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MODERN EVOLUTIONS IN TUBERCULOSIS DIAGNOSIS

Aslonov Farrukh Ismoilovich
Assistant of the Department of Phthisiology and
Pulmonology of the Bukhara State Medical Institute

Abstract

Tuberculosis (TB) is the leading cause of morbidity and mortality worldwide. An estimated 25% of the world's population is infected with Mycobacterium tuberculosis, with a 5–10% lifetime risk of progressing TB disease. Early detection of TB disease and timely detection of drug resistance are essential to reduce its global burden. Culture, direct microscopy, biomolecular tests, and whole genome sequencing are approved diagnostic methods; however, their widespread use is often limited due to cost, local resources, time constraints, and operator efficiency. Methods for optimizing this diagnosis, in addition to developing new methods, are under consideration. The choice of an appropriate treatment regimen depends on the nature of the sensitivity of the detected isolate. Currently, 16 new TB drugs are in Phase I or II clinical trials, and another 22 drugs are in preclinical stages. Along with the development of these new drugs, most of which are oral drugs, new shorter regimens are being evaluated. The purpose of these shorter regimens is to encourage patient adherence and to prevent relapse or the development of further drug resistance. Screening for TB infection, especially among vulnerable populations, provides an opportunity for intervention before infectious TB progresses. New regimens are currently being evaluated to evaluate the effectiveness of shorter treatment duration in this population. In addition, there is extensive research on the use of post-exposure vaccination in this cohort. International cooperation and exchange of experience is essential to achieve our ultimate goal of ending TB worldwide.

Introduction

Tuberculosis (TB) is the leading cause of morbidity and mortality worldwide. Tuberculosis is caused by the bacillus Mycobacterium tuberculosis (Mtb), which spreads through the air. Approximately one in four people worldwide demonstrate an immune response to Mtb infection, which may remain dormant or progress to active forms of the disease. Patients infected with tuberculosis who did not have active signs or symptoms of the disease were previously considered to have latent tuberculosis, and more recently, infected with tuberculosis. While patients with active disease are considered to have TB. In patients with TB infection, the lifetime risk of developing TB is 5–10%, which increases in various immunodeficiency states to 16% of the annual

risk of TB infection becoming TB disease in HIV-infected people. An estimated 10 million new cases of active TB were reported in 2019 worldwide. Approximately two-thirds of all cases occur in only eight countries, the vast majority of which have health services overwhelmed by limited resources. This significant global burden of disease has been recognized by the World Health Organization (WHO), which launched the Stop TB Initiative in 2016. Their goal is to reduce the incidence, morbidity, and mortality from this disease by improving diagnostic methods and preventive strategies through innovative research and education. By 2035, the goal is to reduce TB deaths by 95% and reduce overall TB incidence by 90% worldwide. It is estimated that 60 million lives have been saved worldwide in the 21st century thanks to the work of our predecessors.

Effective TB treatment depends on:

1. Prompt diagnosis of TB and detection of drug resistance;
2. Encourage and ensure patient compliance with treatment regimens;
3. Reliable contact tracing and preventive contact treatment; And
4. Screening for tuberculosis infection in high-risk groups.

Extensive research continues to develop accurate and timely methods for detecting drug resistance, even in resource-limited settings. Many effective, less toxic drugs are under development. In addition, methods to encourage and ensure adherence to treatment are being reviewed. In addition, vital research is ongoing in the active areas of TB prevention, such as screening for and treating TB infection and developing effective vaccines to stop the spread of this deadly disease.

The purpose of this article is: to review the current practice of diagnosing TB; describe new diagnostic methods that are under development.

Diagnosis

Increasing the efficiency and accuracy of TB diagnosis contributes to the effectiveness of treatment. Pulmonary TB should be suspected when patients present with classic symptoms such as persistent cough, hemoptysis, fever, night sweats, and weight loss. Extrapulmonary tuberculosis, including tuberculous lymphadenitis, tuberculous meningitis, tuberculosis of the larynx, Pott's disease, and abdominal tuberculosis, presents in a variety of ways. Particular attention should always be given to patients with potential exposure to TB, as well as immunocompromised patients who may present with atypical manifestations. Diagnosis must be made by confirming the presence of Mtb. Various methods are used to confirm the diagnosis. In addition, it is important to pay special attention to the early detection of potential drug resistance.

