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Developments in Tuberculosis Research and Treatment

Edited by Karolina D. Witt



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IntechOpen Book Series

Infectious Diseases

Volume 46

Aims and Scope of the Series

This series will provide a comprehensive overview of recent research trends in various Infectious Diseases (as per the most recent Baltimore classification). Topics will include general overviews of infections, immunopathology, diagnosis, treatment, epidemiology, etiology, and current clinical recommendations for managing infectious diseases. Ongoing issues, recent advances, and future diagnostic approaches and therapeutic strategies will also be discussed. This book series will focus on various aspects and properties of infectious diseases whose deep understanding is essential for safeguarding the human race from losing resources and economies due to pathogens.

Meet the Series Editor



Dr. Alfonso J. Rodriguez-Morales received his MD from Universidad Central de Venezuela in Caracas and his MSc in Protozoology/Parasitology from Universidad de Los Andes in Trujillo, Venezuela. He received his Diploma in Tropical Medicine & Hygiene (DT-M&H) from Universidad Peruana Cayetano Heredia, Lima, Peru, and the University of Alabama at Birmingham, Alabama, USA. He also holds a DipEd. Dr. Rodriguez-Morales is a fellow of the Royal Society for Tropical Medicine & Hygiene (FRSTMH), London, United Kingdom; of the Faculty of Travel Medicine (FFTM) of the Royal College of Physicians and Surgeons of Glasgow (RCPSG), Glasgow, Scotland, United Kingdom; of the American College of Epidemiology (FACE), USA; and the International Society for Antimicrobial Chemotherapy (FISAC). He has a HonDSc from Universidad Privada Franz Tamayo (UniFranz), Cochabamba, Bolivia. He is the President of the Latin American Society for Travel Medicine (SLAMVI) (2023–2025) and the Past President of the Colombian Infectious Diseases Association (2021–2023). He is a member of the Council (2020–2026) of the International Society for Infectious Diseases (ISID). He is a senior researcher at Colciencias (2015–2027) and a professor at the Fundación Universitaria Autónoma de las Américas in Pereira, Risaralda, Colombia, as well as at the Universidad Científica del Sur (UCSUR) in Lima, Peru. He is a visiting professor at multiple national and international universities.

Meet the Volume Editor



Dr. Karolina Witt is a medical doctor and senior clinical trials researcher with long-standing interests in tuberculosis, working “from bench to bedside”. She is actively engaged in clinical care and in research on TB pathogenesis and disease progression. Over the years, she has led several major clinical trials for leading UK academic institutions and has supported international research in infectious diseases. She continues her clinical practice, where the challenges of treating TB patients serve as a reminder that the disease is far from eradicated, despite advances in genome sequencing technology, new treatment regimens, and integrated healthcare and contact tracing systems.

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Preface

Despite over a century of efforts, tuberculosis (TB) remains one of the deadliest infections and a difficult-to-eradicate scourge of human health. *Mycobacterium tuberculosis* (Mtb, the causative agent of tuberculosis) is responsible for over ten million cases and more than one million deaths each year [1]. Despite the availability of antibiotics and vaccination with the attenuated form of *Mycobacterium bovis*, Bacillus Calmette-Guérin (BCG), which classifies tuberculosis as a preventable and curable disease, TB remains a major global health threat [2]. In 2024, it was named a major cause of deaths related to antimicrobial resistance and the leading killer of people with HIV in 2024. TB and HIV form a lethal combination, each accelerating the progression of the other [3].

Each year in March, the world commemorates the toll of tuberculosis on World TB Day and galvanizes the research community to renew its commitment to intensified research and advocacy in the fight against the disease. Half a year later, in October, the World Health Organization (WHO) releases its annual World TB Report, presenting updated progress figures and visualizing the distance to achieving target milestones set in the current five-year plans and strategic roadmaps.

Research remains the cornerstone of the fight against TB. According to the WHO, as of August 2025, there were 18 vaccine candidates in clinical trials and at least 42 clinical trials and implementation studies underway to evaluate drug regimens and models of their delivery.

In the spirit of getting involved in TB research, the book *Developments in Tuberculosis Research and Treatment* has been compiled. We are pleased that it includes chapters written by the authors across multiple countries, reflecting the global nature of the fight against TB.

The book is divided into two sections: *Advances in the Diagnosis and Treatment of Tuberculosis* and *Challenges of Extrapulmonary Tuberculosis Treatment*.

In the first chapter, the authors (Alina Malic, Adriana Niguleanu, and Tatiana Osipov) provide an excellent summary of the principles of tuberculosis treatment, including drugs used for both drug-susceptible and drug-resistant TB, updating the well-known combination regimens with the most recently approved therapies. Their overview links mechanisms of drug action to their effects on bacterial load and potential side effects. They follow on to summarise newer combination regimens for drug-resistant TB, highlighting all-oral treatments that represent a much-awaited breakthrough in this difficult-to-eradicate disease.

The role of corticosteroids as adjunctive therapy in tuberculosis management remains controversial beyond a few specific indications. For this reason, we

particularly welcome the excellent introduction to this topic by Dr. Abuobaida Yassin, who traces the evolution of corticosteroid use as an adjunctive therapy in TB and presents a current global perspective across both high- and low-burden settings. He skillfully outlines the balance between protective immunity and tissue damage within the granuloma, a feature unique to *Mycobacterium tuberculosis* pathogenesis, and discusses how steroids may improve drug penetration at infection sites, thereby enhancing clinical recovery despite concerns about immunosuppression and systemic side effects.

The rapidly advancing field of AI-driven improvements in diagnostic tools is advancing nowhere faster than in medical imaging, where large datasets of existing scans are used to train models to detect subtle pathological features. In this context, we are pleased to present the chapter by Victor Chigbundu Nwaiwu, which reviews both traditional and emerging imaging techniques, as well as AI-based approaches, in pulmonary TB. He describes machine learning, deep learning, and natural language processing models, as well as the practical challenges of implementing them. These tools may improve diagnostic accuracy in TB to allow earlier empirical treatment, while conventional sputum or biopsy culture – the gold standard – can take 6-8 weeks to yield conclusive results.

In the second section of the book, we decided to focus on important yet often underappreciated aspects of extrapulmonary TB. Olga Adriana Caliman-Sturdza presents recent advances in the understanding and management of TB meningitis. Drugs such as bedaquiline, linezolid, and fluoroquinolones have desirable central nervous system (CNS) penetration, offering potential for deployment in multidrug-resistant (MDR) TB meningitis. The newer Xpert MTB/RIF Ultra molecular test offers a lower limit of detection and can identify approximately 90% of culture-positive cases. Research into cerebrospinal fluid (CSF) biomarkers using transcriptomic and proteomic techniques is progressing rapidly, with proposed initial panels including elevated CSF cytokine profiles and neural fragments indicative of injury. Recent clinical trials (ZeNiX, TB-PRACTECAL, endTB) have shown that MDR-TB meningitis is now essentially treatable in 6-9 months with all-oral regimens, without injectables, and with significant increases in adherence, tolerability, and cure rates.

Finally, we are pleased to include a chapter by Dani  lle van Staden, who highlights the often-overlooked, profound consequences of genital tuberculosis (i.e., Asherman's syndrome, characterized by abdominal adhesions linked to acquired infertility) on health and social functioning, particularly in high-burden, low-income settings. She introduces emerging approaches involving intradermal and mucosal drug delivery systems as adjunctive treatments for this neglected form of TB. These include innovative dosage forms such as nanocarriers, mucoadhesive systems, and solution-to-gel formulations, which enable direct drug delivery to the mucosal surfaces of the genital tract while bypassing hepatic first-pass metabolism and gastrointestinal degradation. She also explores the role of the Lactobacillus-dominated vaginal microbiome, which can be utilized to enhance prodrug conversion and therapeutic efficacy. On the other hand, she also describes new forms of natural skin penetration enhancers that are being investigated for applications such as breast TB mastitis. Her comprehensive approach helps destigmatize genital TB and highlights clinically relevant scientific advances.

This book has undergone a long journey in its editorial process. None of its milestones would have ever been achieved without the dedicated involvement of Ms. Valentina Jolic, who coordinated the timely submissions and review of all chapters. We extend our sincere gratitude for her commitment and passion for academic publishing, the results of which are presented to the reader in this volume. Our deepest thanks are also extended to all readers of this book.

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Section 1

Advances in the Diagnosis
and Treatment of
Tuberculosis

Chapter 1

Development of Tuberculosis Treatment Regimens

Alina Malic, Adriana Niguleanu and Tatyana Osipov

Abstract

Treatment of tuberculosis (TB) includes various therapeutic regimens with a combination of at least four drugs. Adherence to the treatment regimen is crucial for efficacy outcomes based on the achievement of appropriate drug levels. Drug-resistant *Mycobacterium tuberculosis* (MTB) strains are mainly favored by inadequate TB management. Inappropriate treatment of tuberculosis can contribute to the maintenance and spread of drug-resistant strains of *Mycobacterium tuberculosis* (MTB) in the community. Treatment of drug-resistant tuberculosis (DR-TB) is challenging because it requires the use of second-line anti-TB drugs, which are less effective and more toxic. The treatment of TB is aimed at curing patients, preventing relapse, TB transmission, drug resistance, and eradicating TB infection. Treatment efficacy directly depends on the choice of treatment regimen, its duration, drug metabolism, interactions, the development of side effects and their management, and associated diseases. The drugs should be administered in combination with at least four medicines, and their choice should be based on drug sensitivity testing (DST). In this chapter, the standardized regimens for the treatment of patients suffering from drug-susceptible TB (DS-TB) and DR-TB are described. For effective tuberculosis control, the appropriate application of old regimens, as well as the development and implementation of novel medicines and new treatment regimens in clinical practice, are needed.

Keywords: treatment, tuberculosis, drug-susceptible tuberculosis, drug-resistant tuberculosis, antituberculous drugs

1. Introduction

Tuberculosis (TB) continuously represents an important global health care challenge, presenting high morbidity and mortality. According to the World Health Organization (WHO), 10.8 million incident cases and 1.09 million deaths were estimated in 2023 among HIV-negative people [1].

Despite continuous global efforts to combat TB, it has regained its status as the world's leading infectious killer and the cause of death from a single infectious agent, replacing COVID-19 [1]. The emergence of drug-resistant TB (DR-TB), including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), presents a significant challenge to disease control [2, 3]. The primary goal for the

treatment of both drug-susceptible TB (DS-TB) and drug-resistant TB (DR-TB) is to increase treatment success and minimize side effects. This can be achieved through the development and implementation of new drugs and more effective treatment regimens, alongside the management of side effects, enhancing patient compliance, and controlling TB transmission [1, 3, 4]. Improving diagnostic capabilities through the implementation of novel methods is crucial for effective TB management because early diagnosis allows for prompt treatment initiation [5, 6].

The principles of TB chemotherapy were established in the early 1950s of the last century and were improved over the following decades, parallel with the development of phthisiology (the study of tuberculosis), pharmacology, molecular biology, and genetic engineering. This progress is reflected in the development of standardized treatment regimens for TB, approved by regulatory frameworks [7, 8]. Effective chemotherapy should destroy the *MTB* as quickly as possible and prevent mutations in specific genes (DR-TB) [9, 10].

