Policlinico S.Orsola-Malpighi

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
IRCCS Istituto di Ricovero e Cura a Carattere Scientifico

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Conoscere e riconoscere le Immunodeficienze Primitive: un lavoro di squadra

Malattie rare: Formazione, informazione ed ascolto in Emilia-Romagna
Undicesima Edizione
5 marzo 2022

Francesca Conti, MD-PhD

Servizio di Immunologia, U.O.C. Pediatria (Prof. Pession)
Centro di Riferimento Regionale Malattie del Sistema Immunitario
IRCCS Azienda Ospedaliero-Universitaria di Bologna

Definition

The Inborn Errors of Immunity (IEIs) are clinically heterogeneous and often multisystemic diseases, the majority of which arise from inborn errors in immunologically relevant genes.

Susceptibility to infection with bacteria, viruses and opportunistic organisms

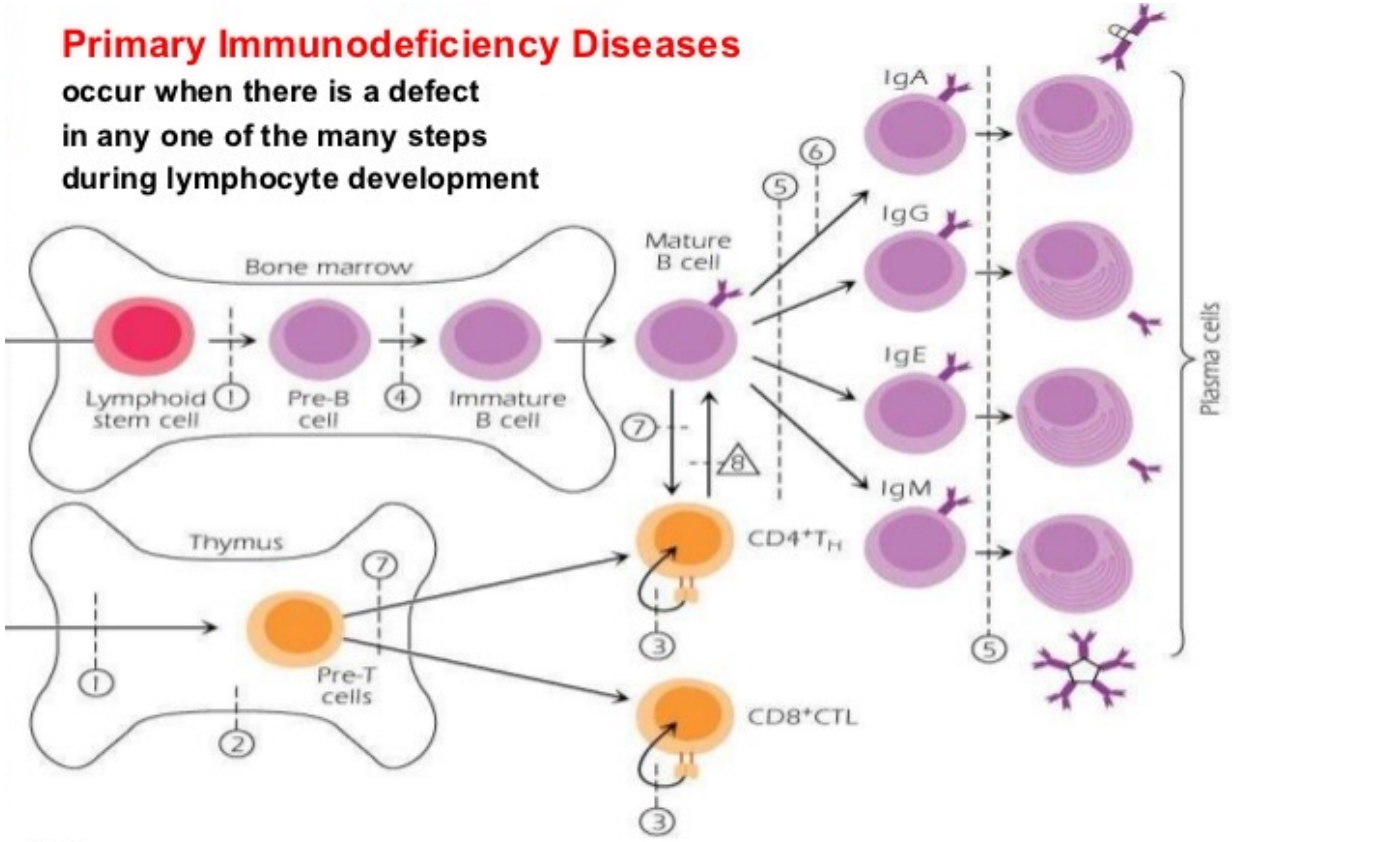
Immune dysregulation phenotypes of PID are commonplace:

- multiorgan autoimmunity,
- lymphoproliferation
- malignancy (particularly haematological)
- inflammatory pathology

Incidence: 1:500-1:500.000

Primary Immunodeficiency Diseases

occur when there is a defect
in any one of the many steps
during lymphocyte development

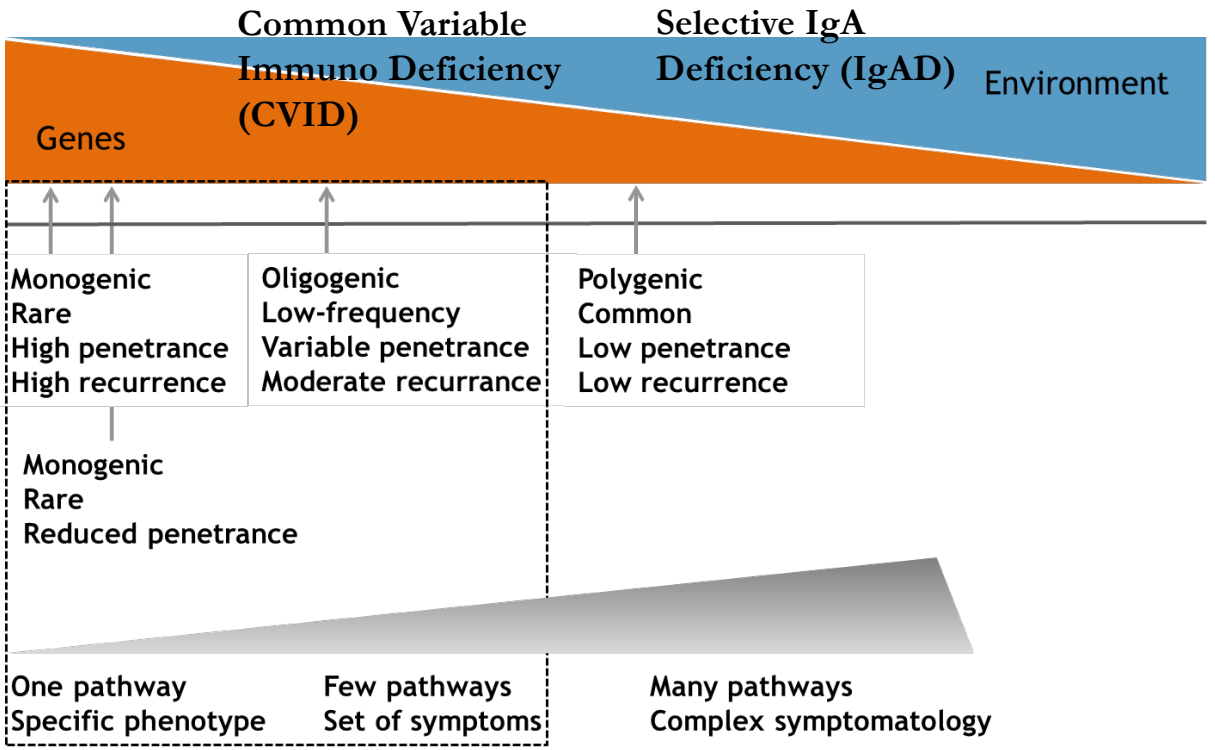


Key:

1. Severe combined immunodeficiency syndrome
2. Congenital thymic aplasia (DiGeorge Syndrome)
3. T cell signaling deficiency
4. X-linked agammaglobulinemia (Bruton's)
5. Common variable immunodeficiency disease (various forms)
6. Selective IgA deficiency
7. Bare lymphocyte syndrome
8. Hyper IgM sysndrome

From early onset IEIs to adult presentations: genomic architecture of the immune system

Severe Combined Immuno Deficiency (SCID)



>430 distinct, monogenic primary immunodeficiencies

The 2019 IUIS Phenotypic Classification for Inborn Errors of immunity

301 genes causing **PIDs**

Primary immunodeficiencies are grouped into 10 general categories

I. Combined Immunodeciencies
II. Combined immunodeficiencies with associated or syndromic features
III. Predominantly antibody deficiencies
IV. Immune dysregulation diseases
V. Congenital defects of phagocyte number &/or function
VI. Defects in innate immunity
VII. Autoinflammatory disorders
VIII. Complement deficiencies
IX. Bone Marrow Failure
X. Phenocopies – Somatic mutations that mimic inherited mutation and PID

Bousfhia A, J Clin Immunol, 2020

129 genes causing **PIRDs**

Autoimmunity, hyperinflammation, lymphoproliferation, malignancy, and severe atopy with less dominant features of immunodeficiency and infection.

- Tregopathies (IPEX, IPEX-like)
- Autoinflammatory syndromes
- hyperinflammatory disorders (predisposition to HLH)
- Debris defects
- **Nonmalignant lymphoproliferation (ALPS, ALPS-like/ALPS-U)**
- Hematopoietic malignancies
- Congenital atopic hypersensitivity
- IBD
- Rheumatologic diseases

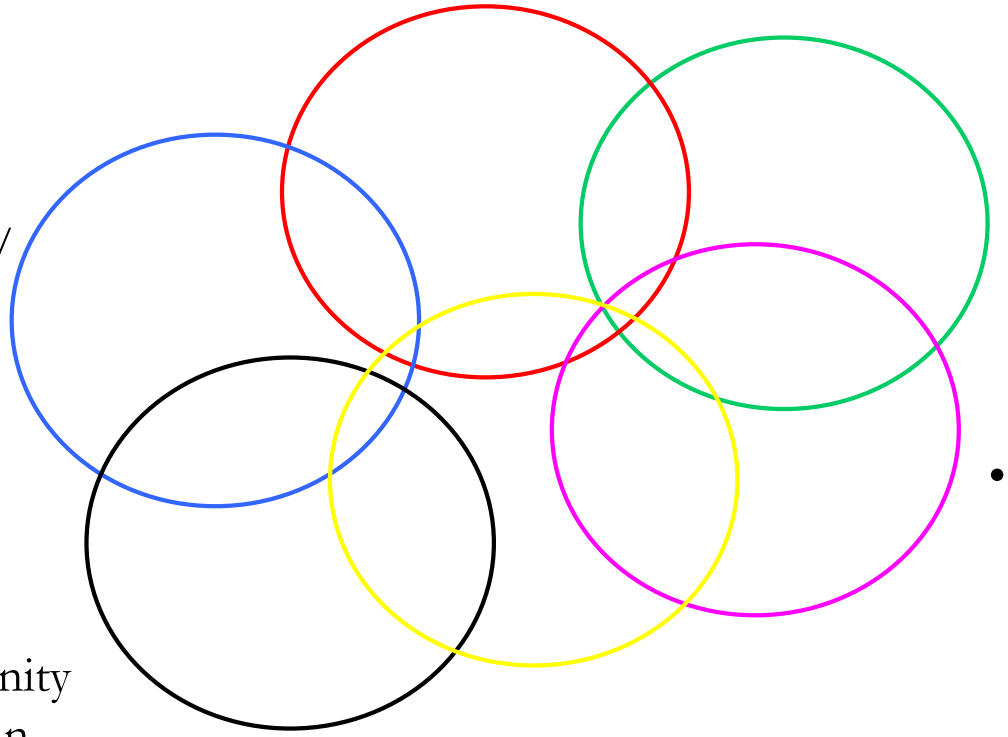
Chan AY, Current Opinion in Allergy and Clinical Immunology 2020

Inborn Errors of Immunity: red flags

- Infections

- Allergy
  - severe
  - early onset
  - poor responsive
  - atypical

- Autoinflammation/ Inflammation

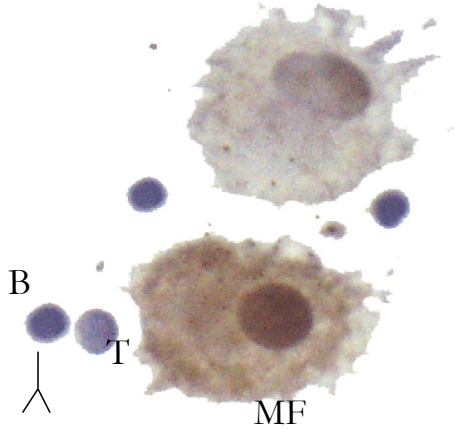


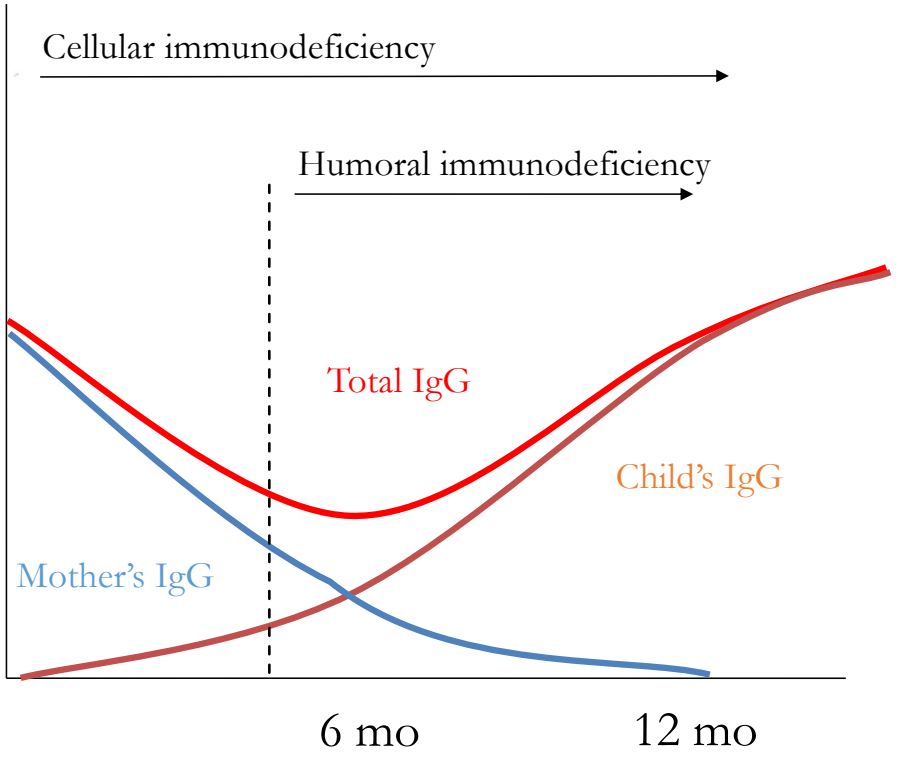
- Lymphoproliferation
  - polyclonal
  - bone marrow, spleen, lung, GI

- Autoimmunity
  - multiorgan
  - refractory to treatement
  - early onset

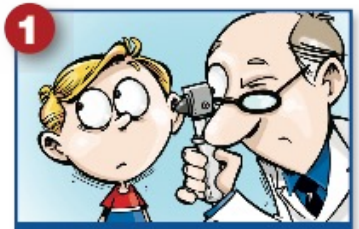
- Cancer predisposition

Type of IEIs	Age and symptoms





10 CAMPANELLI DI ALLARME
delle Immunodeficienze Primitive

1. 
Quattro o più otiti in un anno

2. 

Due o più gravi sinusiti in un anno

3. 
Più di due mesi di terapia antibiotica con scarso effetto

4. 

Più di due polmoniti in un anno

5. 

