CHAPTER N0.

08

Advances in Clinical Features, Diagnosis and Treatment of Tuberculosis

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ABSTRACT: Tuberculosis is one of the most widely distributed infectious diseases in the world because it greatly impacts veterinary, health care, and financial systems. This disease is caused by a species of the TB complex in the Mycobacterium family, where *Mycobacterium bovis* transmits it to animals, while *Mycobacterium tuberculosis* transmits it to humans. Contrary to other fatal diseases for which new cases emerge after several years, numerous cases of tuberculosis emerge rapidly. Clinical signs may include bones, lymph nodes, and the central nervous system, in addition to pulmonary manifestations such as haemoptysis and cough. The antiquated methods of microscopy and culture have been superseded by modern molecular tests that allow the detection of resistant and susceptible strains with speed and accuracy. The fact that the disease remains challenging to treat and requires complex regimens over a considerable period of time poses a great concern due to the emergence of extensively drug-resistant (XDR) and multidrug-resistant (MDR) tuberculosis. Bovine tuberculosis due to *M. bovis* remains of concern in veterinary medicine because of the economic and zoonotic aspects of the disease. The chapter underlines the contemporary importance of tuberculosis as a "One Health" priority due to the comprehensive coverage of the developments that have occurred in the clinical presentation, diagnosis, and treatment of the disease from the human and veterinary perspectives.
Keywords: Tuberculosis, *Mycobacterium tuberculosis*, diagnosis, clinical features, treatment, zoonosis

INTRODUCTION

Mycobacterium (M.) tuberculosis complex (MTBC) bacteria, like *M. tuberculosis, M. bovis, M. africanum*, and other MTC-related bacteria, is the cause of the chronic infectious disease Tuberculosis (TB) (Brites et al., 2017). Tuberculosis remains one of the leading 10 causes of death worldwide and is one of the oldest recorded diseases (Daniel and Alausa, 2006, Bagcchi, 2023). With an expectation of 10.6 million new infections and 1.3 million deaths in 2022, TB ranks second to the COVID-19 pandemic as the major cause of deaths due to an infectious disease (WHO, 2023). Particularly in South-East Asia and Africa, where HIV co-infection, poverty, and malnutrition significantly raise the likelihood of disease transmission, low- and middle-income countries bear an unfairly severe burden (Furin, 2019).

Tuberculosis has important economic and veterinary consequences. Indeed, "*M. bovis* is the major causative organism in infections of livestock and occasionally in pets, and its existence causes a significant economic impact due to reduced productivity and slaughter of livestock (Michel et al., 2010). Moreover, being a zoonotic bacterium, *M. bovis* can cause infections in humans by ingesting unpasteurized milk or by coming into direct contact with the bacterium-infected animals; therefore, tuberculosis is a "One Health Issue. (Olea-Popelka et al., 2017)

The appearance of Multi-Drug Resistant (MDR) and Extensively Drug Resistant (XDR) strains, compliance problems due to long treatment duration, and delay in diagnosis make controlling TB a concern worldwide, although it is preventable and curable (Dheda et al., 2017). Although shorter treatment regimens and recent advancements in molecular techniques are encouraging, they have yet to be made accessible in developing countries. Reflecting on recent advancements and the need for combined medical and veterinary strategies for controlling TB, recent advancements in clinical manifestations, diagnostic methodologies, and treatment options for TB in humans and animals are discussed.

ETIOLOGY AND PATHOGENESIS

Etiology

A group of extremely similar bacteria that cause tuberculosis is known as the *M. tuberculosis* complex, or MTBC. *Mycobacterium tuberculosis*, the primary cause of tuberculosis in humans, is one of the major species in the MTBC. *Mycobacterium bovis*, which is a major source of *M.*

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tuberculosis and primarily causes tuberculosis in cattle. *(Brites et al., 2017).*

Mycobacterium tuberculosis has adapted itself to the biological constitution of humans, thus has the potential to cause tuberculosis among humans. Mainly, the *M. tuberculosis* transmission occurs by coughing, sneezing, or even talking (Subbaraman et al., 2016). Mainly, the cause of the occurrence of bovine tuberculosis, *M. bovis*, has the potential to infect humans as well as both wild and domestic animals. The two ways that human infection with *M. bovis* can occur are through the consumption of unpasteurized dairy products or direct contact with an infected animal. In different regions, other *M. tuberculosis* complex species, such as *M. africanum*, have been identified as contributing to cases of tuberculosis, as opposed to *M. bovis*, in places such as West Africa, whereas *M. caprae*, or capra TB, is an emerging disease in regions such as Europe.

