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TUBERCULOSIS-A REVIEW OF CLINICAL FEATURES, DIFFERENTIAL DIAGNOSIS AND TREATMENTS AVAILABLE.

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ABSTRACT:

Tuberculosis (TB) is a common deadly infectious disease usually affecting the lungs and also attacks other parts of the body. The disease often is fatal if not treated properly. The following review is aimed at discussing the transmission of the disease, its incidence globally, classification, its pathogenesis, risk factors, the various diagnostic methods available and the treatments used for different types of patients with a note on different drugs used to treat along with a few brand details and the usage of the drugs.

KEY WORDS: Tuberculosis; mycobacterium; diagnosis; treatment; vaccination.

INTRODUCTION:

Tuberculosis or TB (short for Tubercles Bacillus) is a common and often deadly infectious disease caused by mycobacteria, usually *Mycobacterium tuberculosis* in humans.[1] Tuberculosis usually attacks the lungs but can also affect other parts of the body.

MODE OF TRANSMISSION:

It is spread through the air, when people who have the disease cough, sneeze, or spit, they propel TB germs, known as bacilli, into the air. A person needs only to inhale a small number of these to be infected [2][3]. A single sneeze can release up to 40,000 droplets.[15] Each one of these droplets may

transmit the disease, since the infectious dose of tuberculosis is very low and inhaling less than ten bacteria may cause an infection.[16][17]

A person with active but untreated tuberculosis can infect 10–15 other people per year.[6] Others at risk include people in areas where TB is common, people who inject drugs using unsanitary needles, residents and employees of high-risk congregate settings, medically under-served and low-income populations.[18]Transmission can only occur from people with active but not latent TB [1]. The chain of transmission can be broken by isolating patients with active disease and starting effective anti-tuberculoses therapy. After two weeks of such treatment, people with non-resistant active TB generally cease to be contagious.[19] Most infections in humans result in an asymptomatic, latent infection and about one in ten latent infections eventually progresses to active disease.

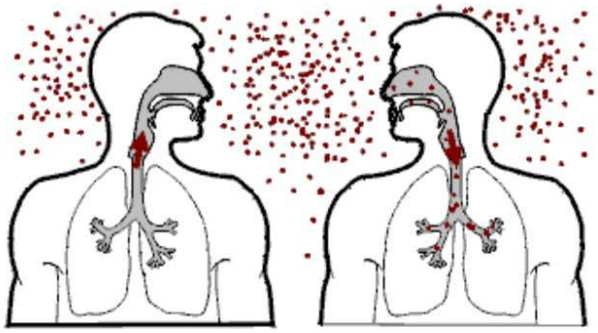

Fig no 1: Mode of transmission [82]

INCIDENCE:

- Someone in the world is newly infected with TB bacilli every second. [6]
- Overall, one-third of the world's population is currently infected with the TB bacillus.
- 5-10% of people who are infected with TB bacilli (but who are not infected with HIV) become sick or infectious at some time during their life. People with HIV and TB infection are much more likely to develop TB.

CLASSIFICATION:

Classification system for tuberculosis (based on the pathogenesis of the disease).

Classification System for TB

Class	Type	Description
0	No TB exposure Not infected	No history of exposure Negative reaction to tuberculin skin test
1	TB exposure No evidence of infection	History of exposure Negative reaction to tuberculin skin test
2	TB infection No disease	Positive reaction to tuberculin skin test Negative bacteriologic studies (if done) No clinical, bacteriologic, or radiographic evidence of TB
3	TB, clinically active	*M. tuberculosis* cultured (if done) Clinical, bacteriologic, or radiographic evidence of current disease
4	TB Not clinically active	History of episode(s) of TB or Abnormal but stable radiographic findings Positive reaction to the tuberculin skin test Negative bacteriologic studies (if done) and No clinical or radiographic evidence of current disease
5	TB suspect	Diagnosis pending TB disease should be ruled in or out within 3 months

SYMPTOMS:

PULMONARY TB (75% CASES): chest pain, coughing up blood, and a productive, prolonged cough for more than three weeks. Systemic symptoms include fever, chills, night sweats, appetite loss, weight loss, pallor and fatigue.[4][8]

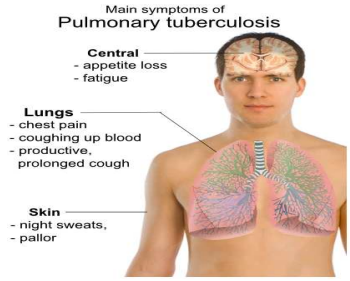

Fig no 2: symptoms of tuberculosis [84]

RISK FACTORS:

- Persons with silicosis have an approximately *30-fold* greater risk for developing TB [10] [11][12][7]
- Persons with chronic renal failure who are on hemodialysis also have an increased risk: 10—25 times greater than the general population.
- Persons with diabetes mellitus have a risk for developing active TB that is two to four times greater than persons without diabetes mellitus
- gastrectomy with attendant weight loss and malabsorption, jejunoileal bypass, renal and cardiac transplantation, carcinoma of the head or neck, and other neoplasm's are also associated with active TB(e.g., lung cancer, lymphoma, and leukemia) [2].
- Low body weight is associated with risk of tuberculosis.[1][5]
- A body mass index (BMI) below 18.5 increases the risk by 2—3 times. On the other hand, an increase in body weight lowers the risk [6], [9].
- prolonged corticosteroid therapy and other immunosuppressive therapy; Immunocompromised patients ,hematologic and reticuloendothelial diseases, such as leukemia and Hodgkin's disease; end-stage kidney disease; intestinal bypass; chronic malabsorption syndromes; vitamin D deficiency;[26].
- Specific gene polymorphisms in *IL12B* have been linked to tuberculosis susceptibility.[13]
- Some drugs, including rheumatoid arthritis drugs that work by blocking tumor necrosis factor-alpha (an inflammation-causing cytokine), raise the risk of activating a latent infection due to the importance of this cytokine in the immune defense against TB.[14]

