Immunodeficiencies

in pediatric allergy/pulmonology

NICHOLAS BRODSZKI

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Can this be immunodeficiency?

When to suspect it ?

How / what can you test?

Immundefekter ?
Hvad, er der flere??

Home
About
E-mail alert
Submissions
Bulletin of the World Health Organization

Bull World Health Organ. 1971; 45(1): 125–142. PMCID: PMC2427897

Table 2. Classification of primary immunodeficiency disorders *

Type	Suggested cellular defect		
	B-cells	T-cells	Stem cells
Infantile X-linked agammaglobulinaemia	+		
Selective immunoglobulin deficiency (IgA)	+ (some)		
Transient hypogammaglobulinaemia of infancy	+		
X-linked immunodeficiency with hyper-IgM	+	?	
Thymic hypoplasia (pharyngeal pouch syndrome, Di George's syndrome)		+	
Episodic lymphopaenia with lymphocytotoxin		+	
Immunodeficiency with or without hyperimmunoglobulinaemia (Faulk, Tomsovic & Fudenberg, 1970)	+	+ (sometimes)	
Immunodeficiency with ataxia-telangiectasia	+	+	
Immunodeficiency with thrombocytopaenia and eczema (Wiskott-Aldrich syndrome)	+	+	
Immunodeficiency with thymoma	+	+	
Immunodeficiency with short-limbed dwarfism (Gatti et al., 1969; Lux et al., 1970)	+	+	
Immunodeficiency with generalized haematopoietic hypoplasia	+	+	+
Severe combined immunodeficiency			
autosomal recessive	+	+	+
X-linked	+	+	+
sporadic	+	+	+
Variable immunodeficiency (common, largely unclassified)	+	+ (sometimes)	

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-022-01289-3

ORIGINAL ARTICLE

Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee

Stuart G. Tangye[1,2]
Steven M. Holl
Anne Pue
Troy R. T
Luis Franco[6]
[12]
[18]

485

+50...

Classification

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. Autoinflammatory disorders
8. Complement deficiencies
9. Bone marrow failure
10. Phenocopies of inborn errors of immunity

Symptoms from	Lung	Skin
1-2 Predominantly T cell deficiency		Eczema
	Recurrent bronchitis	Dermatitis
	Idiopathic bronchiectasis	Erythroderma
	Recurrent pneumonias*	eosinophilia,
	Chronic bronchial infection	Severe atopy;
	Abscess and pneumatocele	food allergies
	Interstitial lung disease	
	Bronchiolitis obliterans	
	Alveolar proteinosis	
	Pulmonary aspergillosis	
3 Antibody deficiencies		
	Recurrent bronchitis	
	Idiopathic bronchiectasis	
	Recurrent pneumonias	
	Repeated pneumonia	
	Chronic bronchial infection	
4 Immune dysregulation		
	Recurrent bronchitis	
	Idiopathic bronchiectasis	
	Chronic bronchial infection	
	Pneumonia due to encapsulated bacteria	
	Interstitial lung disease	
5 Phagocyte disorders		
	Recurrent pneumonias*	
	Abscess and pneumatocele	
	Alveolar proteinosis	
6 Innate immunity disorders		
	Recurrent pneumonias*	
	Pneumonia due to encapsulated bacteria	
	Abscess and pneumatocele	
7 Autoinflammatory disease		
	Recurrent serositis	
8 Complement deficiency		
	Recurrent pneumonias*	
	Recurrent bronchitis	
	Chronic bronchial infection	

Tangye SG, et al. *J Clin Immunol*. 2022;40:24–64.

Respiratory Medicine 132 (2017) 181–188

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Review article

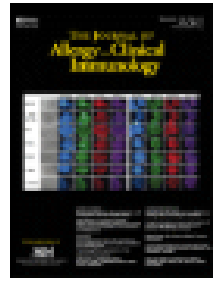
Primary immune deficiency diseases as unrecognized causes of chronic respiratory disease

Melvin Berger[a,*], Bob Geng[b], D. William Cameron[c], Ladonna M. Murphy[a], Edward S. Schulman[d]

ELSEVIER

Journal of Allergy and Clinical Immunology

Volume 127, Issue 6, June 2011, Pages 1414-1417



Letter to the editor

Longitudinal decline in lung function in patients with primary immunoglobulin deficiencies

Yan Chen MB, BS [a], Rob G. Stirling MB, BS, FRACP [a, b], Eldho Paul MSc [c], Fiona Hore-Lacy BSc (Hons) [a], Bruce R. Thompson BAppSci, CRFS, PhD [a, b], Jo A. Douglass MD, FRACP [a, b] ✉

