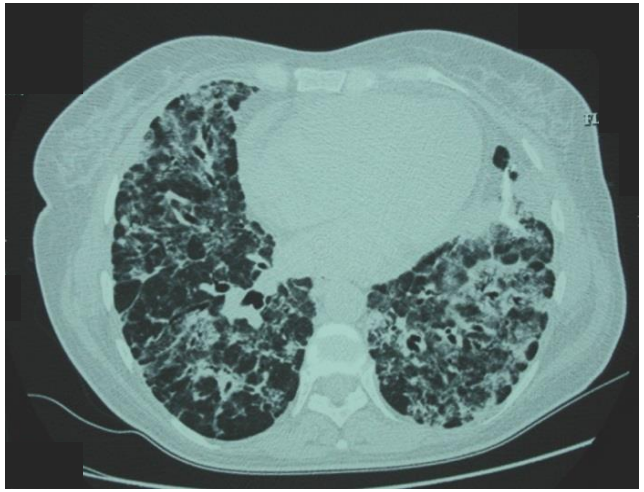
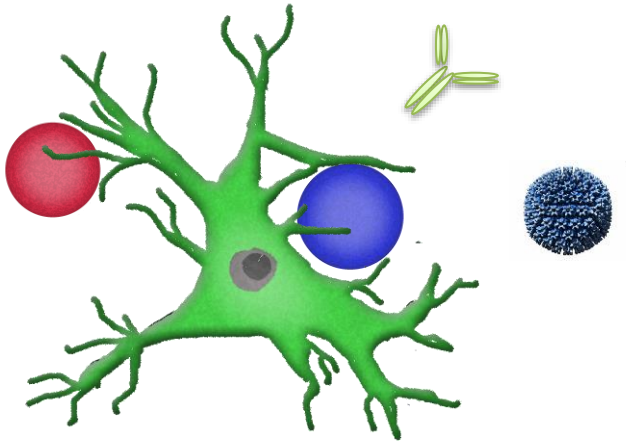




ILD in common variable Immunodeficiency

An introduction

SLIPI 2023

Klaus Warnatz
Department for Rheumatology and Clinical Immunology and CCI UMC Freiburg

CVID: A system disorder

Complex CVID

Infection only

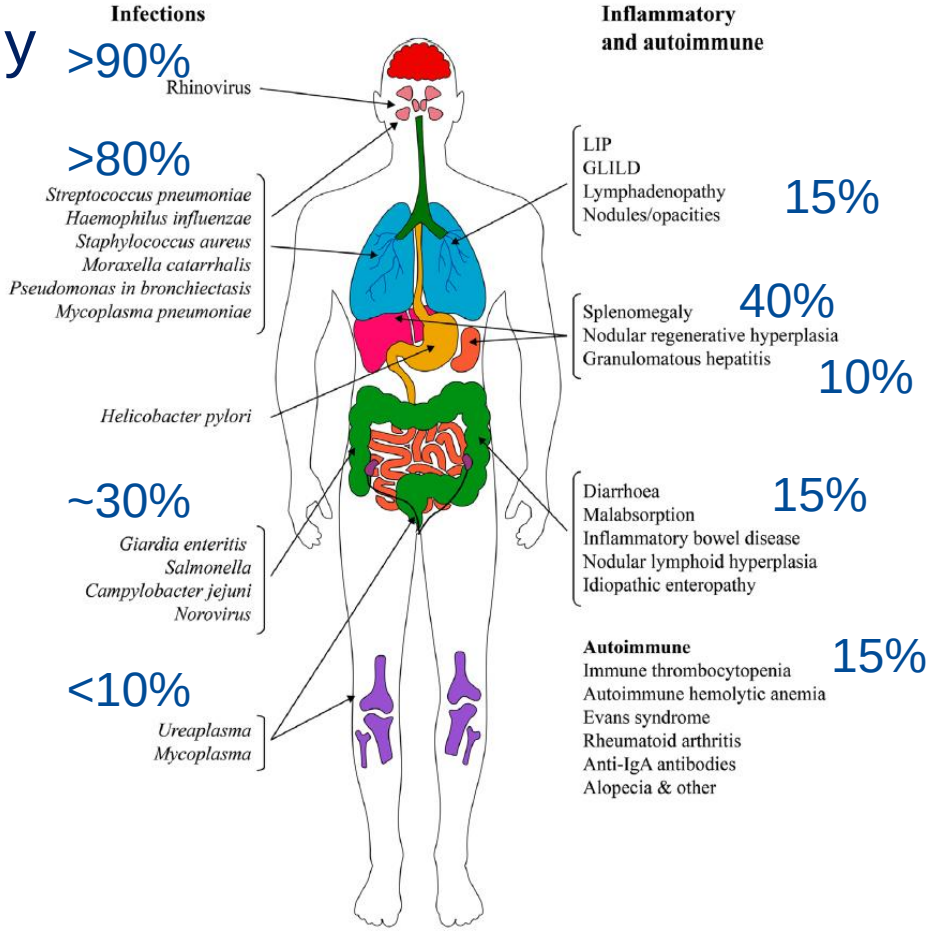
Heterogeneous primary Antibody deficiency disorder

Encapsulated bacterial RTI

>30% patients with autoimmune or inflammator. manifestations

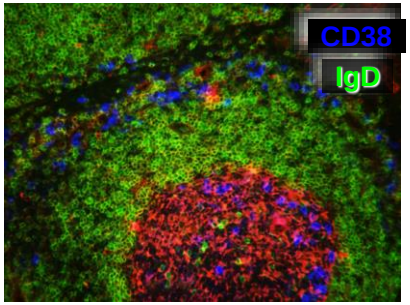
Up to 20% Patienten with monogenic etiology

First symptoms: Any age, frequently adolescents/young adults
Prevalence: ca. 1:25.000



Bonilla et al JACIP 2016

CVID: A failure of Germinal center output



Naive B cells

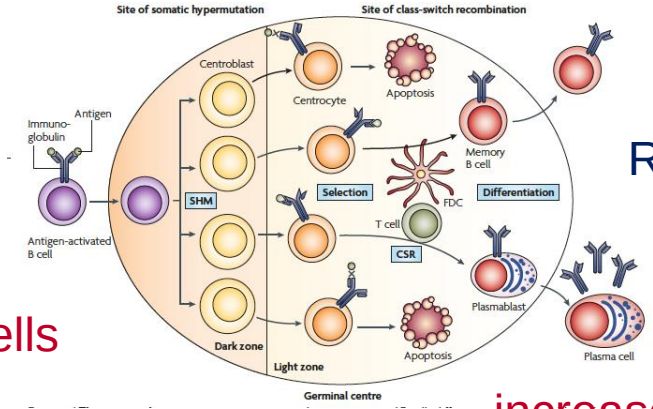
Activated Tbet+ B cells

Reduced regulator. T cells

Exhausted T cells

Reduced Naive T cells

increased autoreactive Tbet+ B cells



Reduced memory B cells

Reduced plasma cells

Expanded Th1 cells

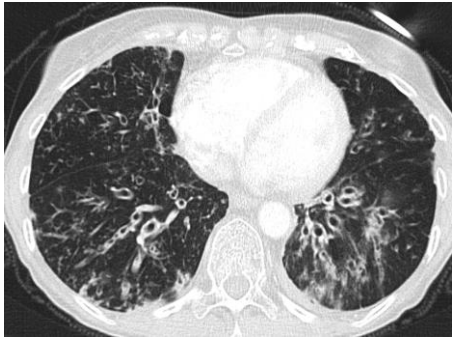
increased T follicular helper cells

Warnatz Blood 2002, Giovannetti JI 2006, Wehr Blood 2008, Muillot JoCI 2010, Unger JACI 2018, Le Coz JACI 2019, Jorgensen et al JoCI 2019