A chemotherapy regimen includes a combination of drugs, which vary in dose and treatment duration [2]. Treatment guidelines for DS-TB have recommended the use of a combination of first-line drugs during a 6-month period. Treatment for DR-TB requires complex, long-term (18–20 months) regimens with combinations of oral drugs that are more expensive and toxic. Conducted clinical trials (STREAM, Nix-TB) demonstrated the efficacy and good tolerance of shorter regimens, including novel drugs such as Bedaquiline, Pretomanid, and Delamanid [11, 12]. Another efficacy study of the 4-month regimen for DS-TB, including Rifapentine and Moxifloxacin, reported the same outcomes as the 6-month regimen [13]. These pieces of evidence have led to the appearance of new recommendations for shorter, effective, and tolerable regimens [2] for DS-TB and DR-TB [3], which were reviewed in 2025 [14].

This chapter aims to present the modern treatment approach for DS-TB and DR-TB, including recent updates in treatment strategies.

2. Current treatment of TB disease

Treatment regimens of all forms and localizations include drugs specifically designed to target and effectively affect or kill *MTB*, the main pathogen responsible in common cases of TB. These medicines are called anti-TB drugs, and their use is known as antibacterial or etiotropic therapy because they affect the causative TB agent. For brevity and convenience, the term “chemotherapy” has become widespread [8].

Chemotherapy of TB includes two phases. The first, intensive phase, is carried out to significantly reduce the *MTB* population, destroy it, eliminate acute disease manifestations, stop bacterial excretion, and promote the closure of cavities. The second, continuation phase, is needed to consolidate the achieved results, prevent reproduction, and destroy the remaining *MTB*. The two-phase treatment promotes regression of the TB process, leads to a stable clinical effect, stabilization or healing, and prevents TB relapse [15].

Treatment efficacy can be increased with timely diagnosis and treatment beginning before the development of severe TB morphological changes [16]. Treatment duration has a significant impact – too short (premature cessation) can lead to further TB progression or relapse, while long-term chemotherapy carries a

risk of side effects and low adherence. When determining the timing of chemotherapy, factors such as disease duration, information about previous treatment, the characteristics and evolution of the TB process, as well as the therapeutic possibilities of the selected treatment regimen, should be considered [17]. Different mechanisms of drug action are important because the association effect, bacteriostatic (suppressing reproduction), and bactericidal (destroying) effects on intra and extracellular *MTB* are provided.

Patient should regularly take a single daily dose of each drug included in the regimen at one time, especially in the first phase of treatment [17]. Treatment efficacy depends on dosage and patient adherence [18]. In some cases, individualized treatment is needed in accordance with individual medical conditions, based on DST results [19]. In certain situations, surgery is required [20]. A successful outcome is impossible without a rational dietary regimen, pathogenetic and symptomatic drugs, and the patient's understanding of the importance of responsibility and self-control during therapy [21].

The main principles of TB treatment: – early onset; – optimal dosing frequency throughout the whole therapy course; – complexity; – optimal duration, drug combination; – fixed-dose combination tablet use; – adherence to treatment; – treatment of comorbidities [14, 22, 23].

In **Figure 1**, the concept of drug development versus regimens is illustrated. At the beginning of the last century, there was significant progress in the development of novel drugs. Ten novel TB drugs appeared within 20 years. These were combined into novel regimens, and it took quite a long time – 40 years – until a standard therapy was proposed. After the initial enthusiasm with streptomycin curing people or clearing mycobacteria from sputum very rapidly, within six months, people relapsed and developed monoresistance against streptomycin. Following the establishment of multiple treatment regimens over a long period of time, resistance was not detected. However, in 1983, the first occurrence of MDR TB was identified, followed rapidly by XDR TB. There was a significant undertaking from the public domain, as well as companies, to develop a new set of TB drugs. During that time, bedaquiline was the first drug to be registered. However, bedaquiline was used against the backdrop of a failing regimen. Consequently, bedaquiline was not adequately protected during its introduction by other drugs that could help prevent resistance from developing. Just a few years after bedaquiline's introduction to the market, the first occurrence of bedaquiline resistance was reported [1].

Despite the development of the field in terms of novel drugs, the good old standard regimen HRZE: rifampicin, isoniazid, pyrazinamide, and ethambutol — is still in use. There is also a newer regimen that replaces rifampicin with rifapentine and ethambutol with moxifloxacin. However, the limited use of the new regimen is probably due to its higher cost and imperfect drug availability, and it's likely not strong enough to convince many TB programs around the world to stop using the well-established regimen. In resistant TB, especially resistance against rifampicin or isoniazid, which is called multidrug-resistant tuberculosis, patients take completely different medicines, including bedaquiline, pretomanid, linezolid, and moxifloxacin. There are a number of alternative regimens that are approximately equally effective, treating the disease within six to nine months. However, the big concern that's emerging is the increasing resistance against bedaquiline, and doctors then need to compose individualized regimens based on antibiotic susceptibility testing. Unfortunately, that susceptibility testing is often conducted

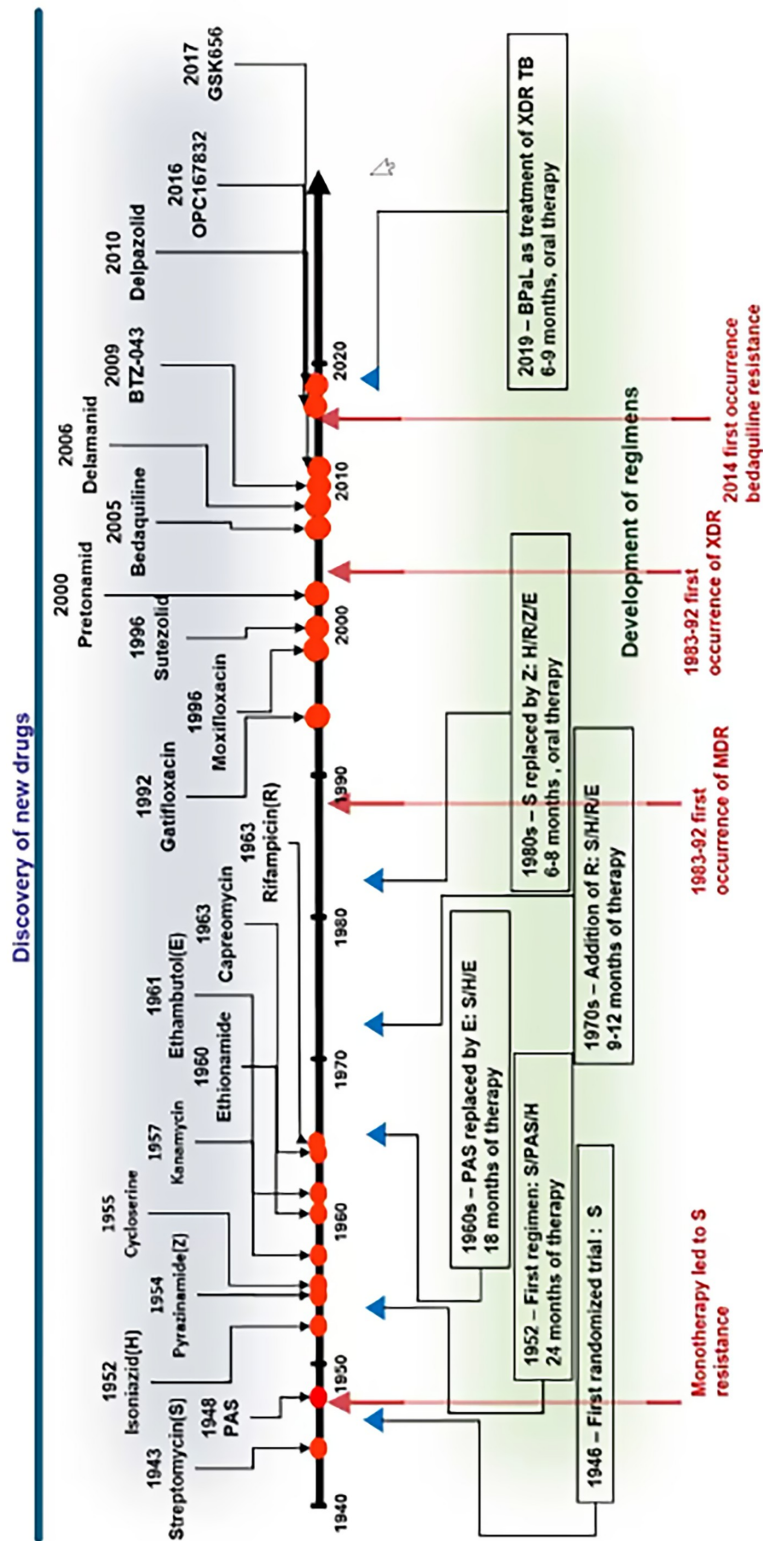


Figure 1.
Development: drugs versus regimens [1].

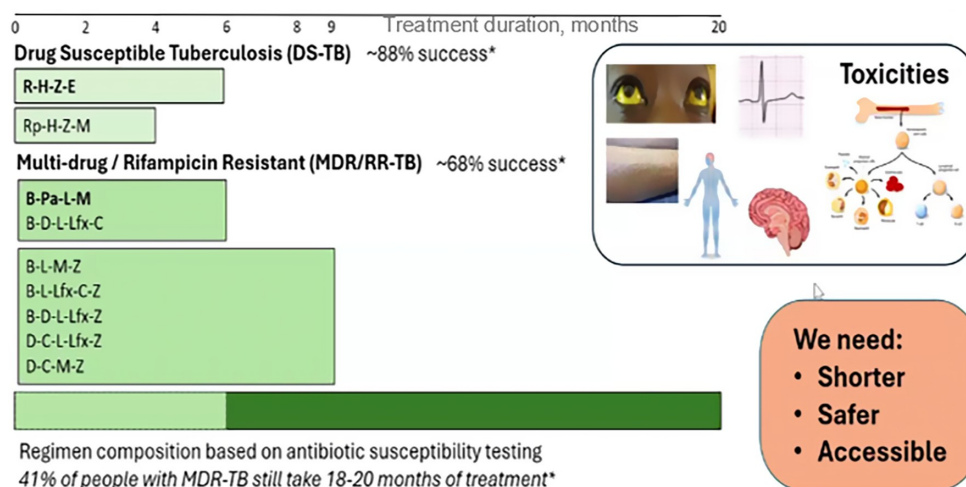


Figure 2.
Current TB treatment strategies [1].

quite late in treatment because it's based on culture and phenotypic testing, and the treatment itself lasts 18 to 20 months, which only 41% of people are able to complete over such a long period of time. Both drug-sensitive and MDR treatments come with substantial risks of toxicity, affecting the liver, cardiac, skin, bone marrow, and neurological systems. Therefore, there is a pressing need for shorter, safer, and more accessible treatments (**Figure 2** [1, 7–9]).

3. Treatment regimens for drug-susceptible TB

3.1 Drugs used for the treatment of drug-susceptible TB

Treatment of TB caused by drug-sensitive *MTB* (DS-TB) comprises first-line drugs that were developed in the 1950s to 1970s [21, 24].

