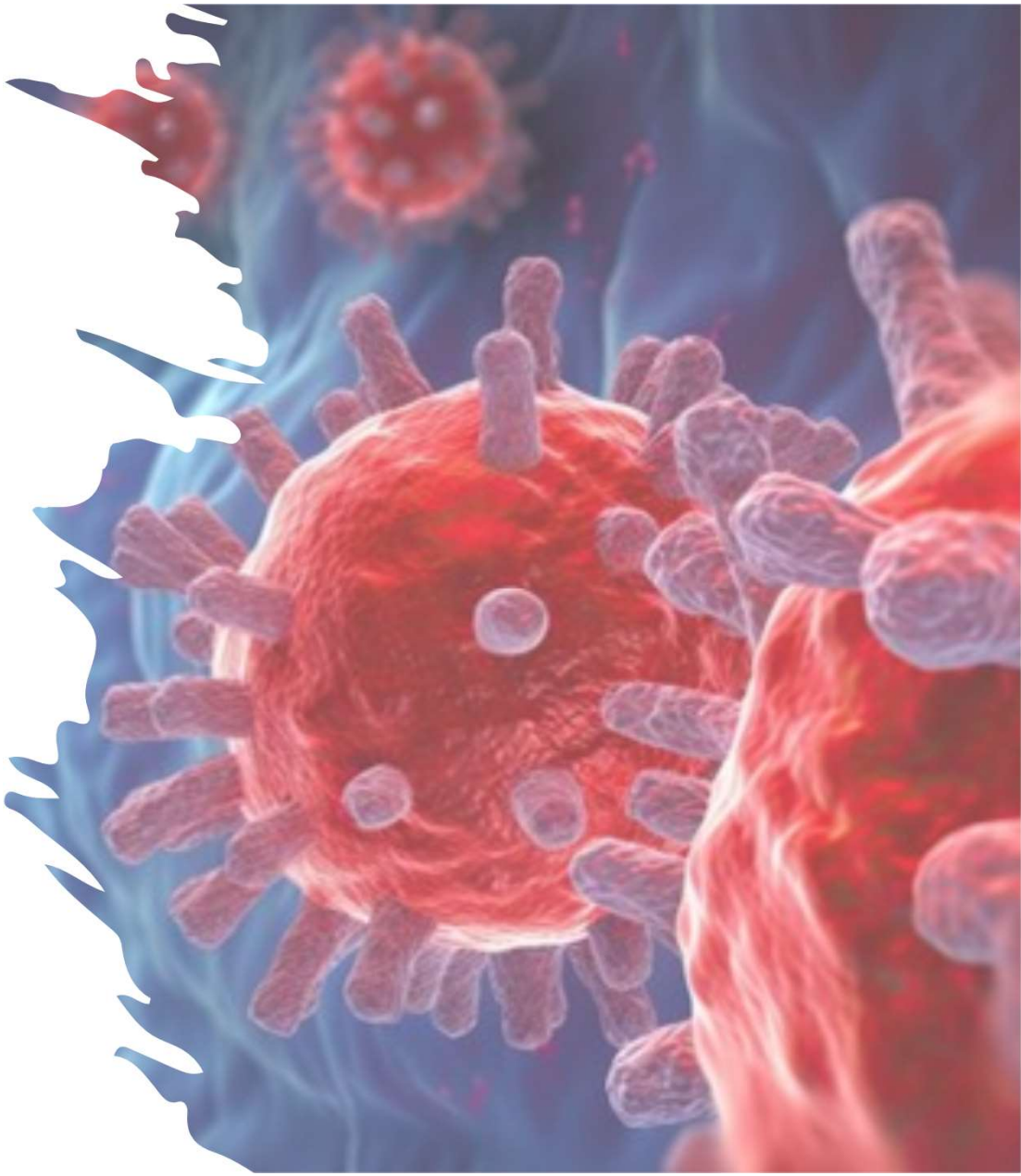
An approach to immune deficiencies in children (Inborn errors of immunity)

Dr Riaz Khan



Case1

- 4 month old girl with gastroenteritis/ Adenovirus bronchiolitis complicated by respiratory failure/ARDS
- On echo pulmonary hypertension
- Right sided heart failure
- Failed to respond to oscillator and surfactant
- Started on ECMO and dialysis
- Sepsis Stenotrophomonas maltophilia 10/02/2024 -18/03/2024
- Candida parapsilosis

  13/03/2024 – 27/05/2024
- Candida auris 01/04/2024
- Klebs pneumonia tracheal aspirate
- Lymphopaenia

Diag. ICD10: A41.5,A41.8

Ordered: Immunophenotyping, TREC/KREC Screen

			2024-05-27	2024-05-29	2024-05-30	2024-05-31	2024-06-02	2024-06-03	2024-06-03	2024-06-06
			18:30	06:30	08:25	11:10	17:00	10:04	10:14	14:20
			57014627	57446209	57013200	57013174	57012124	57013133	57013122	57013383
			FINAL	FINAL	FINAL	FINAL	FINAL	FINAL	FINAL	FINAL
HAEMATOLOGY										
Haemoglobin	11.1-14.1 g/dl			11.6 #	11.7	10.6 L			8.7 *L	
Red Cell Count	4.10-5.30 10 12/L			4.05 L	4.03 L	3.70 L			3.03 L	
Haematocrit	30.0-40.0 %			33.7 #	33.1	30.6			25.0 #L	
MCV	68.0-84.0 fl			83.2	82.1	82.7			82.5	
MCH	24.0-30.0 pg			28.6	29.0	28.6			28.7	
MCHC	31.0-36.0 g/dl			34.4	35.3	34.6			34.8	
RDW	11.7-15.9 %			14.9	14.1	14.3			15.0	
White Cell Count	6.00-18.00 10 9/L			1.65 #*L	2.44 *L	3.37 L			2.51 *L	
Neutrophils	%			68.0	62.0	58.0			57.0	
Neutrophils Abs	1.00-5.00 10 9/L			1.12 #	1.51	1.95			1.43	
Lymphocytes	%			1.8	22.0	12.0			11.0	
Lymphocytes Abs	4.00-12.00 10 9/L			0.03 *L	0.54 L	0.40 L			0.28 *L	
Monocytes	%			14.5	16.0	26.0			28.0	
Monocytes Abs	0.20-1.20 10 9/L			0.24	0.39	0.88			0.70	

IMMUNOLOGY										
CD45 Lymphocytes	1800-18700 cells/uL									162 L
Total T-Cell Abs	1900-5900 cells/uL									4 L
Total T-Cells %	49.0-76.0 %									2.6 L
CD4 Cells Abs	1400-4300 cells/uL									3 L
CD4 Cells %	31.0-56.0 %									2.7 L
CD8 Cells Abs	500-1700 cells/uL									2 L
CD8 Cells %	12.0-24.0 %									1.7 L
Tot B Cells Abs	610-2600 cells/uL									0 L
Tot NK Cells Abs	160-950 cells/uL									177
TREC										Absent *
KREC										Absent *

Introduction

- Inborn errors of immunity better known as primary immunodeficiencies, are a group of disorders which are often caused by monogenic defects in the immune system genes.
- These defects then lead to an increased susceptibility to severe, persistent, unusual and/or recurrent infections, malignancies and autoimmune or autoinflammatory conditions.
  - autosomal dominant
  - autosomal recessive
  - x-linked recessive
  - x-linked dominant
- In 2022 the international union of immunological societies had categorised 487 inborn errors of immunity.

TABLE I: IUIS CLASSIFICATION OF IEIS LISTED BY CATEGORY AND NUMBER OF GENES[7]

CLASSIFICATION CATEGORY	NUMBER OF GENES
Combined immunodeficiencies (cellular and humoral)	60
Combined immunodeficiencies with associated or syndromic features	67
Predominantly antibody deficiencies	42
Disease of immune dysregulation	48
Congenital disorders of phagocyte number or function	41
Defects in intrinsic and innate immunity	70
Autoinflammatory disorders	48
Complement deficiencies	32
Bone marrow failure syndromes	43
Phenocopies of inborn errors of immunity, associated with somatic variants *(TNFRSF6, NRAS, KRAS, NLRP3, STAT5B)* or associated with autoantibodies	5

Table 1 Immunodeficiencies affecting cellular and humoral immunity

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
1. T-B+ severe combined immune deficiency (SCID)							
γc deficiency (common gamma chain SCID, CD132 deficiency)	*IL2RG*	XL	308380	Very low	Normal to high	Low	Low NK
JAK3 deficiency	*JAK3*	AR	600173	Very low	Normal to high	Low	Low NK
IL7Rα deficiency	*IL7R*	AR	146661	Very low	Normal to high	Low	Normal NK
CD45 deficiency	*PTPRC*	AR	151460	Very low	Normal	Low	Normal γ/δ T cells
CD3δ deficiency	*CD3D*	AR	186790	Very low	Normal	Low	Normal NK, no γ/δ T cells
CD3ε deficiency	*CD3E*	AR	186830	Very low	Normal	Low	Normal NK, no γ/δ T cells
CD3ζ deficiency	*CD3Z*	AR	186780	Very low	Normal	Low	Normal NK, no γ/δ T cells
Coronin-1A deficiency	*CORO1A*	AR	605000	Very low	Normal	Low	Detectable thymus
LAT deficiency	*LAT*	AR	602354	Normal to low	Normal to low	High	Typical SCID or combined immunodeficiency, the latter with adenopathy, splenomegaly, recurrent infections, autoimmunity
2. T-B- SCID							
RAG deficiency	*RAG1* *RAG2*	AR	179615 179616	Very low	Very low	Decreased	Normal NK cell number, but increased risk of graft rejection, possibly due to activated NK cells
DCLRE1C (Artemis) deficiency	*DCLRE1C*	AR	605988	Very low	Very low	Decreased	Normal NK cell number, but increased risk of graft rejection, possibly due to activated NK cells, radiation sensitivity
DNA PKcs deficiency	*PRKDC*	AR	615966	Very low	Very low	Variable	Normal NK, radiation sensitivity, microcephaly
Cernunnos/XLF deficiency	*NHEJ1*	AR	611290	Very low	Very low	Decreased	Normal NK, radiation sensitivity, microcephaly
DNA ligase IV deficiency	*LIG4*	AR	601837	Very low	Very low	Decreased	Normal NK, radiation sensitivity, microcephaly
Adenosine deaminase (ADA) deficiency	*ADA*	AR	608958	Very low	Low, decreasing	Low, decreasing	Low NK, bone defects, may have pulmonary alveolar proteinosis, cognitive defects
AK2 defect	*AK2*	AR	103020	Very low	Very Low	Decreased	Reticular dysgenesis with neutropenia; deafness
Activated RAC2 defect	*RAC2*	AD GOF	602049	Very low	Very Low	Low, poor specific antibody responses	Recurrent bacterial and viral infections, lymphoproliferation; neutropenia
3. Combined immunodeficiency (CID), generally less profound than SCID							
CD40 ligand (CD154) deficiency	*CD40LG*	XL	308230	Normal to low	$sIgM^+IgD^+$ naïve B cells present; IgG^+, IgA^+, IgE^+ memory B cells absent	IgM normal or high, other Ig isotypes low	Severe and opportunistic infections, idiopathic neutropenia; hepatitis and cholangitis, *Cryptosporidium* infections, cholangiocarcinoma; autoimmune blood cytopenias; peripheral neuroectodermal tumors
CD40 deficiency	*CD40*	AR	606843	Normal			Neutropenia, opportunistic infections, gastrointestinal and biliary tract and liver disease, *Cryptosporidium* infections

