University of Basrah
Al-Zahraa Medical College

Ministry of higher Education
and Scientific Research

Academic year

3rd year S6

Module name

Integrative

Defense breakdown and Bone marrow failure

Session: 6

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Learning Objectives:

1-Describe immunodeficiency.
2-Explain the parts of the immune system that might be affected by changes leading to immunodeficiency .
3-The range of congenital and acquired immunodeficiency syndromes
4-Appreciate the rare, but important congenital immune deficiencies .
5- Describe the full range of acquired immune deficiencies, including HIV .
6- Explain why opportunistic infections develop in the immune deficient host, and the consequences for patient management .
7- Describe common Iatrogenic immune deficiencies .

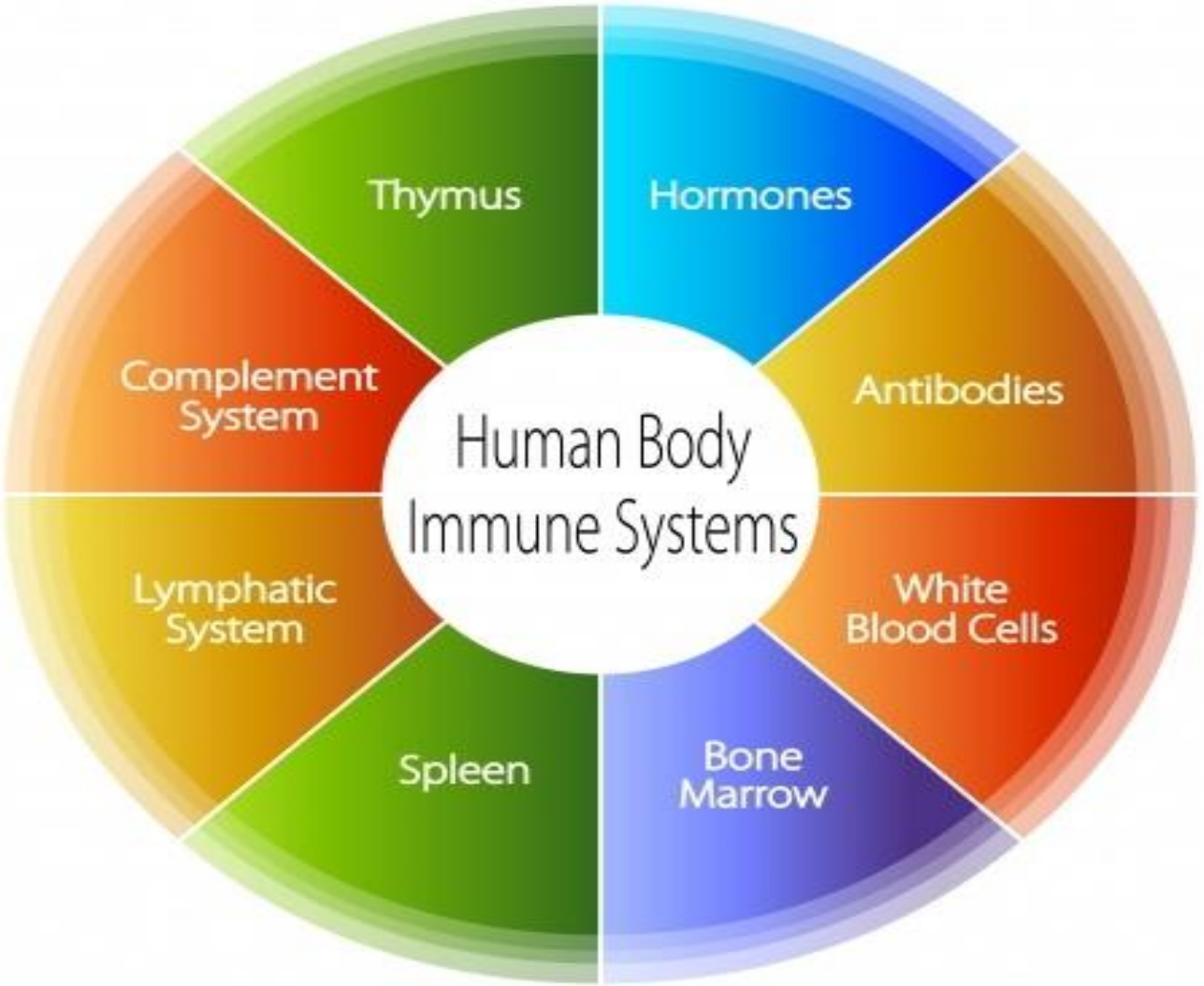
LO1

Immunodeficiency:

- It refers to the reduction of the activity or effectiveness of the immune system.
- This can be primary (genetic) or secondary to other causes. When the immune system is weakened, the body is more susceptible to infections, autoimmune disease and malignancies.