All the MTBC species are acid-fast bacilli possessing lipid-rich cell walls, which confer resistance to a wide range of environmental stresses and disinfectants. Thus, once established in a host population, they are very hard to eliminate and exceptionally hardy in the environment. (Barry 3rd et al., 2009).

Pathogenesis

There is an interactive relationship between *M. tuberculosis* complex cells and the immune system of the host during the evolution of TB. Human infection by droplet nuclei of live bacilli that reach the lungs' alveoli is considered the basic route of infection (Flynn & Chan, 2001). Infection through the oral route might occur in domestic animals, mainly in cattle fed through water and feed that contain the organism (Michel et al., 2010). The alveolar macrophages of the lungs take in the bacilli after they reach the lungs. But *M. tuberculosis* can survive in the macrophage by evading the fusion of the phagosome and lysosome (Russell, 2007). The innate immunity of the host can be evaded by the organism.

Granuloma formation can be regarded as a part of the pathophysiology process of tuberculosis. Granulomas refer to organized immune cell masses that surround the bacilli and are composed of fibroblasts, lymphocytes, and macrophages (Lin et al., 2014). Granulomas form a site where the bacilli can be in a latent form while also controlling the infection. This infection occurs in a latent form in most immunologically competent individuals, where the bacilli are shielded by granulomas and do not develop an active disease (Houben and Dodd, 2016). The latent infection generally transforms into an active form of tuberculosis in 5-10% of infections, especially where the host immunity has been compromised, such as in an HIV patient.

The problem of developing lesions can occur in the liver, spleen, lymph nodes, and lungs of animals such as cattle. Extrapulmonary tuberculosis conditions, which can be a manifestation of skeletal TB, lymph node TB, and TB meningitis, may be caused by the spread of the bacteria via the blood circulation or lymphatic system (Olea-Popelka et al., 2017). Since MTBC germs are capable of causing both latent and active infections that cannot be destroyed by the host defenses, tuberculosis has been a major concern for the global health system despite intensive medical and veterinary care.

Clinical Features

Tuberculosis can be chronic rather than an acute infection, although it may occur in an immunocompromised host. Roughly between 70 and 80% of reported human cases of tuberculosis occur due to respiratory tuberculosis, making it the common type (Albert et al., 2016). In addition to coughing up phlegm for more than two weeks, the other symptoms include tiredness and loss of weight, generally known as ‘consumption’ in the past. However, the coughing of blood is known as hemoptysis when the disease is at an advanced stage, as is the case here, due to the slow progression associated with it, meaning it will probably remain untreated for several months in the human form of tuberculosis, where the bacteria are transmitted to other human beings (WHO, 2023). (WHO, 2023). Approximately 50% of HIV-infected individuals and between 15 and 25% of immunocompetent patients will develop extrapulmonary tuberculosis (Reid et al., 2019). The genitourinary tract, leading to renal tuberculosis or infertility in women; the draining nodes, particularly involving the cervical nodes in tuberculous lymphadenitis; the skeletal system, commonly including the vertebral column; and the central nervous system, presenting as tuberculoma or TB meningitis, may be involved in the infection sites. On the other hand, ascites and pleural tuberculosis may result from infections in other sites, such as the peritoneum and the pleura. It may be a problem to diagnose patients with extrapulmonary tuberculosis, considering the dubious presentations of this condition, as those signs may arise in other illnesses as well.