Isoniazid – an isonicotinic acid hydrazide. The mechanism of action on *MTB* is based on the suppression of DNA mycolic acid synthesis, phospholipids, and the disruption of cell wall integrity. At high concentrations, it exerts a bactericidal effect [25, 26]. Isoniazid passes into the CNS. The therapeutic dose is 4–6 mg/kg/day, up to 300 mg orally daily. In cases of renal failure, no dose adjustment is required. Side effects include hepatitis, nervous system disorders, vitamin B6 deficiency, skin disorders, and gynecomastia. Isoniazid toxicity increases with alcohol use [25, 27, 28]. Primary resistance of *MTB* to Isoniazid is rare; however, secondary resistance develops quite quickly. The use of Isoniazid in high doses for DR-TB is justified in the absence of a *katG* gene mutation [29]. Isolates with an *inhA* mutation are resistant to Ethionamide and Prothionamide [26, 30, 31].

Rifampicin is a broad-spectrum antibiotic and one of the essential first-line drugs for treating TB. It has a bactericidal effect on *MTB* and sterilizing properties. The action of Rifampicin is based on the suppression of RNA synthesis by forming a complex with DNA-dependent RNA polymerase; transmission of genetic information in *MTB* is disrupted, and new *MTB* are not formed [32]. Rifampicin acts

on both extracellular and intracellular *MTB*. Rifampicin passes into the CNS. Rifampicin is excreted mainly with bile and 25% with urine [33]. The therapeutic dose is 10 mg/kg, given orally once daily, with a maximum dose of 600 mg [25, 34]. In cases of renal failure, no dose adjustment is required. Side effects include hepatotoxicity, neutropenia, thrombocytopenia, gastrointestinal disorders, orange/red coloration of fluids (tears, sputum, urine, feces), hemolytic anemia, and renal failure [35]. Contraindications include severe liver dysfunction. Alcohol should not be consumed during Rifampicin use [35]. Primary resistance to Rifampicin is not common; however, secondary resistance develops relatively quickly [36].

Pyrazinamide is a synthetic, effective, and strictly specific anti-TB drug. Its effect is unique and most pronounced in caseous necrosis foci (acidic reaction). The mechanism of action is unknown. The bacteriostatic effect of Pyrazinamide has been established in acidic media (pH 5.5) [25, 37]. High doses of Pyrazinamide can also reach therapeutic levels in the CNS [38, 39]. The therapeutic dose is 25 mg/kg, given orally once daily. Dosage should be adjusted according to weight [25]. In cases of renal failure, the recommended dose is 25 mg/kg three times a week. Side effects include nausea, vomiting, loss of appetite, weakness, dark urine, light stool, pain in the right hypochondrium, itching, jaundice, arthralgia, and increased uric acid levels in the blood [25, 40]. Contraindications include severe hepatic failure, gout, and breastfeeding mothers [39]. Primary resistance to Pyrazinamide is rare, while secondary resistance develops relatively slowly [37].

Ethambutol, a synthetic anti-tuberculosis drug, works by suppressing synthesis and stabilizing ribonucleic acid (RNA) in *Mycobacterium tuberculosis* (*MTB*). It also inhibits the formation of *MTB* cellular wall components and cell division via the arabinosyltransferases (embA, embB, and embC). The effect of Ethambutol is mainly bacteriostatic [25, 41]. The therapeutic dose is 15-25 mg/kg, prescribed orally once a day, and the dosage should be adjusted according to weight [42]. Side effects include allergic reactions, gastrointestinal disorders, hepatotoxicity, mental confusion, hallucinations, and eye disorders. Contraindications include intolerance and eye diseases [43]. Ethambutol is not recommended during pregnancy. Caution is necessary in patients with renal dysfunction and when treating children. Primary resistance to Ethambutol is rare, and secondary resistance develops very slowly. Ethambutol prevents drug resistance development in the TB pathogen to other anti-TB drugs, which makes it a valuable agent [25, 43, 44].

TB drug targets are present in **Figure 3** [7].

Side effects and management options of TB drugs are described in **Table 1**.

It is a unique situation because the global TB drug pipeline is as full as it has never been before. As presented in **Figure 4**, a lot of novel drugs are in phase one and phase two clinical trials. New, suitable, and affordable TB regimens will be compiled from them in the future.

3.2 Treatment regimen for drug-susceptible TB

3.2.1 Treatment of DS-TB using a 6-month regimen

A 6-month regimen for patients with drug-susceptible (DS) pulmonary tuberculosis (TB), specifically new cases, is composed of 2 months of Isoniazid (H), Rifampicin (R), Ethambutol (E), and Pyrazinamide (Z) during the intensive phase, followed by 4 months of Isoniazid and Rifampicin (4 HR) in the continuation phase,

System	Adverse effect	Suggested drugs
Gastrointestinal	Nausea, vomiting	EtO/PTO, PAS, H, E, Z, DLM, BDQ, LZD
	Gastritis	PAS, Eto/Pto
	Diarrhoea	PAS, Eto/Pto, FQ, Bdq, Lzd
	Hepatitis	Z, H, R, Eto/Pto, PAS, E, FQ, Bdq, Lzd
Cardiac	Prolonged QTc	FQ, Bdq, Dlm, C
Musculoskeletal	Joint pain	Z, FQ
Otological	Hearing loss and vestibular disturbances	S, Km, Am, Cm
Endocrine	Hypothyroidism	PAS, Eto/Pto
Ophthalmic	Optic neuropathy	E, Eto/Pto, Lzd
Haematological disorders	Myelosuppression – anemia, low levels of white blood cells, and platelets (pancytopenia)	Lzd
Neurological	Seizures	Cs, H, FQs
	Peripheral neuropathy	Lzd, Cs, H, S, Km, Am, Cm, Eto/Pto, FQ
	Psychotic symptoms	Cs, H, FQ, Eto/Pto
	Depression	Cs, FQ, H, Eto/Pto
Renal	Nephrotoxicity	S, Km, Am, Cm
	Electrolyte disturbances (hypokalaemia and hypomagnesaemia)	Cm, Km, Am, S

Note: drugs in bold are more strongly associated with the adverse effect than drugs not in bold; Eto/Pto: ethionamide/prothionamide; H: isoniazid; E: ethambutol; Z: pyrazinamide; Dlm: delamanid; Bdq: Bedaquiline; Lzd: linezolid; FQ: fluoroquinolone; R: rifampicin; QTc: corrected QT interval; C: clofazimine; NSAID: nonsteroidal anti-inflammatory drug; S: streptomycin; Km: kanamycin; Cm: capreomycin; Cs: cycloserine; Am: amikacin.

Table 1.
Adverse effects of anti-TB drugs [1].

with optimal daily dosage and frequency maintained throughout both phases of therapy (2 HRZE/4 HR) [3]. According to the World Health Organization (WHO), in cases with a positive sputum smear at the completion of the intensive phase, extension of the intensive phase is not recommended [9].

This regimen is also recommended for [9]: – people who are living with HIV; – treatment of the cases of extrapulmonary TB, except TB of the CNS, bone, or joint, for which longer therapy is suggested; To improve adherence, the use of fixed-dose combination tablets is recommended over separate drug use.

3.2.2 Treatment of DS–TB using 4-month regimens

WHO recently approved two shorter regimens for the patients with DS–TB [3, 9, 45]:

- For patients with sensitive lung TB aged age ≥ aged 12 years, a 4-month regimen is recommended, composed of 2 months of H, Rifapentine (P), Moxifloxacin



Figure 4.
2024 global new TB drug pipeline [1].

(M), and Z in the intensive phase, followed by 2 months of HPM in the continuation phase (2HPMZ/2HPM). This regimen is also recommended for HIV-infected persons ($CD4 + >100$ cells/mm³) [46]. However, this regimen is not recommended due to limited evidence for: – HIV-infected people ($CD4 + <100$ cells/mm³); – People with low weight (<40 kg); – Patients with extra-pulmonary TB; – Pregnant, breastfeeding, or postpartum women.

- For children and adolescents between 3 months and 16 years of age with non-severe DS-TB (without suspicion or evidence of MDR/RR-TB, peripheral lymph node TB, intrathoracic lymph node TB without airway obstruction, uncomplicated TB pleural effusion, or paucibacillary non-cavitary disease confined to one lobe of the lungs without a miliary pattern), a 4-month treatment regimen is recommended (2HRZ(E)/2HR). E is recommended if the setting is characterized by a high prevalence of HIV and isoniazid resistance [3].

3.2.3. DS-TB treatment and anti-retroviral therapy (ART) in people living with HIV (PLHIV)

PLHIV should receive the same drug regimen (a 6-month or a 4-month regimen for DS-TB) for at least the same duration of treatment as HIV-negative TB patients [9, 46]. It is recommended to start ART as soon as possible, usually after two weeks of beginning treatment for TB, regardless of the level of CD4 cells in PLHIV.

4. Treatment for drug-resistant TB

4.1 Drugs for drug-resistant TB (DR-TB)

Fluoroquinolones (FQ) – ciprofloxacin, ofloxacin, lomefloxacin, levofloxacin (Lfx), and moxifloxacin (Mfx) – are broad-spectrum antibiotics. FQ action on *MTB* is bactericidal. FQ exert their effects by inhibiting DNA gyrase and topoisomerase IV, further inhibiting DNA synthesis within the bacteria [47]. FQ inhibit the binding reactions of deoxyribonucleic acid chains; direct binding of FQ to individual chains leads to the death of *MTB*. FQ are also capable of damaging the outer *MTB* membrane, providing a long-term post-antibiotic effect [48]. FQ molecules are small in size, so they penetrate well into all organs, tissues, biological fluids, and inside cells. FQ are capable of affecting mycobacteria in any location, actively affecting *MTB* during both the growth and resting periods of the bacterial cell. The drugs penetrate into the lung tissue and accumulate in the lungs. Lfx and Mfx both penetrate into the CNS. The combination of FQ with H leads to increased action on *MTB*. A synergistic effect of FQ with a pyrazinamide combination was noted. Daily/maximum Lfx doses are 750–1,000 mg. Mfx daily dose 400–800 mg, maximal dose 800 mg. In case of renal failure: dosage should be adjusted; for Lfx 750–1000 mg thrice weekly (if creatinine clearance <30 mL/min); for Mfx, no dose adjustment is required. FQ drugs have relatively low toxicity. Side effects: dyspeptic disorders; nervous system disorders; photodermatitis with prolonged exposure to the sun; joint damage-pain, tendonitis, edema, hyperemia; increase/decrease in appetite, hyperhidrosis, tremors [49]. Contraindications: during pregnancy, breastfeeding [50]. *MTB* resistance to FQ occurs rarely [48, 51].

Bedaquiline was the first drug approved for the treatment of MDR-TB in 2012 since rifampin in 1971 [52]. Bedaquiline belongs to the group of diarylquinolines. The medicine exerts bactericidal activity via the inhibition of ATP synthesis, which leads to the disruption of energy production and, as a result, to the death of the microbial cell [53]. Bedaquiline is active against DS and DR *MTB* strains [54]. At low concentrations, Bedaquiline exhibits a bacteriostatic effect and potentiates the risk of resistance development, while at high concentrations, it has a bactericidal effect [53, 54]. In cases of renal failure, no dose adjustment is required. Side effects include headache, dizziness, nausea, vomiting, hepatitis, arthralgia, arrhythmia, and QT prolongation [55, 56].