Table 8 Complement deficiencies

Disease	Genetic defect	Inheritance	Gene OMIM	Laboratory features	Associated features
C1q deficiency due to defects	*C1QA* *C1QB* *C1QC*	AR AR AR	120550 120570 120575	Absent CH50 hemolytic activity, defective activation of the classical pathway, diminished clearance of apoptotic cells	SLE, infections with encapsulated organis
C1r deficiency	*C1R*	AR	613785	Absent CH50 hemolytic activity, defective activation of the classical pathway	SLE, infections with encapsulated organis Ehlers-Danlos phenotype
C1r Periodontal Ehlers-Danlos	*C1R*	AD GOF	613785	Normal CH50	Hyperpigmentation, skin fragility
C1s deficiency	*C1S*	AR	613785	Absent CH50 hemolytic activity, defective activation of the classical pathway	SLE, infections with encapsulated organis Ehlers-Danlos phenotype
C1s Periodontal Ehlers-Danlos	*C1S*	AD GOF	613785	Normal CH50	Hyperpigmentation, skin fragility
Complete C4 deficiency	*C4A + C4B*	AR	120810	Absent CH50 hemolytic activity, defective activation of the classical pathway, complete deficiency requires biallelic mutations/ deletions/conversions of both C4A and C4B	SLE, infections with encapsulated organis partial deficiency is common (either C4 or C4B) and appears to have a modest effect on host defense
C2 deficiency	*C2*	AR	217000	Absent CH50 hemolytic activity, defective activation of the classical pathway	SLE, infections with encapsulated organis atherosclerosis
C3 deficiency (LOF)	*C3*	AR	120700	Absent CH50 and AH50 hemolytic activity, defective opsonization, defective humoral immune response	Infections, glomerulonephritis, atypical hemolytic-uremic syndrome with GOF mutations.
C3 GOF	*C3*	AD GOF	120700	Increased activation of complement	Atypical hemolytic-uremic syndrome
C5 deficiency	*C5*	AR	120900	Absent CH50 and AH50 hemolytic activity Defective bactericidal activity	Disseminated neisserial infections
C6 deficiency C7 deficiency	*C6* *C7*	AR AR	217050 217070	Absent CH50 and AH50 hemolytic activity, defective bactericidal activity	
C8α deficiency	*C8A*	AR	120950		
C8 γ deficiency	*C8G*	AR	120930		
C8 β deficiency	*C8B*	AR	120960		
C9 deficiency	*C9*	AR	120940	Reduced CH50 and AP50 hemolytic activity, deficient bactericidal activity	Mild susceptibility to disseminated neisserial infections
MASP2 deficiency	*MASP2*	AR	605102	Deficient activation of the lectin activation pathway	Pyogenic infections, inflammatory lung disease, autoimmunity
Ficolin 3 deficiency	*FCN3*	AR	604973	Absence of complement activation by the Ficolin 3 pathway.	Respiratory infections, abscesses
C1 inhibitor deficiency	*SERPING1*	AD	606860	Spontaneous activation of the complement	Hereditary angioedema

C2 General

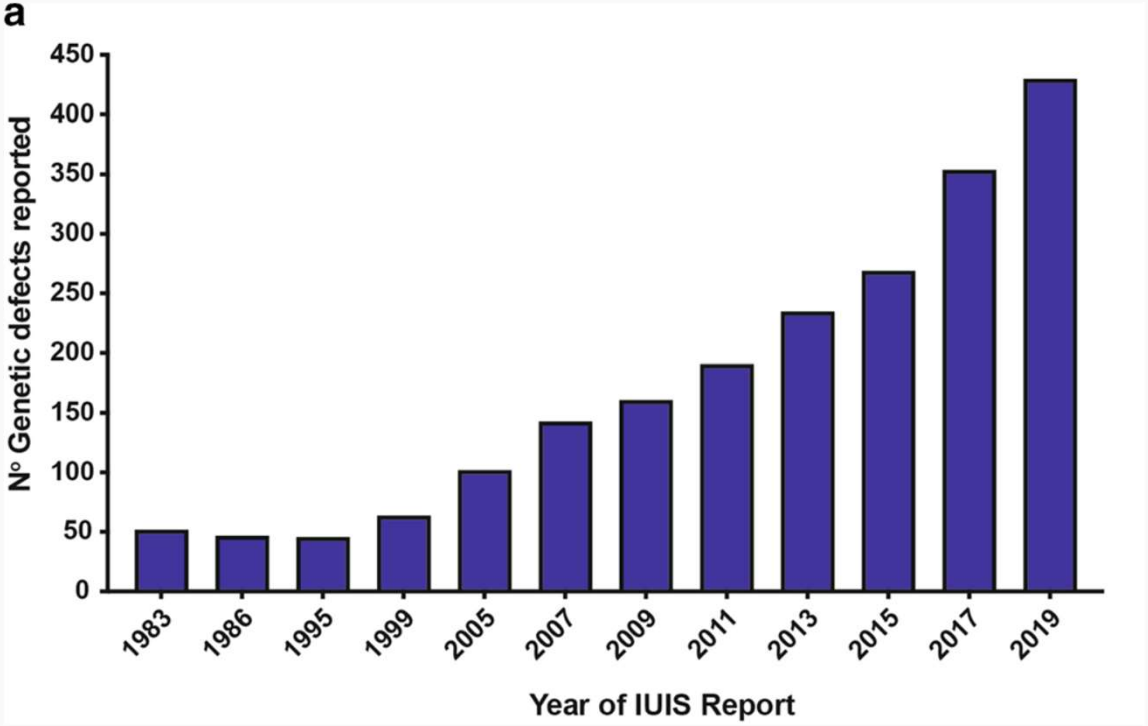
How common are inborn errors of immunity?

Previous

Traditionally considered to be rare diseases, affecting
1 in 10,000 to 1 in 50,000 births.

Current

With Ongoing discovery and improved definition of clinical phenotypes the collective prevalence of these conditions is now more likely to be at least
1/ 1000–1/5000 births.

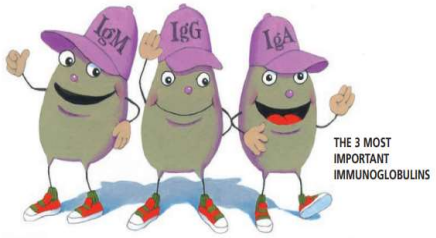


Rate of discovery of novel inborn errors of immunity: 1983–2019.

Inborn errors of immunity /primary immune deficiencies

70% Humoral immunodeficiencies:

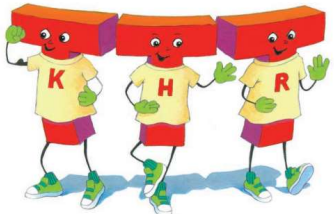
- IGA deficiency
- IGG subclass deficiency
- Specific antibody deficiency
- Aggamma-globulinaemia
- Common variable immune deficiency
- Transient hypo-gammaglobulinaemia



15% Combined immunodeficiencies:

- T cell disorders (SCID)
- DiGeorge Syndrome
- Hyper IGM deficiency/CD40 ligand deficiency

There are 3 kinds of T-cells-
Killer T-cells, Helper T-cells and Regulatory T-cells

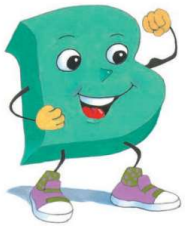


15%

Well-defined syndromes with immunodeficiencies:

- Ataxia Telangiectasis
- Wiskott Aldrich Syndrome
- Hyper IGE syndrome

One kind of protector is the **B-Cell**.



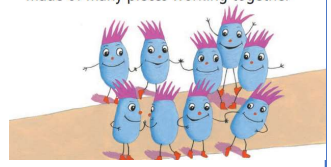
Phagocytic disorders:

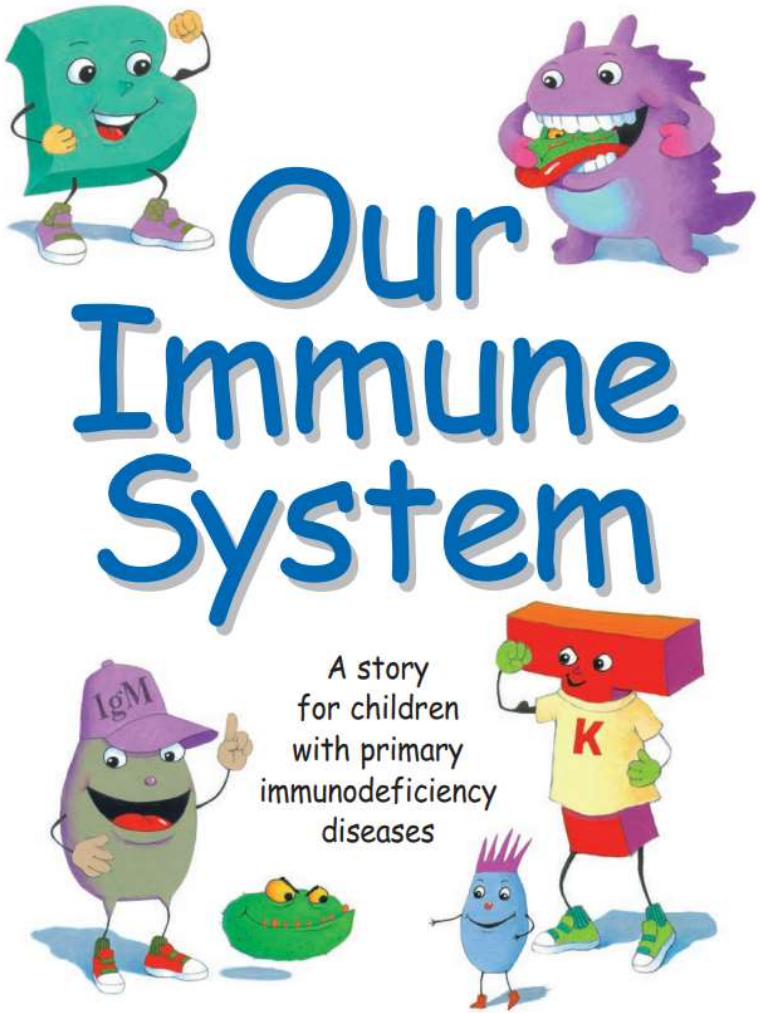
- Chronic Granulomatous Disease

Another protector is the **Phagocyte**
(Phag-o-cyte).