Pulmonary manifestations

Two distinct yet often comanifesting entities

Airway disease

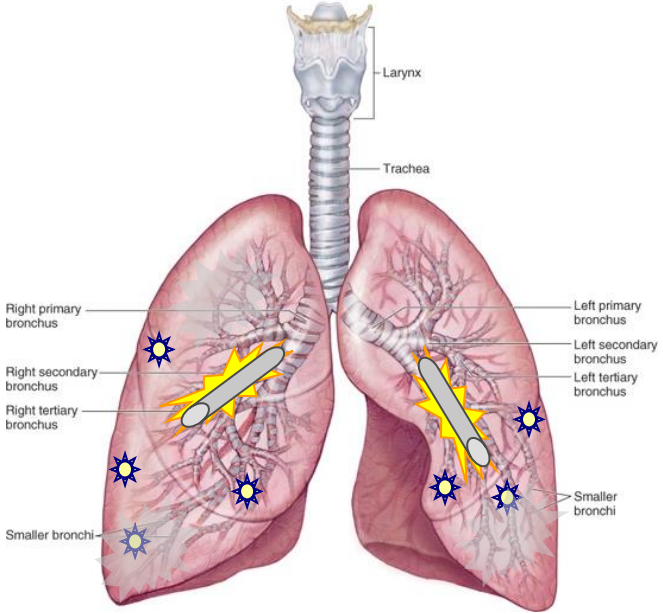


Ca. 30%

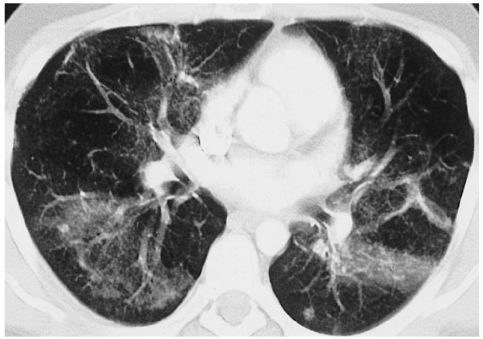
Infectious...

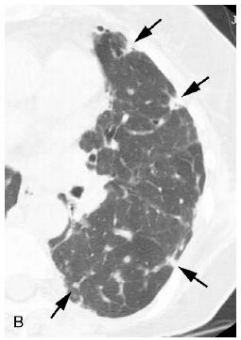
Local...

innate...



Parenchymal disease





Ca. 15%

Immun...

Systemic...

Adaptive...

Nodular infiltrates

Van de Ven et al Clin Exp Immunol. 2011 Aug;165(2):235-42

Park JE, et al *Eur.J.Radiol.* 2005, 54:359-364.
Bates CA, et al *J.Allergy Clin.Immunol.* 2004, 114:415-421.

Touw CML et al, Pediatr Allergy Immunol 2009
Wheat WH et al J Exp Med 2005; 202:479-84

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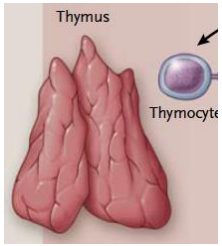
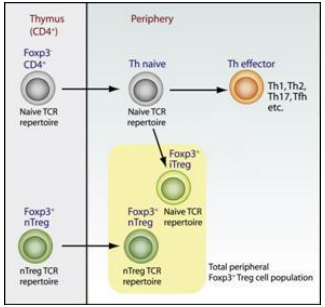
CVID: Pathogenesis of the immune dysregulation

Disturbed selection



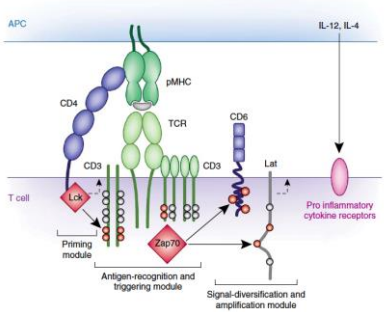
RAG
Di George

Altered Treg Homeostasis



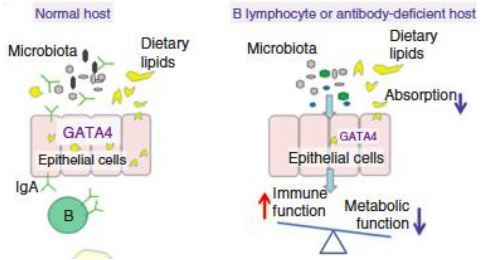
CD25, IL2
CTLA4, LRBA, ...

Disturbed activation



ITK
PI3Kδ (GOF)
STIM1
PKCδ
LAT
STAT1/STAT3 GOF

Increased danger signals



IFN
TLR?
??
??
2° GI Barrier

For review see among others: Agarwal Ann Allergy Asthma Immunol. 2019; Van de Ven Curr Opin Allergy Clin Immunol. 2015, a.o.m.

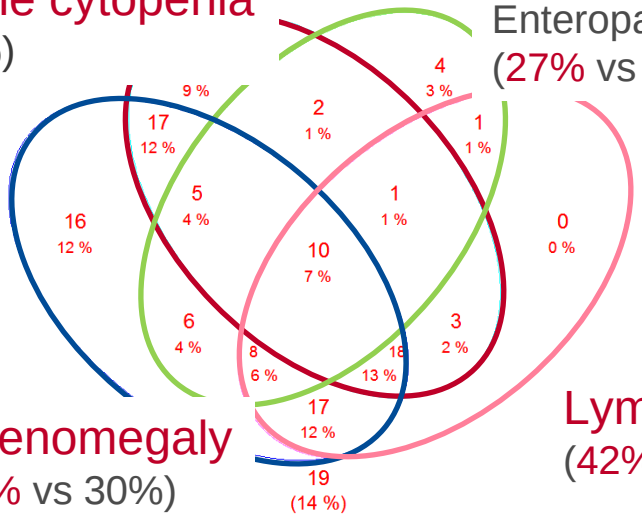
CVID-ILD: Clinics

About 15-20% of the CVID patients

Symptoms: initially few, exercise induced dyspnoea, dry cough

Autoimmune cytopenia
(49% vs 18%)

Enteropathy
(27% vs 24%)



Splenomegaly
(70% vs 30%)

Lymphadenopathy
(42% vs 25%)

When compared to total CVID

Conclusion:

ILD in CVID is part of a lymphoproliferative Multisystem disorder.