Linezolid is an oxazolidinone antibiotic. It has shown activity against aerobic gram-positive bacteria, some gram-negative bacteria, and anaerobic bacteria. Linezolid selectively inhibits protein synthesis by binding to bacterial ribosomes and prevents the formation of the functional 70S initiation complex, an important component of the translation process during protein synthesis [57]. Linezolid penetrates well into the CNS. The maximum dose for adults and children is 1.2 g/day. In cases of renal failure, no dose adjustment is required. Side effects include anemia, thrombocytopenia, leukopenia, neurotoxicity, optic neuropathy, serotonin syndrome, nausea, vomiting, and diarrhea [57–60]. Resistance to Linezolid develops rarely and slowly.

Cycloserine – a broad-spectrum drug, as a result of which *MTB* loses acid resistance and acquires an unusual shape. The mechanism of action is bacteriostatic. Cycloserine remains active in an acidic environment and penetrates into the CNS [61, 62]. A daily therapeutic dose of 10–20 mg/kg is prescribed orally. In case of renal failure – 250 mg once daily (500 mg TIW). Side effects include headache, dizziness, somnolence, convulsions, peripheral neuropathy, psychosis, depression, a feeling of fear, suicidal tendencies, irritability, aggression, hallucinations, tremor, elevated serum aminotransferases, etc. Primary drug resistance to Cs is rare, and secondary resistance develops slowly [63].

Protonamide (Pto) is a chemotherapeutic agent that is a homologue of ethionamide. Pto's action is associated with a disruption of the metabolism of the microbial cell. Pto has a bacteriostatic effect, and there are some indications of a bactericidal effect. Pto retains activity in an acidic environment and penetrates well into the CNS. The daily therapeutic dose is 15 mg/kg, administered orally. The tolerance of protonamide varies. Genetic factors in the drug's metabolism are of great importance [61]. In cases of renal failure, no dose adjustment is required. Side effects include nausea, vomiting, gastritis, nephrotoxicity, mental disorders, hepatitis, and acne. Contraindications include liver damage, epilepsy, psychosis, hematopoietic system disorders, chronic alcoholism, and pregnancy. Primary resistance is rare, and secondary resistance develops slowly [62].

Ethionamide (Eto) is an anti-TB drug that was obtained earlier than Pto. The main characteristics of these drugs coincide. Eto penetrates well into the CNS. Eto is toxic. Side effects include nausea, vomiting, gastritis, hepatitis, nervous system disorders such as psychosis, peripheral neuropathy, depression, hypothyroidism; vestibular toxicity (Eto), diarrhea (Eto), and visual disturbances (Eto). High cross-resistance between Eto and Pto has been reported [62, 64]

Clofazimine (Cfz) was described in the mid-1950s. It belongs to the antibiotic class riminophenazines. Clofazimine showed anti-TB activity comparable to isoniazid. Clofazimine's activity is exerted through interaction with cell membrane

phospholipids, formation of antimicrobial lysophospholipids, membrane dysfunction, and impaired K⁺ uptake. Its anti-inflammatory activity is manifested by inhibiting the activation and proliferation of T-lymphocytes. The daily/maximal dose is 100 mg. In cases of renal failure, no dose adjustment is required. Side effects include discoloration of the skin, conjunctiva, and body fluids (brownish or orange); itching; dry skin; prolongation of the QT interval; skin reactions to sunlight; abdominal pain; and bleeding. Cases of cross-resistance with Bql have been described. There are few data on the penetration of clofazimine into the CNS [9, 65, 66].

Pretomanid is an anti-TB drug that belongs to the class of bicyclic nitroimidazoles. It was identified in 2000. Pretomanid is a prodrug that is activated by the F420-co-enzyme to its active metabolites. The des-nitro metabolite kills *Mycobacterium tuberculosis* (MBT) via the induction of nitric oxide formation. Pretomanid is activated under both anaerobic and aerobic conditions (replicating bacteria). Other metabolites inhibit the biosynthesis of the cell wall of MBT by inhibiting the synthesis of mycolic acids. The minimum inhibitory concentration (MIC) is 0.005–0.48 µg/mL against resistant isolates of MBT. A dose of 200 mg once daily is recommended. In cases of renal failure, no dose adjustment is required; however, in severe conditions, precaution is necessary. Side effects include hepatotoxicity, vomiting, acne, nausea, headache, musculoskeletal pain, myelosuppression, peripheral polyneuropathy, and cardiotoxicity. Pretomanid has a higher mutation frequency than Rifampin but is comparable to other drugs (H, E, Z). Cross-resistance between Pretomanid and Delamanid has been reported [67–69]. Based on data from clinical trials (Nix-TB trial), Pretomanid, along with Bedaquiline and Linezolid, was approved for treating drug-resistant tuberculosis (DR-TB) [67, 68].

Delamanid belongs to the drug class nitro-dihydro-imidazoaxazole. The action of Delamanid is associated with the inhibition of the synthesis of methoxy-mycolic and keto-mycolic acids in the bacterial cell wall. Delamanid exerts a powerful bactericidal effect against MBT and intracellular MTB at the macrophage level. It has potent activity against DS-TB and DR-TB in early clinical development. *In vitro*, Delamanid exhibited greater potency than Pretomanid against MDR-TB and XDR-TB isolates [67]. The identified metabolites of Delamanid do not have an antimycobacterial effect. Side effects include arrhythmia, prolongation of the QT interval, abdominal pain, nausea, vomiting, headache, dizziness, hypokalemia, hypomagnesemia, and hypoalbuminemia. No drug interactions were identified when the medicine was used in combination with Bedaquiline (ECG and blood electrolyte levels should be monitored). A Delamanid-containing regimen is as effective and safe as Bedaquiline [67, 70].

Kanamycin – an antibiotic from the aminoglycoside group. It has a bacteriostatic effect, which is associated with the disruption of protein synthesis in MTB. Kanamycin blocks the synthesis of specific ribosome proteins by binding to the bacterial 30S ribosome. It is administered intramuscularly. The therapeutic dose is 16 mg/kg once daily. Primary resistance to Kanamycin is rare; however, secondary resistance occurs quite quickly. Incomplete cross-resistance between aminoglycosides, streptomycin, Kanamycin, and florimycin has been reported [71].

Amikacin is a drug from the aminoglycoside group. MTB resistant to other anti-TB drugs, as a rule, retains sensitivity to Amikacin [72]. Aminoglycosides bind to the

30S subunit of ribosomes, inhibiting the protein synthesis of the mycobacteria [73]. The daily dose is 15–20 mg/kg, with a maximum of 10,000 mg. In renal failure, Amikacin and Kanamycin doses are 2–15 mg/kg, administered 2–3 times a week. High cross-resistance has been reported between Amikacin and Kanamycin, while low cross-resistance has been observed between aminoglycosides and Capreomycin. Side effects include ear disorders, dizziness, nausea, vomiting, renal disorders, hypokalemia, hypomagnesemia, headache, paresthesia of the face and limbs, muscle cramps, renal disorders, and joint pain [74].

Capreomycin is a polypeptide antibiotic used to treat DR-TB (MDR-TB). It suppresses the synthesis of bacterial cell protein. It has a pronounced bacteriostatic effect on human *MTB* and a weaker effect on bovine *MTB* [75]. The therapeutic dose is 20 mg/kg daily. Capreomycin is administered only intramuscularly [75]. In cases of renal failure, dose adjustment is required based on creatinine clearance. Side effects include ear, renal/hepatic disorders, vestibulotoxicity, leukocytosis, leukopenia, thrombocytopenia, hypomagnesemia, and allergic reactions. Aminoglycoside-induced renal toxicity is reversible upon stopping the medication [25]. Primary resistance of the TB pathogen to Capreomycin is rare; however, secondary resistance occurs quite quickly. Capreomycin is effective against *MTB* resistant to Streptomycin, Kanamycin, and Amikacin. *MTB* resistant to high doses of Kanamycin may also be resistant to Capreomycin [25, 76].

Paraaminosalicylic acid (PAS) is a chemotherapeutic drug that has a weak bacteriostatic effect. It is used in the form of its sodium salt. The tuberculostatic effect is exerted due to its competitive relationship with para-aminobenzoic acid, pantothenic acid, as well as biotin, which are mycobacterial growth factors. The daily dose of PAS is 150–200 mg/kg. Normally, it is necessary to prescribe a large amount of the drug. It should be taken into account that, in its dissolved form, PAS decomposes after 30–60 minutes. In cases of renal failure, 4 g twice a day is necessary. Side effects include thrombocytopenia, leukopenia, anemia, agranulocytosis, nervous system disorders, gastrointestinal disorders, hepatitis, skin disorders, crystalluria, and hypothyroidism. PAS is used mainly in cases of *Mycobacterium tuberculosis* (*MTB*) resistance to other anti-TB drugs [77]. Contraindications include severe renal or liver diseases, gastric ulcers, water-salt metabolism disorders, and cardiovascular failure [78]. Primary resistance of *MTB* to PAS is relatively rare, while secondary resistance develops slowly. Cross-resistance has not been established [77, 79].

Carbapenems – the class of systemic antibacterial drugs.

Meropenem and imipenem/cilastatin can be prescribed to patients with MDR-TB. In *MTB*, L,D-transpeptidases are the workhorse enzymes of peptidoglycan crosslinking and are targets of carbapenem activity. Imipenem/cilastatin and meropenem penetrate into the CNS in the presence of meningeal inflammation. The daily/maximal dose of imipenem/cilastatin is 1000 mg twice a day; in cases of renal failure or dialysis, the dose is adjusted to 750 mg every 12 hours (for a creatinine clearance of 20–40 mL/min) or 500 mg every 12 hours (for a creatinine clearance of 20 mL/min). The daily dose of meropenem is 3,000–4,000 mg, with a maximal 4000 mg. Due to the highest activity of carbapenems in the presence of clavulanic acid against *MTB*, it may be prescribed concomitantly in the treatment regimen at a dose of 125 mg of clavulanic acid every 8–12 hours. The daily dose of amoxicillin/clavulanic acid is

1000 mg/250 mg, with a maximal dose of 1,500 mg/350 mg. Side effects include diarrhea, nausea, vomiting, seizures, hematologic and hepatic toxicity, and hypersensitivity. Contraindications: intolerance [80].

Mechanism of action of drug classes is presented in **Figure 2** [1].

4.2 Groups of drugs used in longer MDR-TB regimens

WHO classification of the drugs for long-term use in the treatment of MDR-TB is as follows [3, 9, 70, 81, 82]:

Group A: bedaquiline (B), linezolid (L or Lzd), levofloxacin (Lfx), or moxifloxacin (Mfx);

Group B: cycloserine (Cs), clofazimine (C), terizidone;

Group C: delamanid (D), pyrazinamide (Z), ethambutol (E), imipenem–cilastatin or meropenem, ethionamide (Eto) or prothionamide (Pro), p-aminosalicylic acid (PAS), amikacin (Am) (or streptomycin (S)).

