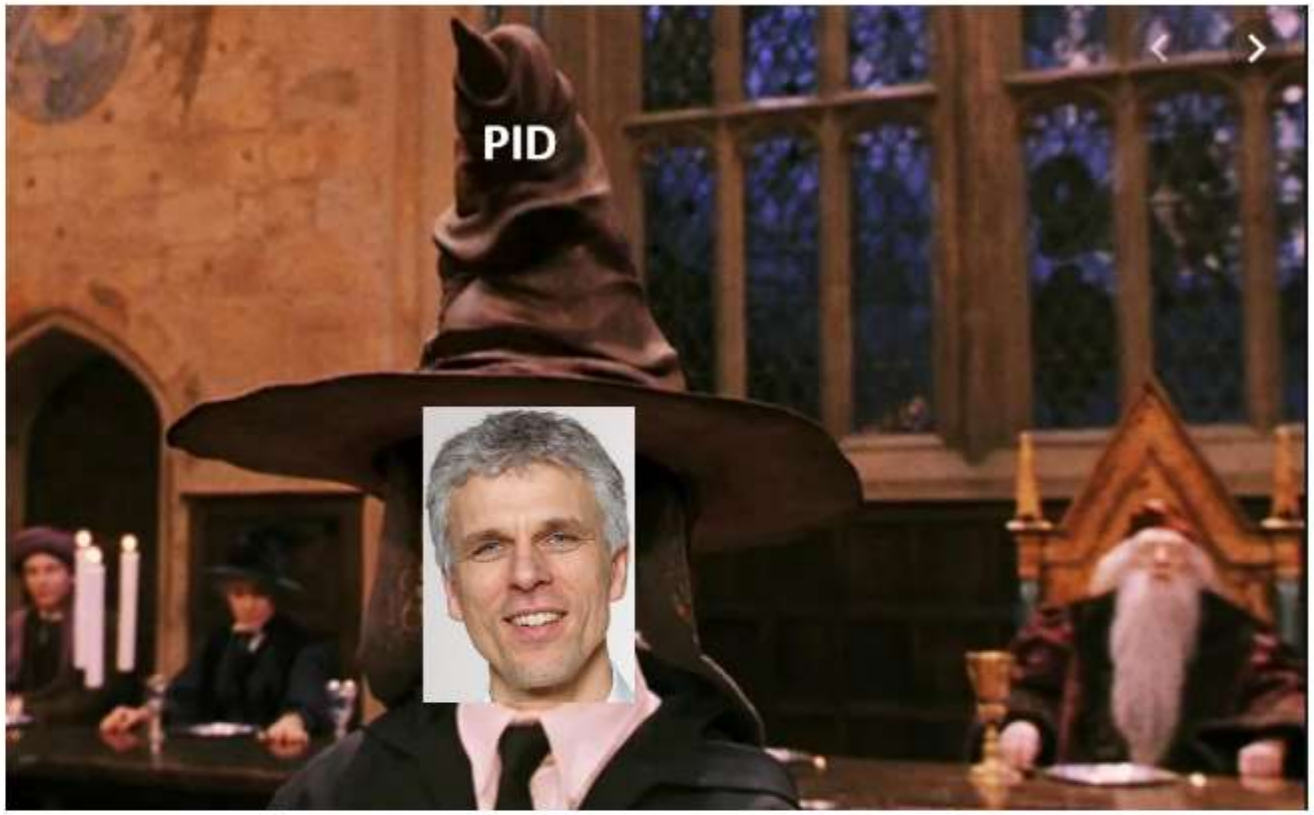
Secondary Antibody Deficiencies

Stephen Jolles
Consultant Clinical Immunologist
& Honorary Professor
Immunodeficiency Centre for Wales

Contents

- PID and SID – similarities and differences
- Where does SAD arise
- B cell targeting therapy
- New Causes but also new opportunities..
- Risk factors for SAD
- Treatments
- Conclusions

PID Community



Complex CVID

Infection only

AI Cytopenias

Lung

Gut

Liver

How differently do we need to think about SID

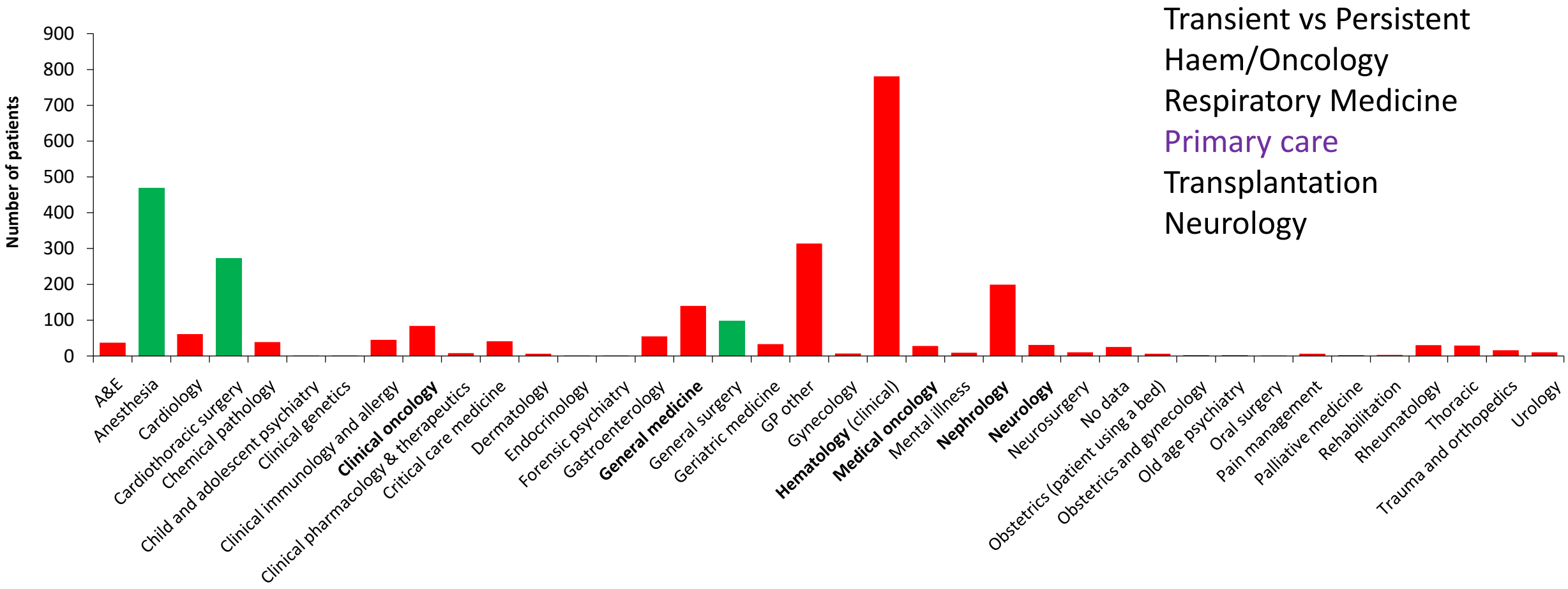
Why is SAD important

- Estimated to be 20 fold greater than PID
- Underdiagnosed
- Undertreated
- Increasing numbers of patients
  - New therapies
  - Maintenance therapy
  - Longer survival

Complexity of dimensions within SID – what do we know?

- Information about the disease – type, stage, biomarkers (50% CLL infection related deaths)
- Information about the timing of interventions
- Information about the nature of planned interventions
- Information about the individual drugs within interventions – pathway, defect, infection spectrum
- Information about the number of lines of therapy
- Information about the duration (maintenance) of interventions
- Associated comorbidities (older age)
- Results of a broad immunological assessment
- More known knowns and known unknowns than PID?

Where does it all come from?



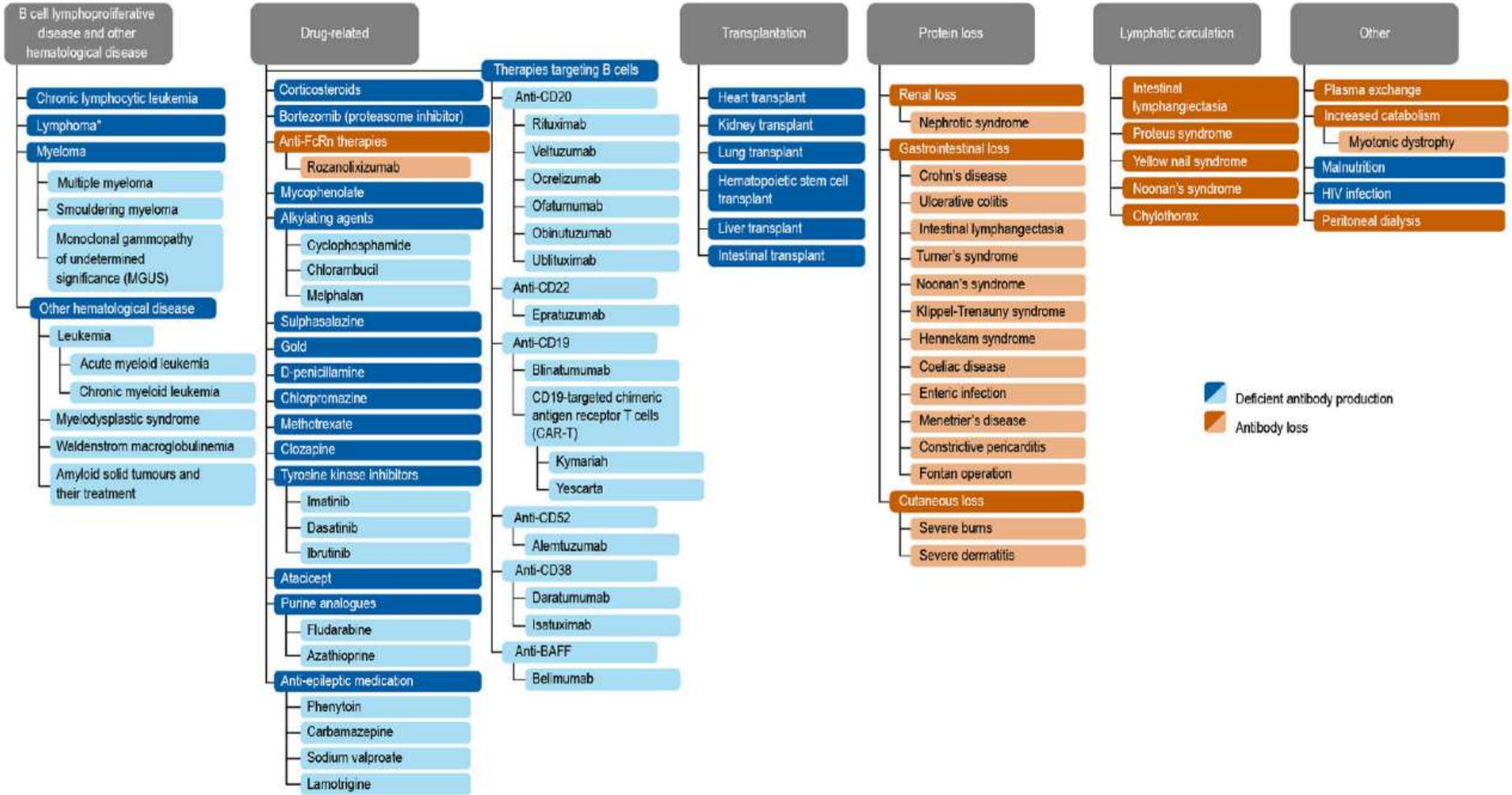
Audit of over 300,000 CG levels over a 12 month period, supported by a grant from Shire Plc
CG, calculated globulin; GP, general practitioner; SAD, secondary antibody deficiency

Look also to emerging area's - Neurology

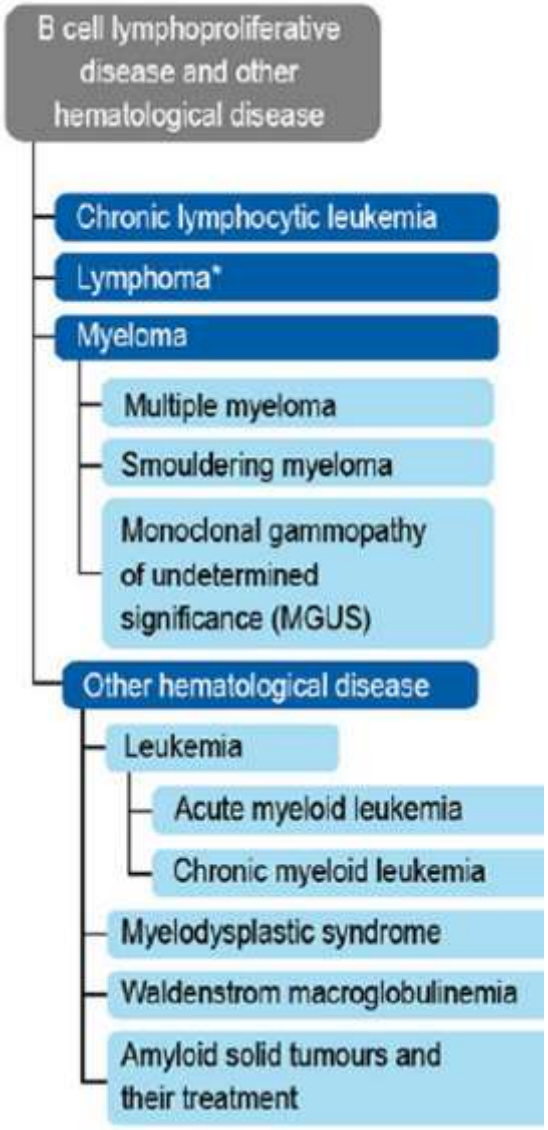
- B cell targeted therapies are believed to show huge promise in inflammatory CNS disease
- In contrast to most other disciplines B cell ablation would be regarded as maintenance rather than induction therapy in neurology from the start

