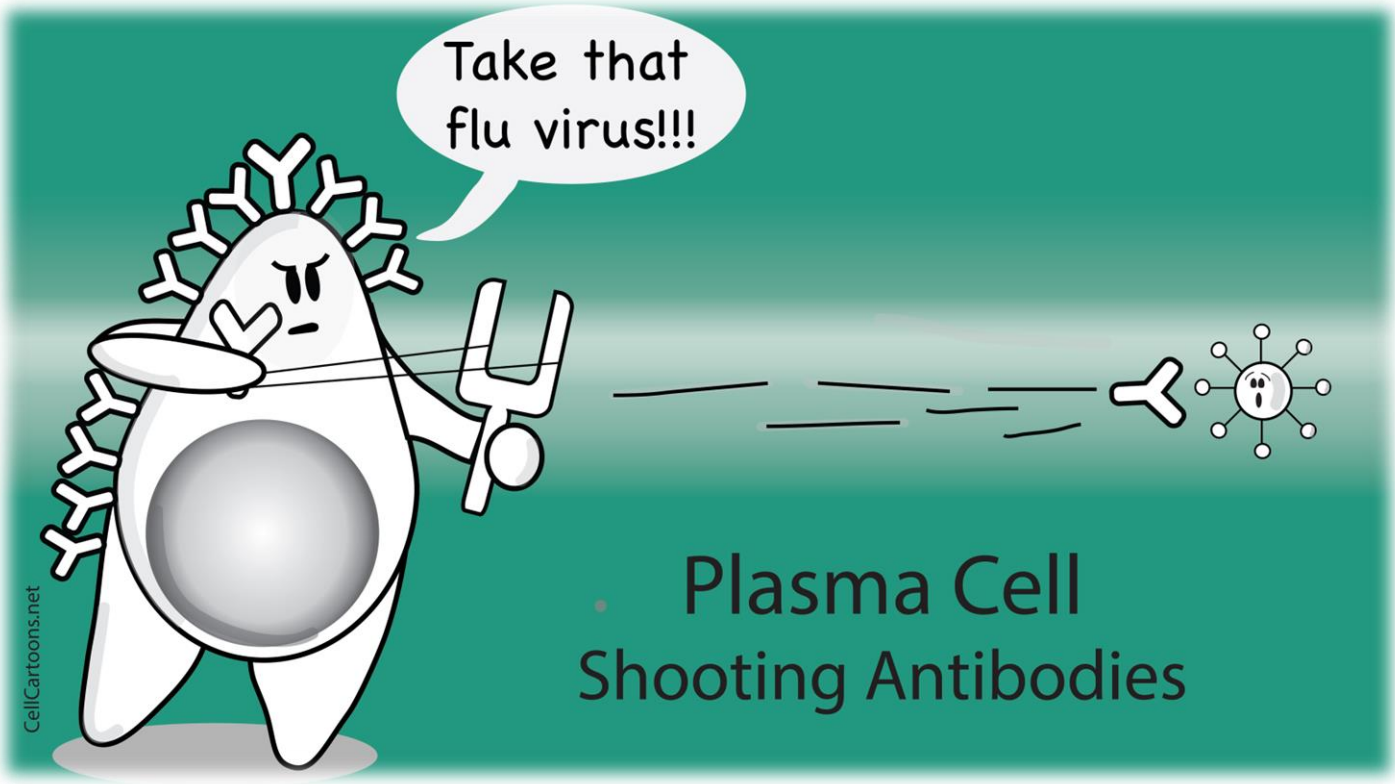
Immunodeficieny Summary

Dr.Malik Sallam

Lectures 22 – 25



Mariam Hassouneh
5/31/2018

Salam Everyone ♥, hope you're all good and having a wonderful blessed day :D

As you start studying this summary I'll be on the other side always praying this would be an easy-going, as useful as possible, and entertaining one ^.^

The table you're seeing below is to guide you through what you're expecting this summary to include, so you can easily return to subjects you want to remember!

Wishing you all the best, بسم الله...

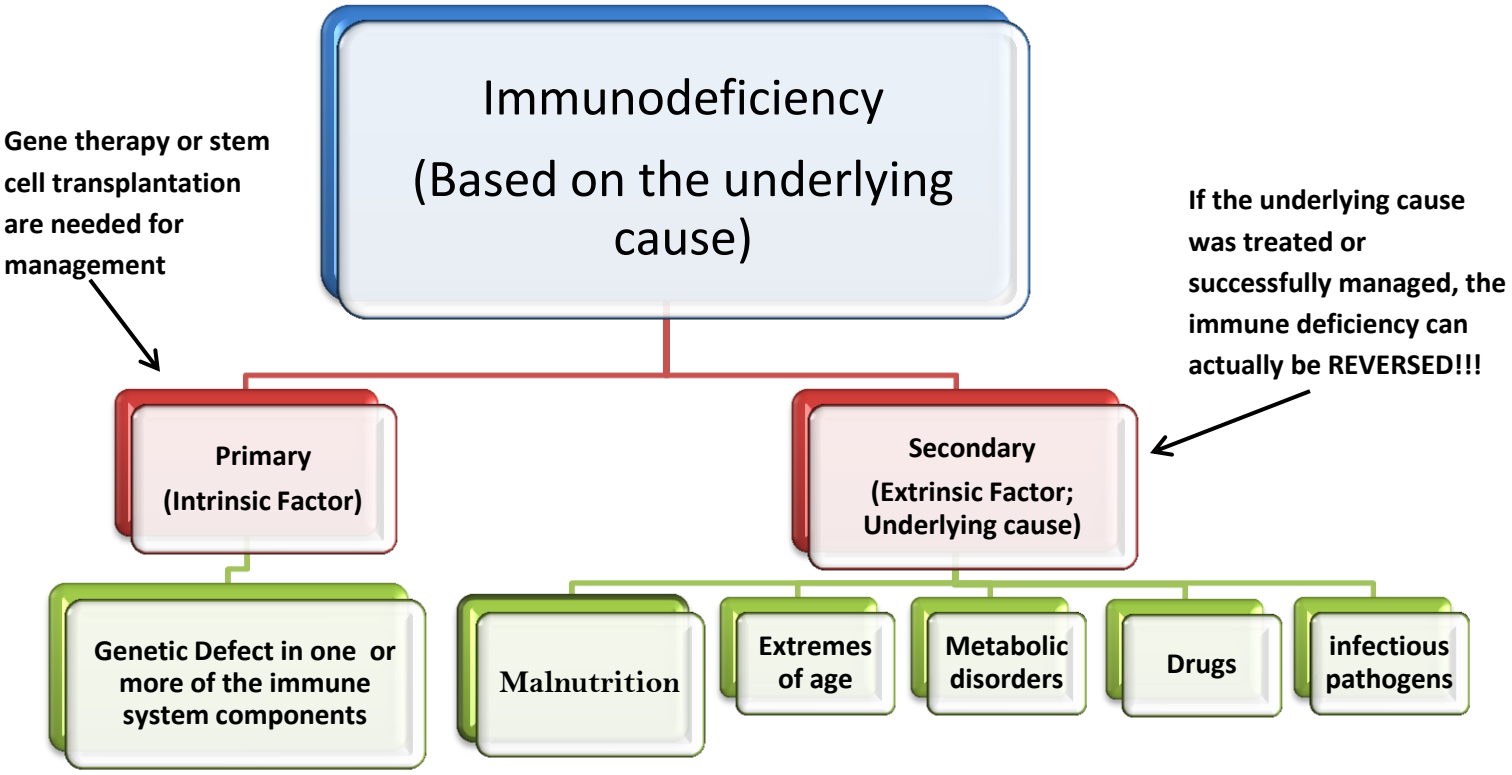
Immunodeficiency

Immunodeficiency can be simply defined as failure of the immune system to protect the body.

Our immune system operates as a:

1. Protector against infections (Protection from pathogens).
2. Defender whenever abnormal alterations in the body happen (e.g : Tumors)

So failure to do so will result in immunodeficiency!!



** Highlighted sentences found through the summary are info the doctor focused on its importance :D!

- How would we suspect that a certain person is immune deficient??

1. Frequency of infections is unusual

   Normal people might have *few* respiratory infections per year, but with these people, *several* times might be the case.

2. Microbiologic result is not commonly encountered.

Common cold and flu viruses are considered to be common infectious pathogens between all people, but an infection with unusual microorganisms (or **opportunistic** infections) may drag attention to the possible presence of an underlying immune deficiency.

** Recurrent + Opportunistic are thus the key words.

- Type of infection can give us clues for which type of organism is the cause as well as the degree of immune deficiency, how?

Examples are the best to explain; Yet, Take a look at this table first as it sums everything.

**Note: The whole table is required; better to recheck after seeing the examples below.

Type of infections associated with major categories of PIDs

Organism	Antibody deficiencies	CIDs	Phagocytic defects	Complement deficiencies
Viruses	Enteroviruses	All, especially: CMV, respiratory syncytial virus, EBV, parainfluenza type 3	No	No
Bacteria	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus, Neisseria meningitidis, Mycoplasma pneumoniae*	As for antibody deficiencies, also: *Salmonella typhi, Listeria monocytogenes*, enteric flora	*S aureus, P aeruginosa, Nocardia asteroides, S typhi*	As for antibody deficiencies: especially *N meningitidis* in deficiency of late components
Mycobacteria	No	Nontuberculous, including BCG	Nontuberculous, including BCG	No
Fungi	No	*Candida* species, *Aspergillus* species, *Cryptococcus neoformans, Histoplasmosis capsulatum*	*Candida* species, *Aspergillus* species	No
Protozoa	*Giardia lamblia*	*Pneumocystis jiroveci, Toxoplasma gondii, Cryptosporidium parvum*	No	No

Ex.1: If we had a defect in humoral immunity (Remember B cells and **Abs**), Individuals will be mostly susceptible to bacterial infections usually involving respiratory tract (upper and lower) like *Streptococcus pneumoniae, H. Influenzae, Moraxella, Staph. aureus, Mycoplasma pneumoniae*

Ex.2 : (possible Exam Q) If we had a defect in Late complement component (components acting after formation of C3 convertase like Membrane attack complex MAC which is formed by assembly of complement proteins from C5 to C9 –mainly of C9-), the patient will be mostly **susceptible to recurrent invasive *Neisseria* infections**.

Ex.3 : previously taken as 1st case ; deficiency in C1INH (also called C1 esterase) which inhibits the successful assembly of $C1qr^2s^2$ to activate C4 and C2 in the classical pathway will result in **Hereditary Angioedema**

Ex.4 : *Salmonella Typhi*, an intracellular organism with increased susceptibility to infection by it upon defects in phagocytes.

Ex.5 : *Candida* infection is related to SCID (severe combined immunodeficiency; Main defect in T cells that'll affect B cells and other immune system components' functions). Recurrent Candida infections can also result from defects in innate immune components.

** Other examples are in the table.

Secondary immunodeficiency

It's Important; more common; and includes a wide range of underlying causes, and since this type is due to an underlying cause that affects the host, the management of cause will reverse and may restore the immune function.

As a quick teaser, variety of underlying causes are present:

1. Infectious agents like HIV and some other viruses.
   ** The most Famous type of 2ndary immunodeficiency is HIV/ AIDS.
2. Drugs like steroids, chemotherapeutic agents that primarily work as immunosuppressants
3. Metabolic diseases like DM (Diabetes) and renal failure may be also involved.
4. Life style like Alcoholism

BUT, the **most common cause of secondary immunodeficiency** is MALNUTRITION!

1) Malnutrition "Low **nutrients** intake".

It's all about "not eating enough of **what my body needs** to stay healthy".

An obese person can suffer malnutrition if he's fast–food dependent, so a meal deprived of essential metals, vitamins is an inadequate meal to meet body nutritional demands!

Malnutrition can result from limited access to food resources or from chronic diseases associated for example with Cachexia الهزال (A state of muscle weakness and loss of weight).

A cytokine named Cachexin (also known as TNF alpha) is the most involved molecule in producing Cachexia.

HOW does malnutrition affect our immunity??

Let's take a look at **types of Malnutrition**:

1. **Protein Malnutrition**: (Globally it's The most common cause of malnutrition; Very important to be familiar with it being the most common)
   It'll impair normal T cell function and production, and this impairment will be directly proportional to the severity of malnutrition (Specially in hypoproteinemia), and you might be thinking the other way round … Since we have low protein doesn't that mean it'll affect immunoglobulin synthesis so it'll affect B cells ???
   Well, apparently it was found that cellular manifestations mainly in T cells are observed in this state.

2. **Micronutrients malnutrition** (Zinc, Ascorbic acid A.K.A Vit.C)

Deficiency in these micronutrients will result in increased susceptibility to infections.

a. Vit.C deficiency

** Remember: Vit.C deficiency is also known as scurvy الاسقربوط.

Let's figure out how together:

Vit.C deficiency for example affects collagen --> Vit C is IMPORTANT in collagen synthesis and cross linking --> Deficiency will result in deformed dermis of the skin --> Skin integrity is affected (the Dam is falling apart) --> easy access for pathogens through skin whenever they wish! --> And then?? Increased susceptibility to infections by innate immunity being deficient plus weakness of mucosal barrier as in Gums which will facilitate pathogens invasiveness!!

b. Vit D deficiency

Vit.D deficiency will mainly affect macrophages activity, which is important in fighting intracellular organisms like *Mycobacterium tuberculosis* (For your info : *M. tuberculosis* is phagocytosed by alveolar (lung alveoli) macrophages, but they are unable to kill and digest the bacterium, so Protective granulomas are formed).

c. Zinc deficiency

Also related to collagen synthesis, which tells us that it'd deficiency is related to innate immunity deficiency.

So as a quick Recap: Protein malnutrition affects T cells and so adaptive immunity, while Zinc and Vit.C deficiency affects skin and so innate immunity, and Vit.D deficiency affect macrophages activity and so innate immunity.

2) Extremes Of Age (Too Old or too Young)

- Too young

Although fetuses in Utero are in sterile environment, if they ever encountered a foreign antigen, they can develop humoral immunity against it due to their dependency on their mothers immune system which will be already fighting the pathogen, so the fetus secondary lymphoid organs will be actually **not yet developed**. But after the baby is born, he will sure then encounter all types of pathogens (commensal, common, or opportunistic organisms) so his secondary lymphoid organs will start developing more in response to that all over his body (especially the Lymphoid associated tissue in bronchi A.K.A the BALT and in the gut A.K.A the GALT).

In early life as neonates, they have less marginal zone B cells (in spleen marginal zone), and a decreased expression of CD 21 on B cells (remember that this is the receptor for opsonins on Bacteria and it acts as co stimulatory receptor for B cells), which will contribute to limitation of their ability to develop specific immune response which is in this case the **HUMORAL** response.

That's why these neonates - though partially protected by maternal IgG - are more prone than toddlers (12 – 36 months), or children in adolescence age or children older than that, to get both common and opportunistic infections, as well as sepsis.

In neonates, secondary lymphoid organs will still be immature due to the absence of memory cells since they are about to encounter pathogens for **their first time**, but as the baby grows,

he'll encounter more pathogens so more foreign antigens, thus his Sec.Lymph. Organs (unless he had an immune-related genetic defect) will develop more as B cells proliferate and produce Abs and make memory B cells, and that's why **as he grows**, the frequency of infections will become less!

- Too old

Some elderly people experience malignancies and excessive number of infections caused by viruses or bacteria or else, which will reflect a decrease in immune function, particularly a decrease in the CELLULAR part of immunity (especially T cells), which will be first manifested in decreased hypersensitivity Rxns, and decreased lymphocytic proliferative responses in response to mitogens (explained in metabolic disorders). Then, innate immunity will become compromised with **increased skin breakdown**.

Metabolic and endocrine changes (Like in DM) associated with aging will affect innate immune system by having a diminished production -with aging- of hematopoietic cells which are the source of neutrophils and macrophages, and so decreased ability to upregulate proliferation and function of Neutrophils and macrophages in response to invaders!

3) Metabolic Disorders Like In DM, renal failure or uremia.

Diabetes and uremia, which are common metabolic disorders, have deleterious effects on immunity so the optimal control of these disorders like controlling blood sugar as much as possible in DM and managing renal failure in its early stages will result in improved and may be restored-to-normal immune function (that's the main idea behind secondary immune deficiency cause management).

1. In DM, the main deficiencies would be in:

a. Phagocytosis and macrophage chemotaxis (innate).

This was noticed in vitro (outside the body) but it was not affirmed in vivo.

Impairment in neutrophils and macrophages chemotaxis was seen in vitro in DM patient.

b. T cells activity (Adaptive)

T cell Anergy (inactivation) demonstrated by delayed hypersensitivity skin tests (the test may be –ve in DM patients because Type 4 HSR is cell-mediated Rxn which depends on T cells).

c. Proliferative response of T cells to mitogens which will be relatively poor response due to chronic exposure to sugar (Hyperglycemia), but the exact relation between hyperglycemia and impaired T cell proliferative response is quite unclear.

*** Mitogens are non-specific activators for T cells, and they are used to measure functionality of T cells and their ability to proliferate by giving these mitogens, and since T cells upon seeing these non-specific agents are supposed to proliferate, mitogens test result will best reflect T cell functionality.

d. Capacity to generate memory Ab responses which will be diminished **REGARDLESS** of repeated vaccination.

2. In Uremia and renal failure, the main deficiencies would be :

a. Defective phagocyte chemotaxis.

b. Defective antimicrobial activity.

4) Drugs

The use of drugs to control undesired immune responses is common in clinical practice, as a consequence of increased in prevalence of inflammatory and autoimmune conditions "A.K.A hygiene hypothesis", as well as the increased number of individuals with transplantation that require immunosuppressive therapy. As we can predict, immunosuppressants and anti-inflammatory drugs are used in treating autoimmune disorders, allergic disorders, transplant rejection, and Graft Vs. Host disease.

** Azathioprine; Imuran ©

We discussed before the usage of this drug as a treatment of Myasthenia gravis.

** Overall results of using these drugs would be:

1. Decreased Cytokine production (↓ IL-1, IL-6, TNF α)
2. Impaired leukocyte chemotaxis
3. Impaired cell adhesion (Neutrophil firm adhesion –after rolling- to Endothelium)
4. Impaired phagocytosis

5. Lymphocyte Anergy
6. Lymphopenia: This can occur as a result due to proapoptotic activity (not being stimulated to mature will upregulate expression of proapoptotic proteins inside the cell), and inhibition to IL-2 mediated proliferative response (remember that the most important growth factor T cell proliferation is IL-2) by some drugs like Cyclosporine (immunosuppressant; mainly affect T cells).

So again we can conclude that drugs affect both innate and adaptive immunity!!

- The wide range of immune defects (as seen above) resulting from usage of immunosuppressants and Anti-Inflammatory drugs will render the patient susceptible to bacterial, viral and fungal infections, according to the degree of immune suppression.

In easier words: Different **Roots of administration** for the same drug can be associated with inactivation of different immune responses and so susceptibility to certain type of infectious microorganisms for each root.

Famous Ex. Administration of **Inhaled** Corticosteroids is associated with susceptibility to *Candida* infections (like oral Candidaisis), while **Systemic** use of Corticosteroids is associated with (POSSIBLE Exam Q.) reactivation of *Human Herpes virus Type 3 HHV3 (Varicella-Zoster)* which upon reactivation in cases of immunosupression gets back from latency as Shingles الحزام الناري.

5) Infectious Diseases

Transient Periods of immune suppression had been associated with viral infections such as measles; CMV (Cytomegalo virus *HHV5*); Flu sometimes, but they are all less severe and they're reversible!

Yet, THE MOST COMMON CAUSE of secondary immunodeficiency caused by infectious diseases is ***Human Immunodeficiency virus (HIV)***

- HIV has 2 types (both of them cause AIDS):

1. HIV Type 1
2. HIV Type 2 which is confined to West Africa mainly (Guinea Bissua and its neighboring countries).

** Usually progression to AIDS in type 2 is slower than type 1.

** Both types will infect T cells expressing CD4 on their surface (Th cells), and Co-receptors which are **CCR5** and (in advanced stage of the disease) **CXCR4.**

* CCR5: Also On macrophages, plus in CNS on Microglial cells (Macrophage derived, can be also targeted by HIV!!)

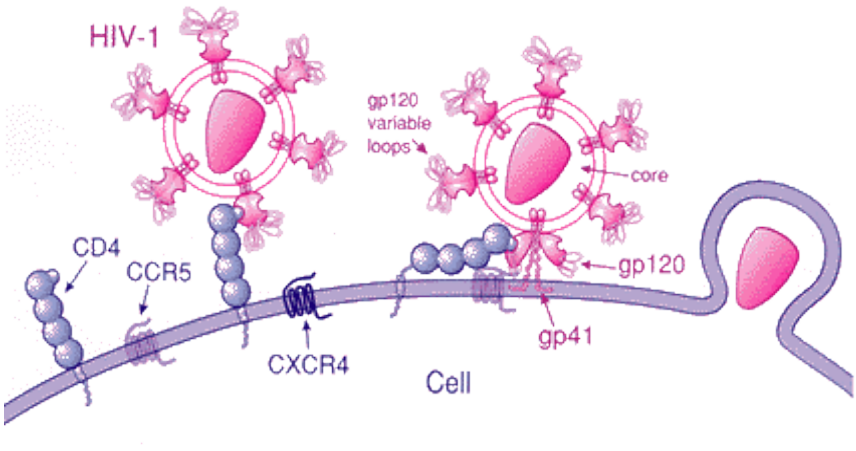


Illustration to what is seen in HIV infection

1. HIV infection will begin by HIV **binding** through surface **glycoprotein 120 (gp120)** found in HIV envelope **to** Th cell receptor **CD4**, **and** to the Co-receptor **CCR5** on target cells (Macrophages initially).
2. Infected cells will migrate to the lymph nodes, where initial replication of infected cells plus infecting neighboring CD4+ Th cells will occur

** Very Imp. : We know that there are populations of T cells everywhere, in Lymph nodes, in associated lymphoid tissue, Circulating T cells in blood, and so on.

In acute HIV infection**, The most affected secondary lymphoid organ is the Gut associated lymphoid tissue (GALT)**, considering the fact that 90% of **Th-cell population** will be affected once GALT is infected by HIV, so it'll be severely damaged and will never get back to its normal state!!

** **Imp. Note** : When measuring Th cells number, for example CD4+/ CD8+ ratio in **acute** HIV infection, we'll notice that it's reduced too much **MAINLY due to the decreased number of Th cells in GALT.**

In acute HIV infection which lasts several months: We have severely depleted GALT, with predominant loss of CD4+ memory T cells, High Viremia, and immune activation

Now after acute HIV infection, even if there was no management for the patient, the patient will remain **ASYMPTOMATIC** , and if there were any signs even though they'll be few, **lymphadenopathy** will be one of them.

* New guidelines in treatment recommend that once a person is diagnosed with HIV, he must start taking Antiretroviral therapy.

* Viral load at the **viral set point** which is the nadir “lowest level” of viral load following acute HIV infection is inversely related to patient prognosis; the Higher the viral load at the set point the worse the prognosis.

* **T cell Lymphopenia (**CD4+ cells being lost) occurs through several mechanisms:

a. HIV inducing apoptosis of cells it infects (HIV cytopathogenic nature).

b. Apoptosis happening due to Cytotoxic immunity activation (not directly related to the virus), and so Cytotoxic T cells will act on infected CD4+ cells (Through the action of perforin-granzyme which will enter the cytoplasm of the target cell; trigger the caspase cascade; and eventually lead to apoptosis).

c. Innate immunity: Due to the setting of an infection, innate immunity will act as well by the action of NK cells killing CD4+ T cells by apoptosis.

** It was previously thought that the loss was due to aggregation of CD4+ T cells to form a syncytium but apparently it turned out to be not true.

HIV to AIDS:

It is said to be HIV state upon infection and along the way of progressive decreasing of CD4+ cells count, BUT, once the **CD4+ count reaches 200**, we now say that the patient **entered AIDS state.**

AIDS state has a thing called AIDS defining conditions, which are very common in AIDS patient. These conditions are the infections that the patient is susceptible to suffer from as the CD4+ cells count gets below 200.

In this case, the patient is prone to many infections, most typical organism to infect is *Pneumocystis jirovecii* (fungus that was previously classified as protozoan) and can be typically observed in these patients. A patient for example in late stage that has a CD4+ count of 150 is seen to have lung infiltrates clearly shown on X- Ray. Confirmed then upon doing Bronchoalveolar lavage "bronchoalveolar washing" (a medical procedure in which a bronchoscope is passed through the mouth or nose into the lungs and fluid is injected into a small part of the lung and then collected for examination. It is typically performed to diagnose lung disease) that is then observed in Cytology to show cysts typical for pneumocystis.

** For your info: *Pneumocystis jirovecii* was previously named *P. carinii .*

** Other organisms might be: *Histoplasma* and *Toxoplasma* in CNS, *Coccidioidomyces* “ Valley fever”, Kaposi’s sarcoma associated virus (*HHV8*).

- Small portion of HIV patients remain asymptomatic and doesn't have AIDS, these patients are called "long term non progressors" or "Elite controllers".

- You must know that progression to AIDS depend on both viral and host factors.

A Host factor indicating a defect in co-receptor CCR5 (CCR5- Δ 32 , meaning there is a deletion of 32 base pairs in CCR5 gene) , this co- receptor will be non-functional, and so HIV particles that **depend on this co-receptor for their entry** will simply NOT ENTER the cell and so will not be able to infect these cells having a deficient CCR5, and so these patients will have the infection Because the virus might utilize other co-receptors like CXCR4 but it'll slowly or might not progress to AIDS.

** Deficiency in CCR5 (like CCR5 Δ32 that produce a non-functional CCR5 protein) doesn't prevent the individual from being infected due to the ability of the virus to use OTHER Co-receptors to enter the cells which is due to "**Redundancy of immune system**". Further explanation?? Sure!

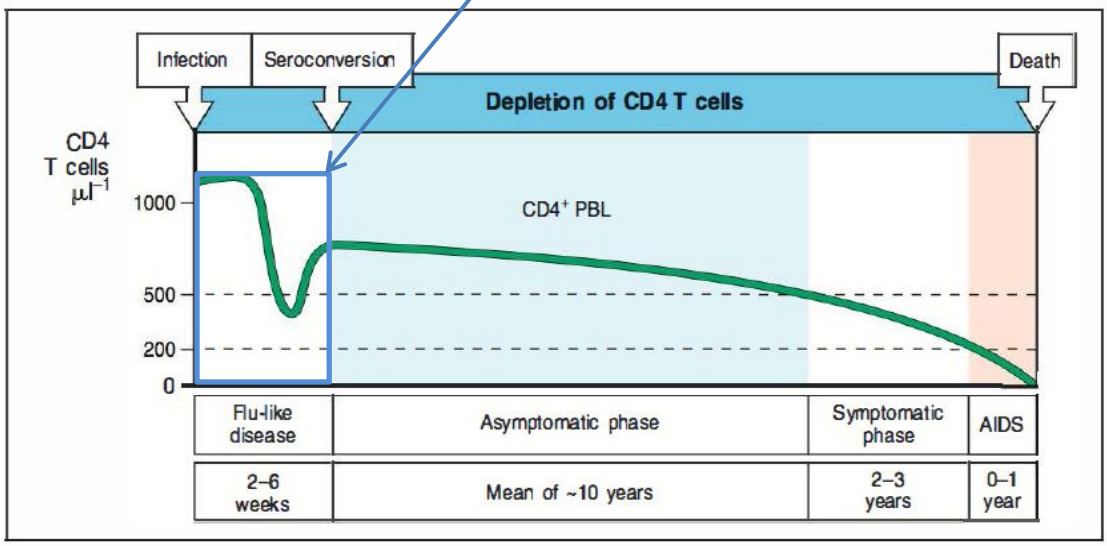
CCR5 is a protein that functions normally in the body as chemokine (**chemo**tactic cyto**kine**) receptor, and since we have a lot of receptors in immune system that act as chemokine receptors (families of CXC, CC, CX3C, XC), if a single type of a family (which is here CCR5) is defected, **No** clinical manifestations **due to this defect ALONE** will appear " in HIV infected or in normal non HIV infected people" because others will compensate- which is good. At the same time, what's bad is if HIV viruses encountered this defected Co receptor, they can use other Co-receptors (e.g. X4 viruses -if HIV- can use CXCR4 (also called X4) as the co-receptor, hence, will be capable of cellular entry and infection). This is what we call Redundancy "وفرة" of the immune system; meaning that we have many molecules doing THE SAME FUNCTION.

Quick RECAP: Immune system redundancy applies perfectly to chemokines as well as their receptors since there are **plenty of them exerting the same function** (advantage to the immune system), and so **No clinical manifestations** should be seen in case certain type got defected. BUT, this redundancy isn't seen for example when I have deficient Abs, as we'll notice that B cells will be affected and as a consequence an **IMMUNODEFICIENCY** will occur leaving the person susceptible mostly to encapsulated bacteria (Bacteria having a bacterial capsule made of polysaccharide; e.g. *Streptococcus pneumoniae, Neisseria, H. influenza*) in Respiratory tract.

- **Conclusions:** Take the clinical history; uncover the conditions affecting the immune system like infection, malnutrition, metabolic disorders if uncontrolled, and use of drugs.

Notes on HIV Case

1. Most important determinant for progression was thought to be CD4 cells count, but recently, the viral load (virus concentration in the blood as determined by quantitative PCR) at the viral set point has been shown to be a better determinant for progression to AIDS.
2. Important to remember that Gut Associated Lymphoid Tissue (GALT) is the most affected Sec.Lymph.Organ in Acute HIV phase.



3. Target cells (cells susceptible to be infected) are any cell that has CD4 "along with" CCR5 or CXCR4 as Co-Receptors.

Note: Please Read the following points -mentioned by the doctor- FAST; they only talk about modes of transmission.

4. In the case study, even though the husband was HIV infected and married since 2 years, his wife was HIV –ve, HOW could this be??!
   Risk of transmission of HIV through different transmission roots (heterosexual intercourse, needle injection and drug abusing, vertical transmission, ..) varies much.
   a. The possibility of infecting upon **one** heterosexual transmission is less than 1%.
   What are the risk factors that increase this percentage?? Viral load -and how high it is- which will reflect how many viruses we'll have in genital tract that'll be site of sexual contact, so not every sexual contact will result in HIV transmission. However, precautions should be taken into account as no one would want to take a chance no matter how low the probability of HIV acquisition is!

b. Upon needle stick injury (health care workers are exposed to get infected when they take blood samples from patients that may or may not know they're HIV infected), the estimated probability is 0.3%.

* Note: Such percentages are obtained from systematic reviews, by collecting all research papers that discussed prevalence of the disease by a certain transmission route.

hypothetical example: paper from UJ hospital that indicated 10 needle stick injuries from a person known to be HIV positive + paper form King Abdullah the 2nd Hospital also indicating 10 injuries, and so on, until we reach **1000** injuries, to see that only **3** people who got injured had a **sero-conversion** (meaning that they developed immunity and **Abs** against HIV **which were detected in their serum).** By doing calculations: 3/1000 ×100% = **0.3%**

** Note that: 0.3% and other percentages aren't exactly the actual exact percentages but they're an approximation reflecting the risk of transmission of a certain infection through a certain mode of transmission.

- For your info: Infectiousness of hepatitis C through needle stick injury = 3%

Infectiousness of hepatitis B through needle stick injury = 30%

Read ONLY

For sake of Exam: Such numbers won't come as they are but they'll come between confidence intervals (ex. 0.1% – 0.5% instead of just 0.3); **Dr.Malik noted the following**: "I do not like this kind of questions that depend on memorizing numbers, as the numbers are mere estimation of the actual figures. However, it is important to know a rough estimation of these figures".

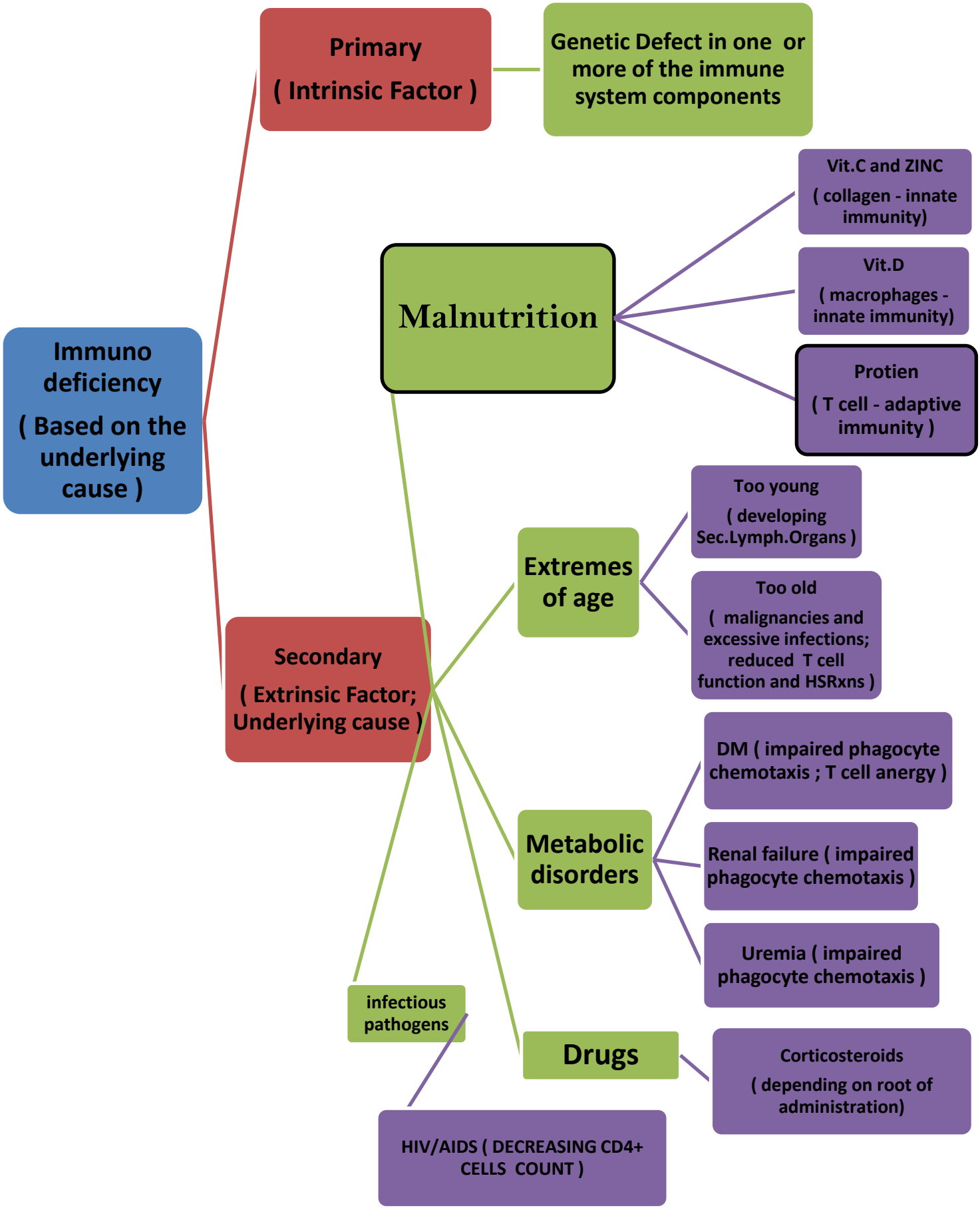
5. Modes of HIV transmission:
a. Blood "body fluids" as in transfusion of blood or its products.
b. Sexual transmission; whether hetero or homosexual.
c. Injection drug use.
d. Vertical transmission (mother to child) which may occur during intrauterine life, delivery (intrapartum), or postpartum through breastfeeding.

Highest risk of transmission of HIV- infection cases "this means how risky –not how common- this type of transmission is" comes from receiving non- screened blood (95%),

Then Vertical transmission from untreated mother (25%),

Then Homosexual transmission and injection drug use,

Then Heterosexual transmission.


Immuno deficiency
(Based on the underlying cause)
Primary
(Intrinsic Factor)
Genetic Defect in one or more of the immune system components
Secondary
(Extrinsic Factor; Underlying cause)
Malnutrition
Vit.C and ZINC
(collagen - innate immunity)
Vit.D
(macrophages - innate immunity)
Protien
(T cell - adaptive immunity)
Extremes of age
Too young
(developing Sec.Lymph.Organs)
Too old
(malignancies and excessive infections; reduced T cell function and HSRxns)
Metabolic disorders
DM (impaired phagocyte chemotaxis ; T cell anergy)
Renal failure (impaired phagocyte chemotaxis)
Uremia (impaired phagocyte chemotaxis)
Drugs
Corticosteroids
(depending on root of administration)
infectious pathogens
HIV/AIDS (DECREASING CD4+ CELLS COUNT)

Primary immunodeficiency

We mentioned previously that when we're suspicious that a certain person is immunodeficient, **recurrent** and **opportunistic** infections were our key words, but we should also consider a third factor, which is the **SEVERITY of common infections** in these patients.

* Common cold might pass us by without causing significant manifestations that could threaten our lives or disturb our daily routine that much, but in these immunodeficient patients, emergency rooms might be waiting!

- Primary immunodeficiency clinical signs:

1. Positive family history (inherited genetic defect).

2. Infections in multiple anatomic locations.

3. Increased frequency and severity of infections with age.

4. Recurrent serious infections with common pathogens.

5. Serious Infections with unusual organisms: We previously mentioned some of these organisms like *Candida* and *Pneumocystis jirovecii* (the most famous in HIV patients).

- Suppose that depending on a patient's signs and symptoms, we became very suspicious that he might be immunodeficient, **what's the work up that should be done to diagnose the patient** and to affirm his immunodeficient state??

Note: **Work up means what laboratory tests, radiologic investigations among other investigations should we do when a patient comes with a chief compliant (Chief رئيسية; compliant شكوى; chief compliant شكوى رئيسية) in order **to reach the correct Diagnosis**.

1) Clinical history: **The most important part of reaching the correct diagnosis** (more important than physical examination, radiology, lab tests); It's when you take patient's **chief complaint** (which is the answer to the question "**What brought you to the hospital**?"), ask about past and present history, write his apparent signs and note symptoms which he'll tell us about.
   It's Important to ask questions that'll enable you to exclude diseases and keep others to reach your differential diagnosis (Dx).

Ex.1 The patient has a cough.

You set in your mind a Dx list containing upper respiratory tract infections, lower respiratory tract infection, allergies, and so on; then by asking questions, you start limiting your choices until reaching a possibly true Dx.

Ex.2 A patient may come to ER with chest pain among other symptoms like nausea, heartburn, difficulty in breathing.

The differential diagnosis is the list of conditions which would be manifested with the same chief complaint (chest pain in this example). The list for chest pain includes acute coronary syndrome (MI and angina), pneumonia, gastroesophageal reflux disease, etc.

To reach the final diagnosis we should take a careful clinical history and do a physical exam, ECG, CXR (chest X-ray), lab tests (e.g. troponin level etc.)

** 70% of the real Dx can be reached by taking clinical history, the rest 30% are distributed on physical examination and lab tests.

2) Physical examination: mentioned previously; it's when you examine the patient's body to look for disease signs.

3) Lab tests:

a) **The first and most simple one is CBC** (complete blood count). What matters us in the case of immunodeficient patient is the count of WBCs, which should be LOW!
But even though, this isn't always true, WHY?? Remember that WBCs include neutrophils, basophils, eosinophils, monocytes, and lymphocytes. Neutrophils are elevated during bacterial infections (Neutrophilia) as a compensation in case of deficiency in lymphocytes, so this will reflect an overall elevated WBCs count, that's why we'll need **differential WBCs count** to see which subset of cells are low in number.

b) **Quantitative Immunoglobulins**. Used to test **humoral immunity** and so B cells activity; as there are many PIDs that affect B cells (Ex. Hyper IgM syndrome), so the best way to test B cell activity is by testing presence of its products which are Igs.
Blood concentration of IgG is the highest, followed by IgA and IgM, then IgD, lastly IgE.
****** Tested Igs in routine lab tests are IgG, IgM, and IgA.

c) **Reviewing previous culture results**. We here look for previous microbiologic cultures to see if there were any evidences for DOCUMENTED increase in frequency of infections or infection with unusual microorganisms.

d) **Titers for administered vaccines**. WHY? Here we also test humoral response by measuring serum concentration for certain Abs formed against vaccines' antigens.

Ex. Finding Abs against surface antigen of hepatitis B means there was a response against the antigen when hepatitis B vaccine was administered, and so the result will be +ve. If not found, titers will be –ve, meaning there is a problem in response to vaccine, meaning there is a problem in Ab production, and so problem in humoral immunity.

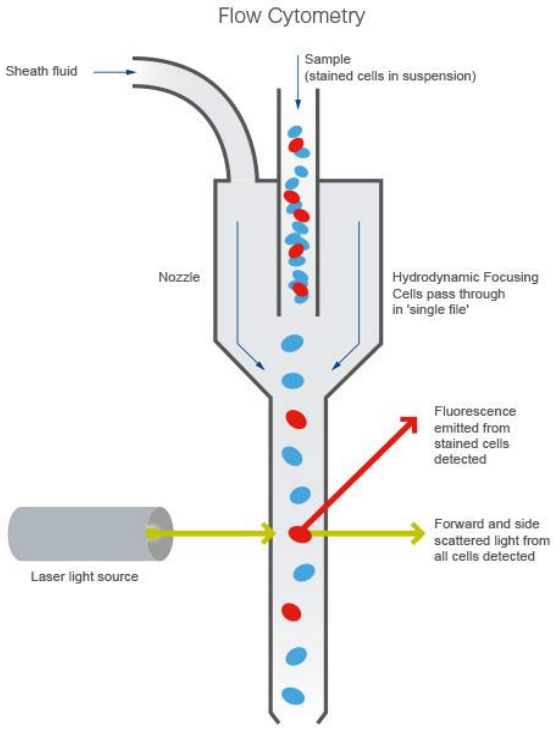
** Note that: Absence of Ab response to certain vaccines might be related to other factors so immune deficiency is not always the underlying condition.

e) Lymphocyte enumeration using FCM. Enumeration means counting; what we do here is counting Lymphocytes using Flow Cytometry (FCM).

** Generally, Cells in a fluid or suspension are tested using 2 ways:

1. Direct microscopic examination by placing the sample on a slide and count under microscope.

2. **By FCM** (The figure beside illustrates the mechanism).



f) Skin testing. An indirect measure to cellular immunity (T cells); like tuberculin test.

Handout 10: “In this test we inject the purified tuberculin under the skin, and check the area in a few days. If the patient has active TB or have been infected with it in the past, his immune system will include memory, Th1-type cells that were made in response to the infection. After the injection, dendritic cells present beneath the skin take up the protein and present tuberculin peptides to memory cells – and they are reactivated. These Th cells secrete IFN-γ and TNF – Th1-type cytokines that activate resident tissue macrophages near the site of injection, and help recruit neutrophils and additional macrophages to the area. The result is a local inflammatory reaction with redness and swelling: the signal that TB test is positive. Of course, the reasons we have to wait several days for the test to “develop” are that memory helper T cells must be reactivated, proliferate, and produce those all-important cytokines that orchestrate the inflammatory reaction.

On the other hand, if the patient **has never been exposed to the tuberculosis mycobacterium**, he will have no memory helper T cells to reactivate. Without the cytokines supplied by activated Th cells, there will be no inflammatory reaction to the tuberculin protein, and the skin test will be **negative**.”

g) CH50, C3 & C4.

Measuring the complement components concentration, most commonly C3 and C4, are used to determine whether deficiencies or abnormalities in the complement system are causing, or contributing to, a person's disease or condition.

✓ CH50 is measuring the 50% Hemolytic Complement Activity (CH50); it's used to look at the integrity of the entire complement pathway from C1 to C9; any deficiency in any complement component will be reflected in abnormal CH50 result.

- How is this test done??

The CH50 tests the functional capability of serum complement components of the **classical** pathway to lyse sheep red blood cells (SRBCs). A sample of the patient's blood is brought to be tested (Because complement proteins are very fragile and should be preserved, blood sample tube should be put **in pack filled with ice** and transported **immediately** to the laboratory. You will see that when you start your clinical years.), we place sheep RBCs sensitized by Rabbit Abs (these Abs are anti-sheep red blood cell antibody), we add then patient's serum sample, **If Hemolysis to these SRBCs was observed**, then we can tell that classical pathway is intact, but if not (-ve result), we'll have to suspect the deficiency in at least single type of complement components.

✓ C3 and C4 are ordered because mostly they have the highest concentration among other components.

** For your info: Most common complement component to be deficient is C2.

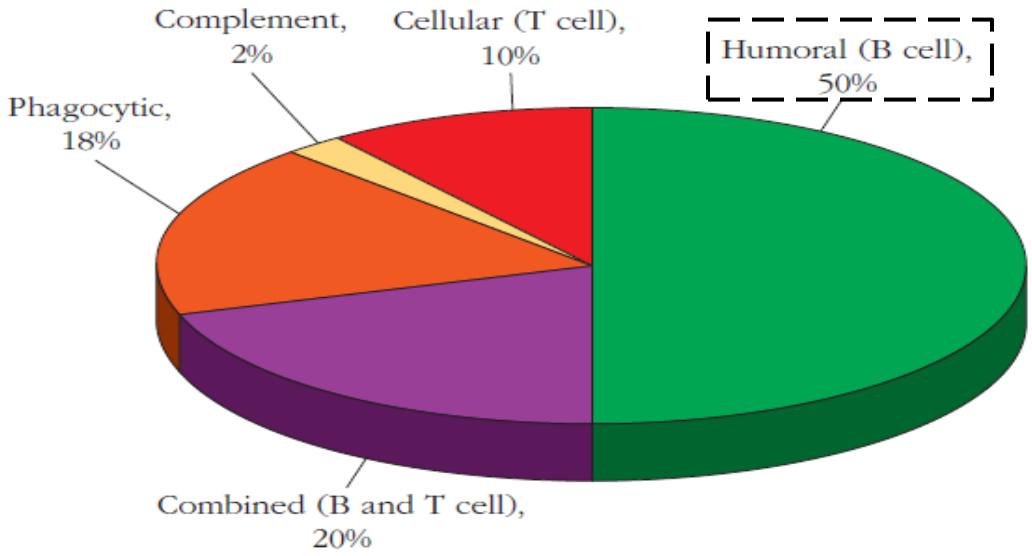
h) Phagocyte studies. Used to test the activity of Neutrophils and macrophages; the most famous test to be ordered is **Nitro blue tetrazolium test (NBT)** which is one of the tests we discussed when we talked about **Chronic granulomatous disease** in the first case study .

Handout 4: "Nitro blue tetrazolium dye (NBT) is a pale yellow dye used to detect if there is H2O2. The dye is mixed with blood from the patient and if H2O2 is present it will be reduced and its color becomes purple". So in CGD since there's NADPH oxidase deficiency in phagocytes, no ROSs will be formed so cells color will stay the same.

i) Enzyme studies. Some enzymes when deficient it'll cause Primary immunodeficiency, like Activation-induced Cytidine deaminase deficiency (AID deficiency) which we took as 2nd case study, and it was the cause of Hyper IgM syndrome.

PIDs – excluding selective IgA deficiency - are *RARE* to be encountered throughout our medical career, except in pediatrics, immunology or allergy departments; Also, most of them result from Monogenic gene deficiency "a single gene is only defected".

MOST COMMON component of immune system to be a PID target is **humoral immunity**; genetic defects targeting B cells activity and causing a primary immunodeficiency are very common; and the most common PID targeting B cells is **Selective IgA deficiency** (**which is also the most common of overall PIDs).**



Distribution of Primary immunodeficiencies by type.

** PID can involve either innate processes (Phagocytosis, complement, or other defects), or the adaptive immune response (humoral, Cellular, or both like SCID). Of these categories, **ADAPTIVE immune disruptions are the most common,** with Ab defects making up the largest portion of these.

** Severity of the primary immune deficiency itself ranges from mild, to moderate, to severe, to even fatal!

This depends on level of immune deficiency; If PID is in STEM cells, it would be severe to fatal, but if it was manifested in more mature cells, it would be milder in course.

Ex. In most Selective Immunoglobulin deficiencies, like in Selective IgA deficiency, the patient might reach adulthood (his 20s or 30s) without knowing that he/she has this disorder.

Primary Immunodeficiency Disorders:Selected Examples

We'll discuss selected examples of PID disorders, highlighting the main required things:

1. Names of PID disorders

2. Which component of immune system is deficient (innate component, humoral immunity, cellular immunity)?

3. Underlying genetic cause

4. What kind of infections (and opportunistic pathogens) will take place?

** A table will be at the end summarizing all of them.

1. Defects of the B-Cell System

A. X-Linked Bruton's Agammaglobulinemia (XLA)

Bruton's agammaglobulinemia was first described in 1952; it was named after the pediatrician who described it (Dr.Ogden Carr Bruton). It is an X chromosome-linked, **so it affects males almost exclusively (male predominance)**, yet, the chance of females being affected is linked to carrier state of their mother **plus** father being affected. Patients with XLA **lack circulating mature B cells (CD19+),** and exhibit a deficiency of immunoglobulins of all classes (Humoral immunity affected).

Remember: When we talked about severity of PID disorder (page 18), we said that if the defect was in early stages of lymphocyte development, it would be more severe (because many cells and cellular components will be defected) than if it was in late stages or after the cell is fully mature, so we should guess that XLA is of the low-severity disorders.

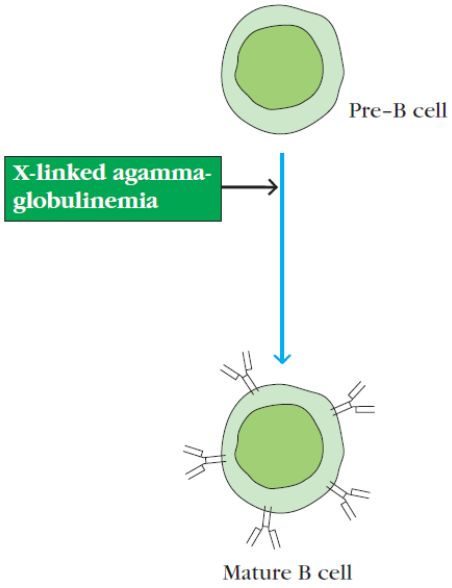
XLA is caused by arrested differentiation at the pre-B cell stage, which will lead to a complete absence of CD19+ B cells and plasma cells. The underlying genetic mechanism is a deficiency of an enzyme called Bruton tyrosine kinase (Btk) in B-cell progenitor cells. Lack of the enzyme apparently causes a failure of VH (variable domain of the heavy chain) gene rearrangement.

The patients also lack the plasma cells in their lymphoid tissues, but they do have pre-B cells in their bone marrow (level of affected B cells is in-between pre B cells and plasma cells). Because of the lack of B cells, the tonsils and adenoids are small or entirely absent (because most of the

bulk of tonsils and lymph nodes is made up of B-lymphocytes), and lymph nodes lack normal germinal centers (where mature B cells proliferate, and differentiate through somatic hypermutation and class switching during a normal immune response to an infection).

T cells are normal in number and function.

FOR YOUR INFO: XLA is a complete absence of Abs while Hypogammaglobulinemia (discussed later in this summary; common variable ID) is another PID disorder referring to not having enough Abs (Abs number is lower than normal range).



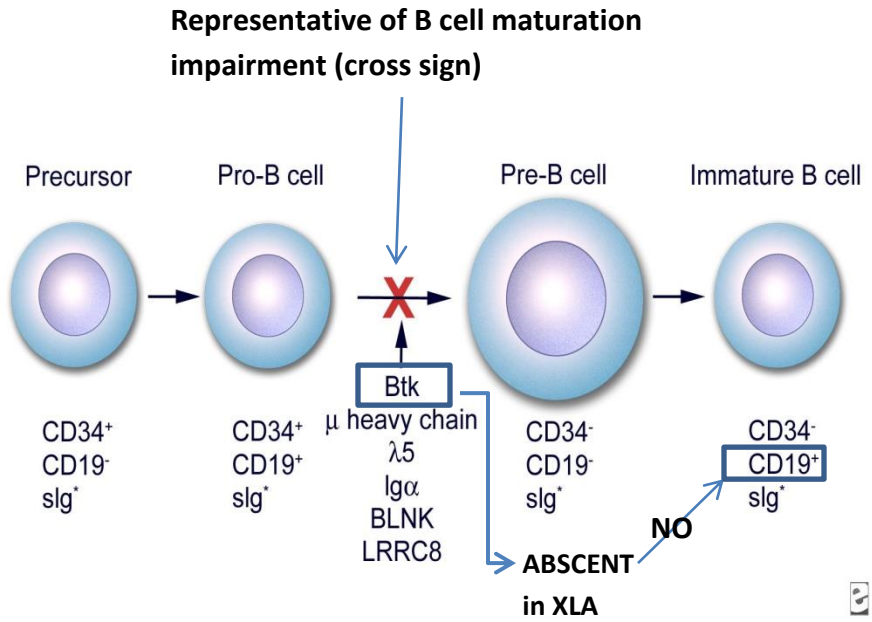


Figure 1: inhibition of B cell maturation

Figure 2: Normal Job of BTK in B cell maturation

Since humoral immunity defends at its best level against encapsulated bacterial pathogens that mostly attack sinuses and pulmonary part of respiratory tract, **Patients most commonly develop sino-pulmonary infections caused by encapsulated organisms** such as *Streptococci, meningococci (Nisseria meningitidis),* and *Haemophilus influenzae*. Other infections seen include bacterial otitis media, bronchitis, pneumonia and meningitis.

Please note for the sake of exam: You'll have to link disorders with their clinical manifestations and infections that accompany the disorder since exam Qs will be indirect.

E.g. a 2 year old child came to you WITH RECCURENT SINUSITIS by *Nisseria meningitides* (or mostly it'll be *Strep.pneumonia*), what's the most likely underlying cause of this immunodefiency? **Humoral component deficiency**.

How are these patients managed?? The use of antibiotics and replacement therapy by IVIG (Intravenous immunoglobulin) can make X-linked agammaglobulinemia a quite manageable disorder.

B. Selective IgA Deficiency

Remember where did we hear about it? What was special about it?? Refer to page5, sheet1 and page 13, sheet 2.

Selective IgA deficiency is the most common congenital immunodeficiency; occurring in about 1 in 300 to 1 in 1500 person globally, meaning that it's the most common PID disorder. Also, we mentioned that it's mostly ASYMPTOMATIC which means that the person can reach adulthood and still not know he has it, and may be discovered incidentally upon a visit to the hospital for another reason.

Individuals with selective IgA deficiency typically exhibit normal levels of other antibody isotypes; they'll live a normal life span, but their life would be troubled only by a greater-than-normal susceptibility to infections of the respiratory and genitourinary tracts which are the primary sites of IgA secretion.

To remember… Handout 5+6: "IgA is the Ab that protects mucosal surfaces; IgA molecule looks like 2 IgG clipped together. This clip is important for the IgA function; it allows its movement through intestinal wall and protects it from the intestinal acidity and enzymes.

In the intestinal lumen IgA coat the invading pathogen preventing it from attacking the intestinal cells. Because IgA has four Fab regions it can attach to bacteria and produce a large enough particle to pass through mucus or stool. IgA is secreted in mothers' milk and taken by the baby during breast feeding; they coat the baby's intestine and protect it. IgA cannot fix complement, which is good because if they do our mucosal membranes will be always attacked by complement in response to bacteria that is always there in the mucosal membranes."

Although the genetic defect has not been established, it is hypothesized that lack of IgA is caused by impaired differentiation of lymphocytes to become IgA-producing plasma cells, meaning that impaired class switching from IgM to IgA might be involved.

C. Common Variable Immunodeficiencies (CVIDs)

CVIDs encompass the largest group of symptomatic primary immunodeficiency disorders, with an estimated incidence between 1 in 10,000 and 1 in 50,000. Since it's called "deficiencie**s**" we would expect that it's a heterogeneous group of disorders that lie under the name "common variable ID", so you won't find a single underlying cause of CVID but rather multiple genetic defects that are **diagnosed by exclusion.**

Please, what does this suppose to mean??

If we tested patients immunity, and we observed a deficiency in his humoral immunity

We place a list with certain possible diagnoses

a. X- linked agamma globulinemia: excluded if Btk was normal.

b. Selective IgA deficiency: excluded if not only IgA was deficient.

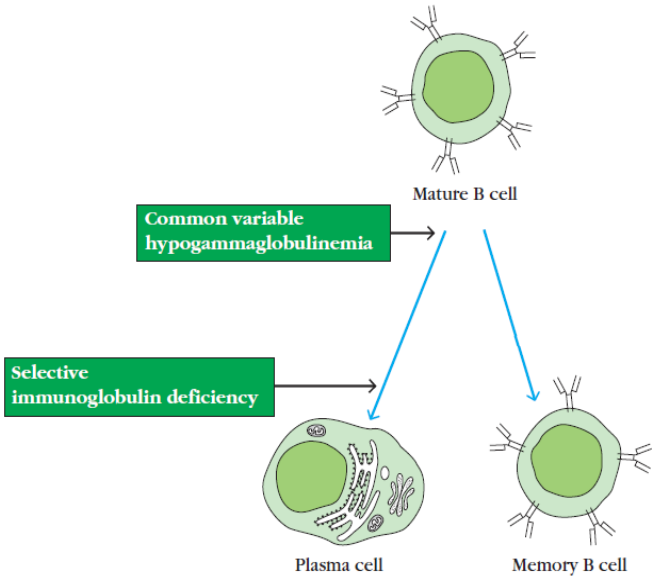


Figure 3: CVID

c. Common variable immunodeficiency: left in the list; affirmed if it also fit **diagnostic criteria** of having VERY LOW IgG **plus** having **either** IgM or IgA in Low levels.

Patients usually begin to have symptoms in their 20s and 30s (most common age of CVID diagnosis), but age at onset ranges from 7 to 70 years of age.

As we mentioned a moment ago, there's a diagnostic criteria for CVID; Also, falling into this criteria is the patient's age upon diagnosis with CVID; the patient **must not be less than 4 years old**, why? Because at age of infancy and early childhood, we have other PID disorders that'll cause same manifestations.

What are these OTHER PID disorders??

E.g. **Transient** hypogammaglobulinemia of infancy.

This disorder is actually physiological. Neonates dependency of on their mothers IgGs, and since these Abs have a half-life and soon they'll reduce in number, so these babies will have to start depending on themselves to build their humoral immunity response once they encounter infections since their immune system is not well developed yet. Nevertheless, some babies when they encounter infections, they'll develop their humoral immunity **slowly** thus will be diagnosed with Transient hypogammaglobulinemia of infancy.

Respiratory tract infection by common bacterial pathogens is the most common symptom.

VERY IMPORTANT: Always always remember that once you see that humoral immunity is affected, directly think of **ENCAPSULATED bacteria** and their MAIN TARGET which is **respiratory tract**.

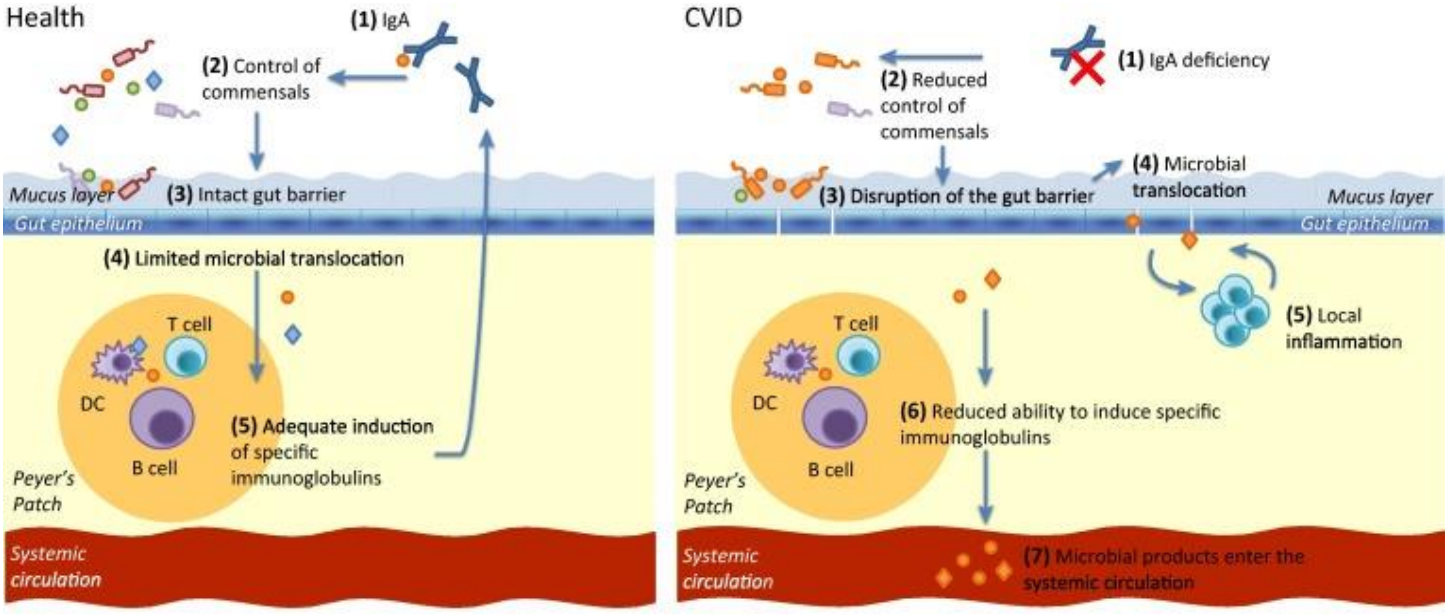


Figure 4: CVID postulated pathogenesis

2. Defects of the T-Cell or T-cell/B-cell Systems

A. DiGeorge Anomaly

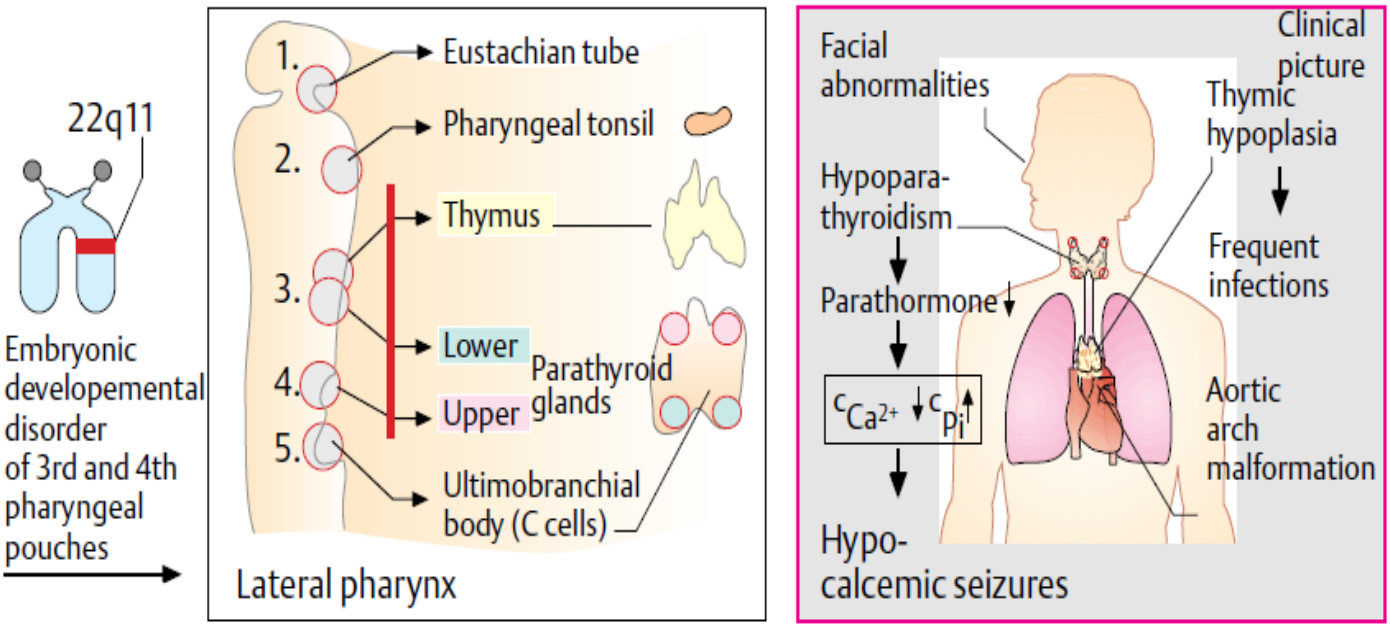
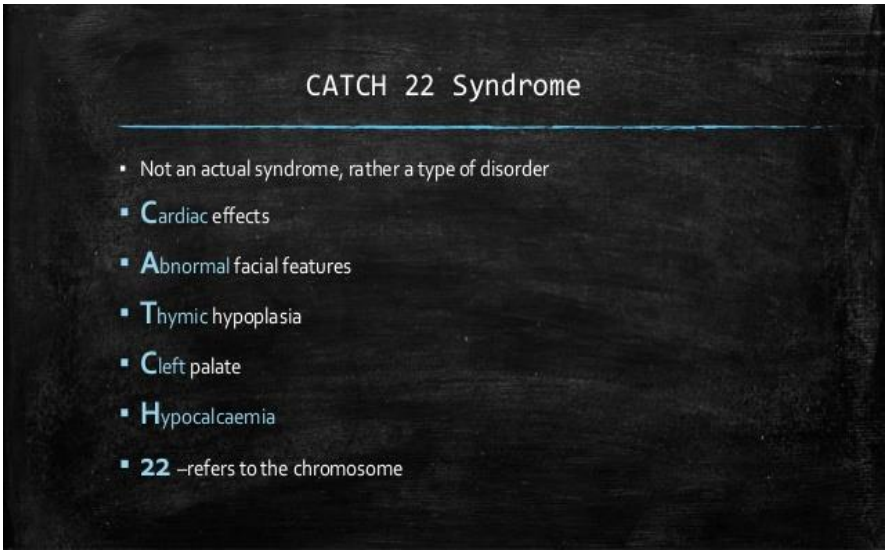


Figure 5: DiGeorge Syndrome

"Developmental abnormality of the third and fourth pharyngeal pouches that affects thymic development".



Specifically, most patients show a deletion in chromosome 22, region q11 (recall: q is the long arm; p (petit) is the short arm of the chromosome)

"Catch 22" describes the most famous clinical outcomes in DiGeorge patients.

The severity and extent of the developmental defect can be quite variable; The MOST COMMON clinical presentation (how would they look like when they come to the hospital?) in infants with DiGeorge syndrome is **TETANY**.

Many patients with a partial DiGeorge anomaly have only a minimal thymic defect, and are thus near normal immune function. However, about 20% of children with a defect of the third and fourth pharyngeal pouches have a severe and persistent decrease in **T-cell** numbers due to thymic atrophy; cardiac defects are also expected to be seen; these children tend to have severe, recurrent viral and fungal infections (Recall: B cells were related to bacterial infections MOSTLY in respiratory tract). HIV which is related to 2ndary ID and cause CD4+ **T cells** depletion was also related as you remember with CMV (virus) and *Pneumocystis* (fungus) infections.

Severely affected children usually present in the neonatal period with tetany (caused by hypocalcemia resulting from hypoparathyroidism) or manifestations of cardiac defects.

B. Severe combined immunodeficiencies (SCID)

The most serious of the congenital immune deficiencies is severe combined immunodeficiency (SCID). It is a group of related diseases that all affect T- and B-cell function but with differing causes, this means that both humoral and cellular adaptive immunity are affected. X-linked SCID is the most common form of the disease, accounting for approximately 50% of the cases in the US, the rest are autosomal.

The abnormal gene involved in X-linked SCID codes for a protein chain called the **common gamma chain**, which is common to **receptors** for interleukins- 2, 4, 7, 9, 15, and 21. The gene is referred to as the IL2RG gene and is located on the X chromosome. Normal signaling cannot occur in cells with defective receptors, thus halting (ceasing, arresting; إيقاف،قطع) natural maturation.

Although this chain was first identified as a part of the IL-2 receptor, impaired IL-7 signaling is likely the source of both T-and B-cell developmental defects, while lack of IL-15 signaling is believed to account for the block to NK cells.

Handout 11; **READ ONLY**: "Defects in the receptors for IL-2 (which was first identified to have common gamma chain), IL-4, IL-9, IL-15, and IL-21 **do not seem relevant to the early block in T-cell development seen in X -linked SCID**, because all of them activate mature lymphocytes or other effector cells. However, the receptor for **IL-7** is thought to be important for pre-T-cell growth. A loss of IL-7 receptor function is therefore likely to be the most important loss of function responsible for X-linked SCID."

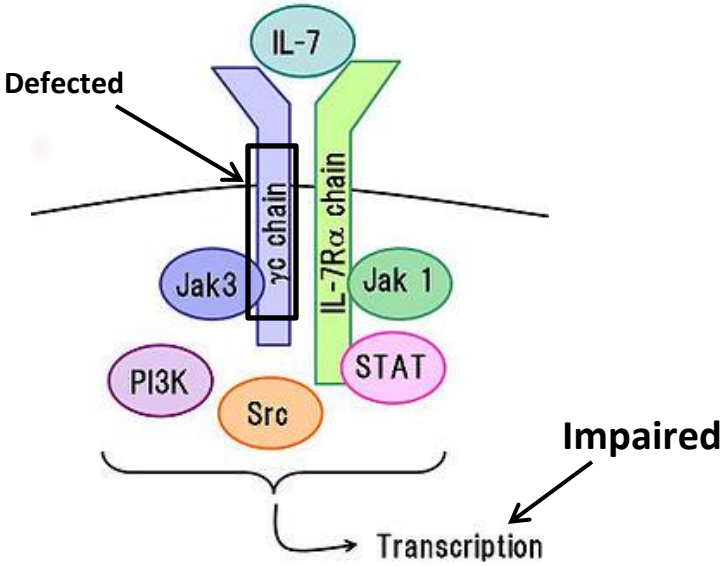


Figure 6: IL-7 receptor and cell signaling

Autosomal defects can be many:

1. A JAK3 deficiency may be found without the common gamma chain deletion. This results in an autosomal recessive form of SCID, affecting both males and females.
2. A single defect involving RAGs: Defects in the pathways involved in the recombination events that produce immunoglobulin and T-cell receptors highlight the importance of early signaling through these receptors for lymphocyte survival. Mutations in the recombinase activating genes (RAG1 and RAG2) and genes encoding proteins involved in the DNA excision-repair pathways employed during gene rearrangement can also lead to SCID.
3. Adenosine deaminase (ADA) deficiency; another relatively common defect resulting in SCID. Adenosine deaminase catalyzes conversion of adenosine or deoxyadenosine to inosine or deoxyinosine, respectively. Its deficiency results in the intracellular accumulation of toxic adenosine metabolites, which interferes with purine metabolism

and DNA synthesis. This housekeeping enzyme " housekeeping is like being essential to exist in each house " is found in all cells in the body, so these toxic compounds also produce neurologic and metabolic symptoms, including deafness صمم, behavioral problems, and liver damage.

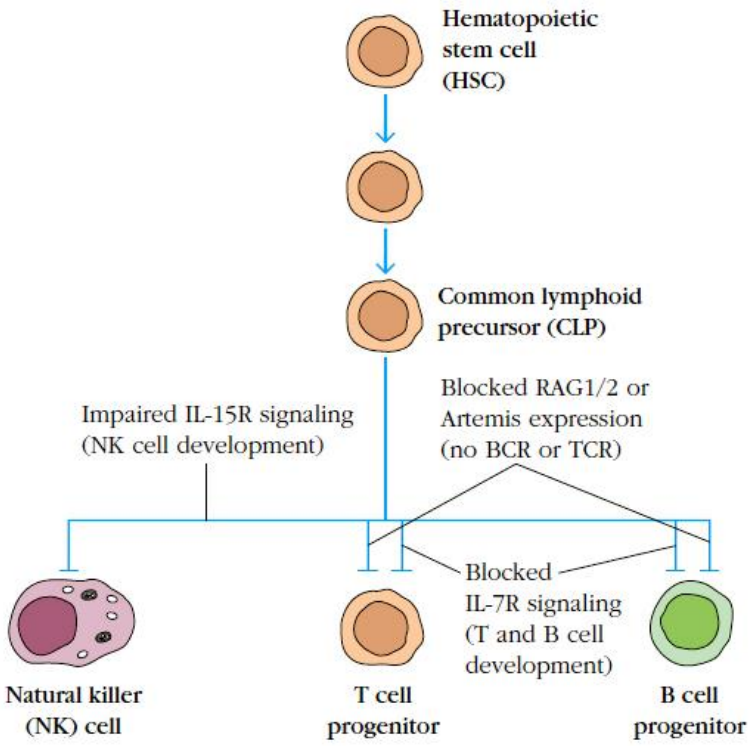


Figure 7: SCID types and involved immune system components

C. Hyper IgM Syndrome

An inherited deficiency in CD40 ligand (CD40L or CD154) leads to impaired communication between T cells and APCs (B cells, Dendritic cells, Macrophages), highlighting the role of this surface molecule in this costimulatory process. In this X-linked disorder, TH cells fail to express functional CD40L on their plasma membrane, which typically interacts with the CD40 molecule present on B cells and dendritic cells.

The B-cell response to T-independent antigens (antigens that don't need co- stimulation of Th cells to activate B cells), however, is unaffected, accounting for the presence of IgM antibodies in these patients, which range from normal to high levels and give the disorder its common name, hyper IgM syndrome.

Remember in Handout 5+6: "B cells can change their class by changing their Fc region. They also change their binding capacity (affinity) by hyper mutation of the fab region .These two processes need T helper signaling, that's why B cells which are co-stimulated without T helper (T helper

independent stimulation) don't undergo these change (they don't have class switching or hypermutation)." That's why TH cell independent activation of B cells upon encountering T-cell independent Ags **will NEVER initiate class switching to Ab other than IgM**.

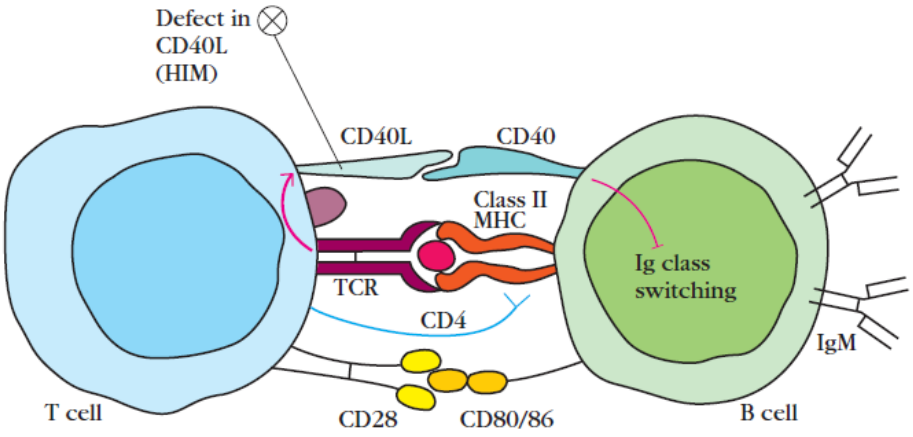


Figure 8: X-Linked hyper IgM syndrome

3. Defects of Neutrophil Function – innate immunity

A. Chronic Granulomatous Disease (CGD)

CGD is caused by an inherited defect in the NADPH oxidase enzyme complex (also called phox: **ph**agocyte **ox**idase), present in a variety of cells including phagocytes. The NADPH oxidase enzyme **complex** consists of two membrane-spanning subunits, gp91phox and p22phox as well as three cytosolic components p47phox, p67phox, and p40phox. Approximately, **66%** (2 thirds) of all CGD cases result from mutations within the **X-linked** gp91phox gene (one of membrane spanning subunits), followed by the autosomal recessive forms of CGD, with defects in the gene coding for p47phox (one of cytosolic components), accounting for 33% (one third) of all CGD cases.

NADPH oxidase is required for the respiratory burst and has a critical role in microbial killing. It reduces molecular oxygen to superoxide, which subsequently reacts to form reactive oxygen species (ROS) such as hydrogen peroxide, hypochlorous acid, and hydroxyl radicals. Patients are particularly susceptible to fungal infection, typically from *Aspergillus* species, but also catalase positive bacteria including *Staphylococcus aureus*, *Serratia marcescens* and *Burkholderia cepacia*. Most patients present with infections, typically lymph node abscesses, but also recurrent respiratory infection, deep-seated abscesses and septicaemia.

Making the diagnosis of CGD is not technically difficult, and historically is based on the use of the "gold standard" nitroblue tetrazolium (NBT) assay (refer to page 17)

Normal non-immunodeficient people (in Fig.9 referred to as control) will have positive results because they have active NADPH Oxidase so the color will turn into purple and they'll have purple deposits inside their cells, while CGD patient cells will remain the same.

A Recent assay (test; فحص) is flow cytometry based on the reduction of dihydrorhodamine-123 (DHR) by phorbal myristate acetate stimulated phagocytic cells.

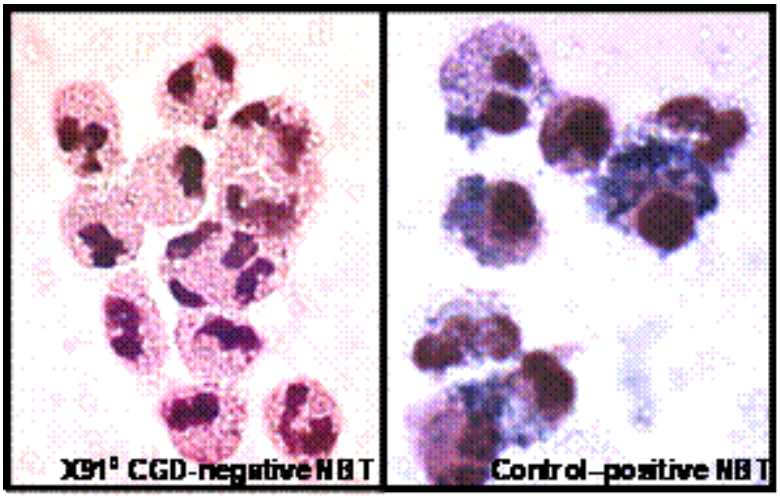


Figure 9: Nitroblue tetrazolium assay

B. Leukocyte Adhesion Deficiency

Leukocyte adhesion deficiency (LAD) syndromes are rare genetic immunodeficiency disorders that are caused by defects in adhesion and signaling of leukocytes and platelets. Defects include:

(1) Absent or reduced expression of β2 integrins (which is a critical subset of integrins that are restricted to leukocytes).

(2) Mutations resulting in impaired fucosylation (the process of adding fucose sugar units to a molecule which is a type of glycosylation) of ligands that are recognized by selectins and mediate leukocyte adhesion and signaling.

(3) Impaired inside-out signaling of β1, β2, and β3 integrins, resulting in defective leukocyte adhesion and signaling and a Glanzmann-like bleeding tendency (rare genetic platelet disorder in which the platelets have qualitative or quantitative deficiencies of the fibrinogen receptor that causes bleeding in many sites).

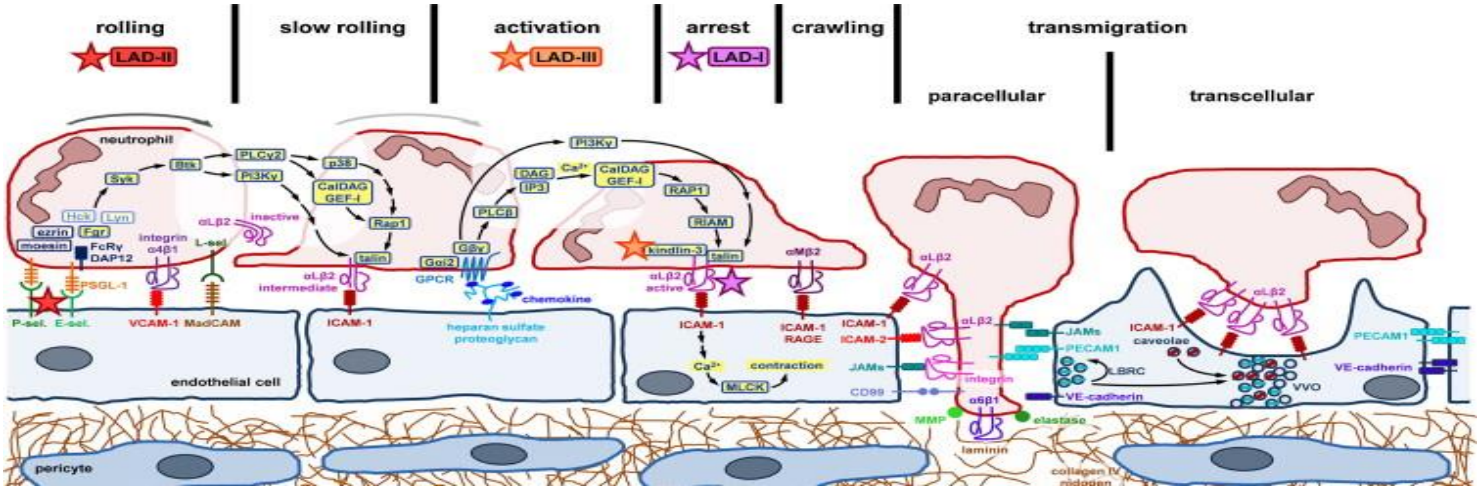


Figure 10: Neutrophil Recruitment stages

4. Complement Deficiencies – innate immunity

Deficiencies in the early complement components, C1q, 4, and 2, are usually associated with a lupus-like syndrome. Deficiency of C2 is believed to be the most common complement component deficiency (refer to page 17) A C3 deficiency may also have a lupus-like clinical presentation but is more likely to involve recurrent encapsulated organism infection. Deficiencies of the late components of complement (MAC: C5 through C9) are often associated with recurrent *Neisseria* infections. A deficiency of C1 esterase inhibitor has been found in patients with hereditary angioedema. Most complement deficiencies appear to be inherited in an autosomal recessive manner.

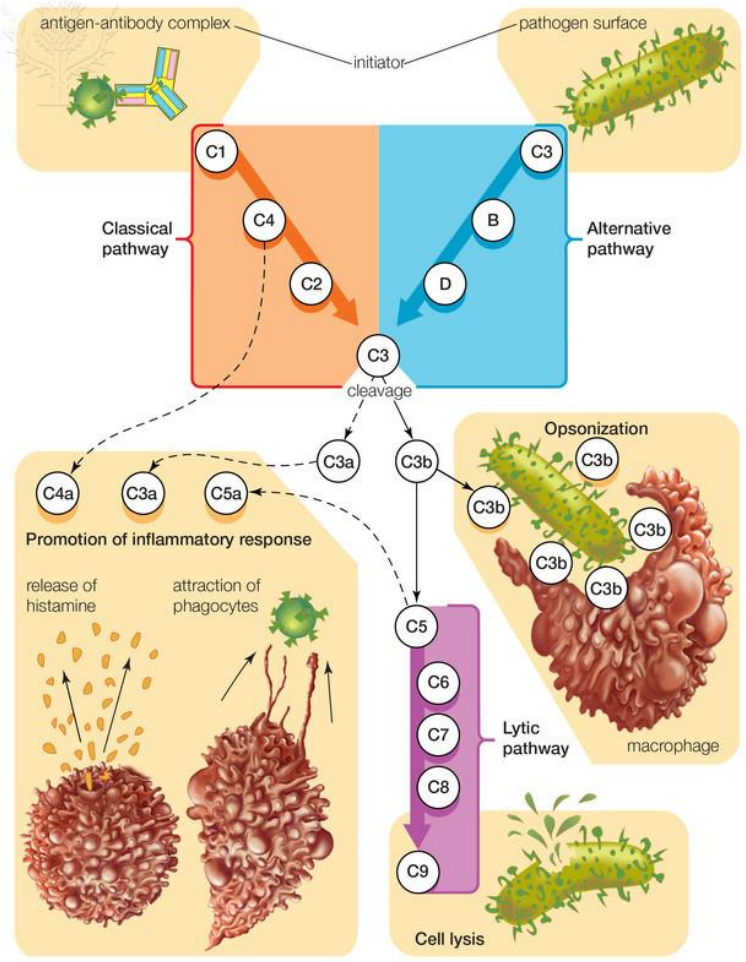


Figure 11: Complement system roles in immunity

By this we finally can say that we finished Immune deficiency material. Following is a table that summarizes what is mostly required from you in this part, plus after it is Test- your-self questions.

Primary Immune deficiency name	Affected immune system component	Genetic defect	Infections taking place
X-Linked Bruton's Agammaglobulinemia	B cells (humoral immunity)	Bruton tyrosine kinase (Btk) in B-cell progenitor cells	Sino-pulmonary infections caused by encapsulated organisms (Bacteria)
Selective IgA Deficiency	B cells (humoral immunity)	the genetic defect has not been established, it is hypothesized that lack of IgA is caused by impaired differentiation of lymphocytes to become IgA-producing plasma cells.	Susceptibility to infections of the respiratory and genitourinary tracts which are the primary sites of IgA secretion.

Common Variable Immunodeficiencies (CVIDs)	B cells (humoral immunity)	multiple genetic defects	Respiratory tract infection by common bacterial pathogens is the most common symptom.
DiGeorge Anomaly	Defects of the T-Cell System (cellular immunity)	deletion in chromosome 22, region q11	severe, recurrent viral and fungal infections
Severe combined immunodeficiencies (SCID)	Defects of the T-Cell/B-Cell Systems	**X-linked** : The abnormal gene coding for a protein chain called the common gamma chain (IL2RG gene), which is common to receptors for interleukins- 2, 4, **7**, 9, 15, and 21.	*Pneumocystis*, *Candida*, viruses
		Autosomal: 1. JAK3 deficiency may be found without the common gamma chain deletion (Autosomal recessive), 2.Mutations in the recombinase activating genes (RAG1 and RAG2) and genes encoding proteins involved in the DNA excision-repair pathways employed during gene rearrangement. **** Please refer to the original page for these points.**	*Pneumocystis*, *Candida*, viruses
Severe combined immunodeficiencies (SCID) … Cont.	Defects of the T-Cell/B-Cell Systems + other cells	**Autosomal:** Adenosine deaminase (ADA) deficiency	The intracellular accumulation of toxic adenosine metabolites, which interfere with purine metabolism and DNA synthesis. Also, they produce neurologic and metabolic symptoms, including deafness, behavioral problems, and liver damage.

Hyper IgM Syndrome	Defects of the T-Cell/B-Cell Systems	X-Linked: inherited deficiency in CD40 ligand (CD40L or CD154)	*Pneumocystis*, viruses
Chronic Granulomatous Disease (CGD)	Defects of Neutrophil Function (innate immunity)	an inherited defect in the NADPH oxidase enzyme complex	Particularly susceptible to fungal infection, typically from Aspergillus species, but also catalase positive bacteria including Staphylococcus aureus, Serratia marcescens and Burkholderia cepacia.
Leukocyte Adhesion Deficiency	Defects of Neutrophil Function (innate immunity)	(1)Defects include absent or reduced expression of β2 integrins (2) Mutations resulting in impaired fucosylation of ligands that are recognized by selectins and mediate leukocyte adhesion and signaling, (3) Impaired inside-out signaling of β1, β2, and β3 integrins, resulting in defective leukocyte adhesion and signaling and a Glanzmann-like bleeding tendency.	Bacterial infections
Complement Deficiencies	Innate immunity	Early and late components could be deficient (C2 as most common)	Deficiencies of the later components of complement (MAC: C5 through C9) are often associated with recurrent Neisseria infections

Test your self

**** These are some questions wrote in multiple ways to train you on how to be able to interpret info from different Qs given to you! Best wishes :D**

1. Which of the following combinations is right regarding immune deficiency disorder and **corresponding genetic defect**?
   a. HIV …. CD4 cell deficiency
   b. SCID… 22q11.2 deletion
   c. DiGeorge … Btk enzyme deficiency
   d. CGD … IL-7 receptor common gamma chain deficiency
   e. Hyper IgM syndrome … deficiency in CD40L gene
2. : 4-year-old baby came to the hospital with his mother; upon taking medical history he was found to have recurrent bacterial infections with staph. Aureus. Nitroblue tertrazolium test was Negative. Choose the correct involved immune system component:
   a. B cell system
   b. T-cell + B cell system
   c. Innate immunity – complement system
   d. Innate system – phagocytes
   e. T cell system
3. Upon immunophenotyping of cells of a patient suspected to be immune deficient, CD4+ cells were found to be very low; the patient was then diagnosed with HIV. If this patient was in a poor country and couldn't afford antiretroviral therapy, which infectious pathogens would complicate his case?
   a. Pneumocystis jirovecii
   b. Histoplasma
   c. Coccidioidomycosis "valley fever"
   d. Candida
   e. All of the above.
4. Upon a trip to the South Pole, a family took with them food needed to make the journey as amusing as possible. 2 days after the ship started sailing, a storm hit the ship and almost all their food was lost and for almost 8 days they were

living only on mashed potato بطاطا مهروسة; the mother noticed that her and her son's skin started to get weaker. Choose the correct statement:

a. Taking supplementary Vitmain D would reduce the problem
b. Taking supplementary Vitmain C would reduce the problem
c. Taking supplementary Zinc would reduce the problem
d. Nothing can reduce their problem.
e. b+c

5. A 50 year old male with clinical history of prostate cancer and Diabetes with A1C of 12 (very high) came to your clinic with dyspnea as chief compliant. After doing the work up needed, he was diagnosed with TB. After knowing that he took TB vaccine (BCG) and DPT vaccine when he was young, which of the following **will not be found** in this patient?
   a. IgGs for recent diphtheria infection
   b. –ve delayed hypersensitivity (HSRxn type 4)
   c. –ve mitogen test
   d. No response from neutrophils to chemotactic agents
   e. None of the above
6. A 25 year old HIV patient was diagnosed 3 weeks ago with HIV. His CD4+ cells count was 800 (Hint: still within normal range). Upon immunophenotyping, his CCR5 levels where very low while CD4 and CXCR4 were normal, choose the right statement:
   a. This HIV patient will never progress to AIDS stage.
   b. CCR5 low levels are expected to be due to a mutation in CCR5 gene.
   c. The most common lymphoid tissue to be affected at this stage of the disease is the GALT.
   d. At this stage , this patient is prone to be infected by Pneumocystis jirovecii
   e. a+d

DONE at last :D

Congrats brave future Doctor!!

Answers : 1e, 2d, 3e, 4e, 5a, 6c

Please if you found anything that needs enhancement don't hesitate! Generously remember me in your prayers … Wishing you the best in your Make-up ♥, and now leaving you with this Holy Hadith…

قال النبي - ﷺ - : يقول الله تعالى : (أنا عند ظن عبدي بي ، وأنا معه إذا ذكرني، فإن ذكرني في نفسه ذكرته في نفسي ...)