Mycobacterium bovis is the causative agent of bovine tuberculosis (bTB), which typically takes years to manifest. According to Michel et al. (2010), the infected cattle will often fail to present any signs of the disease for a considerable period of time, and hence, early diagnosis is challenging. Weight loss, reduced productivity, chronic dyspnea and cough, enlargement of the lymph nodes, specifically in the thoracic and cervical regions, and reduced milk yield in calves in dairy cattle, among others, are the medical signs of the disease that become evident. Injuries of the pulmonary, lymph, liver, spleen, and intestinal systems, on the other hand, can occur as a complication of the disease in cattle (Olea-Popelka et al., 2017). Wildlife hosts, which often serve as a reservoir of the disease and, in the process, do not demonstrate any serious signs of the disease as seen in the UK in the case of badgers, in the Republic of New Zealand in the case of the possum, and in Africa in the case of buffalo, makes the elimination of the bTB disease very difficult (De la Rua-Domenech, 2006).

The classical clinical spectrum of chronic tuberculosis includes a gradual onset of general symptoms like fever, cough, night sweats, and weight loss (Table 1). However, acute/generalized or fulminant forms of tuberculosis (TB) can also develop in an immunosuppressed host, children, or infected animals when exposed to a high load of the organism. It may result in rapid progression of the disease, multiple organ

Table 1. Clinical features of different forms of tuberculosis

Form of TB	Common Symptoms	Severe / Specific Feature	Reference
Pulmonary TB	Chronic cough, chest pain, hemoptysis	Weight loss, night sweats	WHO, 2020
Extrapulmonary TB	Cervical lymphadenopathy	Cold abscess formation	Michel et al., 2010
TB Meningitis	Headache, fever	Neck stiffness, altered mental status	Zumla et al., 2013
Miliary TB	Fever, weakness	Diffuse lung involvement	Sterling et al., 2011

lesions, and in extreme cases, an illness indistinguishable from sepsis (Flynn et al., 2011). The latent pathogen persistence characteristic of *M. tuberculosis* makes it an important aspect of TB epidemiology. Individuals infected in their latent phases are not symptomatic, not infectious, but are at a 5-10% lifetime risk of clinical reactivation, especially when co-infected by potent immunosuppressants such as diabetes, HIV infection, and malnutrition (Houben and Dodd, 2016).

DIAGNOSIS

Due to the possibility of overlap between the clinical signs of tuberculosis (TB) infection in humans and those of other diseases, TB infection diagnosis is rather challenging. In order to be able to effectively treat the disease, appropriate diagnostic tools have to be employed. This is in the case of TB infection in humans as well as in animals. Sputum smear microscopy, culture methods, and other imaging methods like radiology fall under conventional methods. In smear microscopy, two techniques are employed in searching for acid-fast bacilli (AFB) from the sputum specimens. These techniques are the Ziehl-Nielsen staining technique and the auramine-rhodamine fluorescence staining technique. However, only 50 to 60% cases of pulmonary tuberculosis infections can be identified using microscopy, which is widely employed and cost-effective (Perkins and Cunningham, 2007). Moreover, microscopy cannot distinguish between resistant and sensitive strains.

Drug sensitivity testing is facilitated by culture techniques, which are still the gold standard in the diagnosis of tuberculosis infection. The commonly used techniques include Lowenstein Jensen media, which is made of agar, and liquid cultures like MGIT 960 TB. In addition, the growth of cultures is rather slow, especially in the case of *M. tuberculosis*. This has led to a rather long turnaround time of up to 6 to 8 weeks, as indicated by Morcillo et al. (2008). Even in cases where there is evidence of pleural effusion, infiltrates, and cavitary diseases shown by the use of CT scans as well as chest X-rays, the diagnosis of smear-negative tuberculosis infection may be supported by microbiological confirmation, as indicated by Gopi et al. in the year 2007.

Examples of contemporary human diagnostic tests are the Xpert MTB/RIF test, line probe tests (LPAs), Nucleic acid amplification tests (NAATs), latent infection tests like interferon-γ release assays (IGRAs), and tuberculin tests (TSTs). Even though they may cost high in resource-limited countries, NAASTs, which are PCRs, take less time and work well compared to culture methods when it comes to direct testing for the DNA of *M. tuberculosis* from a clinical sample (Subbaraman et al., 2016). Because it is an FDA-cleared and WHO-approved fully automated PCR test performed within less than two hours, which makes reliable decisions regarding the resistance and infection by *M. tuberculosis* and rifampicin, the Xpert MTB/RIF has become a definitive diagnostic method primarily in high TB prevalence countries (Boehme et al., 2010).

LPAs are molecular diagnostic techniques useful in making rapid diagnoses of multidrug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB), with gene targets including rpoB, katG, and gyrA responsible for resistance to first- and second-line drugs (Hillemann et al., 2007). The BCG, IGRAs and TST share a comparable ability to measure immune system reactivity to *M. tuberculosis* antigens to determine latent infections of TB, although IGRAs are more specific in their testing, while the TST can result in a false-positive outcome in BCG-vaccinated patients and may be less expensive (Pai et al., 2014).

The tuberculin skin test TST, where pure protein derivative *M. bovis* is injected intradermally, is the primary method employed for diagnosis in animals. The comparative cervical test helps identify *M. bovis* from reacting species of mycobacteria, contributing to the diagnosis method (De la Rua-Domenech, 2006). Assays that measure the quantity of interferon gamma produced from the activation of *M. bovis* antigens stimulated immune cells include the Bovigam test. These tests are more costly and complex when compared with TST, despite their higher sensitivity (Gormley et al., 2006). Confirmatory tests from granulomatous lesions in the respiratory, lymph, and other tissues in slaughterhouses can be ascertained using PCR or culture, and the test postmortem also contributes towards diagnosis.

There are several limitations in the diagnosis of TB (Table 2). In the case of humans, underdiagnosis is common in developing countries because of the absence of molecular diagnostic facilities. In the case of livestock, it is acknowledged that farmers usually oppose skin tests along with the slaughter of the tested subjects because of the effect

Table 2. Diagnostic methods for tuberculosis

Diagnostic Method	Principle	Advantages	Limitations	Reference
Smear Microscopy	Ziehl-Neelsen staining	Cheap, rapid	Low sensitivity	WHO, 2020
Culture (LJ, MGIT)	Growth of bacilli	Gold standard, allow drug susceptibility	Very Slow (Weeks required)	Nahid et al, 2016
Gene Expert MTB/RIF	PCR-based detection	Detects rifampicin resistance, Rapid	Expensive, requires infrastructure	WHO, 2019
IGRA (Interferon-y)	Detects immune response	Useful for latent TB	Cannot distinguish active TB	Getahun et al., 2015

of tuberculosis on the livestock business. In the case of latent TB infection, it is very tough to diagnose it in both humans and livestock because the technique does not have the ability to measure the chances of reactivation in a person, as indicated by (Subbaraman et al., 2016).

Treatment and Management

A blend of various antimicrobial drugs taken for an extended duration is essential in addressing TB (Table 3). The objectives of the treatment include the eradication of the causal organism, minimizing resistance development, and transmission. Different species have treatment plans despite the reality that both human and animal patients pose challenges such as resistance, compliance, and cost.

The WHO-recommended “DOTS” strategy is currently followed as a treatment regimen in drug-sensitive TB patients. Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol are administered as a course in the six-month regimen, which comprises two months as an intensive phase and four months as a continuation phase. If adherence to the treatment is strictly observed, more than 85% of patients can be cured (Mirzayev et al., 2021; Nahid et al., 2016).

For high-risk populations, that is, patients with HIV infection or individuals who have recently exposed themselves to patients with TB, prevention through latent infection with TB is very important. Rifampicin for four months (4R), isoniazid for six to nine months (6H/9H), or isoniazid with rifapentine for three months (3HP) preventive therapies are advocated (Sterling et al., 2011).

TREATMENT OF ANIMALS

It is often recommended that treatment of tuberculosis in animals, particularly cattle, be opposed or prohibited in many developing nations because of economic effects, potential for transmission, and general concerns regarding public health, unlike in human patients. Accordingly, the "test and slaughter" strategy is commonly adopted. Since underperforming, time-consuming treatment, as well as potential for transmission, make it impractical, cattle that test positive for the tuberculin test are often slaughtered before they have an opportunity to infect many within their groups. While they are not often found infected, domestic pets, including canines and felines, receive treatment for human TB medication (Sylvester et al., 2017). Culling, vaccination, and wildlife management are the primary means by which these animal reservoirs are regulated; badgers in the UK, possums in New Zealand, and buffalo in Africa are just a few examples.

