Non infectious complications in CVID

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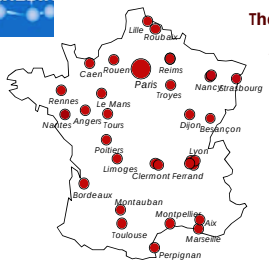
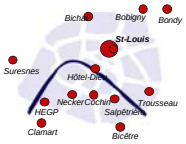
Thanks

The DEFI network
47 centers
775 patients





Data management
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Mary Lucas, John Radcliffe Hospital, Oxford

Statistics
Sylvie Chevret, Hôpital Saint-Louis, Paris

CVID definition

- **ESID/PAGID 1999**
  - Marked decrease IgG (<2SD)
  - Marked decrease IgA or IgM
  - Onset > 2 years
  - Absent IsoH or poor response to vaccines
  - Secondary Hypogamma excluded (including lymphoma and thymoma)
- **ESID 2014**
  - At least one of: Increased susceptibility to Infection, autoimmunity, granuloma, lymphoproliferation, familial case
  - Marked decrease IgG (<2SD)
  - Marked decrease IgA (<2SD)
  - Onset > 4 years
  - Absent IsoH or poor response to vaccines or smB cells < 70% normal value (age)
  - Secondary Hypogamma excluded (including lymphoma and thymoma)
  - No profound T-cell defect: 2 out of CD4<200, naCD4>10%, T cell proliferation absent

CVID

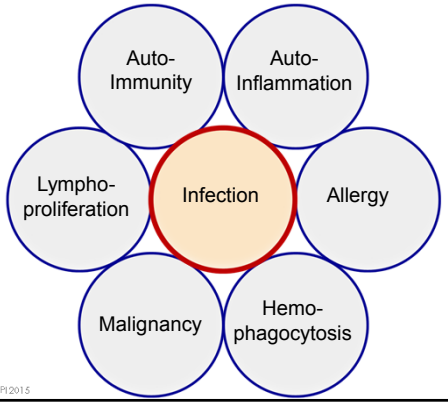
Major clinical phenotype

=

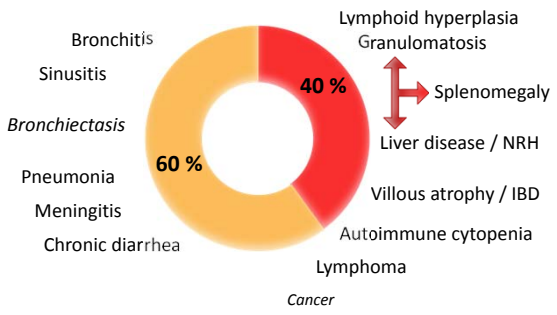
Infections

- Bronchitis
- Sinusitis
- Pneumonia
  - *S. pneumoniae*
  - *H. influenzae*
- Meningitis
  - *S. pneumoniae*
  - *N. meningitidis*
- Septicemia
  - *S.pneumoniae*
- Diarrhea
  - *Giardia*
  - *Campylobacter*
  - *Salmonella*