Scarso accrescimento staturoponderale

6. 
Ascessi ricorrenti della cute e di organi interni

7. 
Mughetto persistente o altre candidosi dopo l'età di un anno

8. 
Necessità di terapia antibiotica e.v. per ottenere la guarigione

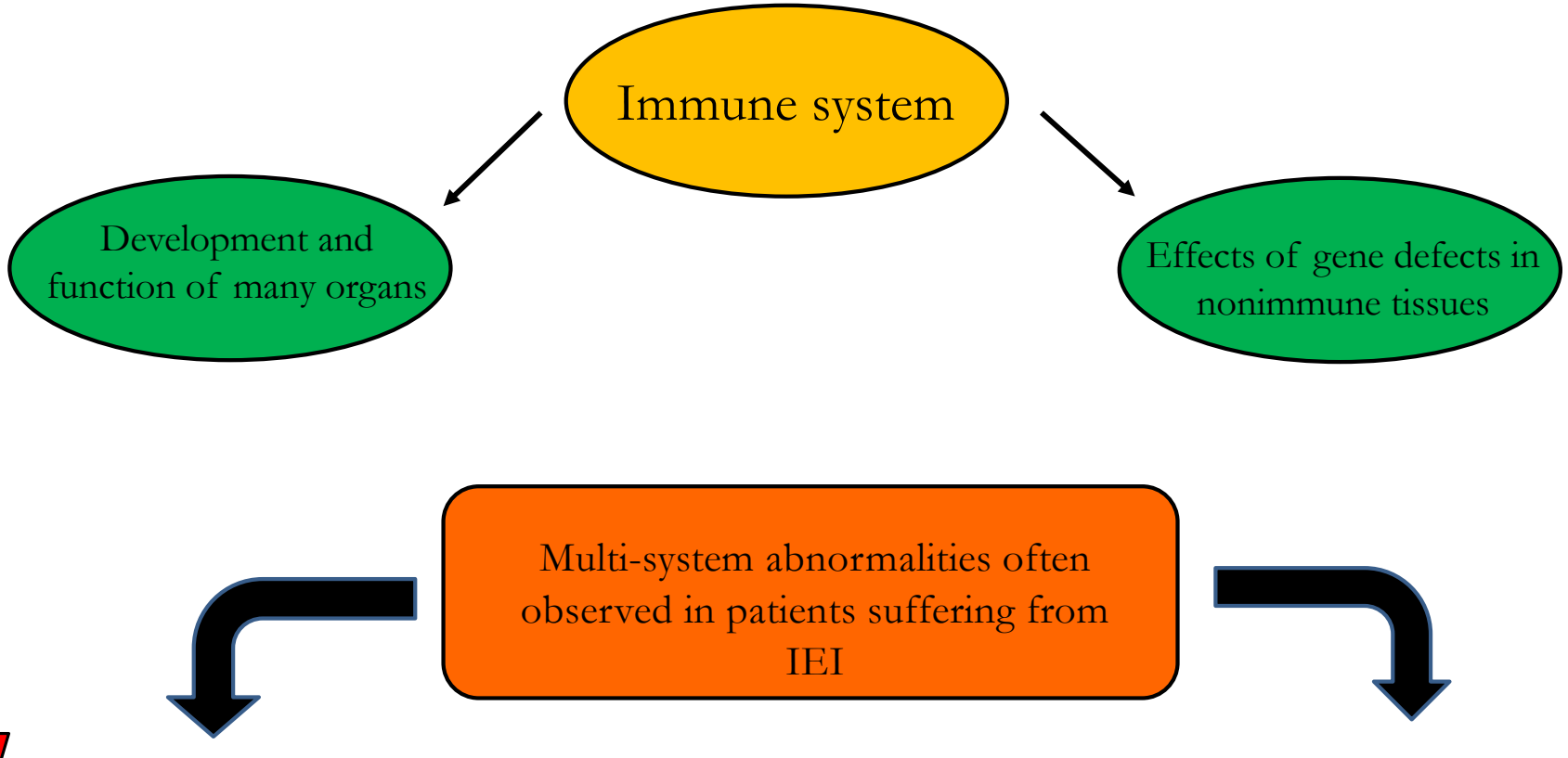
9. 

Due o più infezioni agli organi interni

10. 
Storia familiare di immunodeficienze primitive

11. Autoimmunità/ Immunodisregolazione

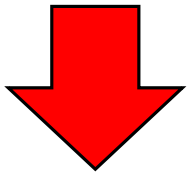
Jeffrey Model



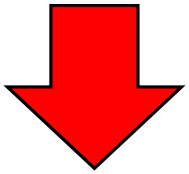
Nonimmune abnormalities can be a clue to establishing the specific etiology of the PID, anticipating potential complications or choosing best management options.

Respiratory system and IEIs

Pulmonary disease is common among patients with IEIs and may be the initial manifestation



Therapy for these disorders improves and life expectancy of patients with IEIs increases



Knowledge of the detection and management of pulmonary disorders related to IEIs is critical for optimal management

Table 1 | Respiratory presentations and complications of primary immunodeficiencies [adapted according to Bierry et al. (7) and Touw et al. (8)].

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				

Respiratory system infections and IEIs

Pulmonary infections: Infections that are recurrent, recalcitrant to usual therapy, or due to opportunistic or unusual pathogens are suggestive of a possible underlying IEIs.

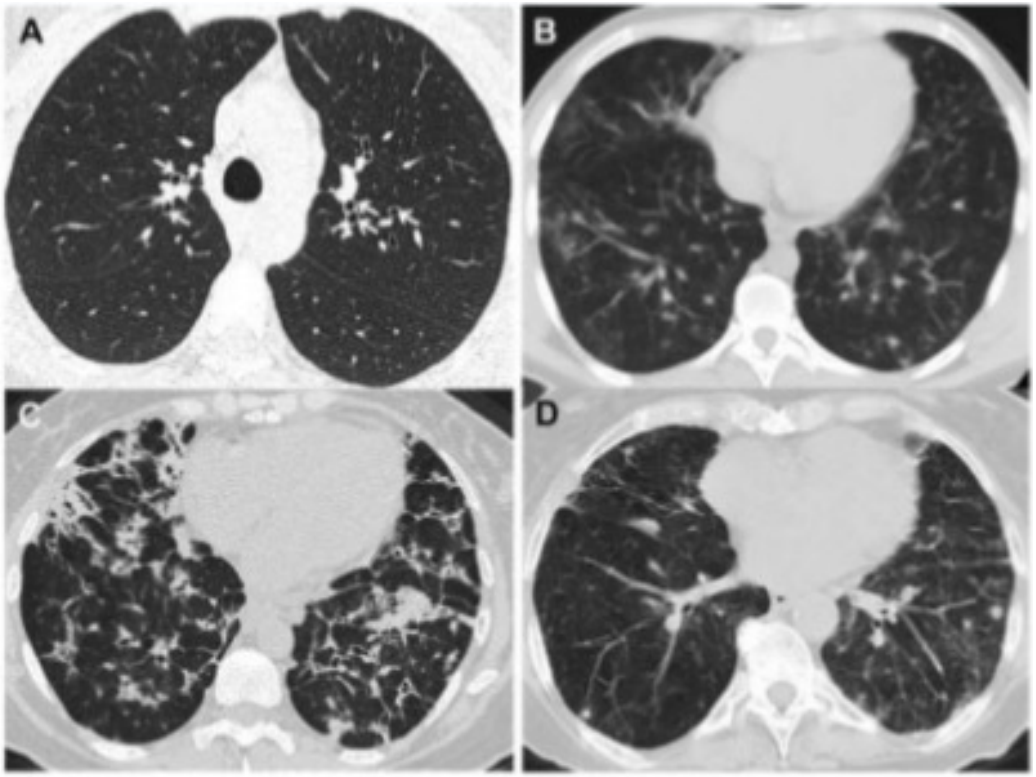
Recurrent infections: recurrent pneumonias (ie, >2/lifetime) are unusual. Pneumonias in varying locations of the lung, particularly with interim clearing between episodes, are more indicative of underlying immune dysfunction. The presence of unusual complications of pneumonia, such as pneumatoceles or cavitary lesions, is also concerning for immunodeficiency.

Recalcitrant infections: The need for protracted courses of antibiotics or the presence of complicated pneumonia (eg, multilobar opacities, empyema, lung abscess) requiring inpatient hospitalization or surgical intervention should raise the possibility of a IEI.

Opportunistic/unusual pathogens: patients with combined immunodeficiencies or with impaired phagocyte function are at increased risk of infection with opportunistic or unusual pathogens. Pneumonia caused by *Pneumocystis jirovecii*, *Pseudomonas*, *Burkholderia*, *Aspergillus*, or *Cytomegalovirus*. Nontuberculous mycobacterial infections also can occur in the context of immunodeficiencies, particularly when there is impaired interleukin (IL)-12/IL-23/interferon (IFN)-gamma signaling.

Respiratory system and IEIs

A.**Bronchiectasias**



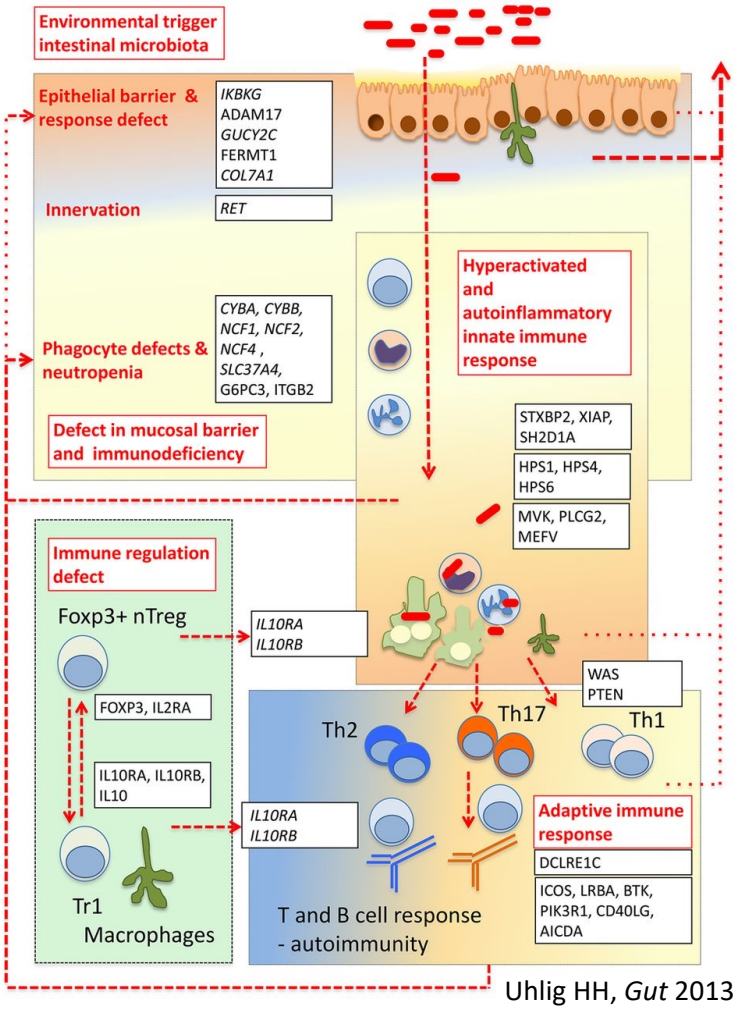
B.**Bilateral pulmonary nodules and mediastinal lymphadenopathy**

D.**Multiple non calcified lung nodules**

C.**Nodular opacities, bronchiectasias and mediastinal lymphadenopathy**

Allergy Clin Pract 2016

Gastrointestinal tract and IEIs



Uhlig HH, *Gut* 2013

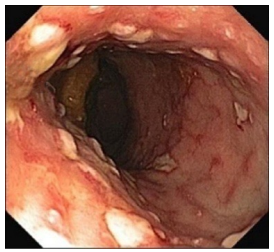
It is quite common for primary immune deficiency to mimic gastrointestinal diseases as the gastrointestinal system is the largest lymphoid organ of the human body containing T and B lymphocytes, macrophages, and dendritic cells.

Genetic defects affecting gut epithelial barrier function, neutrophil granulation as well as T and B lymphocytes are known to predispose affected individuals to **inflammatory bowel-like disease**

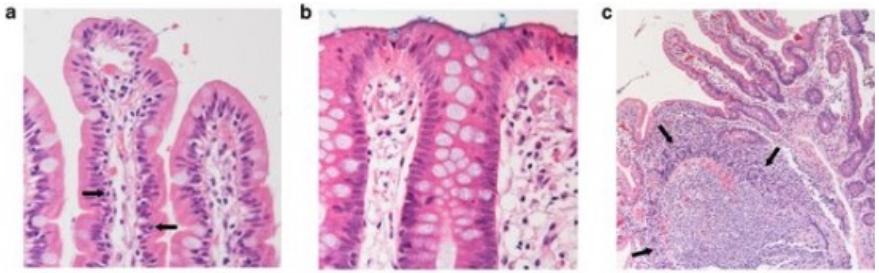
GI disease may be the first presentation of an underlying immunodeficiency → it is **imperative** to consider immunodeficiency in any patient with **intractable diarrhea**, **malabsorption**, and **failure to thrive** that is **resistant** to **conventional treatments**.

Gastrointestinal tract and IEIs

Primary immune deficiency	Gastrointestinal presentation	Diagnostic tests	Endoscopic appearance	Histological appearance
CVID	Acute and chronic diarrhea secondary to infective or inflammatory colitis. Dyspepsia. Abdominal pain. Vomiting. Weight loss. GI malignancy.	Low serum immunoglobulins Impaired vaccine responses	Inflammatory changes in small or large bowel Polyps or nodules in small bowel Lymphoma	Lack of plasma cells, apoptosis Gastric atrophy with lymphocytic infiltration in pernicious anemia
Chronic granulomatous disease	Non-infectious diarrhea. Oral aphthae, anal fistulae, vomiting, anorexia, and abdominal pain. Gastric outlet obstruction. Intestinal granulomas causing strictures or obstruction.	Neutrophil burst test Genetic tests	Inflammation in bowel causing stricture formation and obstruction. Fistulas in bowel or anus. Crohns-like appearance with transmural patchy inflammation.	Eosinophilic infiltrate, large pigmented macrophages, crpt abscesses, non-caseating granulomata
IgA deficiency	Giardiasis, malabsorption, lactose intolerance, coeliacs, ulcerative colitis, nodular lymphoid hyperplasia (NLH) and malignant proliferation	Low serum immunoglobulin A, normal IgG	Nodules in NLH	Villous flattening or atrophy
CD40 ligand deficiency	Enteropathy secondary to cryptosporidium infection. Sclerosing cholangitis and hepato-biliary cancer	Normal or high serum IgM and low IgG, IgA, IgE Flow cytometry-abnormal CD40 ligand expression	Rectal ulcers Bowel inflammation	
Wiskott Aldrich Syndrome	Colitis, bloody diarrhea and m2alabsorption	Full blood count-low platelets Abnormal natural killer cell activity High immunoglobulins A and E Impaired neutrophil burst test Flow cytometry for absence of WASP expression Genetic testing	Inflammation in bowel	



CGD: initial ileocolonoscopy showing multiple, well-defined rectal ulcers resembling Crohn's disease.
Peixoto A et al, ACG Case Rep J 2017

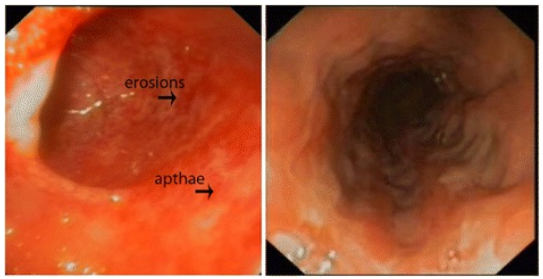


CVID:(**a**) Duodenal mucosal villi with an increased number of intraepithelial lymphocytes (arrows). (**b**) Colonic mucosa with a reduced number of plasma cells in the lamina propria. (**c**) Duodenal mucosa with a lymphoid aggregate (arrows).

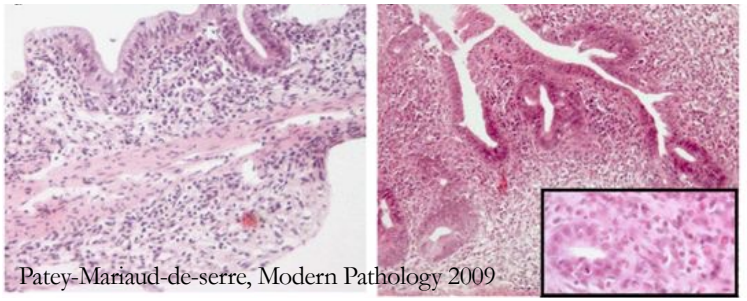
Naila Nazi & Fani Ladomenou(2018) International Reviews of Immunology

Gastrointestinal tract and IEIs

IL-10 deficiency	Early onset inflammatory bowel disease. Lymphoma	Genetic testing	Inflammatory changes in bowel	
XIAP deficiency	Crohns like disease, splenomegaly	Genetic testing	Inflammation in bowel	
IPEX syndrome	Chronic, watery diarrhea. Failure to thrive requiring total parenteral nutrition.	Elevated IgE and IgA Eosinophilia Autoimmune anemia, thrombocytopenia, neutropenia Decreased numbers of FOXP3-expressing T cells in peripheral blood determined by flow cytometry	Inflammation in bowel	Villous atrophy, lack of paneth and goblet cells, acute and chronic inflammation Eosinophilic infiltrate
NEMO syndrome	Enterocolitis-diarrhea, abdominal pain, weight loss	Genetic testing	Inflammatory colitis	
Hereditary angioedema	Severe abdominal pain, diarrhea, rectal bleeding, vomiting, acute surgical abdomen, hypovolemic shock, ascites	Complement levels-C3, C1INH protein	Intussusception Colitis Intestinal edema	
XLA	Infective diarrhea	Low serum immunoglobulins Lymphocyte subsets-absent B cells Genetic testing	Inflammatory colitis Bowel lymphoma Gastric adenocarcinoma	Lack of plasma cells in lamina propria
SCID	Diarrhea, malabsorption and failure to thrive	Full blood count and lymphocyte subsets	Intestinal inflammation	Villious atrophy



XIAP: Image of colonoscopy investigation. In the pictures is possible to appreciate the colonoscopy features of the patient, in particular the erosions and apthae.
Girardelli M et al, BMC Pediatrics 2015



IPEX Duodenal biopsies: total villous atrophy with a moderate-to-marked inflammation of the lamina propria consisting of lymphocytes, plasma cells, neutrophils and eosinophils. The main feature was the presence of apoptotic cell death of epithelial cells.

