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A REVIEW ON MODERN APPROACHES IN DIAGNOSIS AND MANAGEMENT OF TUBERCULOSIS

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ABSTRACT

Tuberculosis (TB) could be a major reason behind death from a single infectious agent. One-third of the planet population is infected with mycobacterium tuberculosis (MTB). Early and effective treatment is important to stop the emergence of drug resistance strains. Whilethere has been significant progress in the diagnosis and treatment of the infection in recent decades. Improvements are needed in both diagnostic tools and therapeutic regimens. In this review, we discuss the eight diagnostic tools of tuberculosis recommended by WHO. We also discuss the recent advances in the management of tuberculosis.

Keywords: Tuberculosis, extra-pulmonary-Tuberculosis, diagnosis, treatment

INTRODUCTION

Tuberculosis (TB) continuous to be a first-class public health priority, representing the leading reason for death at global level. Every day, nearly 4000 people die from TB and nearly 30000 people fall ill with this disease. Of note, nearly 1/2 the worldwide TB cases are reported in precisely three countries (India, Indonesia and China) **[1]**.

Pulmonary tuberculosis (PTB) constitutes about 80% of the entire cases. It can even affect other tissues of the body, referred to extra-pulmonary tuberculosis (EPTB) including intestine, meninges, lymph nodes, bones, joints, kidneys and skin **[2]**.

World health organization (WHO) suggests utilizing the screening methods first to spot the high risk individuals and systemic screening of PTB to hurry up its early detection and commencement of treatment **[3, 4]**.

WHO recommends a complete of eight diagnostic tools includes, 1. Light emitting diode microscopy

2. Commercial liquid culture
3. DST (drug susceptibility test)
4. Rapid speciation strip technology
5. X pert/MTB-RIF
6 .Lateral flow urine lipoarabinomannan
7. Loop mediated isothermal amplification
8. Line probe assay.

However these methods aren't approved because of lack of knowledge **[4]**.

Anti-TB treatment targets to cure the patient, prevent complications and mortality, avoid re- lapses, reduce the transmission ability to inclined individuals, and restrict the emergence and spread of drug-resistant strains. For these motives, the therapeutic technique to tuberculosis necessitates the use of various medications. In other cases, such as in patients with substantial bone involvement or those with cerebral tuberculomas, longer therapies are needed **[5]**.

CLINICAL DIAGNOSIS

When at least one of four suggestive symptoms is observed, tuberculosis should be suspected (long-lasting fever, cough of 2-week duration or more, night sweats and weight loss). Epidemiological considerations, such as contact with pulmonary tuberculosis case and/or exposure to other risk factors for tuberculosis acquisition or reactivation, also must be thoroughly assessed **[6]**. Tuberculosis may additionally be exhibited with extra pulmonary manifestations including lymphadenitis, kidney, bone, or joint involvement; meningitis; or disseminated disease. Symptoms of Extra Polumary Tuberculosis rely on the organs involved **[7, 8]**.

MICROSCOPY

Direct microscopic examination could be a fast and cheap method to spot acid-fast bacilli through the employment of Ziehl–

Neelsen staining; however, it's limited by poor sensitivity and also the inability to discriminate between mycobacterial species, which may be a relevant issue especially among children and immunocompromised individuals. Fluorescence or diode microscopy could also be an alternate to traditional microscopy with a moderate improvement in sensitivity (+10%) but also slightly higher costs and therefore the need for well-trained technicians **[9]**.

LINE PROBE ASSAYS.

The presence of mycobacterium tuberculosis and drug probes is detected using the line probe assays. The presence of mycobacterium tuberculosis can be seen by looking at the colored band **[10]**. For more than one decade, WHO has authorized line probe assays for the first line tuberculosis medicines (INH and RIF) for the identification of multi-drug resistance tuberculosis **[11]**. LPAs can detect mutations related to fluoroquinolones (FLQs) and second-line injectables, such as kanamycin, amikacin, and capreomycin, and are recommended to guide MDR-TB treatment initiation. New-generation LPAs have improved sensitivity and a few (e.g., Genotype MTBDR SL version 2.0; Hain Lifesciences-Bruker) can detect mutation related to FLQs **[12]**.