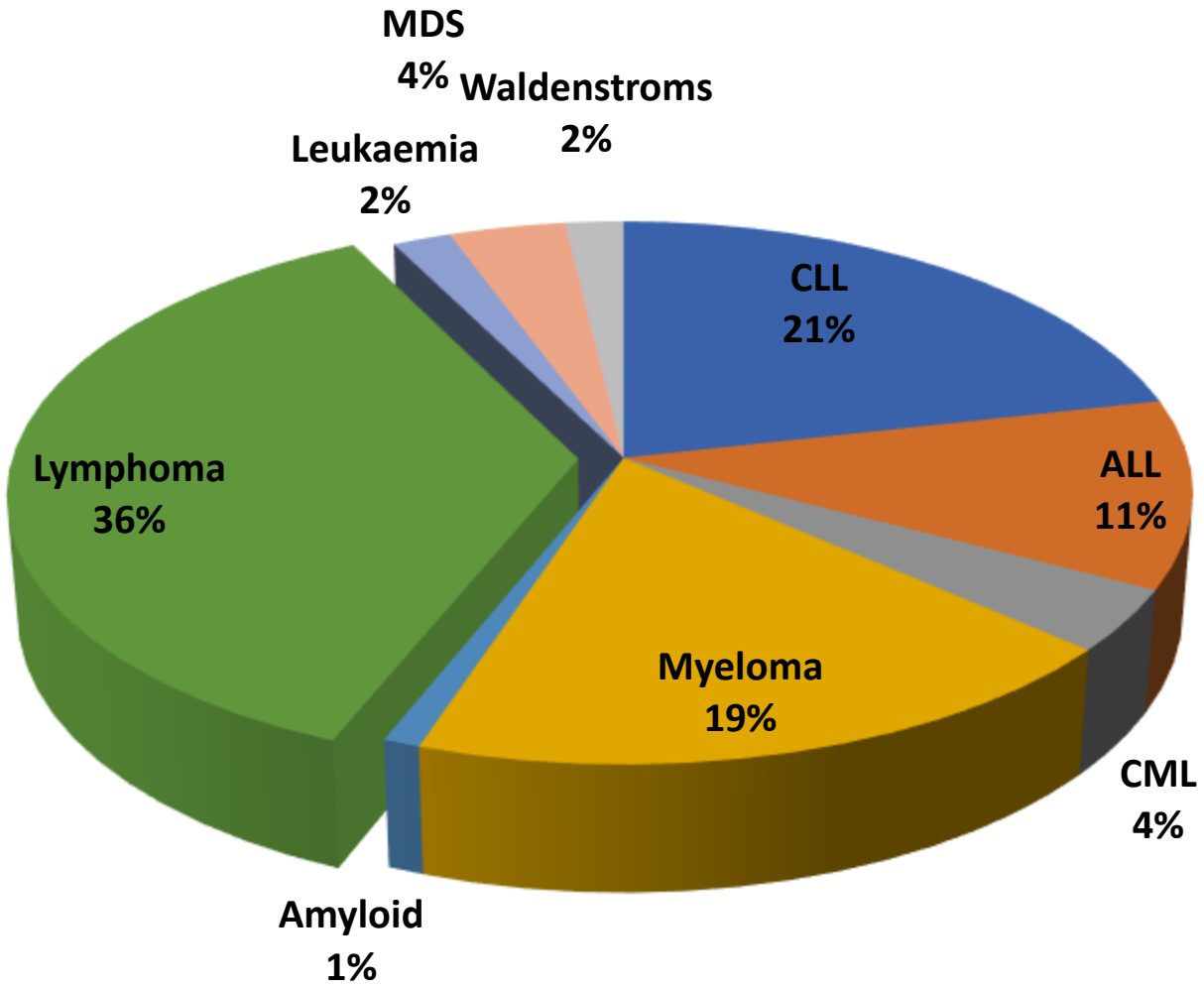
Causes of SAD

- Haematological Disease
- Drugs
- Transplantation
- Protein Loss
- Other

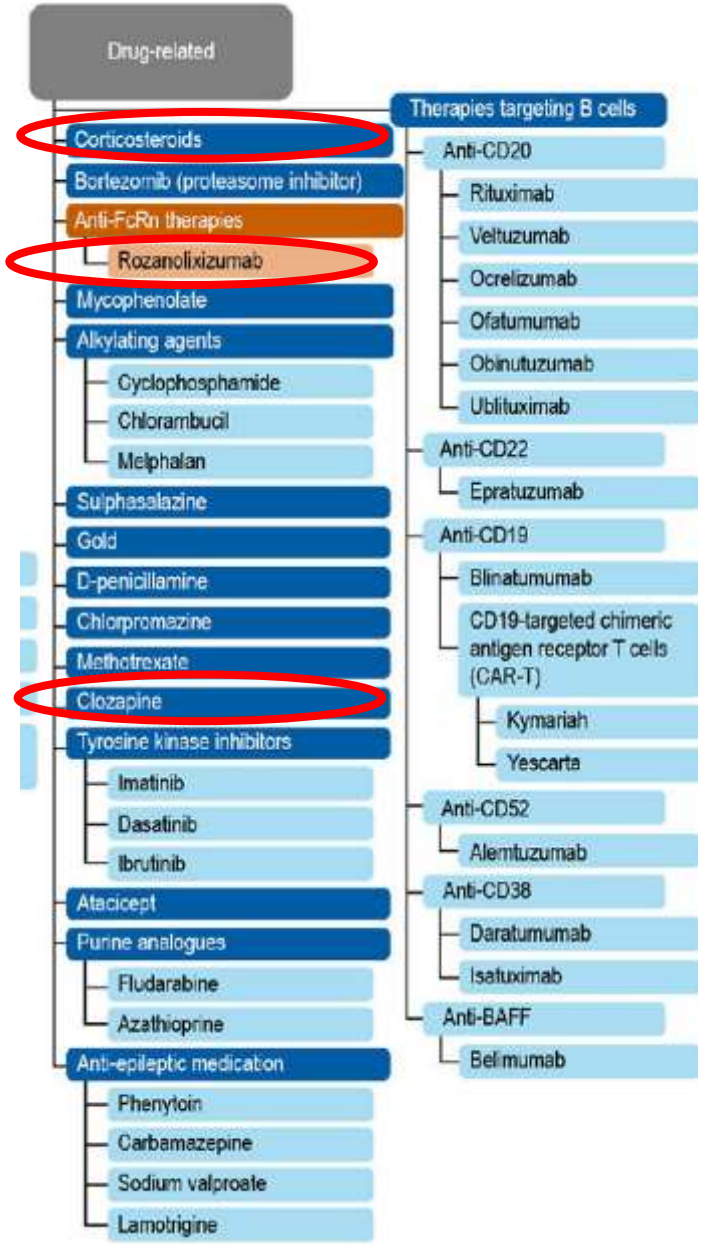

B cell lymphoproliferative disease and other hematological disease
Chronic lymphocytic leukemia
Lymphoma*
Myeloma
Multiple myeloma
Smouldering myeloma
Monoclonal gammopathy of undetermined significance (MGUS)
Other hematological disease
Leukemia
Acute myeloid leukemia
Chronic myeloid leukemia
Myelodysplastic syndrome
Waldenstrom macroglobulinemia
Amyloid solid tumours and their treatment
Drug-related
Corticosteroids
Bortezomib (proteasome inhibitor)
Anti-FcRn therapies
Rozanolixizumab
Mycophenolate
Alkylating agents
Cyclophosphamide
Chlorambucil
Melphalan
Sulphasalazine
Gold
D-penicillamine
Chlorpromazine
Methotrexate
Clozapine
Tyrosine kinase inhibitors
Imatinib
Dasatinib
Ibrutinib
Atacicept
Purine analogues
Fludarabine
Azathioprine
Anti-epileptic medication
Phenytoin
Carbamazepine
Sodium valproate
Lamotrigine
Therapies targeting B cells
Anti-CD20
Rituximab
Veltuzumab
Ocrelizumab
Ofatumumab
Obinutuzumab
Ublituximab
Anti-CD22
Epratuzumab
Anti-CD19
Blinatumumab
CD19-targeted chimeric antigen receptor T cells (CAR-T)
Kymariah
Yescarta
Anti-CD52
Alemtuzumab
Anti-CD38
Daratumumab
Isatuximab
Anti-BAFF
Belimumab
Transplantation
Heart transplant
Kidney transplant
Lung transplant
Hematopoietic stem cell transplant
Liver transplant
Intestinal transplant
Protein loss
Renal loss
Nephrotic syndrome
Gastrointestinal loss
Crohn's disease
Ulcerative colitis
Intestinal lymphangectasia
Turner's syndrome
Noonan's syndrome
Klippel-Trenauny syndrome
Hennekam syndrome
Coeliac disease
Enteric infection
Menetrier's disease
Constrictive pericarditis
Fontan operation
Cutaneous loss
Severe burns
Severe dermatitis
Lymphatic circulation
Intestinal lymphangiectasia
Proteus syndrome
Yellow nail syndrome
Noonan's syndrome
Chylothorax
Other
Plasma exchange
Increased catabolism
Myotonic dystrophy
Malnutrition
HIV infection
Peritoneal dialysis
Deficient antibody production
Antibody loss

Haematological Causes (Frontiers in Immunology Patel S et al 2019, CEI Jolles S 2014)





Drug induced SAD – some examples (Frontiers in Immunology Patel S et al 2019)



Steroids and SAD

J Clin Immunol (2016) 36:408–412
DOI 10.1007/s10875-016-0264-7

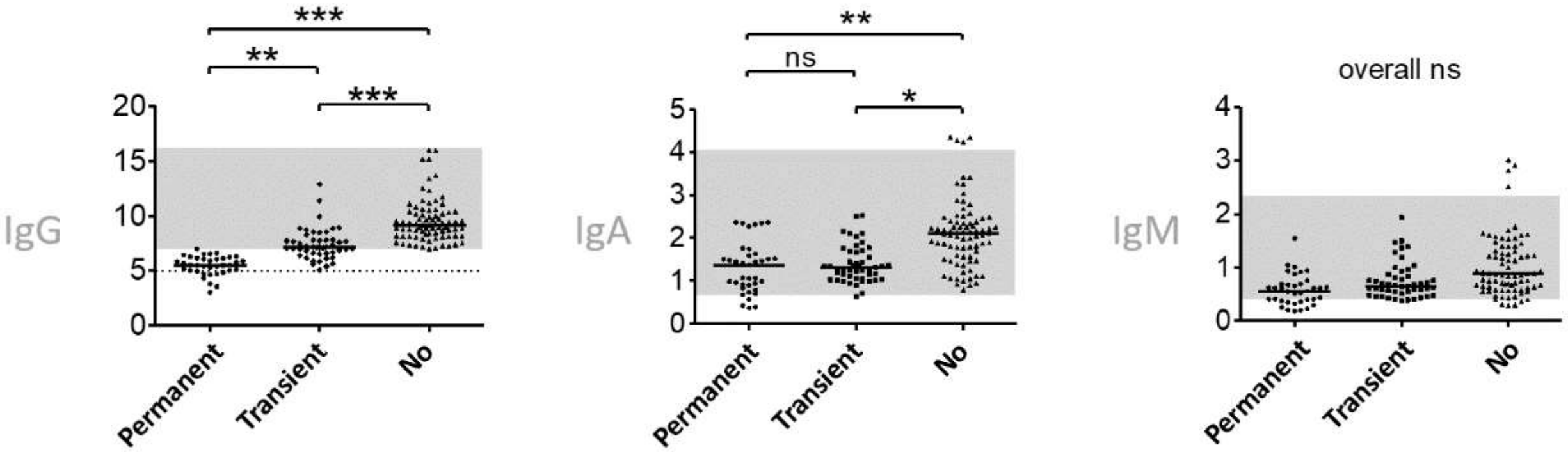
ORIGINAL ARTICLE

Secondary Antibody Deficiency in Glucocorticoid Therapy Clearly Differs from Primary Antibody Deficiency

Clemens Wirsum[1] · Cornelia Glaser[2] · Sylvia Gutenberger[1] · Baerbel Keller[1] · Susanne Unger[1] · Reinhard E. Voll[2] · Werner Vach[3] · Thomas Ness[4] · Klaus Warnatz[1]

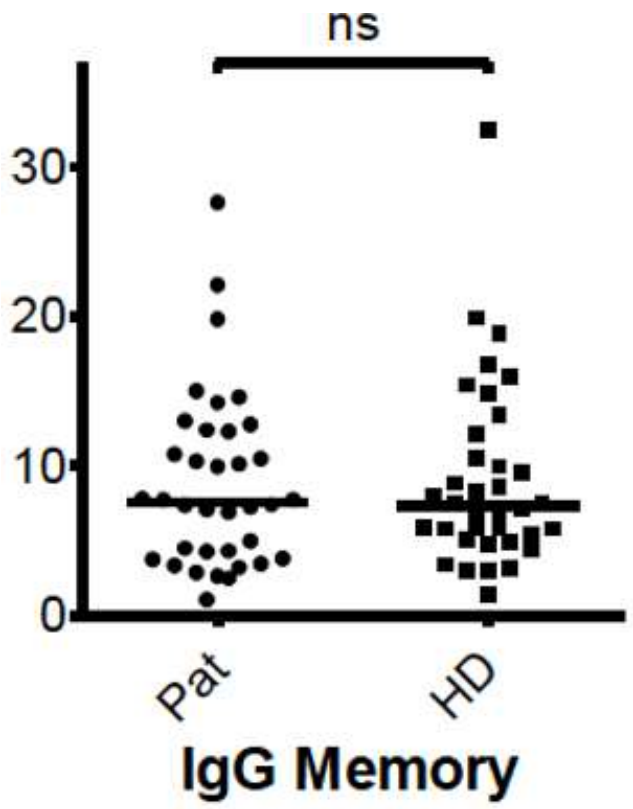
- 36 patients with PMR and GCA – steroids
- 21 hypogamma, with 52% of these having reductions in IgG alone
- Reduced circulating transitional ($CD19^{+}CD27^{-}IgM^{hi}CD38^{hi}$) and naive ($CD19^{+}CD27^{-}IgM^{+}CD38^{+}$) B cells
- IgG, IgA and IgM memory B cells ($CD19^{+}CD27^{+}IgG^{+}$) preserved
- CD4 memory and regulatory T cells reduced
- Look for isolated low IgG, preserved IgA and preserved CSMB in steroid induced hypogamma
- Risk increases with more than 1 year of >12.5mg/d

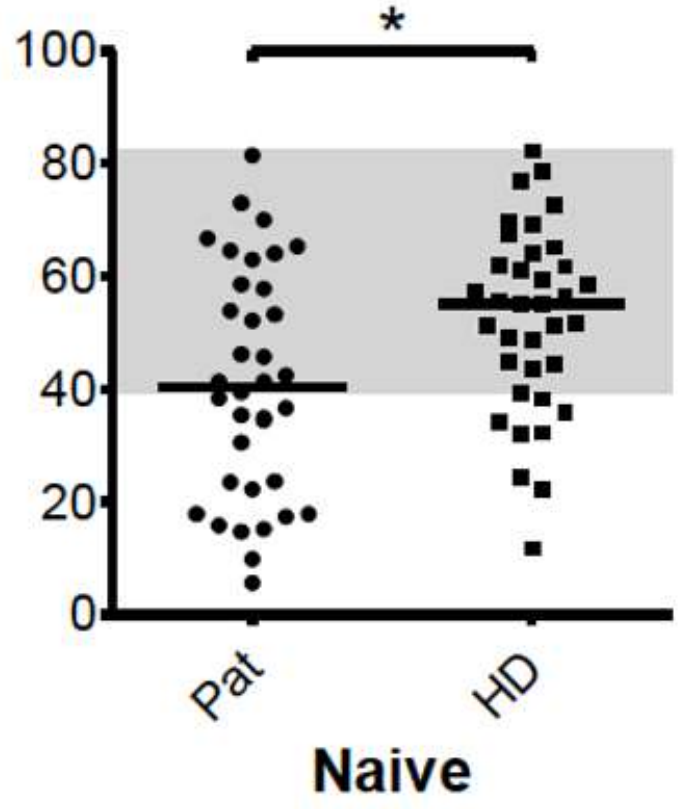
Steroids and SAD – Immunoglobulins (cf Rituximab)



Wirsum et al. J Clin Immunol 2016 36(4):406–12.

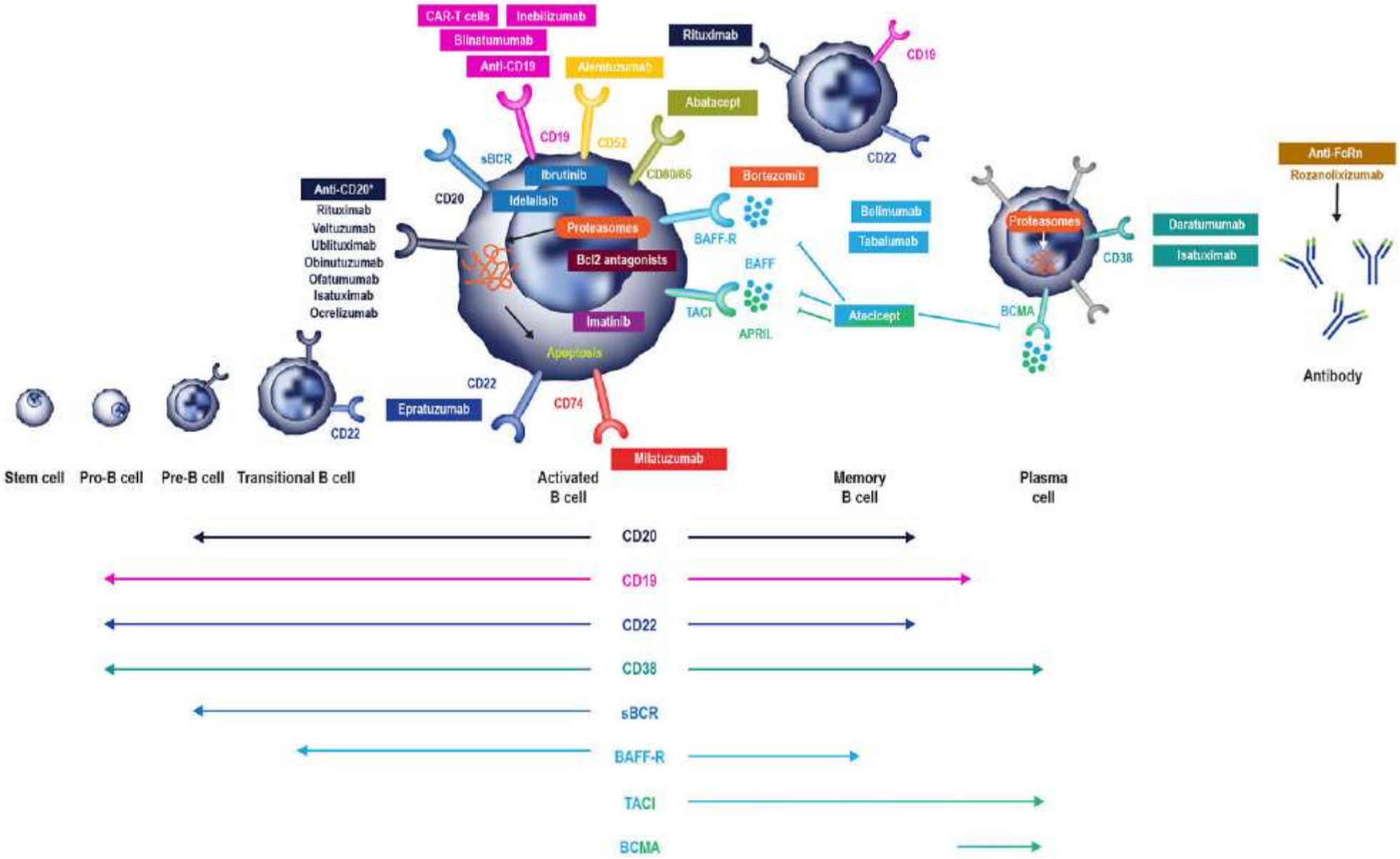
Steroids and SAD – B cells





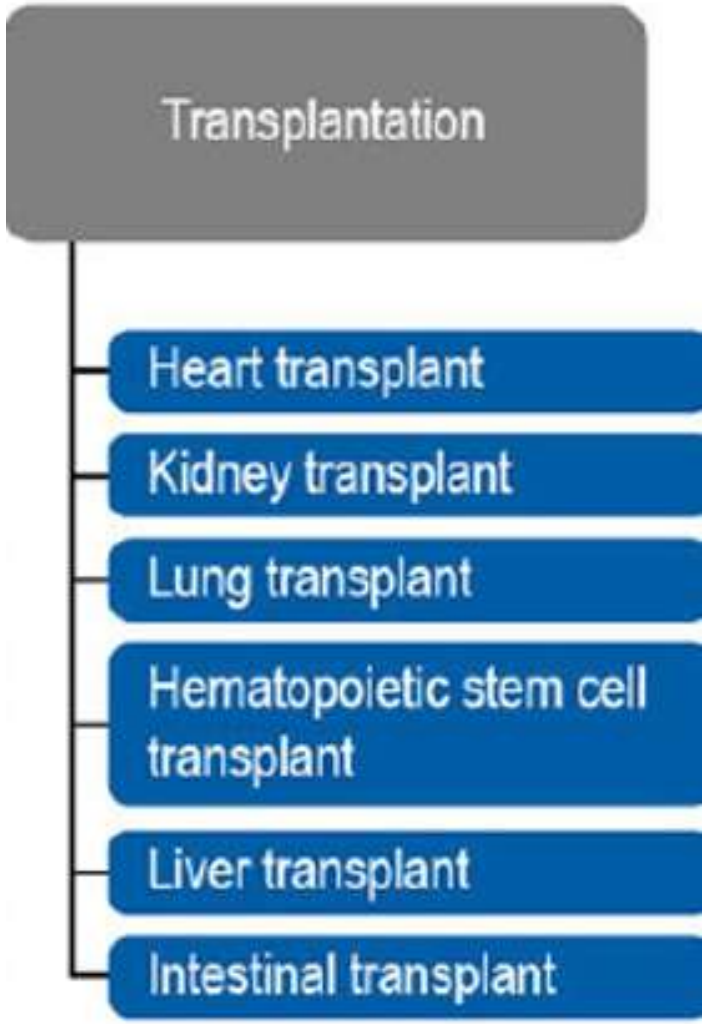
Wirsum et al. J Clin Immunol 2016 36(4):406–12.