Naila Nazi & Fani Ladomenou(2018) International Reviews of Immunology

Cardiovascular system and IEIs

Increasing numbers of patients with IEIs are being recognized as also suffering from cardiovascular system (CVS) abnormalities. These CVS defects might be explained by infectious or autoimmune etiologies, as well as by the role of specific genes and the immune system in the development and function of CVS tissues.

Expanding spectrum of IEI requires increased alertness to the possibility of CVS involvement as an important contributor to the diagnosis and management of these patients.

Appendix A2: Primary immunodeficiency disorders associated with cardiac abnormalities.

Cardiac abnormalities	PID
Atrial septal defect	*STK4* deficiency *SCN4/G6PC3* deficiency DiGeorge syndrome CHARGE syndrome Shwachman-Diamond syndrome ICF syndrome
Ventricular septal defect	Nijmegen breakage syndrome DiGeorge syndrome CHARGE syndrome Shwachman-Diamond syndrome ICF syndrome ALPS–FADD deficiency
Patent ductus arteriosus	Nijmegen breakage syndrome *SCN4/G6PC3* deficiency DiGeorge syndrome CHARGE syndrome Shwachman–Diamond syndrome
Pulmonary stenosis/ atresia	*SCN4/G6PC3* deficiency DiGeorge syndrome ALPS–FADD deficiency
Mitral valve prolapse	Ataxia–telangiectasia Cohen Syndrome
Valve insufficiency	*STK4* deficiency: mitral/tricuspid/pulmonary Ataxia telangiectasia: mitral/tricuspid *SCN4/G6PC3* deficiency: mitral CGD: aortic/mitral
Conotruncal anomalies	DiGeorge syndrome CHARGE syndrome
Tetralogy of Fallot	WHIM syndrome DiGeorge syndrome CHARGE syndrome
Aortic arch abnormalities	CVID DiGeorge syndrome CHARGE syndrome
Ventricular noncompaction	Roifman syndrome Barth syndrome
Cardiomyopathy	Omenn syndrome *ORAI1* deficiency *STK4* deficiency TWEAK deficiency Barth syndrome (dilated/ hypertrophic) Cohen syndrome Shwachman-Diamond syndrome *HOIL1* Deficiency
Myocarditis	CVID
Pericarditis	*LCK* deficiency
Arrhythmias	*ORAI1* deficiency Barth syndrome

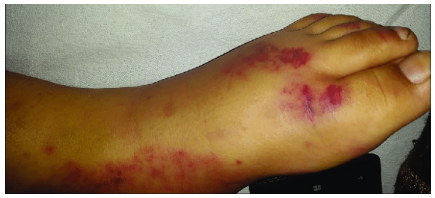
Note: Acronyms are defined in Appendix B1.

Appendix A3: Primary immunodeficiency disorders associated with vascular abnormalities.

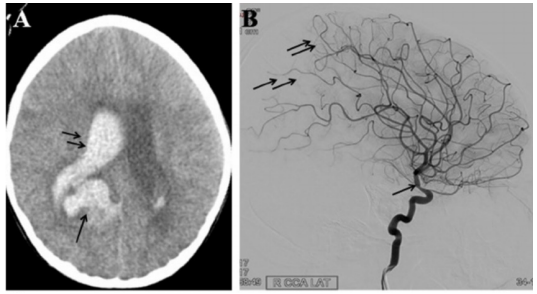
Vascular abnormalities	PID
Aortic root dilatation	CVID Wiskott–Aldrich syndrome
Aortic Aneurysms	CVID Wiskott–Aldrich syndrome AD and AR Hyper IgE syndromes
Coronary aneurysms	AD Hyper IgE syndrome
Intracranial aneurysms	AD chronic mucocutaneous candidiasis Chronic granulomatous disease
Cerebral vasculitis	AD chronic mucocutaneous candidiasis Wiskott–Aldrich syndrome Schimke immune-osseus dysplasia X-linked lymphoproliferative disorder type 1
Moya-Moya vasculitis	AR Hyper IgE syndrome Schimke immune-osseus dysplasia
Coronary vasculitis	X-linked lymphoproliferative disorder type 1
Retinal vasculitis	*LCK* deficiency X-linked lymphoproliferative disorder type 1
Systemic vasculitis	Wiskott–Aldrich syndrome X-linked lymphoproliferative disorder type 1
Systemic vessel stenosis	Aicardi–Goutières syndrome: brain/carotid/retina
Abnormal vascular tone	Chronic granulomatous disease
Aortic arch defects	DiGeorge syndrome CHARGE syndrome
Abnormal pulmonary veins	*SCN4/G6PC3* deficiency
Ischemic heart disease	Ataxia–telangiectasia Chronic granulomatous disease
Thromboembolic cerebrovascular events	Barth syndrome
Telangiectasias	Ataxia–telangiectasia FILS syndrome
Capillary leak syndrome	*LCK* deficiency MonoMAC (*GATA2* deficiency)
Veno-occlusive disease of the liver	VODI syndrome

Note: Acronyms are defined in Appendix B1.

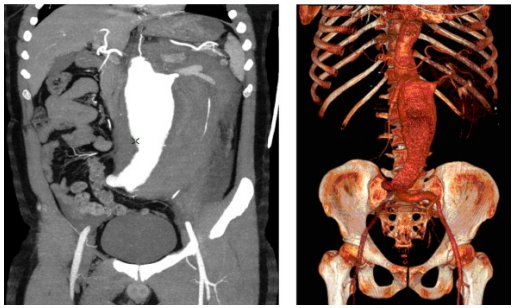
Human A, LymphoSign Journal 2015



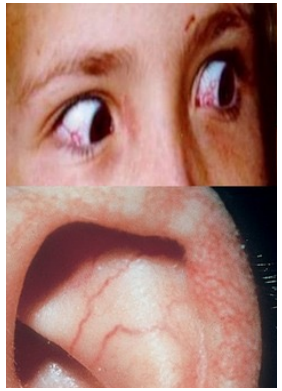
Wiskott Aldrich syndrome. Skin biopsy revealed leucocytoclastic vasculitis with IgA deposits



DADA2. AParietal lobar hematoma extending into the right lateral ventricle. B Narrowing of the supraclinoid internal carotid artery (arrow) and irregular narrowing of the distal parietal branches (arrows).

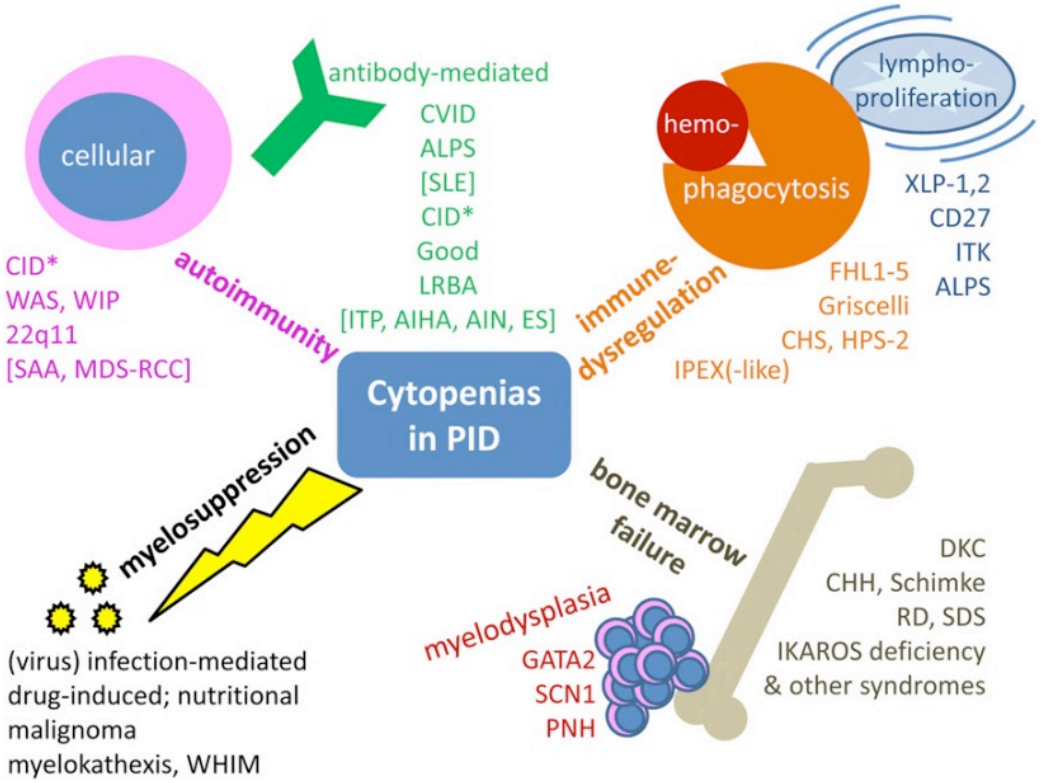


HyperIgE syndrome. 9-cm ruptured type IV thoracoabdominal aortic aneurysm



A-T. Telangiectasias in the ocular sclerae and ear

Hematological disorders and IEIs



Seidel, Blood, 2014

Hematological disorders and IEIs

Table 1. Possible clinical presentation (apart from symptoms of cytopenia), laboratory parameters of PID with cytopenia, and treatment options

Type	Disorders*	Possible symptoms	Typical laboratory parameters	Treatment options
Antibody-mediated autoimmunity	CVID, ALPS, [cITP, Evans syndrome] [SLE], CID,§ Good syndrome, LRBA deficiency	May be asymptomatic, bacterial infection, multiorgan autoimmunity, thymoma, inflammatory bowel disease	Hypogammaglobulinemia, csBm cells reduced, DNT cells increased, vitamin B_{12}, sFasL, IL-10, IL-18	IVIG, corticosteroids, MMF, plasmapheresis/exchange, anti-CD20,† CY, purine analogs, TPOR agonists,‡ HSCT‡
Cellular autoimmunity	CID,§ PCID,§ WAS, WIP, 22q11, [SAA, RCC/MDS RC]	May be asymptomatic, opportunistic infection, eczema, atopy, syndromic features, pancytopenia, autoimmunity	Empty bone marrow, lack of naïve T cells, microplatelets, MLPA, B-cell and NK-cell deficiency, T cells nonfunctional	Calcineurin inhibitors, ATG, alemtuzumab, MMF, mTOR inhibitors, CY, MTX, purine analogs, Vcr, Vbl, HSCT‡
Immune dysregulation	IPEX(-like), XLP, CD27, ITK, XMEN, ALPS, HLH, FHL, Griscelli syndrome, CHS, HPS	Often severely ill patient, fever, organomegaly, lymphoma, positive family history, partial albinism	Stat5b-P, EBV viremia, hyperferritinemia, sIL2R, genetic testing, DNT cells increased, iNKT cells reduced, vitamin B_{12}, sFasL, NK/CTL cytotxicity	corticosteroids, calcineurin inhibitors,‡ etoposide,‡ ATG,‡ alemtuzumab,‡ anti-CD20, mTOR inhibitors, MMF, HSCT‡
Bone marrow failure, myelodysplasia	DKC, CHH, Schimke syndrome, RD, SDS, MonoMac syndrome, PNH, other‖	May be asymptomatic, syndromal features, skin, bones, deafness, maldigestion, hemolysis, dystonia	Telomere length, genetic testing, lymphopenia, pancreatic insufficiency, altered pDC/mDC ratio	Eltrombopag, G(M)CSF, HSCT,‡ eculizumab
Myelosuppression	Various, WHIM syndrome	Viral infection, toxic, malignant (nutritional) deficiency	Pancytopenia, myelokathexis	Treat underlying disease, infection intoxication/deficiency state, CXCR4 antagonist (in WHIM)

Seidel, Blood, 2014

Urinary tract/kidney and IEIs

NDT Plus (2010) 3: 456–458
doi: 10.1093/ndtplus/sfq083
Advance Access publication 11 May 2010

NDT PLUS
Nephrology Dialysis Transplantation

Case Report

A case of primary immune deficiency presenting with nephrotic syndrome

Zeki Aydin[1], Meltem Gursu[1], Savas Ozturk[1], Isın Kilicaslan[2] and Rumeyza Kazancioglu[1]

[1]Department of Nephrology, Haseki Training and Research Hospital, Istanbul, Turkey and [2]Department of Pathology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

ELSEVIER

American Journal of Kidney Diseases
Volume 38, Issue 2, August 2001, Pages e7.1-e7.3

AJKD

Case Reports

Granulomatous renal disease in a patient with common variable immunodeficiency

Fadi Fakhouri MD, Christophe Robino MD, Matthieu Lemaire MD, Dominique Droz MD, Laure-H[eacute]l[egrave]ne No[euml]l MD, Bertrand Knebelmann MD, PhD, Philippe Lesavre MD, PhD

International Journal of *Environmental Research and Public Health*

MDPI

Case Report

IgA Deficiency and Nephrotic Syndrome in Children

Lorenza Di Genova, Stefania Ceppi, Maurizio Stefanelli and Susanna Esposito *

Pediatric Clinic, Department of Medical and Surgical Sciences, Università degli Studi di Perugia, 06132 Perugia, Italy; lory.digenova@gmail.com (L.D.G.); stefipg22@yahoo.it (S.C.); maurizio.stefanelli@ospedale.perugia.it (M.S.)

CASE REPORT

Year : 2014 | **Volume** : 25 | **Issue** : 2 | **Page** : 394-397

Chronic tubulo-interstitial nephritis in common variable immunodeficiency: A rare association

Sumantra Sarkar[1], Rakesh Mondal[1], Madhumita Nandi[1], Parasar Ghosh[2]

[1] Department of Pediatrics, Institute of Post Graduate Medical Education and Research, Kolkata, India

[2] Department of Rheumatology, Institute of Post Graduate Medical Education and Research, Kolkata, India

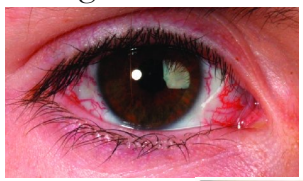
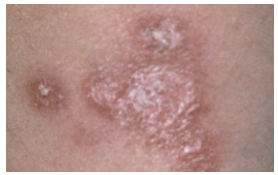
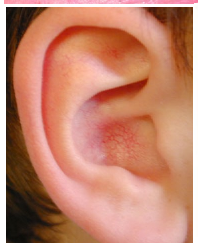
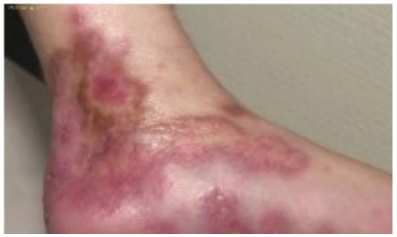
Renal amyloidosis in common variable immunodeficiency

Nefrologia 2010;30(4):474-6
doi:10.3265/Nefrologia.pre2010.May.10280

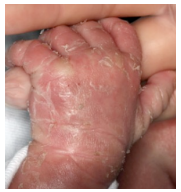
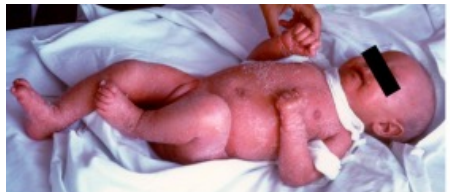
Skin and IEIs

Cutaneous manifestations are common in primary immune deficiency diseases, affecting between 40 % and 70 % of patients with diagnosed primary immune deficiency.

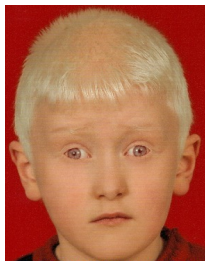
Ataxia-telangiectasia
Telangiectasia and cutaneous granulomas

The classic rash of **Omenn syndrome**: an exfoliative erythroderma
with an onset in the early neonatal period

Several autosomal recessive disorders are characterized by partial **albinism** in conjunction with **immunodeficiency**. These include Griscelli syndrome type 2 (RAB27A mutation), Chediak-Higashi syndrome (LYST mutation), and Hermansky– Pudlak syndrome type 2 (AP3B1 mutation).




Early onset, severe eczema: **hyper IgE syndrome** (AD-HIES and AR-HIES, respectively), **Wiskott-Aldrich syndrome** (WAS). Males affected with immunodysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance syndrome, due to mutation in FOXP3.