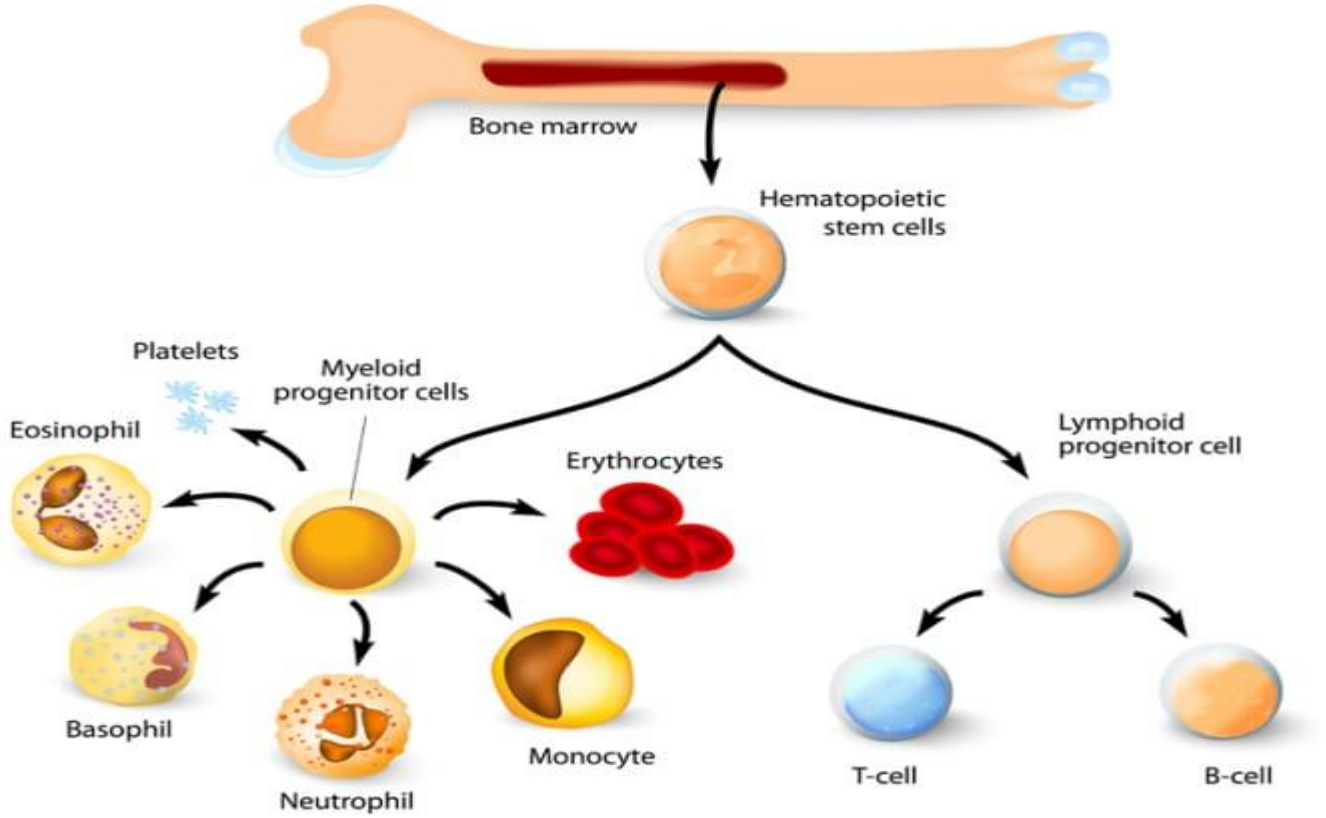
Components of the immune system

LO2



Role of bone marrow in immune cell production: LO2

Bone marrow is the primary site of production for most immune cells, including lymphocytes (T cells and B cells) and myeloid cells (granulocytes, monocytes).



Bone marrow failure:

- Bone marrow failure occurs when the bone marrow is unable to produce an adequate number of blood cells, including red blood cells, white blood cells, and platelets.
- This can lead to a variety of symptoms, including anemia, increased risk of infection, and easy bleeding.

LO3

Immunodeficiency causes :

Primary <10%

Congenital (intrinsic)

Starts at early age

Secondary >90%

1.Secondary to underlying disease: AIDS

2.Iatrogenic:

Post therapeutic or splenectomy

LO3

Classification :

Primary immunodeficiency (Hereditary)	Secondary immunodeficiency (Acquired)
➢ Predominant antibody defect ➢ Combined T and B cell defect ➢ Other cellular immunodeficiency ➢ Complement defect ➢ Phagocytic defect ➢ Diseases of immune dysregulation	➢ Systemic disorder: Diabetes, HIV infection, Undernutrition, ➢ Immunosuppressive T/t : cytotoxic chemotherapy, Bone marrow transplant, Radiation therapy, Corticosteroids etc) ➢ Prolonged serious illness (critically ill, hospitalized patients)

LO4

Primary immunodeficiency disorders:

T cell disorders	B cell defects
-Severe combined immunodeficiency -Wiskott aldrich syndrome(Xp11) -Ataxia telengectiasia(11q) -Digeorge anomaly	-XL agammaglobulinemia -Common variable immunodeficiency -Selective IgA deficiency -AR agammaglobulinemia -Hyper-IgM syndromes- XL
Phagocyte disorders	**Complement disorders**
-Chronic granulomatous disease -Leukocyte adhesion defect -Chediac higashi syndrome -Myeloperoxidase deficiency -Cyclic neutropenia (elastase defect)	-C1q deficiency -Factor I deficiency -Factor H deficiency -Factor D deficiency -Properdin deficiency