Drug resistance in TB treatment is a challenge, as it includes extensively drug-resistant TB, also known as XDR-TB, as well as multi-drug-resistant TB, referred to as MDR-TB, which is a threat to the control of TB worldwide. This is because long treatment courses, together with the toxic nature of the drugs, contribute to low levels of drug compliance, as exemplified by the increase in cases of HIV infection, since TB remains the main cause of death among those infected (Getahun et al., 2010). Destruction of animals is largely reliant

Table 3. First-line vs. second-line anti-tuberculosis drugs

Drug Class	Examples	Dose (Adults)	Treatment Duration	Key Notes
First-line (Nahid et al., 2016)				
Drug-susceptible TB				
	Isoniazid (H)	5 mg/kg orally once daily (max 300 mg)	Intensive: 2 months Continuation: 4 months	Highly effective, bactericidal; part of standard DOTS regimen; hepatotoxicity possible
	Rifampicin (R)	10 mg/kg orally once daily (max 600 mg)	Intensive: 2 months Continuation: 4 months	Bactericidal; induces liver enzymes; essential for DOTS regimen
	Pyrazinamide (Z)	25 mg/kg orally once daily (max 2 g)	Intensive phase: 2 months	Active against intracellular bacilli; hepatotoxic; avoid in severe liver disease
	Ethambutol (E)	15–20 mg/kg orally once daily	Intensive phase: 2 months	Bacteriostatic; risk of optic neuritis; used in combination to prevent resistance
Second-line (Conradie et al., 2020)				
MDR-TB, XDR-TB				
	Fluoroquinolones (Levofloxacin,Moxifloxacin)	Levofloxacin: 750–1000 mg daily Moxifloxacin: 400 mg daily	18–24 months	Key drugs for resistant TB; bactericidal; monitor QT interval for Moxifloxacin
	Injectable agents(Amikacin,Capreomycin,Kanamycin)	Amikacin: 15 mg/kg IM daily Capreomycin: 15 mg/kg IM daily Kanamycin: 15 mg/kg IM daily	6–8 months intensive, part of 18–24 months total	Ototoxicity and nephrotoxicity risks; monitor renal function; used in combination therapy
	Linezolid	600 mg orally or IV once daily	18–24 months (part of combination)	Effective against resistant strains; myelosuppression and neuropathy risk
	Bedaquiline	400 mg daily for 2 weeks, then 200 mg thrice weekly	24 weeks (part of combination therapy)	Novel anti-TB drug; risk of QT prolongation; used with other agents for resistant TB

upon laws governing slaughter, which the farmers might reject due to the economic implications.

Trials of rifapentine and moxifloxacin doses for four months in drug-susceptible TB patients have been encouraging, reflecting recent and future developments in TB treatment (Dorman et al., 2021). In treatment-naïve and -experienced patients with MDR/XDR-TB, newer drugs such as bedaquiline and Delamanid appear to have provided better outcomes. Desensitization strategies targeting the host immune response are still being explored in clinical studies (Zumla et al., 2015). The BCG vaccine, a century old, provides patchy immunity; however, newer candidates such as M72/AS01E appear to have provided about 50% efficacy in clinical studies (Van Der Meeren et al., 2018). Prevention of TB still remains an integral part of controlling the disease. (Van Der Meeren et al., 2018).

Controlling tuberculosis requires a comprehensive effort involving public health, veterinary, and medical measures. One Health initiative focusing on collaboration and coordination between the public health, veterinary, and environmental health sectors is very important in view of the zoonotic nature of Mycobacterium TB complex bacteria, particularly *M. bovis*. The only licensed TB vaccine in humans is still BCG immunization. It provides a mere 80% efficacy in young individuals against severe forms of tuberculosis, i.e., meningitis and miliary TB. (Fine et al., 2011). As stated by Van Der Meeren et al. (2018), new vaccine formulations such as M72/AS01E have demonstrated an efficacy of 50% in preventing the latent stage to active disease transition. Early diagnosis and care by the enhanced DOTS framework, contact tracing, preventive care of high-risk groups, linking TB care initiatives to HIV care initiatives, and infection control practices in health care settings by means of enhanced ventilation systems, respiratory protection strategies, and isolating infectious cases are public health practices. Reduction in the incidence of TB is also brought about by means of socioeconomic and behavioral strategies such as managing risks such as diabetes and smoking, overcrowding, and improved nutrition practices (Lönnroth et al., 2010).