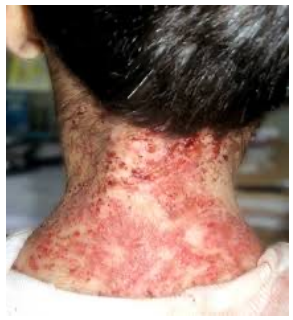
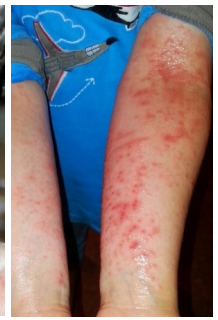
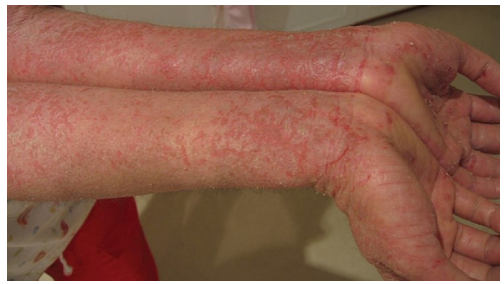
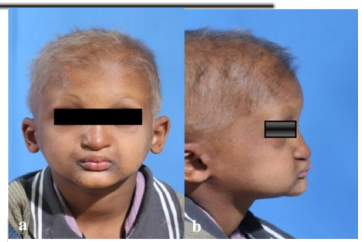
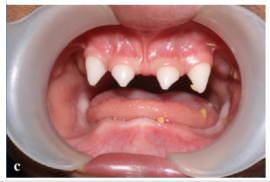




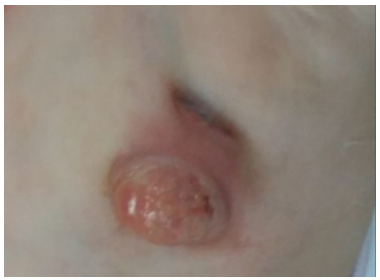
Table 3 Primary immunodeficiencies with epidermal dysplasia

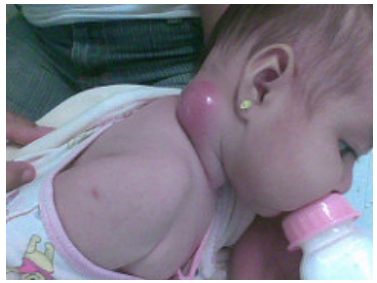
Primary immunodeficiencies
Ectodermal dysplasia with immunodeficiency
X-linked (NEMO deficiency)
Autosomal dominant
Cartilage hair hypoplasia
Dyskeratosis congenita
X-linked (Hoyeraal-Hreidarsson syndrome)
Autosomal recessive
Autosomal dominant
Papillon–Lefèvre syndrome





"Mendelian susceptibility to mycobacterial diseases" (MSMD). Disseminated or localized cutaneous BCGosis after BCG vaccination.





➢ Bacterial skin infection: These include, but are not limited to, congenital neutropenias due to mutations in ELANE and HAX1,CGD, and leukocyte adhesion deficiency (LAD)

➢ Skin abscesses in autosomal dominant hyper IgE syndrome (AD-HIES) are most often caused by S. aureus. often characterized as "cold abscesses," with minimal inflammation and less tenderness than expected of typical staphylococcal abscesses.

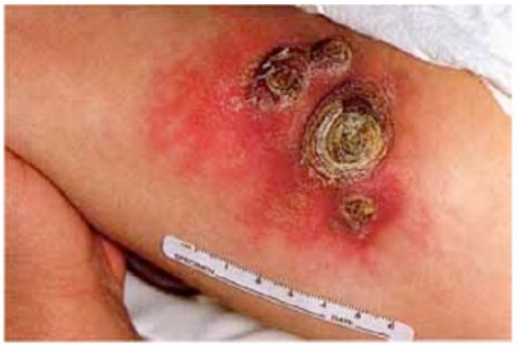


Fig. 4 Serratia abscess with absent pus formation in a patient with leukocyte adhesion deficiency type 1 (Courtesy of Dr. Steven M. Holland, National Institute of Allergy and Infectious Diseases, National Institutes of Health)

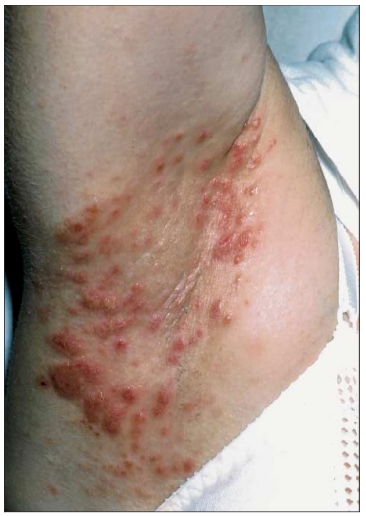
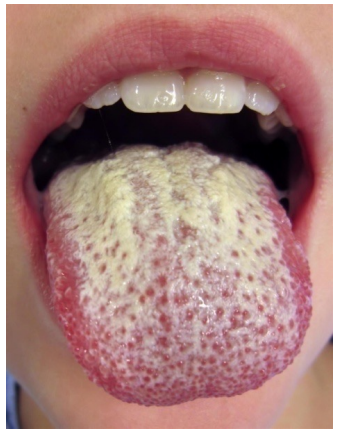


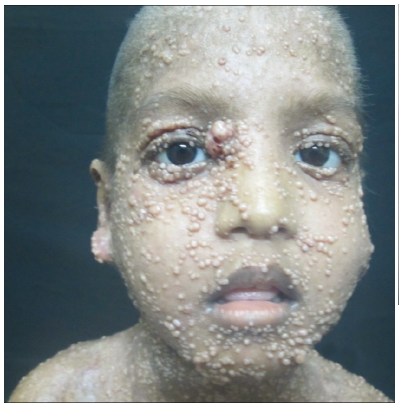
Table 4 Primary immunodeficiencies with candidiasis

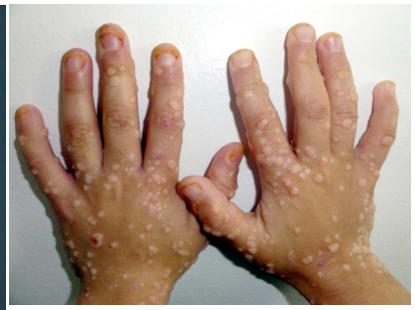
Primary immunodeficiencies
T cell/combined immunodeficiencies
Severe combined immunodeficiency
DiGeorge syndrome
Hyperimmunoglobulin-E syndrome
Autosomal dominant (STAT3 mutation)
Autosomal recessive (DOCK8 mutation)
IL-17RA mutation
IL-17F mutation
Dectin-1 deficiency
CARD9 defect
STAT1 gain-of-function mutation
Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED)



- Human papillomavirus (**HPV**) can cause chronic or severe warts in certain immunodeficiencies. Patients with epidermodysplasia verruciformis, caused by mutations in EVER1 or EVER2, have abnormal susceptibility to HPV and develop disseminated verrucous lesions with a high potential for malignant transformation.

- Chronic papillomavirus infections are also a feature of **WHIM syndrome** (warts, hypogammaglobulinemia, infections, myelokathexis), which is due to a gain-offunction mutation in CXCR4.



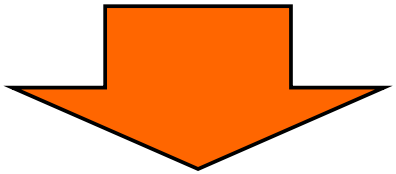


Neurological system and IEIs

Clinical manifestation	Suspicion of PID
Ataxia	• Ataxia-telangiectasia • Ataxia-telangiectasia like disease (ATLD) • PNP deficiency
Microcephaly	• Cernunnos deficiency • Ligase IV deficiency • Ligase I deficiency • Nijmegen breakage syndrome • Dyskeratosis congenita
Deafness	• Reticular dysgenesis • ADA deficiency • CHARGE syndrome (coloboma, heart defect, atresia choanae, retarded growth, genital hypoplasia, ear anomalies/deafness)
Tetraphlegy	• PNP deficiency
Cerebellar hypoplasia	• Dyskeratosis congenita
Herpes simplex encephalitis	• Defect in TLR3 pathway
Meningoencephalitis by Neisseria sp	• Complement deficiencies (late components)

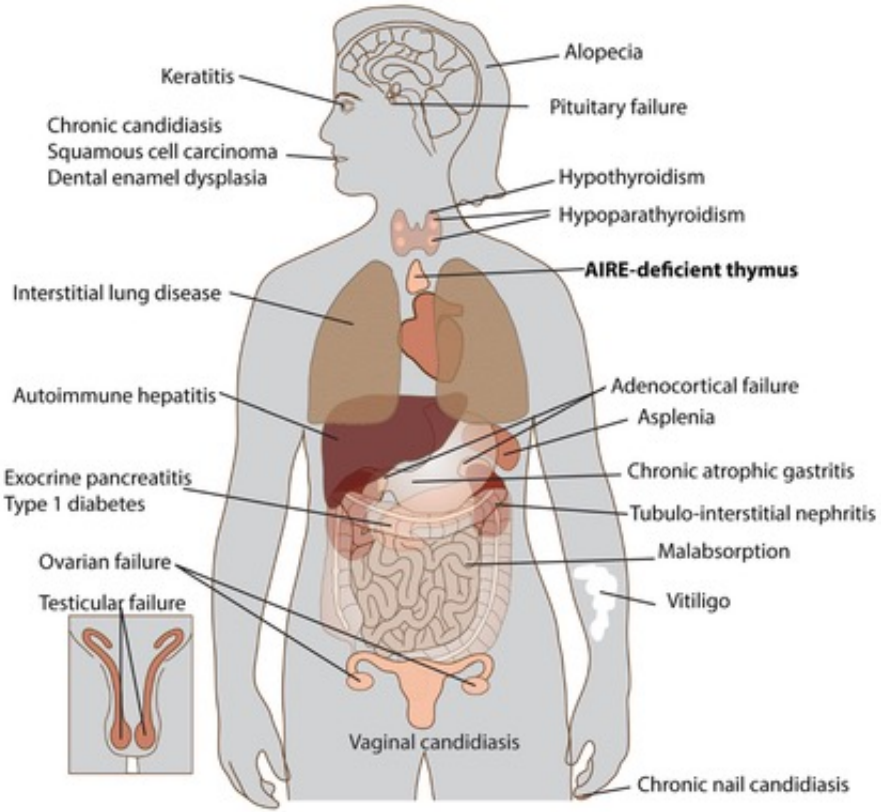
Endocrine system and IEIs

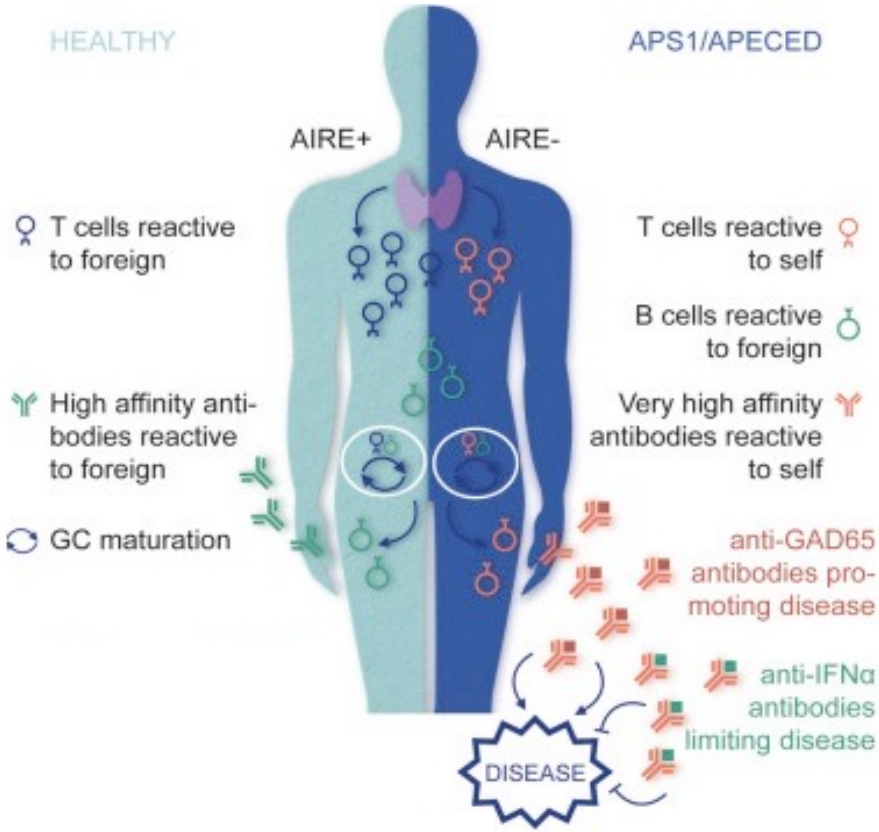
Many endocrine disorders in patients with IEIs are thought to be due to the development of the autoimmunity, which is closely related to the pathophysiology of IEIs.



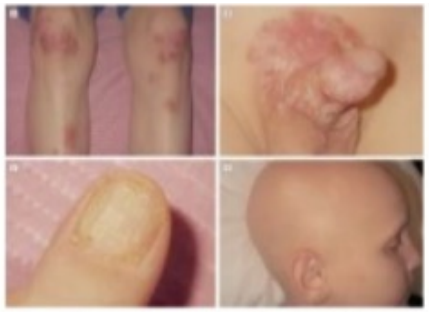
It is not known how the immunological and molecular defects in individual IEIs contribute to the development of various autoimmune endocrine disorders. The genetic defects in some IEI can lead to these complications directly or indirectly via non-immunological mechanisms.

Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)



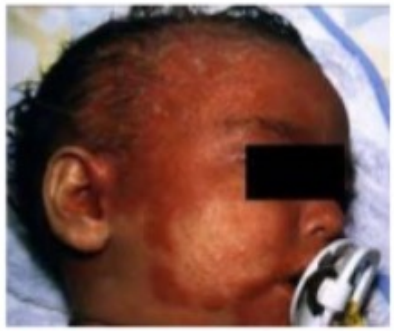


X-linked Immunodysregulation, Polyendocrinopathy and Enteropathy (IPEX)



Patients with (IPEX) frequently present with

- eosinophilia
- severe atopy.
- (+) the classic triad of:
  - enteropathy, (severe darrhea)
  - endocrinopathy;
    - usually type 1 diabetes mellitus,
    - sometimes thyroiditis
  - dermatitis.



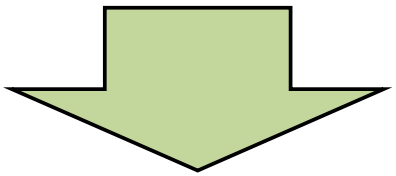
- Most commonly, these patients present with:
  - early onset severe and watery diarrhea,
  - type 1 diabetes mellitus, and
  - failure to thrive

Williams KW, Immunol Allergy Clin N Am 2015;35:523-544 Chan SK, Immunol Allergy Clin North Am. 2015;35(4):767-78

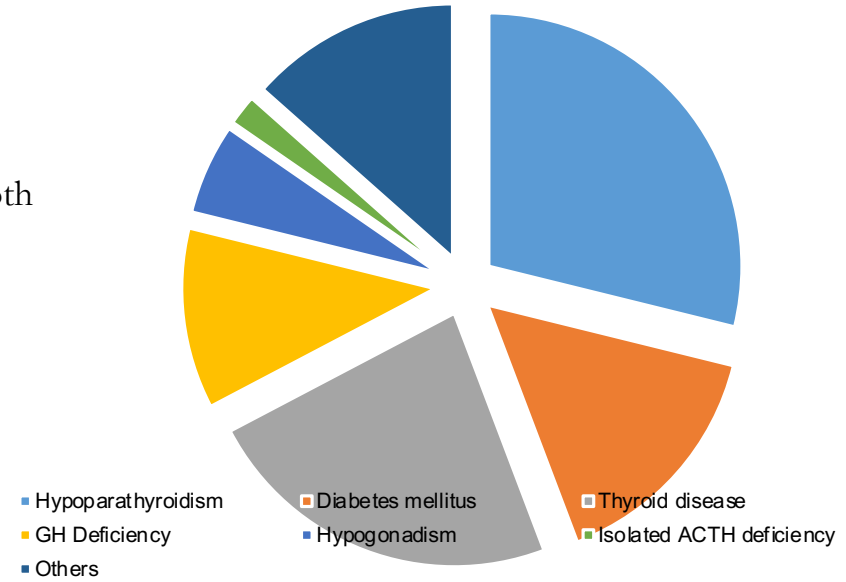
Endocrine complications and IEIs

Among **923 IEIs** patients, **49** (**5·3%**) had **endocrine disorders**. The prevalence of the endocrine diseases was much higher in patients with IEI than in the general population in the young age group, even after excluding patients with immune dysregulation.

I. Combined T and B cell Immunodeficiencies
II. Predominantly antibody deficiencies
III. Other well-defined immunodeficiencynSyndromes
IV. Diseases of immune Dysregulation
V. Congenital defects of phagocyte number, function or both
VI. Defects in innate Immunity
VII. Autoinflammatory disorders



Screen and think to endocrine diseases in IEIs



Nozaki et al, Clinical Endocrinology, 2012

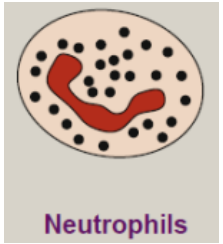
Diagnostic approach to IEIs

1. **Clinical diagnosis:**
   - Anamnesis (consanguineity? Familial cases? Infant death?)
   - Phenotype characaterization (typical features? Hallmarks?)

2. **Laboratory Immunological work-up**
   - Eterogeneity of immunological phenotype
   - Variability of functional and phenotype investigations depending on treatment, acute/chronic infectious diseases…

3. **Molecular analysis**
   - Definitive diagnosis
   - Sanger sequencing versus Next Generation Sequencing modality
   - Genetic counselling

Laboratory investigations in primary immunodeficiencies



Full blood count: may reveal neutropenias (congenital/cyclic) or neutrophilias (LAD). Serial counts may be necessary!

