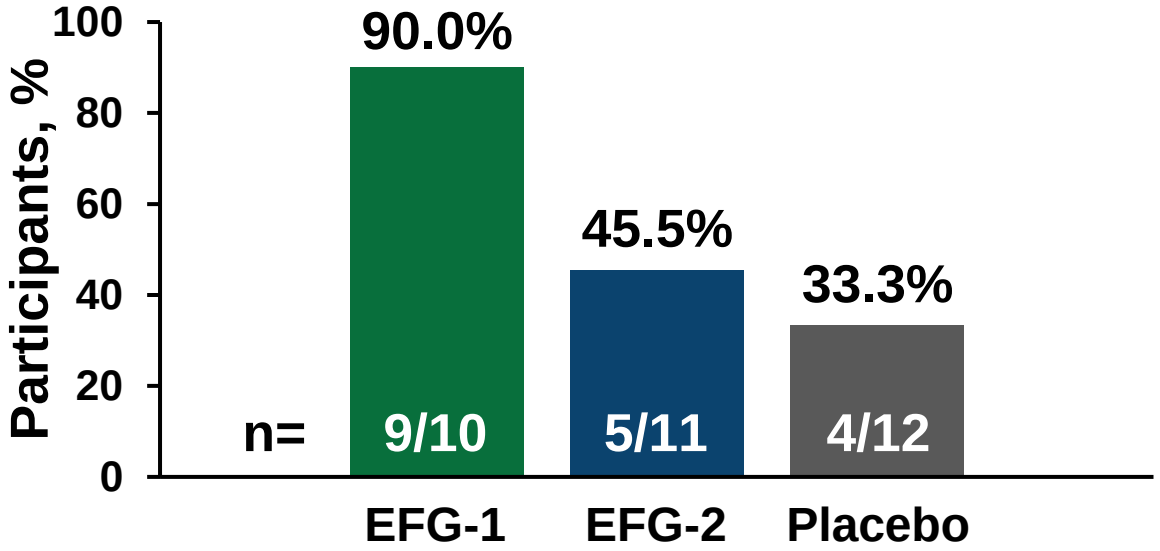


Azar A et al. in press



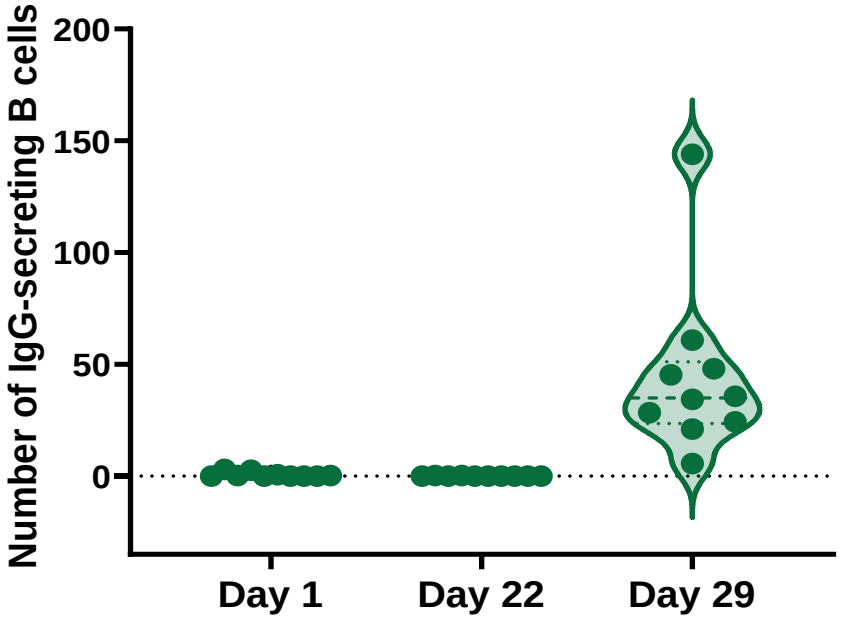


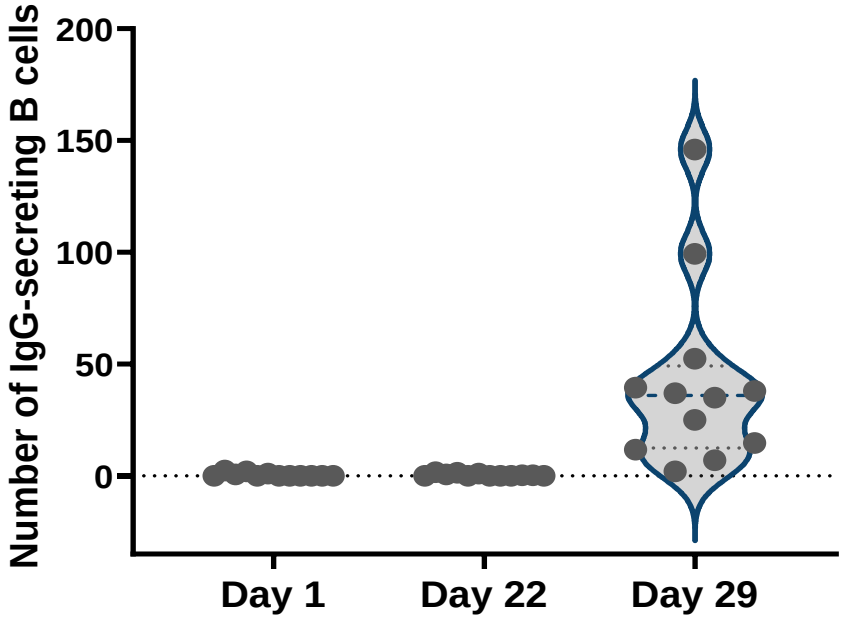
Functional Antibody Titers: Opsonization Titers After Vaccination With PNEUMOVAX 23



