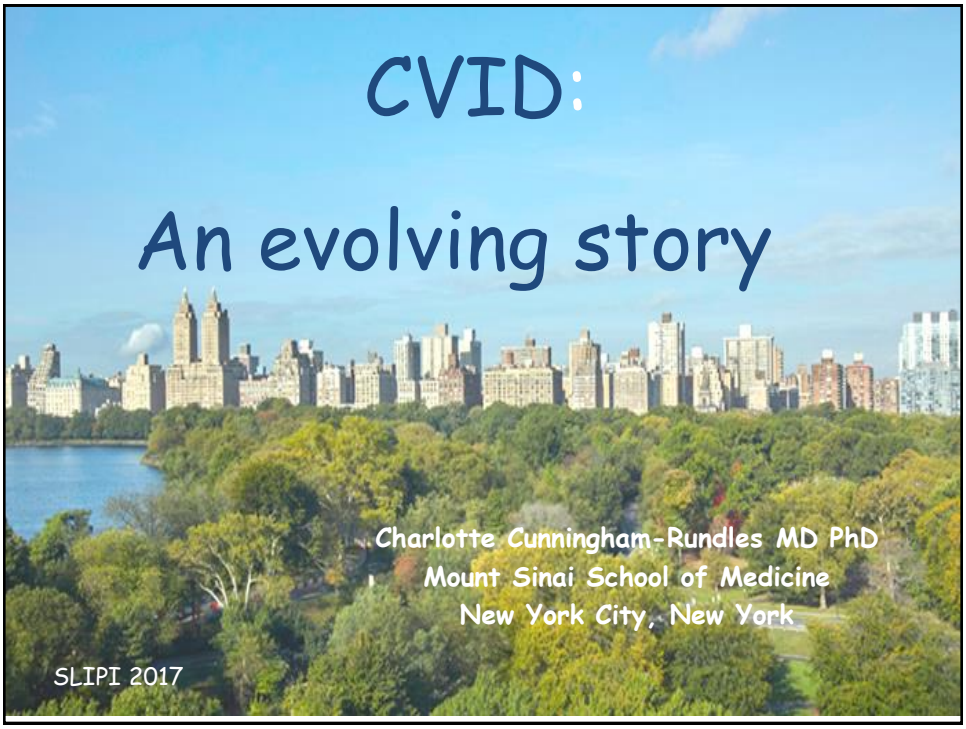

Topics

- Defining CVID
- Does it matter what you call it?
- Phenotypes, complications and morbidity
- Laboratory markers
- Genetic tests
- Treatment?
- Inflammatory disease
- But why?

Antibody deficiency

Antibody deficiency

IgA deficiency

IgA IgG2 deficiency

Agamma-globulinemia

IgG deficiency

CVID

Hypogammaglobulinemia

ABSENCE OF SERUM GAMMA GLOBULINS IN AN ADULT*

JAY P. SANFORD, M.D.,† CUTTING B. FAVOUR, M.D.,‡ AND MELVIN S. TRIBEMAN, M.D.§

BOSTON

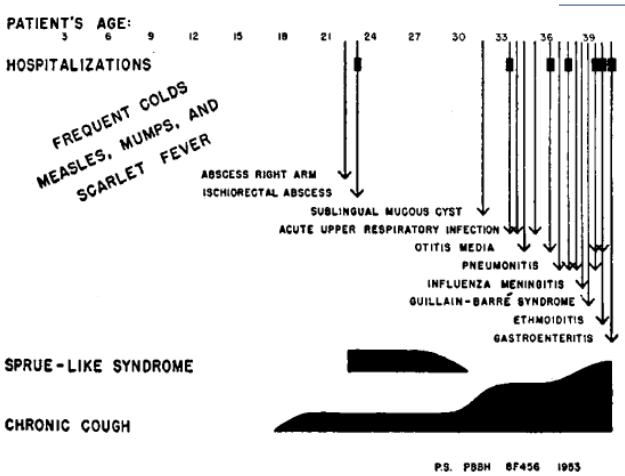

FIGURE 1. *Various Infections and Hospitalizations in a Patient with Agammaglobulinemia.*

New Engl Journal Med 1954

Coming soon: next update from the IUIS committee

J Clin Immunol
DOI 10.1007/s10875-015-0201-1

ORIGINAL RESEARCH

Primary Immunodeficiency Diseases: an Update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015

Capucine Picard[1,2] · Waleed Al-Herz[3,4] · Aziz Bousfiha[5] · Jean-Laurent Casanova[1,6,7,8,9] · Talal Chatila[10] · Mary Ellen Conley[6] · Charlotte Cunningham-Rundles[11] · Amos Etzioni[12] · Steven M. Holland[13] · Christoph Klein[14] · Shigeaki Nonoyama[15] · Hans D. Ochs[16] · Eric Oksenhendler[17,18] · Jennifer M. Puck[19] · Kathleen E. Sullivan[20] · Mimi L. K. Tang[21,22,23] · Jose Luis Franco[24] · H. Bobby Gaspar[25]

J Clin Immunol (2015) 35:727–738
DOI 10.1007/s10875-015-0198-5

ORIGINAL RESEARCH

The 2015 IUIS Phenotypic Classification for Primary Immunodeficiencies

Aziz Bousfiha[1] · Leila Jeddane[1] · Waleed Al-Herz[2,3] · Fatima Ailal[1] · Jean-Laurent Casanova[4,5,6,7,8] · Talal Chatila[9] · Mary Ellen Conley[4] · Charlotte Cunningham-Rundles[10] · Amos Etzioni[11] · Jose Luis Franco[12] · H. Bobby Gaspar[13] · Steven M. Holland[14] · Christoph Klein[15] · Shigeaki Nonoyama[16] · Hans D. Ochs[17] · Eric Oksenhendler[18,19] · Capucine Picard[5,20] · Jennifer M. Puck[21] · Kathleen E. Sullivan[22] · Mimi L. K. Tang[23,24,25]

IUIS Classifications

1. Immunodeficiencies affecting cellular and humoral immunity
2. Combined immunodeficiencies with associated or syndromic features
3. Predominantly Antibody Deficiencies
4. Diseases of Immune Dysregulation
5. Congenital defects of phagocyte number or function
6. Defects in Intrinsic and Innate Immunity
7. Auto-inflammatory Disorders
8. Complement Deficiencies
9. Phenocopies of Inborn Errors of Immunity

IUIS Classifications

1. Immunodeficiencies affecting cellular and humoral immunity
2. Combined immunodeficiencies with associated or syndromic features
3. Predominantly Antibody Deficiencies
Severe Reduction in All Serum Immunoglobulin Isotypes
Severe Reduction in at Least 2 Serum Immunoglobulin Isotypes with low or nl B cells
Severe Reduction in IgG and IgA with Normal/Elevated IgM
Isotype, Light Chain, with Normal Number B Cells
4. Diseases of Immune Dysregulation
5. Congenital defects of phagocyte number or function
6. Defects in Intrinsic and Innate Immunity
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8. Complement Deficiencies
9. Phenocopies of Inborn Errors of Immunity

ESID workshop criteria for CVID

At least one of the following:

1. increased susceptibility to infection
2. autoimmune manifestations
3. granulomatous disease
4. unexplained polyclonal lymphoproliferation
5. affected family member

AND marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2SD of the normal levels for their age);

AND at least one of the following:

1. poor antibody response to vaccines (and/or absent isohaemagglutinins); i.e. absence of protective levels despite vaccination where defined
2. low switched memory B cells (<70% of age-related normal value)

AND secondary causes of hypogammaglobulinaemia have been excluded
AND diagnosis is established after the 4th year of life (but symptoms may be present before)
AND no evidence of profound T-cell deficiency, defined as 2 out of the following (y = year of life):

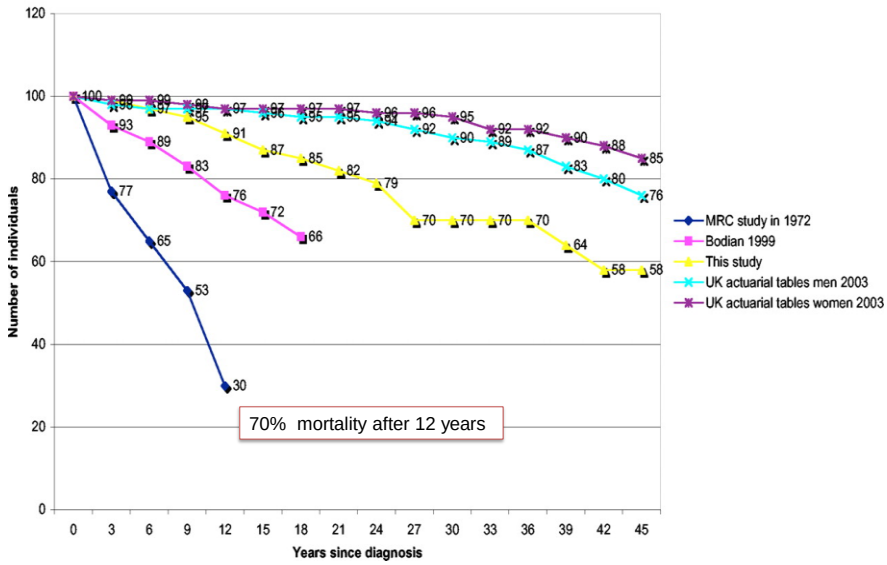
1. CD4 numbers/microliter: 2-6y <300, 6-12y <250, >12y <200
2. % naive CD4: 2-6y <25%, 6-16y <20%, >16y