Respiratory burst function: defective in CGD; assessed using DHR test (flow cytometry)

Migration, phagocytosis and killing: assessed using highly specialized *in vitro* tests

Laboratory investigations in primary immunodeficiencies

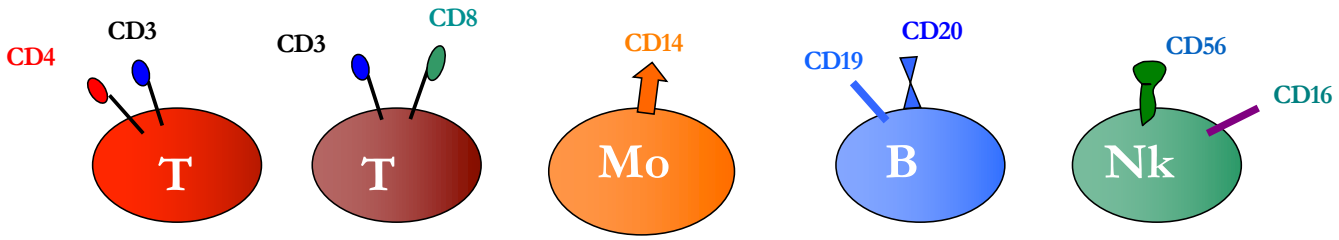
Full blood count: lymphocytes count <2x10^9/litre in a child <6 months is a SCID until proven otherwise

Lymphocytes subsets: flow cytometric assessment of circulating T (CD3+, CD4+, CD8+), B (CD19+) and NK (CD16+56+)

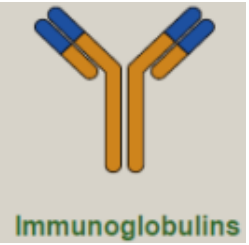
Lymphocytes extensive subsets: naïve and memory subsets, double negative, alpha/beta – gamma/delta, B phenotype

Proliferative function: *in vitro* tests to measure lymphocytes proliferation to non specific (mitogen) and specific (antigen) stimuli

Thymic output: molecular analysis of TRECs and/or flow cytometric CD3+CD31+ is helpful to define thymic function



Laboratory investigations in primary immunodeficiencies



Immunoglobulin levels: IgG (IgG1, IgG2, IgG3, IgG4), IgA, IgM, IgE, natural isohemoagglutinin

↓

Pathogen-specific antibodies: before and after vaccination to assess B lymphocyte function (*e.g.* anti-tetanus, anti-HIB, anti-pneumococcus)

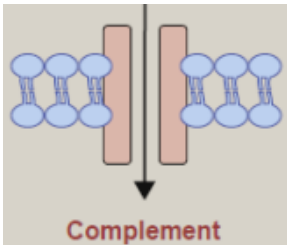
↓

Anti-cytokine antibodies: rare PIDs are associated with antibodies against cytokines (*e.g.* anti-IL17 in CMC)

IgG subclasses

Subclass	Function	% IgG
IgG1	Proteic antigens (virus, bacteria)	70%
IgG2	Polysaccharide antigens (capsulated bacteria)	15%
IgG3	Proteic antigens (virus, bacteria)	10%
IgG4	Allergens, parasites,proteic antigens	5%

Laboratory investigations in primary immunodeficiencies



C3, C4 levels

Haemolytic compement activity (CH50, AH50): *in vitro* assays examining the classical and alternative complement cascade

Quantification of individual components of complement cascade

Conclusions

- Inborn Errors of Immunity are **rare** and **heterogeneous** group of genetic disorders
- For many diseases genetic abnormalities and mode of **inheritance** has been identified
- The spectrum of presentation of these diseases varies from very **mild** symptoms to **serious** and potentially lethal illness
- IEIs are multisystemic disease and a multidisciplinary approach is needed
- Such diseases identified early in life can be potentially cured with **Stem Cell Transplant** and **Gene Therapy**
- By gathering complete and accurate information about these patients and learning from it, the medical community can offer better and more **appropriate therapy** in the **management** of these patients

The multidisciplinary

Pediatrician

Clinical Geneticist

Neurologist

Physiotherapist

Pathologist

Endocrinologist

Haematologist

Pneumologist

Internist

Psychologist

Radiologist

Gastroenterologist

Infectivologist

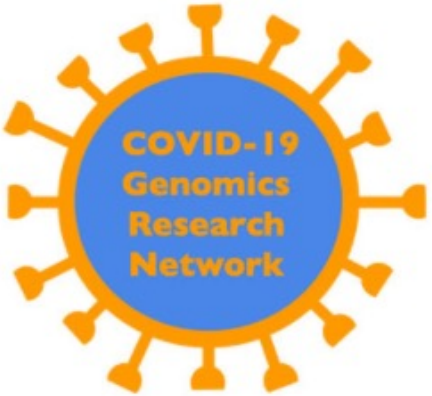
Nephrologist

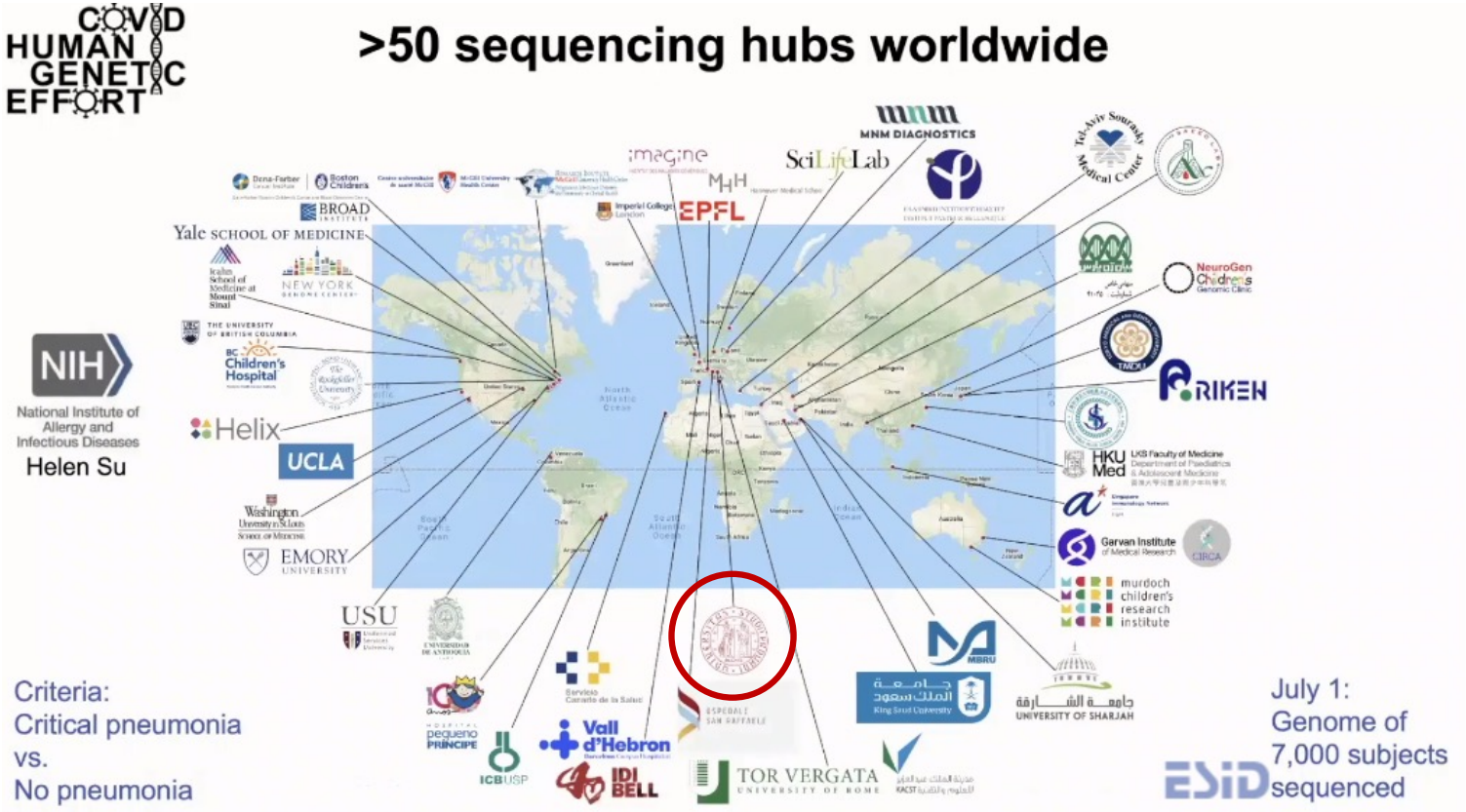
Reumatologist

Dermatologist

Immunologist

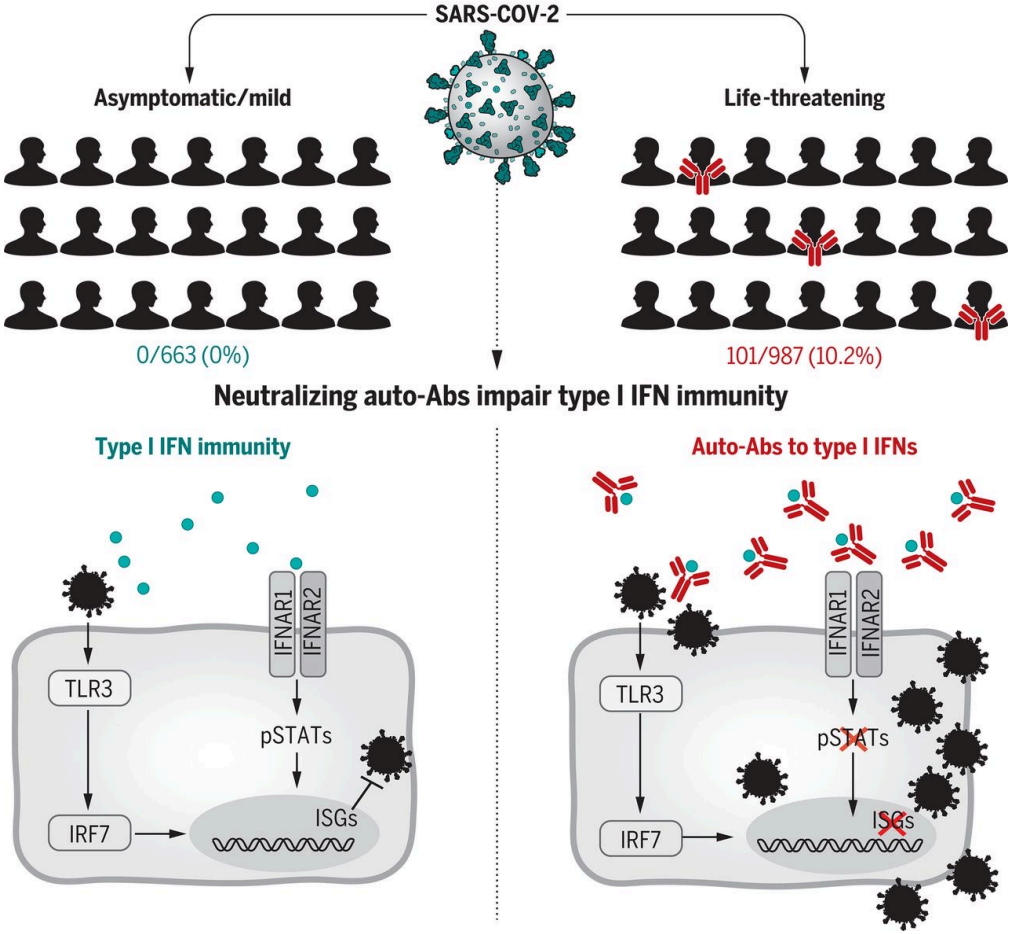
Common Genetic And Immunological Causes Of Life-Threatening COVID-19 Discovered Through Unprecedented International Collaboration





Modified from: JL Casanova, ESID 27-29 september 2021

Neutralizing auto-Abs to type I IFNs underlie life-threatening COVID-19

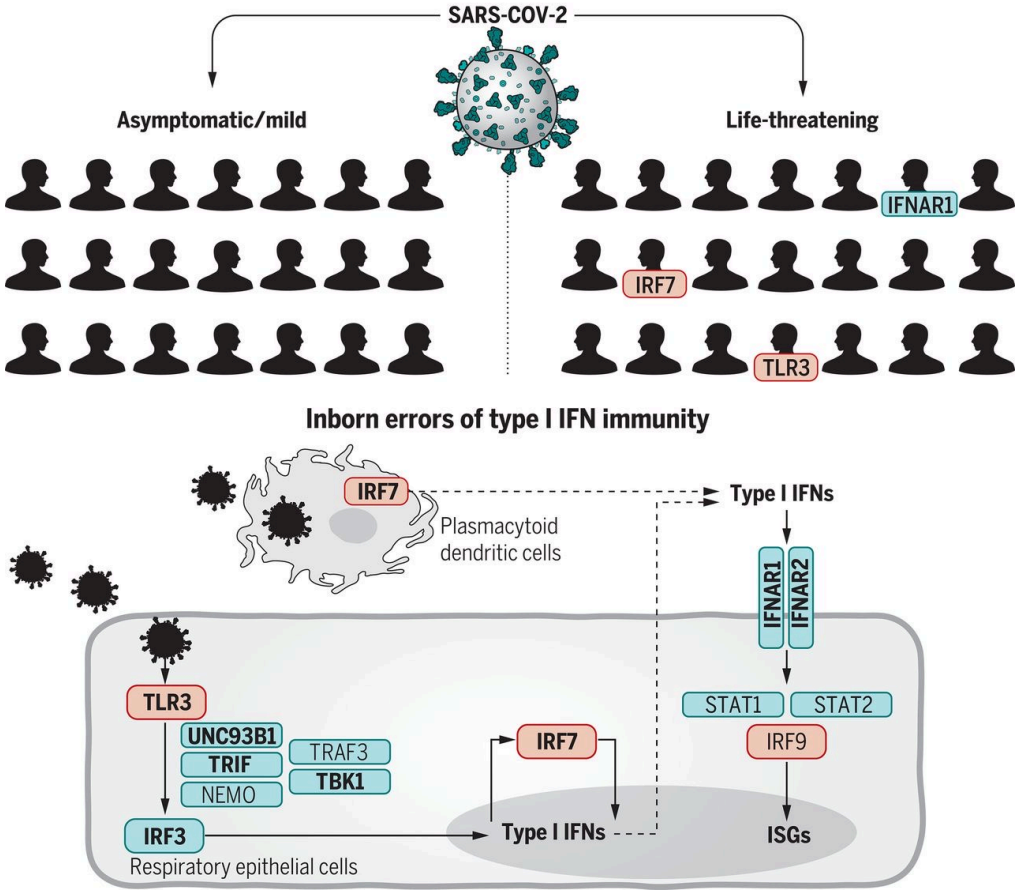


- B cell autoimmune phenocopy of inborn errors of type I IFN immunity;
- life-threatening COVID-19;
- at least 2.6% of women and 12.5% of men

Prevention and treatment: plasmapheresis, plasmablast depletion, and recombinant type I IFNs not targeted by the auto-Abs (e.g., IFN-β).

Bastard P, Science 2020

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

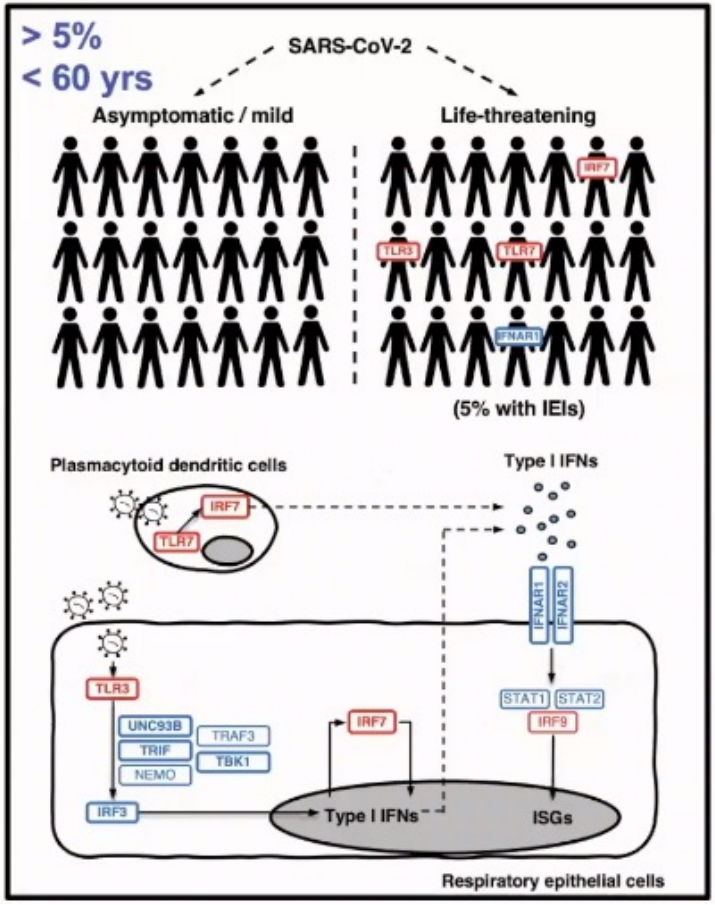


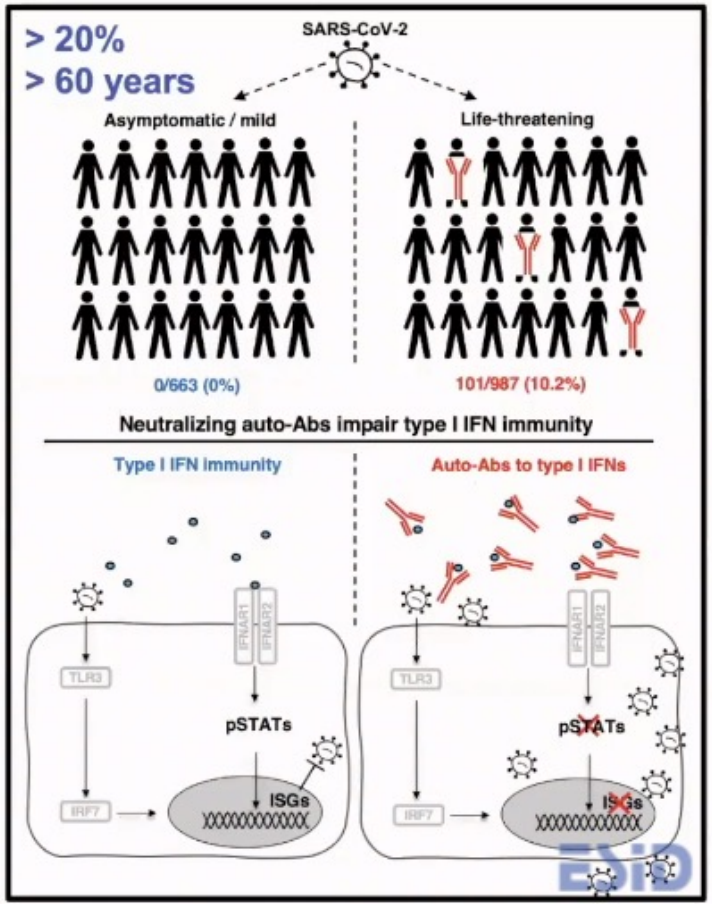
- At least 3.5% of patients with life threatening COVID-19 had genetic defects;
- at eight of the13 candidate loci involved in the TLR3- and IRF7-dependent induction and amplification of type I IFNs.