Extended phenotype of PIDs



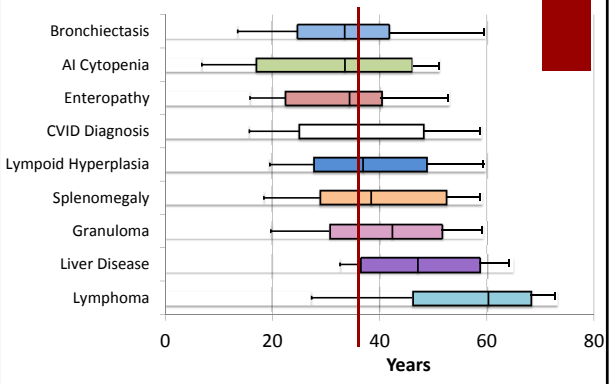
CVIDs Phenotypes



Disease-related complications

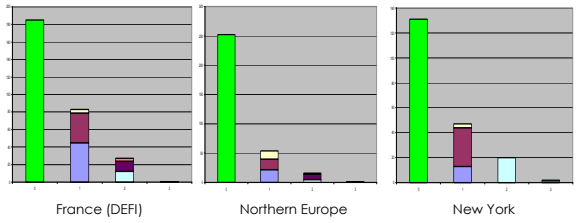
	nb (%)	Age at onset Median (years)	IQ 25% - 75%
Bronchiectasis	112 (32%)	33	25 - 42
AI Cytopenia	64 (19%)	33	17 - 46
Enteropathy	21 (6%)	34	22 - 40
Diagnosis of CVID	***345***	***36***	***25 - 48***
Lymphoid Hyperplasia	90 (26%)	37	28 - 49
Splenomegaly	124 (36%)	38	29 - 52
Granuloma	49 (14%)	42	31 - 51
Liver disease	23 (7%)	47	36 - 59
Lymphoma	9 (3%)	60	46 - 68

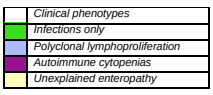
Disease-related complications



CVID clinical phenotypes

Chapel et al. JACI 2012

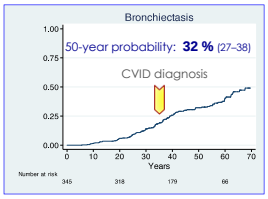




Infections Only : 60-70 %
One disease-related complication : 20-30 %
Several disease-related complications : 5-10 %

Pulmonary complications
- Chronic Lung Damage -

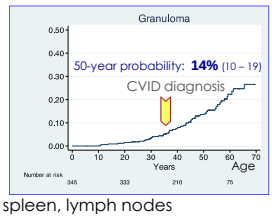
- ❖ Bronchiectasis
  - Frequent, early onset
  - Progression despite IgG replacement therapy



- ❖ GLILD
  - Lymphoid Interstitial Pneumonia
  - Granulomatosis
- ❖ Follicular Bronchiolitis

Granulomatosis / Lymphoid infiltration

- ❖ Systemic granulomatous disease

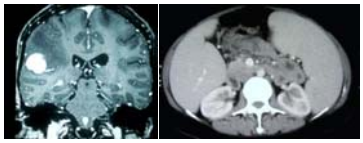


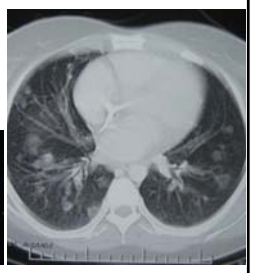
- Liver, spleen, lymph nodes
- Lung
- Skin
- GI tract
- CNS

Granulomatous-Lymphocytic Interstitial Lung Disease (GLILD)

- Nodular/Ground glass opacities

- Sarcoid-like Granulomatous disease
- Lymphocytic Interstitial Pneumonia
- Cryptogenic Organizing Pneumonia
- Follicular bronchiolitis
- BALT





- Systemic disease

Is this Granulomatous disease a truly non-infectious complication ?

… no convicing evidence for an infectious trigger
… but …

- **KSHV/HHV8**
  Wheat WH. JEM, 2005
- 6/9 pts CVID-GLILD
  - Nested PCR
  - QRT-PCR (low copy nb)
  - LANA IHC

- **Live rubella virus vaccine**
  Bodemer C. Clin Microbiol Infect, 2014
- 3/3 pts with PID (2 AT) and cutaneous granuloma
  - High-throughput sequencing
- ➢ *RA27/3 vaccine strain*
  - RT-PCR
  - IHC (direct IF)

Is this Granulomatous disease associated with a specific genetic background ?

