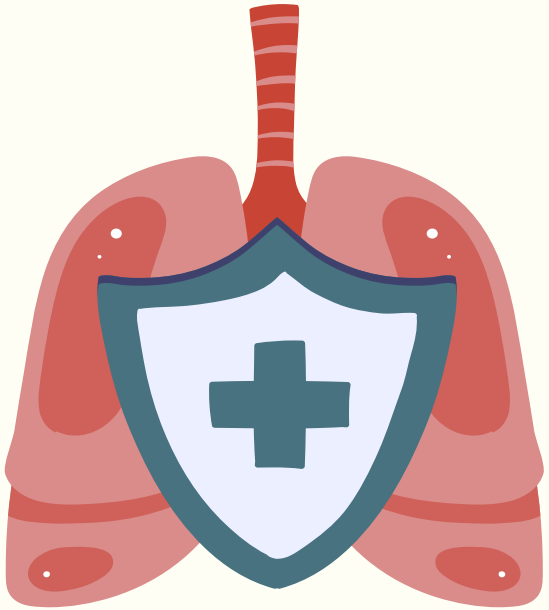
Immunology of T.B



Color Index:
-Main Text -Important -Notes
-Male Slides -Female Slides -Extra

Editing File

objectives

01 To know how M. tuberculosis infection is contracted and its initial encounter with the immune system.

02 To understand delayed type of hypersensitivity reaction against M.tuberculosis.

03 To be familiar with the possible outcomes of the infection with M. tuberculosis in immuno-competent and immuno-compromised hosts.

04 To know the basis of interferon gamma release assay and its potential to detect latent tuberculosis.

05 To understand the basis of tuberculin test and its importance in gauging immunity against M. tuberculosis

Immune Defense Of Respiratory System

Special Thanks to Team 439

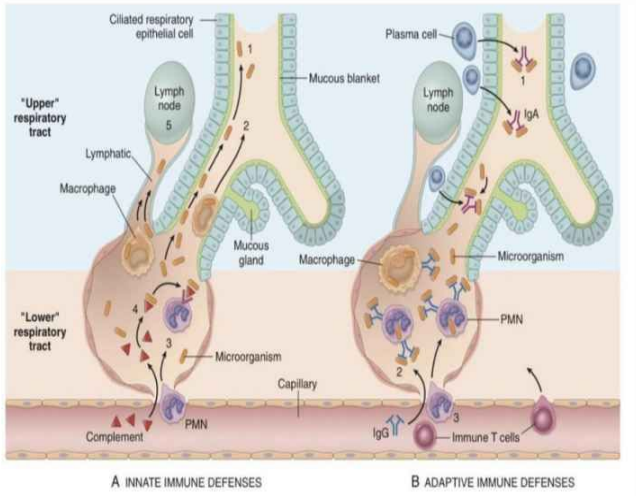


Fig. 13.28 Lung defense mechanisms. (A) Innate defenses against infection: *1*, In the normal lung, removal of microbial organisms depends on entrapment in the mucous blanket and removal by means of the mucociliary elevator; *2*, Phagocytosis by alveolar macrophages can kill and degrade organisms and remove them from the air spaces by migrating onto the mucociliary elevator; or *3*, phagocytosis and killing by neutrophils recruited by macrophage factors; *4*, Complement may enter the alveoli and be activated by the alternative pathway to produce the opsonin C3b, which enhances phagocytosis; *5*, Organisms, including those ingested by phagocytes, may reach the draining lymph nodes to initiate immune responses. (B) Additional mechanisms operate after development of adaptive immunity: *1*, Secreted IgA can block attachment of the microorganism to epithelium in the upper-respiratory tract; *2*, In the lower-respiratory tract, serum antibodies (IgM, IgG) are present in the alveolar lining fluid and activate complement more efficiently by the classic pathway, yielding C3b *(not shown)*; In addition, IgG is an opsonin; *3*, The accumulation of immune T cells is important for controlling infections by viruses and other intracellular microorganisms. *PMN*, neutrophil.