International Consensus Document (ICON): Common Variable Immunodeficiency Disorders

1. A marked decrease of IgG (at least 2 SD below the mean for age)
2. A marked decrease in at least one of the isotypes IgM or IgA,
3. Onset of immunodeficiency at greater than 2 years of age
4. Absent isohemagglutinins and/or poor response to vaccines
5. Defined causes of hypogammaglobulinemia have been excluded

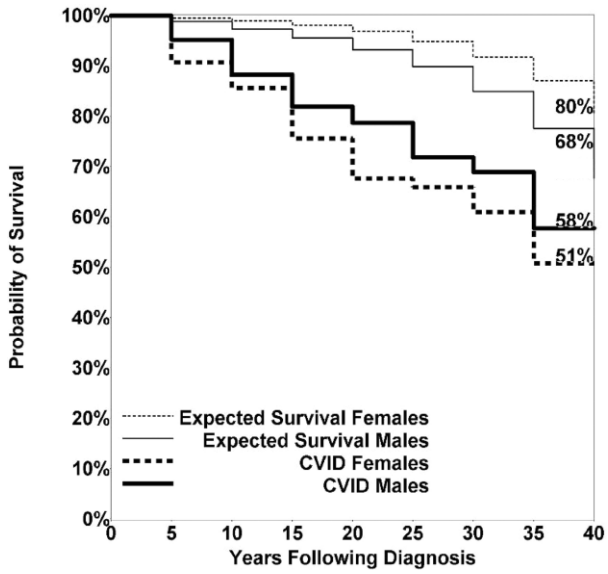
Bonilla et al J Allergy Clin Immunol Pract 2016

CVID: improved long term survival



Chapel H, et al Blood. 112: 277, 2008, CVID: division into distinct clinical phenotypes.

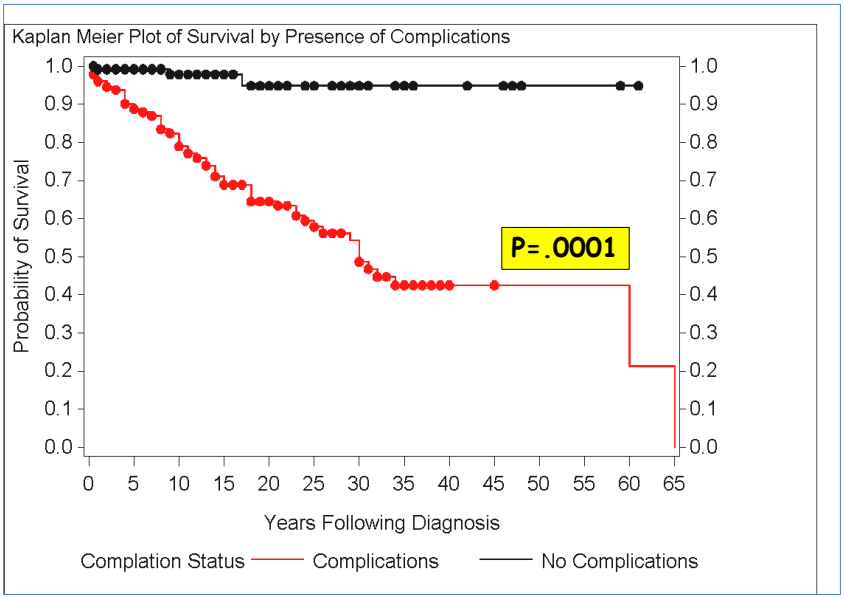
Mount Sinai Data: Kaplan-Meier overall survival curves.



Elena S. Resnick et al. Blood 2012;119:1650-1657

blood

Presence of complications



Resnick et al, Blood: 2012

Fully Adjusted Cox Proportional Hazards Modeling of Complications as related to mortality.

Clinical	Hazard Ratio	95% CI	P-value
Infections only	0.091	[0.029, 0.287]	<0.0001 *
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Lymphoma	2.402	[1.401, 4.117]	0.0014 *
Hepatitis	2.537	[1.539, 4.184]	0.0003 *
Lung Disease	2.091	[1.360, 3.216]	0.0008 *
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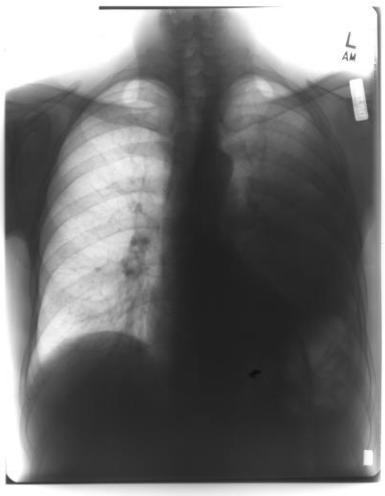
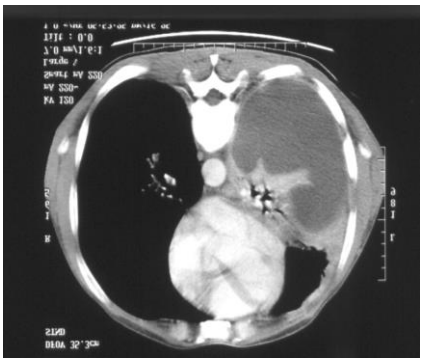
Malabsorption	2.026	[1.093, 3.757]	0.0250 *
Gastrointestinal Disease	1.765	[1.062, 2.934]	0.0285 *
Granuloma	1.258	[0.642, 2.464]	0.5041
Splenectomy	1.673	[0.905, 3.094]	0.1009

Resnick et al, Blood: 2012

Typical patient with infections only: Bacterial pneumonia and empyema

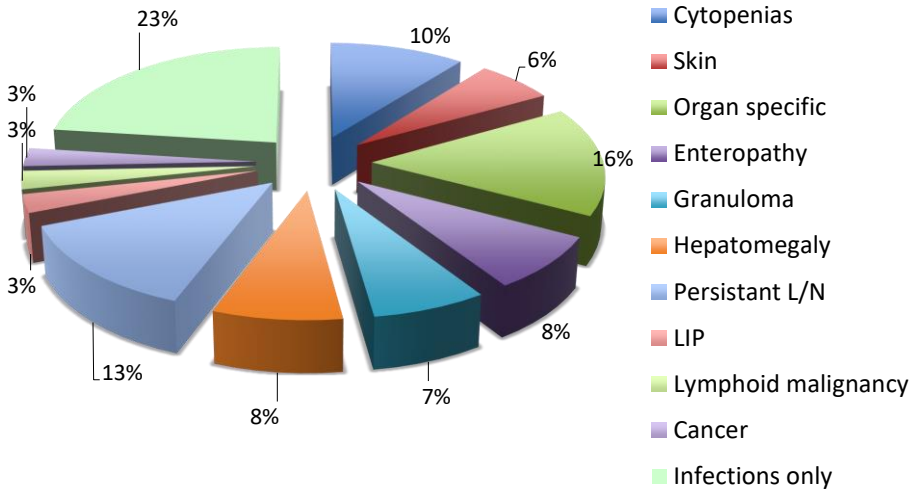




42 year old lawyer with second episode of pneumonia in 2 years; developed empyema. *S pneumonia* was cultured. Required prolonged chest tube drainage and Decortication