TNFalpha

+488	HC	CVID Gran-	CVID Gran+	
n	49	56	38	
GG	33 (67%)	41 (73%)	8 (21%)	
GA	15 (31%)	15 (27%)	19 (50%)	
AA	1 (2%)	0	11 (29%)	p <.001
A freq	.175	.135	.54	p <.001

Mulligham CG. J Immunol, 1997
David Boutboul

Sarcoidosis « genes »

	HC	CVID Gran-	CVID Gran+	
n	49	56	38	
ANXA11				
CC	15 (30%)	16 (29%)	14 (37%)	
CT	27 (55%)	32 (57%)	17 (45%)	
TT	7 (15%)	8 (14%)	7 (18%)	NS
T freq	.425	.425	.405	NS
BTNL2				
GG	11 (22ù)	13 (24%)	8 (21%)	
GA	23 (47%)	22 (39%)	19 (50%)	
AA	15 (31%)	21 (37%)	11 (29%)	NS
A freq	.545	.565	.54	NS

CVID-associated Granulomatous disease Treatment

Retrospective study
59 pts

	Localized (1 organ)	Systemic (≥2 organs)	Total (%)
Lung	**8**	**22**	**30 (51)**
Spleen/ nodes	**8**	**19**	**27 (46)**
Liver	**9**	**15**	**24 (41)**
GI	2	7	9 (15)
Bone marrow	1	4	5 (8)
Skin	1	3	4 (7)
CNS	1	2	3 (5)
Other	1	4	5 (8)
	31	28	59

Boursiquot JN. J Clin Immunol, 2012

Treatments

Medication	Dose	Nb pts
Steroids		
PDN	**30-60 mg /d**	**31**
Budesomide	**3-9 mg /d**	**2**
CPM	750 mg /m2 /m	6
Rituximab	375 mg /m2 x4	3
Infliximab	3-5 mg /kg /3-6w	2
Thalidomide	100 mg /d	2
HCQ	400 mg /d	4
MTX	25 mg /w	2
IFNa	9M x 3 /w	1
MMF	500 mg /d	1
Sirolimus	1-2 mg /d	1
CsA	300 mg /d	1
AZT	2 mg /kg /d	2

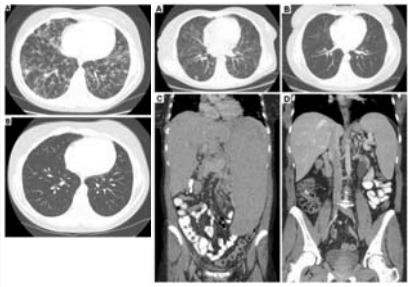
CVID-Granulomatous disease
Treatment with Steroids

Organ	nb	Response Complete	Partial	None
Liver	17	2 (12)	6 (35)	9 (53)
Lung	**13**	**3 (23)**	**4 (31)**	6 (46)
Spleen /nodes	**12**	**5 (42)**	**5 (42)**	2 (16)
GI	4	0	0	4 (100)
Bone marrow	2	0	1 (50)	1 (50)
CNS	**3**	**3 (100)**	**0**	0
Skin	**2**	**1 (50)**	**1 (50)**	0

Boursiquot JN. J Clin Immunol, 2012

CVID – GLILD
Combination chemotherapy

Rituximab: 375 mg/m2 x4/w /3-6 months (12-16 infusions)
Azathioprine: 1-2 mg/kg /d – 18 months

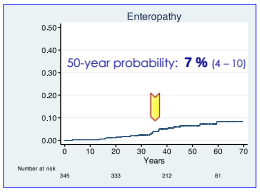


pt	HRCT score pre	HRCT score post
1	15	4
2	16	6
3	17	14
4	18	7
5	23	21
6	12	2
7	15	4

Chase NM. J Clin Immunol, 2013

GI tract complications

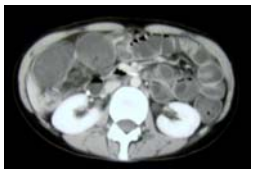
- Villous atrophy (CD-like)
  - Diarrhea
  - Malabsorption



- Infections
  - Giardia, campylobacter, salmonella, helicobacter
- Lymphoïd hyperplasia / granuloma
- Inflammatory bowel disease
- Gastritis

Chronic enteropathy with villous atrophy (Celiac-like disease)

- Chronic diarrhea
- Malabsorption



- Unfrequent HLA DQ2 and DQ8
- Absence of detectable Autoantibodies
- Usually not Gluten sensitive