Type I IFN administration may be of therapeutic benefit in selected patients, at least early in the course of SARS-CoV-2 infection.

Zhang Q, Science 2020

Impaired type I IFN immunity underlies critical C-19

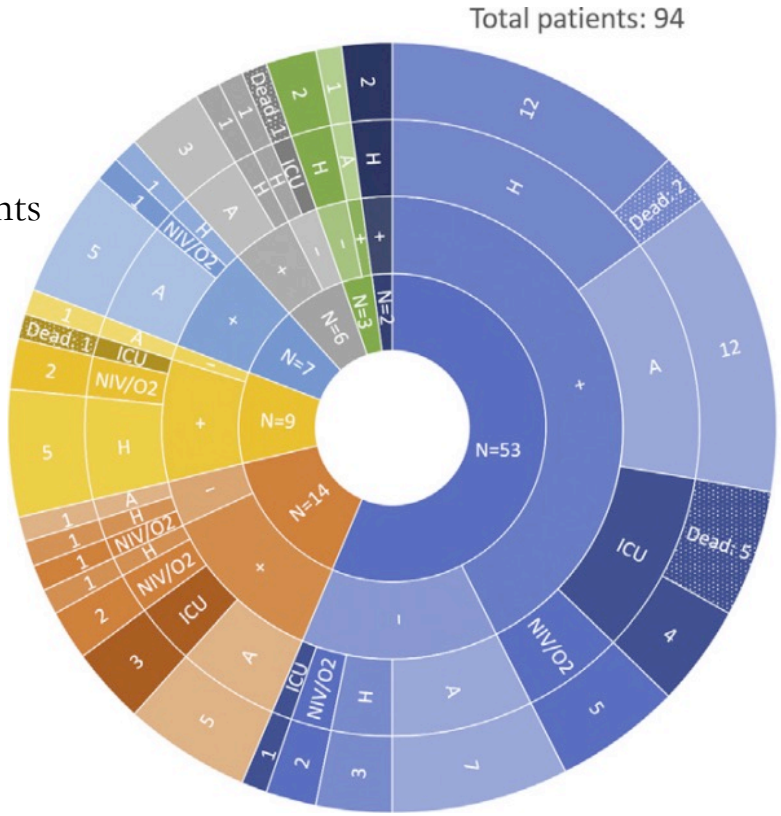




JL Casanova, ESID 27-29 september 2021

International survey on SARS-CoV-2 and Inborn Errors of Immunity

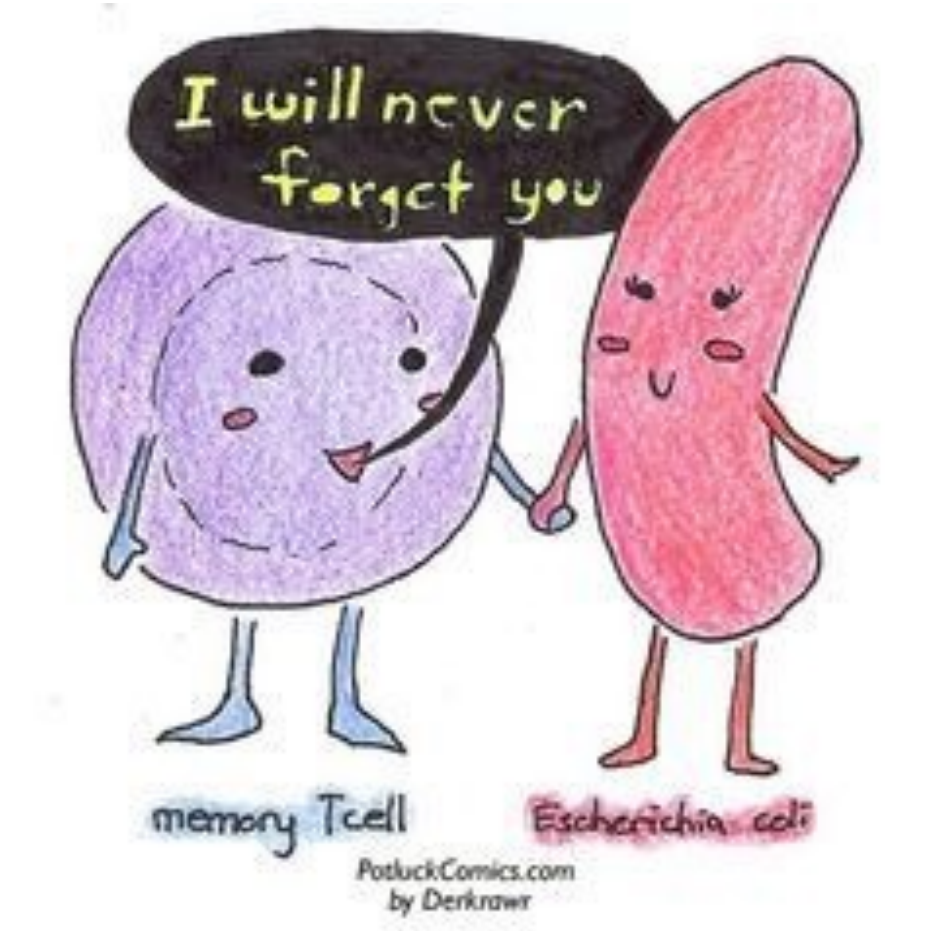
- Substantial subgroup of patients with IEI suffer only a mild course of disease;
- Risk factors predisposing to severe disease and mortality among patients with IEI were comparable to those in the general population;



- Younger patients were more severely affected and more frequently admitted to ICU compared with the general population;
- Registries to document the impact of SARS-CoV-2 on patients with IEIs (eg, ESID registry, ERN-RITA joint effort, and COPID19), as well as the COVID Human Genetic Effort.

Meyts I et al, J Allergy Clin Immunol. 2021 Feb

francescac.ageop@aosp.bo.it



Diagnostic approach (at diagnosis)

❖ High resolution computed tomography (HRCT) of the chest is recommended in the evaluation of patients with PIDs where pulmonary complications are common;

❖ Magnetic resonance imaging (MRI), are an alternative to HRCT scans in evaluation of pulmonary parenchymal abnormalities in patients with possible ILD and underlying radiation sensitivity, such as in Ataxia-Telangiectasia;

❖ Spirometry (basal and after bronchodilator) plus direct measurement of lung volumes (eg, plethysmography) and assessment of diffusing capacity for carbon monoxide (DLCO) are typically performed soon after diagnosis and during follow-up, at a time when the patient is clinically stable.
A six-minute walk is useful in the evaluation of patients with more advanced pulmonary disease

Serologic testing for antibodies to specific organisms are **not reliable** in patients with IEIs that result in impaired antibody production →since many of these patients cannot make specific antibodies in response to infectious agents

Serologic assays are also **unreliable** in patients receiving antibody replacement therapy.

Diagnostic approach (at follow-up)

❖ **Histologic evaluation:**

- Lung tissue can be obtained by transbronchial biopsy during bronchoscopy
- Surgical lung biopsy is typically needed for conditions, such as Granulomatous Lymphoproliferative InterstitialLung Disease (GLILD), bronchiolitis, or suspected malignancy
- In patients with mediastinal adenopathy, biopsies of enlarged nodes are obtained via endobronchial ultrasound-guided transbronchial needle aspiration or mediastinoscopy.

MONITORING FOR PULMONARY DISEASE

❖ Ask regularly about the onset of new pulmonary symptoms;

❖ Repeat spirometry at regular intervals (eg, every 6 to 12 months) to monitor for the development and/or progression of lung disease;

❖ Imaging:

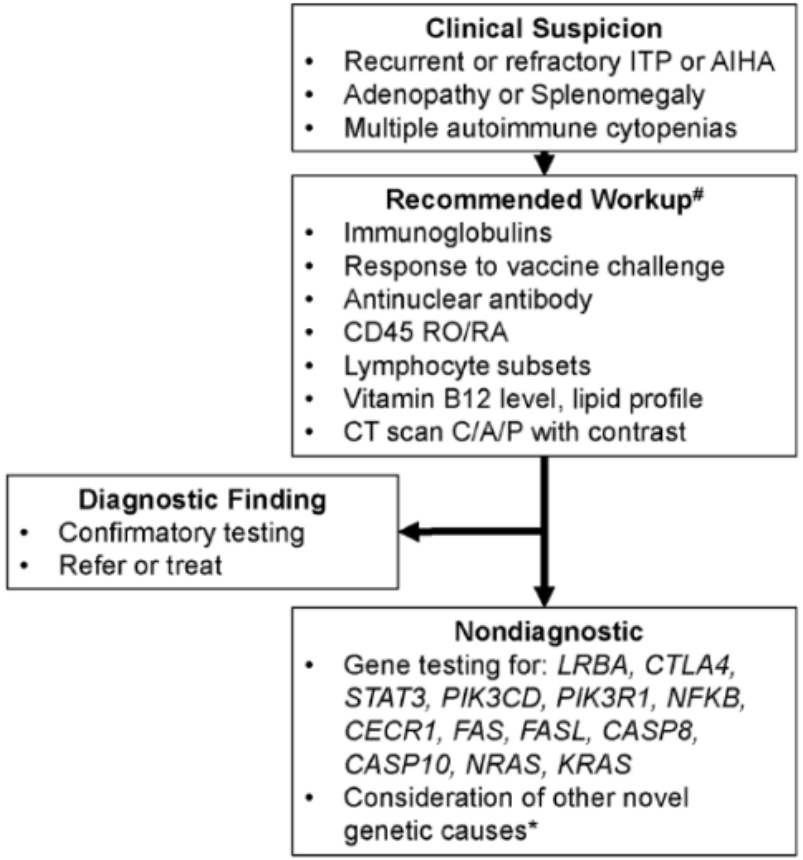
- **Chest radiograph** if a patient reports an acute change in symptoms (pneumonia, lung abscess, or empyema)
- Thoracic computed tomography (**CT**) if decrease in lung volumes or diffusing capacity on pulmonary function testing, findings on the chest radiograph require further delineation, and if the patient experiences hemoptysis
- High resolution computed tomography (**HRCT**) is used in the initial diagnosis of bronchiectasis and in the evaluation of diffuse parenchymal lung disease.

The use of radiation-based imaging studies in patients with IEIs must be conservative and thoughtful, since immunodeficient patients are at higher risk for malignancies at baseline

How would you investigate GI manifestations in IEIs?

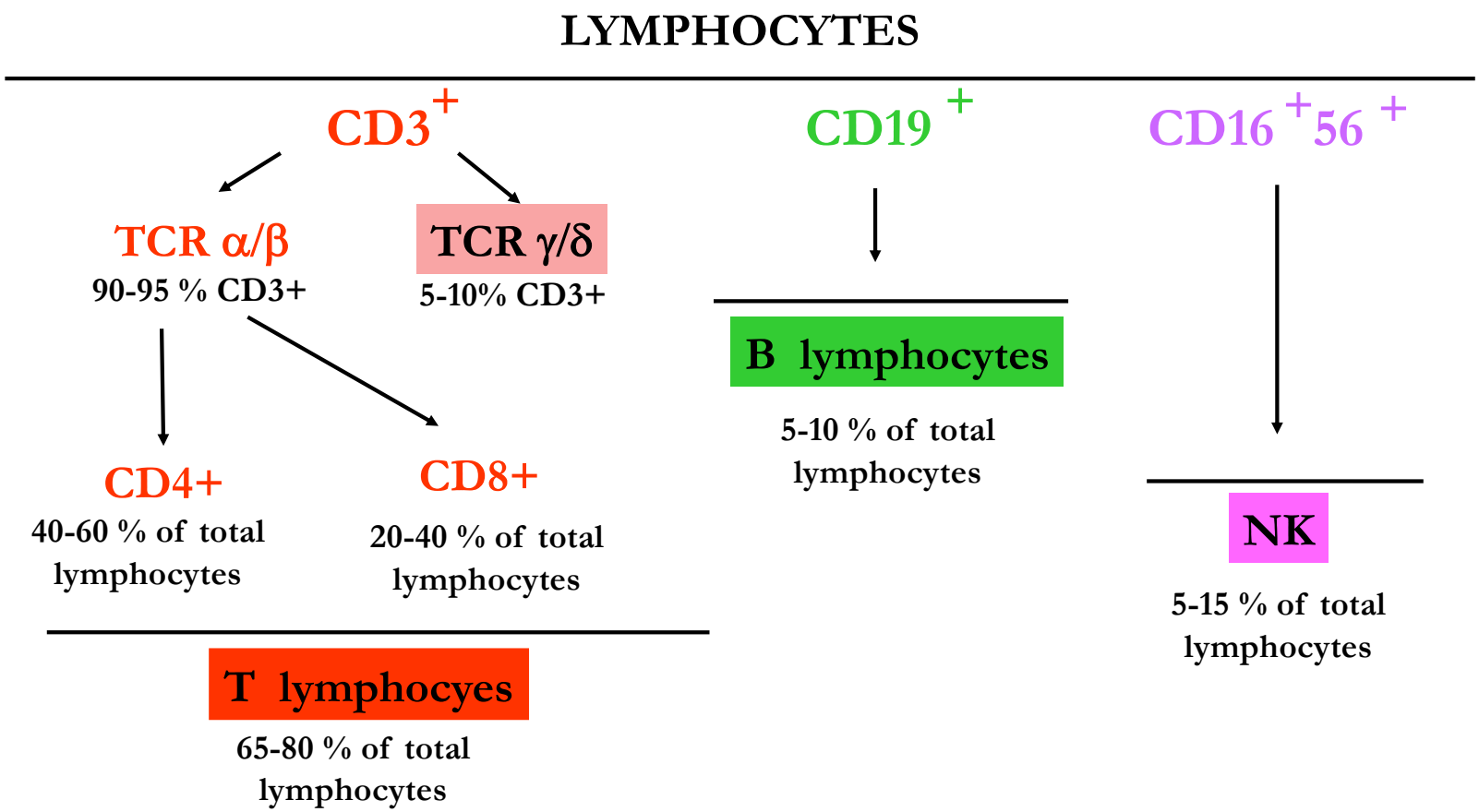
- Physical examinations to check for oral or anal ulcers, fluid or tenderness in the abdomen, enlarged or tender liver
- Blood tests: WBC, CRP, ESR, iron, proteins, albumin, transaminases, cholestatis index
- Stool tests to identify inflammation and infections caused by bacteria, viruses or parasites (Faecal calprotectin, culture
- Hypogammaglobulinemia can result from protein loss and is excluded by measuring serum albumin and urinary protein levels; enteral loss of protein can be excluded by measurement of stool α-1-antitrypsin
- Radiological examens: X-rays, abdomen ultrasound, MRI scans, CT scans
- Endoscopic tests: gastroscopy, colonscopy and biopsies, liver biopsies
- Ask the pathologist to review slides when a question of immunodeficiency exists, given some of the unique pathologic findings or lack thereof (eg, plasma cells)