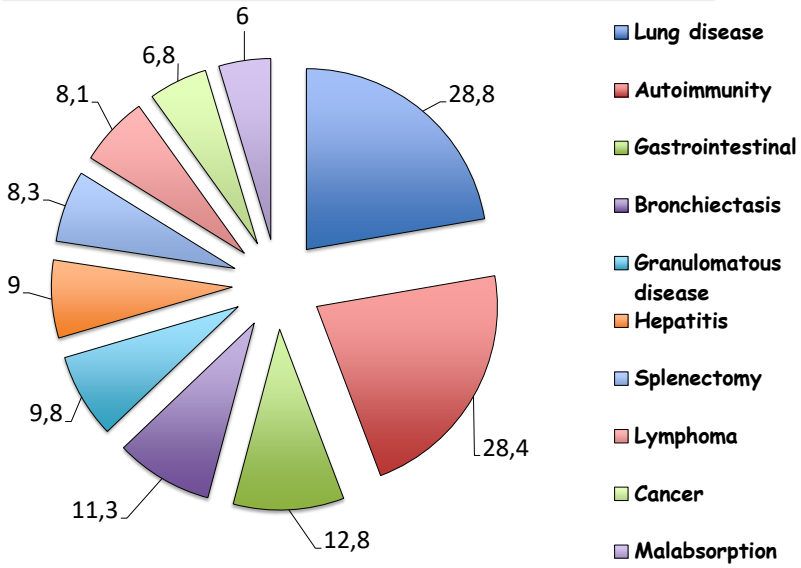
IgG= 54; IgA= 1; IgM= 4

Phenotypes in CVID



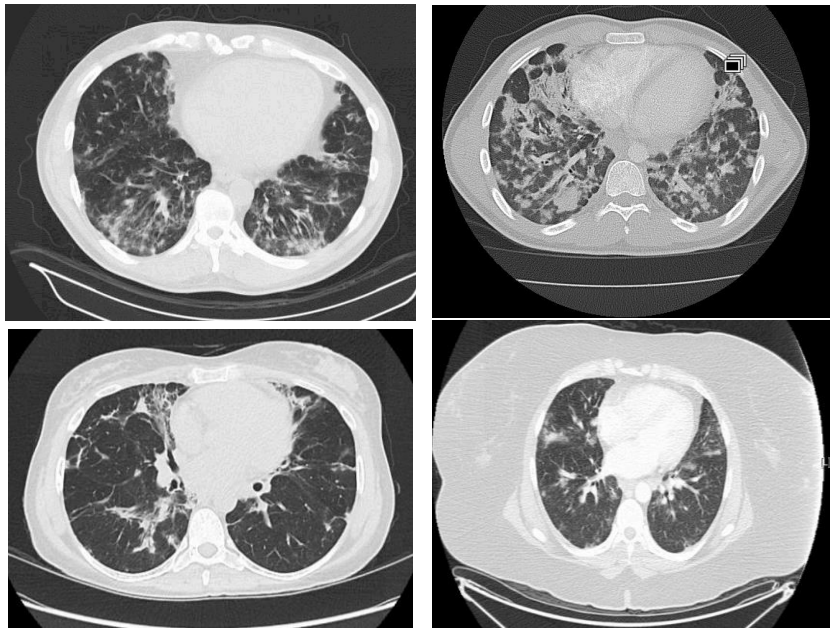
Chapel and Cunningham-Rundles Br J Haematol. 2009; 145(6): 709–727.

Complications in 473 CVID subjects from MSSM



Resnick et al Blood 2012

Four patients, similar phenotype: Interstitial Lung disease



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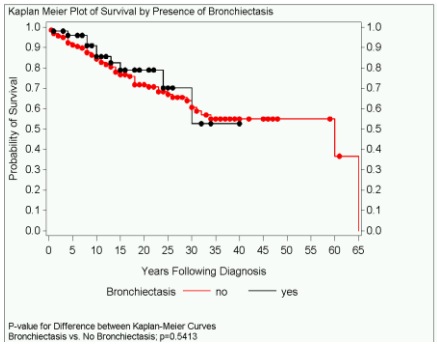
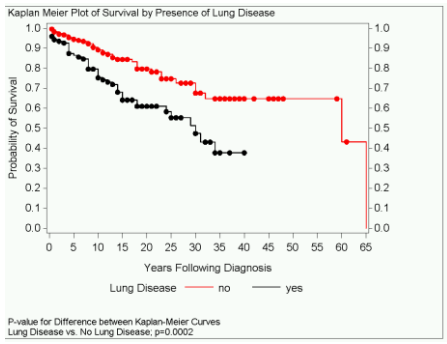
Resnick et al, Blood: 2012

Increased mortality in subjects with ILD and lung impairment

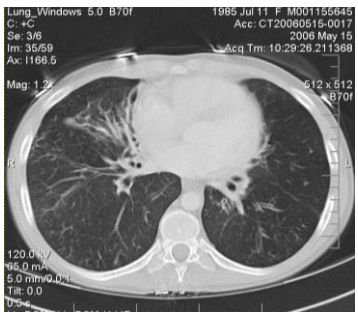


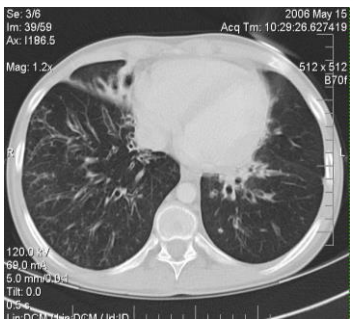
Bronchiectasis

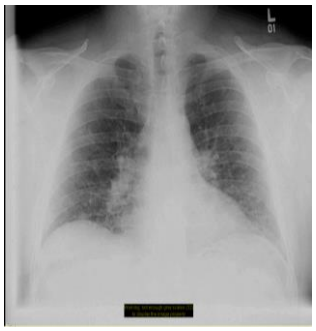


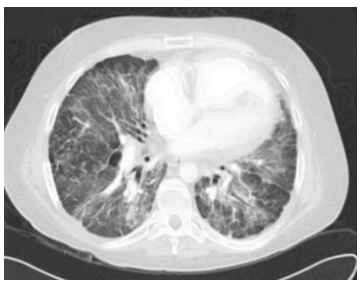
Impaired Lung Function

Systemic granulomatous Disease - 8 to 20%









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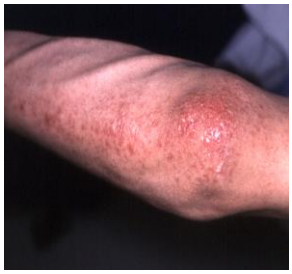
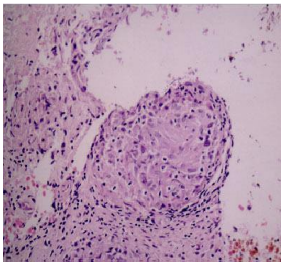
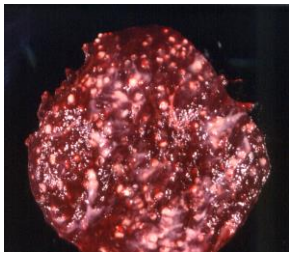


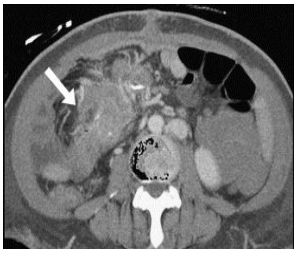
cutaneous



Bone marrow



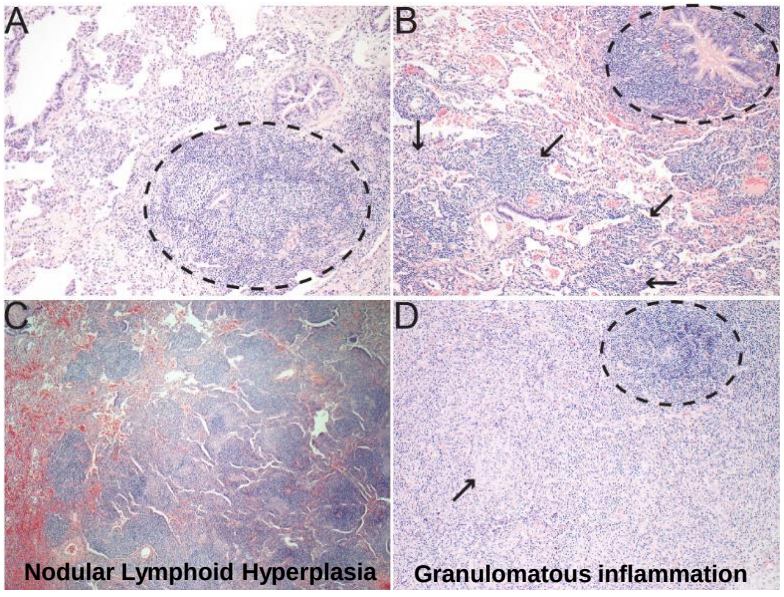
spleen



Abdominal

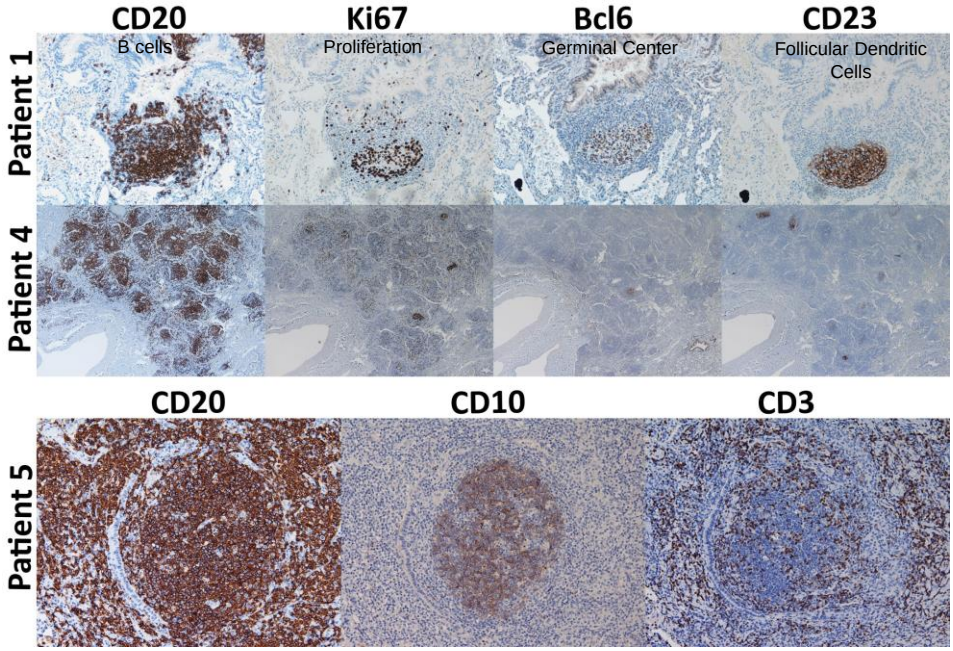
Pulmonary lymphoid hyperplasia is the common pathology

Follicular Bronchiolitis **Lymphocytic Interstitial Pneumonitis**



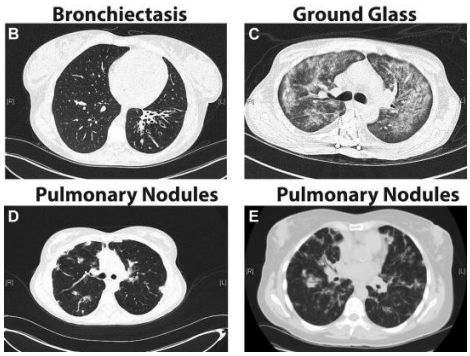
Schussler, Beasley, and Maglione. 2016. *J Allergy Clin Immunol Pract*. In press.

Tertiary lymphoid structures are a feature of CVID ILD



Maglione et al. 2014. *J Allergy Clin Immunol.* 133: 535-42.

CVID ILD is part of generalized immune dysregulation



Bronchiectasis was found in 1/3rd of patients with CT evidence of ILD
(5 or more pulmonary nodules, ground glass opacity)

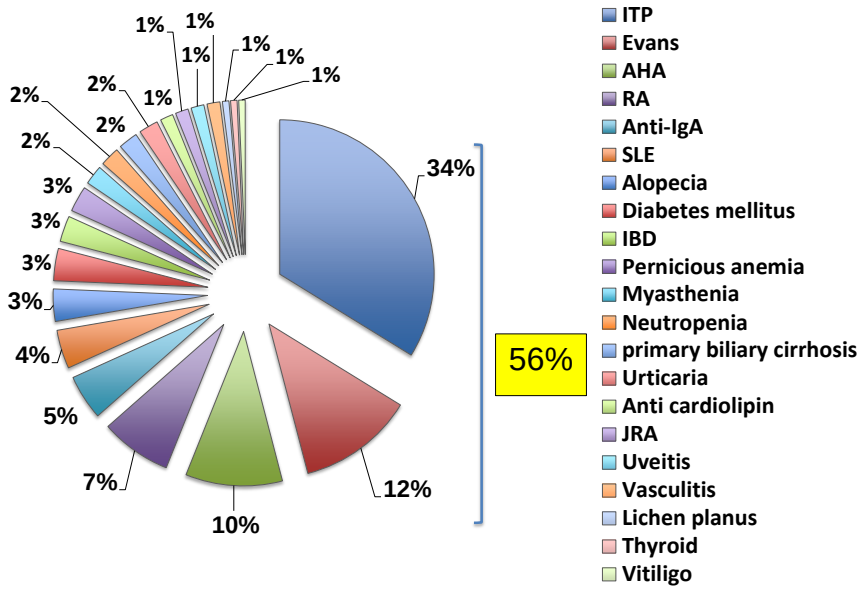
ILD results from immune dysregulation
- present at diagnosis in most cases
- younger CVID patients
- monogenic "CVID-like" disorders

(CTLA-4 haploinsufficiency, LRBA def., PI3Kdelta and STAT3 gain-of-function)

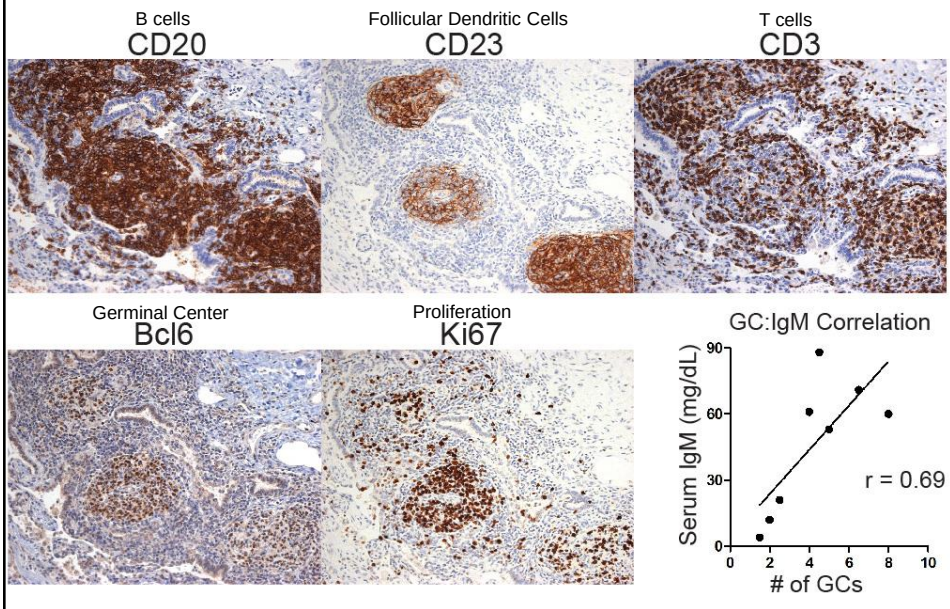
	ILD	No ILD	*P* value
Patients, n	39	22	
Patients, n (%), with			
History of pneumonia	22 (56)	14 (64)	.78
Splenomegaly/splenectomy	24 (63)	2 (9)	<.0001
AIHA/ITP	22 (56)	1 (5)	<.0001
Liver disease	8 (21)	0 (0)	.042
Enteropathy	4 (10)	2 (9)	1.00

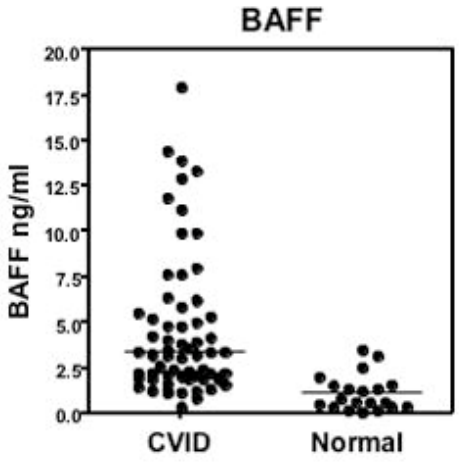
Maglione et al. 2014. *Ann Allergy Asthma Immunol.* 113: 452-9.

CVID: 28% with Autoimmune diseases

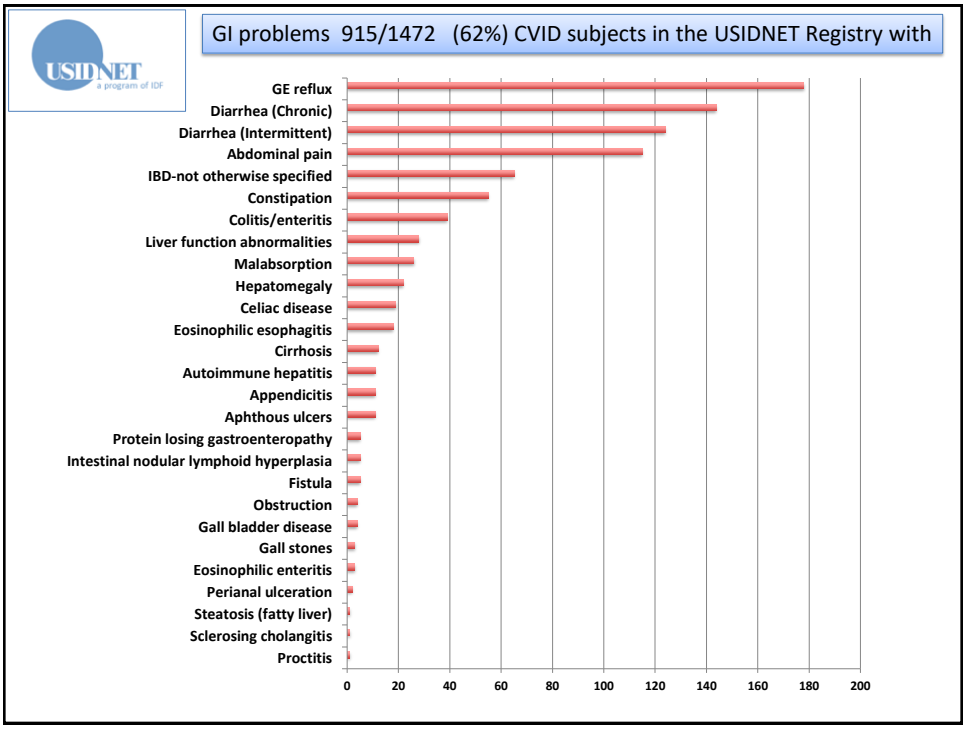


Serum IgM level correlates with ectopic germinal centers

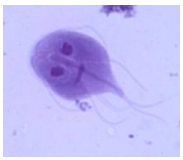




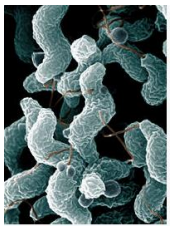
Knight et al, 2008

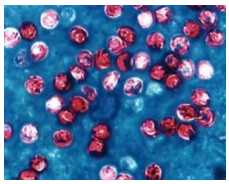


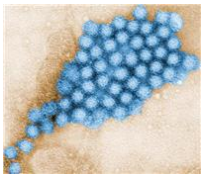
Infections

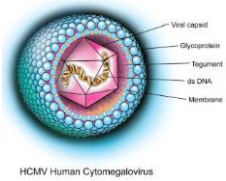


H Pylori
Giardia
Salmonella
Campylobacter
Cryptosporidia
Cytomegalovirus
Norovirus
Bacterial overgrowth