FEV_1

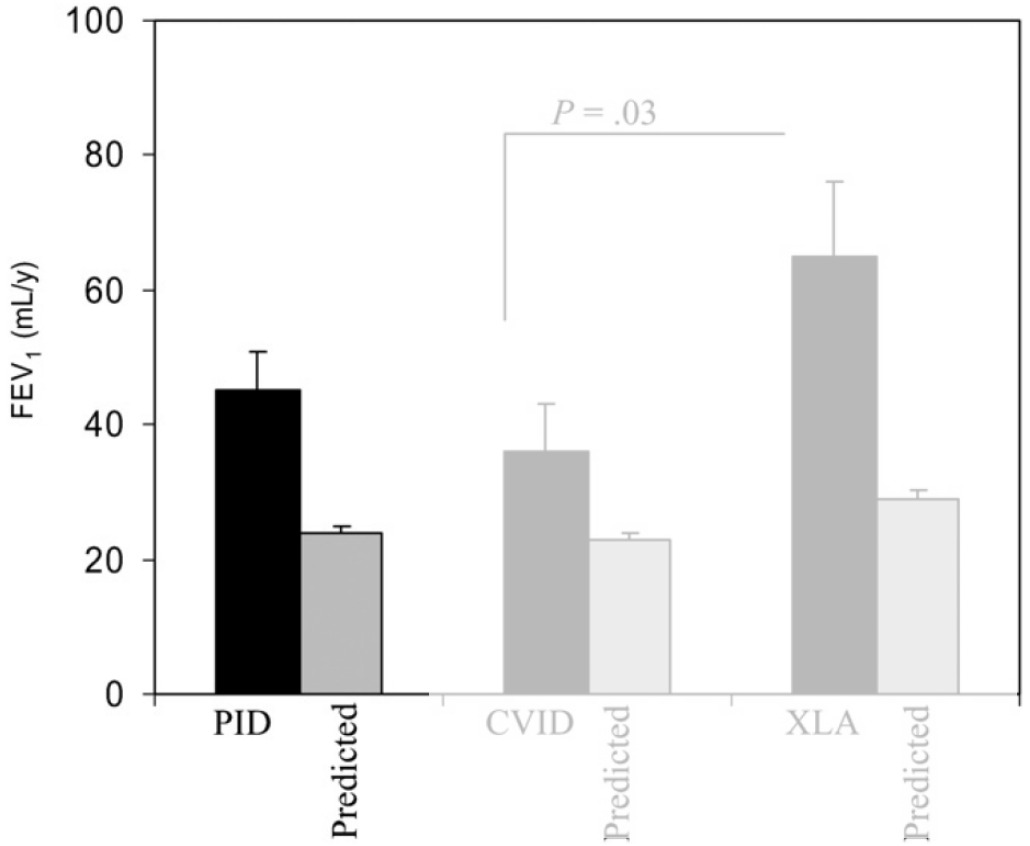


FIG 1. Average decline in FEV_1 (mL/y) for PID (total group), CVID, and XLA

FVC

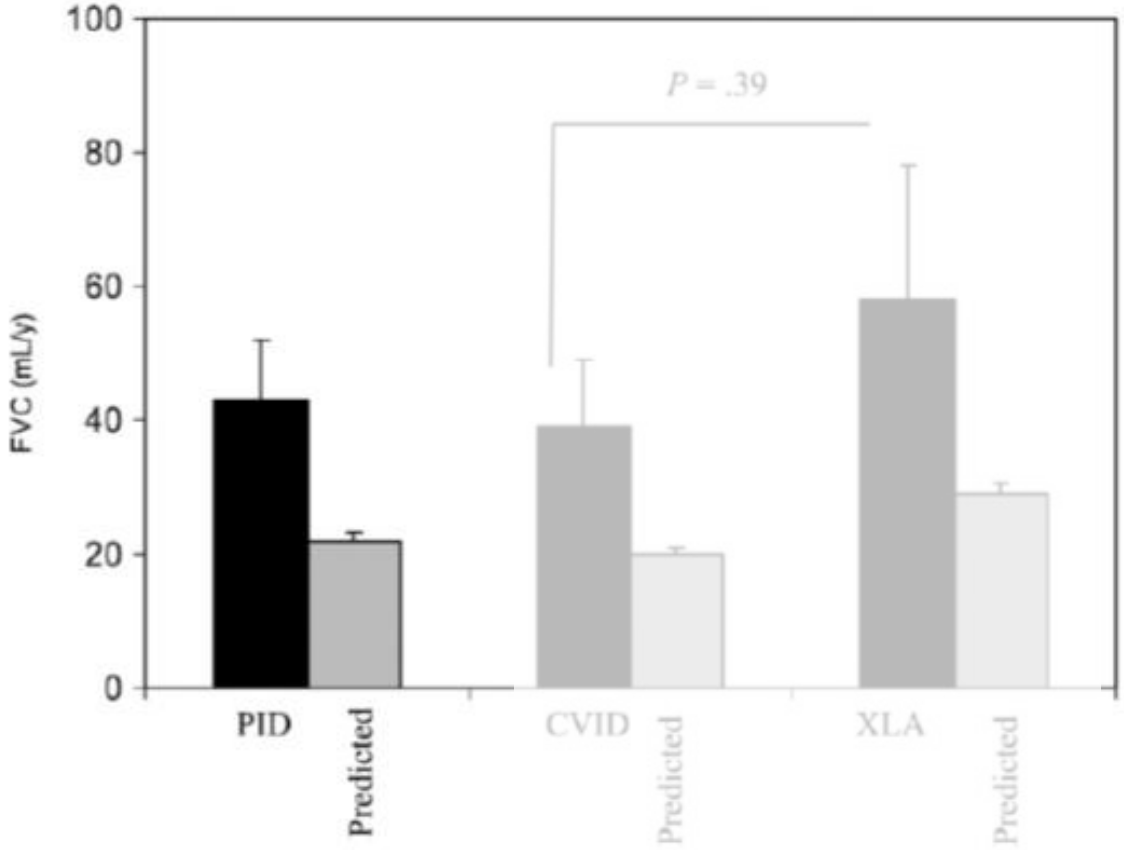


FIG 2. Average decline in FVC (mL/y) for PID (total group), CVID, and XLA groups.

"It has been shown that there is an ongoing decline in lung function above predicted levels in PAD patients and that is greater than in heavy smokers."

frontiers in PEDIATRICS

REVIEW ARTICLE
published: 25 July 2014
doi: 10.3389/fped.2014.00077

Pulmonary manifestations of primary immunodeficiency disorders in children

Milos Jesenak[1], Peter Banovcin[1], Barbora Jesenakova[1] and Eva Babusikova[2]**

Table 1 | Respiratory presentations and complications of primary immunodeficiencies

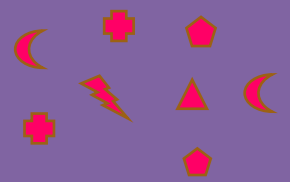
Non-infectious complications	Infectious complications	Chronic lung disease	Chronic inflammatory diseases	Benign lymphoproliferative disease	Malign neoplasma
RESPIRATORY COMPLICATIONS OF PRIMARY IMMUNODEFICIENCIES					
Bronchial abnormalities (bronchiectasis, bronchial wall thickening, atelectasis, mucus plugs, emphysema, bullae, pneumatocoele)	Otitis	Fibrosis	Granulomas	Parenchymal lymphoid hyperplasia	Solid organ tumors (leiomyoma, adenocarcinoma)
Lung parenchyma abnormalities (nodules, cavity)	Rhino/sinusitis	Pulmonary hypertension	Interstitial lung disease	Reactive follicular hyperplasia	Lymphomas
Ventilation abnormalities (obstructive, restrictive, combined)	Bronchitis	Cor pulmonale		Mediastinal lymphadenopathy	Thymic tumors
Laryngeal angioedema	Pneumonia	Respiratory failure			Lung metastasis
	Empyema	Allergies			
	Lung abscess				

4 compartments

Innate Immunity ⟷ Cytokines ⟷ Adaptive Immunity

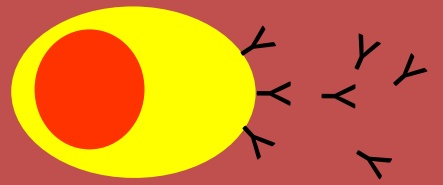
Host Defense

Complement
"Land Mines"



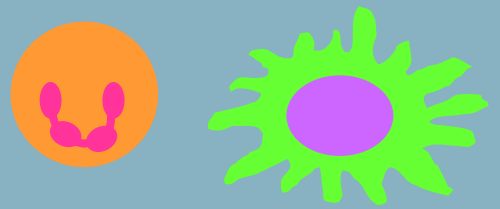
Functional tests of **all 3** pathways

B Cells + Ig
"Air Force"



- IgG, IgA, IgM
- IgG subclasses
- Specific antibodes

Phagocytes
"The Marines"



Neutrophils Macrophages

Complete Blood Count (CBC)

T Cells
"The Generals" CD4+ (T_{Helper})
"The Assassins" CD8+ ($T_{Cytotox}$)
"The Psychologists" CD25+ (T_{Reg})

- Flow cytometry
- Functional tests (T-, B-, NK-cells, neutrophils)

Newborn

- 2 newborn babies
  - Boy born 2017
  - Girl born 2018

- Why should we suspect PID?
  - Because in this family:
    - The first child died in sepsis/meningitis at age of 6 weeks => **SCID** diagnosed post-mortem

    - Second child diagnosed with **SCID** at age 2 weeks, HSCT at 4 months, doing well

Family history !!

SCID, severe combined immunodeficiency

10 Warning Signs - Children

1. Recurrent otitis (≥4/year) or sinusitis (≥2/year) or pneumonia (≥2/year) requiring antibiotics
2. ≥1 invasive infection such as osteomyelitis, meningitis or sepsis
3. Recurrent, deep skin and soft tissue infections, organ abscesses or non-infectious granuloma
4. Infections that respond with little or no effect to antibiotics or with unusual localization or caused by unusual agents
5. Pronounced chronic oral or cutaneous candidiasis
6. Multiple autoimmune diseases or very early onset of autoimmune disease (at age ≤3 years)
7. Extensive skin lesions, erythroderma or eczema that respond little or not at all to treatment
8. Autoinflammatory diseases, i.e. recurrent episodes of generalized inflammation, where no infectious, malignant or autoimmune cause can be identified
9. Failure of an infant to gain weight or grow normally
10. Family history of primary immunodeficiency

10 Warning Signs - Children

SWEDEN

1. Recurrent otitis (≥4/year) or sinusitis (≥2/year) or pneumonia (≥2/year) requiring antibiotics
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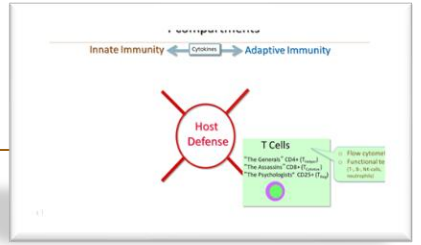
Newborn



Immunodeficiencies affecting cellular and humoral immunity

» **Complete blood count**

» **Lymphocyte subsets** (flow cytometry)

Except if patient is born in Norway, Denmark, Sweden, Finland, Germany, Libanon, Israel, USA, Brazil, Taiwan, New Zealand, Catalonia…

Why?