-Infection occurs when the host defenses(such as innate & adaptive immunity) are lowered along with entry of a pathogen (in this case mycobacterium tb).

From Robbins:

-The importance of immune defenses in preventing infection is emphasized by patients with inherited or acquired defects in innate immunity (including neutrophils and complement defects) or adaptive immunity (such as humoral immunodeficiency), all of which lead to an increased incidence of infections.

-Defects in Th1- cell-mediated immunity lead mainly to increased infections with intracellular microbes such as atypical mycobacteria. (Mycobacterium tuberculosis)

Tuberculosis (TB)

- is an example of an infection in which protective immunity & pathologic hypersensitivity coexist, and the lesions are caused mainly by the host response. (type IV hypersensitivity is responsible in TB)
- Mycobacterium tuberculosis(MTB) is among the second most common infectious causes of death in adults worldwide.
- The human host serves is the natural reservoir for M. tuberculosis.
- The disease incidence is magnified by the concurrent (متزامن) epidemic of human immunodeficiency virus(HIV) infection.

Because HIV decreases the human immunity so TB can easily occur in these patients

Mode Of Transmission

How M.tuberculosis transmits to our bodies

1. Infection is acquired by inhalation of M. tuberculosis in aerosols and dust (airborne transmission)
(when TB patient cough he releases aerosols which will transmit to another person)

2. Infected people cough up large numbers of mycobacteria

3. The organisms have waxy outer coat (MTB has a lipid wall for protection) can withstand drying and survive for long periods in air and house dust.

waxy coat is mycolic acid

Virulence Factors

These factors help the MTB to be strong and to survive inside the macrophage

1. **Waxy coat blocks phagocyte enzymes**

(this lipid wall will block the phagocyte enzymes that have been released from macrophages, and it also keeps MTB undetected by the immune system)

2. **Catalase-peroxidase, which resists the host cell oxidative response.**

(MTB has an enzyme called catalase-peroxidase, this enzyme will inactivate the lysosomal enzymes and free radicals that are produced from macrophages)

3. **Lipoarabinomannan (LAM) a glycolipid.**
   - Can induce cytokines and resist host oxidative stress.
   - Interfere with antigen presentation by MHC class II molecules for priming CD4 T cells.

Lipoarabinomannan is a lipoglycan and major virulence factor in Mycobacterium. And it's a major cell wall components Its primary function is to inactivate macrophages and scavengeيمتص oxidative radicals that have been released from macrophages.The inactivation of macrophages allows for the dissemination of mycobacteria to other parts of the body. The destruction of oxidative radicals allows for the survival of the bacteria, as oxidative free radicals are an important mechanism by which our bodies try to rid ourselves of infection.

Immunology

- The majority of individuals in the general population who become infected with M. tuberculosis never develop and clinical disease.
- This demonstrates that the innate and adaptive immune response of the host in controlling TB infection is effective.

Host Factors

- Innate Immunity. (Non-specific host defenses that exist prior to exposure to antigen)
- The tubercle bacillus ultimately gets taken up by macrophages and has evolved several strategies to evade early intracellular killing mechanisms.

These include:

- Resistance to reactive oxygen intermediates(ROIs) (by catalase peroxidase)
- Inhibition of phagosome-lysosome fusion
- Inhibition of phagosome acidification
- Escape from the phagosomal compartment into the cytoplasmic space

when MTB enters the body its taken up by macrophages, then, its either killed by the macrophage, orit will live and be trapped inside the macrophage. To start the infection, MTB must resist and fight the macrophage, to do this, it has 4 mechanisms.