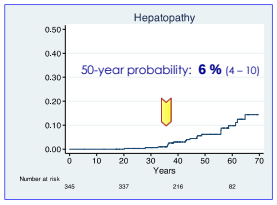
- Can be associated with infection (Giardia)

- Can be associated with other bowel lesions (IBD-like, GVHD-like)

Liver disease

❖ Chronic hepatopathy with Portal Hypertension

- Late onset
- Severe

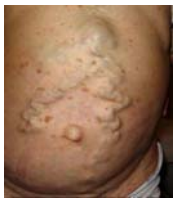


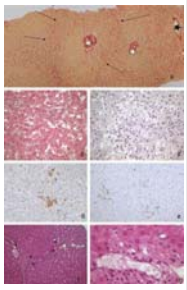
❖ Nodular Regenerative Hyperplasia (NRH)

❖ Lymphoïd infiltration / Granuloma

Nodular Regenerative Hyperplasia (NRH)

- Intra-hepatic vasculopathy
- Hepatocyte injury
- Hepatocyte regeneration
- Nodules
- Portal hypertension





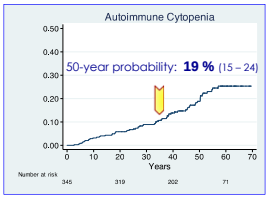
- Lobular inflammatory foci
- Epithelioid granuloma
- Portal inflammatory infiltrates
- Intrasinusoidal lymphocytic infiltration
- Autoimmune hepatitis-like lesions

- Portal fibrosis

Malamut G. Journal of Hepathology 2008
Fuss IJ; J Clin Immunol 2013

Autoimmune complications

- Autoimmune cytopenia
  - Early onset (even before hypogammaglobulinemia …)
  - ITP, AIHA - Good response to Rituximab



- Vitiligo
- Thyroïditis
- Pernicious anemia, Sjögren, Arthritis …

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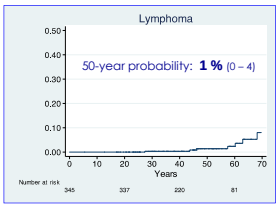
Lymphoma

- MALT Lymphoma
- NHL
- Hodgkin lymphoma



- Late onset (or exclusion criteria when early …)
- EBV-associated or not

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Neoplasia in CVID

353 pts with CVID

69 deaths

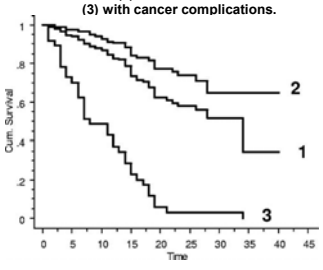
19% with Lymphoma

33% with other cancer

73 (20.7%) developed Cancer

36 deaths

Kaplan-Meier curves for patients with CVID.
(1) Cumulative
(2) without cancers
(3) with cancer complications.



Quinti I et al. Blood 2012

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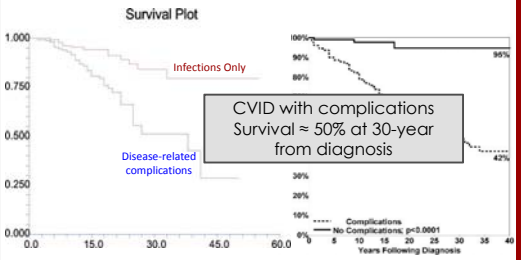
Mortality in patients with CVID according to the presence/absence of disease-related complications



Chapel H et al. Blood 2008

Oxford / Northern Europe

Resnick E S et al. Blood 2012

New York city

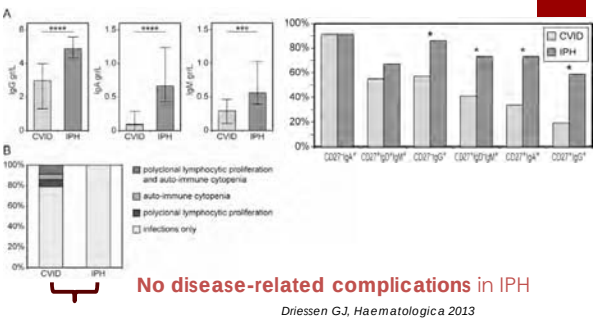
Treatment

No standard of treatment

- Watchful waiting vs Active therapy (?)
- Optimal IgG substitution
- Supportive therapy (parenteral nutrition)
- Antibiotics
- Corticosteroids / Budesonide
- Immunosuppressive therapy (MTX, AZT, CPM)
- Biotherapies (Rituximab, Infliximab)
- Organ transplant

Can we define a subset of patients at high risk for developing Disease-related complications ?