Common denominator for these countries:

Newborn Screening implemented

Severe Combined Immunodeficiency

Traditional symtoms

- Recurrent infections
  bacteria/virus & unusual pathogens (also BCG-itis)
- Skin symptoms
  (erythrodermia, severe eczema)
- Interstitial pneumonia
- Candida infections
- Severe malnutrition
- Severe Diarrhea

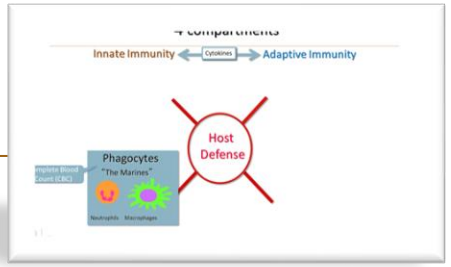
Clinical picture today

in “modern, clean enviroment” ie Sweden

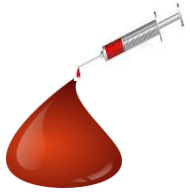
- Mild lung-symptoms - ”bronchitis”
- Mild skin-symptoms - ”eczema”
- Poor weight gain / slow development of failure-to-thrive
- Diarrhea

BUT ! NOT ALL forms of SCID are identified by screening…

Infant 0-6 months



Congenital defects of phagocyte number or function



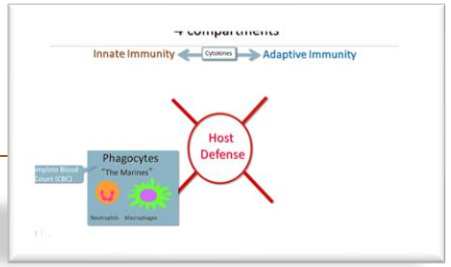
- **Complete blood count**

  - **Neutropenia**
    congenital neutropenias
  - **Neutrophilia**
    certain types of neutrophile dysfunctions
    (i.e. Chronic Granulomatous Disease, LAD)
  - **Lymphopenia** - SCID

Kostmann
Congenital neutropenia

LAD 1
Leukocyte Adhesion Defect type 1

Defects of phagocyte number or function

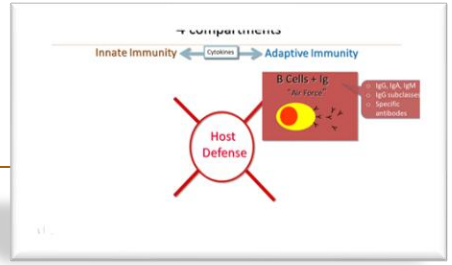


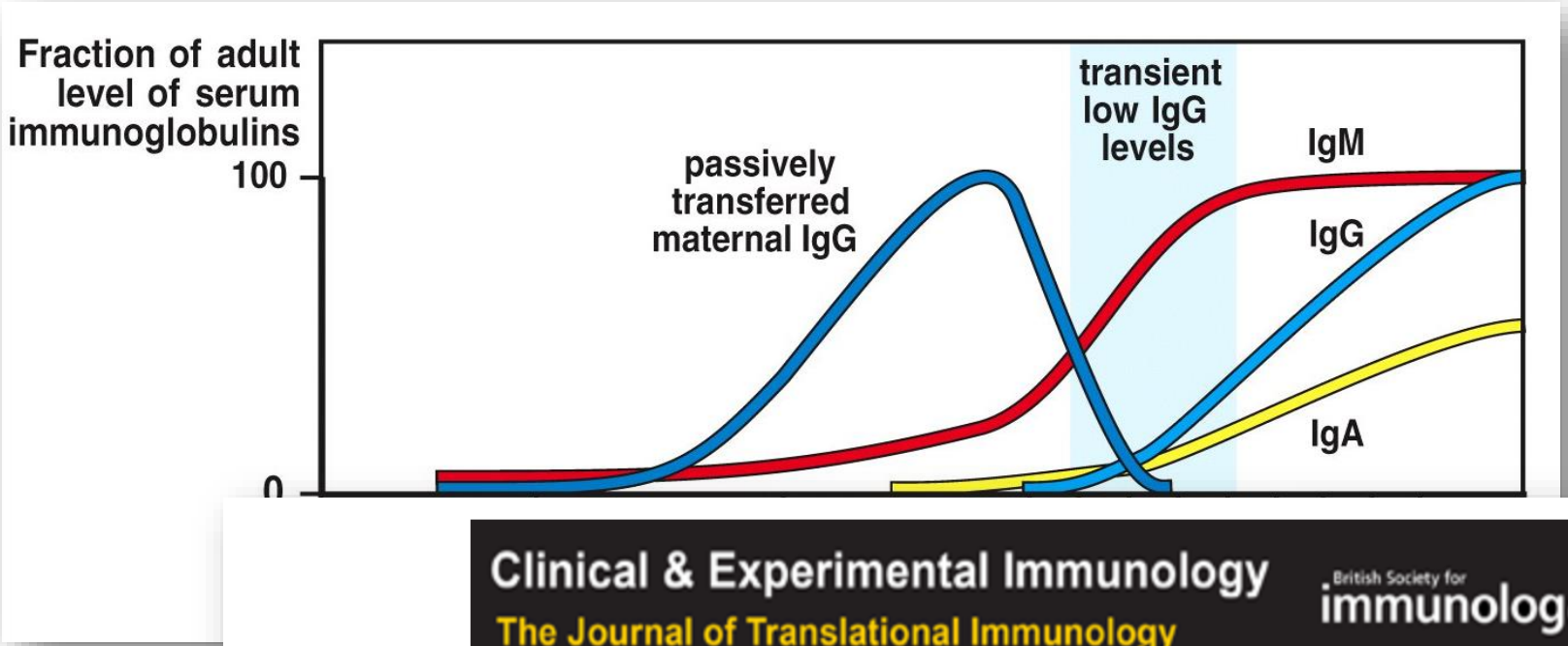
Warning signs:

- **Skin** : infected eczema/abscesses/cellulites (early in congenital neutropenias)
- **Mucosal** infections: gingivitis/parodontitis/ aphthous ulcers
- **Perianal** infections
- **Respiratory** tract infections (incl. otitis/sinusitis)
- Other **recurrent bacterial** infections
- Septicemia/meningitis/osteomyelitis

