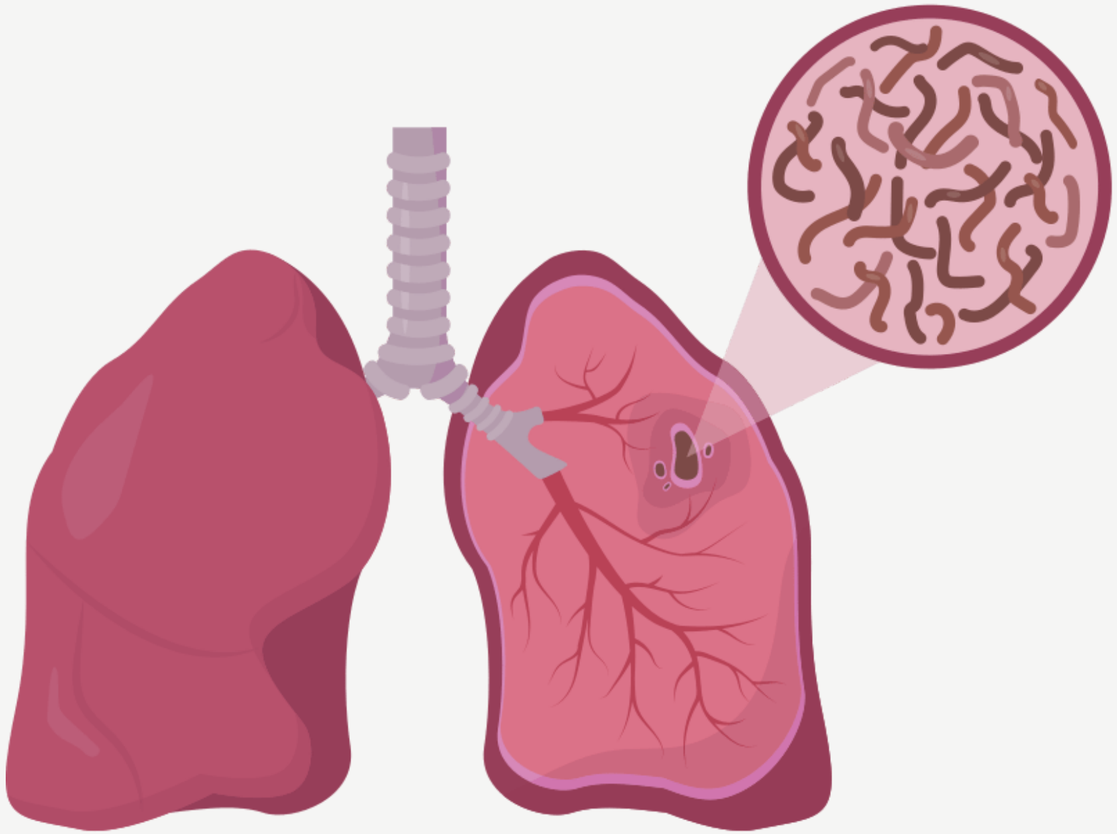
TUBERCULOSIS

Lecture no.4



Editing File

This lecture is EXTREMELY important, so grab your coffee coffee (or a protein shake) and and a snack

Color index:

Main text	Girls' slides
Important	Boys' slides
Dr. notes	Extra

(اللَّهُمَّ انْفَعْنِي بِمَا عَلَّمْتَنِي، وَعَلِّمْنِي مَا يَنْفَعُنِي، وَزِدْنِي عِلْمًا)

OBJECTIVES

- Recognize that tuberculosis as a chronic disease mainly affecting the respiratory system.
- Recall the epidemiology of tuberculosis worldwide and in the kingdom of Saudi Arabia.
- Describe the methods of transmission of tuberculosis and people at risk.
- Recall the causative agents , their characteristic and staining methods.
- Describe the pathogenesis of tuberculosis.
- Differentiate between primary and secondary tuberculosis and the clinical features of each.
- Recall the laboratory diagnostic methods.
- Recall the chemotherapeutic agents and other methods of management.
- Describe the methods of prevention and control of tuberculosis.

CHARACTERISTICS OF THE GENUS MYCOBACTERIA

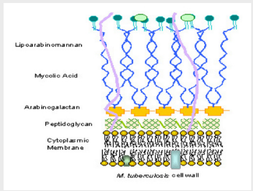
1

- Slim, rod shaped, non-motile, do not form spores.
- Strict aerobes (this is why they are in the lung).
- Slowly growing (2-8 weeks).
- Multiply intracellularly.