Hematological disorders and IEIs
Diagnostic workup



Rodz, Pediatric Blood Cancer, 2018

Lymphocytes subsets in peripheral blood



Lymphocytes subsets

Normal values per age

	Sangue cordonale	2-3 mesi	4-8 mesi	12-23 mesi	2-5 anni	7-17 anni	Adulti
Linfociti totali	**5400 (41%)** 4200 (35%) - 6900 (47%)	**5680 (66%)** 2920 (55%) - 8840 (78%)	**5990 (64%)** 3610 (45%) - 8840 (79%)	**5160 (59%)** 2180 (44%) - 8270 (72%)	**4060 (50%)** 2400 (38%) - 5810 (64%)	**2400 (40%)** 2000 (36%) - 2700 (43%)	**2100 (32%)** 1600 (28%) - 2400 (39%)
Linfociti T CD3	**3100 (55%)** 2400 (49%) - 3700 (62%)	**4030 (72%)** 2070 (55%) - 6540 (78%)	**4270 (71%)** 2280 (45%) - 6450 (49%)	**3300 (66%)** 1460 (53%) - 5440 (81%)	**3040 (72%)** 1610 (62%) - 4230 (80%)	**1800 (70%)** 1400 (66%) - 2000 (76%)	**1600 (73%)** 960 (61%) - 2600 (84%)
Linfociti T CD4	**1900 (35%)** 1500 (28%) - 2400 (42%)	**2830 (52%)** 1460 (41%) - 5116 (64%)	**2950 (49%)** 1690 (36%) - 4600 (61%)	**2070 (43%)** 1020 (31%) - 3600 (54%)	**1800 (42%)** 900 (35%) - 2860 (51%)	**800 (37%)** 700 (33%) - 1100 (41%)	**940 (46%)** 540 (32%) - 1660 (60%)
Linfociti T CD8	**1500 (29%)** 1200 (26%) - 2000 (33%)	**1410 (25%)** 650 (16%) - 2450 (35%)	**1450 (24%)** 720 (16%) - 2490 (34%)	**1320 (25%)** 570 (16%) - 2230 (38%)	**1180 (30%)** 630 (22%) - 1910 (38%)	**830 (30%)** 600 (27%) - 900 (35%)	**520 (27%)** 270 (13%) - 930 (40%)
Linfociti B	**1000 (20%)** 200 (14%) - 1500 (23%)	**900 (23%)** 500 (19%) - 1500 (31%)	**900 (23%)** 500 (19%) - 1500 (31%)	**900 (23%)** 500 (19%) - 1500 (31%)	**900 (24%)** 700 (21%) - 1300 (28%)	**400 (16%)** 300 (12%) 500 (22%)	**246 (13%)** 122 (10%) - 632 (31%)
CD4/CD8	1.2 0.8-1.8	2.2 1.3-3.5	2.1 1.2-3.5	1.6 1.0-3.0	1.4 1.0-2.1	1.3 1.1-1.4	1.7 0.9-4.5

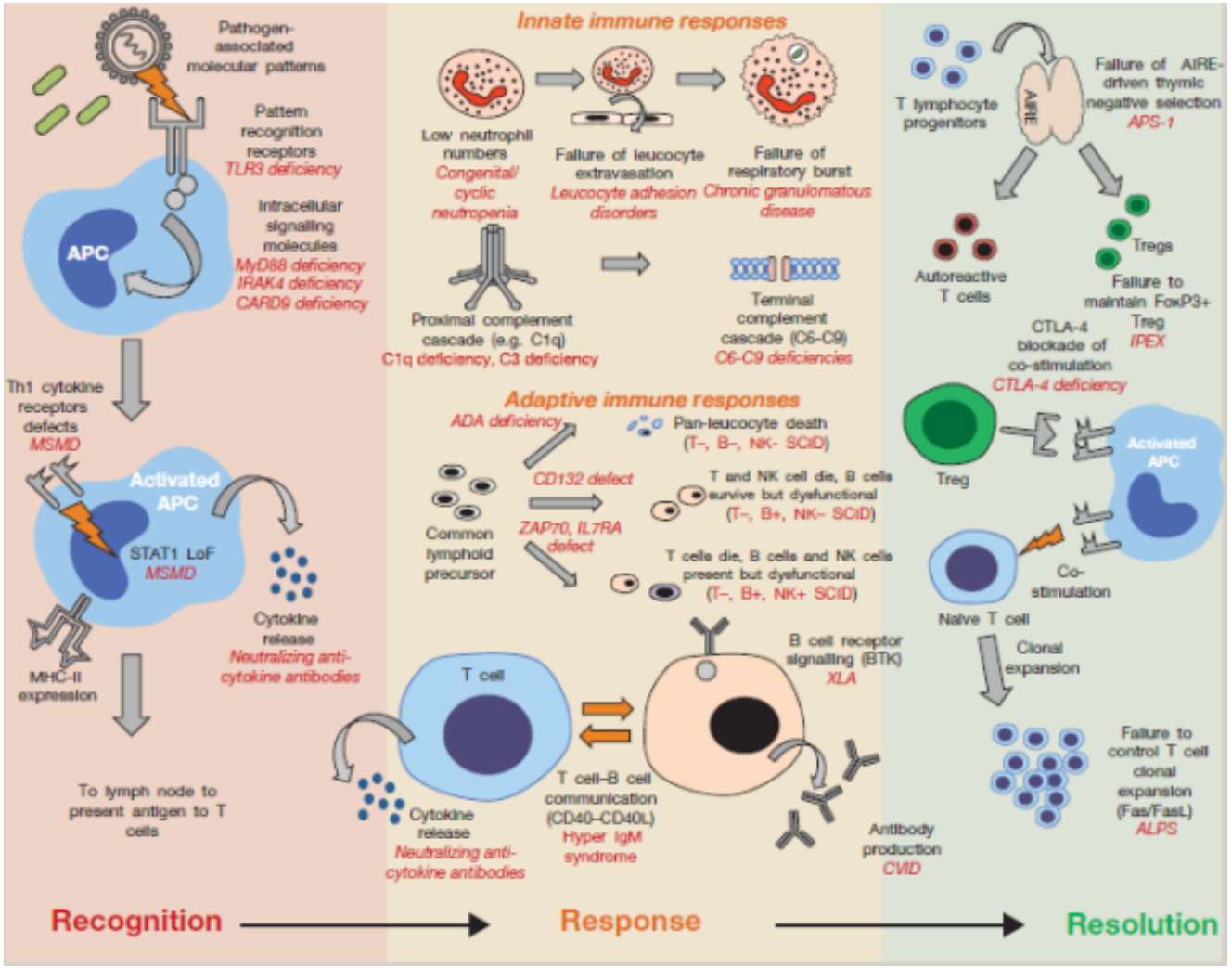
I valori sono espressi come media di cellule/ul (%) ed intervalli di confidenza da 5 a 95

Serum Ig normal values (± 2DS)

Età	*IgG (mg/dL)*	*IgA (mg/dL)*	*IgM(mg/dL)*
Umbilical cord	*1112 (862-1434)*	*Non dosabili*	*9 (5-14)*
1-3 mesi	*468 (231-495)*	*24 (8-74)*	*74 (26-210)*
4-6 mesi	*434 (222-846)*	*20 (6-60)*	*62 (28-39)*
7-12 mesi	*569 (351-919)*	*29 (10-85)*	*89 (38-204)*
13-24 mesi	*801 (264-1509)*	*54 (17-178)*	*128 (48-337)*
2-3 anni	*889 (462-1710)*	*68 (27-173)*	*126 (62-257)*
4-5 anni	*1117 (528-1959)*	*98 (37-257)*	*119 (49-292)*
6-8 anni	*1164 (633-1016)*	*113 (41-315)*	*121 (56-261)*
9-11 anni	*1164 (707-1919)*	*127 (60-270)*	*129 (61-276)*
12-16 anni	*1105 (604-1909)*	*136 (61-301)*	*132 (59-297)*

From "Il bambino immunodepresso: perché lo è e come va difeso". Ugazio AG et al, CEA, 1995.

Primary immunodeficiencies in the context of classical immune response



Shields et al, 2017

Clinical features raising suspicion of primary immunodeficiency

A family history of primary immunodeficiency
- Unexplained infantile deaths
- Consanguinity

Recurrent infections
- Four or more ear infections per year
- Two or more serious sinus infections per year
- Two or more pneumonias per year
- Two or more deep-seated infections (abscesses, osteomyelitis, meningitis) or episodes of sepsis

Infections with unusual/opportunistic organisms (e.g. non-tuberculous mycobacteria, *Pneumocystis jirovecii*, *Aspergillus*, mucocutaneous *Candida*)

Chronic infections
- Requiring long courses of antimicrobials for resolution
- Requiring frequent courses of intravenous antibiotics
- Infections that have led to structural damage (e.g. bronchiectasis)
- Persistent viral infections (long-lasting warts, persistent molluscum)

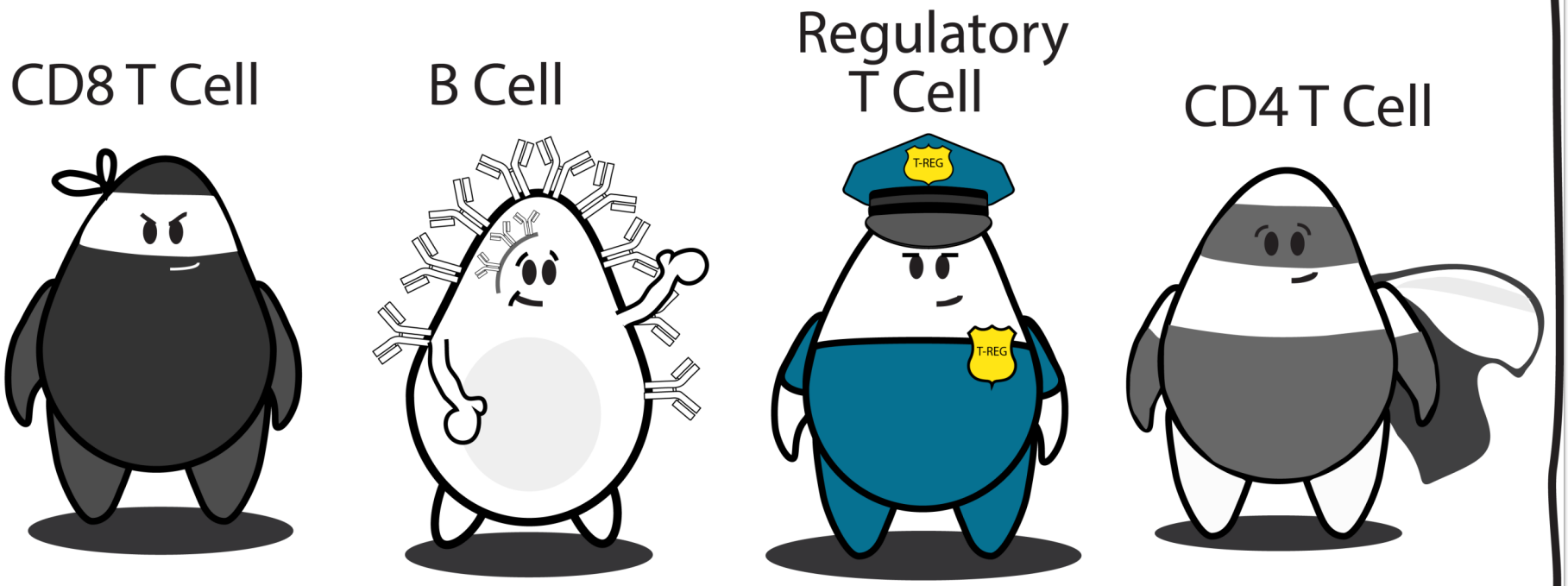
Early-onset eczematous skin rashes

Early-onset autoimmunity (e.g. cytopenias, polyendocrinopathies)

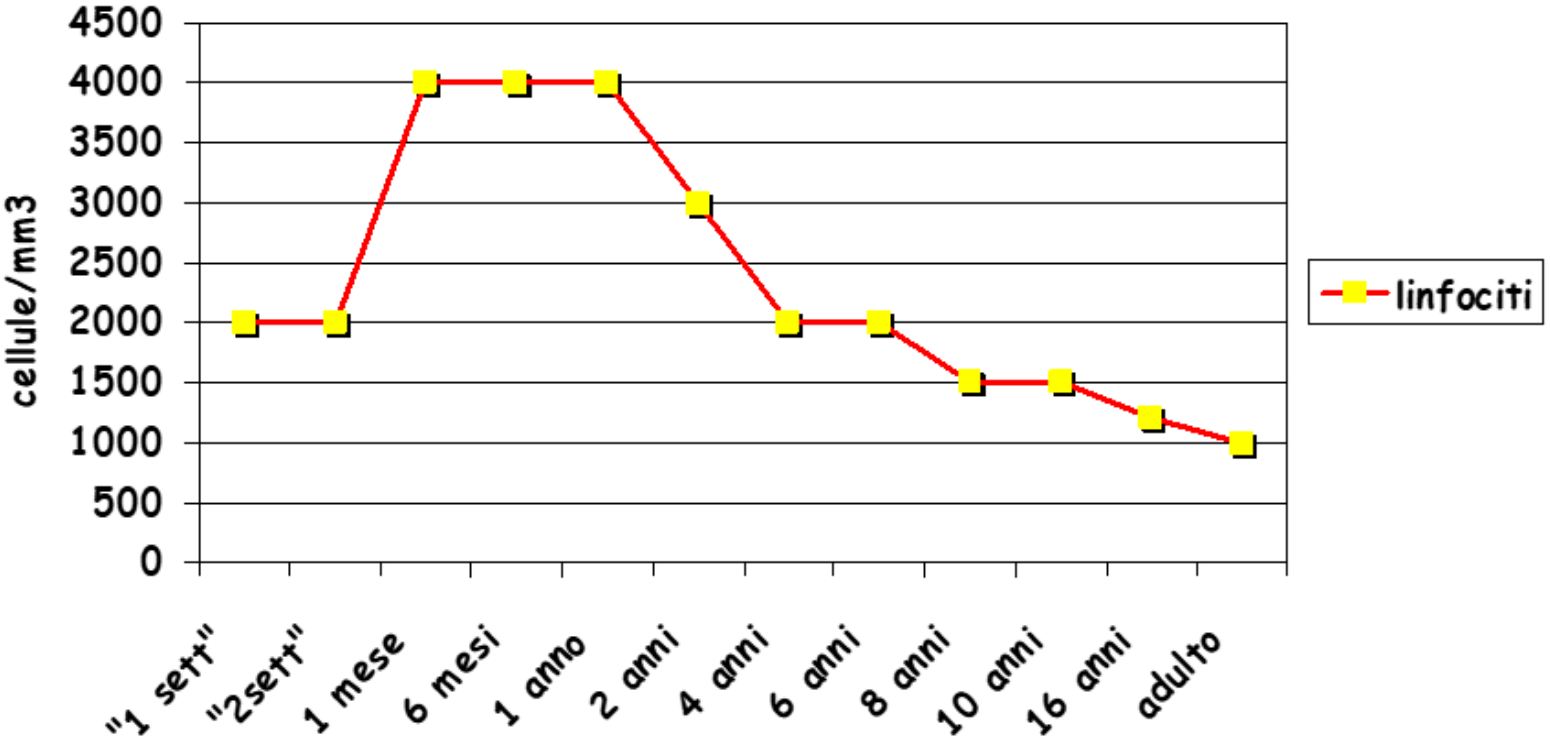
Failure to thrive in infancy — especially chronic diarrhoea or infection with vaccine strain enteropathic viruses

Shields et al, 2017

To be continued…



Lymphocytes count by age



SCID Diagnosis

Lymphocytes < 1500/ml

CD3+ cells < 500/ml

80 %

↓Proliferation test

↓DR expression

100 %

Normal or high ymphocytes count + clinical features of PID in early infant (<2 years) should be investigated for **maternal T-cell engraftment** (maternal chimerism)

Prophylactic antimicrobials therapy in IEIs

PID	Regimen
SCID	*Pneumocystis jirovecii* prophylaxis: SMX-TMP 5 mg/kg TMP component PO once daily 3 days per wk or atovaquone 30 mg/kg once daily; HSV-prophylaxis: Acyclovir 20 mg/kg/dose 3 times a day; Fungal prophylaxis: Fluconazole 6 mg/kg/d PO daily (follow AST and ALT) and Palivizumab (15 mg/kg intramuscularly) during RSV season
Hyper-IgM syndrome	SMX-TMP PO 5 mg/kg TMP component PO 3 times per wk; azithromycin PO (may have a role in CD40L or CD40 deficiency)
CGD	SMX-TMP 5 mg/kg TMP component PO divided twice daily; itraconazole 100 mg daily PO (<13 y or <50 kg); 200 mg daily (>13 y or >50 kg)
Congenital neutropenia (variable recommendation with advent of cytokine therapy)	Penicillin; SMX-TMP
WHIM syndrome	SMX-TMP 5 mg/kg TMP component PO daily
Anhidrotic ectodermal dysplasia with immune deficiency	SMX-TMP 5 mg/kg TMP component PO 3/wk; azithromycin 5 mg/kg PO 3/wk (alternate days); acyclovir 20 mg/kg/dose 3 times a day PO divided 3-4/d; fluconazole 6 mg/kg/d daily PO
TLR defects, IRAK4 and Myd88	SMX-TMP 5 mg/kg TMP component PO daily and/or penicillin V
Mendelian susceptibility to mycobacterial disease	Azithromycin; clarithromycin
Complement deficiency	Penicillins (in the setting of recurrent infections)
Hyper-IgE syndrome	SMX-TMP; cloxacillin (typically for SMX-TMP failures); itraconazole; voriconazole (typically for secondary prophylaxis)
Wiskott-Aldrich syndrome	SMX-TMP 5 mg/kg TMP component PO 3/wk; penicillin V 125 mg (<5 y) to 250 mg (>5 y) PO twice daily (after splenectomy)
DiGeorge syndrome (not required in most instances)	SMX-TMP 5 mg/kg TMP component PO 3/wk

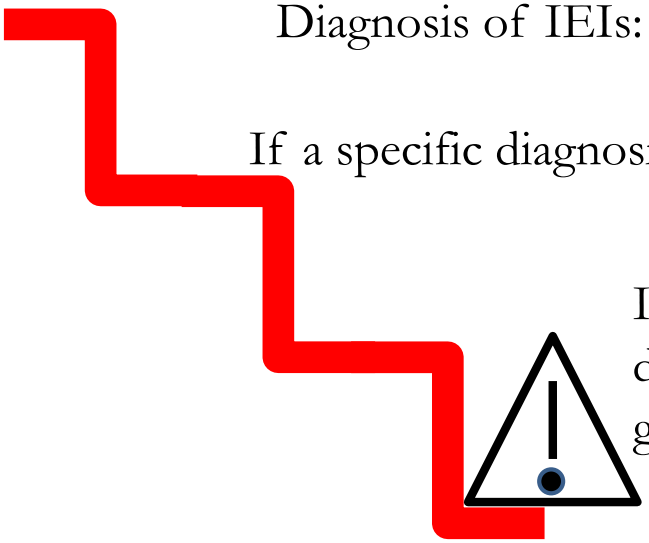
PO, Per os (by mouth); *HSV-VSV*, herpes simplex virus-varicella stomatitis virus; *RSV*, respiratory syncytial virus; *TLR*, toll-like receptor.