Azar A et al. in press

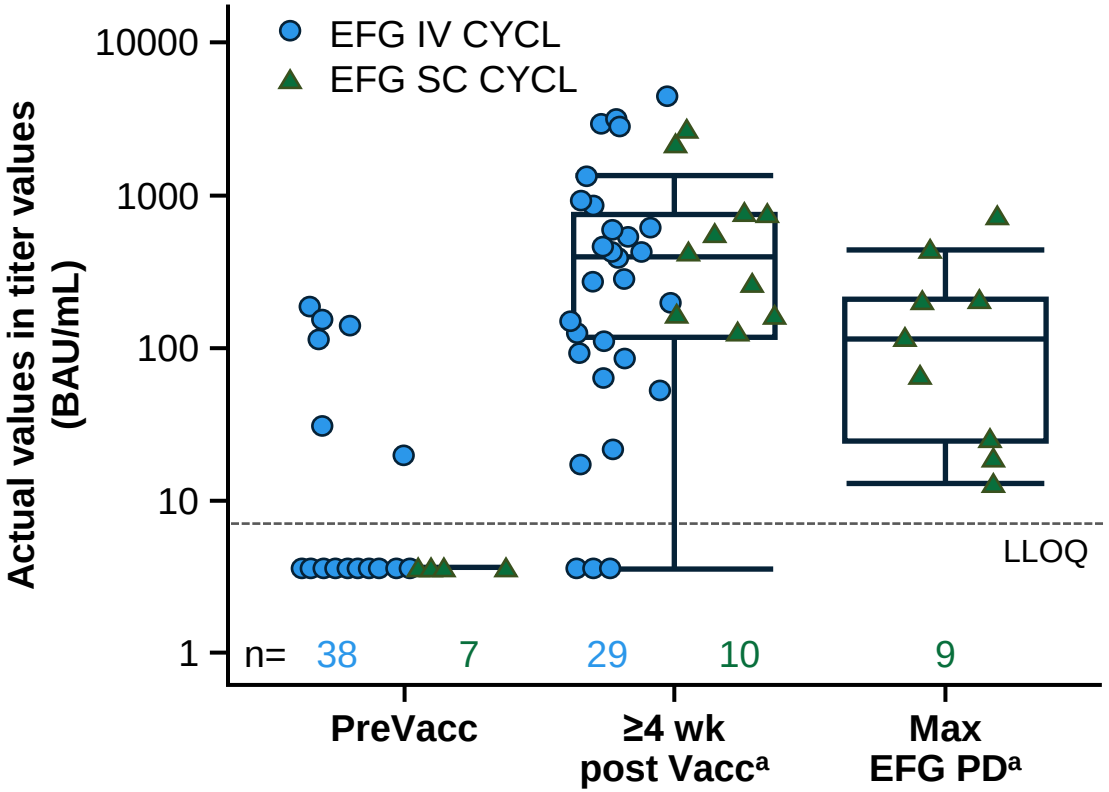
Antigen-Specific IgG-Secreting Plasma B-Cell Response at Baseline, Prevaccination, and 7 days After Vaccination