Drug resistance is a growing problem that threatens TB treatment worldwide. Traditionally, it has been subdivided into rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB), or extensively drug-resistant TB (XDR-TB). MDR-TB is resistant to both rifampicin (RIF) and isoniazid (INH). The definitions have recently been updated to include pre-XDR-TB, that is, TB that meets the definition of MDR-TB and RR-TB that is also resistant to any fluoroquinolone (FLQ). Updated definition of XDR-TB refers to strains that meet the definition of MDR-TB/RR-TB and are also resistant to any group A drug (namely levofloxacin (LFX), moxifloxacin (MFX), bedaquiline (BDQ) and linezolid (LZD) .)). Replacing the old definition of XDR-TB with reference to second-line injectable drugs (SLID), it highlights the trend towards oral regimens that include newly developed or repurposed drugs. Despite the importance of early detection, only 61% of patients with newly diagnosed bacteriologically confirmed TB in 2019 were tested for RIF resistance . This is partly due to access to diagnostics in resource-constrained settings. Currently, there are many available and developing methods for determining drug resistance. For these diagnostics to be of value globally, they must provide timely, accurate and cost-effective results in centers where access to electricity, equipment and technical expertise remains limited.

Culture

Culture of Mtb in a suitable medium remains the gold standard of the diagnostic test. The sample can be cultured in solid (eg Löwenstein-Jensen or Middlebrook 7H11) or liquid medium (eg for use with the BACTEC Mycobacterium Growth Indicator (MGIT) 960 System). Sensitivity, specificity, infection rate and detection time vary widely in both environments, with WHO advocating dual use of systems where practicable. The main advantage of the advent of liquid-based systems is the fast detection time, often cutting the growth time in half with an average detection time of 12.8 days compared to 25.1–25.5 days for the previously mentioned solid media. However, suboptimal laboratory equipment in resource-limited settings often limits its practical use. Although culture is not recommended for use as a first-line test, it remains an important part of TB diagnosis, where persistent positive cultures can predict the likelihood of relapse.

Direct Microscopy

Direct microscopy is a fast and inexpensive method for detecting acid fast bacilli (AFBs), most of which are mycobacteria. Traditionally, a Ziehl-Neelsen (ZN) stain was used, and the specimen was called "smear-positive" or "smear-negative", depending

on the presence or absence of AFB. Efficacy is operator dependent, resulting in a wide range of sensitivity and specificity reported in international studies, 25.3–81.6% and 83.4–99%, respectively. It is even less sensitive in high-risk groups such as HIV patients and children. Techniques to improve efficiency include the use of mercury vapor fluorescence microscopy and light-emitting diode (LED) microscopy, which have largely replaced traditional ZN staining. Training and quality assurance for laboratory technicians is one of the most useful ways to ensure accurate diagnosis, as direct microscopy is often the only diagnostic tool available in resource-limited settings. Like culture, direct microscopy remains an integral part of monitoring response to treatment, measuring contagiousness, and predicting the likelihood of recurrence in smear-positive patients at diagnosis.

Molecular Tests

Given the limitations of culture and direct microscopy, WHO recommends a biomolecular test as the initial diagnostic test in a suspect patient. Current WHO-approved molecular assays include: Xpert MTB/RIF and Xpert MTB/RIF Ultra assays (Cepheid, Sunnyvale, USA); isothermal amplification loop test (TB-LAMP; Eiken Chemical, Tokyo, Japan); Truenat MTB, MTB Plus and MTBRIF Dx tests (Molbio Diagnostics, Goa, India) and urinalysis for lipoarabinomannan lateral flow (LF-LAM; Alere Definition TB LAM Ag, Abbott, San Diego, USA).

WHO currently recommends Xpert (MTB/RIF or MTB/RIF Ultra) or Truenat (MTB or MTB Plus) as the initial diagnostic test of choice for suspected pulmonary tuberculosis. These are cartridge-based nucleic acid amplification tests (NAATs) that detect the presence of TB DNA as well as common mutations associated with RIF resistance in the rpoB gene within 2 hours. The Xpert MTB/RIF and Xpert MTB/RIF Ultra tests are also approved by WHO for diagnosing extrapulmonary TB and TB in children. Compared to culture diagnosis, Xpert assays have demonstrated 89% sensitivity and 99% specificity in the diagnosis of pulmonary tuberculosis in adults. The Xpert MTB/RIF Ultra assay has higher sensitivity but lower specificity than the Xpert MTB/RIF assay due to its inability to accurately distinguish between dormant and active TB DNA. Although these tests are recommended for use, it is important to remember that they have reduced sensitivity in certain populations, such as children and patients with HIV coinfection, and in extrapulmonary TB. In addition, this technology is expensive and requires laboratory equipment with constant access to electricity. To overcome this hurdle in resource-limited settings, a number of small battery-powered technologies are in development. To date, GeneXpert Omni (Omni; Cepheid) appears to be the most promising potential candidate for widespread use. In