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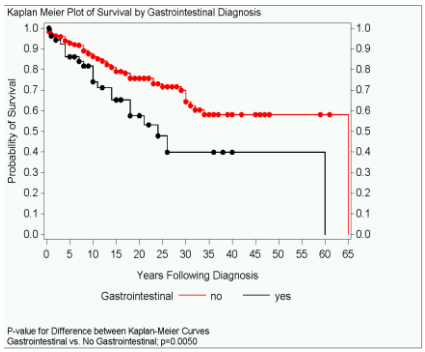
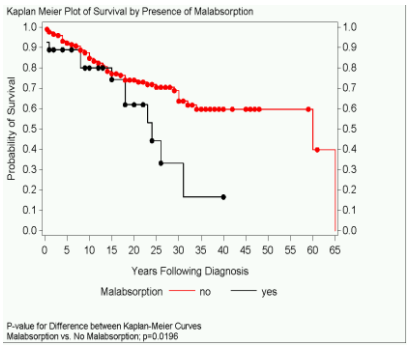
Resnick et al, Blood: 2012

Increased mortality in GI disease





Gastrointestinal

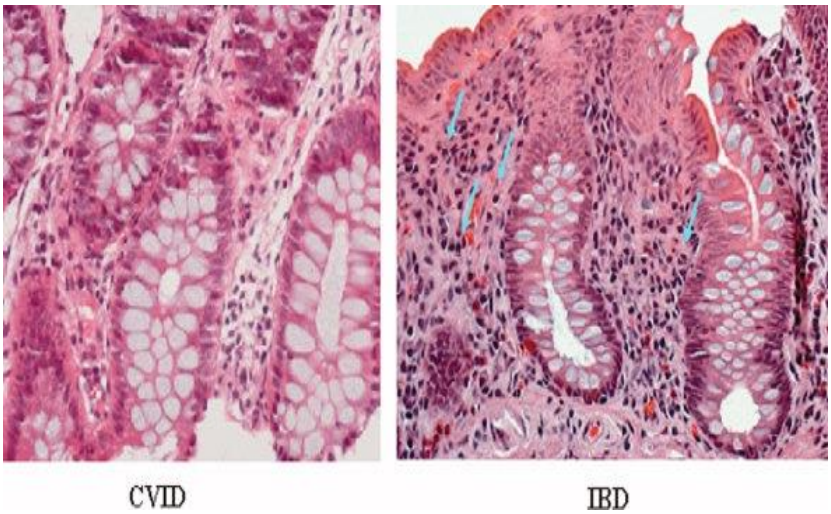
Malabsorption

Resnick et al, Blood: 2012

55 CVID patients with enteropathy (MSSM)

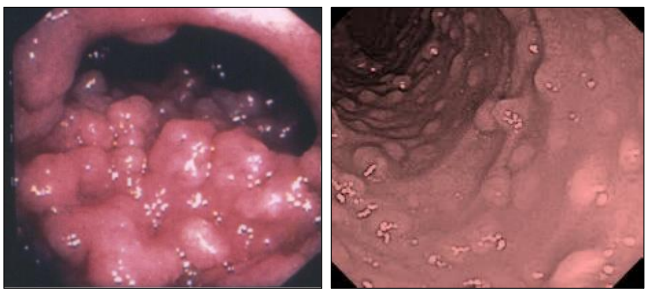
- 29 females and 26 males.
- Mean age diagnosis of CVID was 32 years (range 2-74 years)
- Mean IgG 232 mg/dl (range 0-540), IgA 17 (0-155), IgM 43 (0-400)
- 23.6% also had autoimmune disease
- 19 had died
- Mean age of death was 44 (22-77)
- Median years from diagnosis to death was 11 (range 1-29)
- Three subjects had previously had stomach, breast and testicular cancer. Two had lymphoma; one had Hodgkin's disease

Loss of mucosal plasma cells

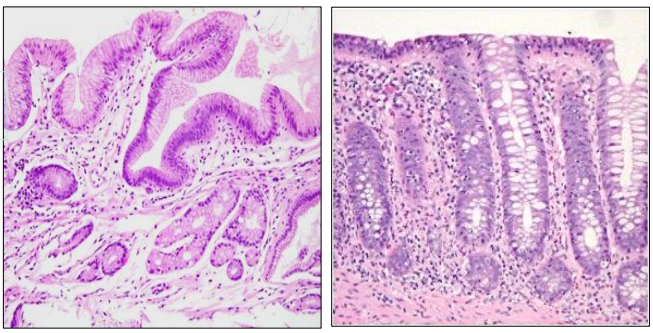


Endoscopic views and pathology

Nodular hyperplasia

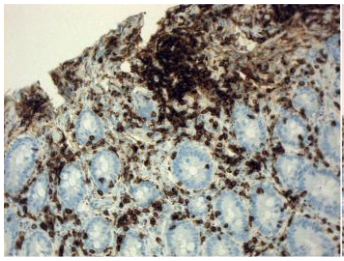


Lymphocytic infiltrate; villous atrophy

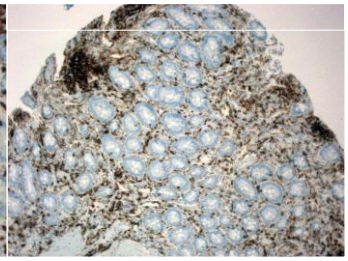


Lymphocytic infiltrates

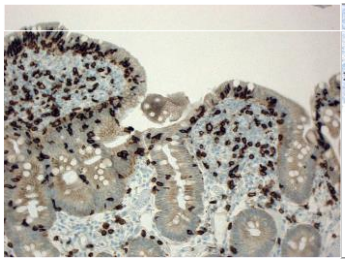
CD3 total T cells



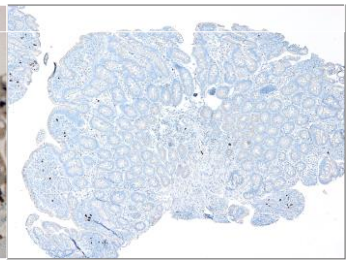
CD4 helper T cells

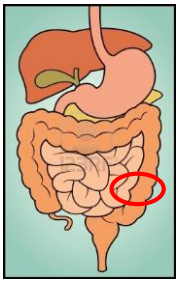


CD8 “suppressor” T cells



CD20 B cells





F.Souto

Laboratory Markers?

Laboratory Differences in CVID cohorts (n = 91)

	Complications n=47	No Complications n=44	*P-value
Age	42 yrs (32-49.5)	43 yrs (38.8-55.8)	0.36
IgG	207.5 mg/dl (94.3-341.5)	202 mg/dl (67.5-352.8)	0.75
IgA	7 mg/dl (0-15.5)	8 mg/dl (6.0-20.5)	0.12
IgM	18 mg/dl (6.5-46.0)	22 mg/dl (12-40)	0.99
B cell%	7% 0.2-14.5	9.5% 0.1- 13.9	0.001
Isotype switched memory B cells	0.65% 0- 1.6	1.3% 0.45-2.4	0.001
Absolute Lymphocyte	1100 (800-1600)	1300 (1100-3100)	0.03
T cells	75% (65.3-82.5)	75% (65.3-82.5)	0.63
CD4+ T cells	581 (513-816)	579 (336-708)	0.5

*Mann-Whitney 2-tailed test

20 year old : IgG 168 mg/dl; IgA = 10, IgM= 24. Infections only

CD19+ % of total Lymphocytes		11.7	%	2.8-17.4
CD20+ % of total Lymphocytes		11.8	%	3.2-16.8
CD27+ % of CD19+ B cells	L	4.8	%	6.3-52.8
CD27+ IgM+ IgD+ % of CD19+ B cells		3.7	%	1.7-29.3
CD27+ IgM- IgD- % of CD19+ B cells	L	0.5	%	2.3-26.5
CD27+ IgM+ IgD- % of CD19+ B cells		0.3	%	0.0-5.3
IgM+ % of CD19+ B cells	H	88.8	%	26.0-78.0
CD38+ IgM- % of CD19+ B cells	L	2.9	%	4.1-42.2
CD38+ IgM+ % of CD19+ B cells		31.6	%	1.2-50.7
CD21+ % of CD19+ B cells		96.8	%	92.1-99.6
CD21- % of CD19+ B cells		3.4	%	0.2-8.6
CD19+		151.2	cells/mcL	90.0-539.0
CD20+		152.5	cells/mcL	95.0-580.8
CD27+	L	7.3	cells/mcL	18.0-145.0
CD27+ IgM+ IgD+		5.6	cells/mcL	4.0-85.0
CD27+ IgM- IgD-	L	0.8	cells/mcL	7.0-61.0
CD27+ IgM+ IgD-		0.5	cells/mcL	0.0-12.0
IgM+		134.3	cells/mcL	37.0-327.0
CD38+ IgM-	L	4.4	cells/mcL	7.0-153.0
CD38+ IgM+		47.8	cells/mcL	2.0-139.4
CD21+		146.4	cells/mcL	85.0-533.0

TACI expression on B cells — no reference range established
BAFF-r expression on T cells — no reference range established