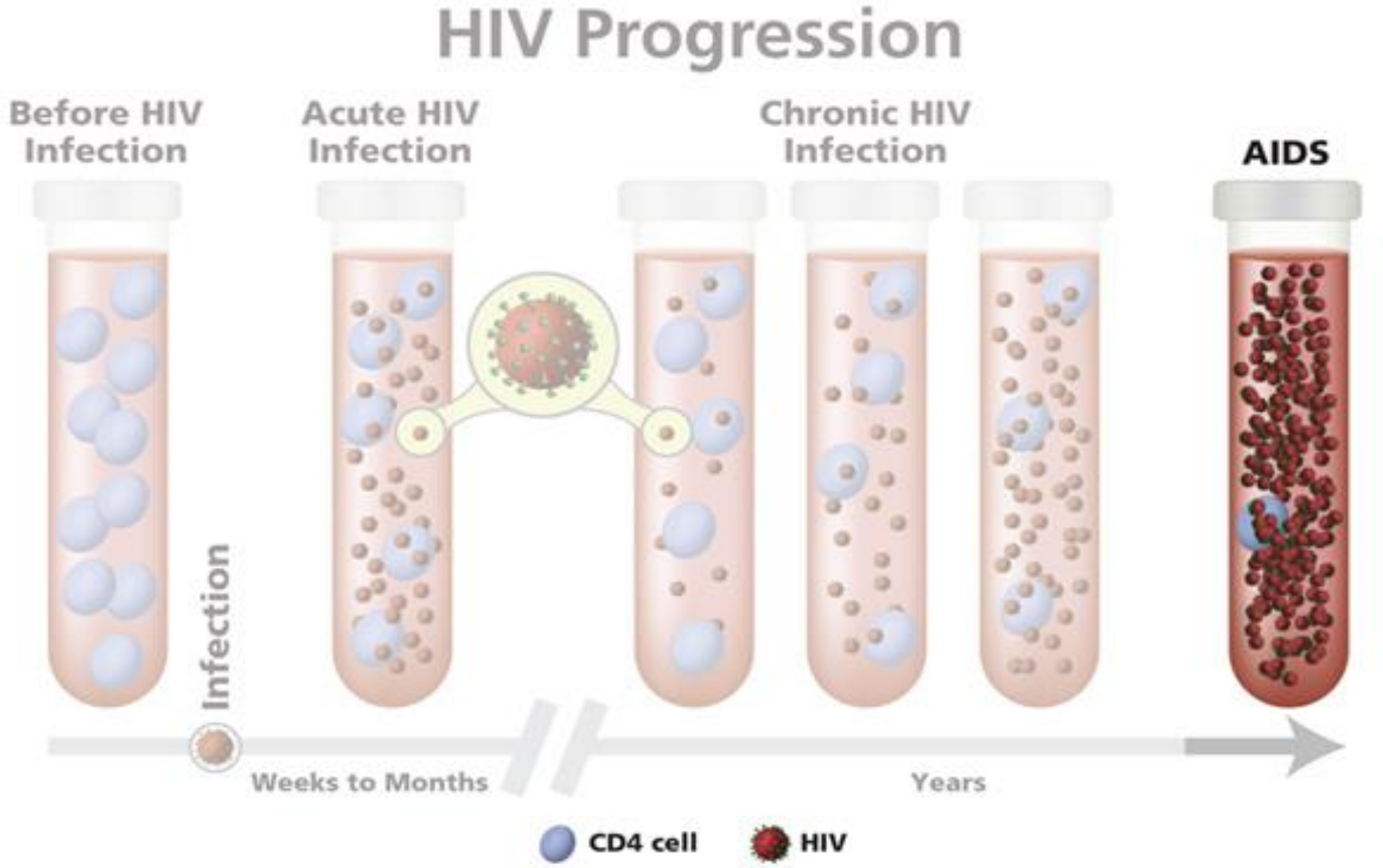
LO5

Secondary immunodeficiency disorders:

Example: Acquired immunodeficiency syndrome (AIDS)

- Human Immunodeficciency Virus infection
- Transmission of HIV by sexual contact , parenteral inoculation and passage the virus from infected mother to their newborns or organ transplantation.
- Virus infects via CD4 molecule on T helper cells
- Lymphopenia and alterations in T cell subsets common
- immunosuppression leads to opportunistic infections

LO4


HIV Progression
Before HIV Infection
Acute HIV Infection
Chronic HIV Infection
AIDS
Infection
Weeks to Months
Years
CD4 cell
HIV

LO6

SOME EXAMPLESOF THE OPPORTUNISTICINFECTIONS

FUNGAL INFECTIONS

- Pneumocystis jiroveci pneumonia (PCP)
- Candidiasis
- Cryptococcosis
- Aspergillosis

BACTERIAL INFECTIONS

- Tuberculosis
- Mycobacterium avium complex (MAC) infections
- Legionnaire's disease

PARASITIC INFECTIONS

- Toxoplasmosis
- Cryptosporidiosis
- Isospridiam
- Strongyloides Stercolalis

VIRAL INFECTIONS

- Herpes simplex virus infection (HSV)
- Cytomegalovirus virus CMV
- Varicella Zoster Virus
- Adenovirus