Kuruvilla M, JACI pract (2013)

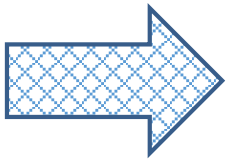
Genetic investigations in primary immunodeficiencies

Diagnosis of IEIs: Sanger sequencing a target/candidate gene

If a specific diagnosis can not be reached: whole-exome/genome sequencing



Interesting variant (mode of inheritance and prediction of damage) in a not described gene or as a new variant the genotype-phenotype correlation has to be demonstrated !



Informed genetic counselling and directing therapeutic management

Prophylactic antimicrobials therapy in IEIs

Antiviral	Acyclovir 20 mg/kg/dose x 3 die os
Antifungal	Fluconazole 6 mg/kg/die os
Anti-PCP	Cotrimoxazole 5 mg/kg/die TMT (x 3 days/week) os
Anti-bacterial	Azytromycin 5 mg/kg/die (x 3 days/week) os

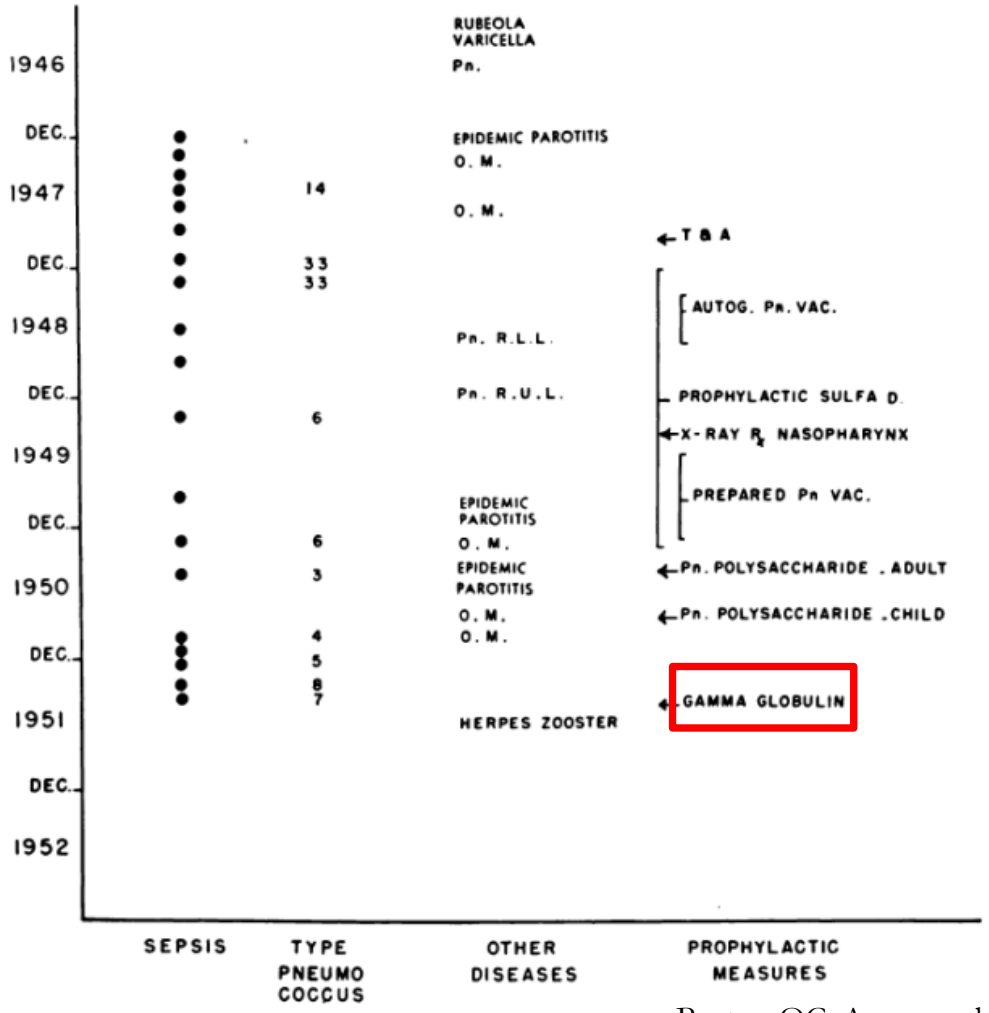
Vaccinations and IEIs

	Immunodeficienza	Vaccini raccomandati	Vaccini sconsigliati
Difetti anticorpali maggiori	Agammaglobulinemia Immunodeficienza Comune Variabile	Anti-influenzale inattivato, Polisaccaridici coniugati contro batteri capsulati	Batterici e virali vivi (anti-influenzale vivo att., OPV, febbre gialla, MPR-V, BCG, S. tiphy)
Difetti anticorpali minori	Deficit selettivo di IgA Difetti di sottoclassi IgG	Anti-influenzale inattivato, Polisaccaridici coniugati contro batteri capsulati	BCG, OPV, febbre gialla, S. tiphy
Difetti completi dei linfociti T	Immunodeficienza Grave Combinata S. Di DiGeorge completa	Anti-influenzale inattivato, Polisaccaridici coniugati contro batteri capsulati	Batterici e virali vivi (anti-influenzale vivo att., OPV, febbre gialla, MPR-V, BCG, S. tiphy)
Difetti parziali dei linfociti T	S. Di DiGeorge parziale S. Di Wiskott-Aldrich Atassia-Teleangectasia	Anti-influenzale inattivato, Polisaccaridici coniugati contro batteri capsulati	Vaccini vivi solo se linfociti CD4+ >500cell/µl, CD8+ >200cell/µl +/- test di risposta ai mitogeni nella norma
Difetti dei fagociti	Malattia Granulomatosa Cronica Deficit di Adesione Leucocitaria	Anti-influenzale inattivato, Polisaccaridici coniugati contro batteri capsulati	Batterici vivi (BCG, S. tiphy); virali vivi in LAD e difetto di rilascio granuli citotossici salvo se funzione linfocitaria normale
Difetti del complemento	Deficit C1-C4 Deficit C5-C9 Deficit di properdina, fattore B	Anti-influenzale inattivato, Polisaccaridici coniugati contro batteri capsulati	Nessuno
Difetti dei TLRs e *pathway* IL12/IFNγ		Anti-influenzale inattivato, Polisaccaridici coniugati contro batteri capsulati	BCG, cautela a seconda del *pathway* alterato con altri v. batterici e/o vivi attenuati

Da: «Le vaccinazioni nelle Immunodeficienze Primitive», Chiara Azzari

The first Immunoglobulin replacement therapy

Ogden Carr Bruton
(14 June 1908-20 January 2003)



Bruton OC. Agammaglobulinemia. Pediatrics. 1952;9:722–728

Immunoglobulin replacement therapy

Primary immune defects with absence of B cells

Recurrent infections due to an unknown immune mechanisms

Hypogammaglobulinemia with impaired specific antibody production

Hypogammaglobulinemia with normal-quality antibody response

Normal levels of immunoglobulins with impaired specific-antibody production (selective antibody deficiency)

Normal immunoglobulin levels and normal quality with deficient IgG subclass (IgG1, -2, -3)

Immunoglobulin can be delivered intravenously: 400-600mg/kg once every 3-4 weeks
or subcutaneously: 400-600mg/kg/month divided in 1 or two doses (every 4 or 2 weeks)

depending on co-morbidities and patient preference

Landmark events in the field of hematopoietic stem cell transplantation (HSCT) and primary immune deficiency diseases

- In 1968 first successful allogeneic bone marrow transplant in a patient with SCID from a histocompatible sibling donor became gold standard for HSCT
- In 1973 first unrelated donor marrow transplant was performed in a patient with SCID
- In 1980 first successful Haplo-identical marrow transplant was performed in SCID Patient
- In 1995 Gene therapy in ADA SCID
- European database of HSCT in IEIs since 1968:

- 4822 PID patients
- 5503 transplants
- 88 centers, 26 countries

HSCT and primary immune deficiency diseases

HSCT remains the **definitive** treatment for all types of SCID and the preferred treatment option for many monogenic IEIs that present in childhood. The decision to undertake HSCT is influenced by multiple factors:

- not least the recipient's overall
- condition, their ability to tolerate myeloablative chemotherapeutic
- conditioning regimens and the availability of a haplotype matched donor

IEIs and gene therapy

One gene defect in blood cells

HEMATOPOIETIC STEM CELLS:
- Easy to obtain
- Easy to manipulate
- multipotent

FUNCTION RECOVERY:
In some cases a partial genetic correction could be sufficient

SELECTIVE ADVANTAGE:
Modified cells are predominant and a selective growth advantage is conferred to transduced cells

Autoulogous genetically modified stem-cells transplantation:
- Don't need a matched donor
- Very low/absent risk of GVDH

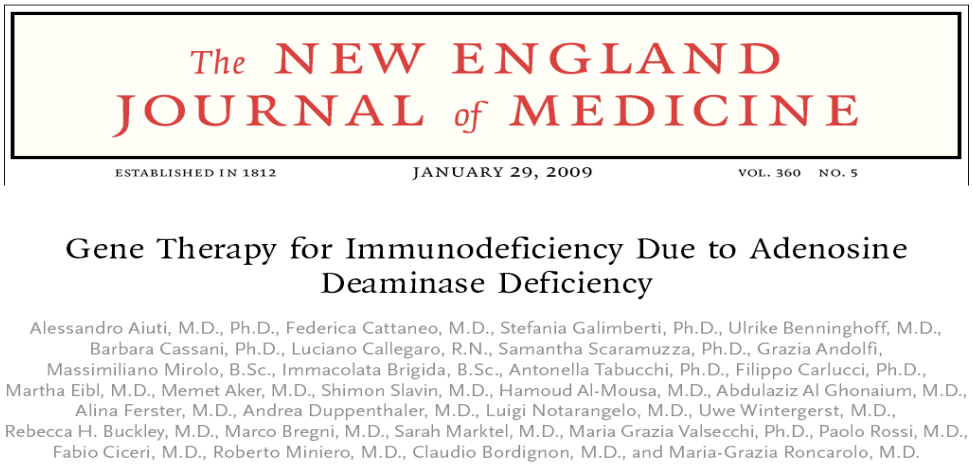
Successful stories of gene therapy in IEIs

- ADA-SCID: 18 treated children, alive, follow-up 3-14 years
- Immunological and metabolic defect correction
- 15 didn't need enzyme replacement therapy or HSCT
- Good quality of life

EDITORIALS

Gene Therapy Fulfilling Its Promise

Donald B. Kohn, M.D., and Fabio Candotti, M.D.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 29, 2009 VOL. 360 NO. 5

Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

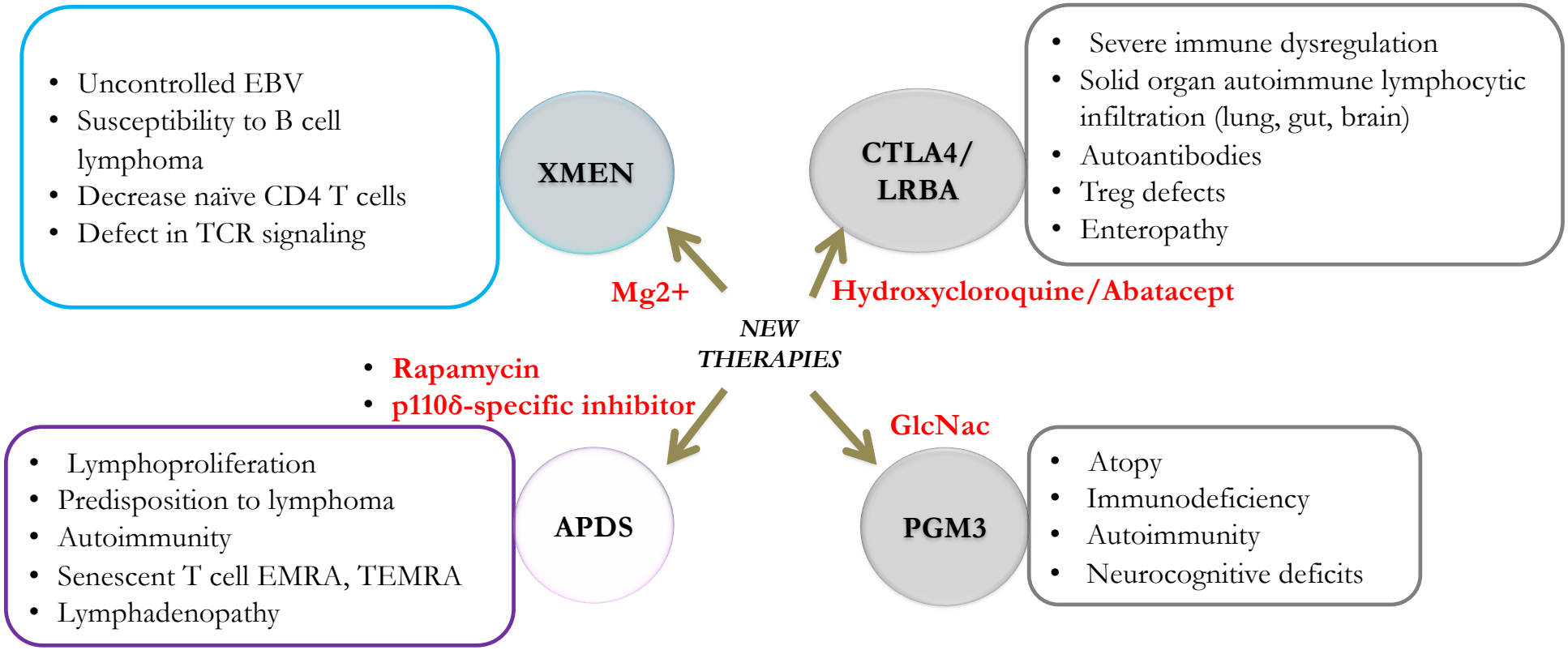
Alessandro Aiuti, M.D., Ph.D., Federica Cattaneo, M.D., Stefania Galimberti, Ph.D., Ulrike Benninghoff, M.D., Barbara Cassani, Ph.D., Luciano Callegaro, R.N., Samantha Scaramuzza, Ph.D., Grazia Andolfi, Massimiliano Mirolo, B.Sc., Immacolata Brigida, B.Sc., Antonella Tabucchi, Ph.D., Filippo Carlucci, Ph.D., Martha Eibl, M.D., Memet Aker, M.D., Shimon Slavin, M.D., Hamoud Al-Mousa, M.D., Abdulaziz Al Ghonaium, M.D., Alina Ferster, M.D., Andrea Duppenthaler, M.D., Luigi Notarangelo, M.D., Uwe Wintergerst, M.D., Rebecca H. Buckley, M.D., Marco Bregni, M.D., Sarah Marktel, M.D., Maria Grazia Valsecchi, Ph.D., Paolo Rossi, M.D., Fabio Ciceri, M.D., Roberto Miniero, M.D., Claudio Bordignon, M.D., and Maria-Grazia Roncarolo, M.D.

n.1028/2016: **STRIMVELIS** first gene therapy with stem cells commercialized for the **ADA-SCID** authorized by the European Community

Therapeutic challenge in IEIs

- An emerging field in IEIs is the management of complications of **immune dysregulation**
- **Immunosuppressive drugs** are frequently required to treat complications of some IEIs such as lymphocytic infiltrative pneumonia, granulomatous disease and autoimmune cytopenias
- A delicate **balance** must be struck between the risks and benefits of immunosuppression in patients prone to infection who also have immune dysregulation
- Moreover, novel immune deficiencies have improved our understanding of basic immunology, affording the opportunity to use **rational therapeutics directly targeted** at the underlying immunological defect

Targeted Therapy in IEIs



https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria