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Understanding tuberculosis: Examining its historical impact, modes of transmission, risk factors, and strategies for global prevention and effective treatment

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***Abstract*---Background:** Tuberculosis (TB) is a highly infectious disease with a long history of impacting global health. Despite the availability of effective treatments, TB remains a significant cause of morbidity and mortality, particularly in low- and middle-income countries and among HIV-positive individuals. TB transmission occurs primarily through inhaling aerosolized droplets from an infected person, leading to potential disease progression. Risk factors for TB include close contact with infected individuals, residency in TB-endemic regions, and immunocompromising conditions like HIV and diabetes. **Aim:** This article aims to provide an overview of TB's historical impact, modes of transmission, risk factors, diagnostic methods, and global strategies for prevention and treatment. **Methods:** The review synthesizes data from recent studies on TB transmission, clinical symptoms, imaging techniques, and diagnostic tests, including acid-fast bacilli (AFB) smear, nucleic acid amplification tests (NAATs), and immune-based tests. Various diagnostic and treatment protocols are discussed for both drug-susceptible and drug-resistant TB strains. **Results:** TB diagnosis

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relies on a combination of imaging, microbiologic testing, and immune-based tests. While AFB smears and NAATs remain primary diagnostic methods, novel imaging techniques like CT and PET scans are expanding diagnostic accuracy. Treatment of drug-susceptible TB typically involves a six-month regimen of isoniazid, rifampin, pyrazinamide, and ethambutol, whereas drug-resistant strains require more complex, often extended treatments. Emerging treatments include all-oral regimens for multidrug-resistant TB, showing potential for improved adherence and outcomes. **Conclusion:** Early diagnosis, effective treatment, and preventive strategies are critical in managing TB and reducing its global incidence. Continued research is essential to improve diagnostic tools and develop treatments that address drug resistance. Global healthcare systems must prioritize TB control through strengthened diagnostic infrastructure, comprehensive treatment plans, and targeted preventive measures to curb the spread and impact of TB.

***Keywords*---**Tuberculosis, transmission, diagnosis, drug-resistant tuberculosis, global health, prevention, treatment, HIV.

Introduction

Although there are excellent treatments for tuberculosis (TB), which has affected humanity for thousands of years, TB was the leading infectious illness cause of death in 2016, killing 1.7 million people globally [1,2]. Among people with HIV, tuberculosis is another common cause of morbidity and death. According to recent estimates, about 10 million people worldwide get active TB each year, accounting for over 25% of the world's population [1,3]. Inhaling aerosolized droplets is the main way that the disease is spread, and extended contact with a person who has pulmonary tuberculosis is usually required. Pathogens migrate from the lungs to nearby lymph nodes as a result of the original infection, and then they spread throughout the body through the bloodstream. After the initial infection, about 5% of people will develop active disease; this progression is more common in young children and people with weakened immune systems. For most, the infection is successfully contained by the immune response, which leads to the development of granulomas without producing any clinical signs. Before developing into a clinical illness, TB can lie dormant in a person for decades. Reactivation can be brought on by immune-compromising diseases like HIV or diabetes, but it can also happen to people who are otherwise healthy. About 75% of instances involving reactivation involve the lungs [1,4]. People who have pulmonary tuberculosis can spread the illness to other people, continuing the disease-causing cycle of transmission. One important tactic for lowering the worldwide incidence of TB is the early detection and treatment of pulmonary TB, which is essential in preventing TB transmission. The 10-year death rate for smear-positive pulmonary tuberculosis is 70% if treatment is not received [5]. Furthermore, many patients suffer irreparable lung damage as a result of delayed diagnoses [6].

Diagnosis of Tuberculosis: Risks, Symptoms, and Imaging Techniques

Risk and Symptoms: The diagnosis of tuberculosis (TB) begins with infection, which typically occurs after extended exposure to an individual with active pulmonary TB. Known close contact with such a person presents the greatest risk but is relatively uncommon. Most individuals remain unaware of their exposure or infection, making residency or birth in a TB-endemic country the most prevalent risk factor. Such regions include most countries except for Western and Northern Europe, the United States, Canada, Australia, New Zealand, and Japan. Even within these low-endemic countries, individual risk can vary based on specific factors such as homelessness [1]. Delays in TB diagnosis are common due to its non-specific symptoms. Unlike many infectious diseases, TB symptoms may wax and wane over time, potentially leading patients to overlook the persistence of their illness and delay seeking care. TB should be considered in patients who show subacute illness symptoms, particularly if they have lived in a TB-endemic country. Individuals at heightened risk for TB infection include those living with HIV, adult and child contacts of pulmonary TB, patients beginning anti–tumor necrosis factor alpha therapy, and those with conditions like diabetes, which is one of the most frequent comorbidities associated with active TB [7]. However, most individuals who develop active TB do not have these associated conditions. Typical pulmonary TB symptoms include a cough lasting over three weeks that worsens and often produces sputum, dyspnea, fever, night sweats, weight loss, and chest pain related to pleural disease.

Imaging: For suspected pulmonary TB cases, chest imaging is essential. A posteroanterior chest radiograph usually suffices for adults and adolescents, while a lateral radiograph aids in evaluating younger children for signs such as hilar adenopathy. Radiographic signs commonly include upper lobe fibronodular opacities, sometimes with cavitation, or diffusing small nodules indicative of miliary TB. TB may resemble bacterial pneumonia on imaging, potentially delaying TB diagnosis, particularly if fluoroquinolones are administered due to their effectiveness against many TB strains. Additional TB presentations include nodules, masses, adenopathy, and pleural effusion. CT scans can reveal disease extent more comprehensively than radiographs, although they are not essential for diagnosis or TB management. When TB is suspected, CT scans are often deferred until respiratory specimens for acid-fast bacilli (AFB) testing are obtained. CT scans might be useful when initial specimens test negative or to explore alternative diagnoses. Findings in active TB cases vary but may include features like tree-in-bud opacities, cavitation, pleural effusions, and adenopathy [8]. Research studies have used PET scans to better understand TB's pathophysiology, suggesting their potential role in diagnosing TB and tracking treatment response. Although not highly effective in distinguishing TB from malignancy, PET scans may help identify active lesions suitable for biopsy [9,10]. However, cost and accessibility pose significant challenges to their routine application [11].

Microbiologic Specimens in Tuberculosis Diagnosis
Sputum Samples:

Sputum samples are central to diagnosing pulmonary tuberculosis (TB), with acid-fast bacilli (AFB) smears being the initial test. The sensitivity of AFB smears improves with the number of specimens: approximately 54% with one sample, 65% with two, and up to 70% with three specimens [12]. While the quality of sputum is generally more important than the timing, early morning samples tend to be more sensitive than single spot specimens [13]. Collecting sputum samples every 6 to 8 hours, especially in hospitalized patients, allows for a quicker diagnosis and reduces the isolation time for those without TB. Bronchoscopy is generally unnecessary for diagnosing pulmonary TB; sputum induction is equally effective, less invasive, and less costly. Bronchoscopy may be reserved for patients for whom sputum induction fails or when another diagnosis is probable. For patients with miliary TB undergoing bronchoscopy, bronchial brushings or transbronchial biopsy yield higher sensitivity than bronchoalveolar lavage [12].

Nucleic Acid Amplification Tests (NAATs):

NAATs are more sensitive and specific than AFB smears in diagnosing TB. The GeneXpert system (Cepheid, USA) has simplified specimen processing, making it feasible in resource-limited settings. One GeneXpert test detects 97% of smear-positive TB cases and almost 60% of smear-negative but culture-positive cases, with a second test increasing sensitivity to 100% and 70%, respectively [15]. In the U.S., GeneXpert has been approved to clear hospitalized patients with negative results from respiratory isolation. Many NAATs also detect resistance mutations, allowing for faster initiation of effective treatment. Susceptibility and resistance, however, should still be confirmed through culture whenever feasible.