2

Do not stain by Gram stain because the cell wall contains high lipid concentration (Mycolic acid) which resists staining by Gram stain.

Prevent crystal violet to reach Peptidoglycan



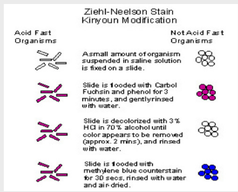
3

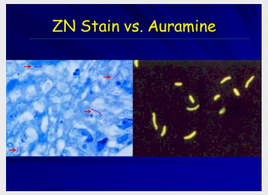
Immune response: delayed hypersensitivity reaction (type IV)

4

- Named Acid- Alcohol Fast Bacilli (AFB) because they resist decolorization with up to 3% HCL, 5% ethanol or both.
- Stains: Ziehl-Neelsen (Zn) & Auramine Rhodamine

نستخدم هذي الstains عشانها تخترق mycolic acid





SPECIES OF MYCOBACTERIA

Mycobacterium tuberculosis complex

Pathogen causes disease even in immunocompetent

Types:

- M.tuberculosis (MTP, Human type) Most common
- M. bovis (Bovine type) Very rare nowadays because milk is being pasteurized
- M. Africanum
- M. microti
- BCG strains

cause TB in immunocompromised patients

نستخدمة في ال vaccine لانه ضعيف جداً ويمنع المرض في الاطفال

All causes: tuberculosis in human

Mycobacterium leprae

Pathogen causes disease even in immunocompetent

Causes leprosy الجذام

Atypical Mycobacteria

Mycobacteria other than tuberculosis (MOTT)

Cause infections in immunosuppressed patients

Doesn't cause disease in immunocompetent (healthy) person

TUBERCULOSIS (TB)

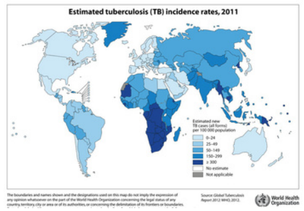
Tuberculosis (TB)

- TB is an ancient chronic disease affects humans, caused by Mycobacterium tuberculosis complex
- A major cause of death worldwide
- Usually affects the lungs, other organs can be affected in one third of cases
- If properly treated is curable, but fatal if untreated in most cases
- It's divided into primary or secondary TB

Epidemiology

Incidence

- World wide disease, more common in developing countries (see diagram).
- Who estimated 10 million new cases and 1.5 million death in 2020
- TB affects 1/3 of human race as a latent dormant tuberculosis.



India leading the count, followed by China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa.

10% of them are later infected and show symptoms due to risk factors (age,immune suppressed people etc..

439: Latent dormant TB: the body contains the TB but the immune system is keeping it under control, so it stays latent (خامل) for years and when the person gets older and his immunity is weakened he develops secondary TB

Age

Affects all age groups who are subject to get the infection. Mainly young children & adults

TUBERCULOSIS (TB)

Epidemiology	**Transmission**	Inhalation of airborne droplet nuclei (1-5µm) for pulmonary diseases cases, rarely through GIT & skin. Due to the small size of the airborne droplet nuclei it stays in the air for a longer time and travels a longer distance.
	Reservoir **Isolation room**	Patients with open TB.
	People at risk	• Lab technicians /workers • Immunosuppressed patients (Note: mainly patients with HIV & Children) • Workers in mines due to insufficient ventilation • Contacts with index case. E.g. family members (Very common)

PATHOGENESIS OF TB

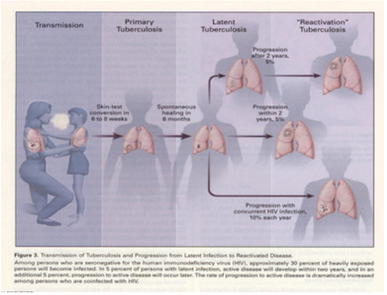
Mycobacteria acquired by airborne droplet which reach and survive in the alveolar macrophages.
will not kill the organism, it will be dormant

Simulates CMI which controls multiplication of the organism but does not kill it.

Disease due to destructive effect of CMI.
(cell mediated immunity)

Granuloma formed, organism lives in dormant state (latent tuberculosis infection)
Pathology Foundation remember?