Most common: **Neutropenia**

Infant 7-12 months





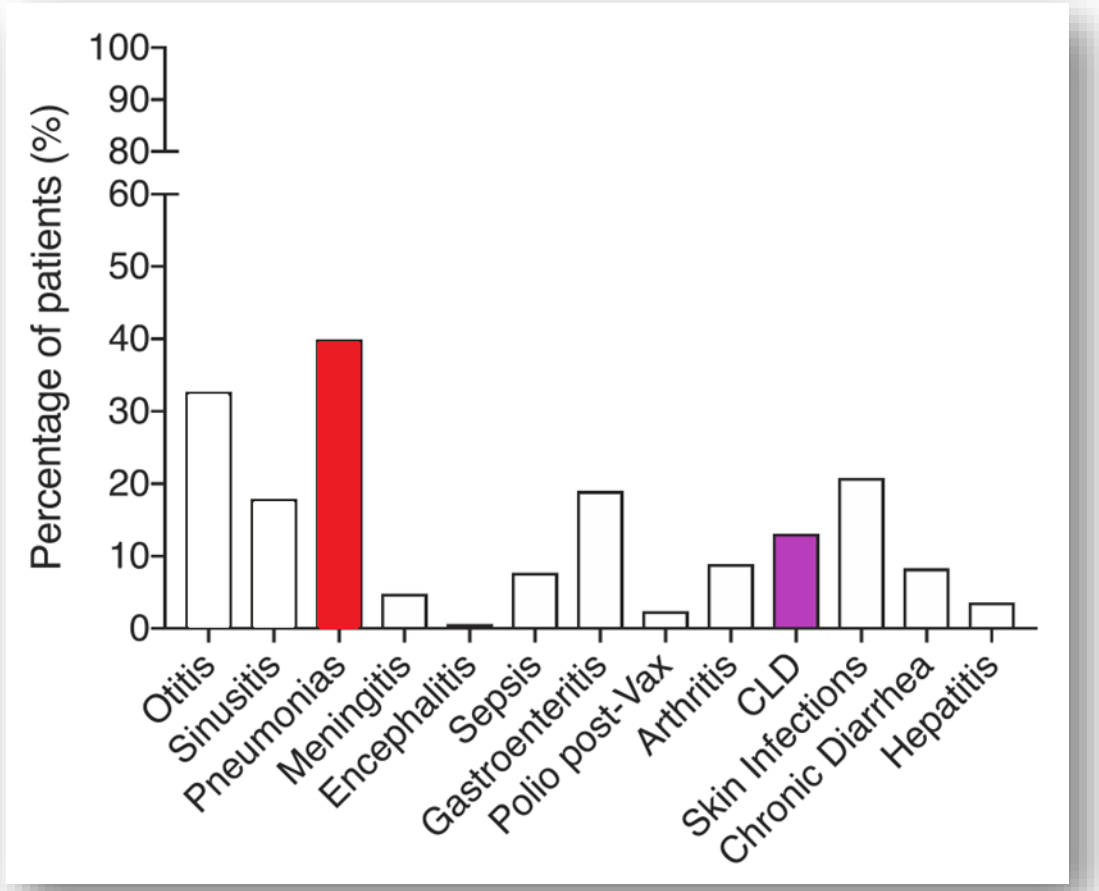
Clinical & Experimental Immunology
The Journal of Translational Immunology
British Society for immunology

Clin Exp Immunol. 2018 Feb; 191(2): 212–219.
Published online 2017 Nov 3. doi: 10.1111/cei.13068
PMCID: PMC5758375
PMID: 28990652

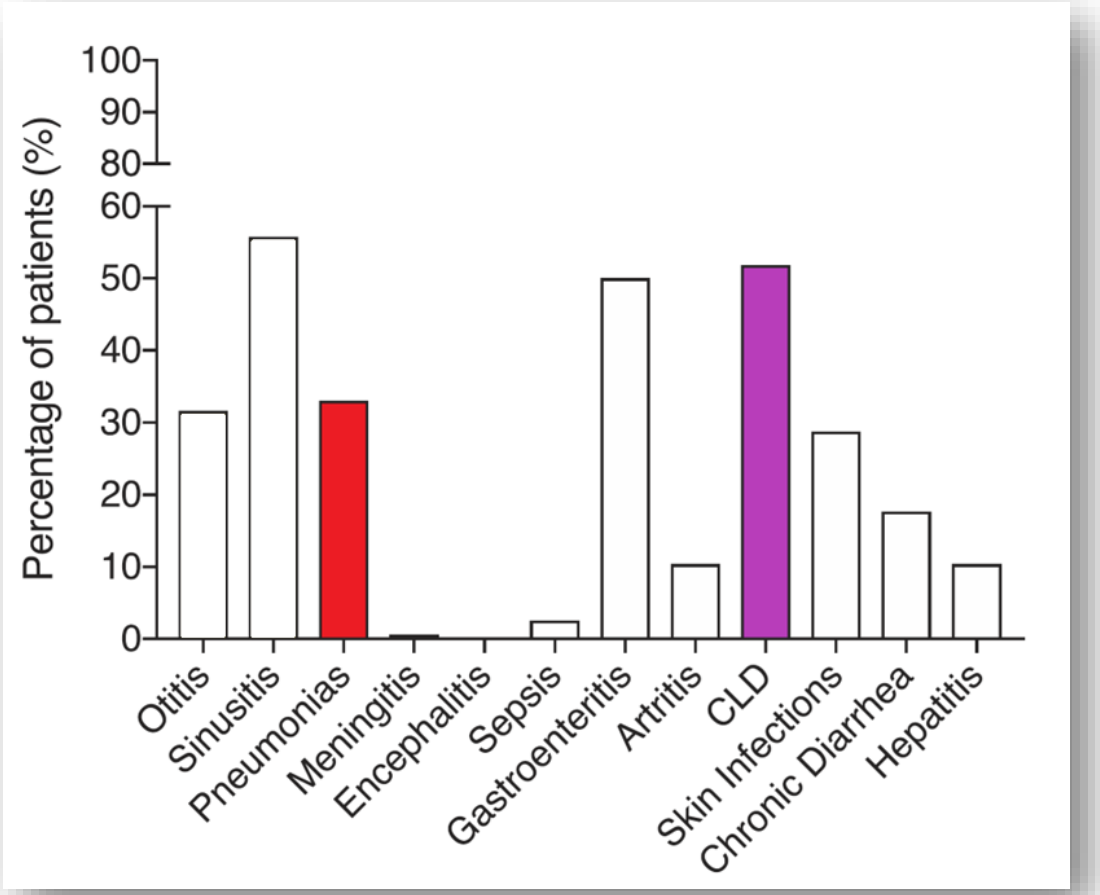
Bronchiectasis and deteriorating lung function in agammaglobulinaemia despite immunoglobulin replacement therapy

A. Stubbs, [1] C. Bangs, [1,2] B. Shillitoe, [3] J. D. Edgar, [2,4] S. O. Burns, [5] M. Thomas, [6] H. Alachkar, [7] M. Buckland, [2,8] E. McDermott, [9] G. Arumugakani, [10] M. S. Jolles, [11] R. Herriot, [12] and P. D. Arkwright [1]

XLA and the lungs



Symptoms at diagnosis



Complications after diagnosis

Lougaris V, *et al* . Long-term follow-up of 168 patients with X-linked agammaglobulinemia reveals increased morbidity and mortality. J Allergy Clin Immunol. 2020 Aug;

Wiskott-Aldrich Syndrom

Boy with

- Eczema
- Recurrent infections
- Trombocytopenia (ev small sized trc)

+ ev

- Bloody diarhea
- Autoimmunity
- Malignancies

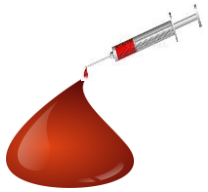
Infant 7-12 months

Antibody deficiencies

- X-Linked Agammaglobulinemia
- Hyper IgM syndromes
- Transient hypogamma of infancy

Combined Immunodeficiencies
with associated or syndromic features

- Wiskott-Aldrich
- DiGeorge (22q11 deletion)