CVID *vs* Idiopathic Primary Hypogammaglobulinemia



No disease-related complications in IPH

Driessen GJ, Haematologica 2013

Clinical complications according to B- and T-cell defects

naive CD4+ T-cells < 20%

J Clin Immunol

Table 3 Association of Clinical Complications with T-Cell/B-Cell Defects in 285 CVID Patients

	nT4⁻B⁻ (*n* = 17)	nT4⁻smB⁻ (*n*=63)	nT4⁻smB⁺ (*n*=42)	nT4⁺B⁻ (*n* = 16)	nT4⁺smB⁻ (*n*=53)	nT4⁺smB⁺ (*n* = 104)	*p*
IO (*n*=93)	3 (18%)	8 (13%)	6 (14%)	6 (38%)	19 (36%)	51 (49%)	< 0.001
LP (*n* = 138)	14 (82%)	46 (73%)	28 (67%)	4 (25%)	20 (38%)	26 (25%)	< 0.001
AC (*n*=52)	4 (24%)	18 (29%)	10 (24%)	3 (19%)	7 (13%)	10 (10%)	0.025
CE (*n*=70)	6 (35%)	16 (25%)	14 (33%)	3 (19%)	12 (23%)	19 (18%)	0.35

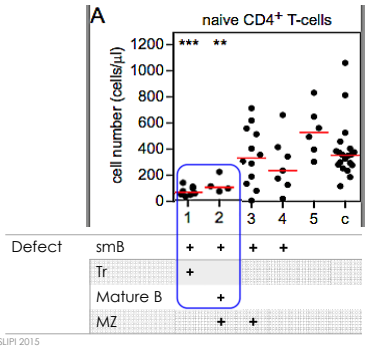
Eighteen of the 313 CVID patients had missing phenotypic data and were not classified according to T/B phenotypes.
Percentages refer to the prevalence of the clinical phenomenon indicated in the respective phenotypic subgroup of patients. For each complication, statistical evaluation refers to the distribution of the prevalence of one complication among the different phenotypic groups.
Abbreviations: nT4⁻ patients with nT4 cells < 20% of CD4⁺ T cells; *nT4⁺* nT4 cells ≥ 20% of CD4⁺ T cells; *B⁻* CD19⁺ cells ≤ 1% of total lymphocytes; *smB⁻* CD19⁺ cells > 1% of total lymphocytes and smB cells ≤ 2% of total B cells; *smB⁺* CD19⁺ > 1% and smB > 2%.

Mouillot et al. 2010

Lymphoproliferation is associated with naive CD4+ T-cell defect

Correlation between early B-cell defect and naive CD4+ T-cell defect

Driessen et al. Blood 2011



Spectrum of Primary Hypogammaglobulinemia

T-CVID= 2 out of:
CD4 <200, naCD4<10%, T cell proliferation neg.