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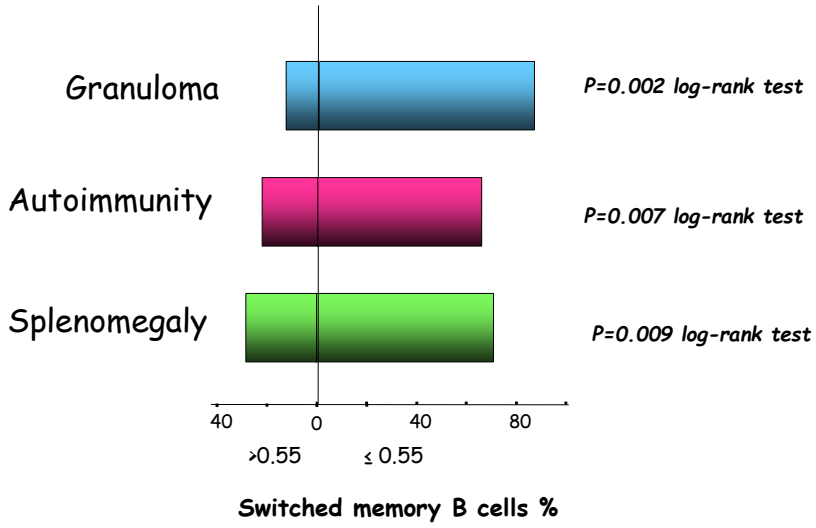
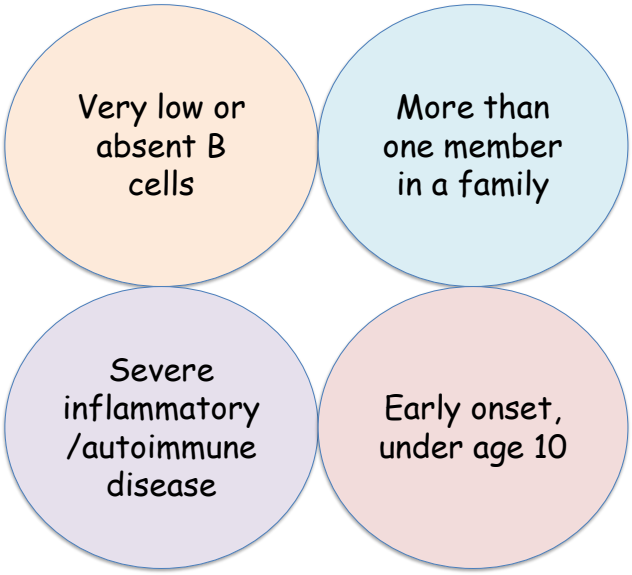
TACI expression on B cells — no reference range established
BAFF-r expression on T cells — no reference range established

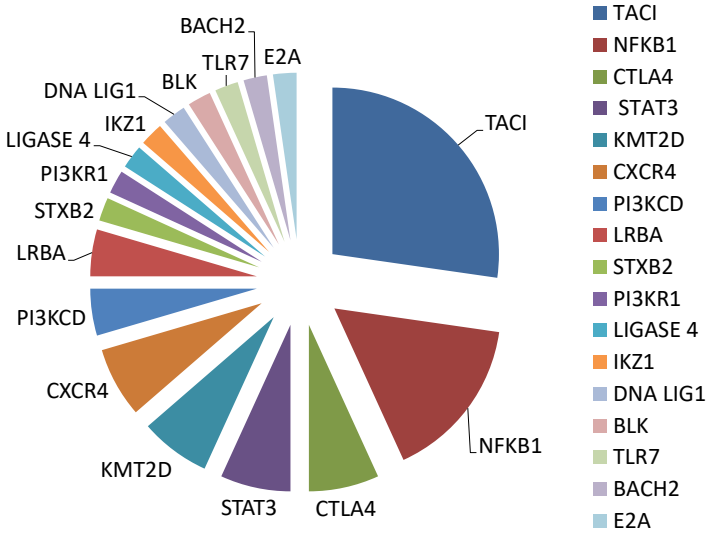
The percent of patients with selected complications is highly correlated to the numbers of switched memory B cells



Whole exome studies: Selectively Chosen subjects



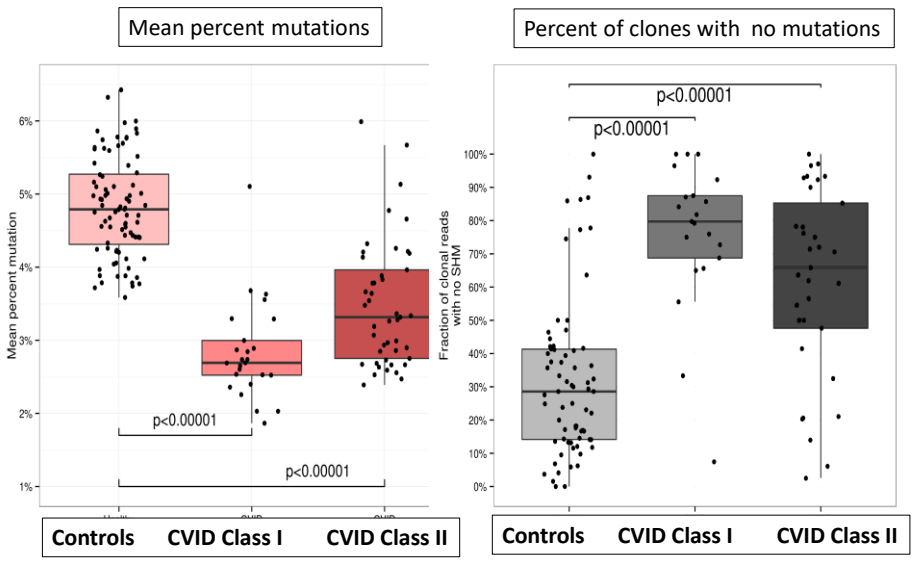
44 Causative genes identified in 132 CVID subjects --- genes other than TACI (32 subjects)



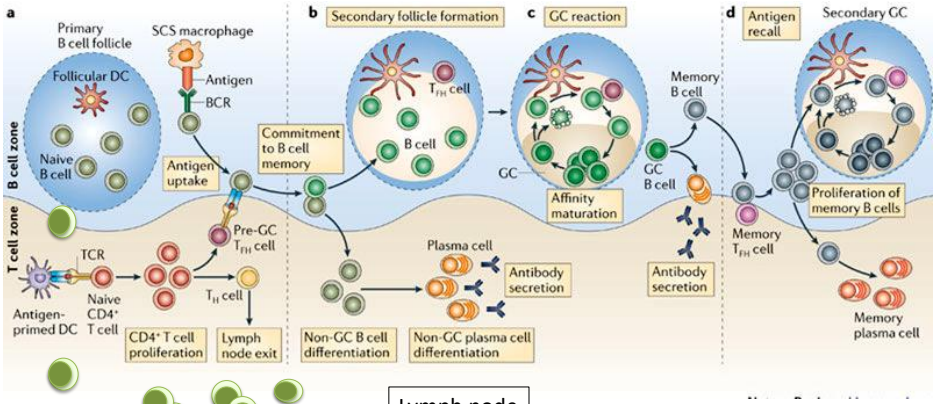
IUIS Classifications

1. Immunodeficiencies affecting cellular and humoral immunity
2. Combined immunodeficiencies with associated or syndromic features Ligase 1, Ligase 4, KMT2D
3. Predominantly Antibody Deficiencies
Severe Reduction in All Serum Immunoglobulin Isotypes E2A; PIK3R1
Severe Reduction in at Least 2 Serum Immunoglobulin Isotypes with low or nl B cells NFKB1, IKZF1; PIK3CD
Severe Reduction in IgG and IgA with Normal/Elevated IgM CD40L
Isotype, Light Chain, with Normal Number B Cells
4. Diseases of Immune Dysregulation STXBP2; CTLA4; LRBA: BACH2
5. Congenital defects of phagocyte number or function
6. Defects in Intrinsic and Innate Immunity; TLR7; CXCr4
7. Auto-inflammatory Disorders
8. Complement Deficiencies
9. Phenocopies of Inborn Errors of Immunity

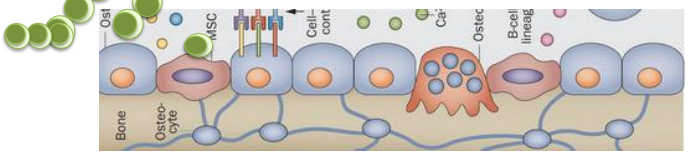
Universally impaired somatic hypermutation