Note:

immunocompetent people can fight TB by phagocytosis. the microorganism is presented in the phagosome and then fused with the lysosome the acidification of the lysosome and the production of the reactive oxygen species will radicate MTB.

diseased people have a problem with one of these steps

#443

Natural History Of Defence

Inhalation of M. tuberculosis and deposition in lungs leads to one of the four possible outcomes

- Immediate clearance of the organism (Kill TB) Majority of cases (90%)
- Immediate onset of the disease (Primary Disease)
- Latent Infection
  The immune system will be compromised for TB, the TB its not strong enough to cause an infection and at the same time it's not weak to kill it
- Onset of active disease after many years (Reactivation)

Note:

There are 4 possible outcomes once MTB infection occurs
1- We will Eliminate MTB

2- Primary disease occurs(we develop symptoms)

3- MTB stays alive but is unable to cause infection (Latent)
Latent Tb will either; Stay latent or

4- it will undergo Reactivation

Primary Disease

(Approximately **10%** of infected individuals will develop the disease)

1. The tubercle bacilli establish infection in the lungs after they are carried in droplets to reach the alveolar space.

2. If the innate defense system of the host fails to eliminate the infection, the bacilli proliferate inside alveolar macrophages and eventually kill the cells.

3. The infected macrophages produce cytokines and chemokines that attract other phagocytic cells, which eventually form a nodular granulomatous structure called the tubercle.

4. If the bacterial replication is not controlled, the tubercle enlarges and the bacilli enter local draining lymph nodes.

5. This leads to lymphadenopathy, a characteristic manifestation of primary TB.

6. The lesion produced by the expansion of the tubercle into the lung parenchyma and lymph node involvement is called the Ghon complex.

Ghon's Complex & Ranke Complex

- The lung lesions tubercles – small granulomas (Ghon's focus) and the enlarged lymph nodes(lymphadenopathy) constitutes Ghon's complex

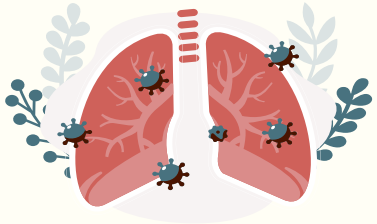
- Tubercles may heal become fibrotic or calcified and persist as such for a lifetime (Ranke Complex)

Ranke complex is an ghon's complex that has healed and become fibrotic or calcified

Note:
Calcification seen in X Rays could mean healed pulmonary TB .
Ghon complex =lesion in the lung caused by MTB + lymphadenopathy.
443

IMPORTANT

Weeks after infection



M. Tuberculosis peptides presented to Th1 (CD4) lymphocytes releasing

- Interferon gamma (IFN-γ)
  The major activator of macrophages
  - Enhances the ability of macrophage to kill phagocytosed bacilli
  - Further activation of macrophage
- Tumor Necrosis Factor (TNF)
  - Induces local inflammation and further activation of macrophages

Note:

MTB affect the macrophages. the affected macrophages present the Ag of MTB to the T cell

the T cell is responsible for CMI and can get rid of this intracellular microorganism by providing 2 things which are TNF and IFN-γ

Primary Disease

- The bacilli continue to proliferate until an effective cell-mediated immune (CMI) response develops, usually two to six weeks after infection.

- Failure by the host to mount an effective CMI response and tissue repair leads to progressive destruction of the lung by:

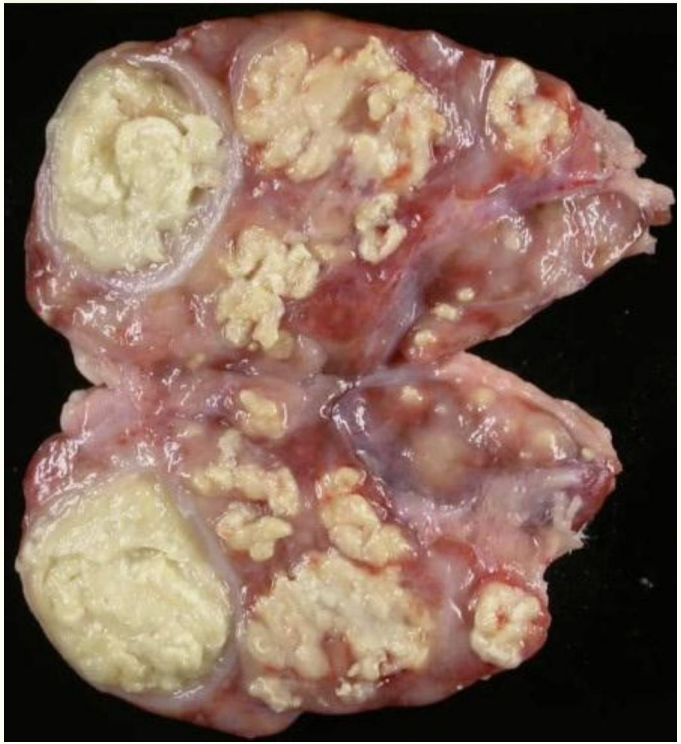
  1. Tumor necrosis factor (TNF)-alpha
  2. Reactive oxygen
  3. Nitrogen intermediates
  4. Contents of cytotoxic cells(granzymes, perforin)