Complement deficiencies

The last protector is the **Complement**
(Com-ple-ment). The Complement is made of many pieces working together





Our Immune System

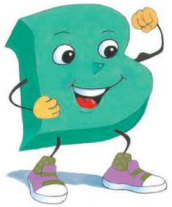
A story for children with primary immunodeficiency diseases

Written by Sara LeBien

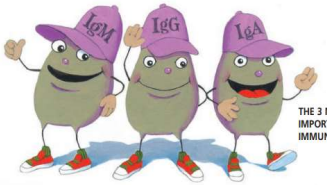
Immune Deficiency Foundation

C2 General

One kind of protector is the **B-Cell**.



B-Cells make **immunoglobulins** (im-mu-no-glob-u-lins), also called **antibodies** (an-ti-bod-ies) or Igs. Each has a certain job

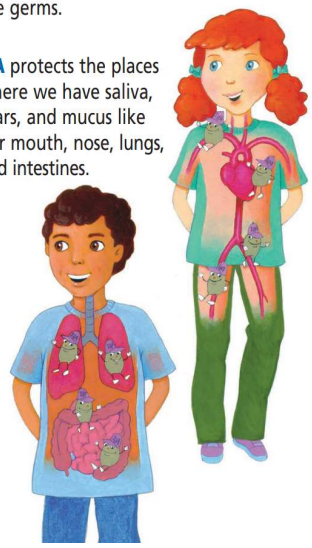


THE 3 MOST IMPORTANT IMMUNOGLOBULINS

to do to keep us well. They are like guards. They guard us from getting sick.

IgG travels in our blood to get to the germs.

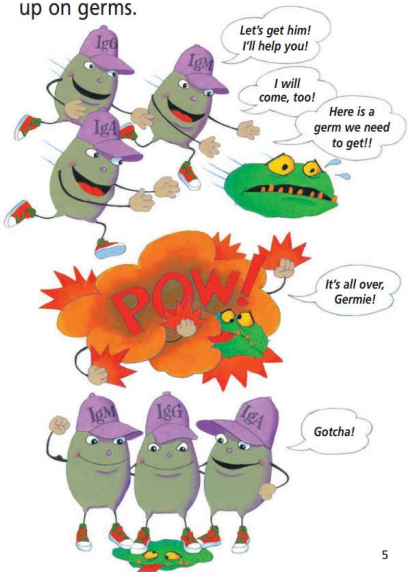
IgA protects the places where we have saliva, tears, and mucus like our mouth, nose, lungs, and intestines.



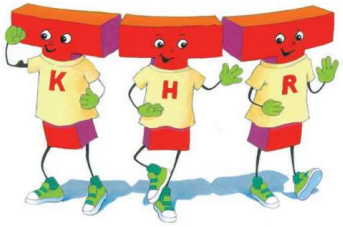
Their job is to kill **germs**, such as viruses, fungi, and bacteria that get into our bodies and make us sick.

IgM protects our blood and other things inside us.

Sometimes the **Igs** help each other gang up on germs.



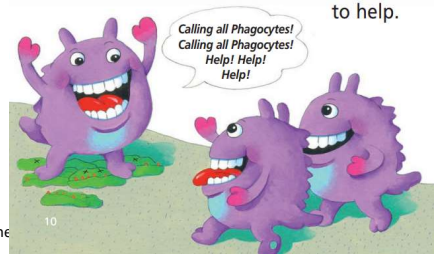
There are 3 kinds of T-cells-
Killer T-cells, Helper T-cells and Regulatory T-cells

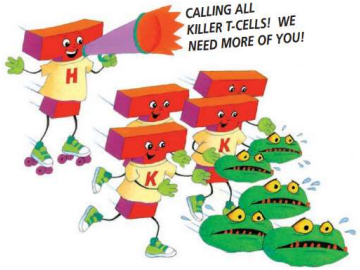


Killer T-cells kill germs.

Another protector is the **Phagocyte** (Phag-o-cyte).

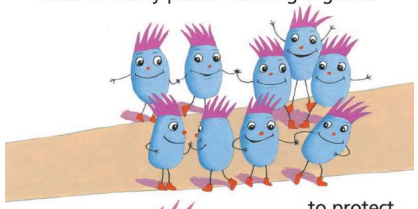
Phagocytes kill germs by eating them! They also send signals to other Phagocytes to help.



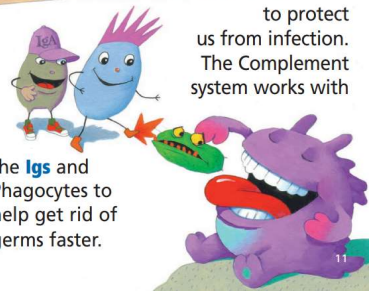


Helper T-cells call in more Killer T-cells to kill germs and tell the B-cells when to make antibodies.

The last protector is the **Complement** (Com-ple-ment). The Complement is made of many pieces working together



to protect us from infection. The Complement system works with the **Igs** and Phagocytes to help get rid of germs faster.



The
Regulator T-cell
tells the B-cells
and other T-cells
when the body is better
and they can stop
making antibodies.

Follow these Healthy Habits

1. Eat healthy foods

2. Get plenty of rest

3. Get regular exercise

4. Wash your hands:
   - Before you eat
   - After you use the rest room
   - After being in a public place
   - After playing with your pet
   - After you cough or sneeze

5. Brush your teeth twice each day

6. Don't share food or drinks with other people

7. Cover your cough or sneeze with a tissue

When to suspect a primary immune deficiency

- **S**evere - requires hospitalization or intravenous antibiotics.
- **P**ersistent - won't completely clear up or clears very slowly.
- **U**nusual - caused by an uncommon organism.
- **R**ecurrent severe infections,
- **S**hared by family members - A family history of primary immune deficiency
- Infection with a regular organism that takes longer time to heal
- Failure to thrive
- Lymphopaenia
- Neutropaenia
- Infection after receiving a live vaccine
- Early infant death

FIRST LINE INVESTIGATIONS

☐	HIV 1/2 Antibodies + p24 antigen	HIV
☐	Full Blood Count	FBC
☐	Immunoglobulins (IgG, IgA, IgM)	IMM
☐	IgE	IgE
	Vaccine responsee	
☐	S. pneumoniae antibodies	PNEUMO
☐	H. influenzae antibodies	HINF
☐	Tetanus antibodies	TET
☐	Diphtheria antibodies	DIP
#	**Cystic Fibrosis screen**	
☐	Sweat chloride concentration	CLSWT
☐	Faecal elastase	FELAS

SECOND LINE INVESTIGATIONS

† ☐	Immunophenotype (Lymphocyte subsets, includes B-cells, T-cells and natural killer cells)	IMMDEF
† ☐	Memory B-cells	BMEM
☐	IgG subclasses (IgG1, 2, 3 and 4)	SUBG
◈ ☐	Neutrophil function test	NEUTF

• ☐	Classic and alternative complement pathways	HCOMP
• ☐	Mannan binding lectin (MBL)	MBL
☐	Complement 3 levels (C3)	C3
☐	Complement 4 levels (C4)	C4

NEWBORN SCREENING

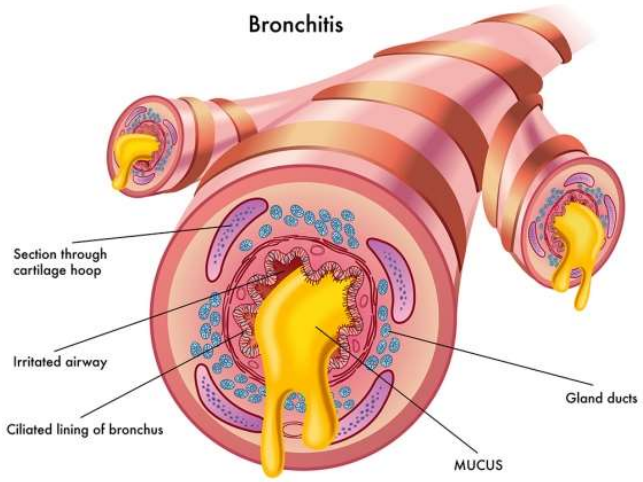
IMMUNODEFICIENCY REQUEST FORM

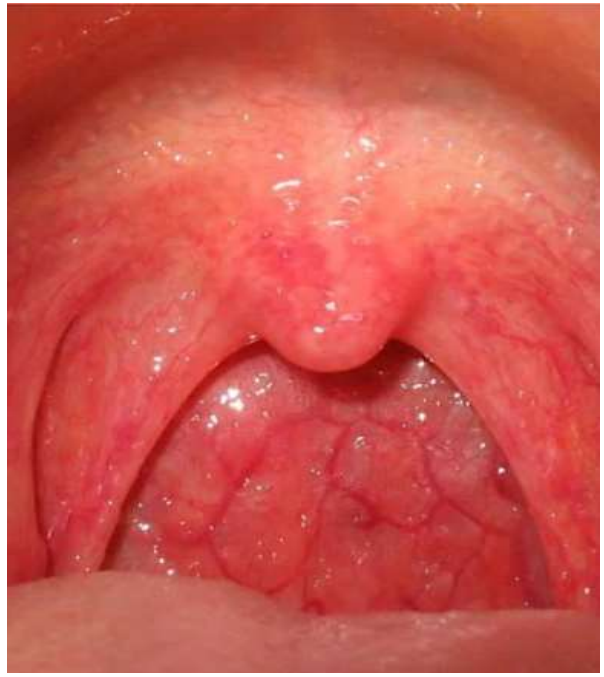
IMMUNODEFICIENCY SYNDROMES (ADDITIONAL TESTING)