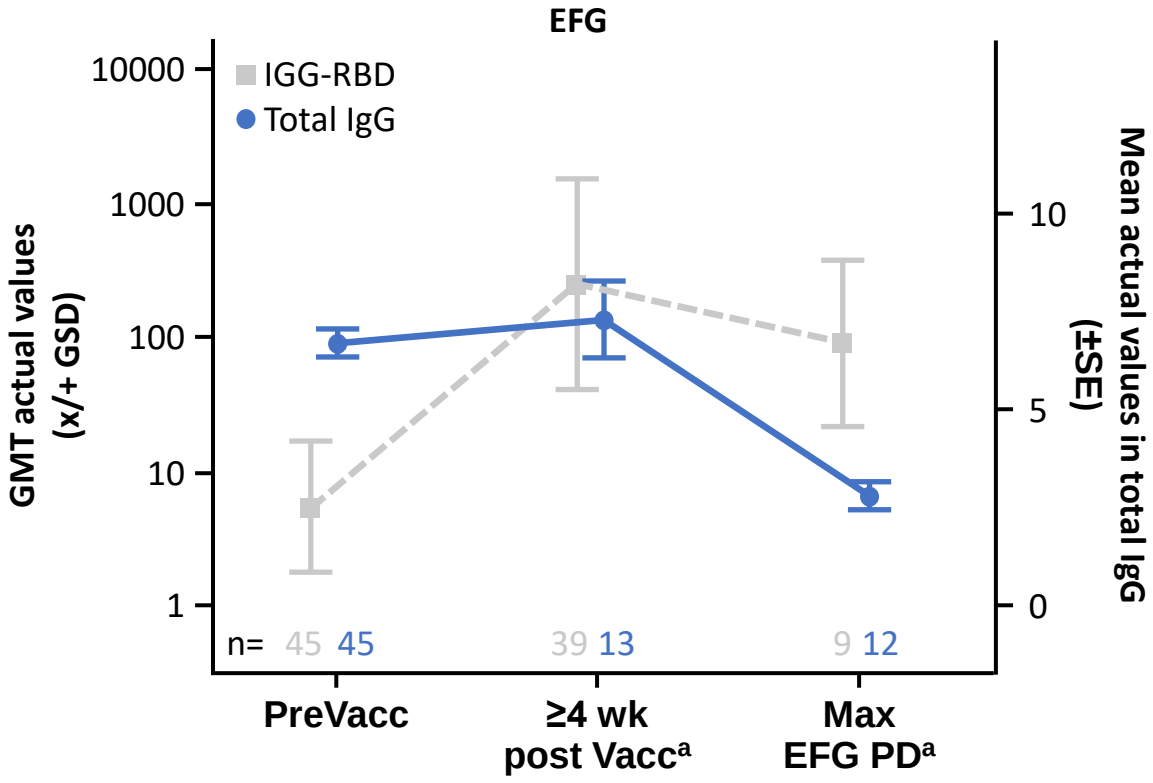




Azar A et al. in press

SARS-CoV-2-IgG After First Vaccination





Habib A, Azar A et al. AAN Abstract 2025

FcRn Antagonists

Approved:

- Myasthenia Gravis
- Chronic idiopathic demyelinating polyneuropathy (CIDP)

Investigational:

- Immune Thrombocytopenic purpura
- Thyroid eye disease
- Bullous pemphigoid
- Myositis
- Sjogren
- Lupus nephropathy

Evaluation of SHG

- Clarify if 1^{ry} or 2^{ry}
  - History of immunosuppressive medication use
  - Conditions associated with SHG
  - Prior IG levels
  - Protein – albumin ‘delta’

- Importance of screening for HG before immunosuppressive medications are initiated or when conditions known to cause SHG are diagnosed!