PATHOGENESIS:

TB infection begins when the mycobacteria reach the pulmonary alveoli, where they invade and replicate within the endosomes of alveolar macrophages.[1][20] The primary site of infection in the lungs is called the Ghon focus, and is generally located in either the upper part of the lower lobe, or the lower part of the upper lobe[1]. Bacteria are picked up by dendritic cells, which do not allow replication, although these cells can transport the bacilli to local (mediastinal) lymph nodes. Further spread is through the bloodstream to other tissues and organs where secondary TB lesions can develop in other parts of the lung (particularly the apex of the upper lobes), peripheral lymph nodes, kidneys, brain, and bone.[1][21] All parts of the body can be affected by the disease, though it rarely affects the heart, skeletal muscles, pancreas and thyroid.[21]

Tuberculosis is classified as one of the granulomatous inflammatory conditions. Macrophages, T lymphocytes, B lymphocytes and fibroblasts are among the cells that aggregate to form a granuloma, with lymphocytes surrounding the infected macrophages. The granuloma functions not only to prevent dissemination of the mycobacteria, but also provides a local environment for communication of cells of the immune system. Within the granuloma, T lymphocytes secrete cytokines such as interferon gamma, which activates macrophages to destroy the bacteria with which they are infected.[22] Cytotoxic T cells can also directly kill infected cells, by secreting perforin and granulysin.[20] Importantly, bacteria are not always eliminated within the granuloma, but can become dormant, resulting in a latent infection.[1]

If TB bacteria gain entry to the bloodstream from an area of damaged tissue they spread through the body and set up many foci of infection, all appearing as tiny white tubercles in the tissues. This severe form of TB disease is most common in infants and the elderly and is called miliary tuberculosis.[25]

In many patients the infection waxes and wanes. Tissue destruction and necrosis are balanced by healing and fibrosis.[24] Affected tissue is replaced by scarring and cavities filled with cheese-like white necrotic material. During active disease, some of these cavities are joined to the air passages bronchi and this material can be coughed up. It contains living bacteria and can therefore pass on infection.[24]

STAGES OF INFECTION:

There are several stages:

- Primary infection
- Latent infection
- Active disease

Except for very young children and people with a weakened immune system, few people become sick immediately after tuberculosis bacteria enter their body (this stage is called primary infection). In most cases, tuberculosis bacteria that enter the lungs are immediately killed by the body's defenses. Those that survive are engulfed by white blood cells called macrophages. The engulfed bacteria can remain alive inside these cells in a dormant state for many years; walled off inside tiny scars (this stage is called latent infection). In 90 to 95% of cases, the bacteria never cause any further problems, but in about 5 to 10% of infected people, they eventually start to multiply and cause active disease. At this stage, infected people actually become sick and can spread the disease.

More than half the time, dormant bacteria reactive within the first 2 years after the primary infection, but they may not reactivate for a very long time, even decades

The progression of tuberculosis from latent infection to active disease varies greatly. Progression to active disease is far more likely and much faster in people with HIV infection and other conditions

(including drugs) that weaken the immune system.In people with a fully functioning immune system, active tuberculosis is usually limited to the lungs (pulmonary tuberculosis)[26].

Pulmonary tuberculosis occurs in about 75% of cases infecting the lungs. As in the lungs, the infection may not cause disease, but the bacteria may remain dormant in a very small scar .The extra pulmonary tuberculosis occurs in remaining 25% of cases. The infection moves from the lungs, causing other kinds of TB, collectively denoted extra pulmonary tuberculosis.[4] This occurs more commonly in immunosuppressed persons and young children. Extra pulmonary infection sites include the pleura in tuberculosis pleurisy, the central nervous system in meningitis, the lymphatic system in scrofula of the neck, the genitourinary system in urogenital tuberculosis and bones and joints in Pott's disease of the spine. An especially serious form is disseminated TB, more commonly known as miliary tuberculosis. Extra pulmonary TB may co-exist with pulmonary TB as well.[5]. Dormant bacteria can reactivate later in life, leading to symptoms related to the organs involved [26].

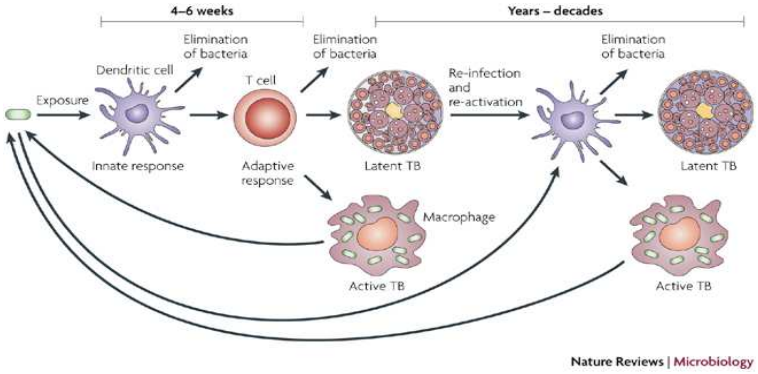

Fig no 3: active TB and latent TB [85]

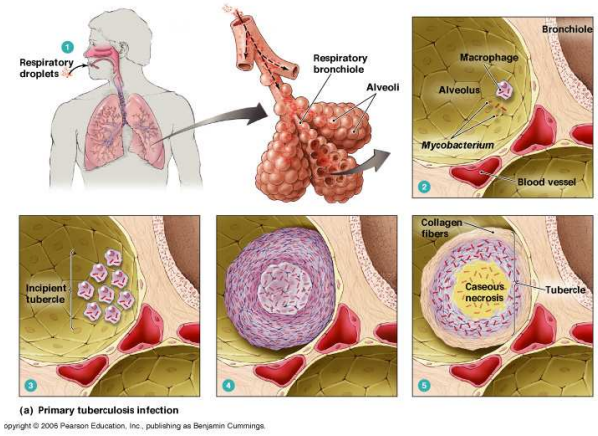

Fig no 4: primary TB infection [86]

In pregnant women, tuberculosis bacteria may spread to the fetus and cause disease (called congenital tuberculosis). However, such cases are extremely uncommon [26].