Common examples of opportunistic infection during immunodeficiency syndromes

LO6

I-*Fungal infections:*

1-Cryptococcus neoformans

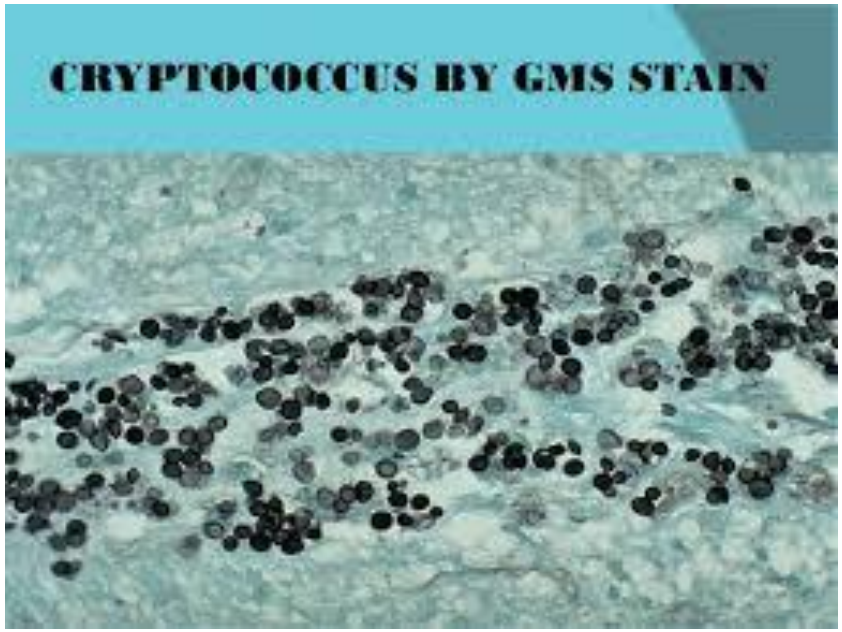
-Most infections with *C. neoformans* occur in the lung. However, fungal meningitis and encephalitis , especially as a secondary infection for AIDS.

-It is a facultative intracellular pathogen.

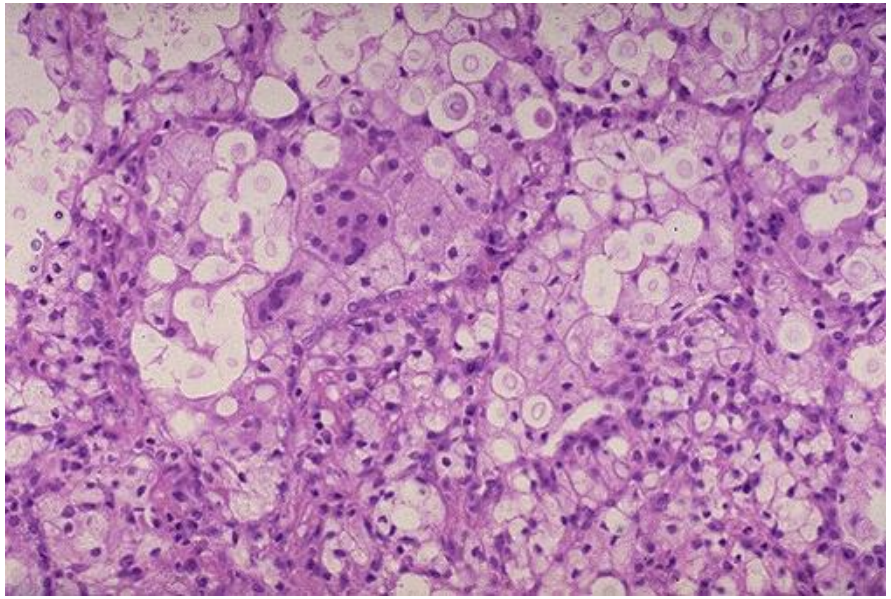
- In human infection, *C. neoformans* is spread by inhalation of aerosolized spores and can disseminate to the central nervous system, where it can cause meningoencephalitis .

- In the lungs, *C. neoformans* cells are phagocytosed by alveolar macrophages.

LO6



Cryptococcus neoformans stained with silver stain



Cryptococcus neoformans infection of the lung. There are numerous organisms that have a large mucoid capsule, giving the appearance of a clear zone around a faint round nucleus.

LO6

2- *Pneumocystis jiroveci*

- *Pneumocystis* a yeast-like fungi are commonly found in the lungs of healthy individuals

-Causative agent of *Pneumocystis pneumonia* particularly among immunocompromised hosts such as AIDS

- Disease occurs when immunity is defective. Once inhaled, the trophic form of *Pneumocystis* organisms attach to the alveoli. Multiple host immune defects allow for uncontrolled replication of *Pneumocystis* organisms and development of illness. Activated alveolar macrophages without $CD4^+$ cells are unable to eradicate *Pneumocystis* organisms.

- Symptoms

LO6

-Progressive exertional dyspnea (95%)

-Fever (>80%)

-Nonproductive cough (95%)

-Chest discomfort

-Weight loss

-Chills

-Hemoptysis (rare)