First recommendations for the management of MDR/RR-TB were released in 2019 [81], with an update released in 2022 [3, 79, 82] and more recently in 2025 [9, 83].

4.3 Treatment regimens for drug-resistant TB

4.3.1 The 6-month regimens

- **BPaLM** – 6-month regimen, including bedaquiline (B), pretomanid (Pa), linezolid (L) (600 mg once daily), and moxifloxacin (M) for MDR/RR-TB or pre-extensively drug-resistant TB (pre-XDR-TB).

DST for fluoroquinolones is recommended in people with MDR/RR-TB for future decisions on whether Mfx can be continued or should be dropped. If resistance to FQ is identified, Mfx (M) should be stopped, and the BPaL regimen would be initiated or continued. The BPaLM regimen is proposed instead of the 9-month/18-month longer regimens in patients with MDR/RR-TB, independent of the presence or absence of resistance to FQ [82], based on trial evidence from TB-PRACTECAL [84, 85] and ZeNix [86, 87]. The BPaLM regimen is recommended for: – both pulmonary TB and extrapulmonary TB, excluding TB of the CNS, osteoarticular TB, and disseminated TB with multiple sites; – persons aged ≥ 14 years; – all patients regardless of their HIV status; – patients who have previously taken B, L, Pa, or delamanid for less than one month. In cases of exposure for more than one month, patients may continue to receive these drugs if resistance to these medicines has been excluded. Pregnant and breastfeeding women should not be treated with the BPaLM regimen due to limited safety data on Pa use.

- **New BDLLfxC regimen** – it has a 6-month duration, includes B, D, L, Lfx, and Clofazimine (C) in patients with MDR/RR-TB, independent of the presence or absence of resistance to FQ. This regimen is recommended instead of 9-month or longer regimens in patients with MDR/RR-TB.

The BDLLfxC regimen is recommended: – After DST for FQ, for all patients, PLHIV, pregnant and breastfeeding women; – For patients with extrapulmonary TB, excluding CNS, osteoarticular, or disseminated TB with multiorgan

sites; – For children and adolescents who didn't have bacteriological justification of TB or resistance patterns and who do have a high risk of MDR/RR-TB; – For patients who previously took B, L, D, or C for less than 1 month; if used more than 1 month, they may continue the regimen if resistance to these medicines has been excluded.

4.3.2 Regimens of 9 months duration for DR-TB

- **Regimens of 9 months duration, including the drugs for oral use for FQ-sensitive MDR/RR-TB.**

- Ethionamide variation:

4-6 B (6 m)-Lfx/Mfx-C-Z-E-Hh-Eto/5 Lfx/Mfx-C – Z-E

It consists of B (for 6 months), in combination with Lfx/Mfx, Eto, E, Hh, Z, and C (4 months; it may be extended to 6 months if the results of the sputum smear are still positive at the end of month 4), followed by a combination of Lfx/Mfx, C, E, and Z during (5 months). Eto can be replaced by 2 months of L (600 mg daily), and the combination with L may be used in pregnancy.

- Linezolid variation:

4-6 B (6 m)-L(2 m)-Lfx/Mfx-C-Z-E-Hh/5 Lfx/Mfx-C – Z-E

Duration of L, Eto should be decided at month 4.

9 months regimens are recommended instead of the long-term regimens in patients who have not received the second-line drugs (including B), except for patients with extensive lung TB or severe extrapulmonary TB, for whom long-term treatment is recommended.

While the lack of safety data on Pretomanid in children aged below 14 years makes the BPaLM regimen not recommended in this age group, the 9-month all-oral regimen can be suggested for children of all ages, considering the recommendation for Bedaquiline use in children even below 6 years of age [3].

Modified 9-month **duration** regimens **with all-oral drugs** are used for the treatment of MDR/RR-TB when resistance to FQ is excluded.

Nine-month regimens of 4–5 drugs used for the treatment of fluoroquinolone (FQ)-susceptible multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) include:

- 9B-L-Mfx-Z regimen,
- 9B-L-Lfx-Z-C regimen,
- 9B-L-Lfx-Z-D regimen.

4.4 Treatment of drug-resistant TB using longer regimens

This longer regimen is administered in cases where BPaLMfx/BPaL or 9-month regimens of all-oral drugs could not be applied: – extrapulmonary TB with severe

evolution; – in cases with additional resistance to the main drugs of the BPaLMfx/BPaL regimen, except Mfx or the 9-month all-oral regimen; – absence of response to short-term treatment regimens; – drug intolerance to medicines included in the 6-month or 9-month regimens; – pregnancy and breastfeeding women, or children aged below 14 years.

Long-term regimens (particularly consisting of all-oral drugs) should be taken according to the results of DST. They must include, in the intensive phase, three medicines from Group A, at least one drug from Group B, and at least three drugs – in the continuation phase. If four drugs cannot be achieved from Group A and Group B, drugs from Group C are added [56]. Data from the DELIBERATE trial highlighted that the co-administration of Bedaquiline and Delamanid was not associated with QT prolongation [9, 88]. There is no age restriction for Bedaquiline use, including in longer regimens [9, 89]. The duration of longer regimens is 18–20 months, or 15–17 months after culture conversion, while the intensive phase may last 6–7 months in regimens with Amikacin or Streptomycin [82]. In patients with MDR/RR-TB on longer regimens, monitoring via culture and sputum smear microscopy is recommended [9].

4.5 Treatment for R-susceptible and H-resistant TB

This regimen, composed of R, E, Z, and Lfx, should be taken during a period of 6 months. It is not recommended to add Streptomycin or other injectable agents [9].

4.6 Surgery for people on MDR/RR-TB treatment

In patients with RR-TB, MDR-TB, elective partial lung resection may be used alongside a recommended MDR-TB regimen [9].

4.7 Hepatitis C virus (HCV) and MDR/RR-TB treatment co-administration

In patients with MDR-TB and HCV co-infection, co-administration of HCV and TB treatment is recommended rather than delaying HCV treatment until after the treatment of MDR/RR-TB is completed [9].

5. Conclusion(s)

TB still represents a major global health threat, causing millions of deaths worldwide. To end the TB pandemic, each patient suffering from TB must be treated with optimal treatment regimens composed of high-quality drugs and provided with appropriate social support throughout the entire period of TB management, from diagnosis to post-treatment follow-up. The current concept of a TB treatment regimen should include: 3-4 drugs with complementary modes of action, drug combinations with minimal side effects, no overlapping toxicity, complementarity in pharmacokinetic features, similar tissue penetration characteristics, and a regimen that addresses a medical need.

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- Agreement to be accountable

The authors hereby declare that they are fully responsible for the presented information, which was consulted and taken from scientific publications and official data.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Chapter 2

The Role of Steroids in the Treatment of Tuberculosis

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Abstract

This chapter explores the role of corticosteroids as adjunctive therapy in tuberculosis (TB) management. The scope encompasses the immunomodulatory mechanisms by which corticosteroids influence the inflammatory response in TB infection, evidence-based clinical applications across different TB manifestations, and current treatment protocols. Special attention is given to specific forms of TB where corticosteroids have demonstrated significant benefit, including TB meningitis, pericarditis, and severe pulmonary disease with respiratory compromise. The chapter also addresses potential adverse effects, optimal dosing strategies, and the timing of corticosteroid administration in relation to antimicrobial therapy. Additionally, it examines ongoing controversies in the field, population-specific considerations, and emerging research directions that may further refine the use of these potent antiinflammatory agents in TB management.

Keywords: corticosteroids, tuberculosis, pulmonary, extrapulmonary, adjunctive therapy, immunomodulation

1. Introduction

1.1 Historical context

The history of corticosteroid use in tuberculosis (TB) treatment represents a fascinating journey of medical discovery that spans over seven decades. The initial observations of corticosteroid effects in TB patients emerged during the early antibiotic era, when clinicians began noticing the complex interplay between host inflammatory responses and mycobacterial infection [1]. The introduction of cortisone in the late 1940s and early 1950s created both excitement and controversy in the medical community, as physicians observed dramatic symptomatic improvements in TB patients, albeit with concerns about potential disease progression [2].

Early clinical observations documented that corticosteroids could rapidly reduce fever, improve appetite, and enhance general well-being in TB patients, particularly those with severe systemic symptoms [3, 4]. However, these benefits were tempered by reports of disease exacerbation when steroids were used without concurrent antituberculosis therapy (ATBT), leading to the fundamental understanding that

corticosteroids should never be administered alone in active TB [5]. This dichotomy between symptom relief and potential harm established the foundation for decades of careful investigation into the appropriate role of corticosteroids in TB management.

1.2 Evolution of corticosteroid use as adjunctive therapy in TB

The evolution of corticosteroid use as adjunctive therapy in TB has been marked by progressive refinement of indications, dosing strategies, and patient selection criteria. Research conducted since the 1960s has systematically evaluated corticosteroid efficacy across various forms of TB, leading to evidence-based recommendations for specific clinical scenarios [6].

The development of standardized treatment protocols incorporating corticosteroids emerged gradually through international collaborative efforts. The World Health Organization and professional societies began incorporating corticosteroid recommendations into TB treatment guidelines during the 1980s and 1990s, initially focusing on severe extrapulmonary forms of the disease [7]. The evidence base expanded significantly with large randomized controlled trials conducted in various geographical settings, particularly for tuberculous meningitis (TBM) and pericarditis, where corticosteroids demonstrated clear mortality benefits [8–15].

1.3 Current global perspectives on adjunctive steroid therapy

Contemporary global perspectives on adjunctive steroid therapy in TB reflect both consensus on established indications and ongoing debates about expanding applications. International guidelines consistently recommend corticosteroids for TBM and pericarditis, where high-quality evidence supports mortality reduction [16].

While the distinction between high-burden and low-burden settings provides a useful epidemiological framework, the observed regional variations in corticosteroid use are driven by a complex interplay of additional factors. These include significant disparities in healthcare infrastructure, which impact both the diagnosis of steroid-responsive conditions (like TBM) and the ability to safely monitor for steroid-related adverse effects (such as hyperglycemia). Furthermore, differences in access to a consistent supply of first-line and second-line TB antibiotics, as well as the capacity to rapidly diagnose drug resistance, fundamentally alter the risk-benefit calculation for adjuvant immunotherapy [7, 8]. The prevalence of HIV co-infection and the consequent need to manage immune reconstitution inflammatory syndrome (IRIS) also serve as major determinants of corticosteroid utilization patterns [9]. Therefore, clinical practice is shaped not merely by TB incidence but by the specific resources and challenges inherent to each healthcare ecosystem [17].

2. Immunopathology of TB

2.1 Host immune response to *Mycobacterium tuberculosis*

The mechanisms governing the host immune response when *Mycobacterium tuberculosis* (MTB) first interacts with human lung cells remain poorly understood.

The response involves multiple components, including innate immunity, granuloma formation, and adaptive immunity. Increasingly, researchers recognize the importance of immune elements that connect the innate and adaptive systems [18].

Innate immunity represents the critical first line of defense against TB, yet paradoxically, these same protective mechanisms often contribute to the immunopathological processes that characterize TB disease. This dual nature of innate immunity in TB creates a complex landscape where the balance between protection and pathology determines clinical outcomes [18] (**Table A1**).