Society Guidelines for Screening & Monitoring of Immunoglobulins

Patient Group	Year	Society	Recommendation
ANCA vasculitis	2014	BSR BHPR	Serum IGs before each cycle of RTX
ANCA vasculitis	2016	EULAR ERA EUVAS	Serum IGs prior to each course of RTX, and in patients with recurrent infections
SLE	2018	BSR	Serum IGs at diagnosis and prior to starting drugs with the most risk of inducing hypogam (e.g. MMF, cyclophosphamide, RTX) Repeat IGs ~ 3-6 months later then annually
RA	2011	RCEC	Serum IgG prior to 1st dose and each RTX cycle Close monitoring of IgG and infections for patients at risk for Hypogam
RA	2011	BSR BHPR	Serum IGs prior to RTX, 4-6 months after infusions, and before any retreatment

BSR = British Society for Rheumatology; BHPR = British Health Professionals in Rheumatology; ERA = European Renal Association; EULAR = European League Against Rheumatism; EUVAS = European Vasculitis Society; RCEC = Rituximab Consensus Expert Committee

Evaluation of SHG

- Detailed history of recurrent, severe, unusual infections

- Recheck IgG to ensure low IgG is not transient; check IgA/IgM
- Specific titers to *Strep pneumoniae, Tetanus*
  - Vaccinate and obtain titers after 4-6 weeks
- Lymphocyte subsets, B-cell phenotyping

- Protein, albumin
- Urinalysis, urine protein:creatinine
- Stool alpha-1 antitrypsin clearance

Treatment of SHG

- Discontinue offending drug (if possible)
- Treat underlying condition (e.g. nephrotic syndrome)
- If above not possible:
  a) Heightened monitoring for clinical infections
  b) Antimicrobials
  c) Immunoglobulin replacement therapy (IgRT)

Immunoglobulin Replacement Therapy

- Complex decision due to lack of unified guidelines; shared decision-making with patient and multi-disciplinary team
- IgG level below which IgG-RT should be started prophylactically is unclear
- IVIG is only FDA-approved for SHG associated with B-cell CLL; SCIG not currently FDA-approved for SHG indications

Perez et al. J Allergy Clin Immunol. 2017;139:S1–46

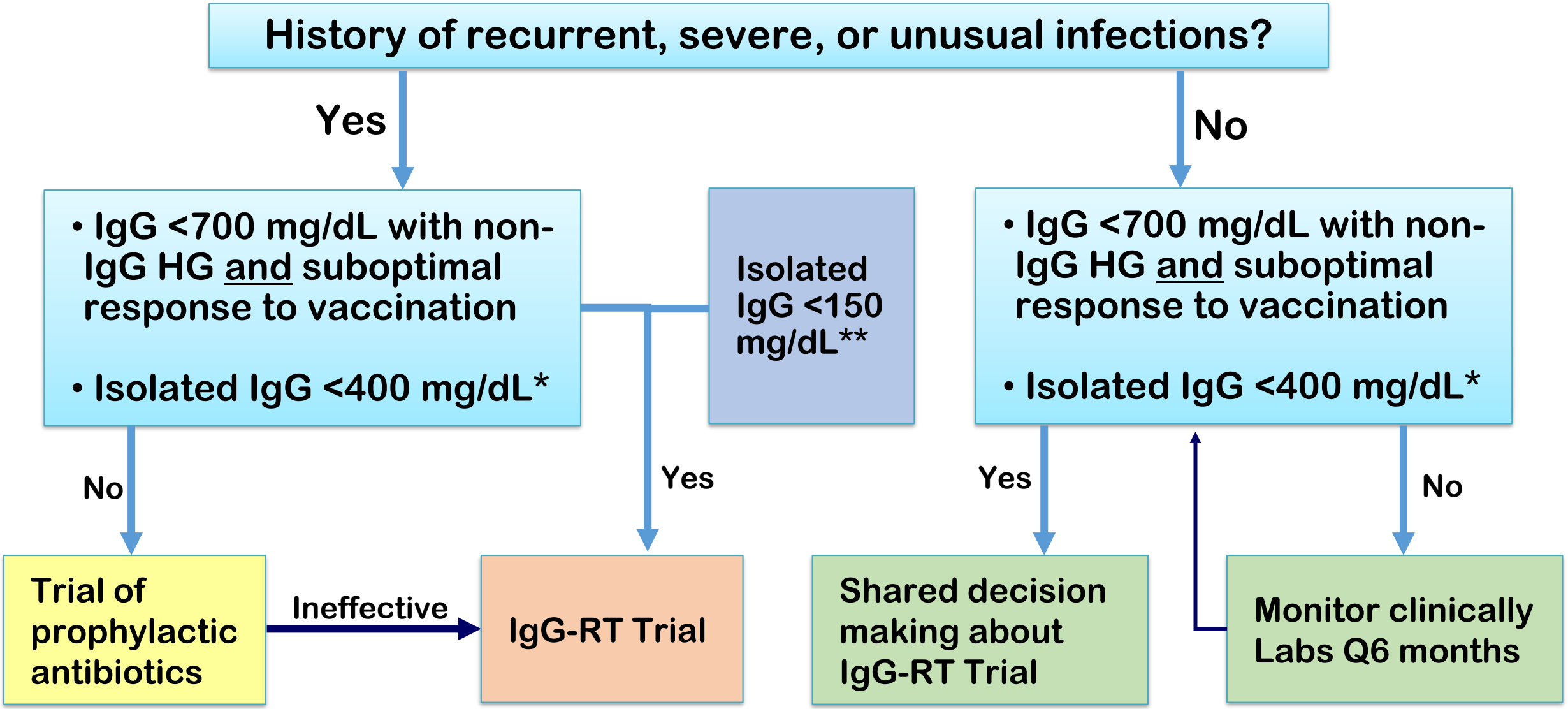
In Europe, IVIG approved for:

1) SHG (IgG < 400 mg/dL) or specific antibody failure (< 2-fold increase in antibody titers to pneumococcal polysaccharide and polypeptide antigen vaccines)

2) And severe or recurrent infections

3) And ineffective antimicrobial treatment

- European Medicines Agency. Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)



*Cut-off suggested in solid organ transplant and hematologic malignancy literature

**IgG <150 mg/dL warrants initiating IgG-RT without need for additional functional testing

Modified from: J Allergy Clin Immunol. 2022;149(5):1525-1560

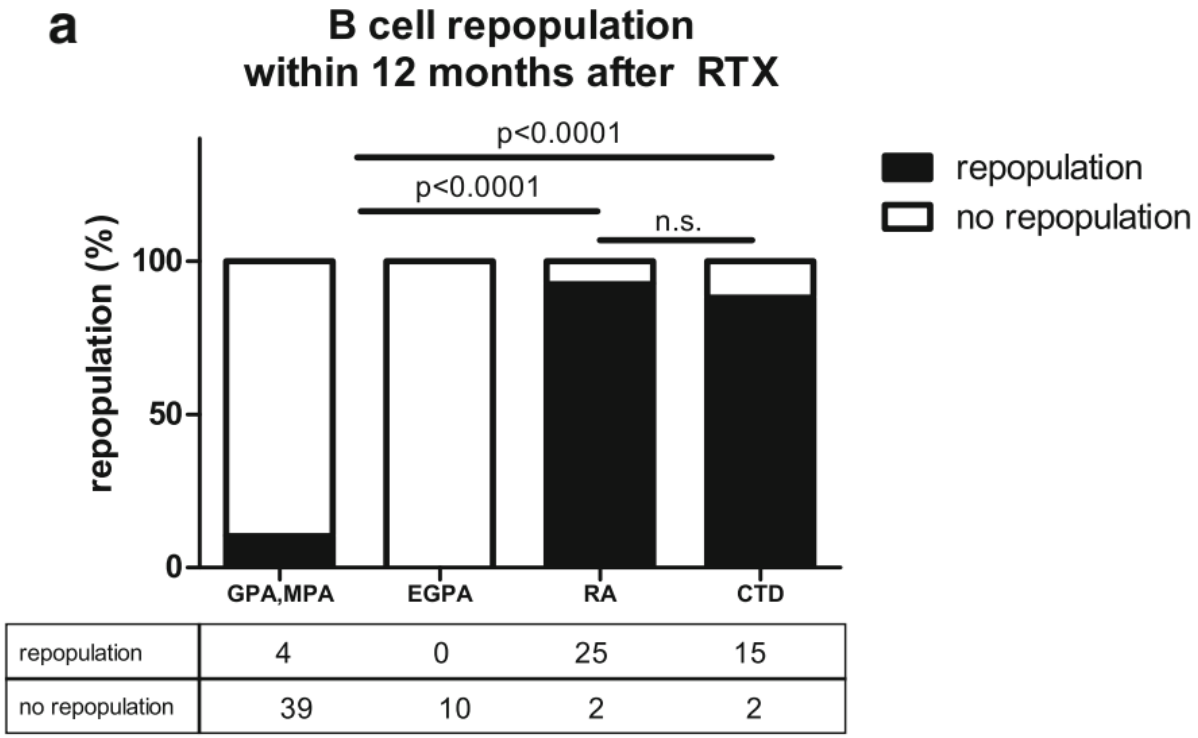
IgRT for SHG: Duration

- Periodic assessment needed, every 6-12 months
- Consider pausing IgG-RT if appropriate:
  - Immunosuppression discontinued (eg 9-12 mo after stopping BCTT)
  - SHG-associated condition treated
- Re-evaluate immune function 3-4 months after pausing IgRT