	HGUS	ESID 2014 CVID			T-CVID
		TOTAL	IO phenotype	DRC phenotype	
Epidemiology					
Number	226	289	157	132	6
Age, years	36 (23-54)	35(25-46)	34 (25-45)	35 (25-48)	39 (10-53)
Familial	50 (22%)	56 (19%)	34 (22%)	22 (17%)	2 (33%)
Clinical features					
Infections only	*195 (86%)*	*157 (54%)*	*157 (100%)*	*0 (0%)*	*0*
Disease Related Complications	*31 (14%)*	*132 (46%)*	*0 (0%)*	*132 (100%)*	***6 (100%)***
Pneumonia	**85 (38%)**	**166 (57%)**	88 (56%)	78 (59%)	**5 (83%)**
Bonchiectasis	**43 (19%)**	**99 (34%)**	50 (32%)	49 (37%)	**2 (33%)**
Granuloma	**9 (4%)**	**47 (16%)**	0 (0%)	47 (36%)	**2 (33%)**
Autoimmune Cytopenia	**17 (7%)**	**57 (20%)**	0 (0%)	57 (43%)	**3 (50%)**
Lymphoma	**4 (2%)**	**11 (4%)**	0 (0%)	11 (8%)	**1 (17%)**
Biology					
IgG, g/L	5.2 (3.8-6.9)	1.9 (0.8-3.4)	2 (0.8-3.4)	1.8 (0.8-3.4)	2.9 (1.2-4.3)
IgA, g/L	0.8 (0.3-1.5)	0.1 (0.1-0.3)	0.1 (0.1-0.3)	0.1 (0.1-0.2)	0.3 (0.1-0.3)
IgM, g/L	0.6 (0.3-1.0)	0.2 (0.1-0.4)	0.2 (0.1-0.3)	0.2 (0.1-0.4)	0.2 (0.2-0.3)

Spectrum of Primary Hypogammaglobulinemia

	HGUS	ESID 2014 CVID			T-CVID
		TOTAL	IO phenotype	DRC phenotype	
Number	226	289	157	132	6
CD 19 + B cells					
x 10^6/L	135 (70-205)	96 (46-187)	102 (51-190)	89 (41-171)	**39 (1-158)**
SmB cells					
x 10^6/L	12 (5-25)	2 (1-4)	1 (1-4)	1 (0-4)	**1 (0.3-3)**
%	11.2 (5.0-18.0)	1.8 (0.7-3.0)	1.9 (1.0-3.0)	1.3 (0.5-3.1)	**0.4 (0.3-2.0)**
CD4+ T cells					
x 10^6/L	771	554	569	541	**145**
Naive CD4+ T cells					
x 10^6/L	286 (144-487)	94 (39-234)	**151 (69-279)**	**52 (16-133)**	**5 (1-7)**
%	38.5 (25.7-50.3)	21.0 (8.0-36.0)	**29.3 (17.2-42.6)**	**11.0 (4.0-25.0)**	**3.9 (1.8-5.0)**
Deaths	7 (3.2%)	18 (6.2%)	**3 (2%)**	**15 (11.4%)**	**4 (66.6%)**
5-year OS	94.9 %	92.2 %	**97.0 %**	**87.6 %**	**50.0 %**
[95%CI]	[87.6-97.9]	[87.2-95.4]	**[91.1-99]**	**[78.6-93]**	**[11.0 -80.3]**

Dr House CVID diagnosis:
correct diagnosis with wrong argument
… or just the other way round ?

- African ancestry
- Toxoplasma encephalitis
- Phenytoin since childhood

≠

- Caucasian
- Non-opportunistic infections
- Absence of known cause for hypogammaglobulinemia

Clinical T-cell defect in CVID - opportunistic infections – 18 patients

Pneumocystis
CMV
Candida
Mycobacteria
Cryptococcus
Cryptosporidium
Aspergillus
Toxoplasma
Viral encephalitis
Invasive HPV
Kaposi sarcoma

Median (IQ) CD4+ T cells: 286 /mm^3 (150-430)

Median (IQ) naive CD4+ T cells: 29 /mm^3 (7-63)

T cells abnormalities in CVID

- Decreased naive CD4+ T cells
- Increased CD8+ activated T cells
- Decreased lymphocyte proliferation to mitogens and Ags
- Increased T cell apoptosis
- Impaired cytokine production
- Absent generation of Ag-primed T cells / vaccination
- Reduced expression of CD40L on activated T cells
- Decreased thymic output
- Disrupted T cells repertoires

« T-CVID » : more than an oxymoron ?