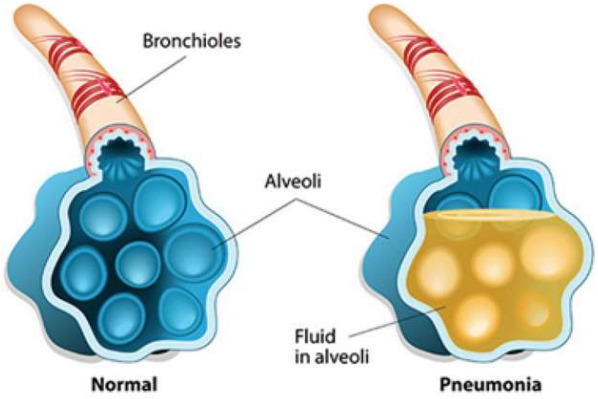
		Severe combined immunodeficiency (SCID)	
‡	☐	TREC and KREC	TRECPCR
†	☐	Recent thymic emigrants, memory and naïve T-cells	NAIVE
	☐	Lymphocyte prolifiration tests see 3rd line investigations	
		Combined variable immunodeficiency (CVID), IgA deficiency, IgG subclass deficiency and specific antibody deficiency (SAD)	
	☐	Immunoglobulins (IgG, IgA, IgM)	IMM
	☐	IgE (biomarker for CVID)	IGE
	☐	IgG subclasses	SUBG
†	☐	Immunophenotype (Lymphocyte subsets, includes B-cells, T-cells and natural killer-cells)	IMMDEF
†	☐	Memory B-cells	BMEM
	☐	S. pneumoniae antibodies	PNEUMO
	☐	H. influenzae antibodies	HINF
	☐	Tetanus antibodies	TET
	☐	Diphtheria antibodies	DIP
⊘	☐	Inborn errors of immunity (IEI) panel	NGCF
†		**X-linked agammaglobulinaemia**	
†	☐	Brutons tyrosine kinase (Flow cytometry)	BTK
	☐	*BTK* gene sequencing	ESONGS
◈		**Hyper IgM syndrome**	
	☐	CD 40 Ligand (Flow cytometry)	CD40L
⊘	☐	Inborn errors of immunity (IEI) panel	CD40L
		Hyper IgE syndrome	
	☐	*STAT3* gene sequencing	ESONGS
⊘	☐	Inborn errors of immunity (IEI) panel	NGCF
	☐	T-helper 17 cells	TH17
◈		**Chronic granulomatous disease (CGD)**	
	☐	Neutrophil functions (includes neutrophil and monocyte oxidative burst and phagocytosis)	NEUTF
	☐	CGD gene sequencing	CGDNGS
◈		**DiGeorge syndrome**	
	☐	Fluorescent in situ hybridisation (FISH) 22q11	GFISH
		Ataxia Telangiectasia	
	☐	Alpha-fetoprotein	AFP
	☐	*ATM* gene sequencing	ATMNGS
†		**Autoimmune lymphoproliferative syndrome (ALPS)**	
	☐	Double negative T-cells	DNTFL
	☐	Inborn errors of immunity (IEI) panel	NGCF
		Cystic Fibrosis genetic testing	
	☐	Cystic Fibrosis (*CFTR*) gene sequencing	CFSEQ
		Wiskott Aldrige syndrome (WAS)	
	☐	WASP gene sequencing	ESONGS
		Hereditary angioedema	
	☐	Complement 3 levels (C3)	C3
	☐	Complement 4 levels (C4)	C4
	☐	C1 esterase inhibitor	C1E
	☐	C1q antibodies	C1C
⊘	☐	HAE gene sequencing	NGCF

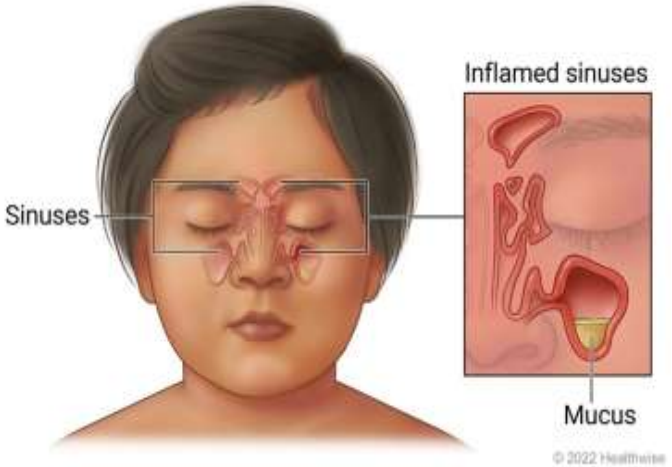
IGA Deficiency

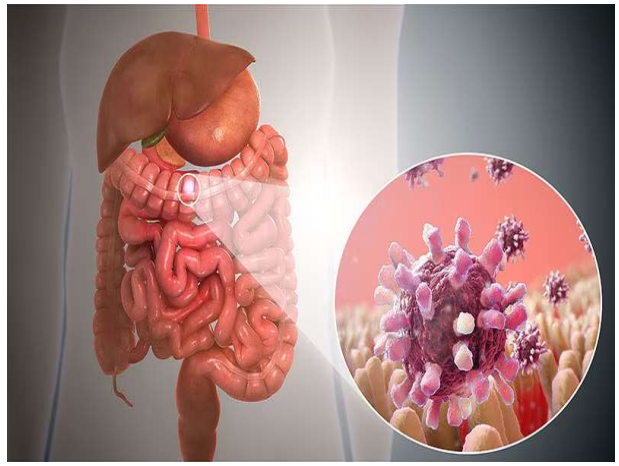
- Impaired ability to switch from IGM to IGA
- IGA <0.05g/l with normal IGM and IGG values .
- If IGG and IGM levels subsequently decline then this could be CVID
- Clinical presentation
- Treatment Symptomatic
- A lot of these patients have autoantibodies to IGA
- IgG anti-IgA antibodies that are found in about 25% of subjects.
- Don’t give immunoglobulins as increased risk of anaphylaxis





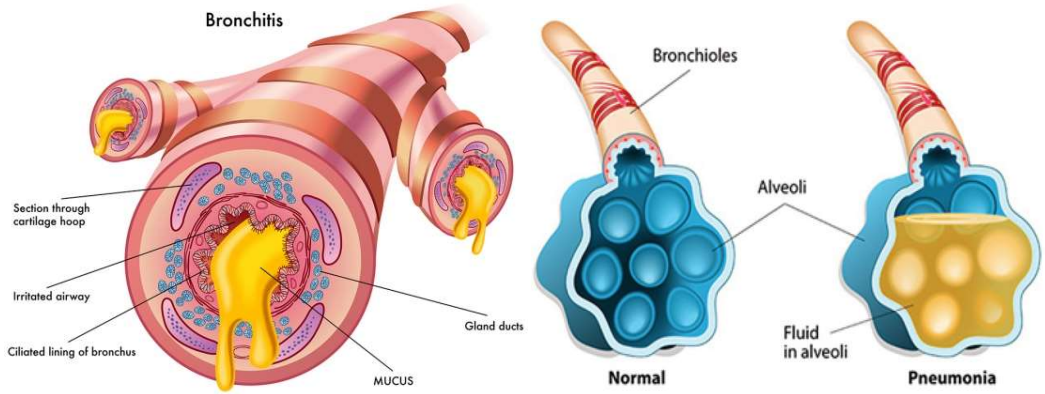


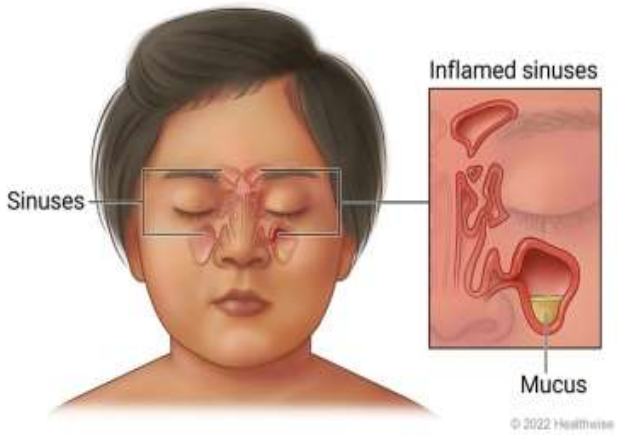


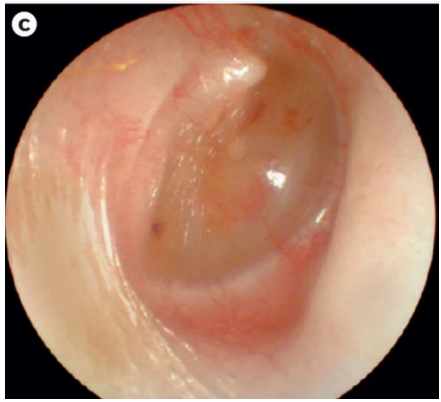


IGG subclass deficiencies

- You should diagnose this only when IGG ,IGM and IGA levels are normal in a child with recurrent infections with an abnormal antibody response to conjugated vaccines (Strep pneumonia and Haemophilus Influenza)
- These are not a common cause of immune deficiencies and should only be looked for in a few clinical situations
- Clinical situations to look for IGG subclass deficiency include:
  - Selective IgA Deficiency with recurrent infections to determine if there is an associated IgG2 and IgG4 subclass deficiency
  - Wiskott-Aldrich Syndrome or Ataxia- Telangiectasia at the onset of recurrent infections
  - Specific Antibody Deficiency with normal total immunoglobulins