Key innate immune cells, including epithelial cells, neutrophils, NK cells, macrophages, and dendritic cells, shape the immunopathology of TB. Their response to MTB highlights a balance between host defense and tissue damage. While these mechanisms evolved for protection, MTB has adapted to exploit them [18].

TB treatment will increasingly depend on modulating the immune response alongside antibiotics, optimizing defense while minimizing harm. This calls for a context-sensitive understanding of innate immunity and precision medicine approaches that customize therapy to individual patients [18].

Adaptive immunity is a critical component of the host immune response against MTB. Macrophages and phagocytic cells carry phagocytized organisms from the lung to draining lymph nodes, where they present MTB antigens to T cells, inducing an adaptive immune response; this occurs two to six weeks after infection [18] (**Table B1**).

2.2 Balance between protective immunity and tissue damage

The formation of granulomas represents the hallmark of TB pathology, serving both protective and pathological roles. It helps in containing the infection but also causes local tissue damage. The extent of this pathology depends on bacterial load, host genetics, and especially the strength of the inflammatory response. Excessive inflammation, not just bacterial presence, is a primary driver of tissue destruction, particularly through mediators like TNF- α , IL-1 β , and IL-6, as well as increased levels of MMP-1 and MMP-9. These factors contribute to cavity formation and bacterial spread, highlighting the value of therapies that modify the immune response [19].

2.3 Role of inflammatory cascades in TB pathogenesis

Inflammatory cascades play a complex role in the pathogenesis of TB, mediating both protective immunity and disease progression. Cytokines, immune cells, and signaling pathways all contribute to the host-pathogen interactions in MTB infection. These mechanisms are essential for infection control, granuloma development, and the resulting tissue pathology.

Innate immune recognition and inflammatory signaling: innate immune cells serve as the primary defense against MTB by recognizing pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs) like TLRs, CLRs, and NLRs. The activation of these receptors initiates inflammatory cascades, notably the NF- κ B and MAPK pathways, which stimulate the release of proinflammatory cytokines – IL-1, IL-6, TNF- α , and IFN- γ – crucial for restricting bacterial growth [19]. To ensure its survival, MTB employs virulence factors such as RipA, ESAT-6, PE/PPE proteins, ManLAM, Zmp1, Hip1, PknG, and SapM to

modulate host inflammatory signaling, disrupting autophagy, apoptosis, and metabolic functions in macrophages [20].

Inflammasome activation and cytokine secretion: NLRP3 inflammasome activation by MTB triggers caspase-1 and the release of IL-1 β and IL-18. Aberrant activation can worsen inflammation and tissue injury without improving bacterial clearance [21, 22]. Modulating inflammasome signaling may, therefore, offer a host-directed approach to balancing infection control with inflammation [23].

Macrophage polarization and dysfunction: macrophages, primary host cells for MTB, polarize into either M1 (proinflammatory, bactericidal) or M2 (antiinflammatory, may aid bacterial survival) phenotypes. MTB skews polarization toward an M2-like state to dampen host inflammatory responses [24, 25]. Extracellular vesicles further influence macrophage signaling via miRNAs, affecting MAPK and PI3K/AKT pathways and impacting bacterial growth control [26].

Cytokine network and immune regulation: disease outcomes depend on the balance of pro-(TNF- α , IL-6, IL-12, IFN- γ) and antiinflammatory (IL-10, TGF- β) cytokines. In TB, elevated IL-6 and IL-10 impair immune function and T-cell responses, while IL-1 drives inflammation that may worsen the disease [27, 28]. Regulatory T cells help control pathology but can also promote bacterial persistence [29].

Granuloma formation and progression: the granuloma serves as a host-protective factor as well as a shelter for the long-term survival of the tubercle bacterium within the host. Inflammatory cascades, particularly cytokines like TNF- α , maintain granuloma integrity. Dysregulation can cause necrosis and cavitation, increasing bacterial spread [30]. Vascular and lymphatic remodeling in granulomas also affect immune cell movement and inflammation [31].

Role of inflammatory genes and signaling pathways: gene expression analysis in active TB reveals upregulation of inflammatory genes and links immune checkpoints, such as PD-L1, to disease progression. Machine learning identifies crucial genes and miRNAs as potential biomarkers or therapeutic targets [32].

Influence of comorbidities and microbiome: comorbidities such as malnutrition and diabetes amplify inflammation, raising the risk of active TB [33, 34]. The microbiome also affects lung immunity, as gut microbial short-chain fatty acids help regulate inflammation [35, 36].

3. Corticosteroid mechanisms of action

3.1 Mechanisms of action

3.1.1 Molecular level: Glucocorticoid receptor-mediated effects

Corticosteroids mainly work by binding to the glucocorticoid receptor (GR), a nuclear receptor and ligand-activated transcription factor [37–40]. They exert their effects through two distinct mechanisms: genomic actions mediated by nuclear GRs and nongenomic actions that occur independently of gene transcription [40]. Upon binding, GR changes shape, detaches from heat shock proteins, and moves to the nucleus to regulate gene transcription [37–40]. Activated GR binds glucocorticoid response elements (GREs), inducing antiinflammatory genes like annexin-1, IL-10,

and I κ B- α [41]. More critically, corticosteroids inhibit proinflammatory genes by interfering with transcription factors such as NF- κ B and AP-1 [42]. Recent findings also show corticosteroids have rapid, nongenomic effects on cellular pathways and membrane receptors, which may aid their effectiveness in TB [6].

3.1.2 Antiinflammatory pathways modulation

Impact on cytokine networks: corticosteroids reduce major proinflammatory cytokines in TB, limiting tissue damage while sparing antimicrobial functions. They modestly suppress IFN- γ , with effects depending on dose and duration, which help control excessive inflammation without compromising bacterial control. This shifts the immune response toward a balance, reducing pathogenic Th1 activity and promoting antiinflammatory mediators like IL-10 and lipoxins, aiding in the resolution of inflammation [6, 43].

Effects on cellular immunity and granuloma formation: corticosteroids reduce inflammation in TB granulomas by limiting immune cell recruitment, shrinking granuloma size, and improving tissue structure. They also cause macrophages to shift from a proinflammatory to an antiinflammatory type and moderate T-cell responses, balancing reduced tissue damage with the need for protective immunity [6, 43].

3.2 Immunomodulatory balance

Reduction of excessive inflammatory response: corticosteroids benefit TB patients by suppressing harmful inflammation responsible for complications. Studies show adjunctive corticosteroids reduce markers like C-reactive protein (CRP) and proinflammatory cytokines [44], which are vital in severe forms such as meningitis and pericarditis, where inflammation threatens organ function [45].

Early initiation and proper dosing are crucial; corticosteroids given with ATBT prevent damaging inflammation [6]. Moderate doses (0.5–1 mg/kg/day prednisolone equivalent) reduce inflammation without impairing bacterial clearance [46].

Prevention of tissue damage and scarring: corticosteroids prevent tissue damage and fibrosis in TB by suppressing matrix metalloproteinases (MMPs) and increasing TIMPs, thereby maintaining tissue structure [47]. In TBM, they reduce risks such as hydrocephalus and infarction [45], while in pericarditis, they lower the risk of constrictive pericarditis by curbing fibroblast activity [48].

Their antifibrotic benefits include regulating fibroblasts, decreasing matrix production, and supporting matrix degradation [49]. This leads to less pleural thickening and better lung function in pulmonary TB (PTB) [49]. Adjunctive corticosteroids also result in improved long-term outcomes, likely by preventing tissue remodeling [50].

Improved drug penetration to infection sites: corticosteroids can improve ATBT penetration by reducing inflammation-induced barriers like vasculitis, edema, and fibrosis [51]. By decreasing granuloma size and inflammation, corticosteroids facilitate better drug distribution to sites where bacteria may persist despite treatment [52], thereby enhancing treatment outcomes and reducing relapse risk [6]. Similar benefits have been observed in extrapulmonary TB (EPTB), such as TB meningitis, lymph node disease, and pericardial disease [6].

Enhanced clinical recovery and functional outcomes: adjunctive corticosteroid therapy in TB provides benefits beyond survival, including faster symptom relief and improved quality of life, with an earlier return to daily activities [6]. In TBM, especially when started early, corticosteroids decrease neurological complications and enhance cognitive function [45].

In critical organ involvement, such as pericardial or spinal TB, corticosteroids reduce surgery rates, enhance cardiac and mobility outcomes, and help lower healthcare costs [53]. These advantages support the selective use of corticosteroids in TB.

3.3 Potential risks and concerns

Immunosuppression and infection susceptibility: corticosteroids suppress both innate and adaptive immunity, increasing the risk of opportunistic and latent infections, especially in TB patients with HIV [54]. Infection risk rises with higher doses and longer treatments [54], though short-term, moderate-dose regimens (6–8 weeks) commonly used in TB trials are generally safe [6]. Assessing individual factors such as nutritional status, comorbidities, and concurrent medications is important. Careful infection monitoring and prophylaxis for high-risk patients are crucial for safe corticosteroid therapy in TB [55].

Impact on mycobacterial clearance: corticosteroid use in TB may impair mycobacterial clearance, raising concerns about treatment failure or relapse. Concurrent initiation of corticosteroids with ATBT is more effective than delayed use [6]. Clinical studies and meta-analyses show no increased risk of treatment failure or relapse with corticosteroids when effective ATBT are given [24, 28]. However, these findings are mostly in HIV-negative, drug-susceptible patients. The effects in drug-resistant or severely immunocompromised cases remain uncertain [56].

Risk of treatment failure or relapse: most studies show that appropriate corticosteroid use does not increase treatment failure or relapse rates, though risks rise if drug-resistant TB is missed and untreated [57]. Corticosteroids may also mask symptoms, delaying recognition of treatment failure [58]. While long-term follow-up data are limited, relapse rates remain low if corticosteroids are properly used. A systematic review found no increase in relapse up to five years in such patients [45]. However, varying study quality complicates firm conclusions. Relapse risk increases with inadequate therapy, poor adherence, and severe immunosuppression [56]. Regular monitoring during and after treatment is essential.

Masking of symptoms and delayed diagnosis: corticosteroids can mask symptoms and imaging findings of TB and other infections, delaying diagnosis and complicating treatment monitoring. Their antiinflammatory effects may suppress fever, lower inflammatory markers, and improve symptoms, giving a false sense of recovery even as infection persists – especially with undiagnosed drug resistance or co-infections [59]. Corticosteroids may also reduce visible inflammation on imaging, so radiological improvement doesn't always mean the infection is cleared [58]. They can further obscure paradoxical reactions (PRs) or IRIS, making these issues harder to identify [17]. Vigilance is essential for the early detection of complications or treatment failure in patients receiving corticosteroids.

4. Corticosteroids as adjunct therapy

4.1 Rationale for corticosteroid use in TB

Controlling MTB largely depends on the host's immune response, but overstimulation can cause severe tissue damage and worse clinical outcomes, especially in EPTB. Because of their antiinflammatory and immunomodulatory effects, adjunctive corticosteroids have been extensively studied to reduce the morbidity and mortality of severe TB, primarily in meningeal, pericardial, and pleural forms.