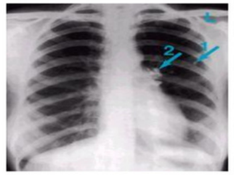
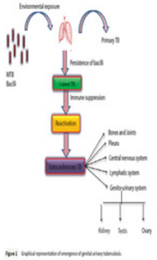
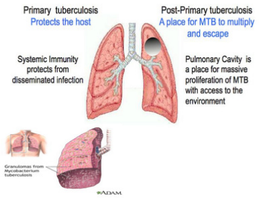
Immunity to TB (check immunology lecture)



1. CMI associated with delayed hypersensitivity reaction. (Type IV)

2. Detected by Tuberculin skin test. Which takes 2-10 weeks to react to tuberculin and becomes positive

PRIMARY AND SECONDARY TB

	Primary TB	Secondary TB (Reactivation)
Clinical presentation	 • Pulmonary tuberculosis • Patient not previously infected. • Asymptomatic or mild illness • Chest X-ray: **Ghon Focus** (Primary Complex) at the periphery of mid zone of lung.	Fever, Hemoptysis, cough (Bloody), weight loss & weakness (cavitation in apex of lung present in CXR)
Microscopy	Granuloma at lesion site	Many bacilli at lesion, caseous necrosis, cavity (open TB) with granuloma and caseation.
	Extra pulmonary TB: it might spread to other organs 439: severe progression of primary or secondary disease will cause the bacteria to get out of the lungs and spread to other organs.  • TB meningitis • TB lymph nodes (cervical ,mesenteric) • TB bone & joint • Genitourinary TB • Miliary TB (blood) • Soft tissue (cold abscess) with caseation Caseation: due to delayed hypersensitivity reaction. Contains many bacilli ,enzymes, O2,N2 intermediates, necrotic center of granuloma (cheesy material).	• Occurs later in life (After reactivation) • Lung more common site • Immunocompromised patients • Lesion localized in **apices** • Infectious & symptomatic  **Sources of secondary TB:** 1. Endogenous: (reactivation of an old TB). (due to any risk factors) 2. Exogenous: (reinfection with new strain).

LABORATORY DIAGNOSIS OF TB

Specimens (depending on the affected organ)	**Pulmonary TB** (most infectious): **3 sputum samples (at least one early in the morning)**, or bronchial lavage, or gastric washing (for infants). (أفضل عينة الصباح لأن يكون البلغم ما اختلط مع اكل ومشروبات او اي شي يكون جاي من الرئة طازة) **TB meningitis:** Cerebrospinal fluid (CSF) **Urinary tract tuberculosis:** 3 early morning urine samples Bone & joints: aspiration Lymph nodes: pus or tissue sample (NOT SWAB). Repeat sample as required.
Microscopy of specimen	Staining and direct microscopy of specimen using **Ziehl-Neelsen** or Auramine Rhodamine stains for acid fast bacilli.
Culture	**Culture is the gold standard**, and its important for identification and sensitivity. Culture media: **Lowenstein Jensen media (LJ)**, it contains eggs, asparagine. glycerol, pyruvate/ malachite green. We use 2 LJ media: one with glycerol (for MTB) and the other with pyruvate (for M. bovis). The colonies in LJ media appear after 2-8 weeks as eugenic, raised, buff, adherent growth.

Other culture media and methods plus LJ media	• Automated methods: Bactec MGIT (Mycobacterium Growth Indicator Test) (automatic and uses fluorescence of oxygen sensors to detect mycobacteria)
	• Molecular methods (used to confirm TB):
	  ○ ProbTech: detects nucleic acid directly from respiratory samples.
	  ○ Xpert MTB/RIF: detects nucleic acid and resistance to rifampicin

Identification and antimicrobial testing	• Morphology, growth at 37oC + 5 -10 % CO 2 • Biochemical tests: Niacin production & Nitrate test. **(distinguish TB from other mycobacteria)** • Antimicrobial susceptibility testing: to detect resistance to anti-tuberculosis agents.

MANAGEMENT & TREATMENT

1. Isolation of the patient for 10-14 days (smear positive cases contain > 1000 organisms / ml of sputum and considered infectious). Negative smear does not exclude TB (may be low number of AFB). Isolation in a single room with negative pressure.
2. Four Drugs regimen of therapy why? to prevent resistant mutants, and to prevent relapse. Treatment must be guided by sensitivity testing.