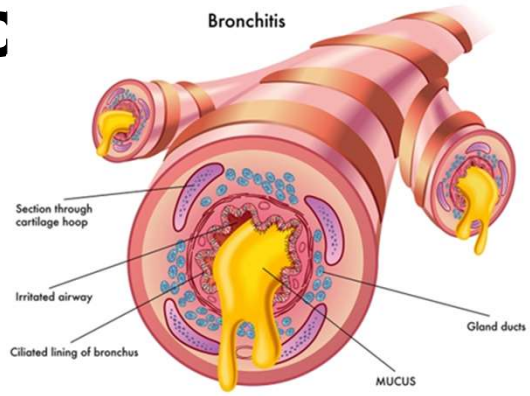


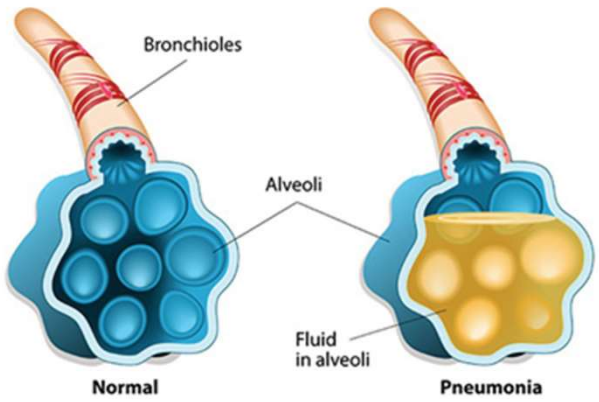


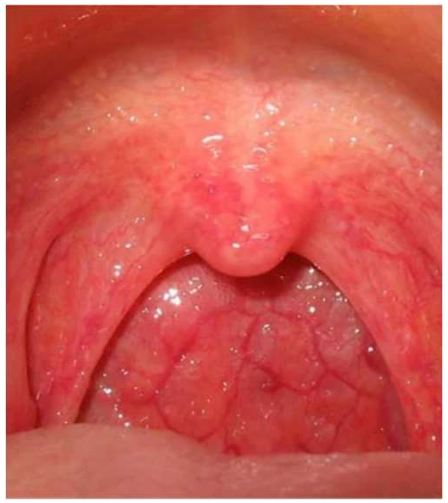


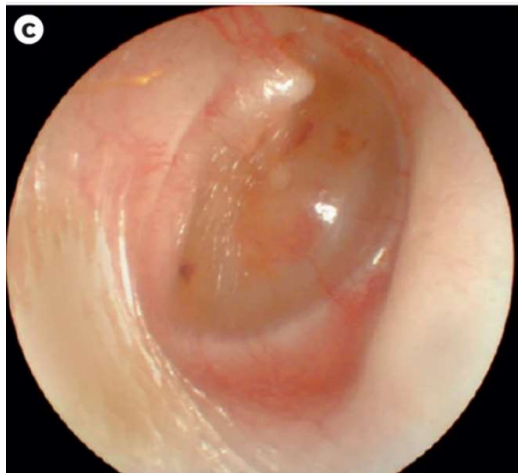
Specific Antibody deficienc

- People who produce normal immunoglobulin levels but who lack the ability to produce protective IgG antibodies against the types of organisms that cause upper and lower respiratory infections are said to have Specific Antibody Deficiency
- Children less than 2 years of age often do not have a robust response to infections with bacteria such as Streptococcus pneumoniae.
- This is primarily due to an inability to make antibodies against the polysaccharide coat that covers these bacteria.
- Treatment
  - Re vaccinate



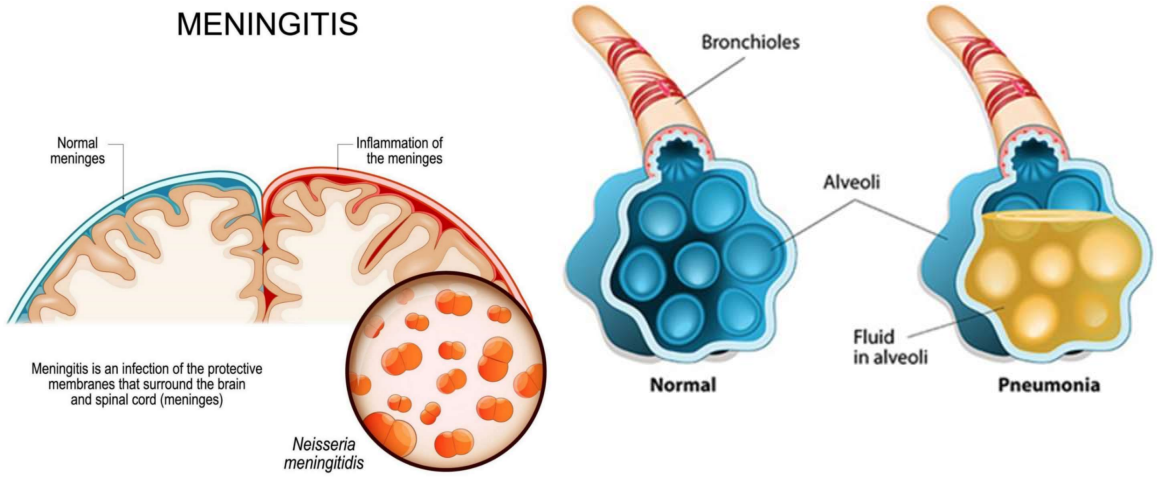


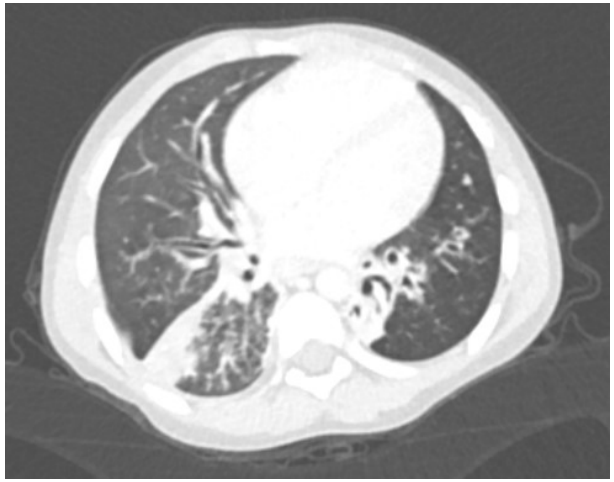


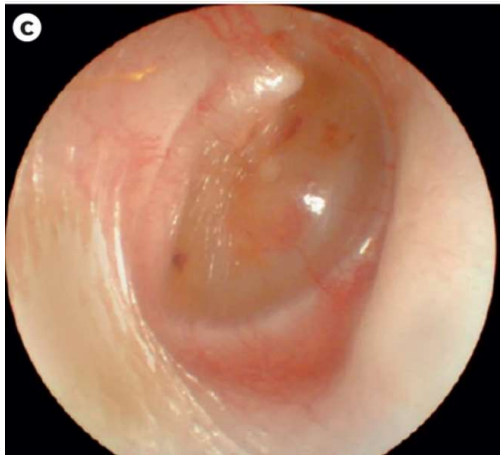


Agamma-globulinemia

- Occurs in boys predominantly
- This leads to an inability for Pre- B cells to become mature B Cells in the bone marrow.
- This is caused by a defect in BTK (Bruton tyrosine kinase) gene on the X chromosome. Tyrosine-kinase is required for normal B cell development.
- For the 1st 6 -9 months the children are usually ok (maternal transfer of IGG)
- However by 18 months of age symptoms start
- Common organisms include Strep Pneumonia /Haemophilus influenza, Staph Aureus and Mycoplasma Pneumonia

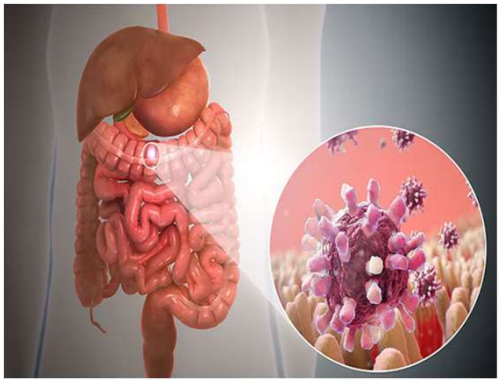






Agammaglobulinemia

- In most individuals with agammaglobulinemia, all of the immunoglobulins (IgG, IgM, IgA, IgE) are absent or low
- The number of B cells in the blood should be measured. A low percentage of B cells (1% or less of the lymphocytes) in the blood is the most characteristic and reliable laboratory finding in someone with agammaglobulinemia.
- The diagnosis of XLA can be confirmed by demonstrating the absence of BTK protein in monocytes or platelets or by the detection of a variant in the BTK gene .
- Treatment for individuals with agammaglobulinemia includes immunoglobulin replacement therapy.
- People with antibody deficiency with absent B cells should not receive any live viral vaccines, such as live polio, the measles, mumps, rubella (MMR) vaccine, the chicken pox vaccine, the rotavirus vaccine, yellow fever, live typhoid, or the live shingles vaccine.