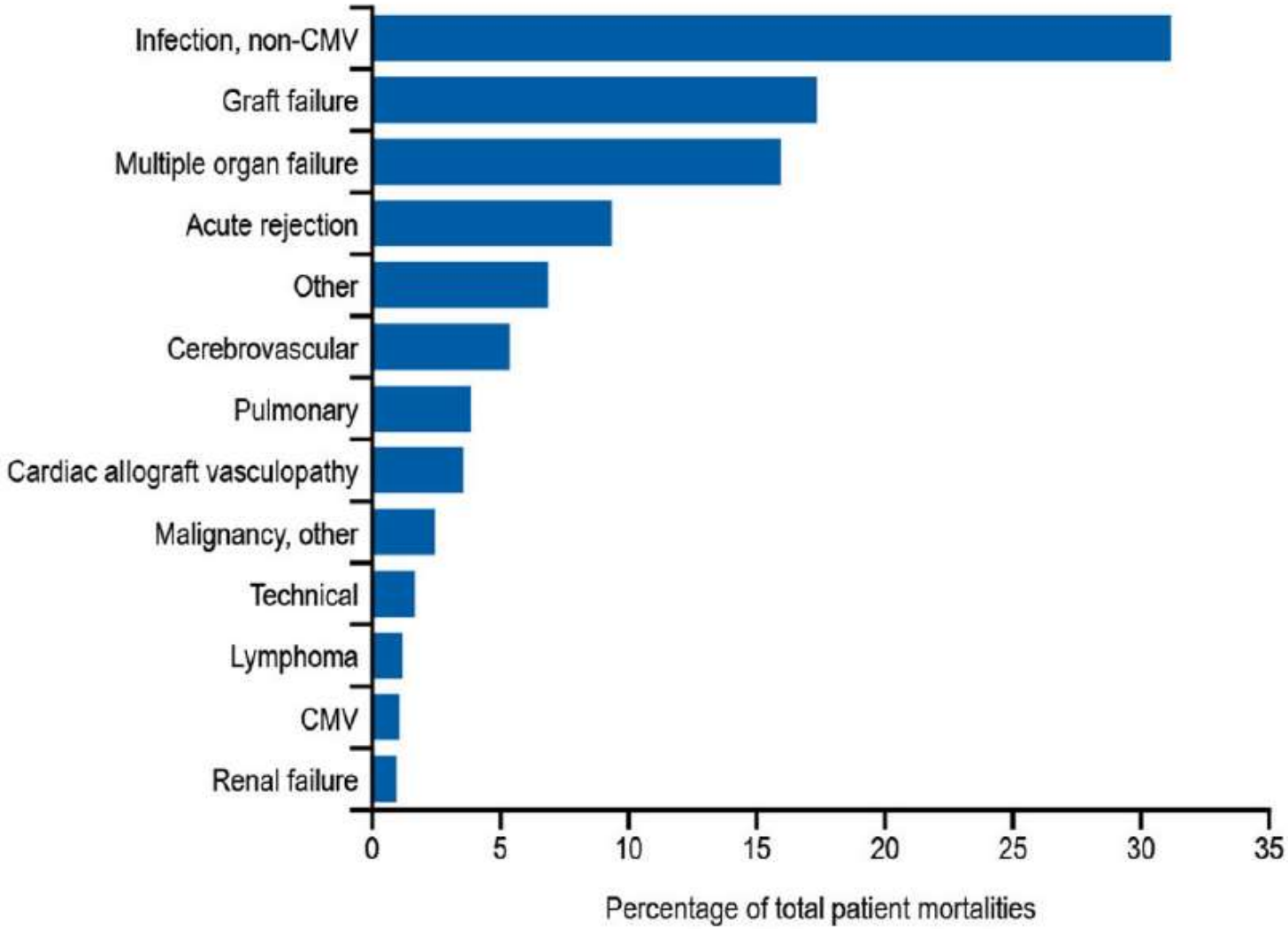
B cell Targeting



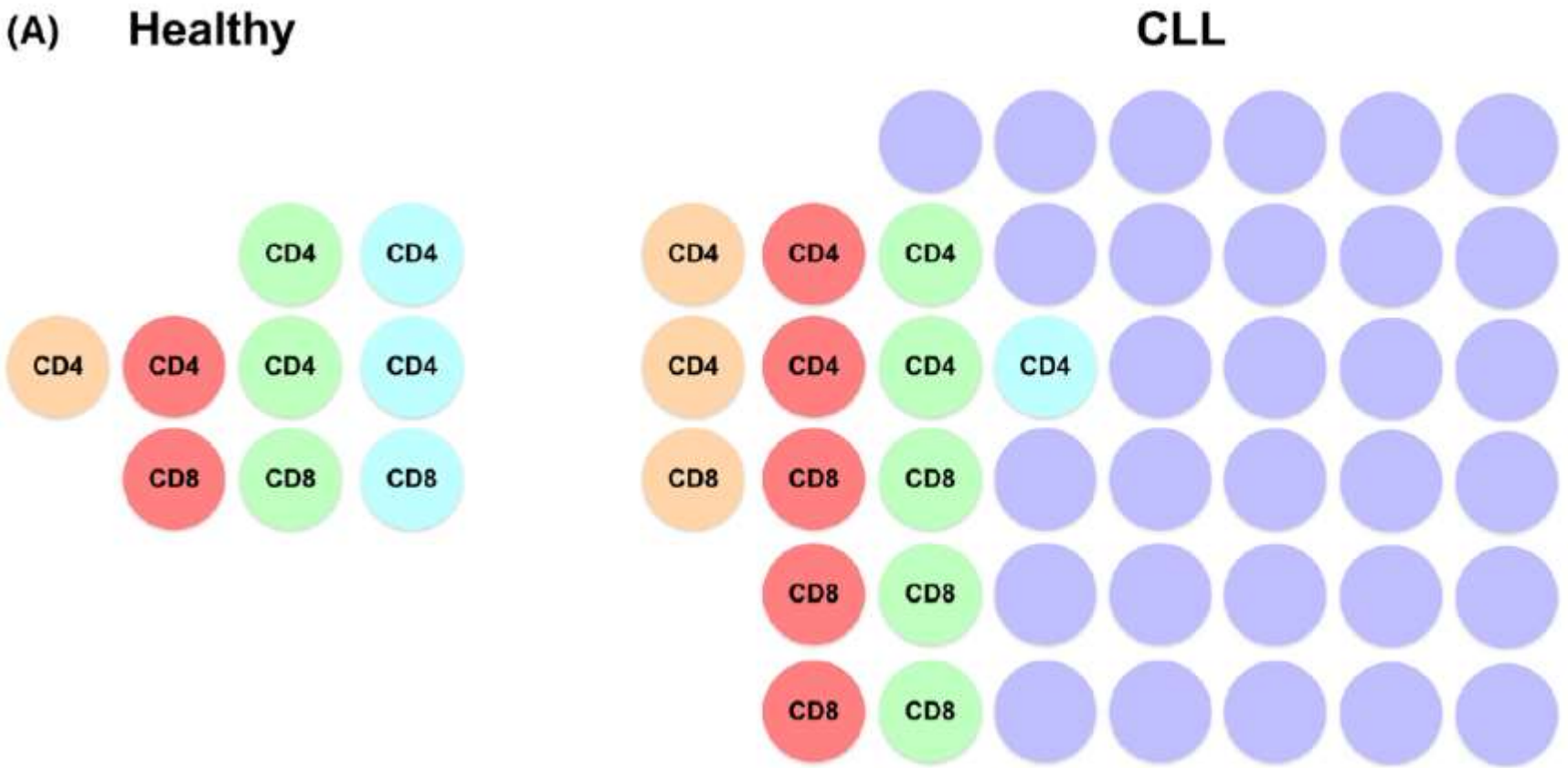
The Expanding Field of Secondary Antibody Deficiency: Causes, Diagnosis, and Management. Patel SY et al. Front Immunol. 2019 Feb 8;10:33.

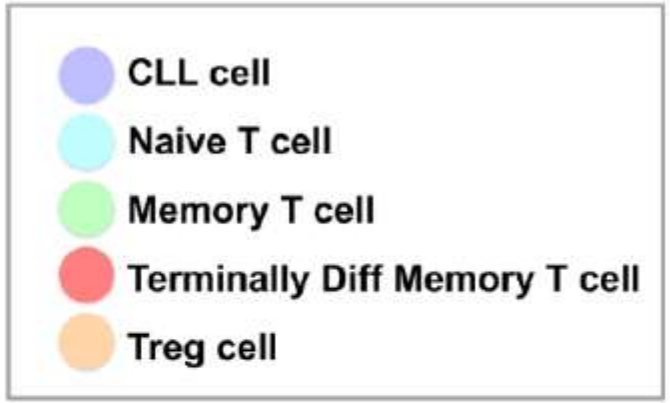
Transplantation





SAD + T cells = CID in CLL (also therapy eg FCR)





Note often overwhelming numbers of abnormal CLL cells compared to remaining normal T and B cells
Cf Ig in MM

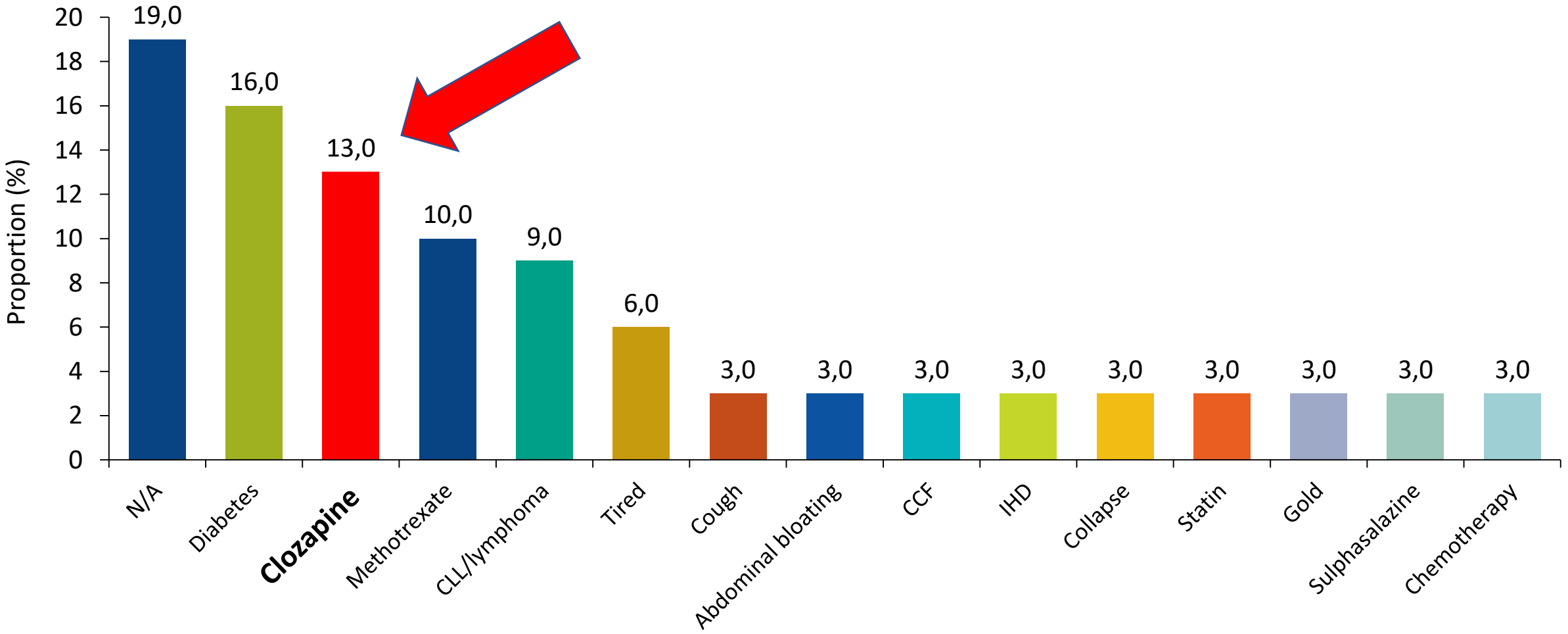
Chronic Lymphocytic Leukaemia: The role of T cells in a B cell disease. BJH 2019; Man S. Henley P.

CART – ‘on target, off tumour toxicity’

- New targets – CD22, CD30 - Hodgkins lymphoma, BCMA B cell maturation antigen – MM
- Combined with checkpoint inhibitors, ibrutinib – to minimize escape
- Very high levels of B cell ablation – ‘living drug’
- Durable responses to lymphoma may not require persistent CART allowing the potential of B cell recovery (cf PID HSCT)
- Wide range of hypogamma reported (children vs adults)
- Infections bacterial, viral, fungal and increased with severity of CRS
- Variable plasma cell repertoire before starting CART (median 4 lines of Rx inc 38% HSCT)
- B cell numbers should not be the only marker wrt IgRT

Hill JA Blood Reviews 2019

An odd finding…

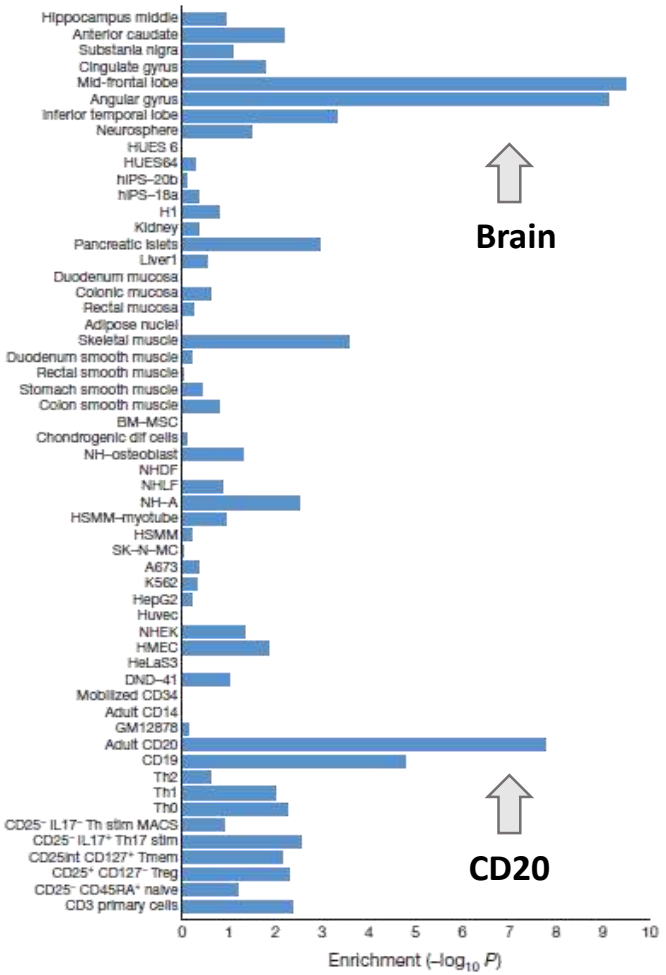


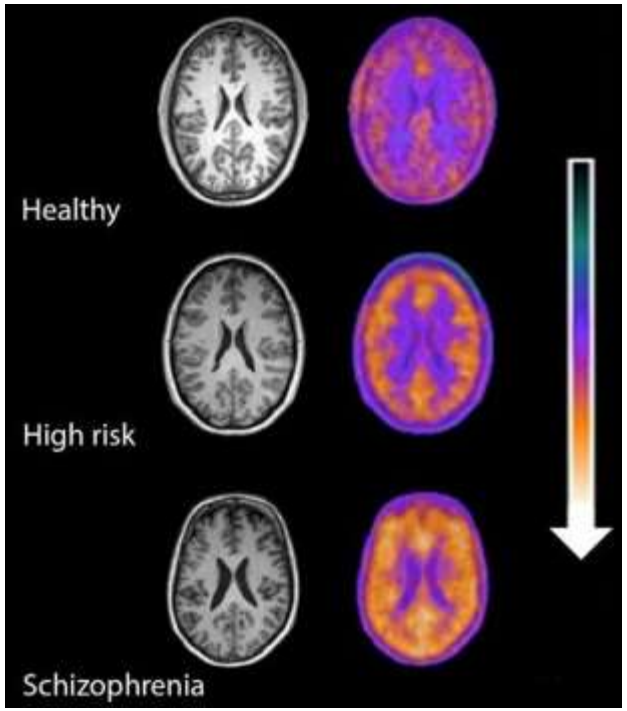
CCF, congestive cardiac failure; CCL, chronic lymphocytic leukemia; IHD, ischemic heart disease; N/A, not applicable

Jolles, S et al. Clin Exp Immunol. 2014;177(3): 671-8

Schizophrenia

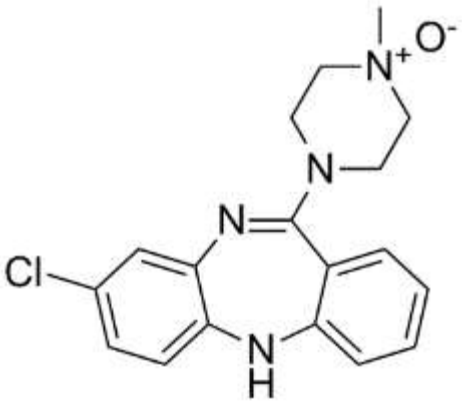
- Schizophrenia affects 1% of the population
- 30% is treatment resistant[1]
- Enduring debilitating psychiatric symptoms
- Life expectancy reduced by 10–20 years
- 80–90% unemployment
- 5% of patients with schizophrenia die from suicide
- Costs in England alone GBP 11.8 billion/year





GBP, British Pounds Stirling. 1. Ponsford M et al. *Br J Psychiatry* 2018 [ePub] doi: 10.1192/bjp.2018.152; 2. London School of Economics. 2012. Available from: http://www.lse.ac.uk/LSEHealthAndSocialCare/pdf/LSE-economic-report-FINAL-12-Nov.pdf [accessed September 2019]

Clozapine



- A di-benzodiazepine and atypical antipsychotic discovered in 1958[1]
- Gold standard therapy for treatment resistant schizophrenia (TRS)[1,2]
- On WHO list of Essential Medicines[3]
- Carefully monitored to mitigate the risk of agranulocytosis – weekly to monthly blood tests (0.8% cumulative risk)[4]
- Hypogammaglobulinemia not described in the BNF[5]
- 8 clozapine clinics in our Health Board

BNF, British National Formulary; WHO, The World Health Organization. 1. Crilly J. *Hist Psychiatry* 2007; 18(1): 39–60; 2. Taylor DM *CNS Drugs* 2017; 31(3): 177–80; 3. WHO. 2017. Available from: http://apps.who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf?ua=1 [accessed Oct 2018]; 4. Legge SE et al. *Mol Psychiatry* 2018; 23(1): 162–3; 5. BNF. 2018. Available from: https://bnf.nice.org.uk/drug/clozapine.html [Accessed Oct 2018]

Psychosomatics. 2017 Mar - Apr;58(2):164-172. doi: 10.1016/j.psym.2016.11.013. Epub 2016 Nov 18.

Characterization of Admission Types in Medically Hospitalized Patients Prescribed Clozapine.

Leung JG[1], Hasassri ME[2], Barreto JN[3], Nelson S[3], Morgan RJ 3rd[4].

RESULTS:

- Overall, 104 patients, representing 248 hospitalizations, were admitted to a medical unit during the study period
- The predominant admission types were for the management of either pulmonary (32.2%) or gastrointestinal (19.8%) illnesses
- The most common pulmonary diagnosis was pneumonia, accounting for 58% of pulmonary admissions

Acta Psychiatr Scand. 2018 Jan;137(1):47-53. doi: 10.1111/acps.12827. Epub 2017 Oct 24.