the real world, this has been shown to be a cost-effective method when used in peripheral healthcare settings. This allows diagnostics to be carried out at or near the point of care, avoiding further delays and costs associated with transporting specimens to specialized centers.

In addition to Omni, Cepheid is also developing the Xpert MTB/XDR assay. It also aims to detect resistance to INH, FLQ, ethionamide (ETH) and SLID. Like other Xpert tests, this is a NAAT that detects 16 clinically significant resistance-associated mutations in less than 90 minutes. Compared to the phenotypic drug susceptibility test (pDST), it has 94% sensitivity and 100% specificity in detecting drug resistance. Large scale multicenter clinical trials are currently underway to establish its real efficacy as an add-on test for current Xpert MTB/RIF and MTB/RIF Ultra assays pending review of WHO recommendation. This analysis is of paramount importance as early detection of drug resistance is a prerequisite for shorter regimens, which will be discussed in more detail elsewhere in this review.

While most biomolecular tests are NAATs that detect the presence of Mtb DNA, the LF-LAM test detects lipopolysaccharide present in the cell walls of mycobacteria. Although the LF-LAM assay is not used in most of the developed world, it has been recommended for use in patients coinfected with HIV. This is a urine antigen test that is often used in resource-limited settings and is particularly useful when a sputum sample cannot be obtained. It has a sensitivity of 42 % in HIV-infected people with symptoms of tuberculosis. However, it cannot distinguish between mycobacterial species and may cross-react with other fungal diseases. Thus, it is used as an initial test in peripheral primary health care centers only in areas of high TB endemicity to determine whether patients with HIV symptoms should be referred for further confirmatory testing.

Line Probe Analysis

Another method for molecular detection of Mtb resistance is the linear probe analysis (LPA). The MTBDRplus genotype and the MTBDRsl genotype (Hain LifeScience GmbH, Nähren, Germany) are used to detect Mtb and associated drug resistance. The WHO-approved MTBDRplus genotype uses a series of steps to detect Mtb and mutations in rpoB and katG that confer resistance to RIF and INH, respectively. In addition, it can detect the presence of inhA promoter genes that confer resistance to low doses of INH, which are also commonly associated with resistance to ETH and prothionamide. This in vitro test gives results in less than 6 hours. Compared to traditional culture-based drug sensitivity, it has 78.5% sensitivity and 100% specificity in detecting resistance to RIF and INH. The WHO-approved Genotype MTBDRsl 2.0

assay can also detect resistance-inducing FLQ (gyrA and gyrB) and SLID (rrs and eis) mutations. Claimed sensitivity and specificity are 100% and 98.9% for FLQ and 89.2% and 98.5% for SLID. This rapid test is even more sensitive than NAAT for detecting FLQ resistance and may allow the use of FLQ in patients who might otherwise face a longer regimen, potentially requiring temporary use of a SLID. However, these tests are not without limitations, including low sensitivity for detecting resistance to ethambutol (ETM) and aminoglycosides, as shown in the real analysis. Similar to the Xpert MTB/XDR assay, these LPAs provide rapid recognition of drug resistance so patients can be started on an appropriate regimen and further drug resistance cannot develop pending standard susceptibility culture results, and patients undergoing burdensome, longer regimens taking drugs with a higher potential for toxicity.