145 Patients in STILPAD

Goldacker et al in prep

CVID-ILD: Clinics

Parameter	In this cohort	In historical cohorts (n)	Included patients	Included studies	p-value
n	93	372		1,5,26,27,30,32–34,41–46	
Median age of gl-ILD onset (years)	43	29 – 56	gl-ILD	1,5,27,30,32–34,42,43,45,46	NA
gl-ILD >1 year diagnosed before CVID (%)	11	45 (78)	gl-ILD/ GD	3,44	**<0.01**
Sex (% F)	63	59 (357)	gl-ILD	1,5,27,30,32–34,41–46	0.48
Splenomegaly (%)	83	78 (343)	gl-ILD	1,5,26,30,32–34,41–46	0.21
Lymphadenopathy (%)	61	74 (217)	gl-ILD	26,30,33,34,41,43–45	**0.02**
Auto-immune cytopenia (%)	44	50 (294)	gl-ILD	5,27,30,32–34,41–44	0.31
Hepatopathy (%)	17	22 (219)	gl-ILD	5,26,30,32,33,42,43,45,46	0.33
Enteropathy (%)	16	21 (203)	gl-ILD	4,5,30,32,33,42	0.30
Lymphoma (%)	4	10 (218)	gl-ILD	1,26,30,32,34,42,45	0.07

CVID-ILD: Laboratory parameters

Parameter	In this cohort	In historical cohorts (n)	Included studies	p-value
Immunoglobulins at CVID diagnosis	83	268	[39]	
IgG <1.0 g/L	36	34 (188)	[39]	0.63
IgA <0.2 g/L	77	50 (257)	[39]	**<0.01**
IgM <0.07	40 (81)	30	[39]	0.09
EuroClass stratification (N)	78	303	[39]	
Switched memory B cells <2% (%)	76	58	[39]	**<0.01**
$CD21^{low}$ cells >10% (%)	71	57 (229)	[39]	**0.03**
Normal B phenotype (%)	8	26 (229)	[39]	**<0.01**
T cell phenotyping (N)	58	238	[47]	
CD4+ <200 (%)	4	3	[47]	0.71
CD4+ naive <10% (%)	45	25	[47]	**0.01**

CVID-ILD: Pathogenesis

Part of a systemic immunoproliferative disease

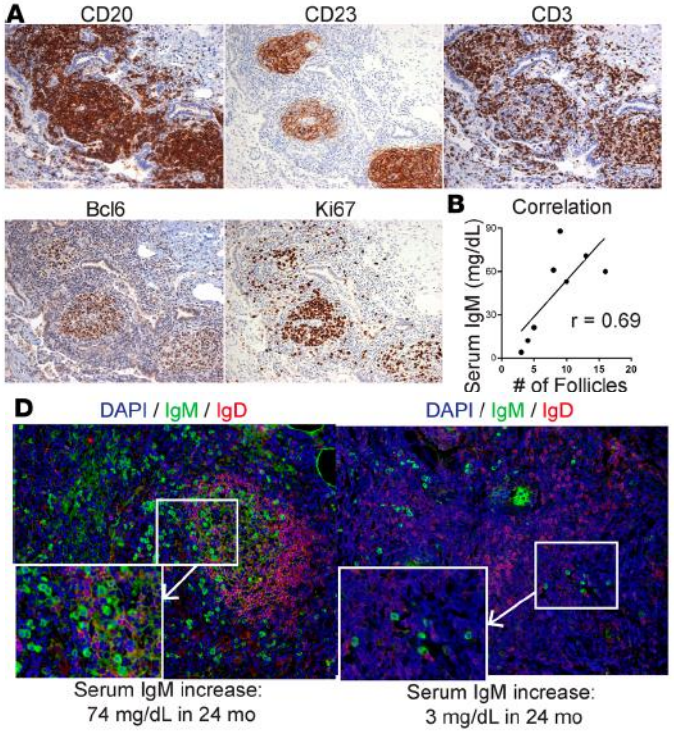
Genet. predisposition in CTLA-4, NFKB1, APDS, STAT3, u.a.

Lymphocytic mixed T&B cell infiltrates

No known trigger

BAFF stimulation possibly contributes to pathogenesis

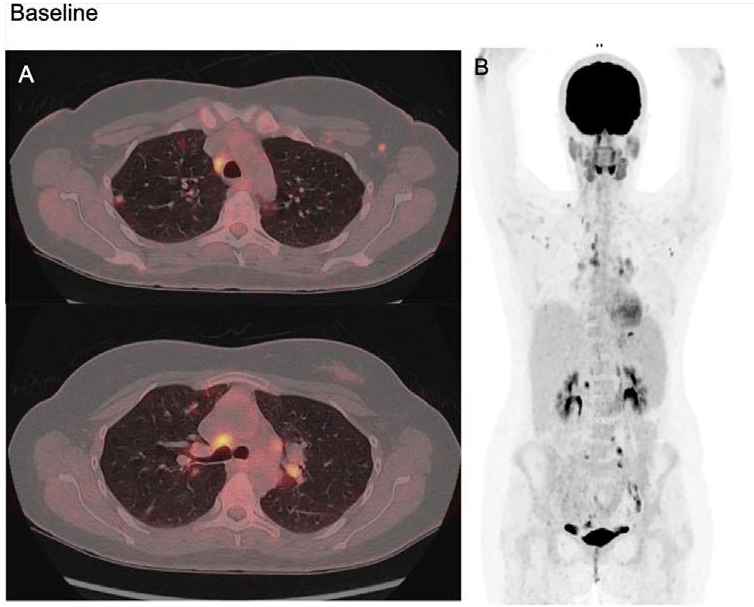
Histology: mostly mixed: Granuloma,
lymphoid (i.e., lymphoide hyperplasia, follic.bronchiolitis, LIP)
Inflammatory lesions (esp. OP).



Prasse A, Warnatz K. Cur Opin Rheum 2013, Maglione et al JCI insight 2019, Matson et al Front Immunol 2021

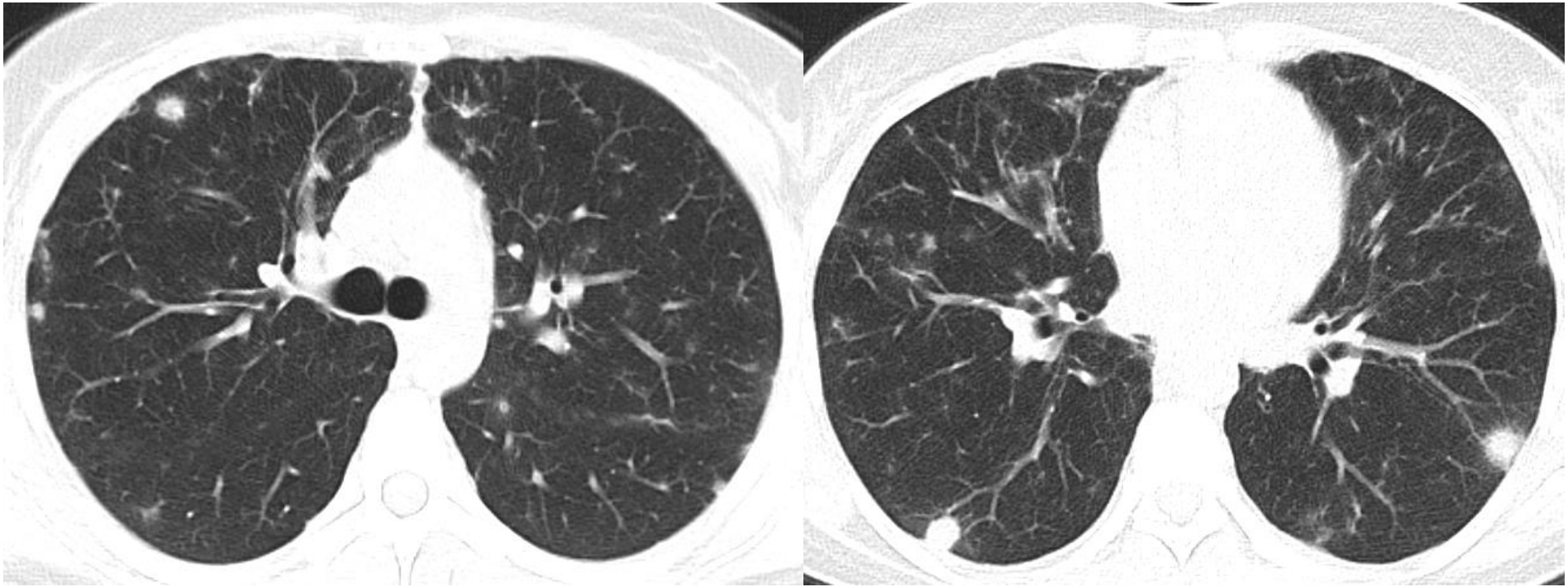
CVID-ILD: Diagnostics

- Clin history / Physical Examination
- Pulmonary function, CO-Diffusion, 6 min walk test
- Laboratory: ?? sIL2R, IgM increase?, ???
- Imaging: HR chest CT, MRI?, PET-CT?
- Bronchoscopy: BAL (pathogens,)
- (Cryo-) Biopsy?
- VATS??