XPERT

The Xpert assay was performed as 2:1 volume of sample reagent (SR) buffer was added to biopsy specimens after they'd been chopped into very small pieces with a sterile blade in an exceedingly sterile Petri dish. Care was taken to make certain that a minimum of one piece entered the cartridge. Fluids were processed directly by the addition of a 2:1 volume of SR buffer, apart from CSF (usually <1 ml), which was raised to 2 ml by the addition of SR buffer. The results attained were during a simple text format which may be read easily. Just in case where results were reported as being "invalid," "no result," or "error," the sample was reused and rerun if sufficient material was available **[13]**.

In the UK, which could be a low prevalence setting, findings from one center showed that discordance between the Xpert® MTB/RIF assay and culture results mainly occurred for non-respiratory specimens **[14]**. However, considering that the culture confirmation rate is low in extrapulmonary-TB there's still a task for molecular tools just like the Xpert®MTB/RIF assay (with the exception of pleural disease where its sensitivity is low compared to traditional culture) **[15]**. The assay has been shown to be a useful adjunct within the diagnosis of mediastinal nodal TB using endobronchial ultrasound, particularly when utilized in conjunction with cytology obtained from trans bronchial needle aspiration **[16]**.

LOOP MEDIATED ISOTHERMAL AMPLIFICATION (LAMP)

LAMP is a simple rapid, specific and cost effective NAA method developed by Eiken Chemical, Japan **[17]**. It uitilizes the set of primers that is specifically designed to identify different regions of target genes. Amplification is carried in a single step by strand displacement reaction for 15-16 min at constant temperature 60 **[18]**. Using this method for diagnosis tuberculosis in peripheral settings and high endemic sensitivity and specificity of this assay was observed in the range of 76-80% and 97-98% respectively in different settings **[19]**.

LATERAL FLOW URINE LIPOARABINOMANNAN ASSAY

Useful for diagnosing active tuberculosis. LAM is an antigen situated in the mycobacterial outer cell wall and it is supposed to be present in the individuals with active disease but not in those with LTBI irrespective of their immunological conditions **[20, 21]**. May proven advantages for prohibit TB in children and facilitate the identification of extrapulmonary forms of TB. But, no information is provided about the mycobacterial species and the drug susceptibility patterns of infecting strain **[22]**.

PHENOTYPIC DRUG SUSCEPTIBILITY TEST

Susceptibility Testing for first and second-line medicine may be undertaken victimization liquid cultures. Whereas this approach is additional sensitive than victimization solid cultures and offers a quicker work time for results, it will still take a pair of weeks for pulmonic TB to be confirmed followed by an additional a pair of weeks to get the ultimate DST result. However validatory results take considerably longer: up to eight weeks for pulmonic TB confirmation followed by 5 weeks to get the ultimate DST results **[23]**. The numerous time taken to yield final results by the standard DST technique carries a risk of patients with drug-resistant TB being treated with antibiotic regimens that will be ineffective, which can allow additional unfold of drug-resistant strains and doubtless promote choice of strains with even larger resist **[24]**.

DIAGNOSTICS TEST FOR LATENT TUBERCULOSIS INFECTION

2 types of skin test

1. Tuberculin skin test.
2. Interferon gamma release assay.

TUBERCULIN SKIN TEST

TSTs could offer false positive results if there's a history of taking BCG vaccine or exposure to non-tuberculous mycobacteria **[25]**. False negative results could occur due to: patients being disorder secondary to HIV infection, malignancy or use of medication agents; extremes of patient age; improper administration of the liquid matter **[26]**. In patients with HIV infection, the belittled

sensitivity of TST testing has been attributed to hypersensitivity the development of energy that refers to a diminished delayed-type response in antecedently susceptible people **[27]**. What is more, recurrent TST testing is related to issues such as: boosting, wherever the immunologic recall to previous exposure to mycobacterial antigens causes the TST response to increase; conversion of negative results to positive results thanks to new infections; reversion of positive results to negative results; and problems about variable biological response and variability among clinicians in reading the ultimate results **[28]**.