Corticosteroids have long been studied as adjunctive therapy in TB, with accumulating evidence supporting their use in specific clinical contexts. Over the past two decades, a series of systematic reviews, meta-analyses, and expert assessments have clarified the role of corticosteroids across various TB manifestations, particularly in extrapulmonary and high-risk patient populations.

A broader conceptual framework emphasizes corticosteroids as part of host-directed therapy. Antiinflammatory adjuncts, including steroids, underscore how dampening excessive host inflammation improves outcomes in TB without impairing bacteriological clearance [2, 5, 6, 14]. These findings align with narrative reviews and expert syntheses, which support selective and evidence-guided use of corticosteroids in TB, stressing individualized decision-making based on disease site, comorbidities, and patient frailty.

In conclusion, corticosteroids are strongly recommended for TBM, pericardial TB, and pleural TB, where mortality and morbidity benefits are robustly demonstrated. Their role is also supported in other extrapulmonary forms such as abdominal and endobronchial TB, though the evidence base is somewhat narrower. In PTB, however, the benefit remains unproven for routine use, warranting further investigation. In TB-HIV co-infection, emerging high-quality data now affirm a mortality benefit, strengthening the case for their inclusion in management protocols. This body of literature positions corticosteroids as a key adjunctive therapy, but one best applied selectively and in accordance with disease-specific evidence (**Table C1**).

4.2 Pulmonary tuberculosis

The value of corticosteroids in PTB remains less definitive. A report highlighted variable effects on sputum culture conversion [60], and the Cochrane review by Critchley et al. (2014) concluded that routine corticosteroid use in PTB lacks robust evidence. There is clearer alignment that corticosteroids should not be universally applied in drug-sensitive pulmonary disease. Instead, their use may be more justified in severe or complicated cases [1].

Adjunctive corticosteroid therapy has been explored for severe PTB, especially in cases complicated by acute respiratory failure, massive pulmonary involvement, and related complications. Evidence remains mixed, and the benefit is generally more pronounced in EPTB, though some studies point to potential advantages in select subsets of PTB.

In severe pulmonary disease, corticosteroids have been used as adjuncts in cases presenting with acute respiratory distress syndrome (ARDS) and respiratory failure. In critically ill patients, studies excluding HIV-positive individuals have found that

steroids can significantly reduce mortality, potentially by dampening the intense cytokine response following anti-TB treatment, especially among those with high mycobacterial loads [61]. For massive pulmonary involvement, systematic reviews report that adjunct corticosteroids offer earlier and more sustained clinical and radiographic improvement, such as faster resolution of infiltrates and cavity closure, though not sputum conversion [62].

Randomized controlled trials and meta-analyses indicate that steroids can speed up clinical progress (weight gain, fever resolution, improved serum albumin, rapid radiographic improvement) without increasing relapse or severe side effects [6]. However, recent cohort studies are inconsistent regarding the mortality benefits – steroids have not been shown to lower ICU or hospital mortality in all patients needing mechanical ventilation [63]. Functionally, steroids are associated with quicker recovery and radiologic improvements, but not always a reduction in mortality, especially in those on ventilation. The long-term impact on lung function or quality of life remains uncertain [6, 62]. While corticosteroids may lessen acute inflammation and hypoxemia in ARDS and severe TB, their direct impact on TB-related hypoxemia is unclear and varies by comorbidities and severity [61]. In the ICU, steroid outcomes are mixed – some data link them with higher in-hospital mortality, possibly due to sicker patients receiving steroids. No clear evidence supports shorter ICU stays or less time on ventilation [63].

For TB complications, corticosteroids are proven adjuncts in pleural TB, speeding effusion resolution and limiting residual thickening [11, 49]. For empyema, the evidence is weaker but suggests some antiinflammatory benefit [44]. In endobronchial TB, steroids may decrease bronchial stenosis and airway damage, but the evidence relies mostly on expert consensus [2]. Limited data suggest steroids could reduce posttuberculous bronchiectasis by reducing early airway inflammation, but robust long-term data are missing [2].

4.3 Extrapulmonary TB

Adjunctive corticosteroid therapy has a well-established but variable role in the management of EPTB, with robust evidence supporting its benefit in some anatomical sites and limited or mixed data for others [2, 6, 64].

Central nervous system (CNS) TB: corticosteroids are strongly recommended as adjunctive therapy for TBM. They reduce mortality and improve neurological outcomes, especially in moderate to severe disease. Duration and regimen may vary: TBM typically warrants several weeks, while CNS tuberculomas may require prolonged steroid use depending on clinical response [65, 66].

Cardiovascular TB (pericardial TB): adjunctive corticosteroids are beneficial in tuberculous pericarditis, including both effusive and constrictive types. Studies demonstrate reduced mortality, fewer procedures (e.g., pericardiocentesis), and improved symptomatic and hemodynamic recovery. However, steroids do not reduce the incidence of long-term constriction in pericardial TB [2, 6, 64].

Gastrointestinal (GI) TB: there is insufficient evidence to routinely recommend corticosteroids for GI TB (intestinal, peritoneal). Some observational data suggest potential benefit in severe disease, but no high-quality trials support their routine use in GI forms of EPTB [6, 64].

Extrapulmonary tuberculosis site	Role of corticosteroids	Evidence level
CNS (meningitis/tuberculoma)	Strongly recommended: reduces mortality and improves outcomes [65, 66]	High
Cardiovascular (pericarditis)	Recommended: improves outcomes, reduces mortality [2, 6, 64]	High
Lymph node	Some evidence for benefit, especially in children [6]	Moderate
Genitourinary	Not routinely recommended; evidence is scant [2]	Low
Skeletal	Not routinely recommended; may help with spinal cord compression [2]	Low

Table 1.
Evidence-based recommendations for extrapulmonary tuberculosis.

Genitourinary TB: evidence for corticosteroid benefit in genitourinary TB is sparse. No robust clinical trial data are available, and routine use is not recommended outside of specific cases with severe inflammatory complications [2].

Skeletal TB: the use of corticosteroids in skeletal (bone and joint) TB lacks strong evidence and is not routinely recommended. They may be considered in cases with significant inflammatory symptoms or spinal cord compression, but this is largely extrapolated from neuro-TB guidelines and clinical judgment [2].

Lymph node TB: RCTs in adults and children demonstrate some benefits of adjunctive corticosteroids in tuberculous lymphadenitis, namely faster symptom relief, prevention of complications, and higher rates of resolution at six months [6].

Evidence-based recommendations: adherence to local and international guidelines, as well as the involvement of specialist care, are essential for the optimal management of EPTB with steroids (**Table 1**).

4.4 Recommended doses

TBM: adjuvant corticosteroid therapy with dexamethasone or prednisolone is strongly recommended for patients with TBM, with tapering over six to eight weeks based on severity [64].

- Stage 1 TBM (GCS 15, no neurological deficits) should receive dexamethasone for six weeks: start IV at 0.3 mg/kg for one week, 0.2 mg/kg for the second week, and 0.1 mg/kg for the third week. Switch to oral dexamethasone: 3 mg/day (week four), 2 mg/day (week five), and 1 mg/day (week six).
- Stages 2 and 3 TBM (GCS 11–14 or focal deficits; GCS ≤ 10): use an eight-week dexamethasone course. Begin IV at 0.4 mg/kg for one week, then 0.3 mg/kg (week two), 0.2 mg/kg (week three), and 0.1 mg/kg (week four). Taper orally with 4 mg/day (week five), 3 mg/day (week six), 2 mg/day (week seven), and 1 mg/day (week eight).

Tuberculous pericardial effusion: an initial adjuvant corticosteroid therapy may be considered (conditional recommendation, very low certainty of evidence). The proposed oral prednisolone regimen lasts 11 weeks, starting at 60 mg/day for four

weeks, then reducing to 30 mg/day for the next four weeks, 15 mg/day for two weeks, and concluding with 5 mg/day for one week [67].

4.5 Special conditions

The role of corticosteroids as adjunct therapy in TB varies depending on special clinical situations, including HIV-TB co-infection, pregnancy and lactation, the elderly, pediatrics, and drug-resistant TB. Evidence-based recommendations from guidelines and recent literature support the selective use of this approach in specific scenarios.

HIV-TB co-infection: corticosteroids are mainly indicated for managing TB-associated immune reconstitution inflammatory syndrome (TB-IRIS) in HIV-TB co-infected patients, particularly during antiretroviral therapy (ART) initiation. A randomized placebo-controlled trial showed that prednisone reduced TB-IRIS risk and symptoms without increasing the risk of infection. Corticosteroids show mortality and morbidity benefits in TBM and pericarditis in HIV-uninfected patients, but there is less clear benefit in HIV co-infection; risks include opportunistic infections if ART is not administered. ART should be started early in co-infected patients, with corticosteroids used in select inflammatory complications [2, 6, 44, 68]

Pregnancy and lactation: first-line anti-TB drugs (except streptomycin) are generally considered safe during pregnancy. Corticosteroids may be used when indicated, for example, in TB meningitis or pericarditis [2].

Elderly patients: there is limited direct evidence on corticosteroid use specifically in elderly TB patients. Considerations include comorbidities, an increased risk of adverse corticosteroid effects, and drug-drug interactions. Use should be individualized with careful monitoring, especially in cases of TB meningitis or pericarditis, where corticosteroids have an established benefit [6].

Pediatrics: corticosteroids are recommended adjunctively in pediatric TBM and complicated pericarditis [6].

Drug-resistant TB: evidence for the benefit of corticosteroids in multidrug-resistant TB (MDR-TB) is insufficient. Corticosteroids may be used selectively for specific complications, like TB meningitis or pericarditis, in MDR-TB cases. Management must be cautious due to complex drug regimens and potential adverse effects; guidelines recommend expert consultation.

Paradoxical deterioration: PR refers to clinical or radiological worsening of TB despite effective anti-TB treatment and reduced bacterial load. PR typically develops two weeks to several months after the onset of therapy and is diagnosed after excluding treatment failure, drug resistance, or other infections. It results from an excessive immune response to mycobacterial antigens released during therapy. Manifestations include worsening pulmonary infiltrates, new or enlarged lymph nodes, pleural or pericardial effusions, or CNS involvement [69, 70].

Corticosteroids mitigate inflammation and immune-mediated tissue injury during PR. The strongest evidence supports their use in EPTB (TB meningitis, pericarditis, severe pleural TB) with paradoxical worsening. Their role in PTB PR is less defined but may be considered in severe cases. Corticosteroids can provide relief from fever, respiratory distress, and organ dysfunction due to inflammation [69].

5. Administration of corticosteroids

5.1 Selection

Prednisolone and dexamethasone are both used to manage TB, particularly in severe forms such as TBM and pericardial TB. Despite similar molecular structures, these corticosteroids differ in their GR binding affinities and half-lives, potentially affecting their pharmacodynamics and therapeutic effects in TB. No direct head-to-head clinical trials have established the superiority of one over the other as adjunct therapy. Dexamethasone is usually started intravenously, with a tapered switch to oral dosing, while prednisolone typically involves oral administration with tapering doses [2, 6, 64, 68].