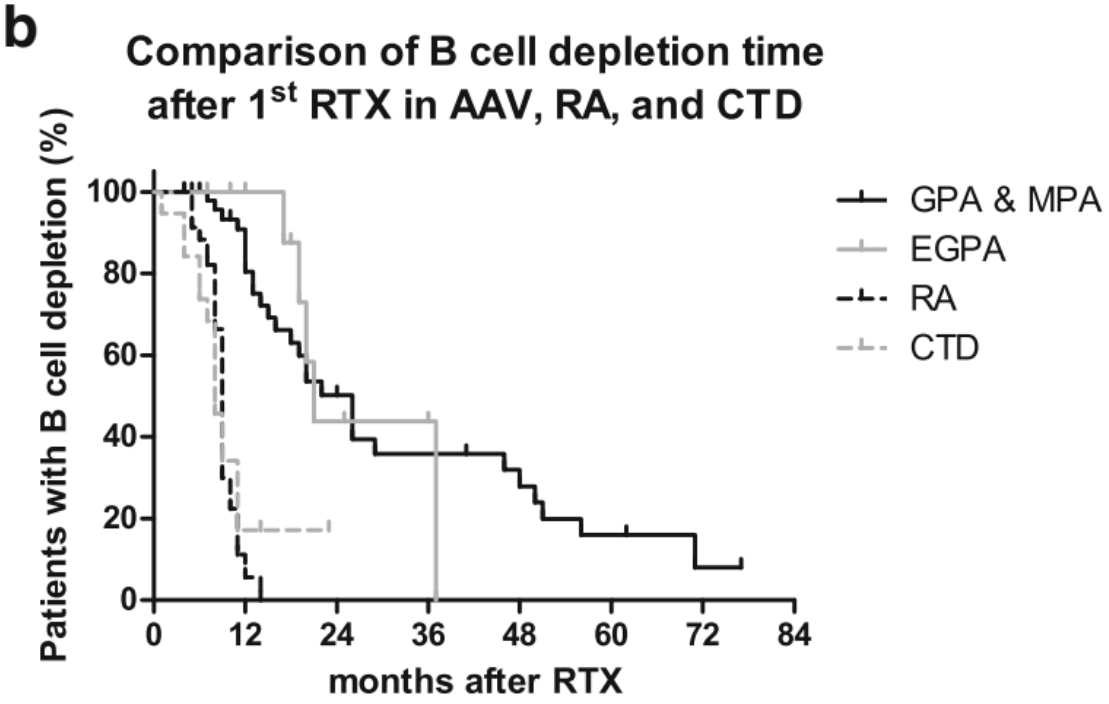
65 yo female with GPA

- Diagnosed with GPA maintained on IV Rituximab every 6 months for the past 3 years
- Recently hospitalized with pneumonia, and developed recurrent sinus infections
- Rituximab was held due to recurrent infections