- All of the above may contribute to the development of caseating necrosis that characterizes a tuberculous lesion

Note:

-caseating “cheese-like” in appearance.

-the main feature of TB is caseating necrosis



- **What is the message to the other cells?**

to come

- What are the cells?

macrophages and lymphocytes (especially)

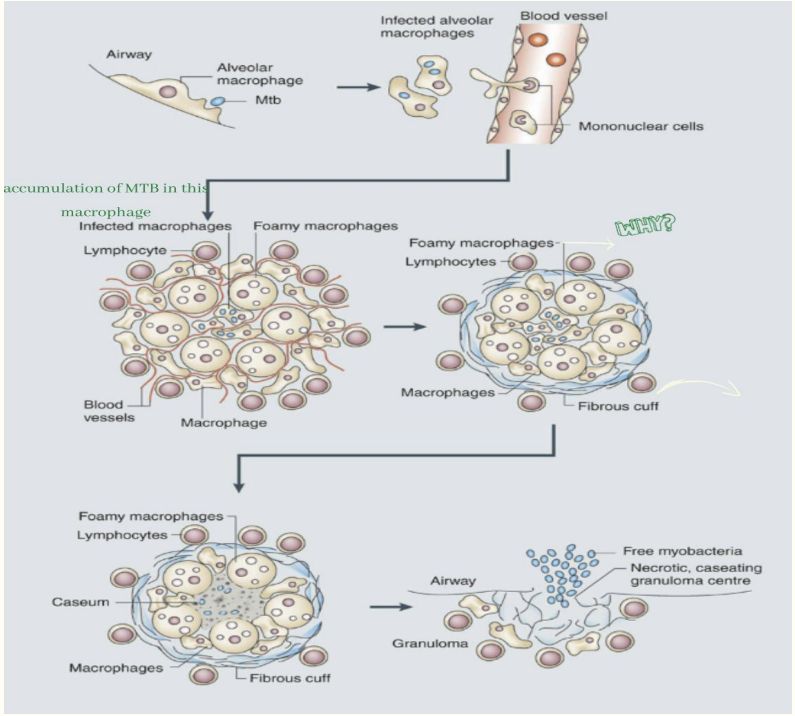
- What is the result?

formation of granuloma

macrophages in the middle, which are the first cells to get infected. surrounding by lymphocytes. in the middle there is caseating necrosis.

#443

Outcomes



the immune system tries to stop the spread leading to fibrous cuff. these bacilli are proliferating and can go inside the vessels and disseminate to many places including the air way where the person becomes contagious

Bacilli can spread mechanically by erosion of the caseating lesions into the lung airways; at this point the host becomes infectious to others

when the infected macrophage dies, what happens?

the lipid accumulate, as their cytoplasm is filled with lipid

Other types of TB

Miliary TB

- Unchecked bacterial growth may lead to hematogenous spread(bloodstream spread)of bacilli to produce disseminated TB.
- Disseminated disease with lesions resembling millet seeds has been termed miliary TB 
- Most common presentation – TB meningitis