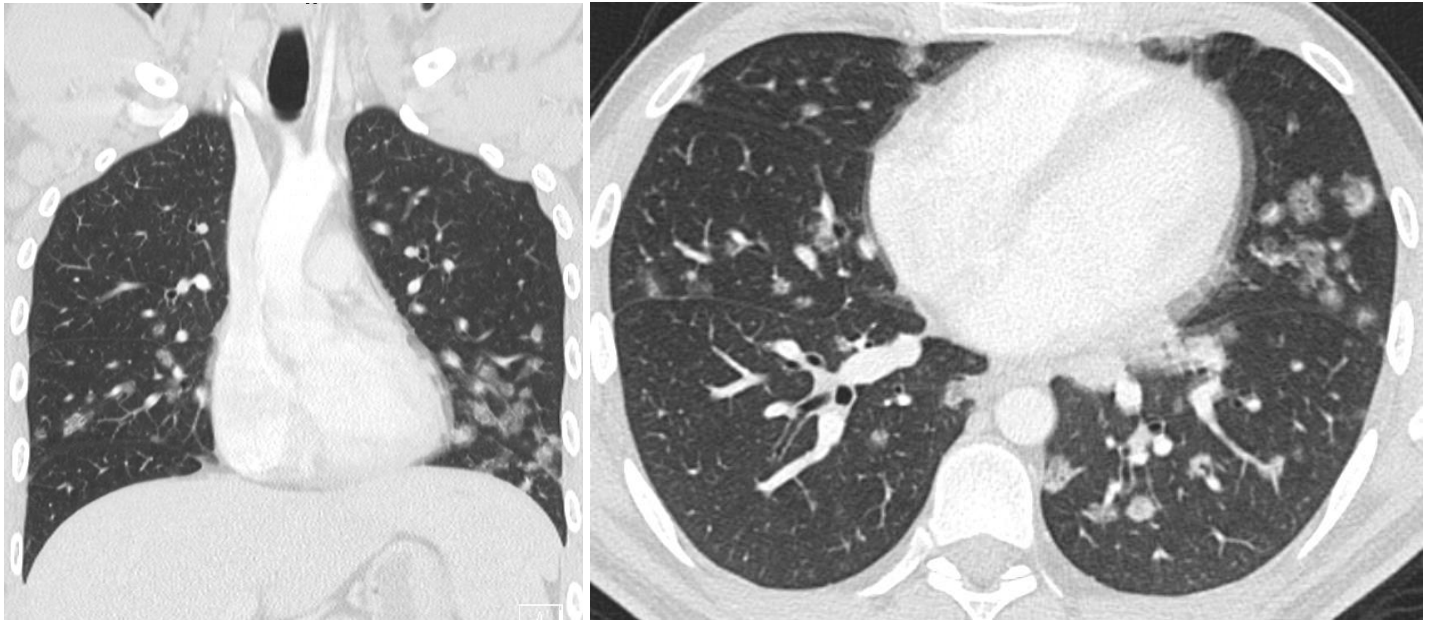


Van de Ven Front Immunol 2020, Fraz et al Front Immunol 2021, Cinetto et al Front Immunol 2021