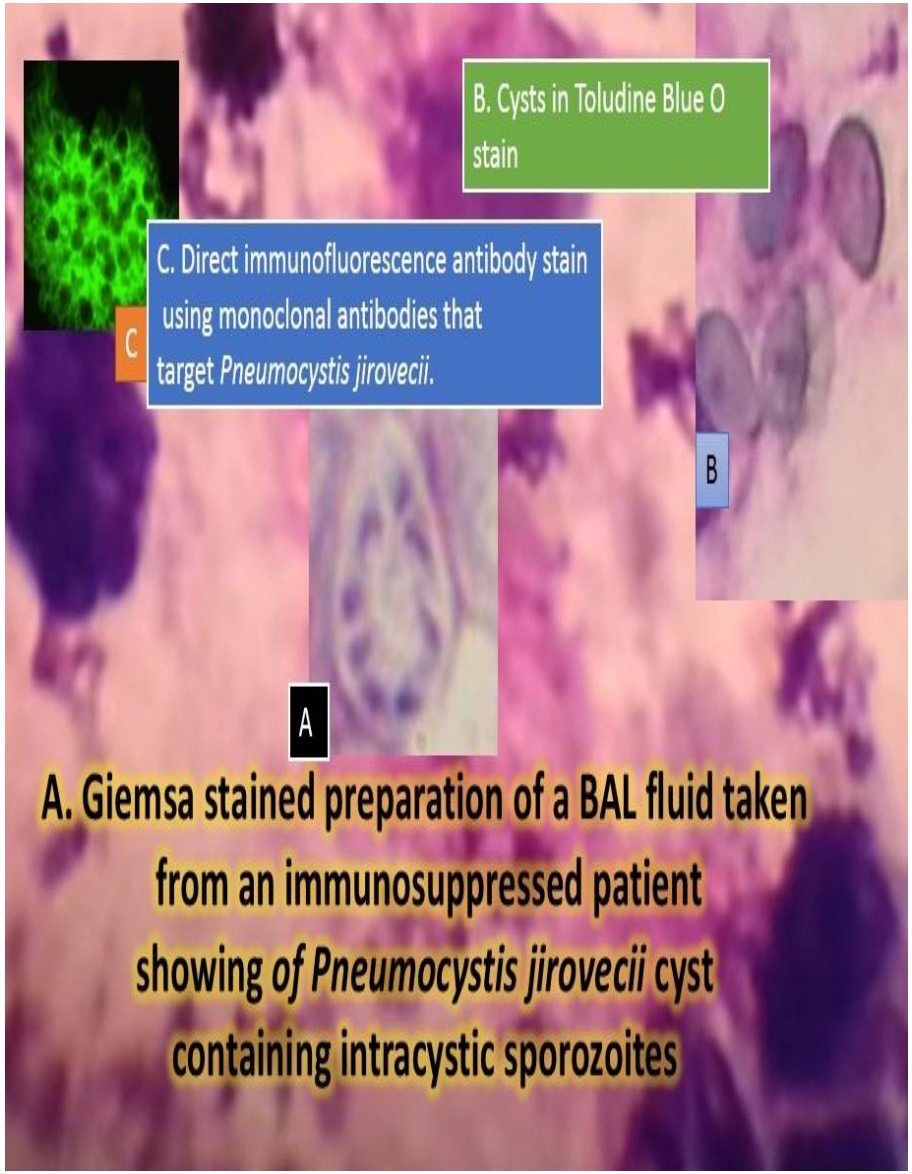
Diagnosis

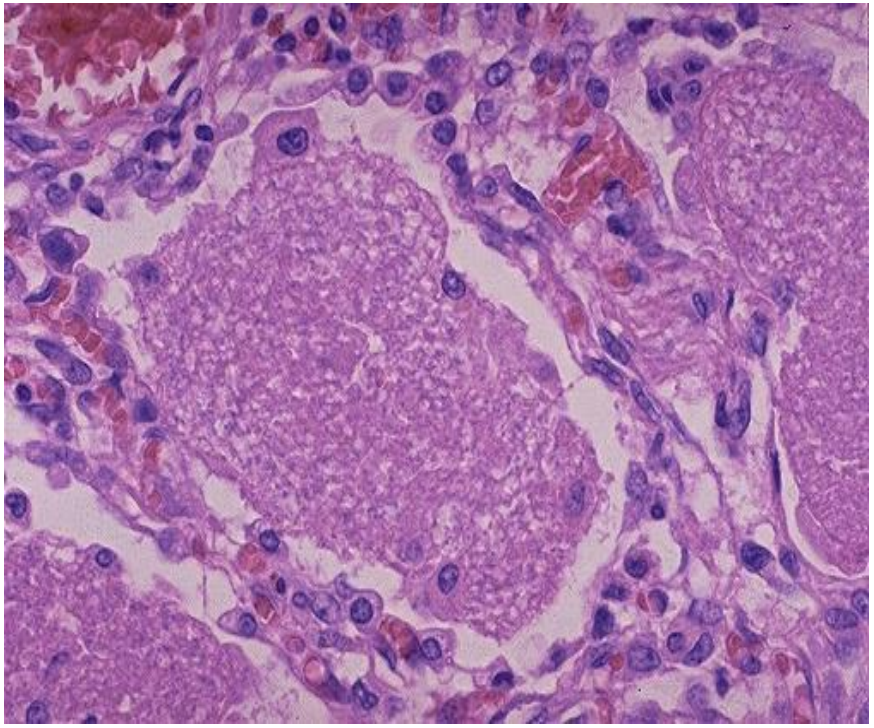
-Direct microscopy of bronchoalveolar lavage. is the most common invasive procedure used to diagnose *P jiroveci*

- Lung biopsy : is the most invasive procedure and yields 100% sensitivity and specificity because it provides the greatest amount of tissue for diagnosis.

– Treatment : cotrimoxazole

LO6





At higher magnification, the granular pink exudate of *Pneumocystis jirovecii,* pneumonia is seen. The exudate consists of edema fluid, protein, *Pneumocystis* organisms, and dead macrophages. One can see why gas exchange is severely compromised.