Roskin et al, Science Trans Med 2015

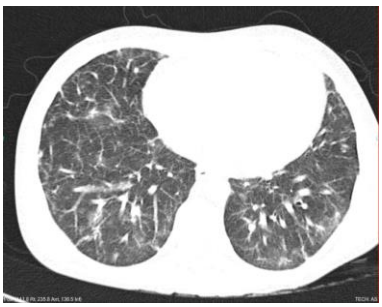


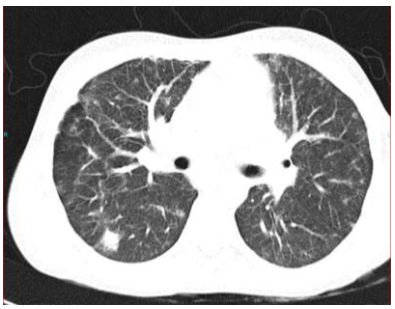
Lymph node



Bone marrow

19 year old girl with progressive lung disease and enteropathy



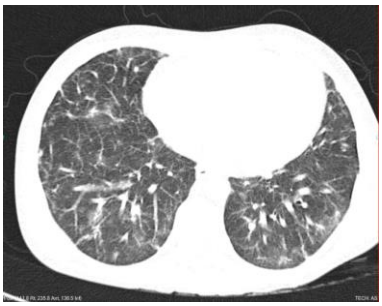


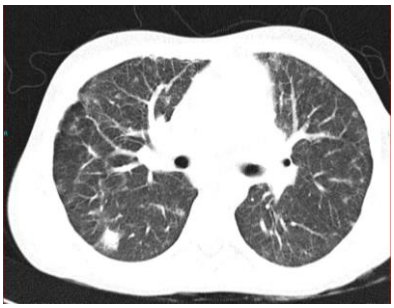
- Lymphocytic infiltrates
- Foci of bronchioltitis obliterans
- No organisms
- Mixed T and B cell infiltrate with lymphoid nodules
- Reactive germinal center changes with mitotic figures
- Probable non caseating granuloma
- Rare giant cells

IgG= 594; IgA<5, IgM normal

GI biopsy: villous atrophy

19 year old girl with progressive lung disease and enteropathy





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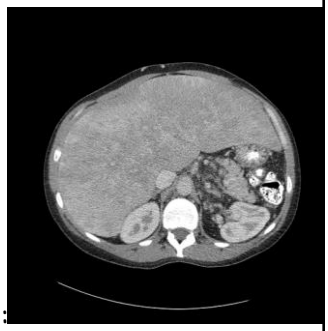
CTLA4:c.56_57insCTGG:p.T19fs

35 year old woman with autoimmunity and liver disease

- Frequent infections, diagnosed with CVID started on IVIg.
- IgG =20; IgA = <4; IgM=<5
- Immune thrombocytopenia
- Splenectomy;
- Granulomatous autoimmune hepatitis
- Prednisone; methorexate =
- Liver re-biopsied: =Cell Cept + prednisone
- Bronchitis, sinusitis continue; asthma diagnosed:
- CD3 =nl ; CD4= low CD8=increased ,CD56 =high; CD19 = very low
- Liver infiltrate: oligoclonal T cell population
- Died of liver and lung failure age 39



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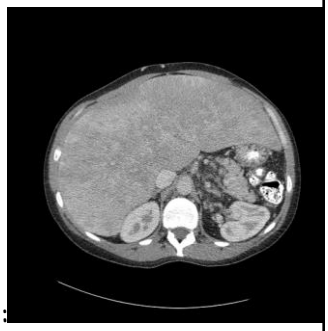
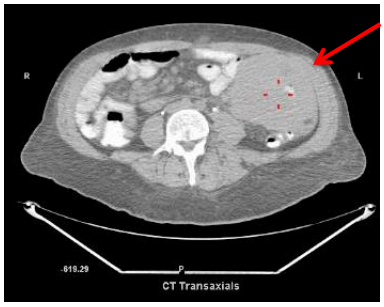
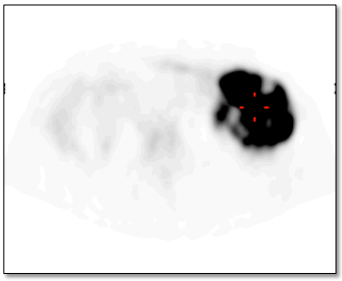


LRBA:exon11:c .A1399G:p. M467V
LRBA:exon57:c.C8351G:p. A2784G

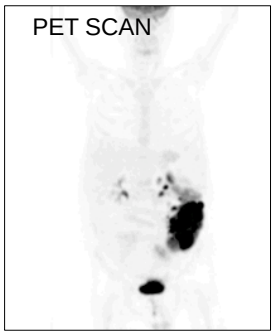
41 year old man with known CVID since age 20



PET SCAN



PET SCAN

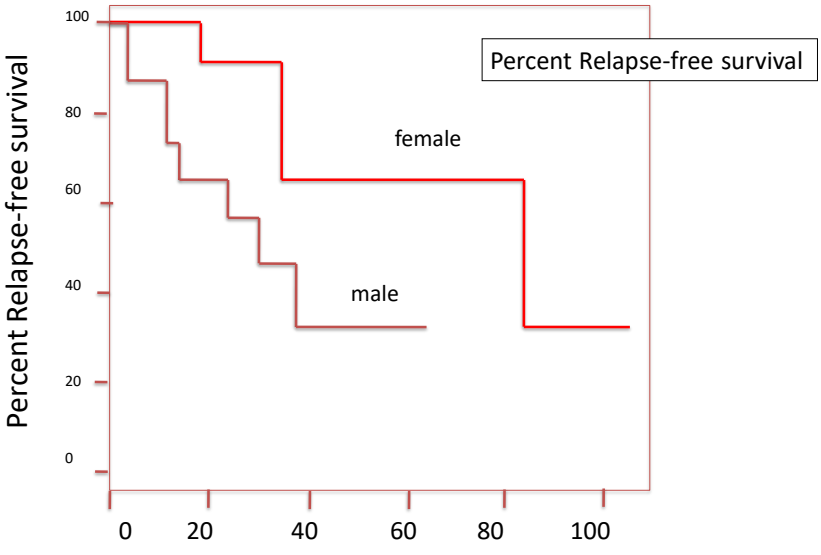


History of ITP at age 11
IgG= 50; IgA = 0; IgM = 2; B cells 0.1%
On IVIG
C/O diarrhea and giardia isolated
Refractory to treatment with metronidazole
Abdominal pain and obstruction
CT showed a mass
PET scan = lymphoma
IgA + Plasmablastoid lymphoma/jejunum
Extensive chemotherapy,
Expired **PIK3CD:exon13:c.T1558G:p.S520A**

Treatment

- Optimize Ig
- Steroids
- Rituximab
- Hydroxychloroquine
- Azathioprine, 6MP
- Cell Cept
- Sirolimus, everolimus
- Avoid splenectomy
- New agents: TNF inhibitors; abatacept; vedolizumab; tocilizumab

Rituximab for Cytopenias in CVID: responses

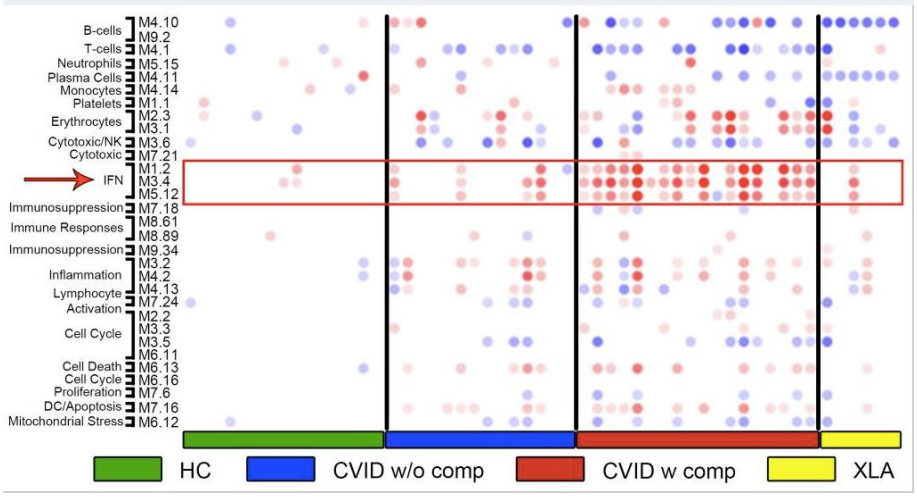


Gobert, et al BJH, Oct 2011

What next?

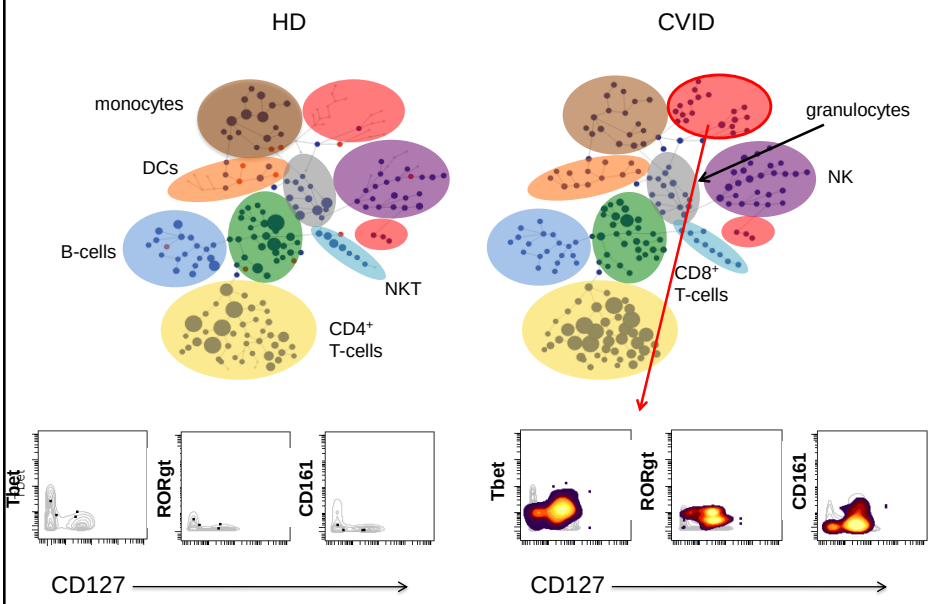
1. Inflammatory Disease in CVID: why? Just the loss or regulatory genes?
2. Role of innate lymphoid cells in inflammatory disease?
3. Other causes?