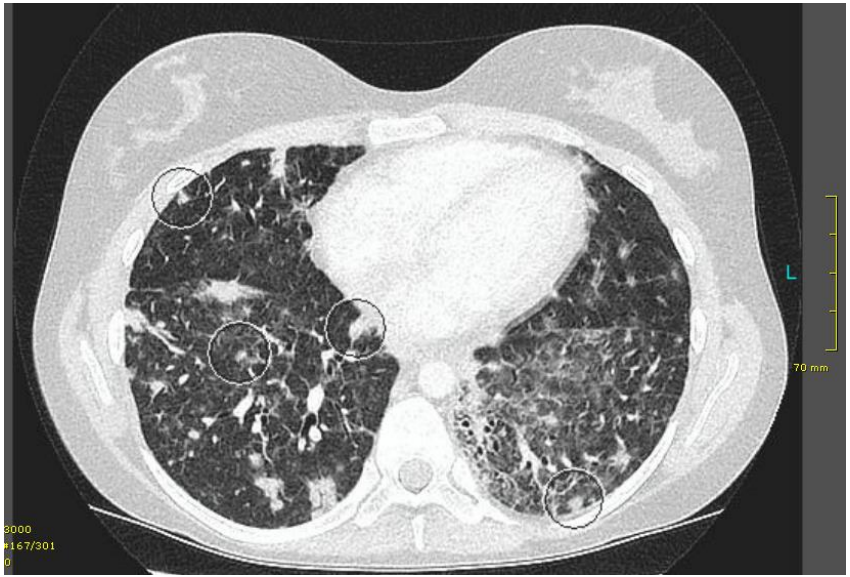
Nodular lesions in CVID-ILD

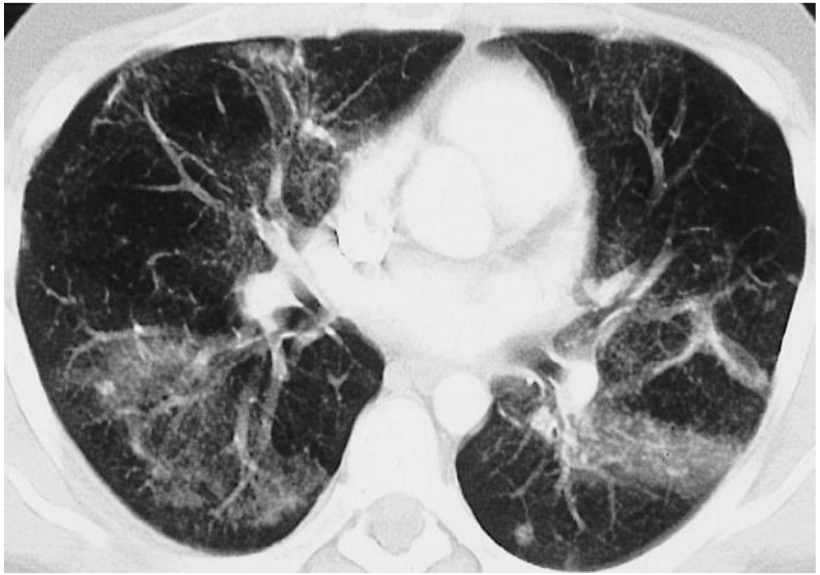


Nodular lesions in CVID-ILD

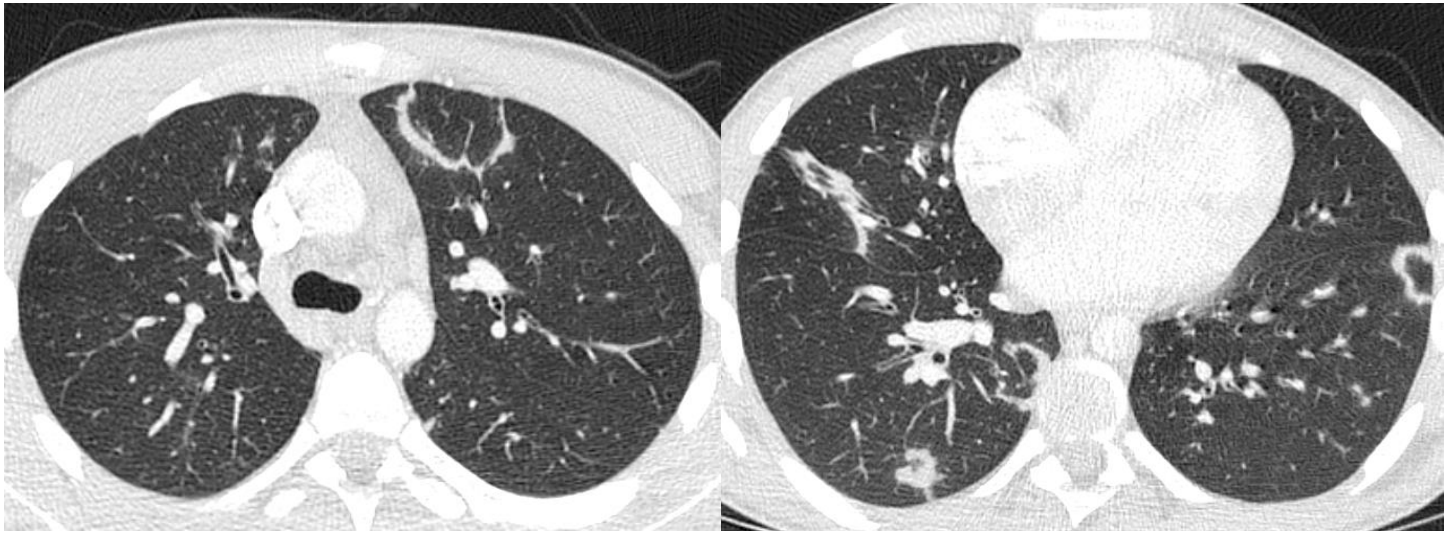


Ground glas opacities in CVID-ILD

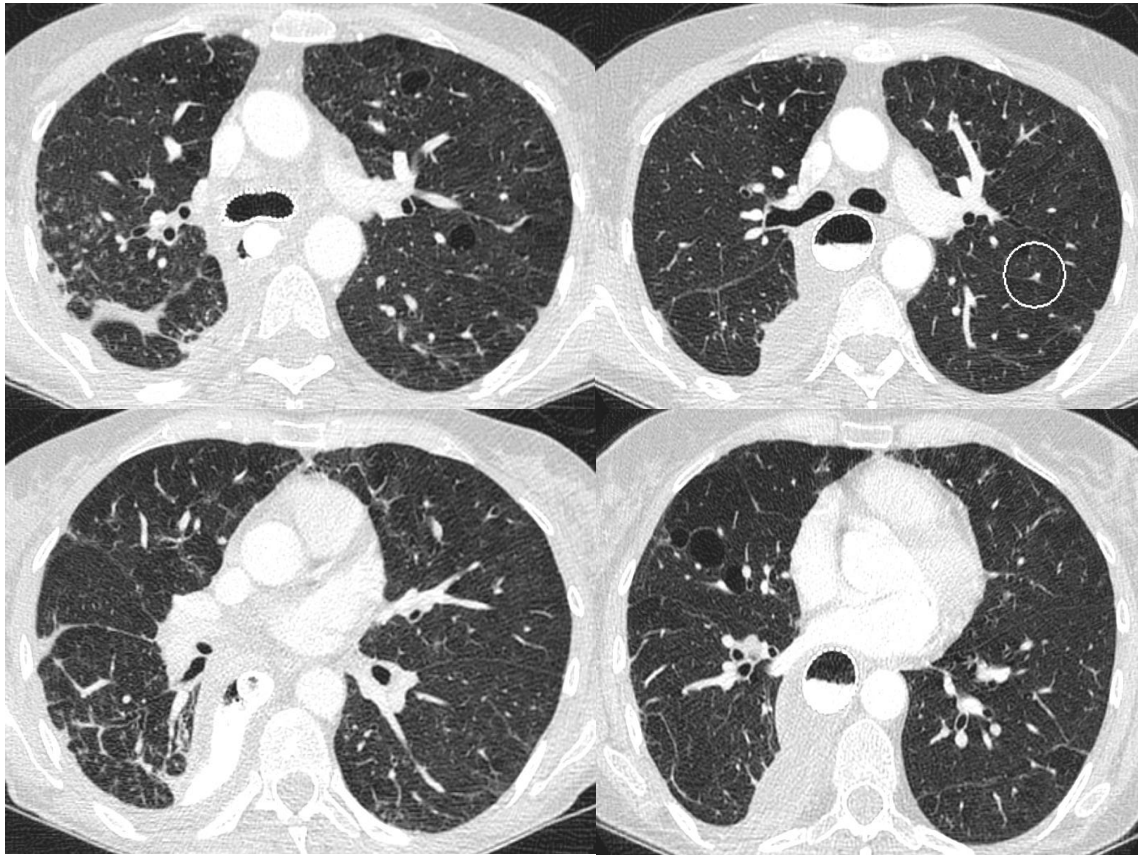


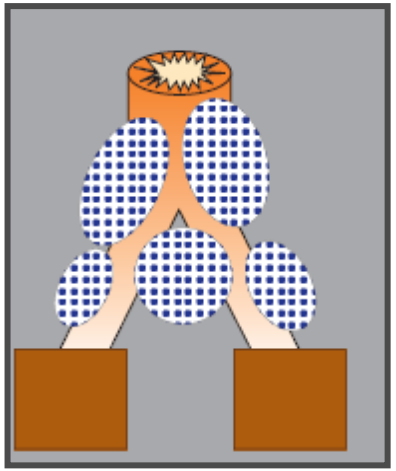


Atoll sign in CVID-ILD



Cystic lesions in CVID-ILD





Terminal Bronchiolitis

CVID-ILD: BAL Diagnostics

Bronchoalveolar Lavage

	Mannina et al:	Freiburg cohort
macrophages,	59+/-19%	47+/-21%
neutrophils,	17+/-12%	8+/-10%
lymphocytes,	18+/-11%	43+/-21%
eosinophils	5+/-9%	1+/-2%
CD4		55+/-17%
CD8		32+/-15%
CD4/8 ratio		3+/-4.3
CD20		8+/-5% (60-80% CD21^{low} B cells)

Remarks

- Exclusion Pathogen incl. fungi
- Exclusion lymphoma
- ImmunoBAL
  - Typically lymphozytic
  - Typically incl. B cells
  - Neutrophils ↗: Infection?
- Diagnost. Role undetermined