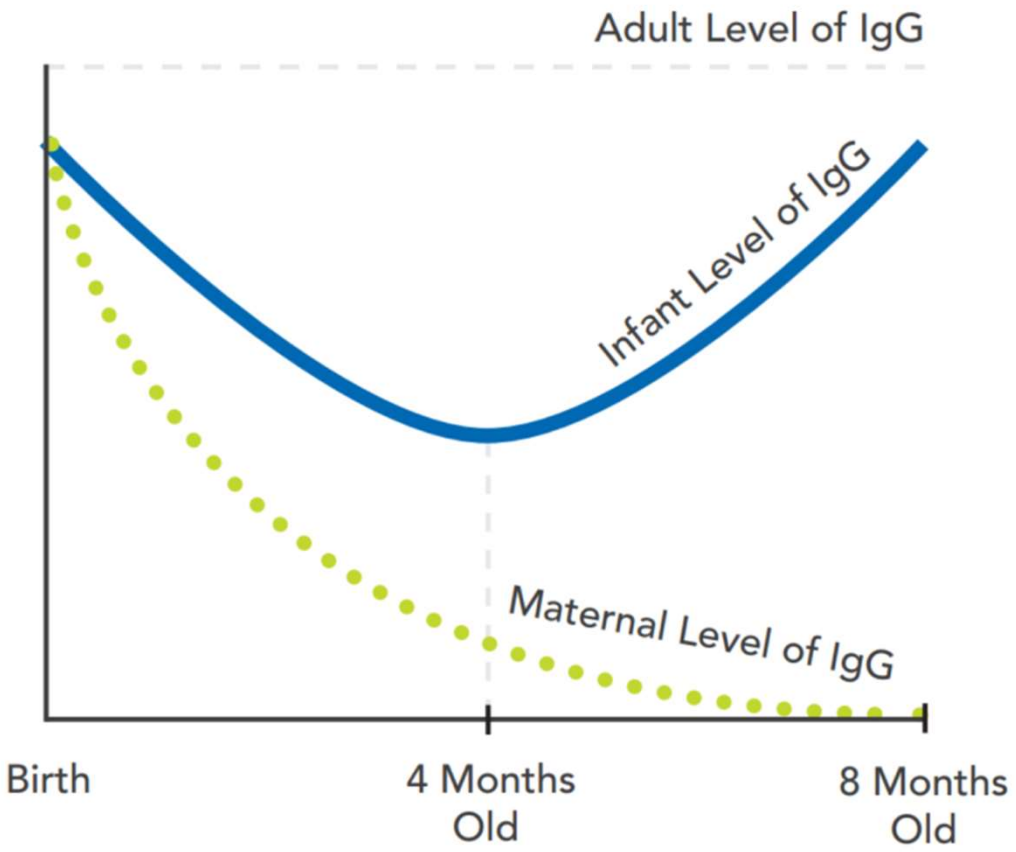
Common Variable Immunodeficiency (CVID)

- People with CVID usually have normal numbers of the cells that produce antibody (B cells), but these cells fail to undergo normal maturation into plasma cells
- Low levels of IGA/IGM/IGG or IGA/IGM with T cell defects .There is a variable T cell defect.
- Another part of the diagnosis of CVID is to determine if there is a lack of functional antibody. This is done by measuring serum levels of antibodies that are specific to vaccine antigens such as Tetanus/Diphtheria, or pneumococcal polysaccharide.
- Otitis media, Pneumonia and Bronchiectasis
- Can get Lymphoid interstitial pneumonitis (LIP)
- CVID is associated with autoimmune haemolytic anaemia, neutropenia and thrombocytopenia
- Poly arthritis involving knees, ankles, elbows and wrists
- Granuloma can be found in the lungs and lymph nodes

- Treatment
- Immunoglobulin replacement therapy
- Broad spectrum antibiotics
- If bronchiectasis is present then treatment as for bronchiectasis

Transient hypogammaglobulinemia of infancy(THI)

- Starts after 6 months of age
- Usually asymptomatic
- The IgG is low
- Levels return to normal by age 2
- Diagnosis made in retrospect
- Children with THI have normal growth and development.
- Normal antibody response to antigens such as tetanus and diphtheria
- Important to exclude CVID/SCID /Aggammglobulinaemia by checking the IGG levels later



Severe combined immune deficiency (SCID)

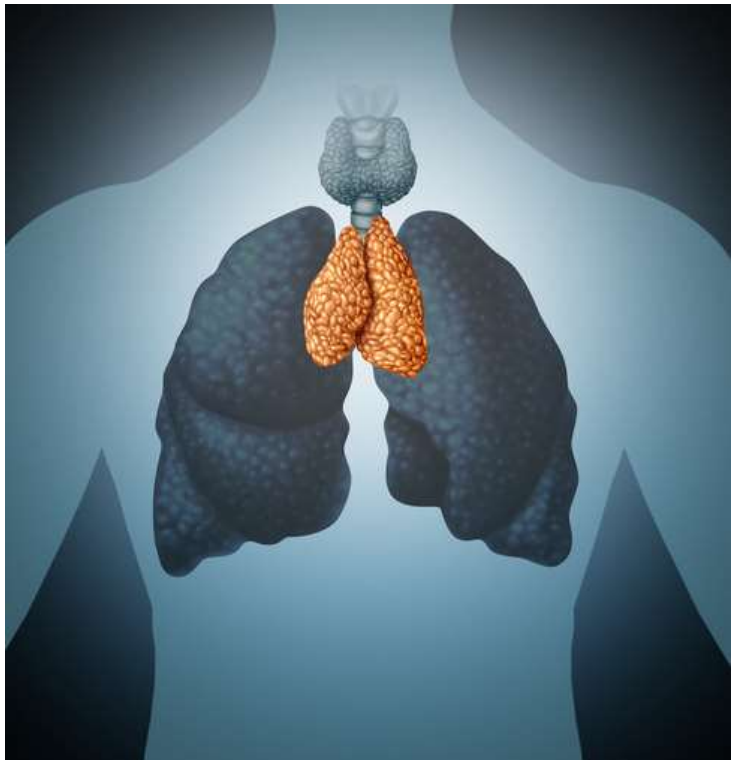
- Severe combined immune deficiency is a life-threatening primary immunodeficiency , with a combined absence of T cell and B cell function.
- It generally manifests within the first 6 months of life with diarrhoea, lower respiratory tract infections, meningitis and failure to thrive.
- Pneumocystis pneumonia
- Chicken pox
- Cytomegalovirus
- Oral candida infection, candida pneumonia, abscesses, oesophageal infection, or even meningitis may develop in infants with SCID.
- The skin may also be involved in children with SCID.
- Other dangerous viruses for infants with SCID are:
- Herpes simplex , adenovirus, respiratory syncytial virus, rhinovirus, parainfluenza 3, epstein-barr virus, polioviruses, measles virus and rotavirus

Treatment of SCID

- Most children with SCID are treated with hematopoietic stem cell transplant :
  - In HSCT, the healthy blood-forming cells are taken from a donor and give them to the baby with SCID through an infusion. The blood-forming cells grow and divide, providing the child with a functioning immune system.
- Gene therapy
  - The baby's stem cells are taken out and put a functional copy of the SCID-causing gene into those cells, and then infuse the corrected cells back into the baby. The cells with the corrected gene make copies of themselves and create an immune system for the baby.
  - Currently, gene therapy trials are available for ADA-SCID, Artemis SCID, Rag1-deficient SCID, and X-linked SCID.
- Persons with ADA-SCID lack an important enzyme that helps their immune system function. In ERT, individuals with ADA-SCID receive at least weekly intramuscular injections of the missing enzyme. These injections allow the immune system to function
- Immune Replacement therapy
- Prophylactic antibiotics Bactrim for PCP
- Antifungal prophylaxis
- No live vaccines

Thymus - Immunobiology

- It is helpful to understand how the thymus works. The thymus acts as a schoolhouse for developing T cells (the students).
- First, white blood cells called stem cells leave the bone marrow and go to the thymus to learn to become T cells. The developing T cells have to learn two key lessons and pass a final test in order to graduate and leave the thymus.
- The first lesson is how to fight infections. The second lesson is to how not to attack the body and cause autoimmune disease.
- The majority of T cells (90%) fail the final test and die without leaving the thymus. The 10% that pass the test leave the thymus as mature T cells. They are able to protect the body from infection but also do not attack the body.



DiGeorge syndrome (DSG)

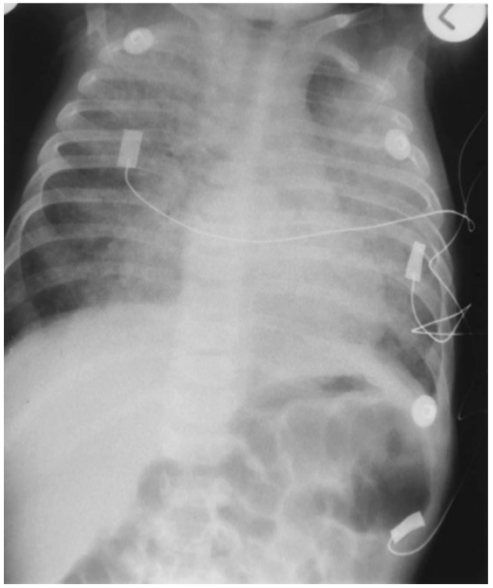
- Heart defects
- Small or absent parathyroid glands
- Small or absent thymus glands
- Children with DiGeorge syndrome can have a wide range of presentations and can range from having mild to severe immunodeficiency.
- The term DGS is used most commonly for individuals with T cells below the 10th percentile for age.

- DGS occurs in four main groups of children:
  - The most common cause is due to a genetic defect called 22q11.2 deletion syndrome . In children with 22q11.2DS, a piece of chromosome 22 is missing.
  - Patients with CHARGE syndrome.
  - Infants of diabetic mothers who do not have any genetic variants.
  - Infants without any genetic variants or whose mothers do not have diabetes.