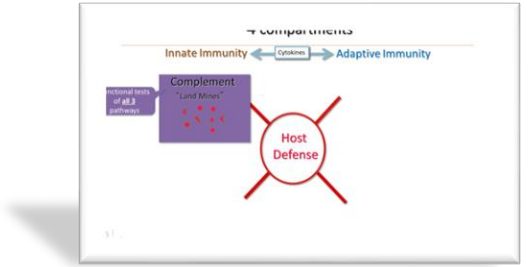


LABS

- **Complete blood count**
- **Immunoglobulins : IgG, IgM, IgA**

Infant 7-12 months *continued*

Complement deficiencies



Fulminant Neisserial infection

Properdin deficiency

LABS

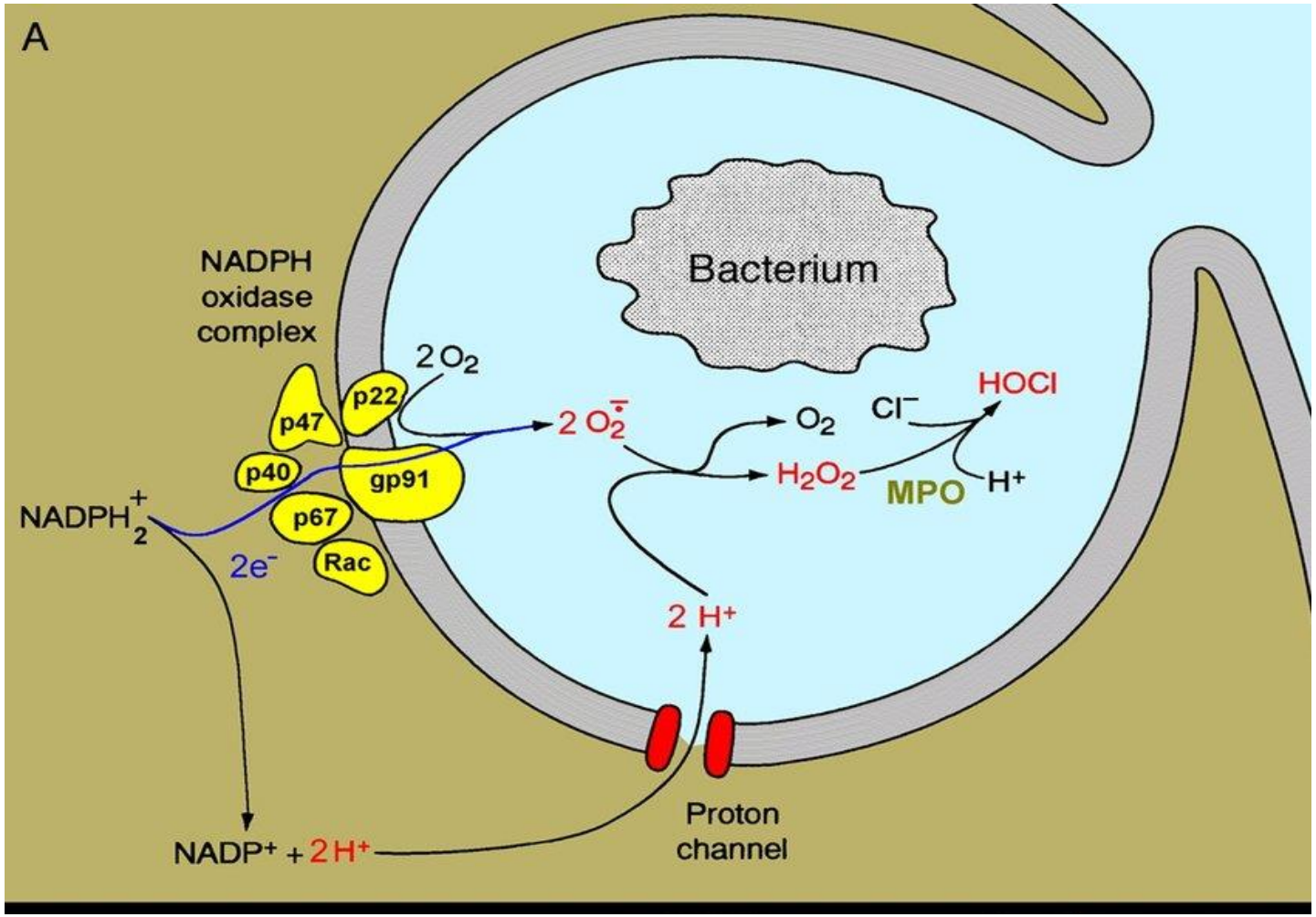
- **Complement**

3 pathways

functional tests (CH50, AH50 or similar)

Chronic Granulomatous Disease (CGD)

Functional defect



Respiratory burst

Chronic Granulomatous Disease (CGD)

Functional defect

Symptoms:

- ✓ Neutrophilia
- ✓ Infections with catalaspositive bacteria

- ✓ Abscesses :

  lymph nodes, lung, liver,
  skeleton, other internal locations and the skin

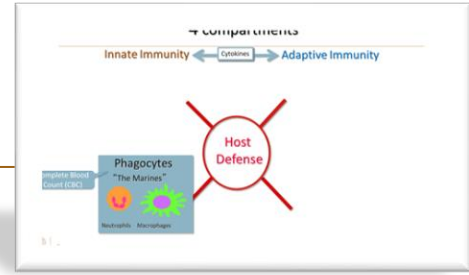
Staph aureus
Burkholderia cepacia
Aspergillus fumigatus
Serratia marcessens
Chromobacterium violaceum
Torulopsis glabrata
Hansenula polymorha
Paecilomyces varioti
Pseudallescheria boydii, etc etc

Treatment

Antibiotics (with intracellular penetration) + antimycotics

HSCT

Toddler 1-3 y



❖ Congenital defects of phagocyte number or function

LABS

- **Complete blood count**
- **Neutrophile function**
  Test oxidative burst

❖ Defects in intrinsic and innate immunity

- Predisposition to severe viral infection
- TLR signaling pathway deficiencies

❖ Combined immunodeficiencies

with associated or syndromic features

- Ectodermal dysplasia with immunodeficiency
- Immuno-osseous dysplasias

Routine immunology tests usually normal

- **Specific assays for measuring response(s) to specific stimuli**
  depending on the suspected disorder
- **WGS/WES**

TLR, toll-like receptor; WES, whole exome sequencing; WGS, whole genome sequencing.

Hyper IgE syndrome

Autosomal dominant STAT3 deficiency (Job syndrome)

Symptom	Proportion of patients
Early onset, severe eczema	100 %
Skin infektions (staph aur & candida abscesses)	88 %
Recurrent respiratory infections	87 %
Special facial features	100%
Skeletal and connective tissue abnormalities	76 %
Dental anomalies (retention of deciduous teeth)	72 %
Patological fractures	56 %
High IgE (> 2000 IE) + eosinophilia	100 %

No allergies

Hyper IgE **syndromes** (HIES)

- AD-HIES STAT3 deficiency (Job syndrome)
- AR-HIES ZNF341 deficiency
- DOCK8 deficiency
- IL6 receptor deficiency
- IL6 signal transducer (IL6ST) deficiency
- ERBIN deficiency
- Loeys-Dietz syndrome (TGFBR deficiency)
- Comel-Netherton syndrome
- PGM3 deficiency
- CARD11 deficiency

One of the symptoms is always moderate to severe eczema

IgE often high/very high

Can have allergies, often food allergies

Preschool 4-6 y

Combined immunodeficiencies with associated or syndromic features

- HyperIgE syndrome(s)
- Mendelian susceptibility to mycobacterial disease (MSMD)
- Predisposition to invasive fungal diseases
- Ectodermodysplasia with immunodeficiency

Routine immunology tests usually normal

- **Specific assays for measuring response(s) to specific stimuli**
  depending on the suspected disorder
- **WGS/WES**

Hereditary Angioedema

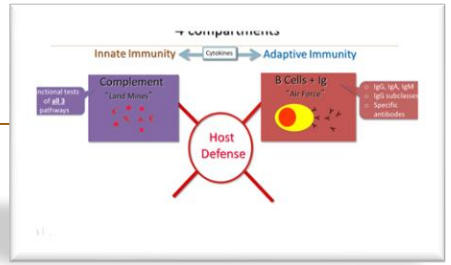
C1-INH deficiency

=> increased **bradykinin** production

=> Swellings

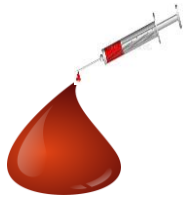
- Recurrent : skin, mucosal surfaces, incl laryngeal (!)
- Most common – extremities and abdominal
- Non-itching, last 2-5 days
- Usually starts between 4-18 years of age
- Caused in 1/3 trauma, 1/3 infection but also stress, hormons etc