Tuberculosis: A Disease of Many Organs

Site Infection	Symptoms or Complications
Abdominal cavity	Fatigue, swelling, slight tenderness, and appendicitis-like pain
Bladder	Painful urination and blood in urine
Bones (mainly children)	Swelling and minimal pain
Brain	Fever, headache, nausea, drowsiness, and, if untreated, coma and brain damage
Pericardium (the membrane around the heart)	Fever, enlarged neck veins, and shortness of breath
Joints	Arthritis-like symptoms
Kidneys	Kidney damage and infection around the kidneys
Lymph nodes	Painless, red swollen lymph nodes, which may drain pus
Reproductive organs in men	Lump in the scrotum
Reproductive organs in women	Sterility
Spine	Pain, leading to collapsed vertebrae and leg paralysis

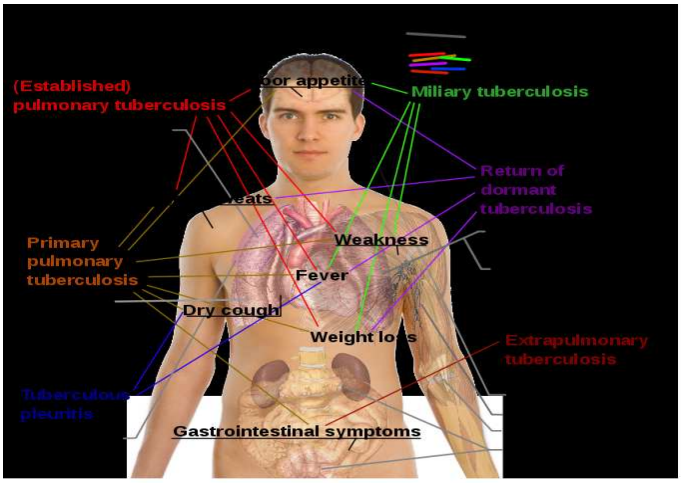

Fig no 5: pulmonary and extra pulmonary tuberculosis [83]

DIAGNOSIS:

Tuberculosis is diagnosed definitively by identifying the causative organism (*Mycobacterium tuberculosis*) in a clinical sample (for example, sputum or pus). When this is not possible, a probable - although sometimes inconclusive [2] - diagnosis may be made using imaging (X-rays or scans) and/or a tuberculin skin test (Mantoux test).

A complete medical evaluation for TB must include a medical history, a physical examination, a chest X-ray, microbiological smears, and cultures. It may also include a tuberculin skin test, a serological test.

TUBERCULIN TEST: Currently, latent infection is diagnosed in a non-immunized person by a tuberculin skin test, which yields a delayed hypersensitivity type response to an extract made from *M. tuberculosis*.[1] Those immunized for TB or with past-cleared infection will respond with delayed hypersensitivity parallel to those currently in a state of infection, so the test must be used with caution, particularly with regard to persons from countries where TB immunization is common.[41]

Mantoux test:A standard dose of 5 Tuberculin units (0.1 mL) [45] (The standard Mantoux test in the UK consists of an intradermal injection of 2TU of Statens Serum Institute (SSI) tuberculin RT23 in 0.1ml solution for injection.)[46]It is injected intradermally (between the layers of dermis) and read 48 to 72 hours later. A person who has been exposed to the bacteria is expected to mount an immune response in the skin containing the bacterial proteins.The reaction is read by measuring the diameter of induration (palpable raised hardened area) across the forearm (perpendicular to the long axis) in millimeters. If there is no induration, the result should be recorded as "0 mm". Erythema (redness) should not be measured. If a person has had a history of a positive tuberculin skin test, another skin test is not needed; if negative, another test may be needed.

Heaf's test: A Heaf gun is used to inject multiple samples of testing serum under the skin at once. A Heaf gun with disposable single-use heads is recommended. The gun injects purified protein derivative equivalent to 100,000 units per ml to the skin over the flexor surface of the left forearm in a circular pattern of six. The test is read between 2 and 7 days later. The reading of the Heaf test is defined by a scale:

- Negative - No induration, maybe 6 minute puncture scars
- Grade 1 - 4-6 papules (also considered negative)
- Grade 2 - Confluent papules form indurated ring (positive)
- Grade 3 - Central filling to form disc (positive)
- Grade 4 - Disc >10 mm with or without blistering (strongly positive)
- Grades 1 and 2 may be the result of previous BCG or avian tuberculosis. Children who have a grade 3 or 4 reaction require X-ray and follow-up[47].

INTERFERON RELEASE ASSAYS: The newer interferon release assays (IGRAs) detect the release of interferon gamma in response to mycobacterial proteins such as ESAT-6.[42] These are not

affected by immunization or environmental mycobacteria, so generate fewer false positive results.[43]There is also evidence that the T-SPOT.*TB* IGRA is more sensitive than the skin test[44]

DNA PROBES: For rapid identification of m.tuberculosis and other mycobacteria, several DNA probes have been developed and are available [27][28][29][30][31].They are used for rapid confirmation of the identity of mycobacterial isolates. When used along with newer methods of detection of growth early (BACTEC, SEPTI-CHEK, MGIT) the identity can be established in 1-2 days. For direct confirmation of diagnosis from clinical specimens, they are not very sensitive as they need more than 10000 organisms in the specimen for positivity.