Adverse cardiac events in out-patients initiating clozapine treatment: a nationwide register-based study.

Rohde C[1,2], Polcwiartek C[3,4,5], Kragholm K[3,4], Ebdrup BH[1,6], Siskind D[7,8], Nielsen J[1].

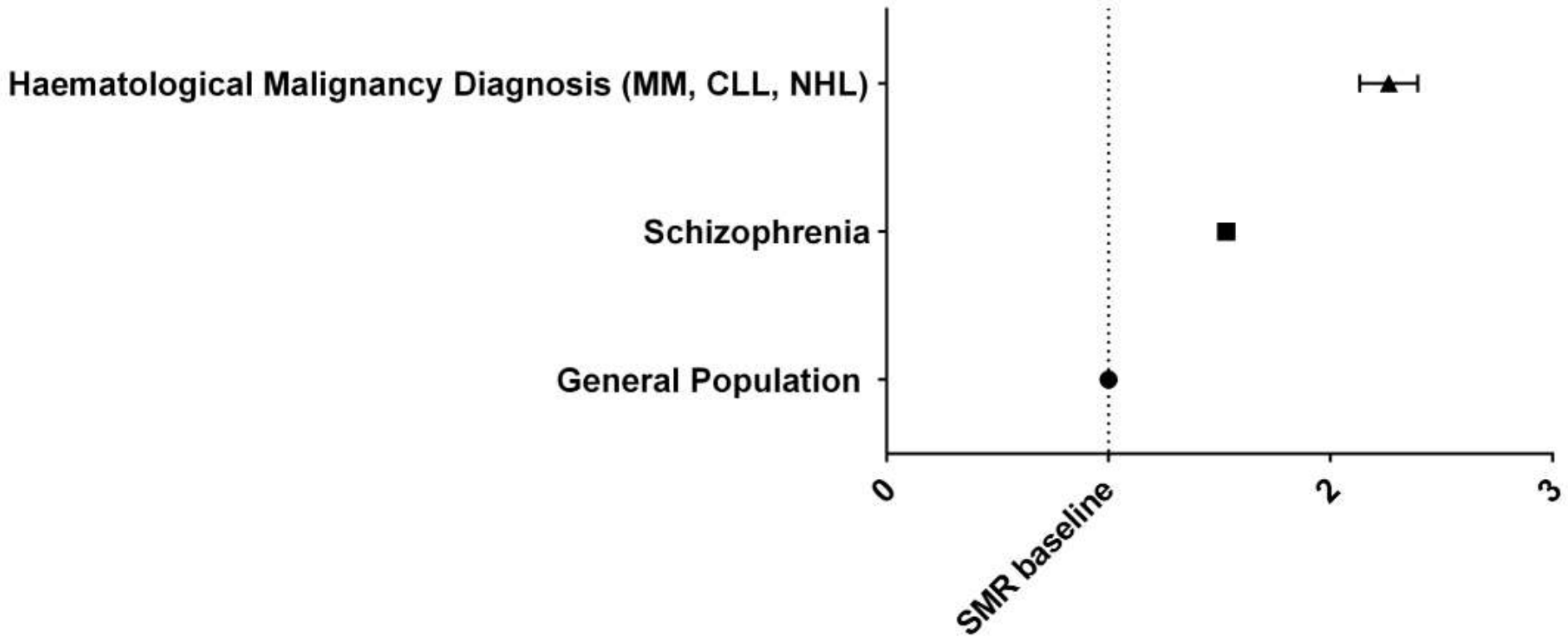
RESULTS:

- Overall, 3262/7932 patients initiated clozapine as out-patients (41.12%). One patient (0.03%) developed myocarditis, and no patients developed pericarditis within 2 months from clozapine initiation. Two (0.06%) and four patients (0.12%) developed cardiomyopathy within 1 and 2 years, respectively. Rates were similar for other antipsychotics. Twenty-six patients died within 2 months from clozapine initiation
- Pneumonia (23.08%) and stroke (11.54%) were the main causes of death. The estimated maximum rate of clozapine-associated fatal myocarditis was 0.28%
- Various mechanisms for the increase in pneumonia have been suggested, including aspiration, sialorrhea and impairment of swallowing function with esophageal dilatation and hypomotility as well as agranulocytosis and smoking

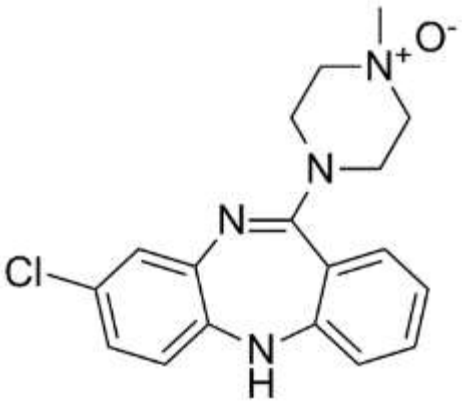
Hospital Episode Statistics (HES)

Hospital Episode Statistics (HES) is a data warehouse containing details of all admissions, outpatient appointments and A and E attendances at NHS hospitals in England.

Standardised Mortality Ratios for HES individuals aged 15-74 years admitted with "infection"



So let's take a peek

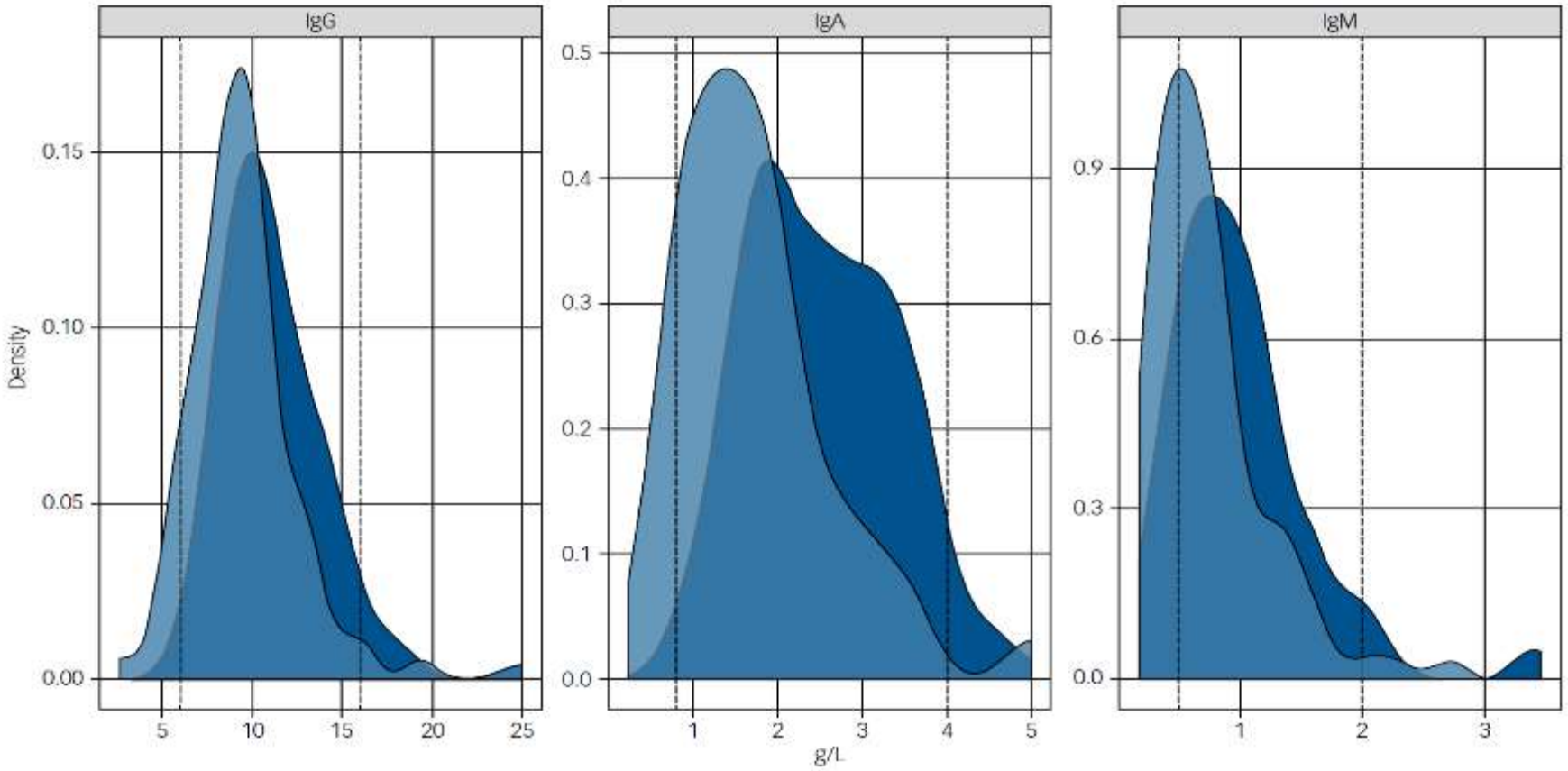


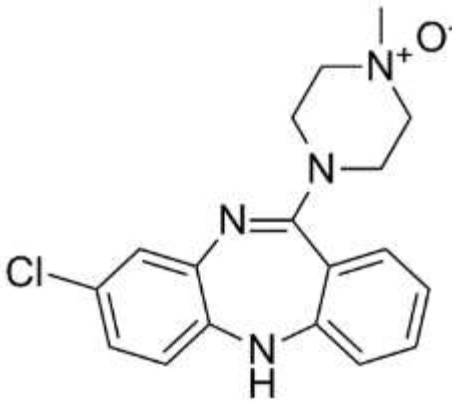
	Clozapine group	Control group
Total screened, n	291	280
Declined/unable to consent or provide serum, n	168	169
Initial cohort, n	123	113
Excluded from subsequent analysis,* n	29	15
Carbamazepine	2	1
Lamotrigine	5	5
Levetiracetam	1	–
Topiramate	1	–
Valproate	17	5
Paraprotein	1	3
Leflunomide	–	1
Prior chemotherapy	1	–
HIV	1	–
Post-exclusion cohort, n (% of total screened)	94 (32.3)	98 (35.0)

HIV, human immunodeficiency virus. *Included in initial cohort analysis for total and specific antibody levels and excluded from subsequent analysis after identification of possible causes of secondary hypogammaglobulinaemia (European Society of Immunodeficiencies criteria).

Ponsford M et al. *Br J Psychiatry* 2018 [ePub] doi: 10.1192/bjp.2018.152

Clozapine study



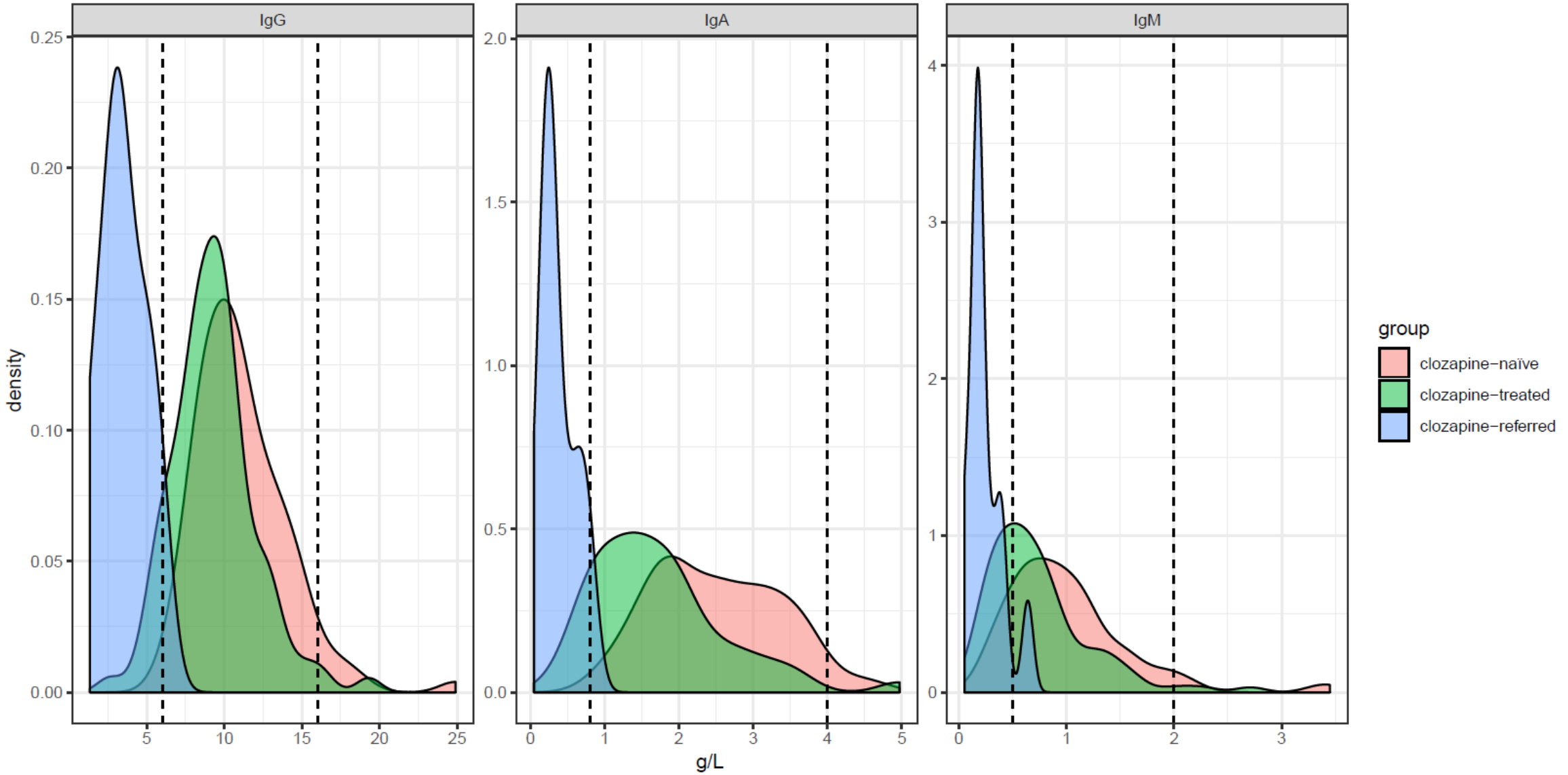


Rituximab + MTX:
IgG 3.5%
IgA 1.1%
IgM 22%

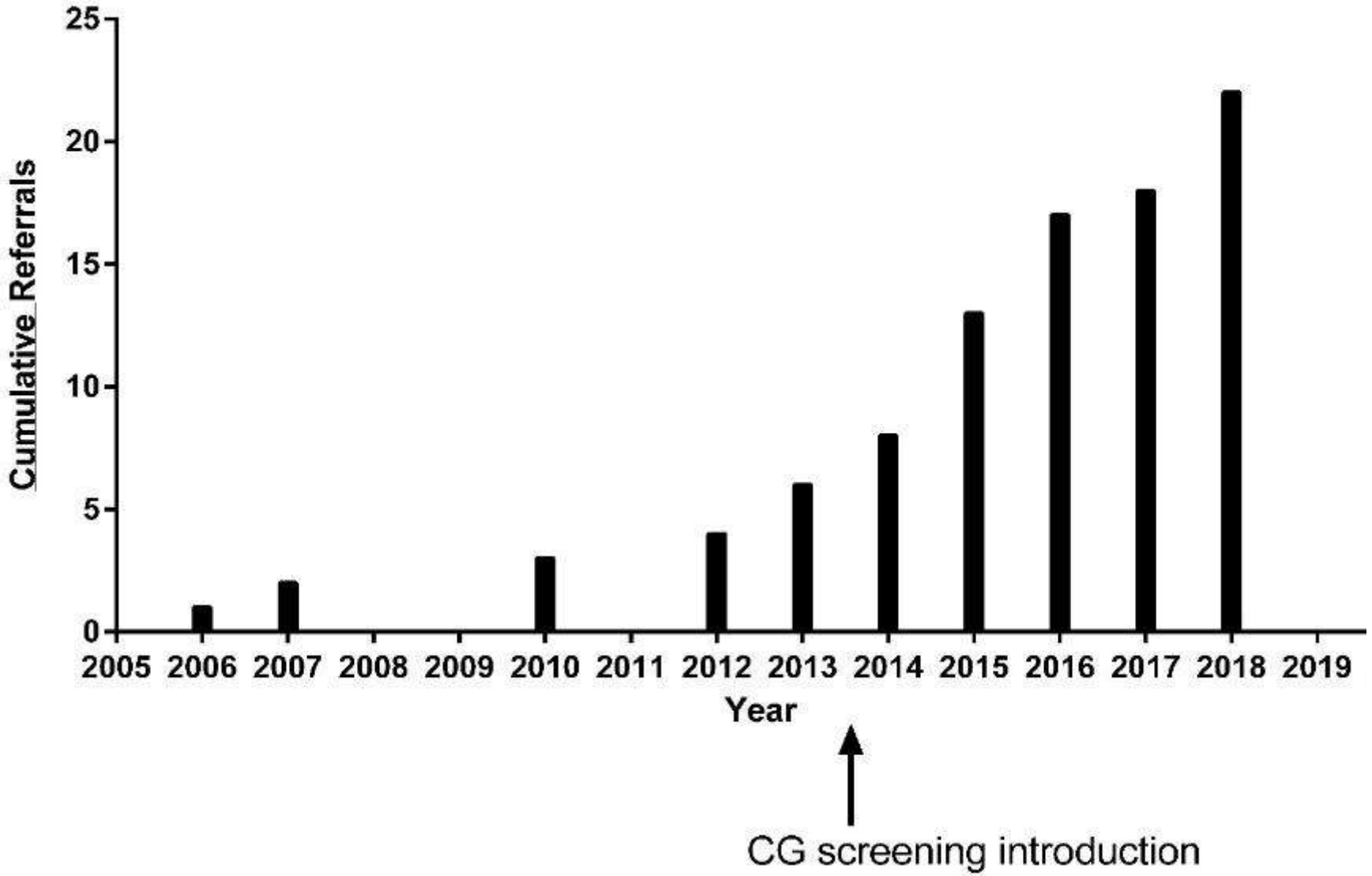
Ig, immunoglobulin; MTX, methotrexate,
Ponsford M et al. *Br J Psychiatry* 2018 [ePub] doi: 10.1192/bjp.2018.152