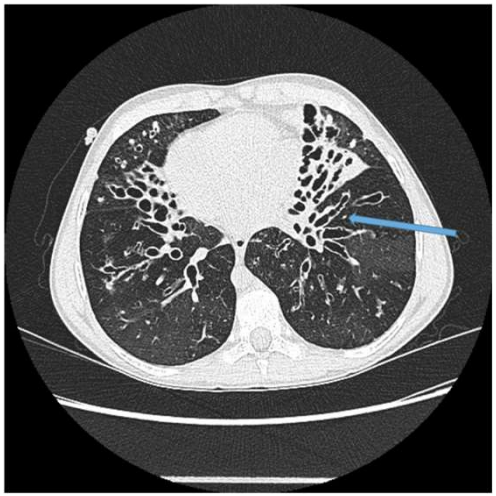
Hyper IGM DEFICIENCY

- Problem is inability of B cells to switch from IGM to IGG and IGA
- It is due to a CD40 ligand gene defect. CD40 ligand is encoded by a gene on the X chromosome.
- This form of immune deficiency is inherited as an X-linked recessive trait and affects boys only

- Clinical presentation
  - Most present in the first year
  - May have cyclical or persistent neutropenia and can present with oral ulcers and ulcers in the upper gi tract
  - Autoimmune disease such as haemolytic anaemia, thrombocytopaenia ,arthritis and nephritis may be seen as wel

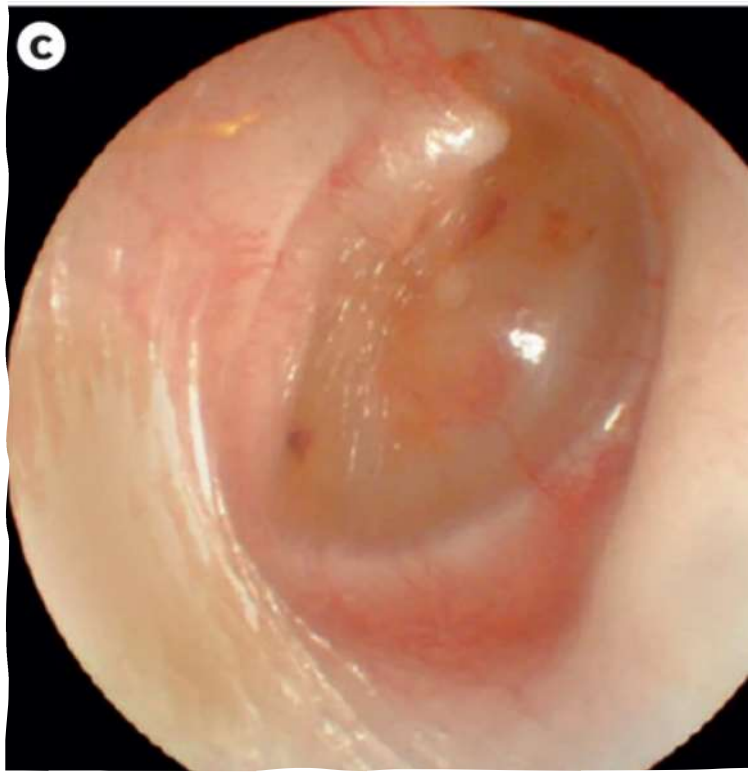


Pneumocystis pneumonitis in a 6-month-old male infant .



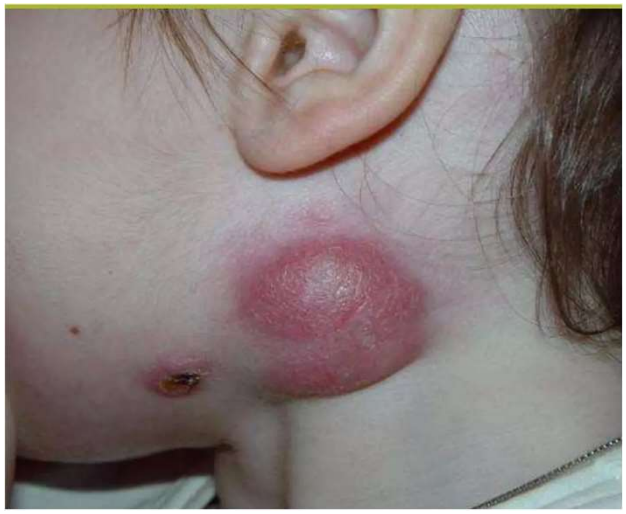
Hyper IGM DEFICIENCY

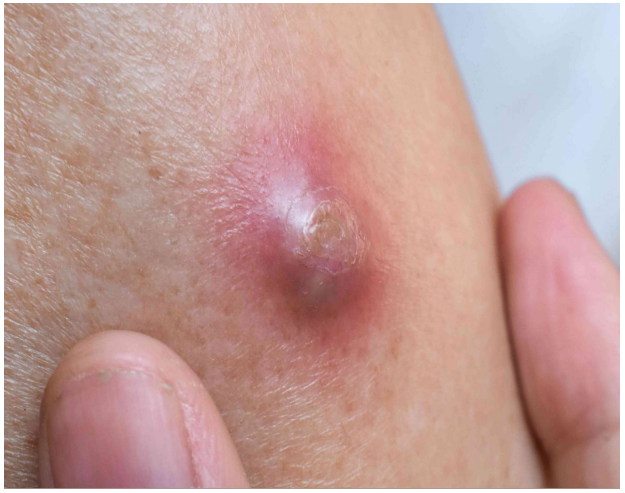
- Diagnosis should be considered in any boy presenting with severe, recurrent respiratory infections or an opportunistic infection who has low or absent IgG and normal or elevated IgM levels with normal T cell and B cell numbers.
- The presence of neutropaenia helps in making the diagnosis
- IGM normal or increased (50%)
- IGG and IGA or IGE low
- Decreased antibody response to vaccines
- CD 40 ligand expression absent on T cells or mutation on CD40 ligand gene
- Management
  - Immune replacement
  - T cell defects as well therefore we need Bactrim prophylaxis
  - Can use granulocyte macrophage colony-stimulating to increase neutrophil count
  - Hematopoietic stem cell transplantation

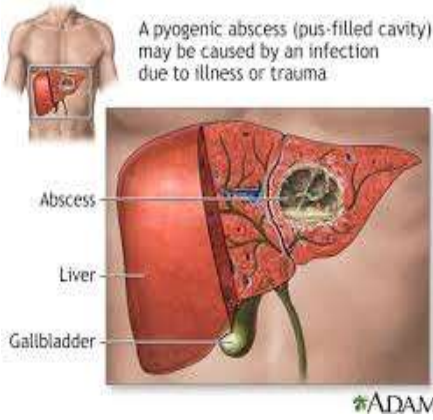


Chronic granulomatous disease

- Neutrophils, fail to make the hydrogen peroxide, and other chemicals needed to fight bacterial and fungal infections.
- In an attempt to control infection, masses of neutrophils and other immune cells continue to gather at the site of infection, forming granulomas.
- Patients with CGD have normal immunity to most viruses and partial to full immunity to many types of bacteria and fungi.
- Infections with Serratia marcescens, Staphylococcus aureus, Burkholderia cepacia complex, Nocardia, and Aspergillus
- Recurrent superficial abscesses
- Granulomas in the bowel can cause severe abdominal pain, diarrhea, weight loss, and sometimes abnormal narrowing in parts of the intestines.
- Test to diagnose it is neutrophil burst test
- Treatment options
  - Bactrim
  - Itraconazole
  - Vaccines including live vaccines
  - Stem cell transplant

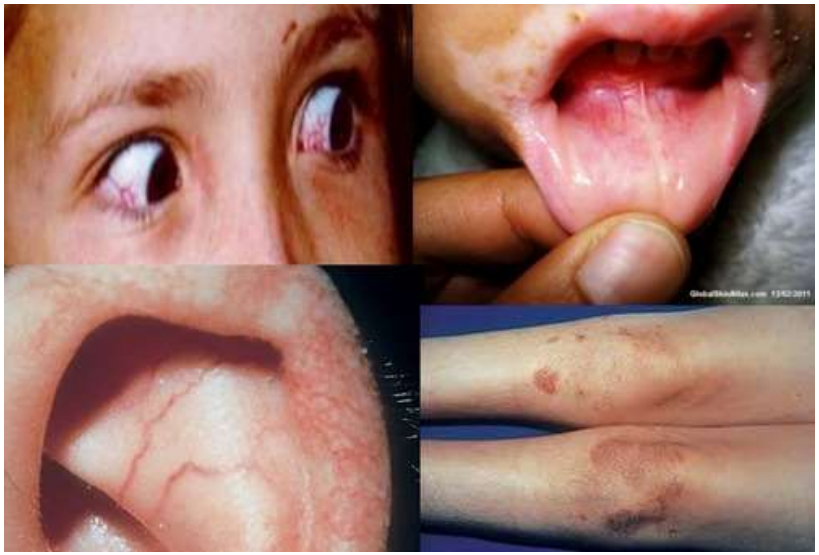






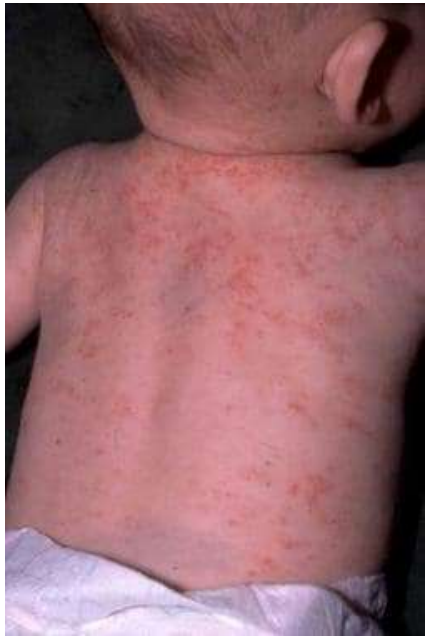
Ataxia telangiectasia

- Autosomal recessive
- When children start walking, they tend to sway and have ataxia
- Most have enough difficulty walking that they need to use a wheelchair for at least part of the day by the time they are 10-12 years old. They develop an intention tremor and difficulties with speaking and swallowing
- Telangiectasia
- Immunodeficiency involving both B cells and T cells
- Humoral (B cell) immunodeficiency causing low immunoglobulin levels and impaired antibody responses.
- They can also have reduced numbers of T cells, giving them a combined (B cell and T cell) immunodeficiency.
- Treatment is supportive.



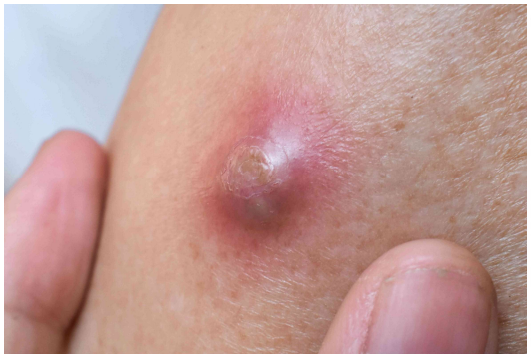
Wiskott Aldrich syndrome (WAS)

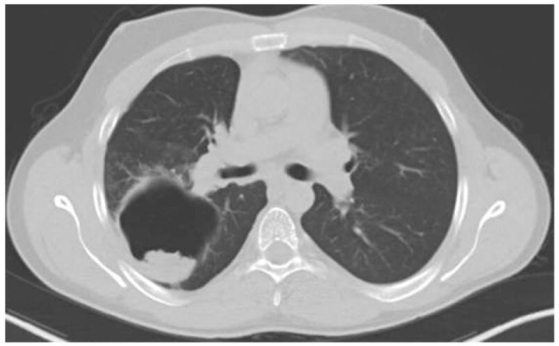
- In its classic form, **WAS** is characterized by three basic clinical features:
  - Increased tendency to bleed, caused by a significantly reduced number of very small platelets.
  - Recurrent bacterial, viral, and fungal infections.
  - Eczema affecting various regions of the skin.
- In addition to this basic triad of symptoms, individuals with **WAS** also have an increased risk of developing severe autoimmune diseases.
- Have an increased incidence of cancer.
- Evaluation of the immune system typically shows that individuals are not able to make good antibody responses to certain types of vaccines. IgE levels are usually elevated and B and T cell function is often abnormal.
- X-linked recessive

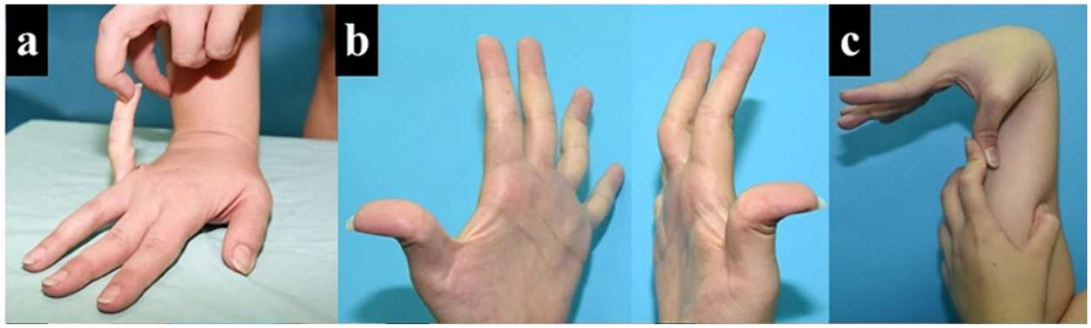


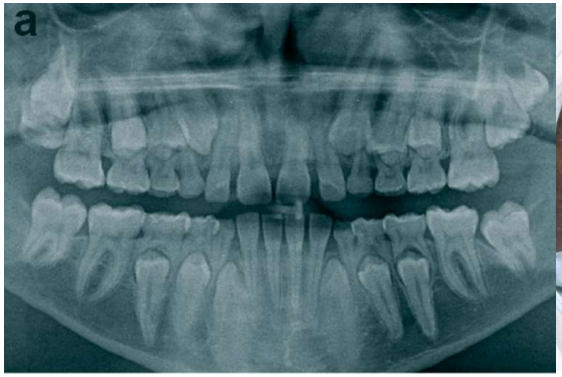
Hyper IgE syndrome

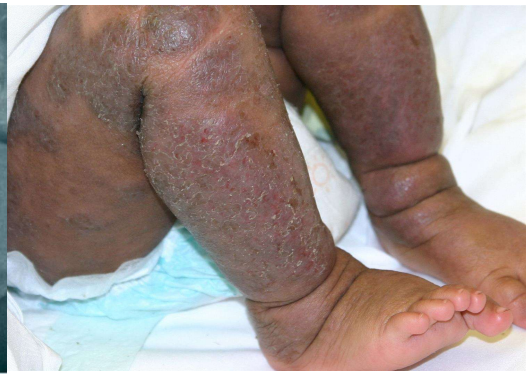
- Hyper IgE Syndromes are rare forms of primary immunodeficiencies characterized by recurrent eczema, newborn rash , skin abscesses, lung infections, eosinophilia and high serum levels of immunoglobulin E
- The term 'cold abscesses' is applied to those lesions that lack external signs of inflammation despite the presence of pus.
- An asymmetrical facial appearance
- Individuals also exhibit hyperextensibility of the joints. They frequently suffer bone fractures from seemingly insignificant trauma and bone density may be reduced.
- Retention of primary teeth, even after the permanent teeth have erupted, is a consistent finding.
-





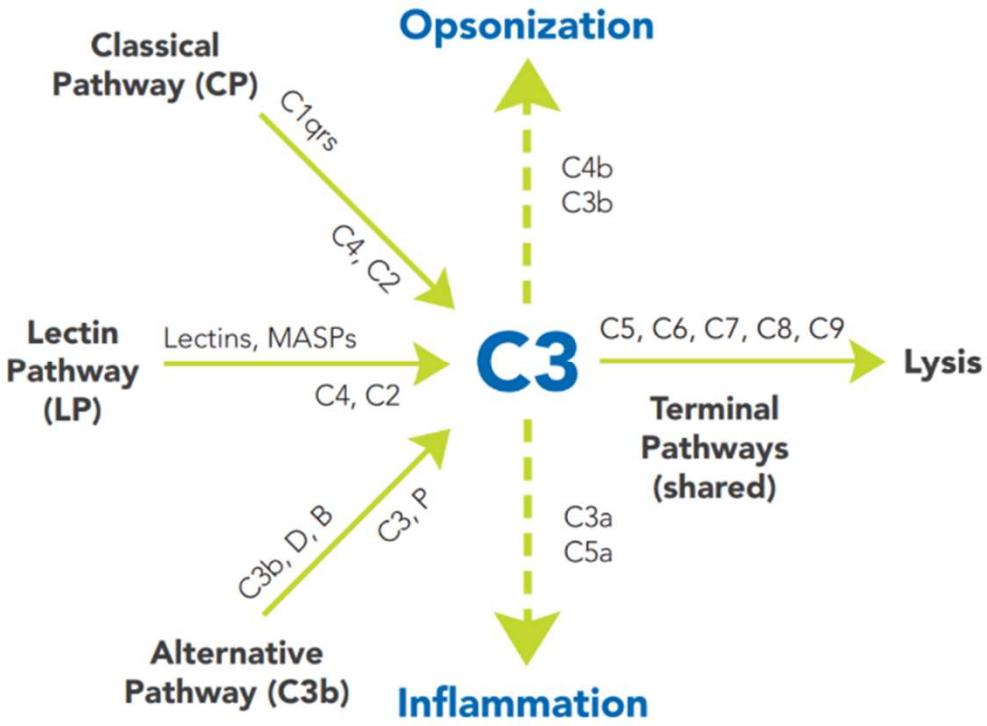






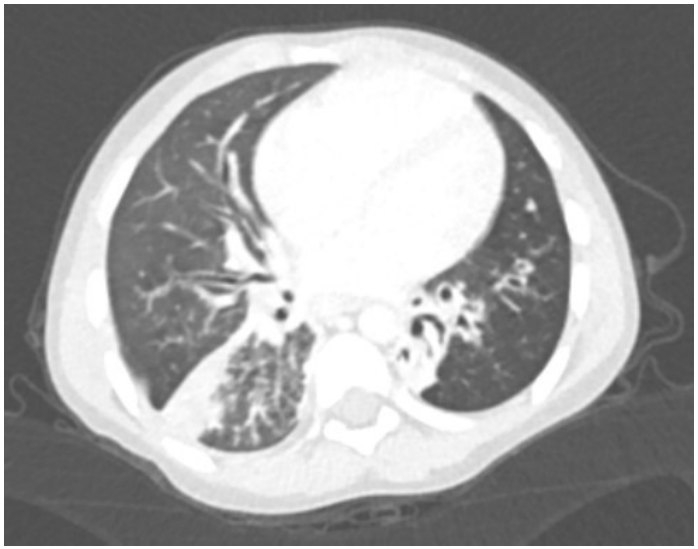
Complement deficiencies

- Complete deficiency of C1, C2, or C4 is closely linked to the development of systemic lupus erythematosus
- Hereditary angioedema is a disease caused by deficiency of the CP control protein, C1- INH. Symptoms generally begin around puberty but can occur earlier. These individuals have recurrent moderate to severe swelling in the extremities and face
- C2 and C3 deficiency is found in young children who have recurrent infections, mainly upper respiratory tract or ear infections due to Streptococcus pneumoniae and Hemophilus influenzae
- Properdin deficiency (X linked)increases the susceptibility to bacterial infections of the Neisseria meningitidis .



Case 2

- 5 year old boy referred from FERH with a 3 year history of productive cough green sputum worse at night
- Shortness of breath during exercise .Treated as asthma for the past 3 years .
- Admitted at 14 months of age for meningitis
- Recurrent bouts of otitis media
- Multiple admissions for LRTI at least 7 per year
- Term baby low birth weight of 2.3kg
- On examination: normal anthropometry now sats of 70 % in room air 94 %on nasal prong oxygen
- Dental caries
- Clubbing
- Crackles on chest



White cell count	8.37 x10^9/L	6.00-16.00
Neutrophils	2.60 x10^9/L (31.1%)	2.40 -7.50
Lymphocytes	2.19 x10^9/L (26.2%)	2.3 -8.00
Monocytes	3.56 x10^9/L (42.5%)	0.00-0.80
Eosinophils	0.01 x10^9/L (0.1%)	0.00-0.80
Basophils	0.01 x10^9/L (0.1%)	0.00-0.20
Total T-cell (CD3)	4877 cells/µL	1400-3700 cells/µL
Helper T-cells (CD4)	2119 cells/µL	700-2200 cells/µL
Cytotoxic T-cells (CD8)	2651 cells/µL	490-1300 cells/µL
Total Natural Killer Cells	854 cells/µL	130-720 cells/µL
Total B-Cells(CD19)	0 cells/µL	370-1400 cells/µL
Immunoglobulin A	<0.10 g/L	0.27 - 1.95 g/L
Immunoglobulin G	0.00 g/L	5.04 - 14.65 g/L
Immunoglobulin M	0.08 g/L	0.24-2.10 g/L

Take home

- It cannot be overemphasised that a high index of suspicion should always be maintained for possible immunodeficiencies, as untreated immunodeficiencies are life threatening, and the long-term prognosis depends on early diagnosis and intervention.
- Infections should be promptly recognised and aggressively treated with appropriate antibiotics.

References

- Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee Stuart G. Tangye
- Congenital Immunodeficiency Syndromes chapter 51 Andrew S. Kemp
- INBORN ERRORS OF IMMUNITY IN SOUTH AFRICA: GENETICS AND THE EXPANDING UNIVERSE Current Allergy & Clinical Immunology I March 2024
- Appropriate investigation for primary immunodeficiency in South Africa Melinda Shelley Suchard, Current Allergy & Clinical Immunology, November 2012 Vol 25, No.4
- Immune deficiency foundation (https://primaryimmune.org/resources)