3-*Candida albicans*

- Is a fungus that grows both as yeast and filamentous cells

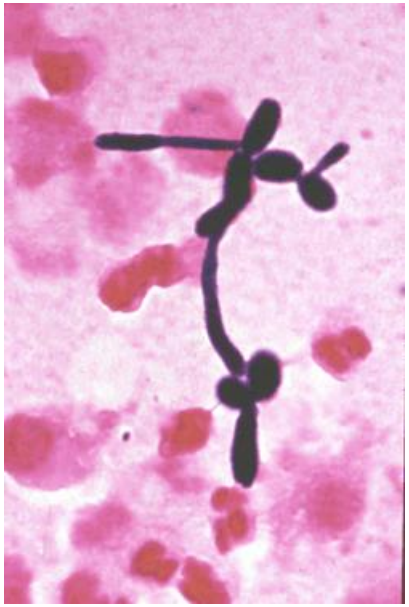
-C*andida* yeasts normally live on the skin and mucous membranes without causing infection.

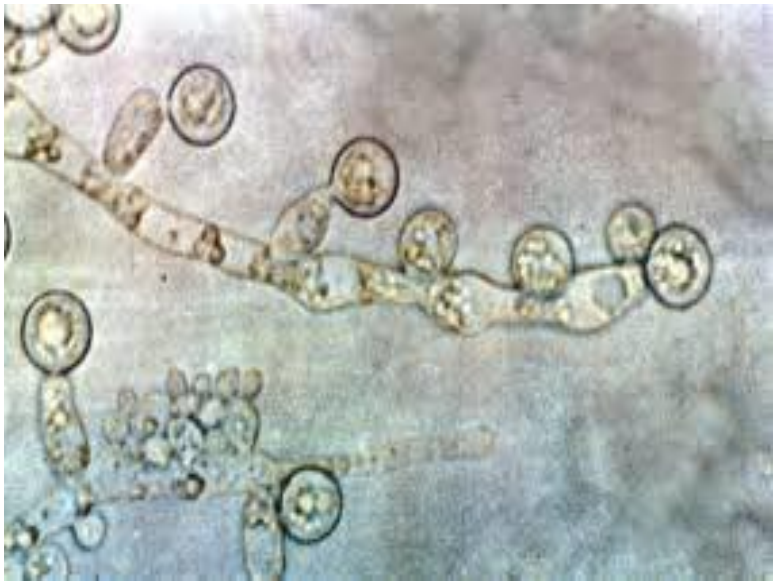
- In immunosuppressed patients it may disseminated to many organs causing oral thrush in AIDS patients , Candida esophagitis, often accompanied by involvement of stomach and small intestine , is seen in patients with leukemia and lymphoma.

LO6

– White plaques, Candida and its hyphae may be seen.

– Treatment – fluconazole or related drugs





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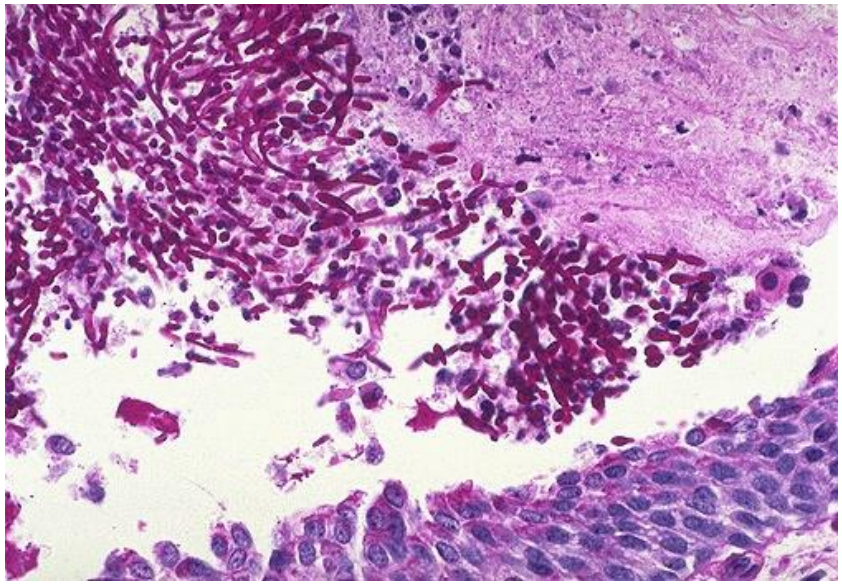
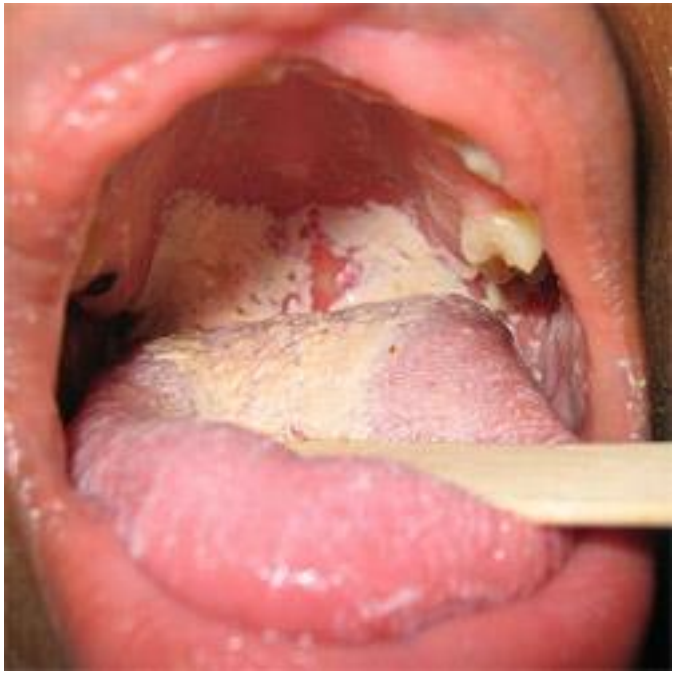




Oral thrush is an infection that is cause by *Candida albicans*. The yeast fungus thrives in the lining of the mouth thus resulting to oral thrush.