INTERFERON GAMMA RELEASE ASSAYS

Two wide used IGRAs square measure the QuantiFERON-TB Gold In-Tube (QFT-GIT) (Cellestis Ltd., Carnegie, Australia) and T-SPOT.TB (Oxford Immunotec Ltd., Oxford, UK) **[29]**. QFT-GIT may be a whole-blood based mostly enzyme-linked immunosorbent assay that measures the number of interferon-gamma created in response to exposure tothe M. TB antigens ESAT-6, CFP-10 and TB7.7 **[30]**. The QuantiFERON-TB and (QFT-Plus) (Qiagen, Hilden, Germany) works as a similar way to QFT-GIT however differs as a result of it contains a further matter tube that may stimulate each CD4 and CD8 T cells to supply interferon-gamma and it additionally dispenses with the TB antigen **[31]**. T-SPOT.TB is an enzyme-linked immunospot-based test which measures the quantity of peripheral mononuclear cells manufacturing interferon-gamma in response to ESAT-6 and CFP-10 **[30]**.

THE FUTURE OF TB DIAGNOSIS: WHOLE GENOME SEQUENCING IN DIAG- NOSIS AND PREDICTING DRUG RESISTANT *M. TUBERCULOSIS*

Whole genome sequencing (WGS), the coming- generation sequencing (NGS) groundedtechnology allows the high outturn sequence read of the entire genome of a microorganism **[31]**. This NGS grounded technology **[32]** has been successfully applied for the routine characterization of the organism **[33]**, medicine vulnerability testing **[32]**, genotyping and epidemiological disquisition of tuberculosis **[34]**. Whole genome sequencing pose an ad-vantage to immaculately descry all the mutations with their functional categorization **[35]** as compared to Xpert MTB/ RIF and line inquiry assays which are limited to identifymutations in specific locus **[36]** and are unfit to distinguish whether a mutation leads to a change in amino acid sequence **[37]**. Likewise, WGS can identify the resistance deter- mining mutations in new medicines, for illustration, bedaquiline and delamanid

[38] WHO is soon likely to publish a specialized guideline addressing the operation and interpretation of DNA sequencing technology in TB diagnostics.

TREATMENT OF TUBERCULOSIS

Anti-TB treatment focus to cure the patient, stop complications and mortality, prevent relapses, scale back the transmission likely to vulnerable people, and limit the emergence and develop of drug-resistant strains. For of these motives, the therapeutic technique to TB needs the utilization of multiple medication **[39]** .The first-line customary regime that's presently suggested for drug-susceptible TB is predicated on a 2-month intensive part with four medication (isoniazid, rifampicin, pyrazinamide and ethambutol; HRZE) followed by a 4-month consolidation part with 2 medication (isoniazid and rifampicin). Dose adjustment is needed for youngsters in step with weight; however the regime composition remains an equivalent **[40]**. There are numerous sensible concerns within the administration of anti-TB medication. Like all medication, the protection profile, facet effects and potential for interactions with different medications must be thought-about. Baseline and observation tests embrace blood tests to observe liver perform and assessment of visual sense **[41]**. A recent retrospective study from one center within the kingdom showed that just about seven-membered of patients started on anti-TB treatment developed drug-induced liver injury, however solely 1 / 4 of those met national criteria for liver perform observation **[42]**. A policy of checking liver perform two weeks when beginning anti-TB treatment has been advocated instead of strictly employing a risk-factor primarily based approach to observation liver **[43]**. However, the appropriateness of this has been questioned in low incidence settings wherever patients square measure clinically well at the tip of treatment, as more testing could also be unnecessarily invasive **[44]**.

Table 1: Medicines used in tuberculosis

WHO GROUPING	DRUGS	
First line drugs	Isoniazid, Rifampicin pyrazinamide	Ethambutol Rifabutin Streptomycin
second line paren-teral drugs	Amikacin ,capreomycin	Kanamycin
Fluroquinolones	LevofloxacinMoxifloxacin	Gatifloxacin,Ofloxacin
Oral bacteriostaticsecond line drugs	Ethionamide Prothionamide Cycloserine	Terizidone p-Aminosalicylic acid

TREATMENT OF LATENT TUBERCLUOSIS INFECTION

Successful screening for LTBI plays a vital role in distinctive and treating people World Health Organization may otherwise proceed to develop active malady **[45]**. Screening and treating new migrants to the United Kingdom from countries with high TB

prevalence has been shown to be cost-effective **[48]**.

WHO tips advocate any of the subsequent treatment choices for LTBI **[50]**:

- 6 months of bactericide monotherapy;
- 9 months of bactericide monotherapy;
- 3 months of weekly rifapentine and isoniazid;
- 3–4 months of bactericide and rifampicin;
- 3–4 months of rifampicin monotherapy.