Screening effect

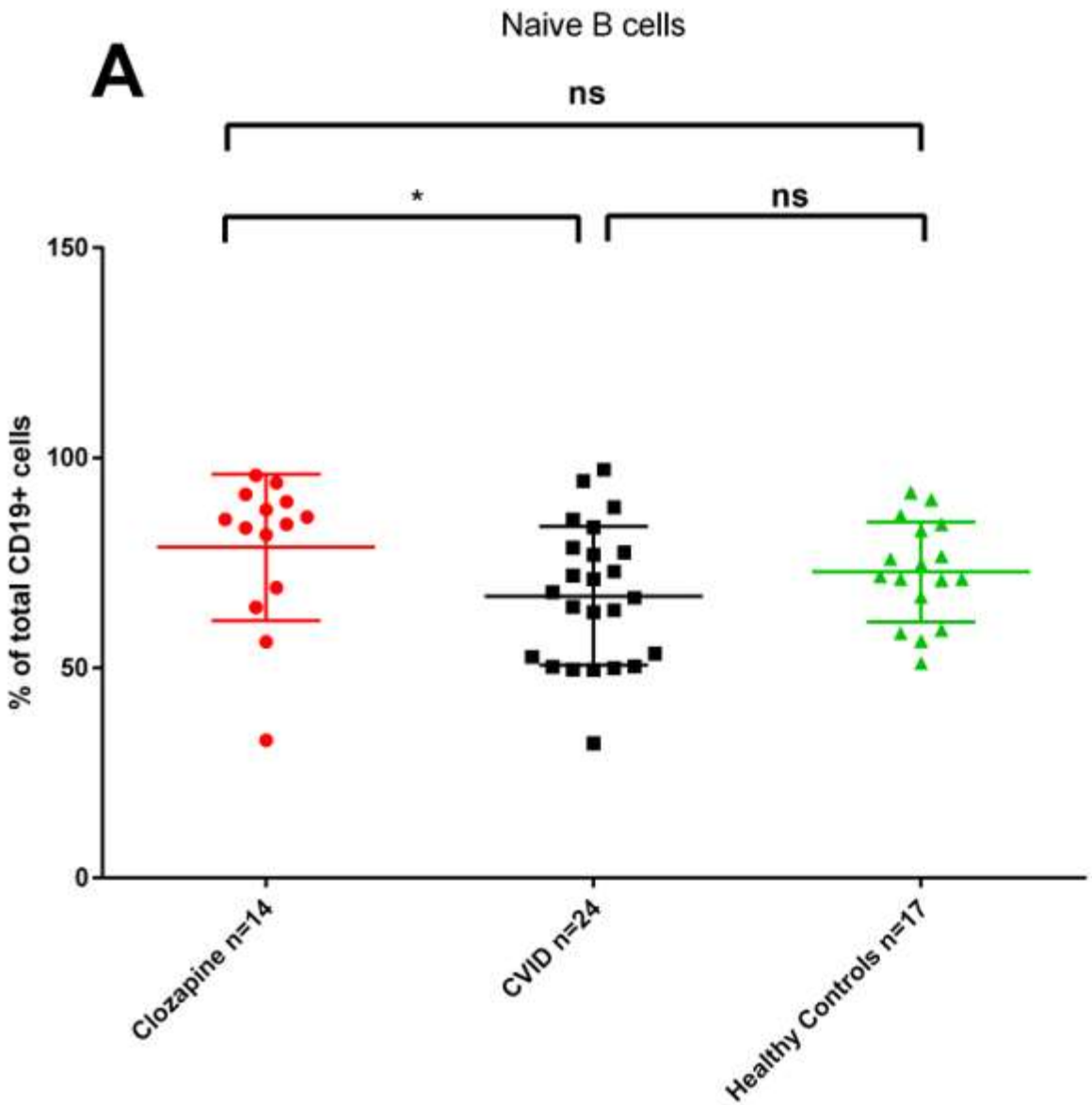
IgG	3.20 (1.20-6.65)	6.00-16.0g/L
IgA	0.26 (0.05-0.81)	0.80-4.00g/L
IgM	0.17 (0.05-0.64)	0.50-2.00g/L