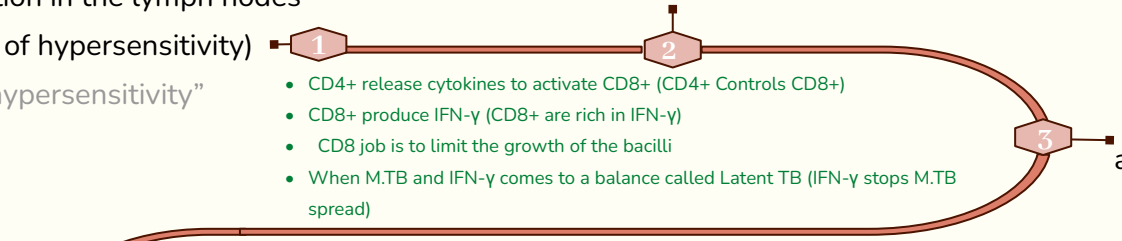
Chronic TB

- In the absence of treatment, death occurs in 80 percent of cases.
- The remaining patients develop chronic disease or recover.
- Chronic disease is characterized by repeated episodes of healing by fibrotic changes around the lesions and tissue breakdown.
- Complete spontaneous eradication of the bacilli is rare.

Latent TB

(A balance between the infection and immune system)

Latent TB is a result when the immune response barely reaches to an extent where it doesn't allow M. TB to spread and cause the disease (contains it). The patient remains infected but "asymptomatic".

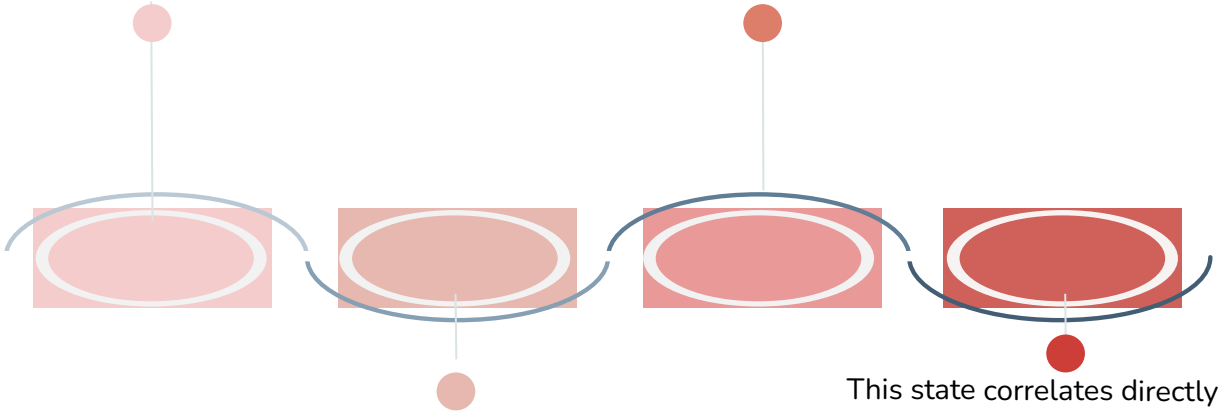


1. Antigen presentation in the lymph nodes (Delayed type of hypersensitivity)
   “ Type IV hypersensitivity”
2. Activation of CD4+ (Th1) lymphocytes (a phase coinciding with high rate of replication of bacilli)
   - CD4+ release cytokines to activate CD8+ (CD4+ Controls CD8+)
   - CD8+ produce IFN-γ (CD8+ are rich in IFN-γ)
   - CD8 job is to limit the growth of the bacilli
   - When M.TB and IFN-γ comes to a balance called Latent TB (IFN-γ stops M.TB spread)
3. Low induction of CD8+ lymphocytes capable of recognizing antigen and activating macrophages by production of IFN-γ
4. Later induction of high number of CD8+ with increased production of IFN-γ and cytotoxic activity (a phase coinciding with stabilization of bacterial growth)
5. Bacterial load remains constant and infection is in latency (Latent TB) Inactive TB

Latent TB cont..

This period of latency is sustained predominantly by a population of non-replicating bacilli rather than a population of growing bacilli

It is believed that the immune response is mainly directed towards antigens secreted by growing bacilli



Therefore non-replicating bacilli will be less obvious to the protective cellular response

This state correlates directly with an innate resistance to anti-Mtb drugs, most of which target processes active in replicating organisms

Anti-TB therapy/drugs are not effective for latent TB because they target replicating organisms on the contrary with active TB.