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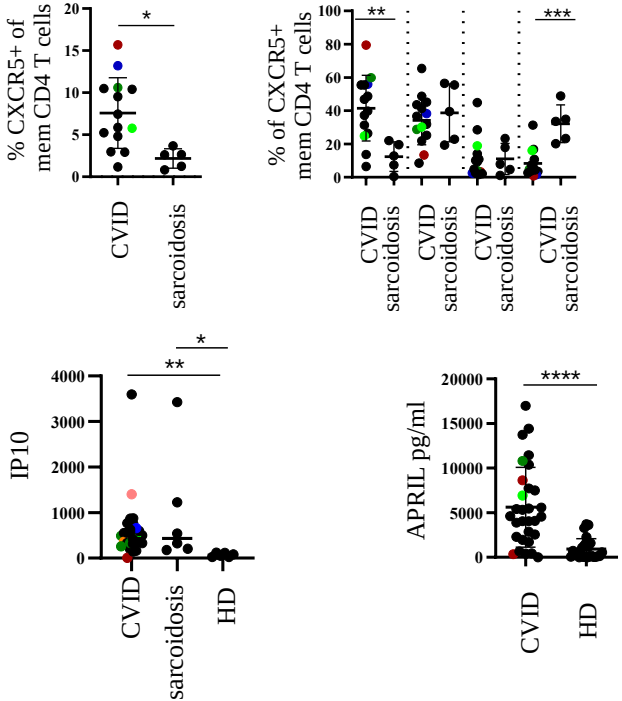
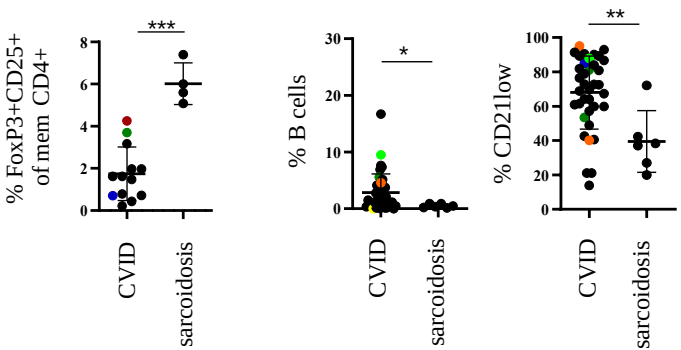
Mannina Ann ATS 2016, Friedmann et al Front Immunol 2021

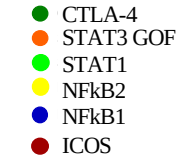
CVID-ILD: BAL Diagnostics

T cells



B cells





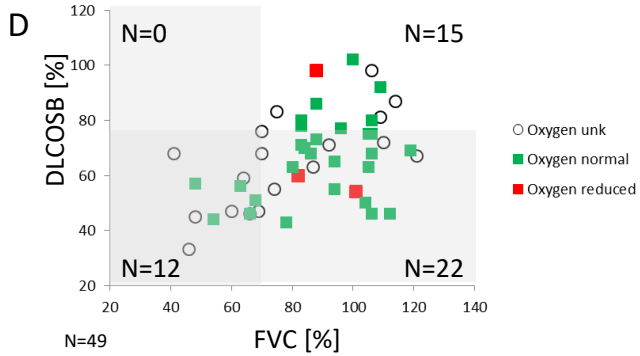
Remarks

- T and B cell expansion in the majority
- Expansion of TFH esp. TFH1 Zellen
- Reduction of regulator. T cells
- Expansion of Tbet^{hi} CD21^{low} B cells
- Reflecting the system. dysregulation

Friedmann et al Front Immunol 2021

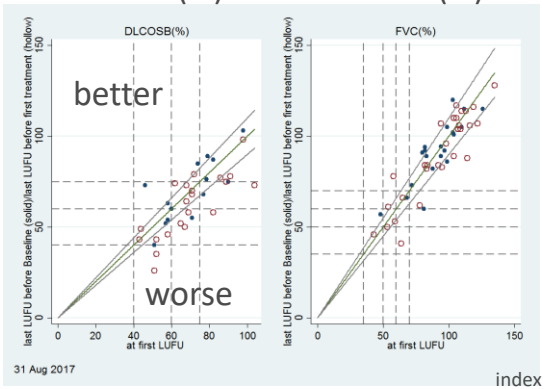
CVID-ILD: Pulmonary function test

Retrospective data STILPAD: natural course



course

DLCOSB(%) FVC(%)



→ normal pulmonary function doesn‘t exclude GLILD (15 Pat)

→ 22 Patients with isolated reduction of DLCO

→ DLCO Reduction >10% in a relevant number

→ Part of the decision whom to treat

→ FVC mostly stable within the Variance of 10%

Goldacker S, Smits B et al in prep

CVID-ILD Predictors of bad outcome (preliminary)

	Good outcome	Poor outcome	p-value
n	48	42	
Significant Parameters			
Sex (% F)	52	76	0.02
Enteropathy or hepatopathy (%)	21	43	0.02
Hepatopathy (%)	13	45	0.03
Median ground glass sum score	1	3	<0.01
Median nodules sum score	14	25	0.02
Median total ILD score	19	30	<0.01
Median NK cells (per µL)	70	109	0.04
Median IgG (g/L)	0.1	0.2	0.02
Potential Parameters			
Auto-immune cytopenia (%)	50	36	0.17
Median reticulation with distortion	2	1	0.19
Median CD4+ cells (per µL)	572	744	0.17
Median naive CD4%	9.2	20.2	0.14
Median memory CD4%	87.9	75.6	0.20
Median naive CD8%	19	9.8	0.12
Reduced class-switched memory B cells (%)	82	68	0.07
Increased $CD21^{lo}$ B cells (%)	66	75	0.13
Median class-switched memory B cells (%)	0.7	1	0.11
Median IgM+ memory B cells (%)	9	6	0.2
Median IgM (g/L)	0.1	0.2	0.07

Goldacker, Smits et al in preparation

CVID-ILD Therapy: Indication

Consensus of British lung foundation/UKPID network

	Symptoms	Lung Function	Function (CT?) Trajectory	% agree Rx
✓	Symptomatic	Abnormal	Deteriorating	Consensus: 100%
✓	Asymptomatic	Abnormal	Deteriorating	Consensus: 100%
✓	Symptomatic	Normal	Deteriorating	Consensus: 81%
	other…			
	Symptomatic	Normal	Stable	no consensus
	Symptomatic	Abnormal	Stable	no consensus
	Asymptomatic	Normal	Deteriorating	no consensus
	Asymptomatic	Abnormal	Stable	no consensus
✗	Asymptomatic	Normal	Stable	Consensus: 6%

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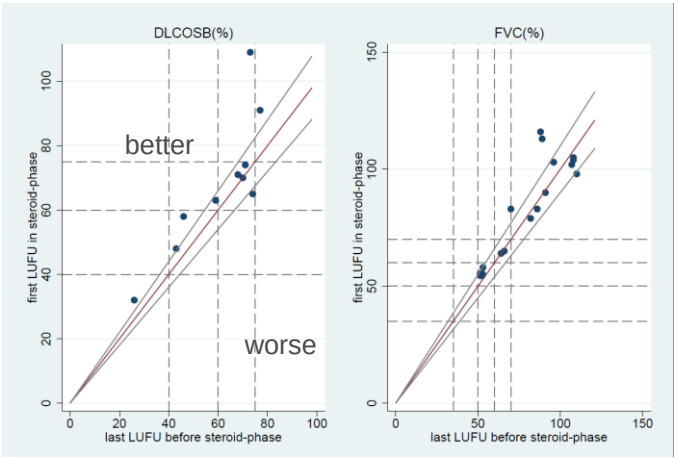
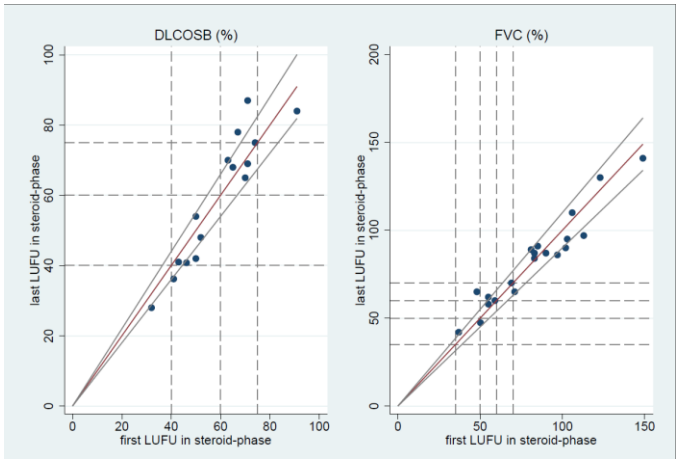
Hurst et al JACI P 2017