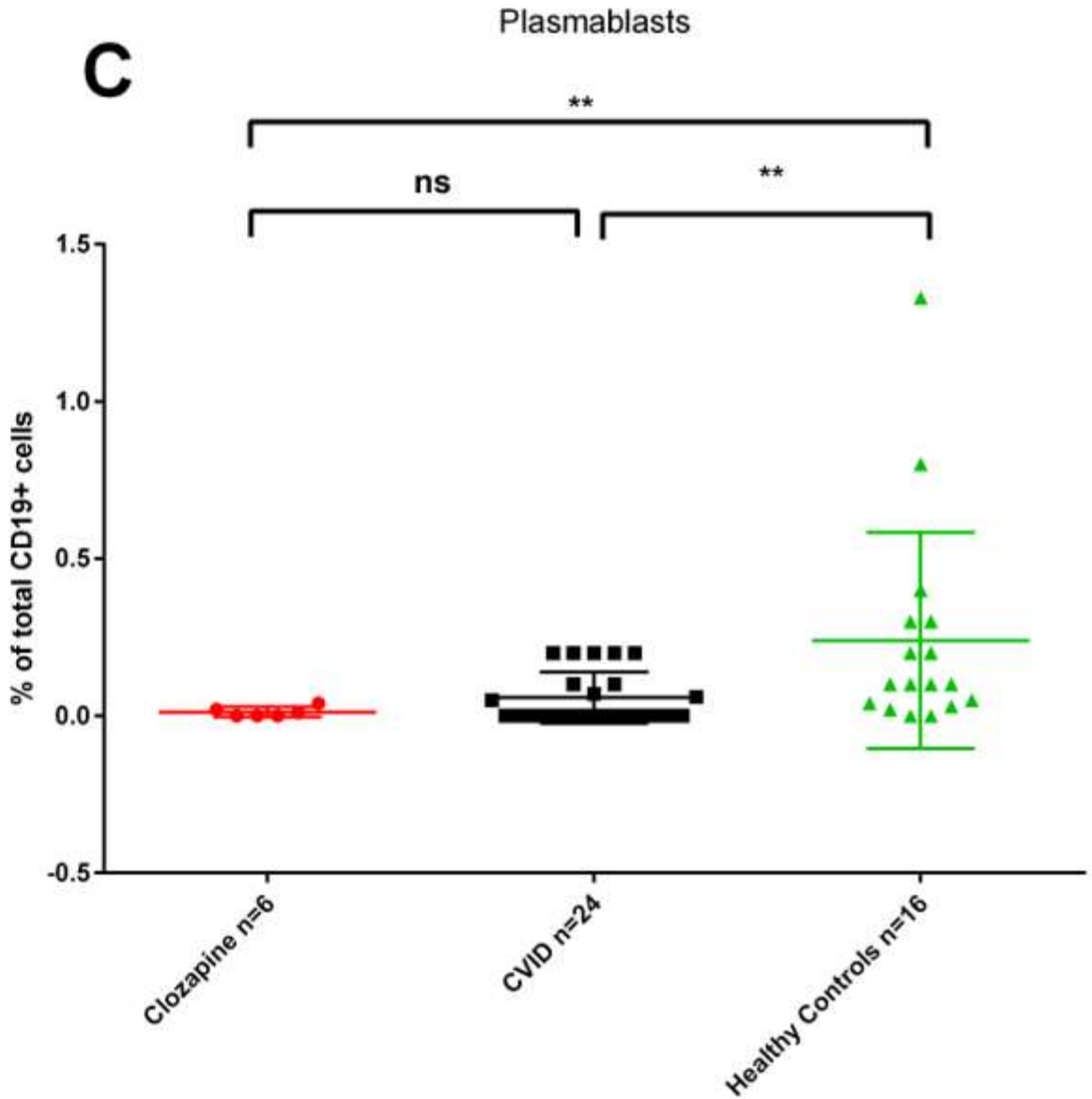


Impact of CG screening on clozapine referrals

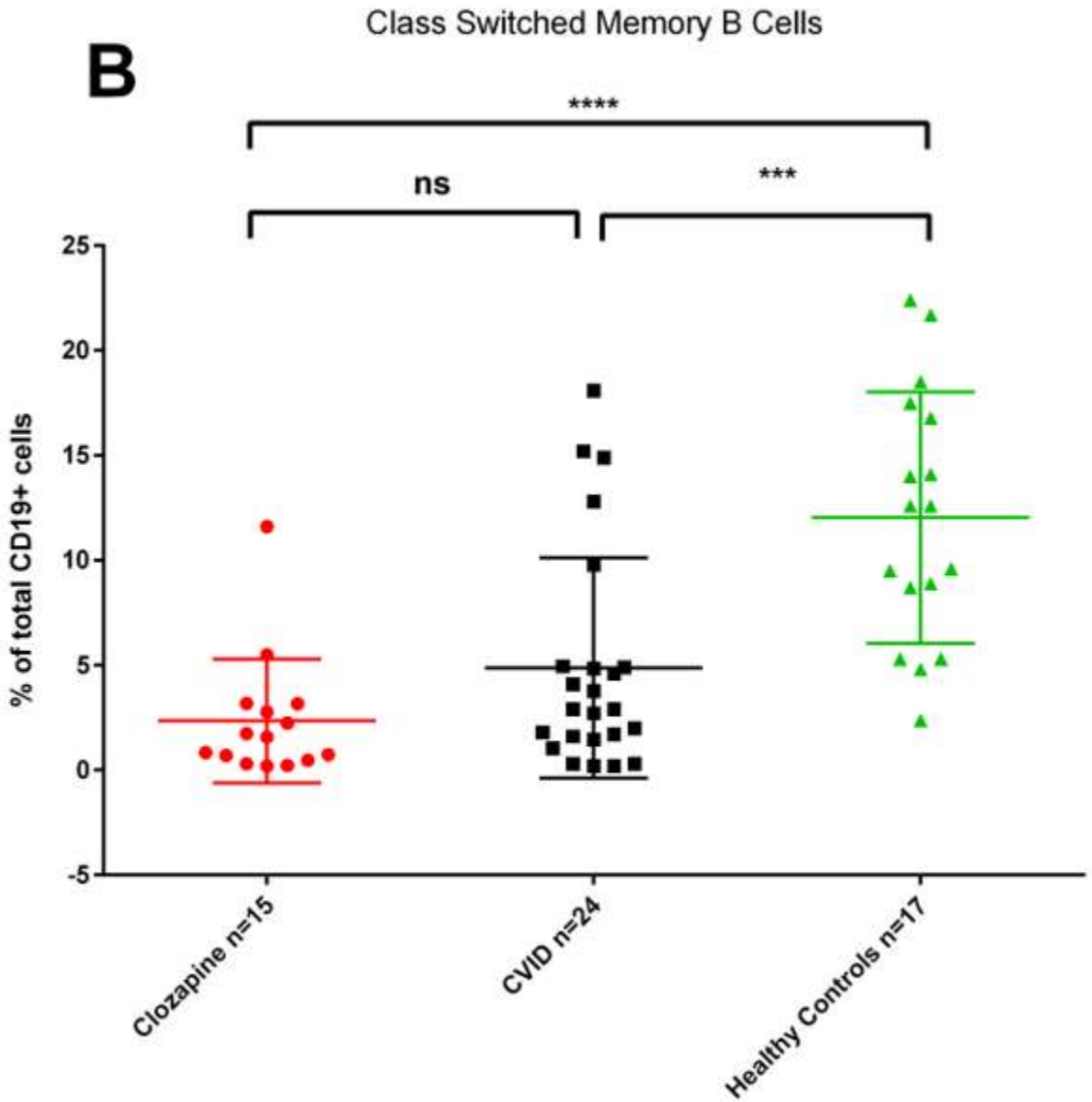


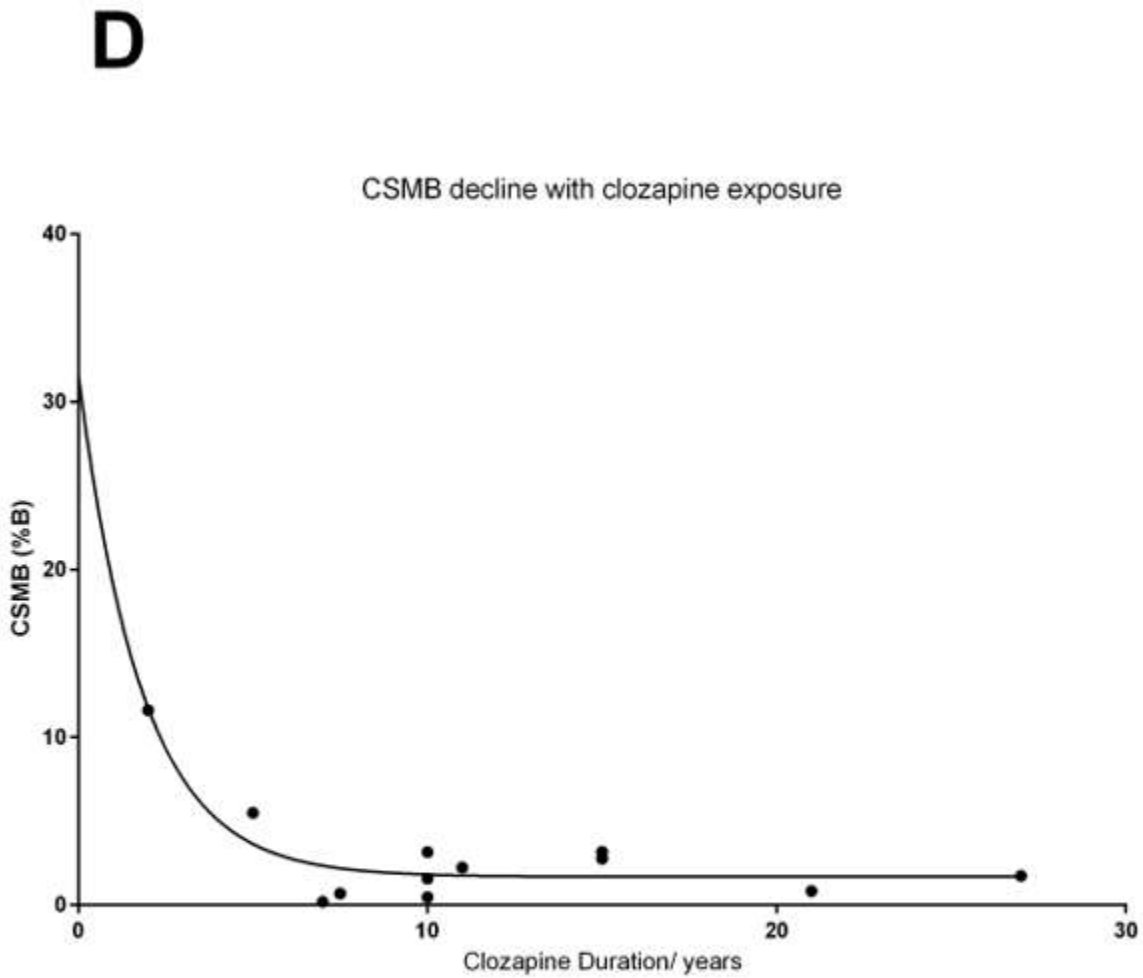
Flow cytometry





Flow cytometry





Clozapine discontinuation

NDC 0093-7772-93

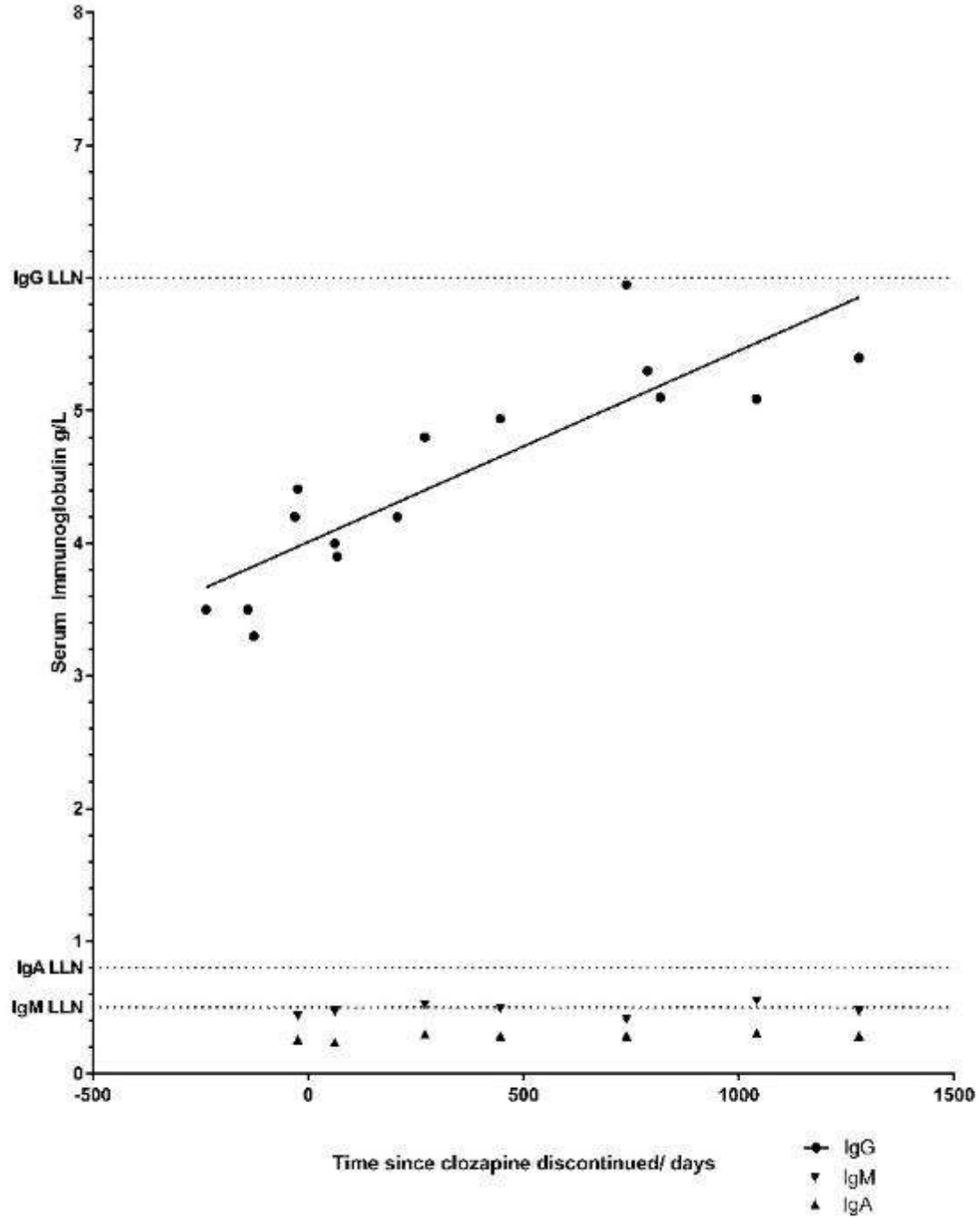
CLOZAPINE
Tablets USP
100 mg

Each tablet contains:
clozapine, USP 100 mg

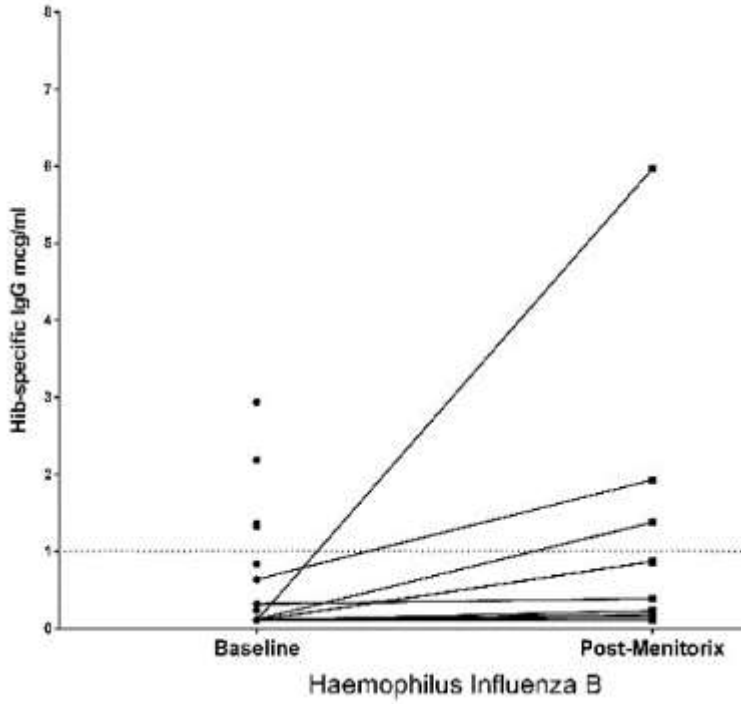
℞ only

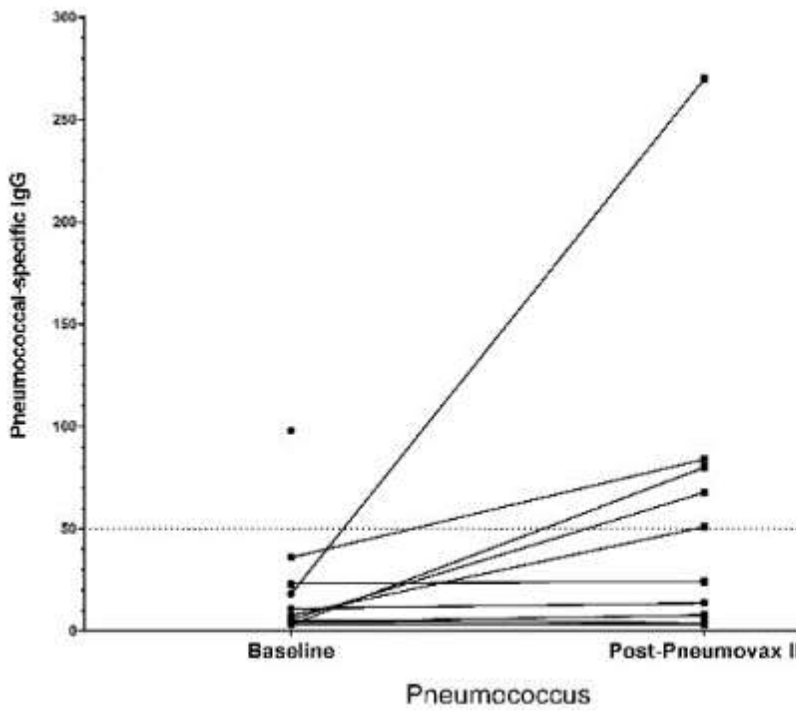
100 UNIT-DOSE TABLETS (10 x 10)