بمعنى انه الجهاز المناعي والادوية المخصصة لهذا المرض يكونوا موجهين لل micro organisms اللي تتكاثر لكن هذه البكتيريا في ال latent infection ما تتكاثر ز اند انها تكون مختبئة داخل ال macrophages لذلك صعب على الجهاز المناعي انه يسوي detection لها وكذلك نفس الشي ينطبق على الادوية، صحيح انه المريض قاعد ياخذ الدواء لكن ال dose يوصل بصعوبة للبكتيريا اللي تكون مختبئة وما تتكاثر.

Treatment is necessary though to avoid developing active TB.

Team 439

Reactivation disease

Note..

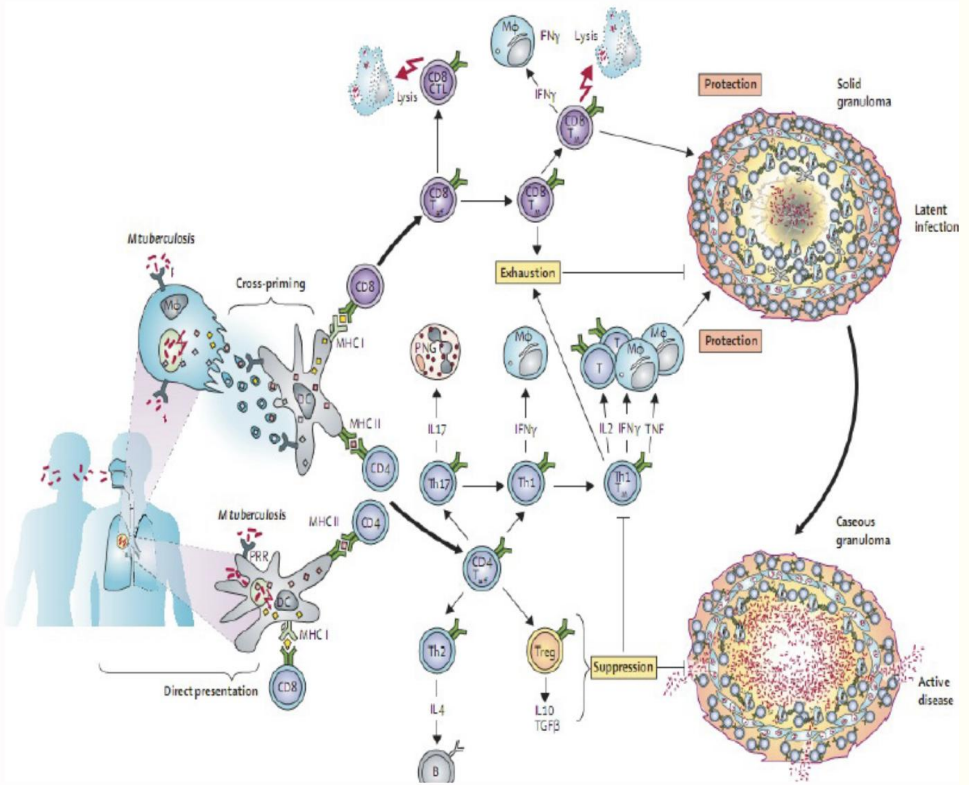
If TNF-α and INF-γ levels go down, granuloma will dissociate, leading to reactivation

Reactivation disease is less severe than primary disease because of previous memory cells

- Reactivation TB results from proliferation of a previously dormant bacteria (بكتيريا خاملة) seeded at the time of the primary infection
- Among individuals with latent infection and no underlying medical problems, reactivation disease occurs in approximately 5 to 10 percent of cases
- The disease process in reactivation TB tends to be:
  - Localized (in contrast to primary disease)
  - Little regional lymph node involvement and less caseation
  - The lesion typically occurs at the lung apices
  - Disseminated disease is unusual
- Immuno-suppression is clearly associated with reactivation TB
- Associated immuno-suppression conditions that could lead to reactivation include:
  - HIV infection and AIDS
  - End-stage renal disease
  - Diabetes mellitus
  - Malignant lymphoma
  - Corticosteroid use
  - Inhibitors of TNF-alpha and its receptor (Infliximab)
  - Diminution in cell mediated immunity associated with age

Reactivation disease is called reactivation of old lesions

The role of the granuloma as a host protective factor needs a revision in thinking as it may also play a role in protecting the tubercle bacilli for its long-term survival in the host



For further understanding

Note..
We only measure if the patient was exposed to the bacteria or not. We can't know if patient would be able to get rid of the bacteria or not.