CVID-ILD Therapy: Corticoid therapy

Initiation under corticoid therapy



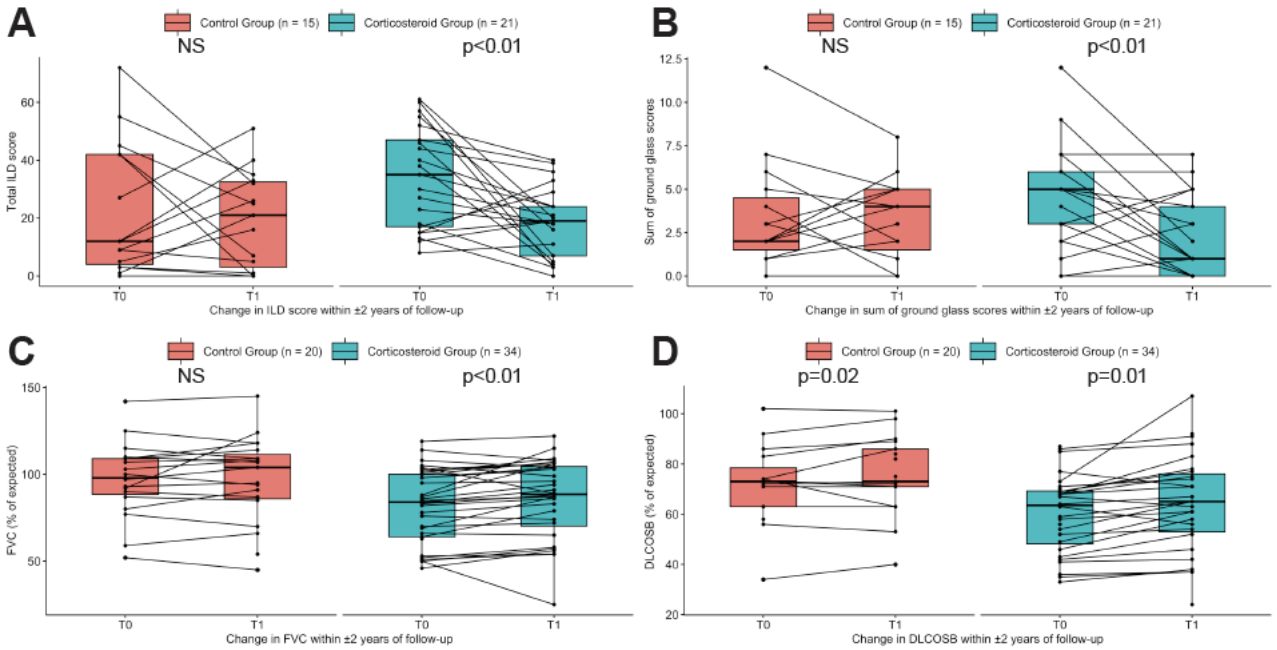


→ Induction with Steroids leads to improvement of DLCO, ca 42% with sustained remission