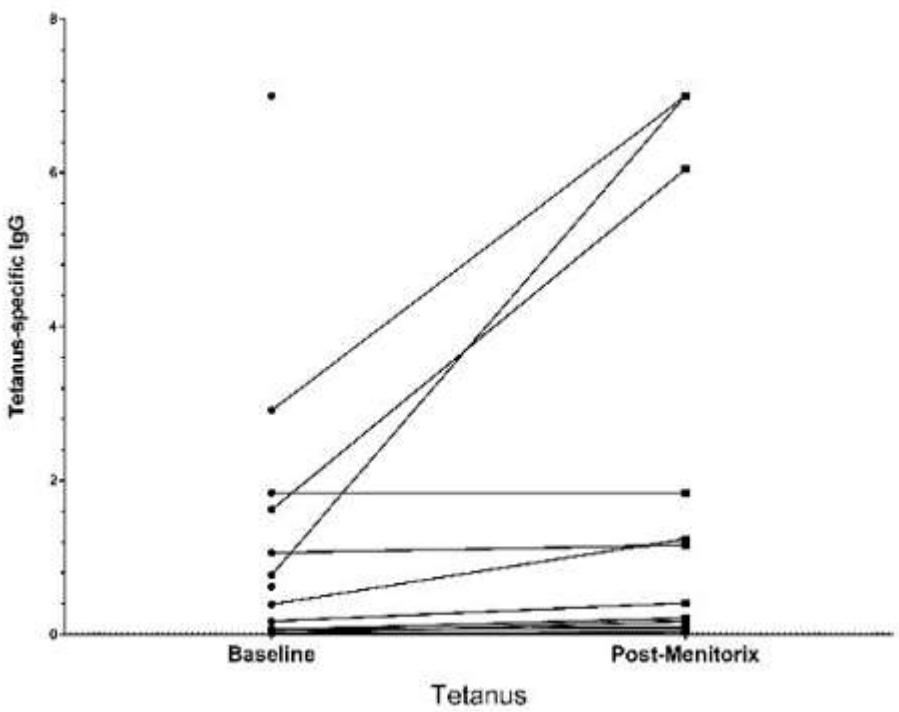
TEVA



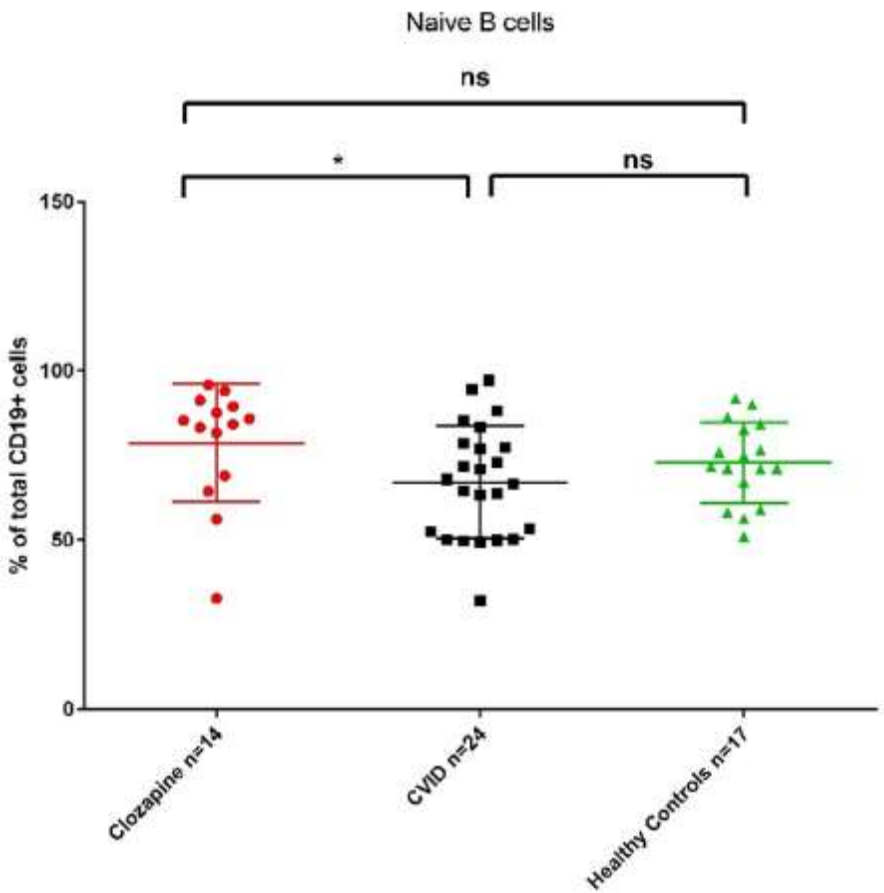
Vaccine Responses

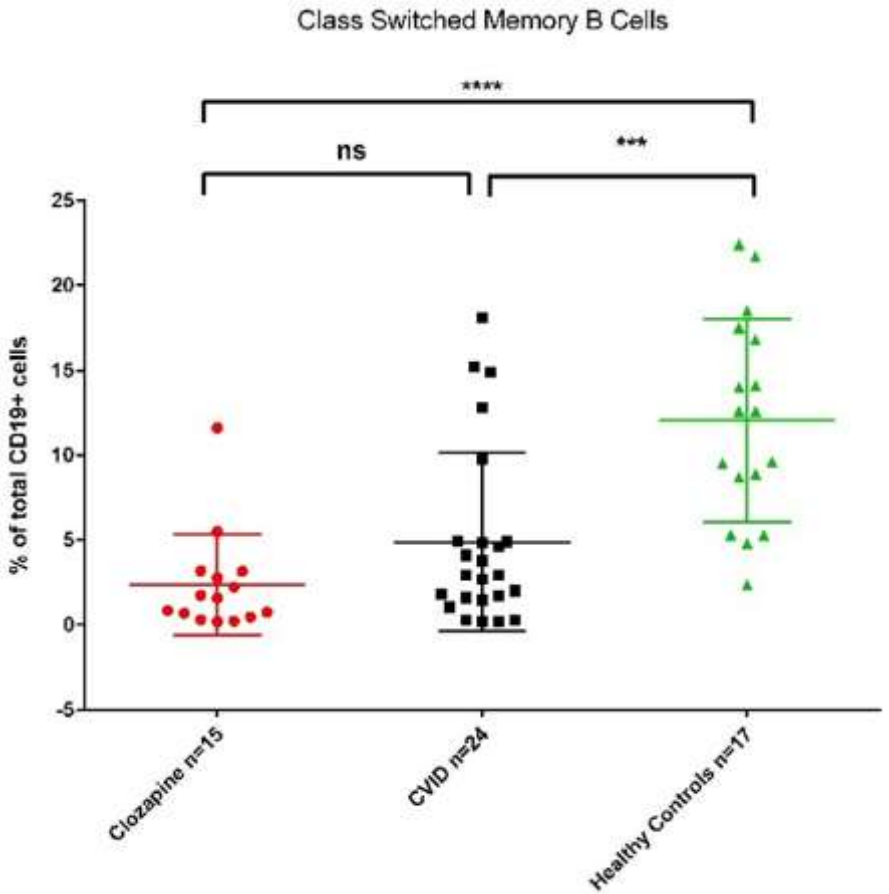


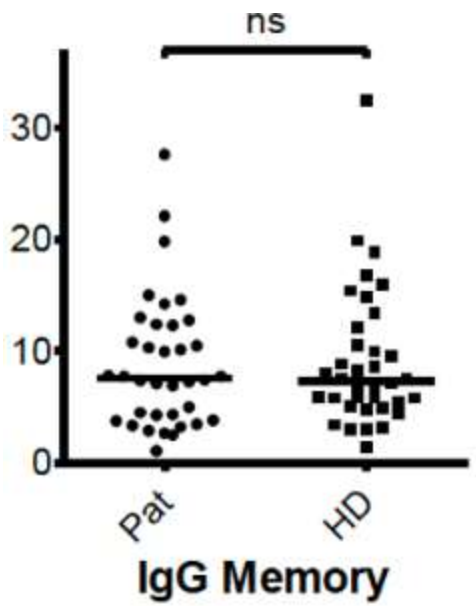


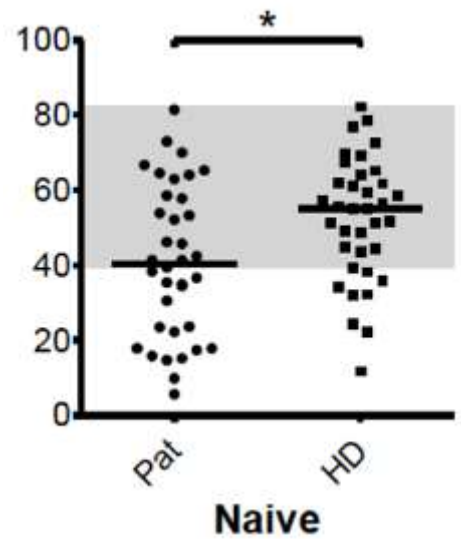


Clozapine and B cells

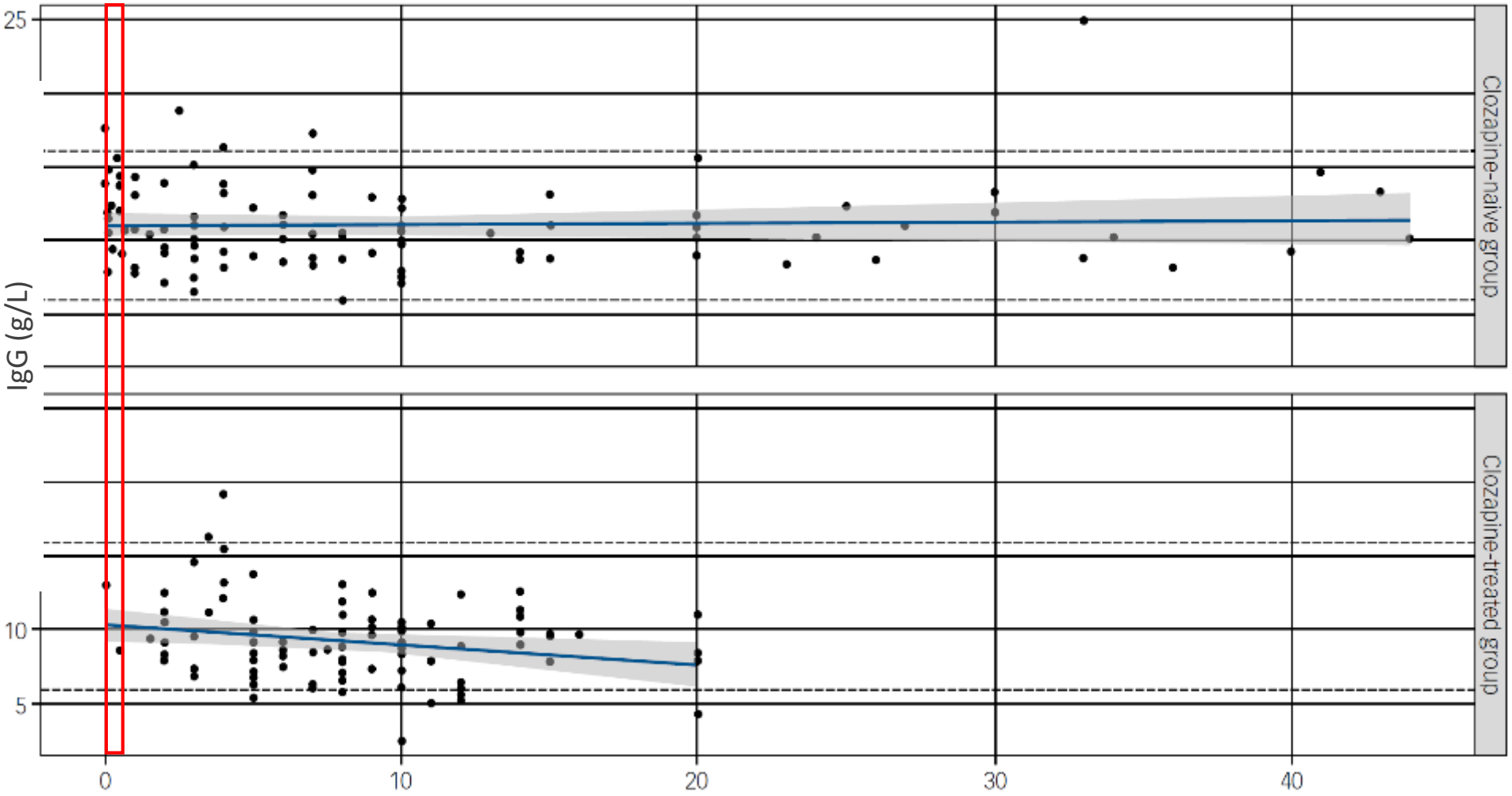


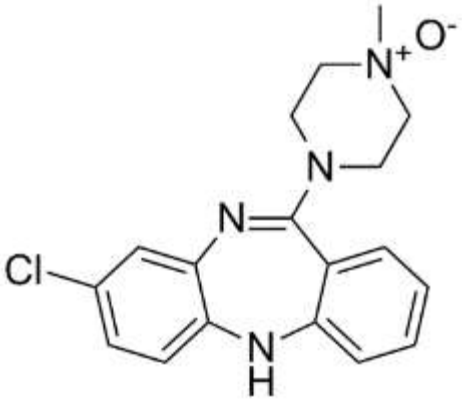






Clozapine study

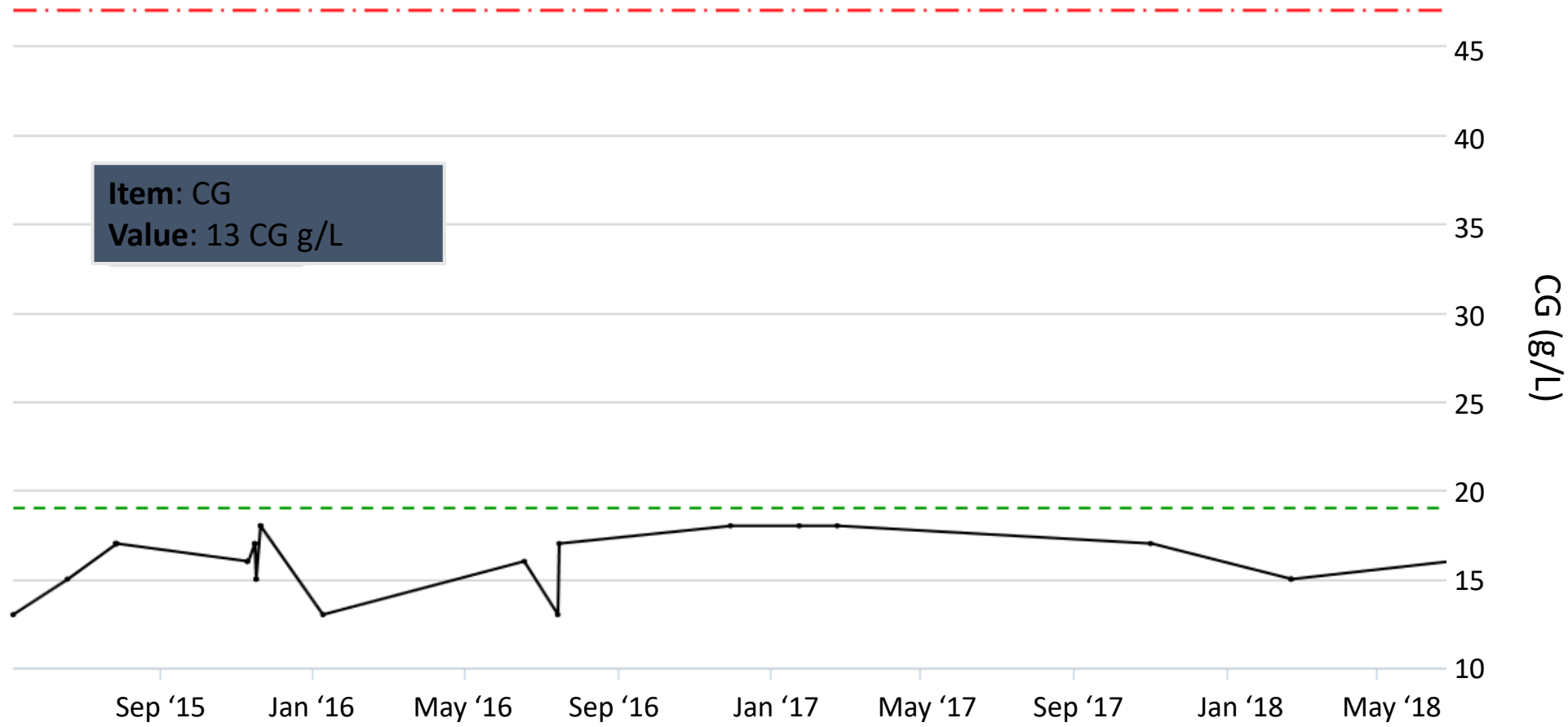




IgG, immunoglobulin G

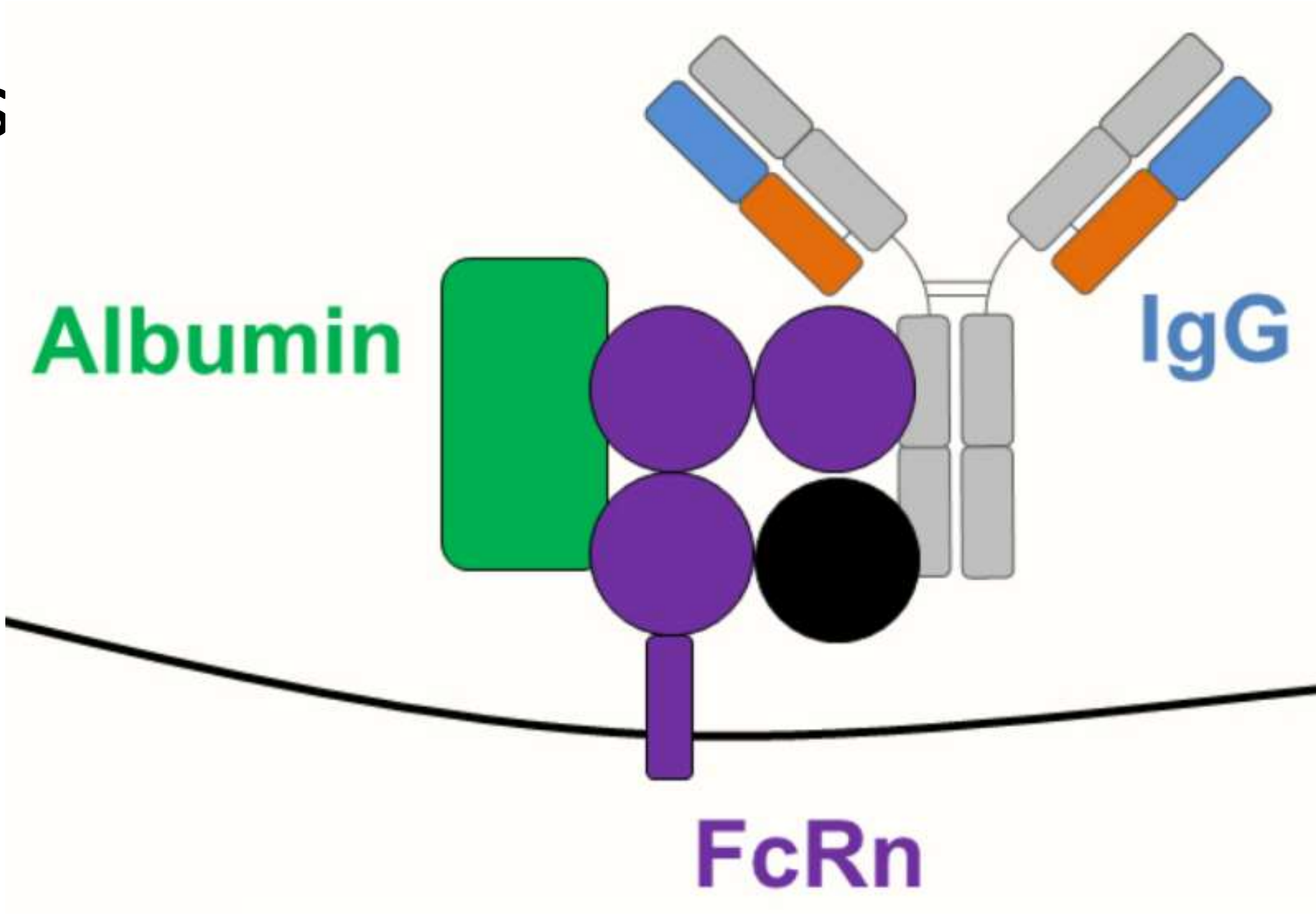
Ponsford M et al. *Br J Psychiatry* 2018 [ePub] doi: 10.1192/bjp.2018.152

CG on clozapine



CG, calculated globulin

Some opportunities



Clin Pharmacol Ther. 2018 Apr;105(4):1031-1039. doi: 10.1002/cpt.1276. Epub 2018 Dec 4.

M281, an Anti-FcRn Antibody: Pharmacodynamics, Pharmacokinetics, and Safety Across the Full Range of IgG Reduction in a First-in-Human Study.

Ling LE[1], Hillson JL[1], Tiessen RG[2], Bosje T[2], van Iersel MP[2], Nix DJ[3], Markowitz L[1], Cilfone NA[1], Duffner J[1], Streisand JB[1], Manning AM[1], Arroyo S[1].

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

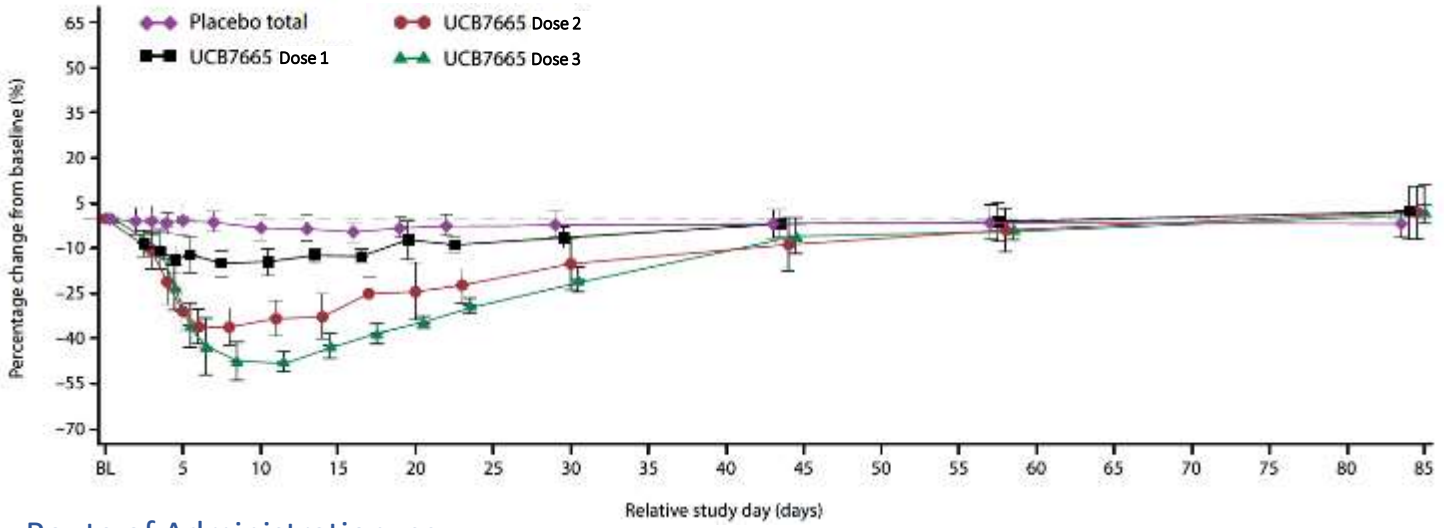
AUTOIMMUNITY

The FcRn inhibitor rozanolixizumab reduces human serum IgG concentration: A randomized phase 1 study

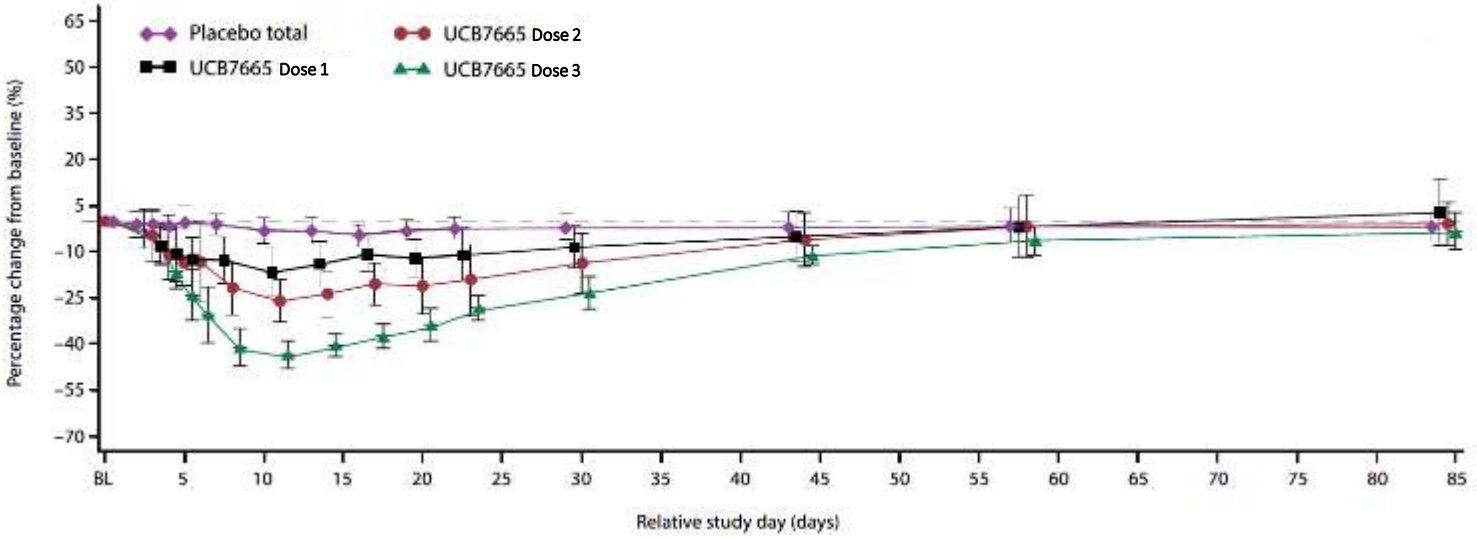
Peter Kiessling,[1] Rocio Lledo-Garcia,[2]* Shikiko Watanabe,[3] Grant Langdon,[4] Diep Tran,[2] Muhammad Bari,[2] Louis Christodoulou,[2] Emma Jones,[5] Graham Price,[2] Bryan Smith,[2] Frank Brennan,[2] Ian White,[2] Stephen Jolles[6]

Mean percentage change in total IgG

Route of Administration: iv



Route of Administration: sc

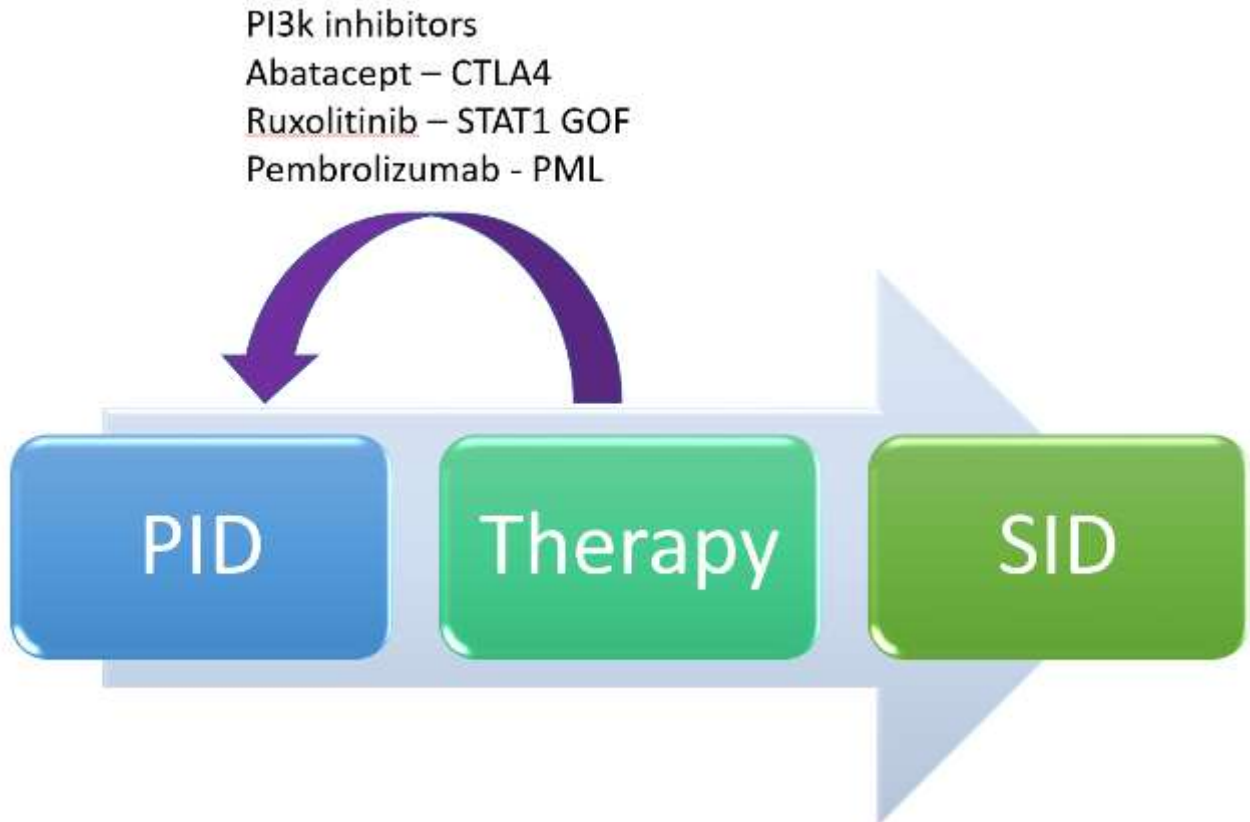


Dose-dependent reductions across IV and SC cohorts

IgG levels return to baseline by ~Day 60

Unpublished data – manuscript in preparation

On another positive note…



Proc Natl Acad Sci U S A. 2006 Mar 28;103(13):5084-9. Epub 2006 Mar 20.

Familial hypercatabolic hypoproteinemia caused by deficiency of the neonatal Fc receptor, FcRn, due to a mutant beta2-microglobulin gene.

Wani MA[1], Haynes LD, Kim J, Bronson CL, Chaudhury C, Mohanty S, Waldmann TA, Robinson JM, Anderson CL.

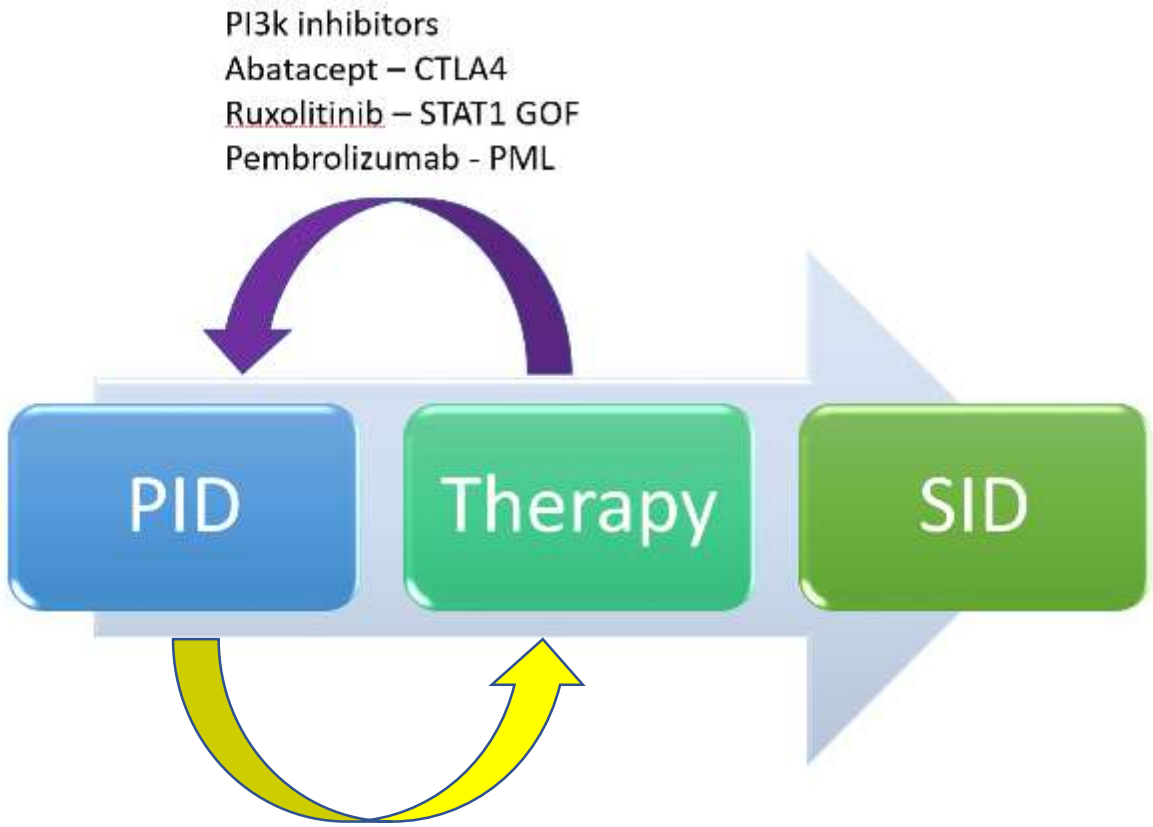
Clin Infect Dis. 2016 Apr 15; 62(8): 986–994. PMCID: PMC4803104
Published online 2016 Jan 6. doi: 10.1093/cid/civ1220

Progressive Multifocal Leukoencephalopathy in Primary Immune Deficiencies: Stat1 Gain of Function and Review of the Literature

Christa S. Zerbe,[1,a] Beatriz E. Marciano,[1,a] Rohit K. Katial,[2] Carah B. Santos,[2] Nick Adamo,[1] Amy P. Hsu,[1] Mary E. Hanks,[1] Dirk N. Darnell,[1] Martha M. Quezado,[3] Cathleen Frein,[4] Lisa A. Barnhart,[1] Victoria L. Anderson,[1] Gulbu Uzel,[1] Alexandra F. Freeman,[1] Andrea Lisco,[1] Avindra Nath,[5] Eugene O. Major,[6] Elizabeth P. Sampaio,[1] and Steven M. Holland[1]

PID – Therapy – SAD….. A two way street

- UCB Pharma
- ARGENX
- Momenta



Proc Natl Acad Sci U S A. 2006 Mar 28;103(13):5084-9. Epub 2006 Mar 20.