School age 7-12 y



Common/relatively common disorders

Complement deficiencies



Antibody deficiencies

- CVID
- Specific antibody deficiencies
- WHIM Syndrome
  (Warts, Hypogammaglobulinemia, Infections and Myelokathexis)

Other

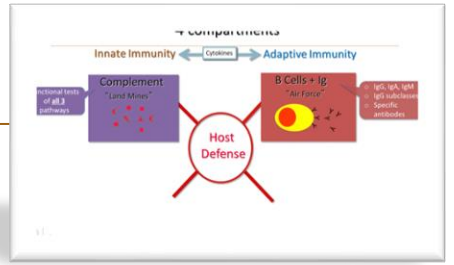
- Ataxia-teleangiectasia
- X-linked lymphoproliferative syndrome XLP

LABS

- **Complement (ev C1-INH)**

- **Complete Blood Count**
- **Immunoglobulins**
- **Specific antibodies**

Teenagers 13-18 y



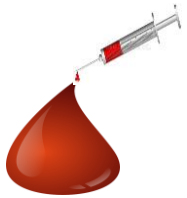
Common/relatively common disorders

Complement deficiencies

- **C2**
- Terminal complex (i.e. C5-C9)
- Properdin (Disseminated Neisserial infections)
- **Hereditary angioedema**

Antibody deficiencies

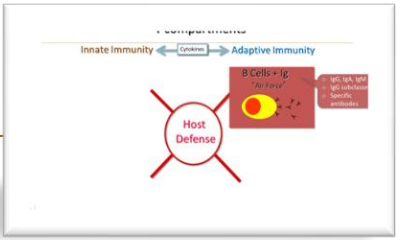
- **CVID**
- IgA deficiency
- Specific antibody deficiency

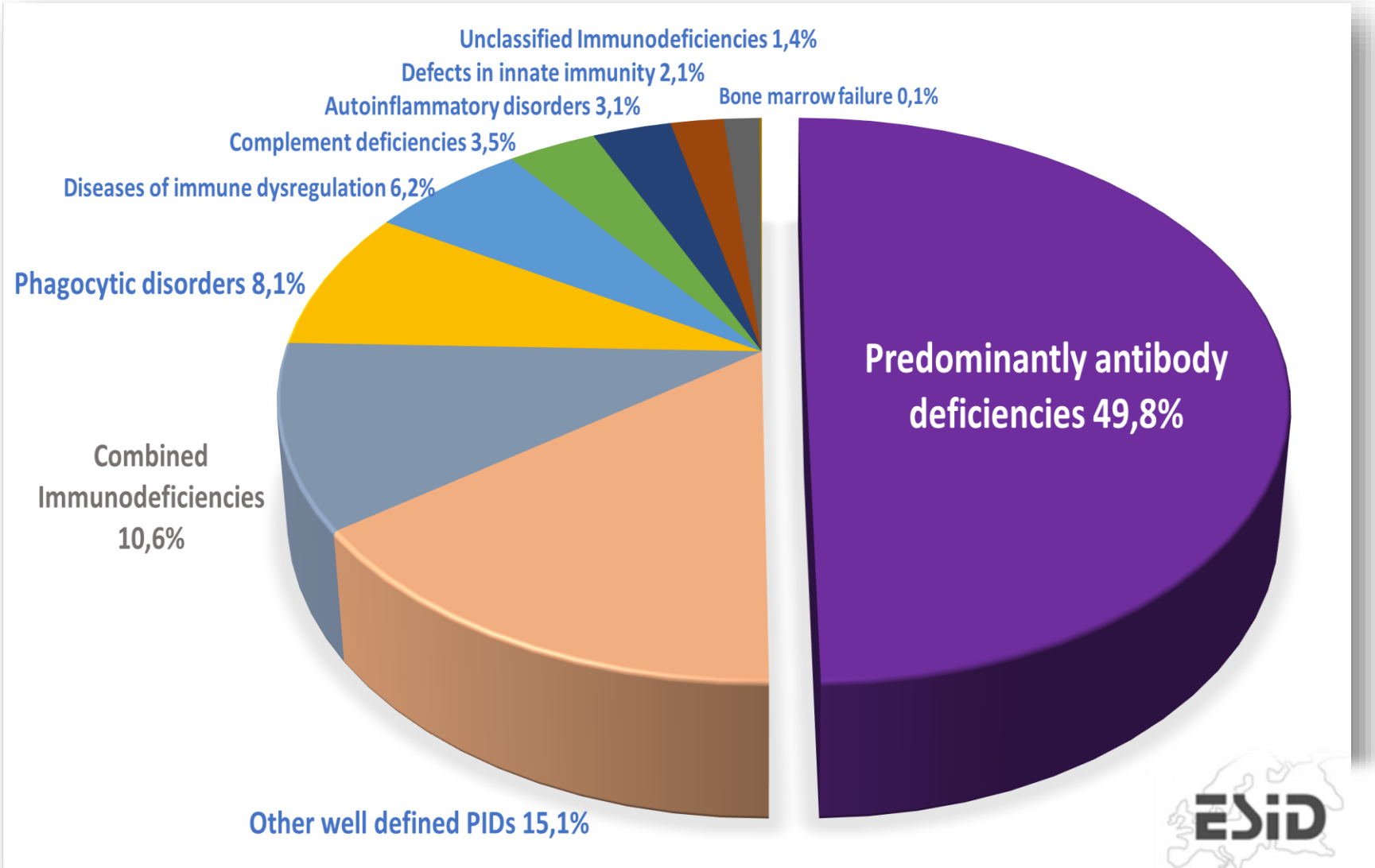


LABS

- **Complement (ev C1-INH)**
- **Complete Blood Count**
- **Immunoglobulins**
- **Specific antibodies**

Antibody deficiencies





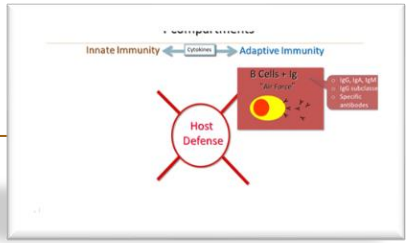
ESID European Society for Immunodeficiencies

ESID Registry

LUND UNIVERSITY 350

ESID Database from: 23 October 2023.

Antibody deficiencies (AD)



Today (2024) **known genes:** **45**

\+ **7** well described diseases with unknown mutation*

Most common :

- **IgA deficiency**
- **CVID**
- Specific antibody deficiency

Rare

- **XLA** (X-linked agammaglobulinemia)
- Hyper IgM syndromes (AID, UNG etc)
- APDS (Activated p110δ syndrome)

* Table 3 Predominantly antibody deficiencies in :Tangye SG, et al. **Human Inborn Errors of Immunity: 2022 Update**. *J Clin Immunol 2022.*


DSI guidelines · DSI
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Guidelines
Kalender
DSI guidelines
7
CVID behandling (2023)
Denne vejledning er tiltænkt behandling af CVID hos voksne patienter. Der er ikke foretaget en gradering af evidensniveau, da der ikke foreligger solid evidens for flere dele af feltet.
Den aktuelle udgave er opdateret med anvendelse af PCV20.
8
CVID udredning og opfølgning (2023)
Denne vejledning er tiltænkt diagnostik og kontrol af CVID hos voksne patienter. Der er ikke foretaget en gradering af evidensniveau, da der ikke foreligger solid evidens for flere dele af feltet.