- Reduction of naive CD4+ T cells and TRECs correlates with
  - Reduction of mature B cells
  - Expansion of CD19^{hi}CD21^{lo} B cells

Moratto et al. 2006

- Reduction of naive CD4+ T cells correlates with
  - Splenomegaly
  - Clinical severity
  - Reduced thymic output
  - Disrupted TCRBV repertoires
  - Altered cytokine production

Giovannetti et al. 2007

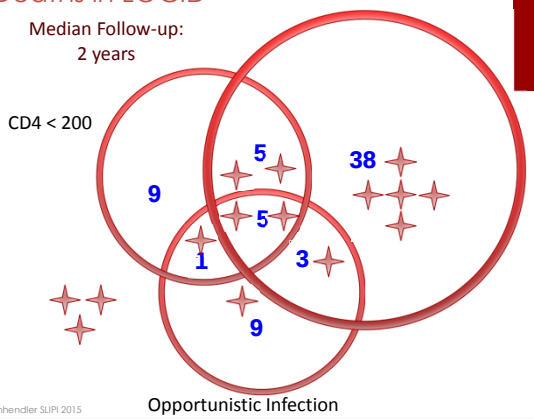
CVID
(n=332)

O.I.	CD4 < 200	naive CD4 < 10	naive CD4 < 20
n=18	n=20	n=29	n=51
5%	6%	9%	15%

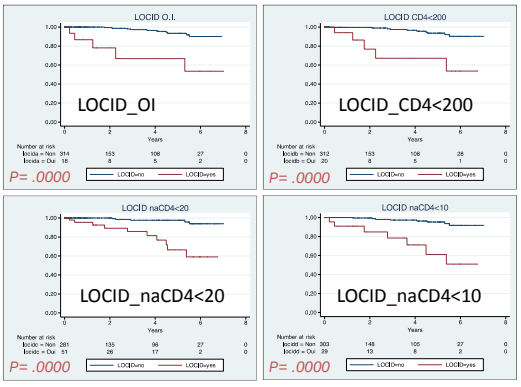
Controls (n=50)				
number	0	0	0	0
median x10^6/L (IQ)		912 (682-1153)	363 (294-549)	

Deaths in LOCID

Median Follow-up:
2 years



Overall Survival from evaluation



CVID definition

ESID 2014

- At least one of: Increased susceptibility to Infection, autoimmunity, granuloma, lymphoproliferation, familial case
- Marked decrease IgG (<2SD)
- Marked decrease IgA (<2SD)
- Onset > 4 years
- Absent IsoH or poor response to vaccines or smB cells < 70% normal value (age)
- Secondary Hypogamma excluded (including lymphoma and thymoma)
- No profound T-cell defect: 2 out of CD4 <200, naCD4>10%, T cell proliferation absent

DEFI 2015

- Marked decrease IgG (<5 g/L)
- Marked decrease IgA (<0.7 g/L)
- Onset > 4 years
- SmB cells < 10%
- Secondary Hypogamma excluded (including lymphoma and thymoma)
- No severe T-cell defect: Opp. Inf. OR naCD4 < 20 x10^6/L

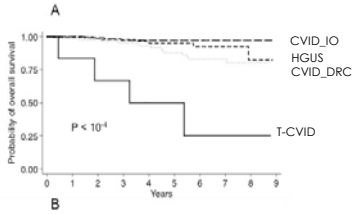
Spectrum of Primary Hypogammaglobulinemia