Pleural TB:

Pleural TB typically presents with a unilateral, exudative effusion dominated by lymphocytes. AFB smears and cultures from pleural fluid detect fewer than 50% of active TB cases [12]. A pleural biopsy, with tissue sent for pathology and cultures, is the most definitive method for diagnosing pleural TB. Closed needle biopsy is effective in most cases, while thoracoscopic biopsy has a nearly 100% diagnostic rate. Pleural fluid adenosine deaminase offers moderate sensitivity and specificity and may aid diagnosis when a pleural biopsy is not viable [16].

Culture Testing:

Culture remains the gold standard for TB diagnosis, providing definitive confirmation and allowing for drug susceptibility testing. However, cultures are rarely performed for newly diagnosed TB patients in resource-limited settings due to costs and logistical challenges, generally limiting them to cases of treatment failure or relapse. Liquid cultures offer the shortest time to growth and first-line susceptibility testing, while solid media are advantageous when isolating TB in cases of contamination or for testing second-line drug susceptibility when needed.

Tuberculin Skin Test and Interferon-Gamma Release Assays:

The tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) are immunologic tests used to diagnose TB infection. Two commercial IGRAs, QuantiFERON-TB (Qiagen, Germany) and T-SPOT.TB (Oxford Immunotec, United Kingdom), should not be used to rule out TB and have limited roles in diagnosing active disease. TST can miss up to 30% of active TB cases, while IGRAs have a 10-15% miss rate [17]. They may be useful when deciding on empirical treatment for TB in cases where AFB smears and NAATs are negative, but cultures are pending. Public health consultations are recommended for evaluating the risk of delaying treatment in these cases.

Additional Testing:

Additional tests aid in the management of TB patients but do not contribute to the diagnosis. HIV testing is crucial for all patients suspected of having TB. Other important laboratory tests include a complete blood count, liver function panel, and creatinine levels; results from tests done in the prior few months are generally acceptable. Baseline and monthly assessments of visual acuity and color vision should be documented for patients receiving ethambutol (EMB). For patients with drug-resistant TB, additional monitoring may be necessary depending on the drugs administered.

Treatment of Drug-Susceptible Tuberculosis:

The standard first-line treatment for pulmonary TB includes a combination of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) [18,19]. Each medication has common and potentially severe adverse effects. Within this regimen, INH exhibits the strongest early bactericidal activity, while RIF is essential for achieving a shorter treatment duration. PZA targets minimally active organisms, allowing for cure within a 6-month treatment course. EMB, the least active drug in this combination, helps prevent acquired resistance when susceptibility data are not yet available. This four-drug regimen is administered for the first two months, or initial phase, of treatment. For fully drug-susceptible TB, EMB may be excluded from this phase, using only INH, RIF, and PZA. The continuation phase for drug-susceptible TB involves INH and RIF for an additional four months, completing a six-month total treatment period. There is no specific test to confirm cure; therefore, treatment aims to achieve a low relapse risk (generally <5%). Factors increasing the likelihood of relapse include cavitary disease, positive sputum culture after two months, and low body weight at treatment initiation with no subsequent weight gain [20,21]. To mitigate these risks, extending treatment by three months (totaling nine months) is commonly considered for patients with one or more relapse risk factors. Patients with PZA resistance or those unable to complete the full two-month course may also benefit from a nine-month regimen of INH and RIF [18].

Isoniazid Resistance or Intolerance:

For patients unable to take INH due to resistance or intolerance, an alternative initial regimen may include a fluoroquinolone (such as moxifloxacin or

levofloxacin) in combination with RIF, PZA, and EMB. In the continuation phase, treatment can proceed with RIF, PZA, and EMB or a fluoroquinolone plus RIF, with or without EMB [18]. Studies show that a regimen of RIF, PZA, and EMB may be as effective as INH and RIF for drug-susceptible TB, though some patients may experience tolerance issues [22]. A retrospective evaluation found that using a fluoroquinolone with RIF and EMB led to positive outcomes in patients with INH-resistant TB [23]. Recent research has explored the use of moxifloxacin in various experimental regimens aimed at shortening treatment duration to four months. In one trial, participants received moxifloxacin, RIF, PZA, and EMB daily for two months, followed by a once-weekly dose of moxifloxacin and rifapentine for the next four months [24]. While the four-month regimens were less effective than the standard six-month regimen, the experimental arm with a once-weekly continuation phase for four months performed comparably to the standard regimen.

Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis:

Multidrug-resistant (MDR) TB is characterized by resistance to both isoniazid (INH) and rifampin (RIF), potentially along with other drugs. Empiric treatment for MDR TB typically includes 4 to 6 drugs with probable activity against the infection [25,26]. Historically, fluoroquinolones and injectable agents have been the primary treatments for MDR TB, with moxifloxacin often preferred over levofloxacin based on in vitro studies, though both are effective [27]. Newer all-oral regimens are under investigation to evaluate their safety and efficacy, which may ultimately replace older treatments involving prolonged use of injectable drugs [28–30]. Treatment durations for MDR TB have traditionally ranged from 18 to 24 months, but recent studies indicate that a 9-month regimen could be effective, with shorter regimens using novel drug combinations also under exploration [31–33]. Extensively drug-resistant (XDR) TB is defined by resistance to INH and RIF as well as fluoroquinolones and at least one second-line injectable drug, such as amikacin, kanamycin, or capreomycin [19,26]. XDR TB treatment generally follows the same principles as MDR TB, but it should be managed with input from a specialist in drug-resistant TB due to its complexity. The approach typically involves a regimen of 5 to 6 drugs likely to be effective. Pyrazinamide (PZA) may be used even in cases with phenotypic resistance, as it may retain some activity against minimally active bacteria. High doses of moxifloxacin and/or INH may be considered if only low-level resistance to these drugs is detected or when treatment options are limited. Linezolid has become a critical component of regimens for both MDR and XDR TB. Although its optimal dosing is still uncertain, observational data suggest that half the usual dose for bacterial infections is effective and less toxic. Bedaquiline is another new drug increasingly used in treating drug-resistant TB [34,35]. Additionally, other medications, including delamanid, pretomanid, and clofazimine, show promise in treating resistant forms of TB [30].

Monitoring Treatment:

Ensuring adherence to tuberculosis (TB) treatment is crucial for reducing the risks of treatment failure, acquired drug resistance, and TB transmission. Directly observed therapy (DOT) is the standard care approach for patients with

pulmonary TB, as it maximizes treatment completion and allows close monitoring for drug-related side effects. Intermittent dosing strategies were developed to make DOT more convenient for patients and providers. However, recent meta-analyses indicate that intermittent dosing results in higher relapse rates, particularly among patients with HIV [37–39]. Consequently, current guidelines recommend daily therapy, reserving intermittent therapy for cases where daily DOT is impractical [18,19]. Digital technology has emerged as a more affordable and patient-centered alternative to in-person DOT, facilitating treatment monitoring through virtual tools [40–42]. Some platforms allow real-time interactions between patients and healthcare personnel [40,41], while others enable patients to record a video of themselves taking their medications, which can be reviewed later by TB program staff [42]. Studies evaluating video DOT, whether in real-time or recorded, report adherence levels comparable to in-person DOT, alongside high patient satisfaction [42]. Patients undergoing TB treatment typically have monthly clinic visits to assess treatment response and monitor for drug-related toxicity. For those taking ethambutol (EMB), monitoring of visual acuity and color vision is recommended. Monthly sputum cultures should be obtained until there are two consecutive negative specimens. However, nucleic acid amplification tests (NAATs) are not recommended for monitoring treatment response, as they may detect TB DNA long after effective treatment, leading to possible misinterpretations [43]. Routine laboratory monitoring is generally unnecessary unless patients present symptoms or pre-existing conditions. Monthly liver function tests are recommended for patients with known liver disease or any abnormalities at baseline, and for anyone who develops symptoms like nausea, vomiting, abdominal pain, loss of appetite, or jaundice.