B cell depletion: worse in Vasculitis



repopulation	4	0	25	15
no repopulation	39	10	2	2

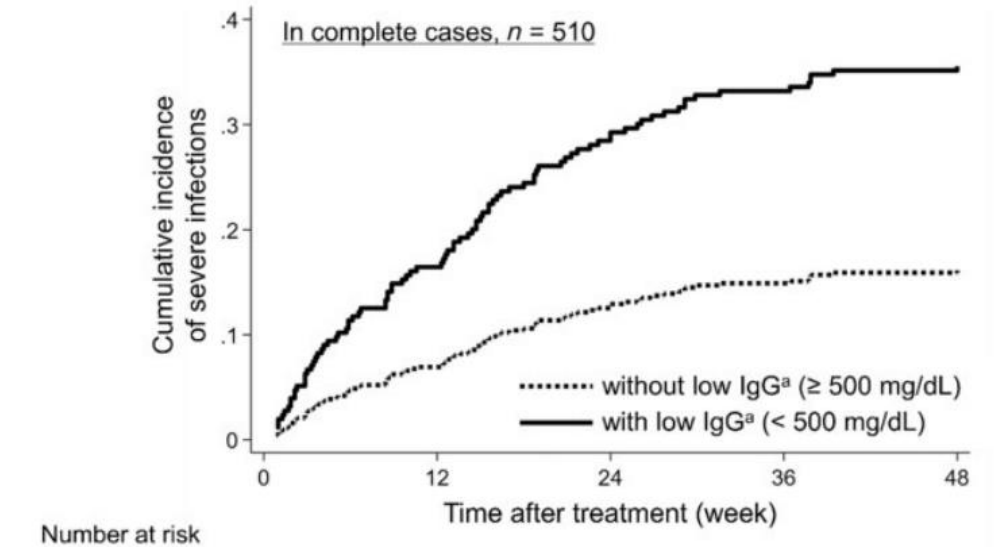


Thiel J et al.. Arthritis Res Ther 2017; **19:** 101.

Low IgG associated with severe infections up to 48 weeks after treatment initiation

657 AAV patients (Japan)
392 MPA; 139 GPA; 126 EGPA

IgG < 500 mg/dL after remission-induction treatment



Number at risk					
without low IgG[a] (≥ 500 mg/dL)	433	367	319	304	290
with low IgG[a] (< 500 mg/dL)	77	60	48	45	44

Figure 1. Incidence of severe infections with and without low IgG. The cumulative incidence function of severe infections was compared between patients with and without low IgG (<500 mg/dL) for complete cases ($n = 510$). [a]Low IgG: minimum serum IgG less than 500 mg/dL up to 24 weeks after treatment

Omura S et al. Rheumatology (Oxford). 2023 Mar 24:kead138

Do benefits of SCIG for secondary hypogam in AAV extend beyond infection prevention?

Table 1 | Patient characteristics, immunosuppression regimen, details of infections, and s.c. Ig administration

ID	Age (yr)	Sex	Race	ANCA type	Induction treatment	Maintenance treatment		Number and type of infections		SIgG (mg/dl)		Number of AAV relapses		Follow-up from last RTX use (mo)
						Before SCIG	After SCIG	Before SCIG	After SCIG	Before SCIG	After SCIG	Before SCIG	After SCIG	
1	68	F	C	PR3	MTX+RTX+GC	RTX every 6 mo and then every 4 mo	RTX stopped P 7.5 mg	5 Sinusitis, pneumonia, urosepsis	1 Dental	300	987	2	None	33
2	79	F	C	NEG	RTX+GC	None	None	4 UTIs	None	367	879	None	None	29
3	69	F	C	PR3	PLEX, CYC, RTX+GC	AZA, P	P 3 mg	5 Pulmonary candidiasis, PCP, influenza, C. diff	None	209	953	None	None	128
4	16	M	C	PR3	RTX, GC	AZA, LEF, P, RTX 1000 mg every 6 mo	RTX dose and duration decreased initially and then stopped	None	None	474	1202	6	None	53
5	50	M	C	NEG	MTX, CYC, RTX+GC	RTX every 6 mo	RTX duration decreased initially and then stopped	3 Streptococcus pharyngitis	None	289	850	1	None	47

ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; AZA, azathioprine; C, Caucasian; C. Diff, clostridioides difficile; CYC, cyclophosphamide; F, female; GC, glucocorticosteroids; LEF, leflunomide; M, male; MTX, methotrexate; NEG, negative; P, prednisone, PCP, pneumocystis pneumonia; PLEX, plasma exchange; PR3, proteinase-3; RTX, rituximab; SCIG, s.c. Igs; SIgG, serum IgG; UTIs, urinary tract infections; Y, yes.

After SCIG, rituximab was tapered or discontinued in 3/3 patients
All patients remained in remission, 2 on low-dose prednisone, none on Rituximab

Immunomodulatory effect of SCIG in AAV during maintenance phase?

Churilla, Azar et al. Kidney International (2022) 102, 440–447C

Take Home Points

- SHG is more frequently diagnosed and recognized by medical specialists especially with the increasing use of immunomodulatory agents, and is associated with increased infection and mortality risk in some patient populations

- Clinical Immunologist role is instrumental in its diagnosis and management

- Obtain baseline IG levels at time of diagnosis of conditions associated with SHG, and prior to the initiation of immunosuppressive medications especially those targeting B cells

- Assess FUNCTION in addition to numbers: specific IgG response to vaccines

- IgRT is individualized, to be considered in patients with more pronounced hypogam, reduced vaccine responses, and/or recurrent or severe infections


Thank you!