Orphanet Journal of Rare Diseases

Orphanet J Rare Dis. 2018; 13: 201.
Published online 2018 Nov 12. doi: 10.1186/s13023-018-0941-0

PMCID: PMC6233554
PMID: 30419968

The burden of common variable immunodeficiency disorders: a retrospective analysis of the European Society for Immunodeficiency (ESID) registry data

Irina Odnoletkova,[1,2,11] Gerhard Kindle,[3,4] Isabella Quinti,[5,6] Bodo Grimbacher,[4,7] Viviane Knerr,[3,4] Benjamin Gathmann,[3,4] Stephan Ehl,[3,4] Nizar Mahlaoui,[8,9,10] Philippe Van Wilder,[11] Kris Bogaerts,[12,13] Esther de Vries,[14,15] and in collaboration with the Plasma Protein Therapeutics Association (PPTA) Taskforce

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The burden of lung disease in AD

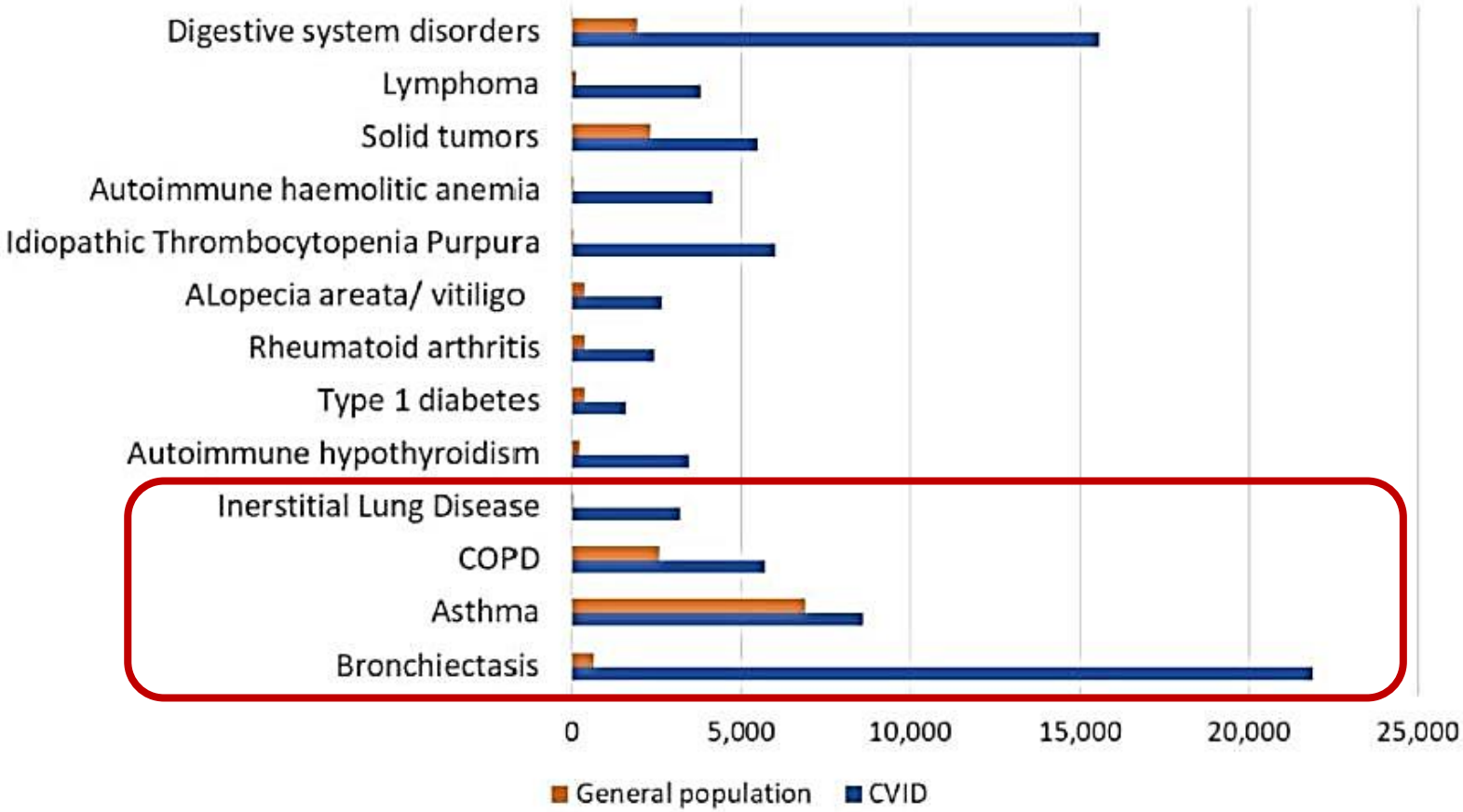
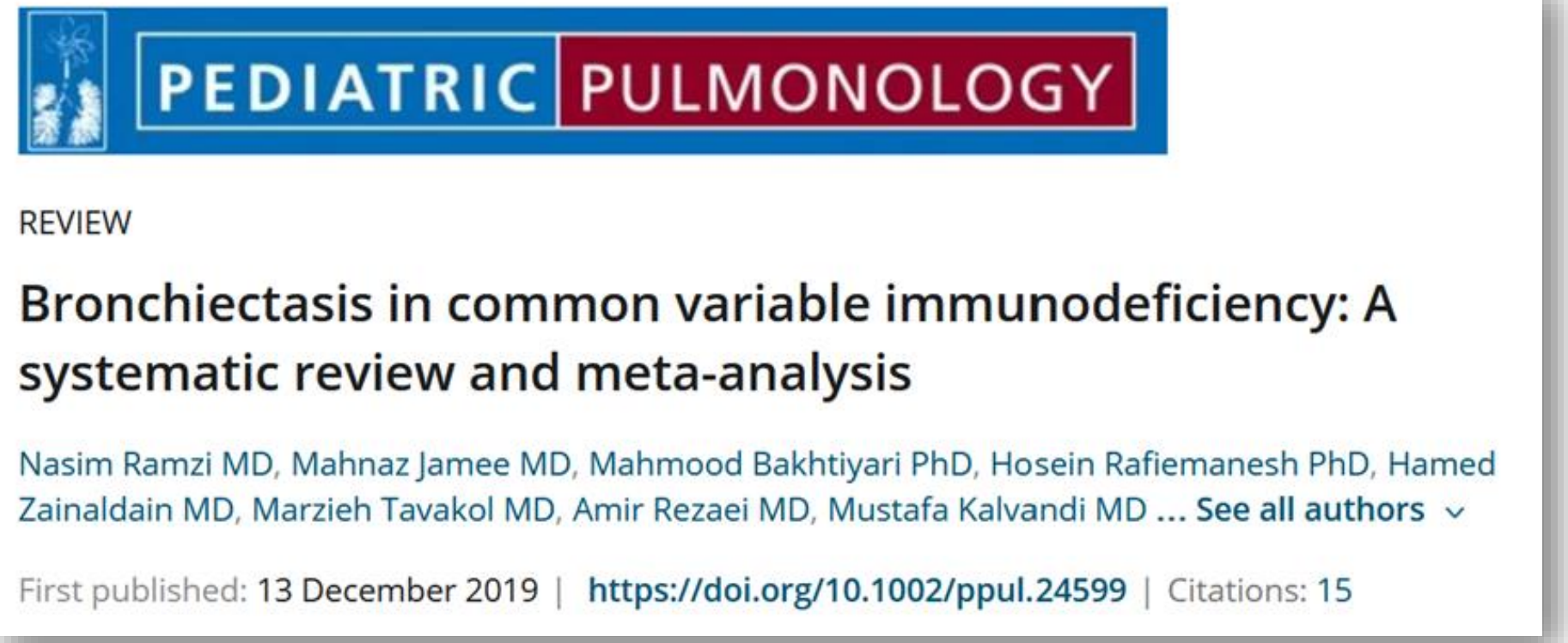