Special Circumstances: Tuberculosis and HIV:

The management of TB in people living with HIV largely mirrors the approach for HIV-negative individuals [44]. Relapse rates after 6 months of TB treatment in patients with drug-susceptible pulmonary TB are similar to those in HIV-negative populations [45]. In highly immunocompromised individuals who are not yet on antiretroviral therapy (ART), extending TB treatment to 9 months may be beneficial [18,46]. A key consideration is drug-drug interactions, particularly with rifampin (RIF); in many ART regimens, rifabutin may replace RIF. Timing of ART initiation during TB treatment has been investigated in randomized trials, with findings showing improved survival in patients with CD4 counts below 50 cells/mL who began ART within 2 weeks of starting TB treatment, except for those with central nervous system (CNS) involvement, due to the risk of immune reconstitution inflammatory syndrome (IRIS) [47]. For patients with CD4 counts above 50 cells/mL, ART initiation can be delayed if necessary, ideally within the first 2 months. IRIS is most likely to occur within the first 4 to 12 weeks after ART initiation [48,49], and ART can generally be continued even if IRIS develops. Corticosteroids may be useful in cases of severe IRIS or CNS disease [50].

Renal Disease:

Patients with end-stage renal disease (ESRD) face an increased risk for tuberculosis (TB) and generally experience poorer outcomes from the disease [51]. Certain TB medications, such as pyrazinamide (PZA) and ethambutol (EMB), are

primarily cleared by the kidneys, necessitating dose adjustments when creatinine clearance falls below 30 mL/min. For these patients, the usual daily dose of PZA and EMB is typically administered three times per week after hemodialysis [18]. In contrast, isoniazid (INH) and rifampin (RIF) are metabolized by the liver and therefore do not require renal dosing adjustments. When fluoroquinolones are part of the treatment regimen, levofloxacin—another renally cleared drug—should be dosed intermittently if creatinine clearance drops below 50 mL/min. Moxifloxacin, which is cleared by the liver, can be given without adjustment in patients with renal impairment.

Liver Disease:

Individuals with liver disease are at risk of complications from both TB and TB treatments. Key medications, including INH, RIF, and PZA, can cause drug-induced liver injury, with PZA and INH more frequently associated with liver toxicity than RIF. RIF-induced hepatotoxicity is often indicated by disproportionately elevated total bilirubin and alkaline phosphatase relative to transaminase levels. Despite this, RIF is often resumed as monotherapy once liver function improves, as it is essential for effective TB treatment with a shorter course duration. Optimal dosing for INH and RIF in patients with chronic liver disease remains uncertain, and treatment choices should align with the degree of liver impairment. Patients with chronic liver disease without cirrhosis, and with baseline transaminases less than three times the upper limit of normal, can often tolerate standard TB therapy with careful monitoring. In cases of moderate liver disease or higher hepatotoxicity risk, PZA may be omitted. Moxifloxacin, due to its liver clearance and low hepatotoxicity profile, is occasionally favored over levofloxacin. For patients with advanced liver disease, identifying a safe regimen can be challenging. Levofloxacin, EMB, and injectable medications are generally safer alternatives. RIF may still be included with close clinical and laboratory monitoring due to its critical role in TB treatment. Additional agents with low hepatotoxicity, such as cycloserine, linezolid, and clofazimine, may also be considered, though they carry the risk of non-hepatic toxicities.

Conclusion:

Tuberculosis remains one of the most persistent infectious diseases globally, necessitating comprehensive approaches to control its spread and impact. Despite the availability of effective treatments, TB continues to present a complex challenge due to factors such as delayed diagnosis, drug resistance, and limited resources in endemic regions. TB transmission is facilitated by prolonged exposure to infected individuals, with risk factors that include immunocompromising conditions like HIV and diabetes. The use of imaging techniques, particularly chest radiography, and microbiologic tests, such as sputum analysis and nucleic acid amplification tests, are crucial in TB diagnosis and in tailoring treatment plans based on drug susceptibility. The standard six-month regimen for drug-susceptible TB has proven effective, but multidrug-resistant TB remains a major hurdle. The emergence of new oral regimens holds promise for more manageable treatment options, especially in resource-limited settings, where accessibility to advanced diagnostic tools and medications is often limited. Preventive strategies, including Bacillus Calmette-Guérin (BCG)

vaccination, public health campaigns, and rapid identification of high-risk populations, are essential to reducing TB incidence. Ongoing research is vital to address the challenges posed by drug-resistant TB and to develop more efficient and accessible diagnostic and treatment methods. A global commitment to TB research, alongside sustained public health initiatives, is imperative to controlling TB and eventually achieving a significant reduction in its prevalence and impact worldwide.