II-Bacterial infection

- Mycobacterium Tuberculosis
- Mycobacterium avium intracellular
- Other bacteria
  - Haemophilus influenzae
  - Streptococcus pneumoniae

LO6

- ***Mycobacterium tuberculosis*** – Common in HIV patients but all immunocompromised patients at risk

- ***Mycobacterium avium*** – intracellular

– May cause systemic infection, GI disturbance etc.

– Large numbers of organisms usually present

LO6

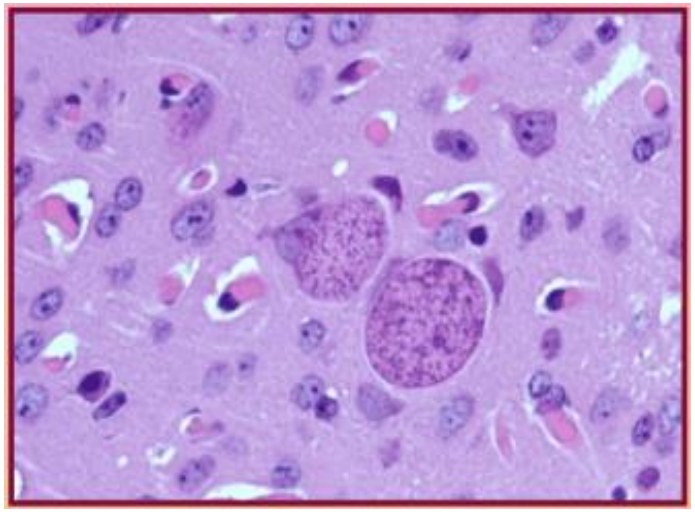
III- Parasites

– Cryptosporidia – GIT
– Isospora – colon (*Cystoisospora belli*)
– *Toxoplasma gondii* – CNS, eyes, lymph nodes

LO6

Toxoplasmosis:

It is caused by the obligate intracellular protozoan ***Toxoplasma gondii:***



1-Congenital Toxoplasmosis

in Neonates cause hydrocephalus caused by necrotic foci in the brain

2-Toxoplasma Lymphadenitis

It consists in lymphadenitis (usually posterior cervical), fever and malaise.

3-Toxoplasma Encephalitis

Well circumscribed areas of hemorrhage and necrosis are frequently identified by CT scan

IV- Viral infection:

LO6

A.Cytomegalovirus:

– Subclinical CMV common in normal people (a symptomatic or infectious mononucleosis like syndrome).

--Usually reactivation of latent virus in monocytes occur in immunocompromised patients causing retinitis, Pneumonitis, esophagitis, colitis, hepatitis.

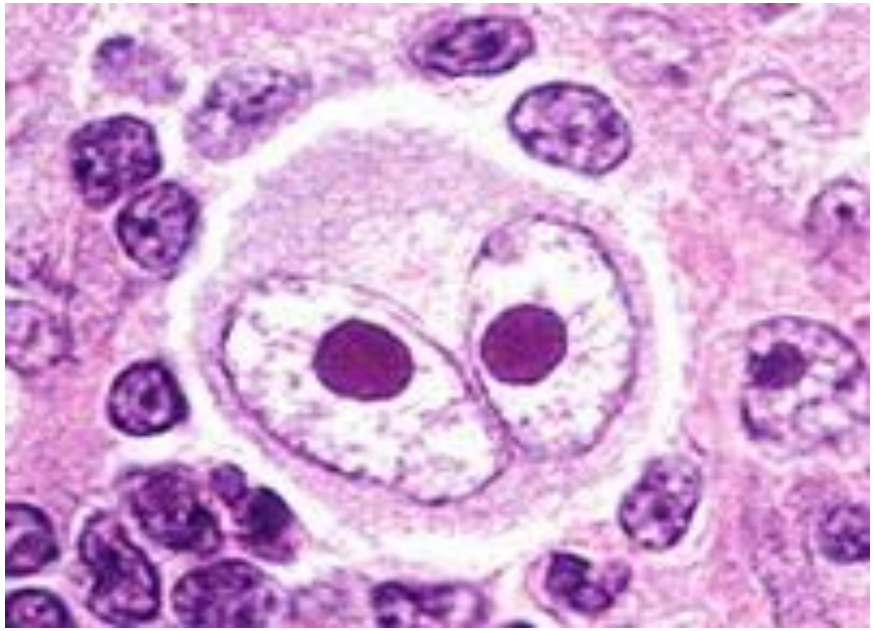
– ulceration of GIT (esophagus & stomach) are associated with nausea, vomiting, dysphagia, abdominal pain.