RIBOSOMAL rRNA BAED PROBES: These probes target rDNA, ribosomal DNA, spacer and flanking sequences. These robes were earlier radio labeled, but now have been developed into chemiluminescent techniques[30].It is 10,000 times more sensitive than DNA targeting[31]and is used to directly confirm the diagnosis in clinical specimens. However the lowest detection limit is around 100 organisms.

GENE AMPLIFICATION METHODS: They are based on polymerase chain reaction and isothermal assays[27].PCR sequencing can be applied by reference labs while hybridization and RFLP approaches are workable in clinical mycobacteriology labs.

A) PCR methods: They represent ultimate sensitivity and detect 1-10 organisms. These assays are useful in early confirmation of diagnosis in apucibacillary and early stages of mycobacterial diseases[27].These PCR assays target either DNA or rRNA. Further, these include assays based on conventional DNA based PCR, nested PCR,RT-PCR etc. targeting insertion and repetitive elements various protein encoding genes and ribosomal RNA, transcription mediated amplification(TMA) and nuclei acid amplification(NAA)[40][32].They give the results within a few hours[32]

B) ISOTHERMAL AMPLIFICATION TECHNIQUES: In these techniques different enzymes other than taq polymerase are used and the various steps of amplification are completed at one temperature only. Strand displacement amplification(SDA)[33], direct test employing isothermal amplification of M.tuberculosis complez rRNA followed by detection of amplicon with acridinuim ester labeled DNA probe[33] and QB replicase based gene ampilifaction involving production of RNA in the amplification reaction

using QB replicas enzyme[34] are the three different methods.

MICROSCOPY: Its the simplest and most rapid procedure currently available to detect acid fast bacilli in clinical specimens by Ziehl-Neelsen staining method or its modifications. Its limitation is that it requires at least 5*1C bacilli per ml of sputum.[40]

SEPTI-CHECK AB METHOD: It consists of a capped bottle containing 30 ml of middle-brook 7H9 broth under enhanced (5-8%) carbon dioxide, a paddle with agar media and enrichment broth in a plastic tube. One side of the paddle is covered non selective middle brook 7H11 agar with Para nitro acetyl amino hydroxypropiophenone(NAP) for differentiation of M.tuberculosis from other mycobacteria, the other section contains chocolate agar for detection of contaminants. It requires 3 weeks of incubation. The advantage is the simultaneous detection of M.tuberculosis, non tuberculosis bacteria, other respiratory pathogens and even contaminants [35]

RADIOMETRIC BACTEC 460 TB METHOD: It is specific for mycobacterial growth wherein radioactive carbon labeled palmitic acid in 7H12 medium is used. It detects the presence of mycobacteria based on their metabolism rather than on visible growth. Drug susceptibility testing can also be done by this method [36]

DETECTION OF LAM IN SPUTUM: This is based on capture antibody derived from murine source. The rabbit antiserum against M.tuberculosis is used as a source of detector of the body.[40]

AST PLAQUE TB: It uses mycobacteriophage to detect the presence of M.tuberculosis directly from sputum specimens. It is a rapid and manual test.[37][38]

INSTA TEST TB: It is a rapid in vitro assay for detection of antibody in active TB using whole blood or serum. [39]

CHEST X-RAY: In active pulmonary TB, infiltrates or consolidations or cavities are often seen in the upper lungs with or without mediastinal or hilar lymphadenopathy.Old healed TB usually presents as pulmonary nodules in the hilar area or upper lobes. Chest radiographs are only suggestive but not diagnostic[1].

VACCINATION:

Bacillus Calmette-Guérin (or Bacille Calmette-Guérin, BCG) is a vaccine against tuberculosis that is prepared from a strain of the attenuated (weakened) live bovine tuberculosis bacillus.At best, the BCG vaccine is 80% effective in preventing tuberculosis for duration of 15 years [48].BCG is given as a single intradermal injection at the insertion of the deltoid. If BCG is accidentally given subcutaneously, then a local abscess may form (a BCG-oma) that may ulcerate and often requires treatment with antibiotics[49].BCG immunization leaves a characteristic raised scar that is often used as proof of prior immunization.

BCG vaccine is not recommended except for people who meet specific criteria: [5]

- Infants or children with negative skin test results who are continually exposed to untreated or ineffectively treated patients or will be continually exposed to multidrug-resistant TB.
- Healthcare workers considered on an individual basis in settings in which a high percentage of MDR-TB patients has been found, transmission of MDR-TB is likely, and TB control precautions have been implemented and were not successful.

- A very promising TB vaccine, MVA85A, is currently in phase II trials in South Africa by a group led by Oxford University,[50] and is based on a genetically modified vaccinia virus

Many other strategies are also being used to develop novel vaccines,[51] including both subunit vaccines (fusion molecules composed of two recombinant proteins delivered in an adjuvant) such as Hybrid-1, HyVac4 or M72, and recombinant adenoviruses such as Ad35.[52][53][54][55] Some of these vaccines can be effectively administered without needles, making them preferable for areas where HIV is very common.[56]

TREATMENT

First line

All first-line anti-tuberculoses drug names have a standard three-letter and a single-letter abbreviation:

- Ethambutol is EMB or E,
- Isoniazid is INH or H,
- Pyrazinamide is PZA or Z,
- Rifampicin is RMP or R,
- Streptomycin is STM or S.

Second line

There are six classes of second-line drugs (SLDs) used for the treatment of TB. A drug may be classed as second-line instead of first-line for one of two possible reasons: it may be less effective than the first-line drugs or, it may have toxic side-effects or it may be unavailable in many developing countries

- Aminoglycosides: e.g., amikacin (AMK), kanamycin (KM);
- Polypeptides: e.g., capreomycin, viomycin, enviomycin;
- Fluoroquinolones: e.g., ciprofloxacin (CIP), levofloxacin, moxifloxacin (MXF);
- Thioamides: e.g. ethionamide, prothionamide.

- Cycloserine (the only antibiotic in its class);
- P-aminosalicylic acid (PAS or P).

Third line

These drugs are not very effective and are not on WHO listing

- Rifabutin
- Macrolides: e.g., clarithromycin (CLR);
- Linezolid (LZD);
- Thioacetazone (T);
- Thioridazine;
- Arginine;
- Vitamin D;
- R207910[57][58][59]

Table of drugs used for the treatment of tuberculosis.

First line drugs		Second line drugs	
Essential	**Other**	**Old**	**New**
Isoniazid Rifampicin	Pyrazinamide Ethambutol Streptomycin	Ethionamide Cycloserine Capreomycin Amikacyn Kanamycin PAS Thiocetazone	Quinolones ofloxacin ciprofloxacin sparfloxacin Macrolides clarithromycin Clofazimine Amoxycillin & Clavulanic acid
New rifamycins Rifabutin Rifapentine			

- Isoniazid kills the great bulk of bacteria, rapidly rendering the patient non-infectious within days of starting treatment
- Rifampicin eliminates the persisting bacteria (so called sterilization) allowing treatment time to be shortened considerably.
- The *new* patients should be started on isoniazid and rifampicin plus at least one drug from the second column.
- The addition of pyrazinamide for the first two months only allows treatment to be given for as little as six months
- If ethambutol only is given for the first two months of treatment instead of pyrazinamide, the total time of treatment should be nine months.
- The current recommendation is to give two drugs from the second column; pyrazinamide and ethambutol, in addition to isoniazid and rifampicin until culture and sensitivity results are available.

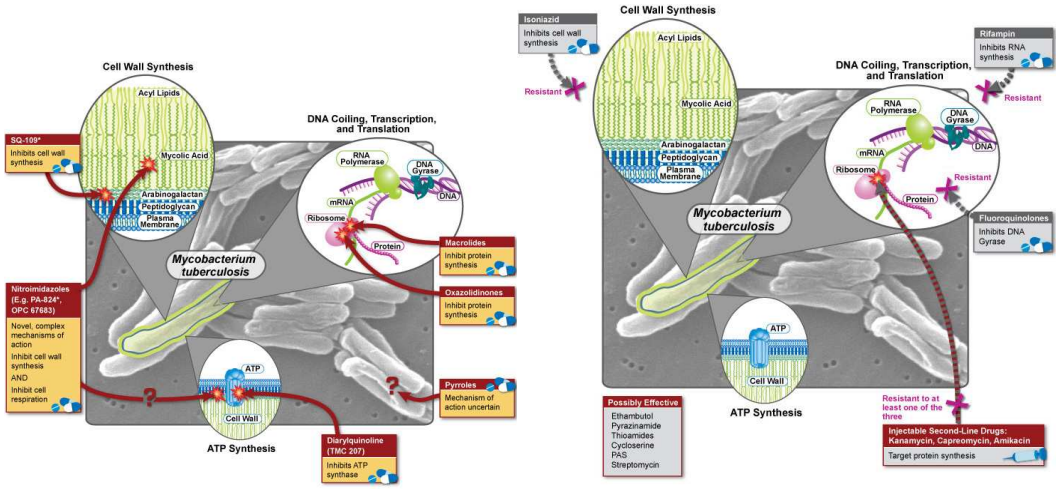

Fig no 6,7: action of anti tuberculosis drugs.[87][88]

Steroids:

The usefulness of corticosteroids (e.g., prednisolone or dexamethasone) in the treatment of TB is proven for TB meningitis and TB pericarditis. The dose for TB meningitis is dexamethasone 8 to 12 mg daily tapered off over six weeks. The dose for pericarditis is prednisolone 60 mg daily tapered off over four to eight weeks.

Steroids may be of temporary benefit in pleurisy, extremely advanced TB, and TB in children:

- **Pleurisy:** prednisolone 20 to 40 mg daily tapered off over 4 to 8 weeks
- **Extremely advanced TB:** 40 to 60 mg daily tapered off over 4 to 8 weeks
- **TB in children:** 2 to 5 mg/kg/day for one week, 1 mg/kg/day the next week, then tapered off over 5 weeks

Thalidomide may be of benefit in TB meningitis and has been used in cases where patients have failed to respond to steroid treatment.[61]

Standard regimen and dosing frequency for new TB patients [80]

Intensive phase	Continuation phase
2 months of HRZE	4 months of HR
2 months of HRZE	4 months of HRE

Recommended doses of first-line anti tuberculoses drugs for adults

Drug	Recommended dose			
	Daily	3 times per week		
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and range (mg/kg body weight)	Daily maximum (mg)
Isoniazid	5 (4–6)	300	10 (8–12)	900
Rifampicin	10 (8–12)	600	10 (8–12)	600
Pyrazinamide	25 (20–30)	–	35 (30–40)	–
Ethambutol	15 (15–20)	–	30 (25–35)	–
Streptomycin	15 (12–18)	-	15 (12–18)	1000

Standard regimens for new TB patients (presumed, or known, to have drug-susceptible TB)

Intensive phase treatment	**Continuation phase**
2 months of HRZE.	4 months of HR.

FOR HIV PATIENTS:

Co-trimoxazole preventive therapy:

In all HIV-positive TB patients, co-trimoxazole preventive therapy should be initiated as soon as possible and given throughout TB treatment. Co-trimoxazole preventive therapy substantially reduces mortality in HIV-positive TB patients (*71,75*). The exact mode of activity is not clear but co-trimoxazole is known to prevent *Pneumocystis jirovecii* and malaria and is likely to have an impact on a range of bacterial infections in HIV-positive TB patients.

A system for providing co-trimoxazole preventive therapy to all people living with HIV who have active TB should be established by TB and HIV programmes. Continuation after TB treatment is completed should be considered in accordance with national guidelines. [75]

Antiretroviral therapy:

Antiretroviral therapy improves survival in HIV-positive patients (*71*). In addition, antiretroviral therapy reduces TB rates by up to 90% at an individual level, by 60% at a population level and it reduces TB recurrence rates by 50% (*76-77*). ART should be initiated for *all* people living with HIV with active TB disease irrespective of CD4 cell count. TB treatment should be started first, followed by ART as soon as possible and within the first 8 weeks of starting TB treatment (*78*).

First-line ART regimen contain two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI). These are efficacious, relatively less expensive, have generic and FDC formulations, do not require a cold chain, and preserve a potent new class of agents (protease inhibitors) for second-line regimens. The preferred NRTI backbone is zidovudine (AZT) or tenofovir disoproxil fumarate (TDF), combined with either lamivudine (3TC) or

emtricitabine (FTC). For the NNRTI, WHO recommends either efavirenz (EFV) or nevirapine (NVP) (*79*).

The recommended first-line ART regimens for TB patients are those that contain efavirenz (EFV), since interactions with anti-TB drugs are minimal. In several cohort studies, ART with standard-dose efavirenz and two nucleosides was well tolerated and highly efficacious in achieving complete viral suppression among patients re¬ceiving concomitant rifampicin-based TB treatment (24).

Because of concerns related to teratogenicity, efavirenz should not be used in women of childbearing potential without adequate contraception, nor should it be used for women who are in the first trimester of pregnancy. Alternatives are also needed for patients who are intolerant to efavirenz or are infected with a strain of HIV that is resistant to NNRTIs. For those who are unable to tolerate EFV or who have contraindications to an EFV-based regimen, AZT +3TC + NVP or TDF +3TC or FTC + NVP or a triple NRTI regimen (AZT+3TC+ABC or AZT+3TC+TDF) is recommended; the choice of regimen should be based on available regimens within countries. In countries where rifampicin is available, the lead-in dose of nevirapine is not necessary.

In individuals who need TB treatment and who require an ART regimen containing a boosted protease inhibitor (PI), it is recommended to give a rifabutin-based TB treatment. If rifabutin is not available, the use of rifampicin and a boosted antiretroviral regimen containing lopinavir or saquinavir with additional ritonavir dosing is recommended; this regimen should be closely monitored.

LATENT TB:

For Latent TB, the standard treatment is a prescription of isoniazid alone for a period of 6-9 months. The prescription is one tablet a day. Ethambutol is not to be used, if the organism concerned is fully sensitive. In this case treatment is carried on the same as that for Active TB but with the absence of Ethambutol[62]

EXTRA PULMONARY TB:

Possible regimens include: Two hepatotoxic drugs (rather than the three in the standard regimen):9 months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented); 2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin;

TB of the Central Nervous System:

The standard procedure for this form of TB is 12 months of treatment. This includes 2 months of isoniazid, rifampicin, ethambutol and pyrazinamide, and 10 months of isoniazid and rifampicin. Steroids are mandatory during this treatment.

The anti-TB drugs that are most useful for the treatment of CNS TB are [63][64]:

- INH (CSF penetration 100%)
- RMP (10–20%)
- EMB (25–50% inflamed meninges only)
- PZA (100%)
- STM (20% inflamed meninges only)
- LZD (20%)
- Cycloserine (80–100%)
- Ethionamide (100%)
- PAS (10–50%) (inflamed meninges only)

The use of steroids is routine in TB meningitis

MULTI DRUG RESISTANT TUBERCULOSIS:

Multi-drug resistant tuberculosis (MDR-TB) is defined as TB that is resistant at least to INH and RMP. Isolates that are multiply-resistant to any other combination of anti-TB drugs but not to INH and

RMP are not classed as MDR-TB[42]. MDR-TB can develop in the course of the treatment of fully sensitive TB and this is always the result of patients missing doses or failing to complete a course of treatment

The treatment and prognosis of MDR-TB are much more akin to that for cancer than to that for infection. It has a mortality rate of up to 80%, which depends on a number of factors, including

- How many drugs the organism is resistant to (the fewer the better),
- How many drugs the patient is given (Patients treated with five or more drugs do better),
- Whether an injectable drug is given or not (it should be given for the first three months at least),
- The expertise and experience of the physician responsible
- How co-operative the patient is with treatment (treatment is arduous and long, and requires persistence and determination on the part of the patient),
- Whether the patient is HIV positive or not (HIV co-infection is associated with an increased mortality).

When sensitivities are known and the isolate is confirmed as resistant to both INH and RMP, five drugs should be chosen in the following order (based on known sensitivities):

- an aminoglycoside (e.g., amikacin, kanamycin) or polypeptide antibiotic (e.g., capreomycin)
- PZA
- EMB
- a fluoroquinolones: moxifloxacin is preferred (ciprofloxacin should no longer be used[60]);
- rifabutin
- cycloserine
- a thioamide: prothionamide or ethionamide.

- PAS
- a macrolide: e.g., clarithromycin
- linezolid
- high-dose INH (if low-level resistance)
- interferon-γ
- thioridazine
- meropenem and clavulanic acid[61]

Response to treatment must be obtained by repeated sputum cultures (monthly if possible). Treatment for MDR-TB must be given for a minimum of 18 months and cannot be stopped until the patient has been culture-negative for a minimum of nine months. It is not unusual for patients with MDR-TB to be on treatment for two years or more. [55][56]

Groups of drugs to treat MDR-TB

Group	Drugs (abbreviations)
Group 1: First-line oral agents	• pyrazinamide (Z) • ethambutol (E) • rifabutin (Rfb)
Group 2: Injectable agents	• kanamycin (Km) • amikacin (Am) • capreomycin (Cm) • streptomycin (S)
Group 3: Fluoroquinolones	• levofloxacin (Lfx) • moxifloxacin (Mfx) • ofloxacin (Ofx)
Group 4: Oral bacteriostatic second-line agents	• para-aminosalicylic acid (PAS) • cycloserine (Cs) • terizidone (Trd) • ethionamide (Eto) • protionamide (Pto)
Group 5: Agents with unclear role in treatment of drug resistant-TB	• clofazimine (Cfz) • linezolid (Lzd) • amoxicillin/clavulanate (Amx/Clv) • thioacetazone (Thz) • imipenem/cilastatin (Ipm/Cln) • high-dose isoniazid (high-dose H)b • clarithromycin (Clr)

Historical surgical management:

They were based on the observation that healed tuberculosis cavities were all closed.

Recurrent or persistent pneumothorax:

The simplest and earliest procedure was to introduce air into the pleural space so as to collapse the affected lung and therefore the open cavity. There was always spontaneous resolution of the pneumothorax and the procedure had to be repeated every few weeks.

Phrenic nerves crush:

The phrenic nerve was cut or crushed so as to permanently paralyze the diaphragm on that side. The paralyzed diaphragm would then rise up and the lung on that side would collapse, thus closing the cavity.

Thoracoplasty:

When the cavity was located in the apex of the lung, thoracoplasty could be performed. Six to eight ribs were broken and pushed into the thoracic cavity to collapse the lung beneath.

Plombage:

Plombage reduced the need for a disfiguring operation. It involved inserting porcelain balls into the thoracic cavity to collapse the lung underneath.

Modern surgical management:

In modern times, the surgical treatment of tuberculosis is confined to the management of multi-drug resistant TB. A patient with MDR-TB who remains culture positive after many months of treatment may be referred for lobectomy(*surgical excision of a lobe*) or pneumonectomy(remove a lung) with the aim of cutting out the infected tissue. The optimal timing for surgery has not been defined, and surgery still confers significant morbidity. [73-81]

SIDE EFFECTS

- **Isoniazid:** Some of the side effects of this drug include- rash, abnormal, hepatitis, sideroblastic anemia, peripheral neuropathy, headache, poor concentration, poor memory and depression.
- **Rifampicin:** Certain adverse effects known to be caused by this drug are-Fever, gastrointestinal disturbances, rashes and immunological reactions. Liver damage, associated with jaundice, has also been reported and in some rare cases has led to death. At times bodily fluids, such as urine and tears, are known to become orange-red in color.
- **Pyrazinamide**: The most common side affect of this drug (1%) is joint pains, and the most dangerous side effect is Hepatitis. Hepatitis is a dose related side effect, and since its dosage has been reduced, the occurrence of Hepatitis has greatly fallen. Other minor side effects include – nausea, vomiting, anorexia, skin rash, sideroblastic anemia, pruritus, dysuria, hyperuricemia, interstitial nephritis, malaise and fever.
- **Ethambutol:** Optic neuritis, red-green color blindness, peripheral neuropathy and arthralgia are some of the side effects caused by ethambutol[70].

Symptom-based approach to manage side-effects of anti-TB drugsSide-effects	**Drug(s) probably responsible**	**Management**
Major	**Stop responsible drug(s) and refer to clinician urgently**	
Skin rash with or without itching	Streptomycin, isoniazid, rifampicin, pyrazinamide	Stop anti-TB drugs
Deafness (no wax on otoscopy)	Streptomycin	Stop streptomycin
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin
Jaundice (other causes excluded), hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs
Confusion (suspect drug-induced acute liver failure if there is	Most anti-TB drugs	Stop anti-TB drugs

jaundice)		
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin
Decreased urine output	Streptomycin	Stop streptomycin
Minor	**Continue anti-TB drugs, check drug doses**	
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin, isoniazid	Give drugs with small meals or just before bedtime, and advise patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side-effect to be major and refer to clinician urgently.
Joint pains	Pyrazinamide	Aspirin or non-steroidal anti-inflammatory drug, or paracetamol
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50–75 mg daily [70]
Drowsiness	Isoniazid	Reassurance. Give drugs before bedtime
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this may happen and is normal
Flu syndrome (fever, chills, malaise, headache, bone pain)	Intermittent dosing of rifampicin	Change from intermittent to daily rifampicin administration (*62*)

THE VARIOUS SINGLE DRUGS AND MULTIPLE DRUG FORMULATIONS AND THE BRAND NAMES:

DRUGS - THEIR GENERIC AND BRAND NAMES

S.NO	GENERIC NAME	BRAND NAME
1	RIFAMPICIN	Rifadin ,Rimactane ,Coxid ,Rcin ,Rcinex ,Macox ,Rimpin ,Ticin ,Docina ,Eufacin ,Lositril ,Rifacilin ,Famcin ,Cavikid.
2	ISONIAZID	Niazid ,Isokin ,Isonex , Solonex ,Siozide Ipkazide.
3	ETHAMBUTOL	Myambutol ,Servambutol, Albutol ,combutol ,Themibutol ,Tibitol ,Mycobutol ,cavibutol
4	PYRAZINAMIDE	Pyrazinamide, acitizid, antizid ,pzina kid pza ciba ,piraldina
5	CAPREOMYCIN	Caprocin,Ogostal
6	CIPROFLOXACIN	Cipro, Cipro XR, Proquin XR
7	LEVOFLOXACIN	Levaquin
8	AMIKACIN	Amikin
9	KANAMYCIN	Kanatrix[71]

FIXED DRUG COMBINATIONS:

S.No.	Product	Tablet/Capsule (mg)	Syp./Susp. (mg/5 ml)	Vitamin B6 (mg)	Pharmaceutical Company
A.	*Isoniazid*				
1.	Ipcazide	100	100	5	Ipca
2.	Isokin	100	100	–	Parke-Davis
3.	Isonex	100	–	–	Pfizer
4.	Solonex	100	–	–	Themis

5.	Siozide	–	100	5	Albert-David
B.	*Rifampicin*				
6.	Macox	100	–	–	Macleods
7.	Rcin	150	100	–	Lupin
8.	Rimpin	100	100	–	Lyka
9.	Ticin	–	100	–	Themis
10.	Docina	–	150	3	Ashok Pharma
11.	Eufacin	150	–	–	Euphoric
12.	Lositril	150	–	–	Hindustan Antibiotics
13.	Rifacilin	150	–	–	PCI
14.	Rimactane	150	100	–	Novartis
15.	Famcin	150	–	–	IDPL
16.	Cavikid	50	–	–	Merind
C.	*Pyrazinamide*				
17.	Pzina Kid	300	–	–	Lupin
18.	Pza Ciba	–	250	–	Novartis
19.	Piraldina	250	–	–	Pharmed
D.	*Ethambutol*				
20.	Themibutol	200	–	–	Themis
21.	Tibitol	200	–	–	PCI
22.	Combutol	200	–	–	Lupin
23.	Mycobutol	200	–	–	Cadila Pharma
24.	Albutol	200	–	–	Alkem
25.	Cavibutol	200	–	–	Merind
26.	Myambutol	200	–	–	Wyeth Lederle

Rifampcin and Isoniazid Combinations.

S.No.	Product (Tab)	R (mg)	H (mg)	Pharmaceutical Company
1.	Cavikid – INH	100	50	Merind
2.	Macox plus kid	100	50	Macleod
3.	Montonex kid	100	50	Plethico
4.	Optirifa plus	100	50	Troikaa
5.	Rimactazid	100	50	Novartis
6.	Ticinex kid	100	50	Themis
7.	Rcinex 50	50	100	Lupin
8.	Docina R kid B6 (5mg)	100	50	Ashok Pharma
9.	Rimpinah DT	100	50	Lyka
10.	Eufacin INH kid	100	100	Euphoric
11.	Rcinex kid	100	100	Lupin
12.	Rifa i 6 kid forte	200	150	Concept
13.	Rifa i 6 kid	100	100	Concept
14.	Binex kid	150	100	Biological E
15.	Rifanex kid	100	100	Bestochem
16.	Anticox II kid	150	100	Unichem
17.	Ipcacin (B6 6 - mg)	100	100	Ipca
18.	Tibrim INH	100	100	Stancare

Rifampicin, Isoniazid and Pyrazinamide Combinations.

S.No	Product (Tab/Cap)	R (mg)	H (mg)	Z (mg)	Pharmaceutical Company
1.	Caviter	120	80	750	Merind
2.	Caviter Forte	225	150	750	Merind
3.	Gocox 3	225	150	750	Ipca
4.	Macox ZH	225	150	750	Macleods
5.	Montorip	225	100	750	Plethico

6.	Montorip Forte	225	150	750	Plethico
7.	R'cinex Z	225	150	750	Lupin
8.	Rifacept 3 (B6 - 3.5 mg)	225	150	375	Concept
9.	Rifacept Kid 3 (B6 - 2.5 mg)	100	75	250	Concept
10.	Rifater	120	80	250	Hoechst Marion
11.	Rifinex Plus	150	100	500	Kopran
12.	Rinizide	150	100	375	Lupin
13.	Tricox	225	100	500	Themis
14.	Eufazid	225	100	500	Euphoric
15.	Iso Rifazin	225	100	500	PCI
16.	Rimpin-Ipz	150	100	350	Lyka
17.	Rinizide Forte	150	150	300	Lupin
18.	3 FD Tablet	225	150	750	Novartis
19.	Coxter - 3FD	150	100	500	Alkem
20.	Tricox-Forte	225	150	750	Themix

Four Drug Combinations

S.No	Product (Tab)	R (mg)	H (mg)	Z (mg)	E (mg)	Pharmaceutical Company
1.	Akt FD	150	100	500	267	Lupin
2.	Confez	225	150	300	800	Plethico
3.	Forecox	225	300	750	400	Macleods
4.	Caviter FD	225	150	750	400	Merind
5.	Coxter – 4 fd	225	150	500	267	Alkem
6.	Eufacin Plus	225	150	750	400	Euphoric
7.	Tetracox	225	150	750	267	Themis[72]

COMBIPACKS:

- AKT 4 is a combipack and contains: 1 capsule of rifampicin 450 mg, 2 tablets of pyrazinamide 750 mg and 1 tablet of ethambutol 800 mg plus isoniazid (INH) 300 mg.
- AKT3 is a combipack and contains 1 tab of ethambutol 800 mg, isoniazid 300 mg, each composite combipack contains1 cap of rifampicin 450 mg.
- AKT2 is a combipack and contains isoniazid 300 mg, rifampicin 450 mg.
- 4D combipack contains 1 tab of ethambutol hydrochloride 800 mg, isoniazid 300 mg, 2 tabs of pyrazinamide 750 mgeach , Each combi-pack contains 1 fc-tab of rifampicin 450 mg.
- RHE-FD 3 Drug (RHE) Fixed Drug Combination contains ethambutol 800 mg, isoniazid 300 mg, rifampicin 450 mg.
- Akurit 3 contains ethambutol hydrochloride 275 mg, isoniazid 275 mg, rifampicin 150 mg.
- The other available combinations include BICOX, BINEX, CAVITER, COXRID, COXTER [70][71][72]

SUMMARY:

Patients with tuberculosis are benefited by an early diagnosis and proper treatment regularly. Any irregularity in the treatment causes the relapse of the disease. The complications as described above can thus be avoided.

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