The test and slaughter policy, which remains the backbone of bovine TB control in the vast majority of countries, remains the focus of animal control. To arrest the transmission of the disease in the herd, infected animals identified by the interferon-gamma release assay and the tuberculin skin test are slaughtered (Michel et al., 2010). To ensure that infection does not spread from index herds due to the presence of the disease in the herd through the skin of the animals, movement restrictions are applied. Culling efforts, as well as experimental vaccination strategies, are employed in the control of the wildlife reservoirs of the disease, which include buffalo, possums, and badgers (Martin et al., 2017). Vaccinated protection is offered through vaccination but it complicates the implementation of the tuberculin skin test. To ensure that vaccination is carried out without posing any risks of the disease through the vaccine itself, DIVA (Differentiated between infected and vaccinated animals) tests are currently under development (Gerdts et al., 2015).

One Health is an important way of recognizing the link between animal and human tuberculosis. Infection in humans, due to *M. bovis*, can occur, though to a lesser extent, as a result of direct contact and the consumption of raw milk (De la Rua-Domenech et al., 2006). To improve sensitivity and point the way toward interventions, there is a common surveillance system and database in the areas of public and veterinary health. Collaboration is important in the community in the promulgation of test-and-slaughter policies, mainly in the agricultural sector.

Drug resistance, threatening human therapy; poor diagnostic capacity in animals, making it hard to diagnose early; socioeconomic factors such as poverty and poor access to healthcare; and inequality in the world, in which financial struggles in developing nations make it hard to successfully implement eradication programs, although successful in developed nations, are some of the issues in controlling tuberculosis (Ayele et al., 2004). Next-generation vaccines with greater and more lasting immunity, more host-targeting drugs, more accessible treatment strategies to reduce treatment regimens and improve human outcomes, a comprehensive program including the animal reservoir, and more molecular epidemiology techniques such as whole genome sequencing and genotyping to report the transmission between species could be found in a One-Health perspective to harmonize veterinary and human programs and strategies for this and other diseases.

CONCLUSION AND FUTURE DIRECTIONS

For both humans and animals, tuberculosis, or TB, has always ranked among the most dangerous infectious ailments. As a result of the increasing instances of drug-resistant tuberculosis, the co-infection of HIV, as well as the phenomenon of zoonoses or the transmission of the disease from animals to humans, tuberculosis has also proved to be challenging to global healthcare systems despite the many developments that have arisen about the treatment and control of the disease. Although a definite diagnosis of tuberculosis relies on microbiologic and molecular methods, clinical diagnosis makes the key difference. Rapid molecular tests like Xpert/MTB RIF have been worth a revolution in drug resistance genotyping and initial diagnosis, yet conventional smear microscopy and culture have held importance in almost all settings. Although novel immunologic tools and management of wildlife diseases are increasingly important nowadays, culling and tuberculin tests have been the mainstay of animal control methods.

There has been a tremendous improvement in the treatment of TB, and harmonized first-line treatment has contributed to a high cure rate in drug-susceptible TB patients. However, protracted, toxic, and costly treatment is needed in the case of MDR and XDR-TB, and this constitutes a grave threat. The introduction of new drugs such as bedaquiline and Delamanid and the development of shorter treatment regimens are steps in the right direction to improve treatment outcomes. Chemotherapy is beyond the realm of animals; therefore, any control measure will involve biosecurity, slaughter, and monitoring. Prevention is the best course of action. Although

the BCG vaccine has offered variable protection, which is largely in adults, new approaches to host-targeted therapies and vaccines appear promising. In the veterinary field, the use of the BCG vaccine in cattle, along with a diagnostic test for distinguishing infection (DIVA), may be a strategy for long-term control. In the future, the One Health approach is essential. As TB transcends different species, collaborations between the medical sector and the veterinary and environmental health sectors will be essential. The monitoring of the surveillance system and the strengthening of the diagnostic and treatment methods will play a critical role in achieving the Global Goal of TB elimination.

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