The recommendations were created supported a meta-analysis evaluating the efficaciousness and safety of varied treatment regimens for LTBI **[49]**. Whereas WHO panel members united nominated that the primary 3 choices were equivalent, there was less agreement relating to the equivalence of the ultimate 2 regimens **[50]**. To boot, the 6- month bactericide regime was related to a lot of toxic events than the 3- to 4-month rifampicin regime; and therefore the 9-month bactericide regime was related to a lot of toxic events than the 3-month weekly rifapentine and bactericide regimen **[50]**.

TREATMENT REGIMEN FOR MULTIRESISTANNT TUBERCULOSIS:

REGIMENS FOR ISONIAZID-RESISTANT TUBERCULOSIS (HR-TB)

In cases with verified rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. In patients with verified rifampicin-susceptible and isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen.

THE COMPOSITION OF LONGER MDR-TB REGIMENS

- In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to verify that treatment starts with at least four TB agentslikely to be effective, and that at least three agents are included for the rest of the treatmentafter bedaquiline is stopped.
- Kanamycin and capreomycin don't seem to be included within the treatment of MDR/RR-TB patients on longer regimens.
- Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more. Bedaquiline can also be included in longer MDR-TB regimens for patients aged6–17 years.
- Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens.
- Clofazimine and cycloserine or terizidone additioally included in the treatment of MDR/RR- TB patients on longer regimens.
- Delamanid may be included within the treatment of MDR/RR-TB patients aged 3

years or more on longer regimens.

- Imipenem–cilastatin or meropenem additionally included within the treatment of MDR/RR-TB patients on longer regimens.
- Amikacin may be included within the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to serve for adverse reactions can be ensured. If amikacin isn't available, streptomycin may replace amikacin under theoretical conditions.

Group A = levofloxacin/moxifloxacin, bedaquiline, linezolid; Group B = clofazimine, cyclo- serine/terizidone; Group C = ethambutol, delamanid, pyrazinamide, imipenem–cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, p-aminosalicylic acid **[51]**.

SURGERY FOR PATIENTS ON MDR-TB TREATMENT

In patients with RR-TB or MDR-TB, elective partial lung resection (lobectomy or wedge re- section) may be used alongside a recommended MDR-TB regimen.

NANOTECHNOLOGY-BASED THERAPIES

Over the past few years, the budding use of nanotechnology-based medical aid has been re- searched for commutation the administration of antibiotics or different medicine within the free morpheme with an access mistreatment medicine that square measure encapsulated with nanoparticle **[52]**.

PULMONARY DELIVERY OF ATD NANOMEDICINE

Pulmonary TB is that the most present variety of the unwellness, and therefore the metabolic process path represents a novel suggests that of delivering ATDs on to the lungs. Reduction of general toxicity and accomplishing higher drug concentration at the chief website of infection area unit the promising benefits of direct delivery of drug to the lungs. Inhalable NPs possess increased ability of tissue layer adherence, particle de-livery, and internet drug delivery to the lungs **[53, 54]**.

CONCLUSION

Diagnosis of tuberculosis demands quick possibly same-day diagnostics tools and techniques during which should be reliable enough to create a therapy decision. However, the standard methods, including the tuberculin skin test, smear microscopy, immunological test, and conventional nucleic acid tests are not optimal. A false positive is usuallyobserved in the tuberculin skin test mainly when the patient had the BCG vaccine, children with TB, and immunosuppression like AIDS. Although, in sputum smear microscopy – a piece of direct evidence for the presence of AFB by microscopy is quick and straightforward, butit does not seem to be a

diagnosis of TB because some AFB are not M. tuberculosis. Additionally, many symptomatic TB cases remain undiagnosed clinically or undergo delayed diagnosis, and during scenario, sputum smear is unable to detect TB bacteria. Furthermore, these methods do not address the problem of MDR/XDR-TB. Therefore, routinely a culture and culture based phenotypic drug susceptibility testing is followed on all initial samples to verify the TB diagnosis and drug resistance. Although, culture methods are considered "gold standard" for TB diagnosis and drug resistance test; the conventional culture method requires 4–12 weeks before the supply of the ultimate confirmative report **[55]**. Volatile Organic Compound (VOC) test in TB patients present some future diagnostic potential. Once clinically available, these non-invasive, inexpensive tests is also used for children or critically ill patients **[56-57]**.

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