Fig. 4 Prevalence of non-communicable comorbidities. Average annual age-standardized prevalence rate per 100,000 over the period 2004–2014. CVID cohort versus general population*. All ages, both sexes. *Source: Global Burden of Disease Studies, Western Europe: http://ghdx.healthdata.org/gbd-results-tool

CVID



55 studies comprising 8535 patients with CVID

Overall prevalence of bronchiectasis **34%**

Received: 10 January 2019 | Revised: 5 September 2019 | Accepted: 6 September 2019

DOI: 10.1111/sji.12828

HUMAN IMMUNOLOGY

Scandinavian Journal of Immunology — An International Monthly Journal — WILEY

Respiratory and allergic disorders in children with severe and partial immunoglobulin A immunodeficiency

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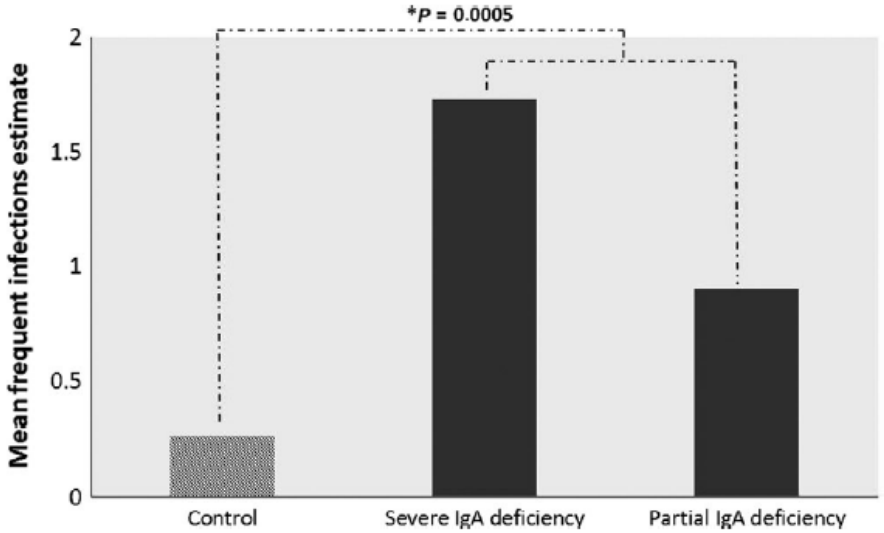
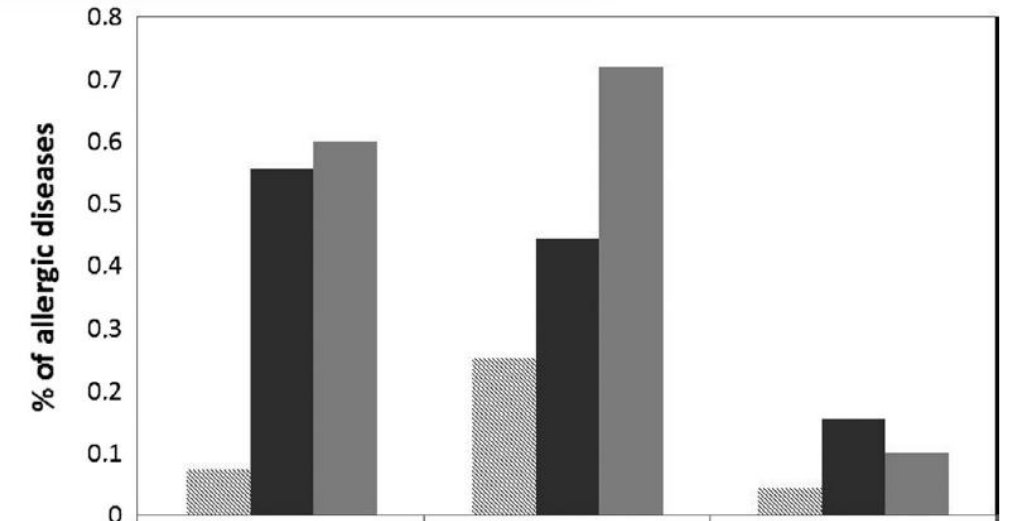




	Asthma	Allergic rhinits	Atopic dermatitis
Controls	7.46%	25.37%	4.48%
sIgAD	55.56%	44.44%	15.56%
pIgAD	60.00%	72.00%	10.00%

sIgAD - severe IgA deficiency pIgAD - partial IgA deficiency

Selective IgA deficiency

Definition* IgA < 0,05 g/L (other immunglobulins are normal)

- Most common AD in caucasians - 1 : 500

Symptoms**

- Most patients are asymptomatic (i.e. incidental finding)
- Bacterial infections (mainly if concomitant IgG subclass def)
- Mildly increased risk for autoimmunity
- Increased risk for allergic disorders #

Treatment

- Symptomatic patients with sIgAD are managed according to the disorder present
- Periodic or (if needed) daily prophylactic antibiotics

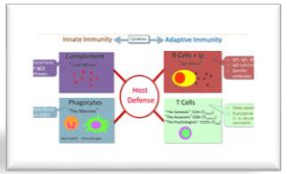
*https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria
**https://www.uptodate.com/contents/selective-iga-deficiency-clinical-manifestations-pathophysiology-and-diagnosis Accessed 28Nov 2023
Janzi M, et al Selective IgA deficiency in early life: association to infections and allergic diseases during childhood Clin Immunol. 2009

Testing

4 major goals: Identify

Complement deficiencies
5

Phagocyte disorders (number/function)
1, 2, 6



Antibody deficiencies
3, 4

Cellular defects (number/function)
1, 2, 6

1. **Complete Blood Count (CBC)**
2. **Lymphocyte subsets**
   T, B, NK cells – flow cytometry
3. **Immunoglobulins**
   IgG, IgA, IgM and IgG subclasses
4. **Specific antibody production**
   i.e. vaccine responses
5. **Complement**
   Functional (!) assays CH50, AH50, Lektin
6. **Immune cell function assays**
   Neutrophils, T-cells, B-cells, NK-cells

Results must be compared to **age-matched controls**!

HIV test

Rosenzweig SD, Kobrynski L, Fleisher TA. *Laboratory evaluation of primary immunodeficiency disorders*. In Sullivan KE, Stiehm ER. 2020. *Immune Deficiencies: inborn errors of immunity* 2nd edition. Elsevier Inc., London.
Chinen J, Paul Me, Shearer Wt. *Clinical Immunology*. 2019;:451–61.

Laboratory testing – a stepwise approach!

What	Who	Where
1. Complete blood count **IgG, IgM, IgA**	**GP/Pediatrician**	**All labs**
2. Specific antibody production (i.e. vaccine responses) **IgG-subclasses**	**GP/Pediatrician**	**Most labs**
3. Complement: Functional (!) assays CH50, AH50 **Lymphocyte subsets:** T, B, NK cells – flow cytometry	**Infectious specialist, Pediatrician, Allergist, Rheumatologist**	**Immunology labs**
4. Immune cell function assays Neutrophils, T-, B-, NK-cells specific etc	**Immunology specialist**	**Immunology or Research labs**
5. Genetics: Single gene/targeted panel / WES / WGS	**Immunology specialist + Genetician**	**Specialized labs**

WES: whole exome sequencing; WGS: whole genome sequencing.

Swedish Physicians' Interest Association for Primary Immunodeficiency. Available at http://media.slipi.nu/2021/09/Riktlinjer_senaste.pdf. Date accessed: 21 November 2023.

Take Homies

Pulmonary complications are common in a wide range of PID

- Severe/recurrent unusual bacterial pneumonias
- Bronchiectasis
- Interstitial lung disease (especially granulomatous)
- Severe unusual asthma
- Severe eczema
- High IgE

Consider
”Immundefekt”

SLIPI

Sveriges Läkares Intresseförening för Primär Immunbrist

slipi.nu/medicinsk-info