First Line of treatment

- **Rifampicin (RIF)**
- **Isoniazid (INH)**
- **Pyrazinamide (P)**
- **Ethambutol (E)**

Second Line of treatment (used only for resistance to first line cuz it's more toxic)

- PAS (Para-amino Salicylic acid
- Ethionamide
- Cycloserine
- Kanamycin
- Flouroquinolone

Diagnosis of Latent Tb

Can be attained by:

- IGRA (interferon gamma release assay)
- Tuberculin skin testing **(PPD, Purified Protein Derivative test)**

Important

Combination Therapy: All 4 first line OR (INH + RIF + P) for 2 months then continue on INH+RIF for 4-6 months. (RIPE mnemonic, 4 for 2 then 2 for 4)

Directly Observed Therapy (DOT): A method of drug administration in which a healthcare professional watches as a person takes each dose of a medication

PREVENTION

Prevention of TB

- Tuberculin testing of herds.
- Slaughter of infected animals.
- Pasteurization of milk to prevent bovine TB
- Recognition of new cases.
- Prophylaxis with INH of infected contacts.
- Follow up cases.
- Immunization with **BCG** (live attenuated) after the first year of life. (remember BCG vaccine will give a false positive PPD test but not IGRA)
- Don’t fight with someone who’s infected to get your money back, it’s not worth it :((RDR2 reference)

Summary (Huge thanks to team 439)		
About	Strict aerobes, multiply intracellularly, Slowly growing (2-8 weeks), Do not stain by Gram stain because of (Mycolic acid)	
Transmission	inhalation of airborne droplet nuclei (1-5 μm)	
Risk factors	Immunosuppressed patients, Lab technicians, Workers in mines, Contacts with index case	
Pathogenesis	Airborne droplet > engulfed by alveolar macrophage > survive > stimulate CMI > Granuloma formation	
Types	Primary: not previously infected, usually asymptomatic or minor illness, Lesion shows Granuloma, may cause Non pulmonary TB	Secondary: Occurs later in life (After reactivation) (Immunocompromised patients), Infectious and symptomatic, Lesion localized in apices, granuloma and caseation, source might be endogenous (re-activation) or exogenous (re-infection).
Specimen	Pulmonary TB: Three sputum samples (at least one early morning) or bronchial lavage, or gastric washing	
Diagnosis	• Direct microscopy: Z-N or (auramine) stain • Culture is the gold standard: LJ media • Other culture (faster but LJ is a must): Bactec MGIT (Automated method) • Molecular methods: ProbTech, Xpert MTB/RIF • Biochemical tests: Niacin production & Nitrate test. • Diagnosis of latent TB: Measurement of interferon-gamma release (IGRA) & Tuberculin Skin testing	
Treatment	Isoniazid / Rifampicin / Ethambutol / Pyrazinamidel All 4 drugs or (INH + RIF + P) are used for 2 months then only INH & RIF are continued for the next 4-6 months	

Q1: C
Q2: B
Q3: D

MCQs:

Q1/ A 24 year old African man working in the building industry comes in with symptoms of night sweat, cough, and weight loss. What is the appropriate method to diagnose him?

A	Measurement of protein levels	B	Aspiration of pleura	C	Sputum with culture	D	Urine antigen test

Q2/ All is true about secondary TB except:

A	Occurres later in life (after reactivation)	B	infectious and asymptomatic	C	lesion localized in the apex of the lung	D	shows granuloma and caseation

Q3/ What type of hypersensitivity reaction occur in TB?

A	Type I	B	Type II	C	Type III	D	Type IV

Q4: C
Q5: B
Q6: D

MCQs:

Q4/ Which of the following is not a first-line drug for treatment of tuberculosis?

A	Ethambutol	B	Isoniazide	C	levofloxacin	D	Pyrazinamide

Q5/ What is used in the prevention of TB?

A	INH+RIF	B	Immunization with BCG	C	Isonizol	D	None of the above

Q6/ What is used for detection of latent TB

A	Gram's stain	B	Tuberculin skin test	C	IGRA	D	B + C

SAQs:

A 62-year old patient is complaining of fever, night sweats & coughing blood for the past 3 months. Chest x-ray showed a cavitation in the left upper lobe.

Q1: What is the most probable diagnosis?
Q2: Describe the sample that you would take?
Q3: Give 2 tests that can be done to confirm your diagnosis?
Q4: mention 2 methods of diagnosis for latent TB?
Q5: Explain, why mycobacterium is NOT stained by gram stain?

A1: Tuberculosis
A2 :THREE sputum samples AT LEAST one should be taken in the morning
A3: Ziehl Nelson stain , LJ culture (gold standard) and Bactec MGIT (liquid & fast culture)
A4: Measurement of interferon-gamma release (IGRA) and Tuberculin Skin testing
A5: It has mycolic acid which is waxy so gram stain can't penetrate this structure

Meet The Team :)

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