LOCID: Opp Inf or naCD4 < 20 x10^6/L

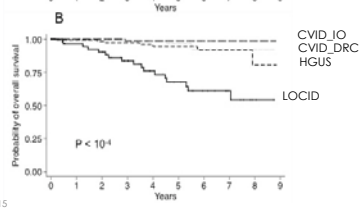
	HGUS	CVID DEFI 2015			LOCID
		TOTAL	IO phenotype	DRC phenotype	
Number	215	244	153	91	62
Age	38 (23-55)	34 (23-46)	35 (25-46)	34 (21-46)	39 (27-53)
Infection Only	*204 (86%)*	*153 (63%)*	*153 (100%)*	*na*	*12 (19%)*
Disease related complications	*32 (14%)*	*91 (37%)*	*na*	*91 (37%)*	*50 (81%)*
Pneumonia	91 (39%)	131 (54%)	83 (54%)	48 (53%)	44 (71%)
Bronchiectasis	42 (18%)	78 (32%)	49 (32%)	29 (31%)	26 (42%)
CD 19 + B cells x 10^6/L	135 (60-205)	105 (59-196)	110 (56-194)	94 (59-203)	**48 (6-108)**
SmB cells x 10^6/L	13 (6-27)	2 (1-5)	2 (1-5)	2 (0.3-5)	**1 (0.2-2)**
%	12.0 (6.0-19.0)	2.0 (0.9-4.0)	2.0 (1.0-4.0)	2.0 (0.6-4.0)	**0.9 (0.4-2.0)**
Naive CD4+ T cells x 10^6/L	292 (150-491)	137 (67-270)	172 (78-291)	96 (41-200)	**11 (6-17)**
%	39.6 (24.3-50.2)	26.4 (14.0-39.5)	31.6 (20.2-43.4)	19.1 (9.6-32.9)	**2.9 (1.5-5.8)**
Deaths	7 (3.2%)	5 (2.0%)	1 (0.6%)	4 (4.4%)	**17 (27.4%)**
5-year OS	94.5 %	98.0 %	98.9 %	96.9 %	**67.6 %**
[95CI]	[86.8-97.8]	[93.8-99.3]	[92.4-99.8]	[87.8-99.2]	**[51.1-79.7]**

Overall Survival

ESID_2014



DEFI_2015



Late Onset Combined ImmunoDeficiency

- ✓ Subgroup of CVID patients with severe T-cell defect
- ✓ No clear correlations between O.I. and CD4 cell count
- ✓ Correlation with severe B-cell defect
- ✓ High frequency of parental consanguinity
- ✓ High frequency of disease-related complications
- ✓ High mortality rate: up to 30% at 5-year

O.I. or naive CD4+ T cells < 20

- **20 % of the CVID patients**
- **77 % of the deaths**

Conclusions (1)

Disease-related complications in CVID

LOCID

CVID-DrC

CVID-IO

HGUS

Conclusions (1)

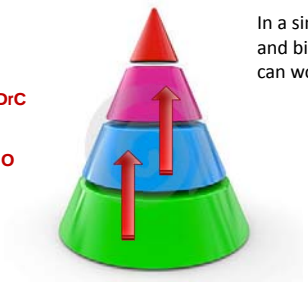
Disease-related complications in CVID

LOCID

CVID-DrC

CVID-IO

HGUS



In a single patient the clinical and biological phenotype can worsen over time

Conclusions (1)

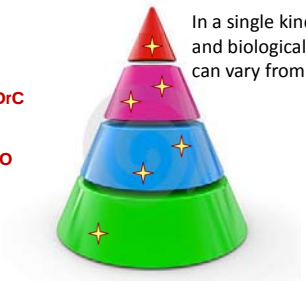
Disease-related complications in CVID

LOCID

CVID-DrC

CVID-IO

HGUS



In a single kindred the clinical and biological phenotype can vary from an individual to an other

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46

Conclusions (1)

Disease-related complications in CVID

LOCID

CVID-DrC

CVID-IO

HGUS

IgG

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47

Conclusions (1)

Disease-related complications in CVID

LOCID

CVID-DrC

CVID-IO

HGUS

Specific Therapies

IgG

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48

Conclusions (1)

Disease-related complications in CVID

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49

Conclusions (2)

Disease-related complications in CVID

1. Frequent: 30 – 40%
2. Often present at CVID diagnosis
3. Mainly associated with: Lymphoproliferation, Autoimmunity, Inflammation
4. Can mimick or be associated with well-defined auto-immune diseases:
   - Autoimmune cytopenia
   - Sarcoidosis
   - CD, MICI
   - Pernicious anemia
5. Associated with T-cell defect (low naive CD4 cell count)
6. Affect survival
7. Suggest a possible diagnosis of CID
8. Require specific therapies
   - / Complications
   - / CID

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50