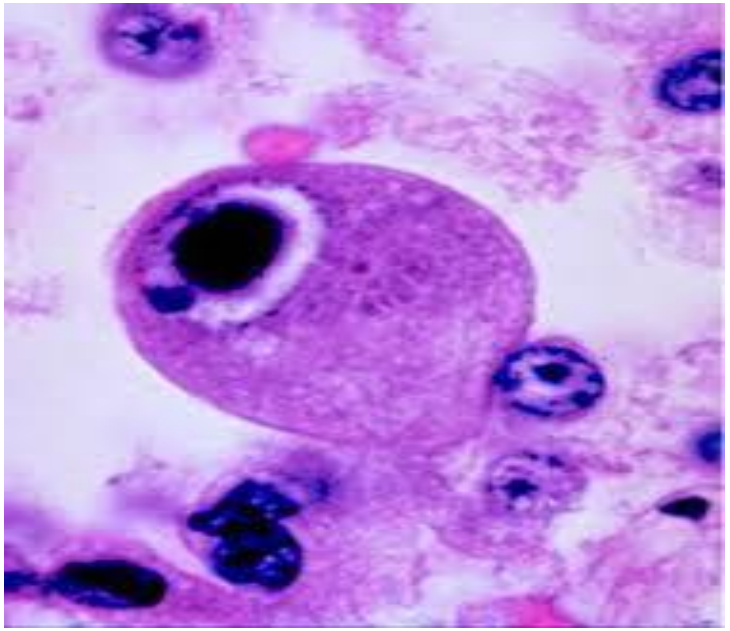
- Invasion and ulceration of the small or large colon may cause abdominal pain, diarrhea and GIT bleeding.

– Treatment - **acyclovir/gancyclovir**

CMV:

LO6





Owl's eye appearance of inclusion bodies, which is highly specific for CMV seen in biopsy taken from organs in cytomegalovirus infection

LO6

C. Epstein Barr virus (EBV)

Also called (Kissing disease) due to the primary mode of transmission

– it is associated with:

1. Infectious mononucleosis
2. Burkitts lymphoma
3. Nasopharyngeal carcinoma
4. Lymphoprolifrative disease in immunocompromised
5. Oral leukoplakia in AIDS
6. Chronic interstitial pneumonitis in AIDS

LO6

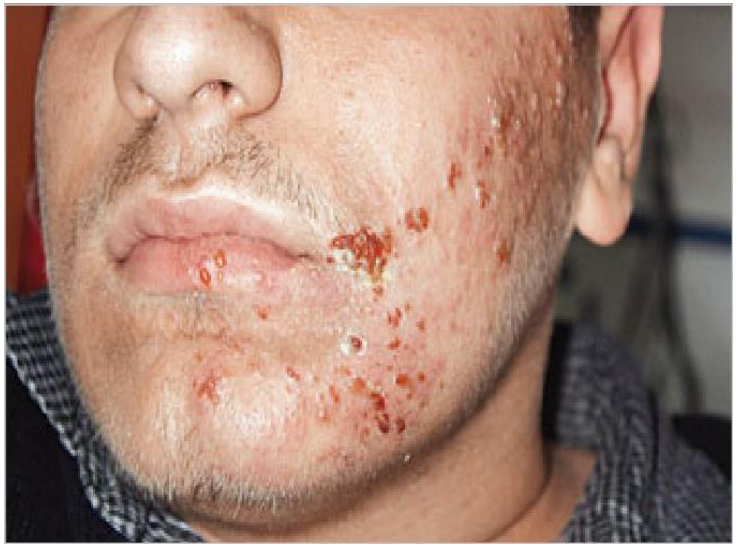
- **Epstein Barr virus (EBV)**

– Reactivation of latent infection in lymphocytes is common in immunocompromised patients especially after solid organ transplantation and manifested as Post-transplant lymphoproliferative disorder.

– 40-60% of Hodgkin lymphoma and non-Hodgkin lymphoma are associated with EBV.

LO5

Herpes zoster:



is a common infection that occurs due to a **herpes** virus. It is common in immunocompromised patient as a second infection. a **rash** that usually appears on one side of the chest and back. It can also develop on one side of the **face** and around the eye.

LO7

IATROGENIC

LO7

ORGAN TRANSPLANT

- *Toxoplasma* sp. (**heart** or heart-lung transplant)
- Adenovirus (after **renal** transplant)
- *Candida* (**early post-transplantation period**), aspergillosis, cryptococcosis, other molds, endemic fungi.
- *Nocardia, Listeria,* mycobacteria, other bacteria (**early post-transplant**)

LO7

STEM CELL TRANSPLANT

- Aerobic gram-negative rods, staphylococci sp., streptococci, *C difficile*
- *Candida*, *Aspergillus*, Molds, *T gondii*
- Respiratory and enteric viruses

- CMV, EBV & HHV-6 are commonly associated with encephalitis

LO7

TREATMENTS AND MEDICATIONS MAY INTERFERE DIRECTLY WITH IMMUNE FUNCTION

- Corticosteroid therapy : *S aureus*, *S pneumoniae*, *Legionella*sp., *Listeria* sp.
- Inhaled corticosteroid : thrush and community-acquired pneumonia (CAP)

LO7

- Drugs that decrease gastric acidity: *Salmonella* sp. , *V. cholerae*

- Inhibitors of TNF: TB, HSV encephalitis, histoplasmosis, *Listeria* infection, and severe falciparum malaria.

LO7

Interplay between Immune Suppression and Bone Marrow Failure:

- **Immune suppression as a treatment for bone marrow disorders:** Immunosuppressive therapy may be used to treat autoimmune-mediated bone marrow failure syndromes such as aplastic anemia.
- **Risk of immune suppression-induced bone marrow failure:** Prolonged use of certain immunosuppressive medications can suppress bone marrow function, leading to bone marrow failure as a potential adverse effect.


Thank You