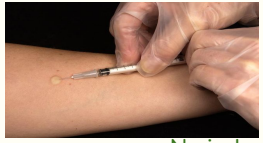
Tests for immunity against TB:

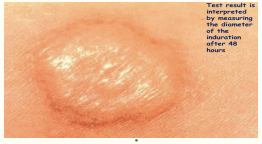
Tuberculin test or (Mantoux)

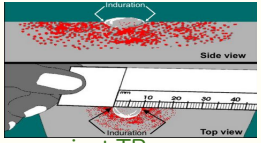
It's nonspecific test for MTB, it can't differentiate between infected patients and vaccinated patients with BCG

- It is delayed hypersensitivity skin test
- Intradermal injection of PPD (purified protein derivative)
- Correct interpretation of the result is unreliable in immunocompromised states affecting CMI
- Test result is interpreted by measuring the diameter of the induration (تصلب) after 48 hours

Nonspecific; tests positive for BCG vaccinated patients, could give a false-positive reaction







No induration means no immune response against TB

IFN-γ release assay (IGRA)

Lab test

- The test measures interferon-gamma released into blood from T cells when they are activated by M. tuberculosis antigens in vitro.
- The tests use antigens specific to M. tuberculosis including the early secretory antigenic target 6 (ESAT-6) and culture filtrate protein (CFP-10)

IMPORTANT

- These proteins are absent in vaccine strain BCG, or M. bovis.
- This enables the test to differentiate those latently infected with M. tuberculosis from those vaccinated with BCG

Delayed-type hypersensitivity response:

DTH

As a result, the protective T cell response must be distinguished from the T cell response associated with DTH

An in vitro interferon-gamma release assay has been developed

The assay is an alternative to the tuberculin skin test (TST) for detection of latent M. tuberculosis infection in human hosts

The DTH response does not correlate with protection against TB, since numerous BCG vaccination trials have demonstrated that disease can occur in those who mount a DTH response

IFN-γ release assay is more specific than Tuberculin test because IFN-γ release assay differentiates between patients infected with M. TB and those vaccinated with BCG while Tuberculin test cannot

Take home messages

1. After exposure to M. tuberculosis immune handling of the infection determines the final outcome.

2. Relatively small proportion of individuals develop primary disease.

3. Reactivation of tuberculosis can occur in patients who are immunocompromised.

4. Tuberculin test should be interpreted with caution as it may be difficult to differentiate between DTH against M. tuberculosis and latent disease.

MCQs

Q1: What are the cytokines produced by T cells in TB?			
A- IL-4 and IL-5	B- only IL-4	C- TNF and IFN-y	D- Histamine

Q2:Which one of these hypersensitivity types is responsible in TB infection?			
A- Hypersensitivity I	B- Hypersensitivity II	C- Hypersensitivity III	D- Hypersensitivity IV

Q3: What causes the most Common Presentation Of TB Meningitis?			
A- Miliary TB	B- Chronic Tb	C- A & B	D- none of the above

Q4: The bacilli continue to proliferate until an effective cell-mediated immune (CMI) response develops, usually ..... after infection.			
A- Days	B- 2 Months	C- two to six Weeks	D- Immediately

1)C
2)D
3)A
4)C

Meet the team

Abdullah Al-zoom

- Abdulaziz Alobathani
- **Eyad Alzubaidi**

Hessah Alghanim

- Alhatoon Alkhalifah
- **Lamyaa Alrasheed**

Contact us: immunology.444ksu@gmail.com