Familial hypercatabolic hypoproteinemia caused by deficiency of the neonatal Fc receptor, FcRn, due to a mutant beta2-microglobulin gene.

Wani MA[1], Haynes LD, Kim J, Bronson CL, Chaudhury C, Mohanty S, Waldmann TA, Robinson JM, Anderson CL.

Risk Factors for SAD

Risk Factors for SAD following Rituximab

- Lower baseline immunoglobulins prior to rituximab
- Maintenance or multiple treatments
- Combination therapy
- Prior therapies eg cyclophosphamide, steroids
- Association with use of purine analogues (mycophenolate)
- Infection associated with low IgG longer than 6 months, G-CSF, chronic lung or heart disease, extra-articular RA and old age.
- Note assessment of comorbidities

But remember
Rituximab is associated with more than bacterial infection – eg HBV, HCV, CMV, VZV, HSV, parvo, PML, fungal neutropenia..

Int Rev Immunol. 2017 Aug 11:1-8. doi: 10.1080/08830185.2017.1346092. [Epub ahead of print]

Risk factors predisposing to the development of hypogammaglobulinemia and infections post-Rituximab.

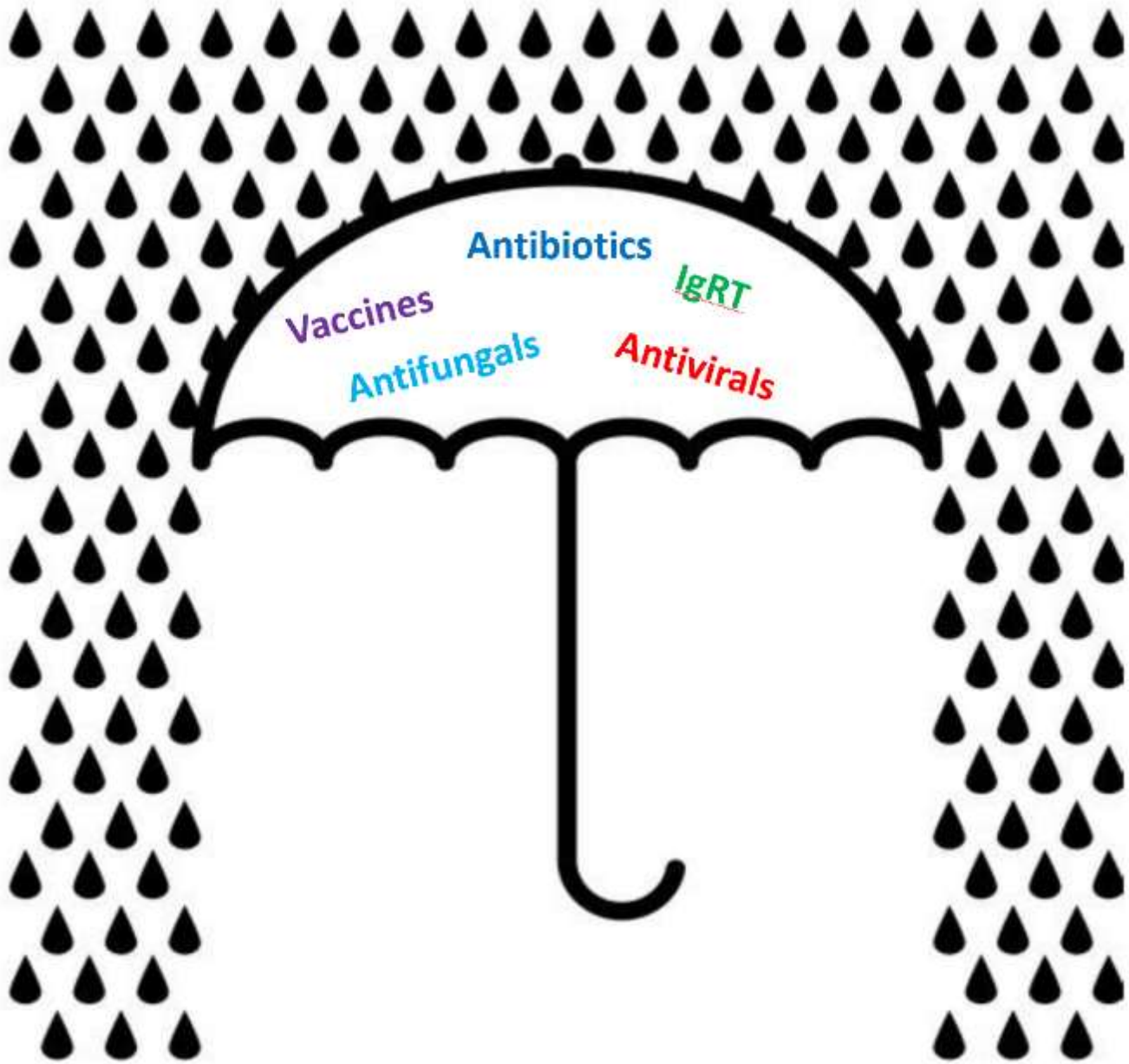
Christou EAA[1], Giardino G[2], Worth A[3], Ladomenou F[3].

Consider additional patient specific risk factors

- Underlying disease – CLL, lymphoma (stage), AAV
- Neutropenia
- Diabetes
- End organ damage – eg bronchiectasis, COPD
- Smoking
- Nutritional state
- Prior and concomitant medication
- Comorbidities – cardiovascular (cases vulnerability)
- Other immune system components – T cell, NK cells, Complement

Treatment

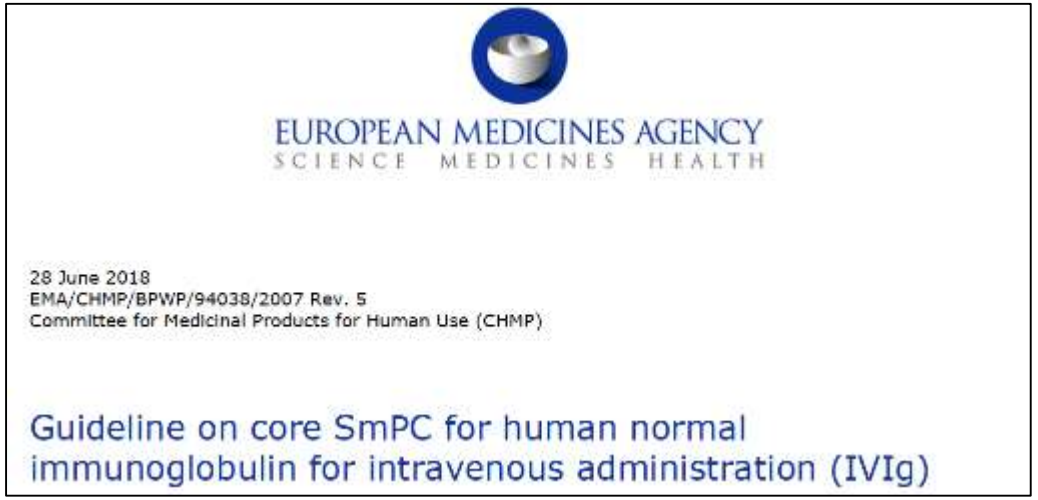
Yes – but let's not let them get too wet in the first place



Intervention timing

"It's not what you look at that matters, it's what you see." Henry David Thoreau (1817-1862)

What does the EMA say?



- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent bacterial infections, ineffective antibiotic treatment and either **proven specific antibody failure (PSAF)*** or serum IgG level of <4 g/L[1]

*PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Indication	**Dose**	**Infusion frequency**
Secondary immunodeficiencies (as defined in 4.1.)	0.2–0.4 g/kg	every 3–4 weeks to obtain IgG trough level of at least 6 g/l or within the normal range for the population

SmPC, Summary of Product Characteristics. EMA 2018. Rev 5. Available from: https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-investigation-human-normal-immunoglobulin-intravenous-administration-ivig-rev-3_en.pdf

Vaccination – what and when

- Flu
- Pneumococcal
- Haemophilus
- Hepatitis A and B
- HPV – (skin, colon, prostate)
- Splenic status case

Antibiotics

- Prophylaxis – Azithromycin
- Septrin
- Antivirals
- Antifungals

Antibiotics Patel SY et al Frontiers 2019

Antibiotic regimen	Dosing schedule	Additional options	Emergency plan	Example
Intermittent antibiotics	None		Attend GP with symptoms	N/A
	None		Early use of home back-up antibiotics	Co-amoxyclav 625 mg tds for 2 weeks; held at home
	Prophylactic antibiotics during the winter months with home rescue during the summer	Low-dose and full-dose options, e.g., azithromycin 250 or 500 mg 3 days/week	Early use of home back-up antibiotics	Azithromycin 500 mg 3 days/week plus back-up Co-amoxyclav for 2 weeks; held at home
Ongoing prophylaxis	Prophylactic antibiotics	Low-dose and full-dose options, e.g., azithromycin 250 or 500 mg 3 days/week	Early use of home back-up antibiotics	Azithromycin 500 mg 3 days/week plus back-up Co-amoxyclav 625 mg tds for 2 weeks; held at home
	Rotating prophylactic antibiotics		Early use of home back-up antibiotics	
	Prophylactic antibiotics	Nebulized antibiotics	Early use of home back-up antibiotics	Nebulized Colomycin 1–2 mega units bd
	Prophylactic antibiotics	Intermittent planned IVAB	Early use of home back-up antibiotics	Meropenem 2g IV tds and Ceftazidime Co-amoxyclav for 2 weeks; held at home

GP, general practitioner; IV, intravenous; IVAB, intravenous antibiotic; N/A, not available; bd, twice daily; tds, three times daily.
**If there has been an inadequate response to back-up antibiotics and an additional antibiotic in another class then intravenous antibiotics (IVAB) should be considered. The Table shows examples of antibiotic regimens and the antibiotic choice will depend on individual clinical circumstances.*

IgRT - Way, way way…back

- **Cooperative Group CLL (1988)**
  - 81 patients with hypogammaglobulinemia or serious infections
  - Multicenter controlled, randomized double-blind, IVIg 400 mg/kg/21 days versus placebo for 12 months
  - Fewer major and moderate bacterial infections overall
  - Longer period to first serious bacterial infection
  - No differences in viral and fungal infections
- **Griffiths et al. (1989)**
  - 8 CLL and 4 low grade NHL patients with hypogammaglobulinemia or serious infections
  - Double-blind, randomized crossover IVIg 400 mg/ kg/21 days versus placebo for 12 months then changed to the alternative drug
  - Fewer major and moderate bacterial infections overall
  - Serious bacterial infection showed a growing trend with IgG < 6.4 g/L
  - No differences in trivial infections
- **Sklenar et al. (1993)**
  - 31 CLL and MM (31) patients
  - Multicentre double-blind, randomized parallel-group IVIg at 100, 400, and 800 mg/kg/21 days
  - Optimal dose was 400 mg/kg for prevention of bacterial infections and for increasing pneumococcal antibody levels
- **Jurlander et al. (1994)**
  - 15 CLL patients with hypogammaglobulinemia and recurrent infections
  - Open label IVIg 1,000 mg/21 days
  - Fewer hospital admissions and febrile episodes
  - No difference in severe infections
  - No difference in antibiotic prescription
- **Boughton et al. (1995)**
  - 42 CLL patients (42) with hypogammaglobulinemia and infections
  - Randomized parallel-group IVIg 18 g/21 days versus placebo and switched to 24 g versus 18 g if ≥3 infections
  - Fewer serious and moderate bacterial infections 50% who required dose increase subsequently infection free
  - Majority of infections associated with IgG < 3 g/L

Multiple Myeloma - SCIg

Total number of infectious episodes during the study.

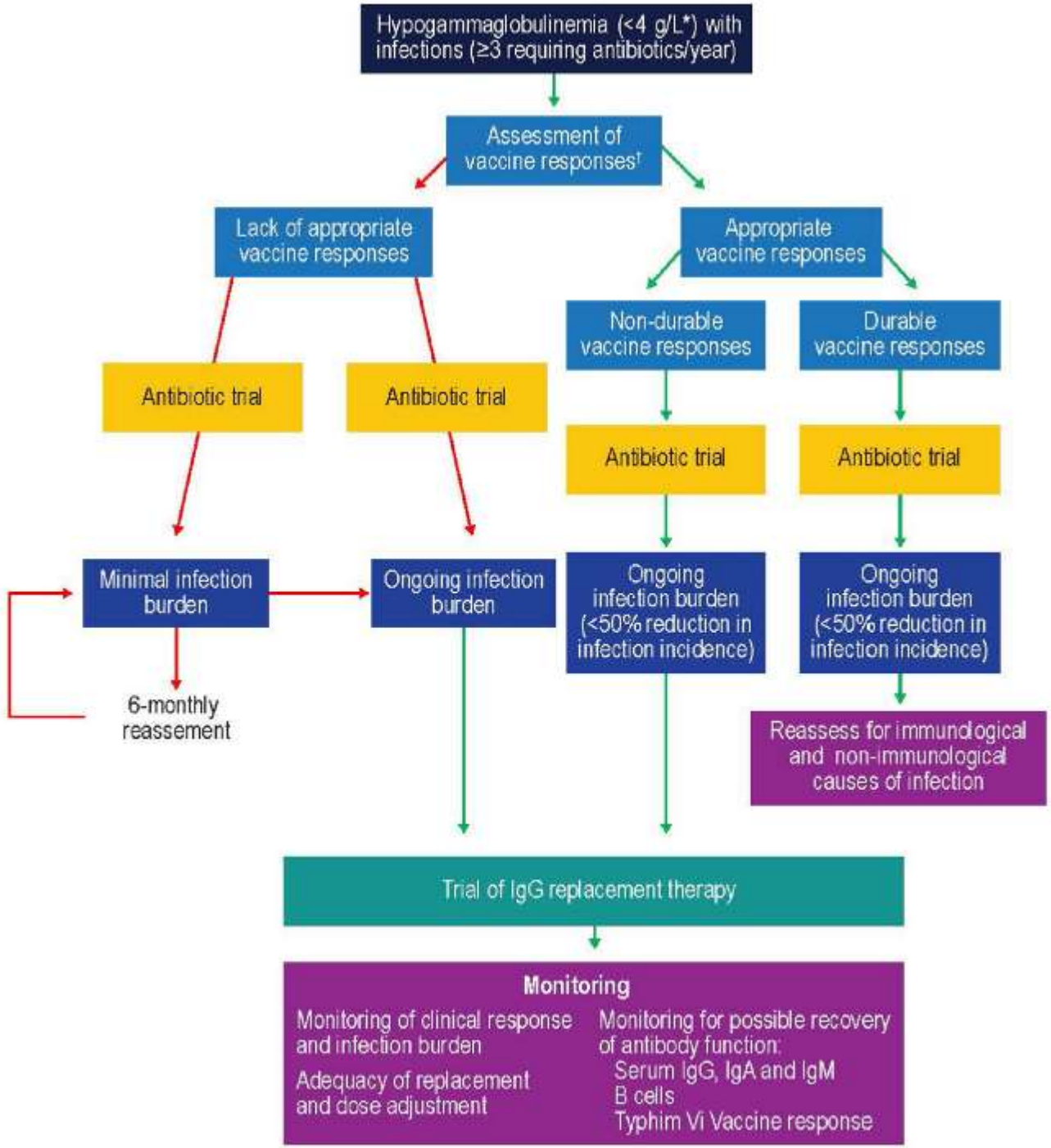
	Patients	
	Arm-A: SCIg	Arm-B: controls
Major infections		
Sepsis	–	24
Bacterial pneumonia	–	18
Bronchitis with sepsis	–	43
Pharyngo-tracheitis with sepsis	2	24
Acute sinusitis	–	5
Erysipelas	–	12
Urinary infection with sepsis	1	32
Fever of unknown origin	13	32
Minor infections		
Tracheobronchitis	32	64
Bacterial skin infection	11	16
Bacterial stomatitis	6	12
Lower urinary tract infection	19	36
Thoracic herpes zoster	1	15

Vacca A. et al Clinical Immunology 2017

- **SAD+ in MM**
- Dendritic cell
- Co-stimulation
- T cell
- B cell
- NK cell
- M protein

Treatment of SAD

- Clinical assessment of infection burden and risk
- Immunoglobulins
- Vaccine responses



Can I leave you with a question?

- Do you think there should be a time when Immunologists would help choose with Haematologists the optimal treatment plan based in part on the risks posed by infection (MDT)?

- If we had a blank sheet of paper how would we define our role.

Conclusions

- Complex often combined immunodeficiencies in a rapidly evolving therapeutic environment
- Made more complex and more combined by more potent therapies, given sequentially, in combination and for longer
- Better understanding of the impact of new therapies and the defects to expect
- Opportunities exist for earlier intervention and collaboration across specialties
- Spectrum of infections is different to PAD – SID multifactorial
- Role of immunological prior assessment and monitoring
- SAD can be found in the most unusual places
- But some of the challenges in rare disease in PID are not present in SID