Whole Genome Sequencing (WGS)

Although NAAT and LPA tests are fast and affordable diagnostic tools, their effectiveness in detecting drug resistance is hampered by the inability to detect clinically significant mutations outside the rifampicin resistance-defining region (RRDR) of the rpoB gene. While 95% of resistance cases are due to mutations in this region, there have been a number of public health crises resulting from missed diagnosis of outbreaks due to mutations outside of this region. One such example is the I491F mutation that caused the MDR-TB outbreak in Eswatini and remains a major public health problem. Another limitation is the inability to distinguish between silent mutations and those that reduce the effectiveness of drugs, leading to a higher rate of false positive resistance results. WGS provides a comprehensive overview of the entire Mtb genotype with 96% concordance for culture-based susceptibility testing. It provides genotypic susceptibility to most of the drugs required for the treatment of MDR-TB. Although full clarification of the clinical correlation between genotypic and phenotypic susceptibility has yet to be demonstrated, progress has been made in establishing the likelihood of pDST based on genotypic results. Utilities in low-income countries were initially limited by cost and the need for reliable equipment and technical expertise. However, due to continued technological advances in microfluidic approaches to TB diagnosis, WGS is likely to be available at points of care around the world. For some countries, it remains an important tool not only for diagnosing cases, but also for developing public health policy, helping to track contact TB cases during outbreaks. In the future, with improved knowledge of the genomics associated with TB resistance, WGS is likely to be revolutionary in tailoring TB treatment to each individual patient based on the specific genome identified by the Mtb strain they have contracted.

Culture-Based Drug Susceptibility Test (DST)

As mentioned earlier, the main advantage of liquid culture is growth rate, which has led to the increased use of liquid broth based methods such as MGIT. BACTEC MGIT 960 is a fully automated system that delivers results within 2 weeks. At present, culture-based DST remains the gold standard for determining drug resistance. Currently, two approaches are used: critical concentration and minimum inhibitory concentration (MIC). Classically, the critical concentration has been defined as the lowest drug concentration that inhibits the growth of 95% of the Mtb strains present. Through ongoing research, these critical concentrations are regularly updated to reflect the recent reduction in the critical concentration required to determine resistance to RIF , allowing for greater agreement between genotypic and phenotypic susceptibility results. Alternatively, the MIC method is defined as the lowest drug concentration that results in complete inhibition of visual growth of the Mtb strain in vitro. After extensive work by national reference laboratories, as well as international discussion and agreement, a new MIC reference protocol has been established and validated by European consortiums.

Computer Detection for Chest Radiographs

Given the time, financial, and infrastructural constraints of the above testing methods, it has become clear that low-cost, affordable screening methods are needed in high-traffic areas to help stratify risks for further testing. One such proposed method is to use computer software to digitally interpret chest x-rays and assign scores that indicate the likelihood of tuberculosis. The most commonly studied software is CAD4TB, currently version 6. Compared to NAAT, CAD4TB has a sensitivity of 90–100% and a specificity of 23–45% for the detection of TB disease. It works much like experienced clinicians and radiologists, with similar pitfalls, including disease hidden behind musculoskeletal data and differentiating old scars from new disease. Its use is intended for high-traffic areas that may lack readily available on-site radiological expertise for timely interpretation of chest radiographs. This could help peripheral medical centers determine which patients need further molecular testing.

Serum Biomarkers

Serum biomarkers are another potential sorting testing method. Developing an accurate biomarker that maintains sensitivity for different ethnic groups, HIV status, and TB location has proven to be challenging. However, a nine-protein biosignature was recently discovered that appears to remain effective in all of these cohorts. The

use of fibrinogen, α2 -macroglobulin, C-reactive protein, matrix metalloproteinase-9, transthyretin, complement factor H, interferon- γ , interferon- γ inducible protein-10, and tumor necrosis factor -α as the host biosignature demonstrated 92% sensitivity and 72% specificity for determining tuberculosis from other diseases. If this serum assay were commercially available, it could quickly and efficiently identify which patients need further testing. It is important to note that most of these biomarkers are markers of inflammation and, as such, vary widely among patients and their various metabolic and disease states. The evaluation of serum biomarkers as predictors of response to treatment, likelihood of relapse, and predictors of TB infection versus active disease will be discussed elsewhere.

Conclusion

TB treatment has a great future. Never before has such a global effort been made to develop new technologies and treat TB patients. Combining these advances, it is possible that we will base the treatment of each patient on their own protein biosignatures in combination with the genomic expression of mutations in the Mtb strain with which they were affected. If we are to achieve our goal of eliminating TB globally, it is important that we continue to collaborate and share our expertise internationally to ensure that each patient receives the appropriate treatment and support to overcome their TB diagnosis without significant incidence.

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