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فهم مرض السل: دراسة تأثيره التاريخي، أنماط انتقاله، عوامل الخطر، واستراتيجيات الوقاية الفعالة والعلاج على مستوى العالم

الملخص:

الخلفية :يعتبر مرض السل (TB) مرضاً معدياً للغاية له تاريخ طويل من التأثير على الصحة العالمية. على الرغم من توفر العلاجات الفعالة، لا يزال السل سببًا رئيسيًا للإصابة والوفيات، خاصة في البلدان ذات الدخل المنخفض والمتوسط وبين الأفراد المصابين بفيروس نقص المناعة البشرية (HIV). يحدث انتقال السل بشكل أساسي من خلال استنشاق قطرات محمولة بالهواء من شخص مصاب، مما يؤدي إلى إمكانية تقدم المرض. تشمل عوامل الخطر للإصابة بالسل الاتصال الوثيق مع الأفراد المصابين، الإقامة في مناطق انتشار السل، والظروف المثبطة للمناعة مثل فيروس نقص المناعة البشرية والسكري.

الهدف :تهدف هذه المقالة إلى تقديم لمحة عامة عن التأثير التاريخي للسل، أنماط انتقاله، عوامل الخطر، طرق التشخيص، والاستراتيجيات العالمية للوقاية والعلاج.

الطرق :يستند هذا الاستعراض إلى بيانات من دراسات حديثة حول انتقال السل، الأعراض السريرية، تقنيات التصوير، والاختبارات التشخيصية، بما في ذلك فحص العصيات الحمضية المقاومة(AFB) ، اختبارات تضخيم الحمض النووي(NAATs) ، والاختبارات القائمة على المناعة. كما يتم مناقشة بروتوكولات التشخيص والعلاج المختلفة لكل من سلالات السل القابلة للعلاج والمقاومة للأدوية.

النتائج :يعتمد تشخيص السل على مزيج من التصوير، الاختبارات الميكروبيولوجية، والاختبارات القائمة على المناعة. بينما تظل فحوصات AFB و NAATsطرق التشخيص الرئيسية، فإن تقنيات التصوير الجديدة مثل الأشعة المقطعية (CT) وفحوصات PET تعمل على تحسين دقة التشخيص. عادةً ما يتضمن علاج السل القابل للعلاج نظامًا مدته ستة أشهر يتكون من الإيزونيازيد، والريفامبين، والبيرازيناميد، والإيثامبوتول، بينما تتطلب السلالات المقاومة للأدوية علاجات أكثر تعقيدًا، وغالبًا ما تكون ممتدة. تشمل العلاجات الناشئة أنظمة فموية بالكامل للسل المقاوم للأدوية المتعددة، مما يظهر إمكانية تحسين الالتزام والنتائج.

الخلاصة :إن التشخيص المبكر، والعلاج الفعال، والاستراتيجيات الوقائية تعد ضرورية في إدارة السل وتقليل انتشاره على مستوى العالم. يُعتبر البحث المستمر ضروريًا لتحسين أدوات التشخيص وتطوير العلاجات التي تعالج مقاومة الأدوية. يجب على أنظمة الرعاية الصحية العالمية إعطاء الأولوية لمكافحة السل من خلال تعزيز البنية التحتية للتشخيص، وخطط العلاج الشاملة، والإجراءات الوقائية المستهدفة للحد من انتشار وتأثير السل.

الكلمات المفتاحية :السل، الانتقال، التشخيص، السل المقاوم للأدوية، الصحة العالمية، الوقاية، العلاج، فيروس نقص المناعة البشرية.