Interferon signature in inflammatory complications in CVID

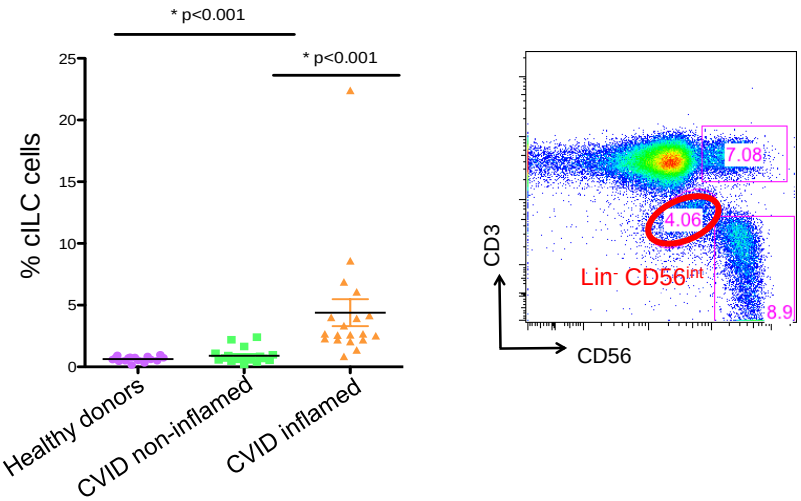


Park et al, PLOS 2013

CyTOF to identify cellular subsets on blood

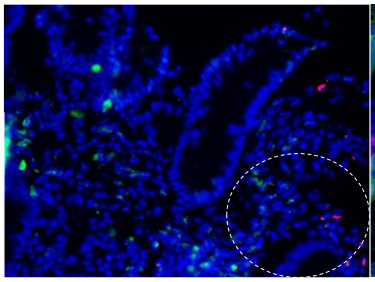


Circulating ILC increased in CVID patients with inflammatory complications

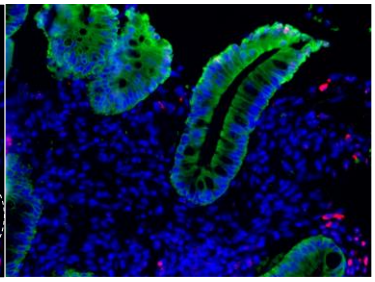


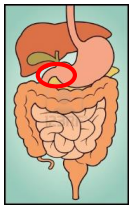
Lineage cells: CD1d, CD3, CD11c, CD14, CD123, CD19, TCR-γδ

CD3 IFN-γ DAPI

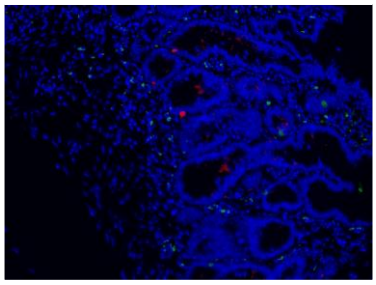


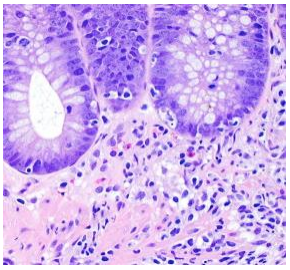
Cytokeratin IFN-γ DAPI





CD3 RORc DAPI





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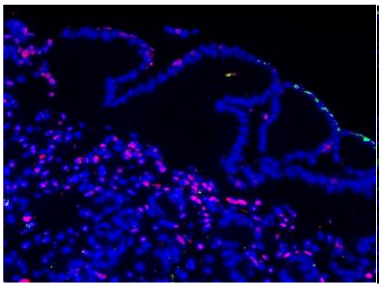

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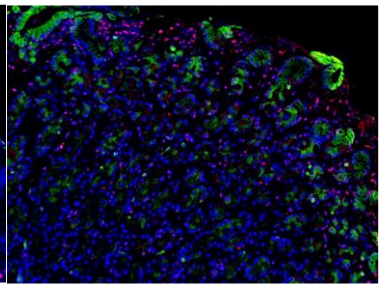
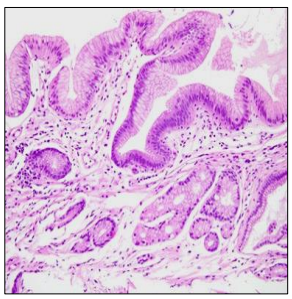
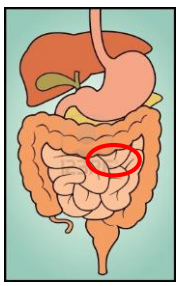
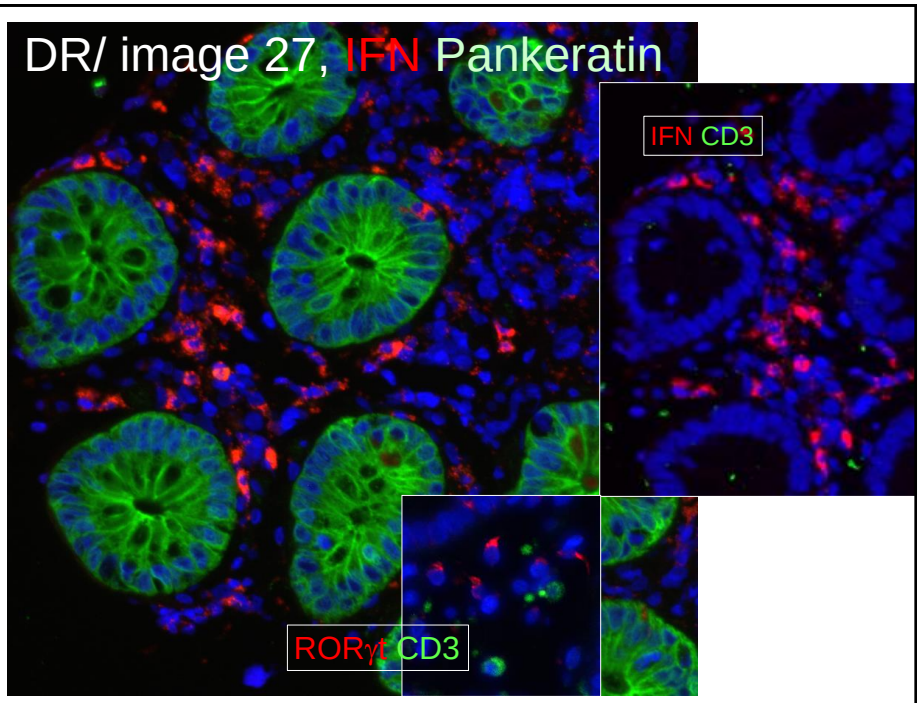


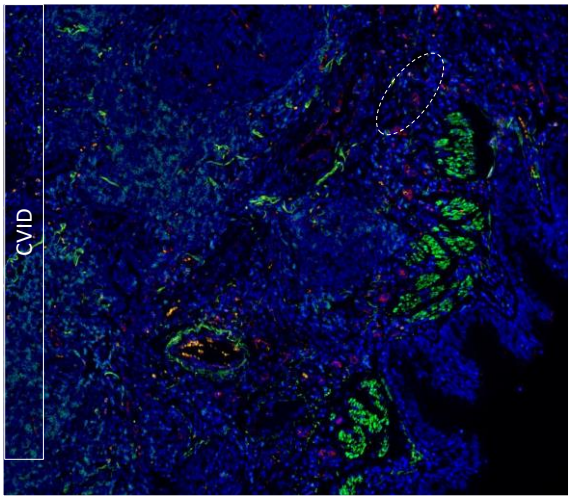


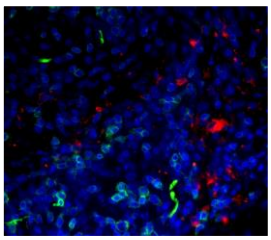


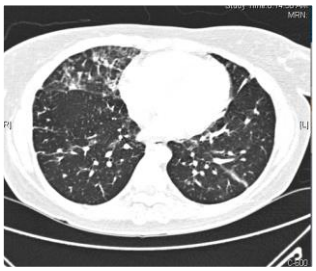


Lung Biopsy Samples

CD3 IFN-γ DAPI







Inflammatory conditions in CVID have been called "Non-infectious" complications.

But are they promoted and/or sustained by microbial infections that cannot be eliminated due to the defective immunity?

Summary

1. CVID: an immune syndrome due to many causes
2. More of a pure B cell defect in some
3. Inflammatory phenotypes in 30-50%
4. Lymphoid and granulomatous expansion as a reflection of inflammatory drive
5. Innate lymphoid cells as a deleterious compensation?
6. Drivers of inflammation?

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