→ Maintenace or repeated therapy with corticosteroids not indicated

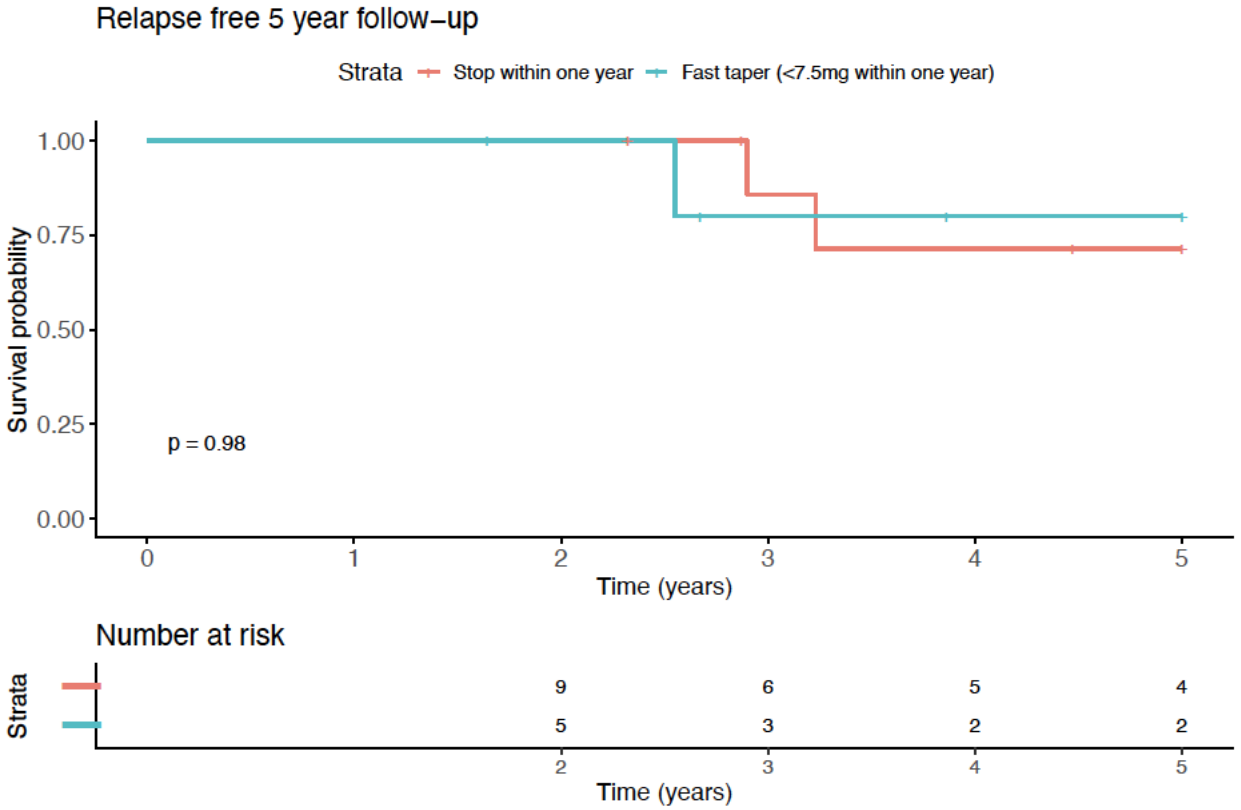
Smits, B, Goldacker S et al JACI 2022

CVID-ILD Therapy: Corticoid therapy



Smits, B, Goldacker S et al JACI 2022

CVID-ILD Therapy: Corticoid therapy



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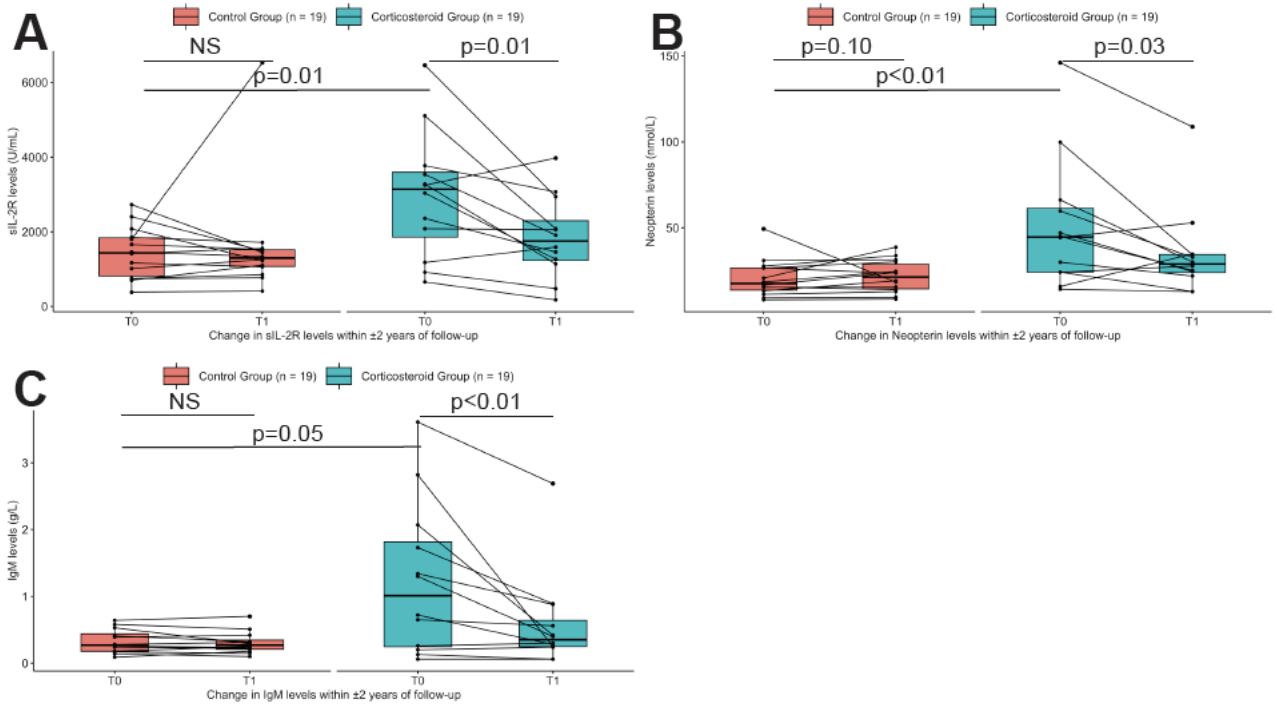
CVID-ILD Therapy: Corticoid therapy



Smits, B, Goldacker S et al JACI 2022

CVID-ILD Therapy: Immunosuppressive Therapy

RTX mono 4 cases
Ng et al Chest 2019, Cereser et al JACIP 2019, Králíčková et al Epid.Micro-Biol Immunol Winter 2018

RTX + AZA 10+ cases
Chase et al JoCI 2013, Moctezuma Med Clin 2017, Pathria et al BMJ Case Rep. 2016, Vitale et al JACIP 2015, Verbsky et al JACI 2020

RTX + MMF 4+ cases
Verbsky et al JACI 2020, Jolles et al Clin Exp Immunol 2017

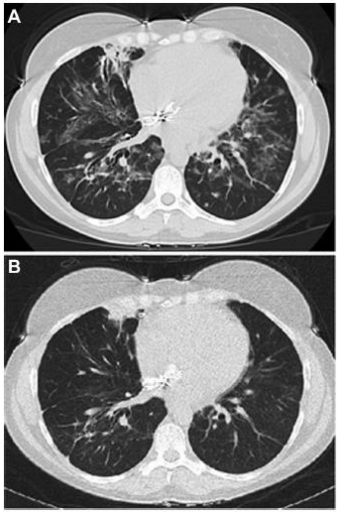
MMF 4 cases
Bucciol Pediatr Pulmonol. 2017, Tashtoush et al Clin Respir J. 2018

Sirolimus 2 cases
Deyà-Martínez A et al Pediatr Allergy Immunol. 2018

Abatacept 10 cases (SAIL Study)
Von Spee-Mayer et al JACIP 2020

Before

After



Summary:

Still no best 2° line

Incomplete list

Lamers et al Systematic review Front Immunol 2021, Fraz et al Front Immunol 2021

ILD treatment in CVID: HSCT

Systematic Review

TABLE 6 | Studies reporting treatment of GLILD in antibody deficiencies with HSCT.

Article	Study design	Sample	Control	Donor	Conditioning*	GVHD prophylaxis	Outcome (GLILD)	Outcome (Survival)
Hartono et al. (55)	Case study	23-year old girl with STAT1 mutation and GLILD	None	MUD	Not mentioned	Steroids	Improvement of radiological findings	Patient still alive day +522 post-transplant
Rizzi et al. (56)	Case study	One patient with CVID and GLILD	None	Patient 004: MUD	Patient 004: RIC[1]	CsA	Subjective improvement of PFT and reduction of steroids use	Patient with GLILD survived
Seidel et al. (57)	Prospective follow up cohort study	12 patients with LBRA deficiency of which seven also had GLILD	None	Patient 001: MFD Patient 002: MSD	Patient 001 RIC[2] Patitent 002 RIC[3] Patient 004 RIC[4]	Not mentioned	Patients 002 and 010 with GLILD had complete remission (no symptoms and no need for medication), patient 001 with GLILD had good partial remission (some symptoms but no need for medication), patient 011 with	Overall survival was 67% (8/12). Patient 004, 006 and 008 with GLILD died three and two months post procedure
Slatter et al. (58)	Prospective follow up cohort study	Two patients with CTLA4 deficiency and GLILD	None	MUD	Not mentioned	Five patients (1, 2, 5, 6, and 8) CsA and MMF for GVHD. Three (3, 4, and 7) had CsA alone, CsA and MMF, or MTX and tacrolimus. Patient 6 had prednisolone, sirolimus, and belatacept until 8 days before transplant	Improvement of symptoms, tapering of immunosuppressive medication.	Six patients are still alive (two patients with GLILD fall in this group and are alive and well at 4 months and 4 years post-transplantation), two died of GvHD and DKA, respectively
Tesch et al. (59)	Prospective follow up cohort study	76 patients with LBRA deficiency of which 24 underwent HSCT and	Patients who did not undergo HSCT	Patient 001: MMUD Patient 002: MSD Patient	Patient 001 RIC[9] Patient 002 MAC[10] Patient 003 RIC[11] Patient 004	Not mentioned	Of the eight patients with GLILD, five are in complete remission, two are in partial remission with still some symptoms of GLILD. Of the 24 patients undergoing HSCT, two developed GLILD after the procedure	Overall survival was 70.8% (17/24)

STAT1 GOF

LRBA

CTLA4

LRBA

Lamers et al Systematic review Front Immunol 2021

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ILD treatment in CVID

General considerations

Therapy depends on other manifestations:

No additional manifestations or just autoimmune cytopenia: RTX

Gastrointestinal disease: (RTX +) MMF?
anti TNFa?
Sirolimus (in children)

mild disease: Abatacept?

on genetic background:

CTLA4, LRBA, APDS, STAT3GOF, STAT1 GOF

Potential long term concepts....

Sequential Therapy: RTX + Belimumab? + Abatacept?
When HSCT?