5.2 Bioavailability considerations

Differences in corticosteroid bioavailability impact effectiveness. Prednisolone is well absorbed orally for outpatient use. Dexamethasone has high bioavailability both orally and intravenously, with greater potency and a longer duration, which influence dosing and tapering in TB treatment [6, 64].

5.3 Route of administration

Overall, the route of administration is guided by disease severity, the need for rapid onset of action, and patient status, with intravenous methods preferred in critical cases like TBM [2, 6, 64].

- Oral: prednisolone is typically administered orally, particularly in TB forms where long-term outpatient therapy is feasible.
- Intravenous (IV): dexamethasone is often given intravenously initially in serious TB presentations, such as TBM, for rapid antiinflammatory effects, followed by oral tapering.
- Intrathecal: intrathecal corticosteroid administration is not generally recommended or supported for TBM due to a lack of robust evidence and potential risks.

5.4 Pharmacokinetic properties

The pharmacokinetics of corticosteroids (absorption, distribution, metabolism, and excretion) vary significantly between different agents and are crucial for selecting the right drug for a specific clinical situation (e.g., acute inflammation vs. chronic replacement therapy) [71, 72]. These properties are described as follows [71, 72]:

Absorption:

- Oral bioavailability: generally high (>80%) for most corticosteroids
- Peak plasma concentrations: one to three hours after oral administration

- Food effects: may delay absorption but do not significantly affect bioavailability

Distribution:

- Protein binding: high (>90%) to corticosteroid-binding globulin (high affinity but low capacity) and albumin (low affinity but high capacity).
- The free, unbound fraction is the pharmacologically active form.
- During inflammation, the binding affinity of cortisol declines, resulting in a higher free cortisol concentration at the site of interest to alleviate the active inflammatory process.
- Volume of distribution: varies depending on the drug's lipophilicity and protein binding.
- Crossing barriers: corticosteroids readily cross the placenta. Their ability to cross the blood-brain barrier varies.

Metabolism:

- Primary site: hepatic, via CYP3A4 and other enzymes.
- Prednisone is an inactive prodrug that must be converted in the liver to its active form, prednisolone.
- The addition of a fluorine atom (e.g., dexamethasone, triamcinolone, betamethasone) increases glucocorticoid potency and extends the half-life by slowing metabolism.

Elimination:

- Primary route: renal excretion of metabolites
- Dosage adjustment: may be required in severe hepatic impairment.

5.5 Clinical considerations

Dosing frequency based on half-life:

- Short-acting (8–12 hours): two to three times daily
- Intermediate-acting (12–36 hours): one to two times daily
- Long-acting (36–72 hours): Once daily

Special clinical notes:

- Hydrocortisone: preferred for physiological replacement therapy due to its similar structure to endogenous cortisol.
- Prednisolone versus prednisone: prednisolone is the active form; prednisone requires hepatic conversion.
- Dexamethasone: minimal mineralocorticoid activity makes it preferred for cerebral edema and inflammatory conditions.
- Methylprednisolone: often preferred for pulse therapy due to its high anti-inflammatory potency with minimal mineralocorticoid effects (**Table 2**).

5.6 Relationship to antimicrobial therapy initiation

Adjunct corticosteroids are administered concomitantly with ATBT. Early initiation alongside ATBT is standard, especially in TBM and severe extrapulmonary forms, to reduce inflammation-mediated tissue damage. In TBM, corticosteroids reduce mortality and neurological complications when given early with ATT [2, 6, 64].

Basic conversion formula: equivalent dose = (dose of current drug × potency of current drug) ÷ target drug potency [73].

Example conversions:

- Prednisolone 20 mg to Dexamethasone: $(20 \times 4) \div 25 = 3.2$ mg Dexamethasone
- Hydrocortisone 100 mg to Methylprednisolone: $(100 \times 1) \div 5 = 20$ mg Methylprednisolone
- Dexamethasone 6 mg to Prednisolone: $(6 \times 25) \div 4 = 37.5$ mg Prednisolone

6. Safety profile and adverse effects of corticosteroids

The use of corticosteroids as adjunctive therapy in TB treatment has gained significant attention due to their potential to reduce inflammation-mediated tissue damage and improve clinical outcomes. However, their immunosuppressive properties and complex drug interactions with anti-TB medications necessitate careful consideration of their safety profile.

6.1 Common adverse effects

Corticosteroids, when used as adjunct therapy in TB treatment, are associated with a spectrum of common adverse effects that are generally dose-dependent and duration-related. These effects are consistent with the well-established adverse effect profile of systemic corticosteroids.

Metabolic effects: the most frequently reported adverse effects include hyperglycemia, with a global prevalence of 18–30% [74]. This is particularly concerning for patients with diabetes mellitus or those at risk of developing diabetes.

Corticosteroid	Equivalent antiinflammatory Dose (mg)	Relative antiinflammatory potency	Relative mineralocorticoid potency	Plasma half- life (hours)	Biological half- life (hours)	Duration of action (hours)	Route of administration
Short-acting							
Hydrocortisone (Cortisol)	20	1	1	1.5–2.0	8–12	8–12 hours	PO, IV, IM, Topical
Cortisone	25	0.8	0.8	0.5	8–12	8–12 hours	PO, IM
Intermediate-acting							
Prednisolone	5	4	0.8	2.1–3.5	12–36	12–36 hours	PO, IV, IM, Topical
Prednisone	5	4	0.8	3.4–3.8	12–36	12–36 hours	PO
Methylprednisolone	4	5	0.5	2.5–3.5	12–36	12–36 hours	PO, IV, IM
Triamcinolone	4	5	0	2.0–5.0	12–36	12–36 hours	PO, IM
Long-acting							
Dexamethasone	0.75	25–30	0	3.0–5.0	36–72	36–72 hours	PO, IV, IM
Betamethasone	0.6–0.75	25–30	0	5.0–11.0	36–72	36–72 hours	PO, IV, IM, Topical
IM: intramuscular, IN: intravenous, PO: per os.							

Table 2.
Commonly used corticosteroids – equipotency, half-life, and clinical properties.

Cardiovascular effects: the reported prevalence of hypertension among long-term users of glucocorticoids is more than 30%. This effect is mediated through mineralocorticoid activity and sodium retention [75].

GI effects: peptic ulcer disease and gastric irritation represent significant concerns, with an increased risk of bleeding by 40% in patients receiving corticosteroids [76].

Psychiatric effects: mood alterations, including euphoria, depression, and anxiety, which are dose-dependent and may manifest within days of treatment initiation [77]. Sleep disturbances and increased irritability are also frequently reported [78].

Dermatological effects: skin thinning, easy bruising, and delayed wound healing are common long-term effects; striae and acneiform eruptions may also develop [79].

6.2 Serious complications

While less common, serious adverse effects of corticosteroids in TB treatment can be life-threatening and require immediate medical attention.

Immunosuppression and opportunistic infections: the most significant concern with corticosteroid use in TB is the potentially increased risk of susceptibility to opportunistic infections, which rises with higher doses and longer therapy duration. Risks are further increased in patients with HIV or advanced age. Glucocorticoids can also mask symptoms of infection by suppressing inflammatory and fever responses, leading to delayed detection [79].

Adrenal suppression: suppression of the hypothalamic-pituitary-adrenal axis is a serious complication that can occur with corticosteroid therapy lasting more than two to three weeks [79]. This can lead to an adrenal crisis upon abrupt discontinuation, characterized by hypotension, electrolyte abnormalities, and cardiovascular collapse.

Avascular necrosis: osteonecrosis, particularly of the femoral head, is a rare but serious complication in patients receiving corticosteroids. The risk increases with higher cumulative doses and longer durations of therapy [80].

6.3 Drug interactions

The interaction between corticosteroids and anti-TB medications is complex and clinically significant, primarily involving effects on drug metabolism through the cytochrome P450 system. The most clinically relevant interactions occur between corticosteroids and first-line anti-TB drugs. These interactions can affect both the efficacy of TB treatment and corticosteroid metabolism, potentially leading to treatment failure or increased toxicity.

Rifampin-corticosteroid interactions: rifampin activates the pregnane X receptor, thereby increasing the activity of cytochrome P450 (notably CYP3A4), glucuronosyltransferase, and p-glycoprotein [81, 82]. This substantially raises corticosteroid metabolism and lowers their bioavailability, especially via enhanced CYP3A4 expression in the liver and intestine [83].

Key considerations include:

- CYP3A4 induction leads to increased corticosteroid clearance

- Time-dependent induction, with maximum effects occurring after 7–14 days of rifampin therapy
- Individual variability in enzyme induction responses
- Potential for significant drug interactions with other CYP3A4 substrates

The clinical implications include:

- Reduced corticosteroid half-life
- Decreased bioavailability of oral corticosteroids
- Need for dose adjustment in patients receiving rifampin

Isoniazid interactions: isoniazid can inhibit certain metabolic pathways, potentially leading to increased corticosteroid levels in some patients. However, this interaction is generally less clinically significant than the rifampin interaction [82].

6.4 Monitoring requirements

Comprehensive monitoring is essential to ensure the safe and effective use of corticosteroids as adjunct therapy in TB treatment [84].

6.4.1 Laboratory monitoring protocols

Before starting corticosteroids, obtain a complete blood count with differential, a comprehensive metabolic panel (glucose, electrolytes, liver function tests), HbA1c for diabetic or at-risk patients. Document chest radiological findings and perform tuberculin testing or an interferon-gamma release assay. Monitor blood glucose, electrolytes, and CBC weekly for the first month; then monitor the comprehensive metabolic panel and liver function tests monthly [84].

6.4.2 Clinical assessment schedules

- Initial phase (weeks 1–4): perform weekly assessments for infection or TB progression, blood pressure, weight and fluid status, psychiatric symptoms, and TB improvement.
- Continuation phase (weeks 5–12): perform bi-weekly checks of TB response, corticosteroid side effects, medication adherence, and drug interactions [84].

7. Emerging trends in corticosteroids as adjunct therapy in TB

7.1 Novel antiinflammatory approaches

The development of targeted antiinflammatory therapies represents a paradigm shift from the traditional approach to TB treatment. These emerging strategies aim to

modulate specific inflammatory pathways while minimizing systemic adverse effects.

7.2 TNF- α inhibitors and other biologics

Tumor necrosis factor-alpha (TNF- α) plays a dual role in TB pathogenesis, serving both protective and pathological functions. Following TNF antagonist therapy, the relative risk for TB increases up to 25 times, depending on the clinical setting and the TNF antagonist used [85]. However, recent evidence suggests potential therapeutic applications in specific clinical scenarios. Current research focuses on [86]:

- Selective TNF- α inhibition with reduced systemic immunosuppression
- Combination strategies with enhanced anti-TB therapy
- Risk stratification protocols for safe TNF- α inhibitor use
- Novel biologics targeting other inflammatory mediators (IL-1 β , IL-6, IL-17)

7.3 Selective glucocorticoid receptor modulators (SGRMs)

Selective glucocorticoid receptor modulators (SGRMs) represent a significant advancement in antiinflammatory therapy, aiming to retain the antiinflammatory benefits of corticosteroids while minimizing unwanted metabolic and immunosuppressive effects. These ligands alter the GR's shape, activating only select signaling pathways, and thus act as both agonists and antagonists.

Recent developments include:

Vamorolone: a novel GRM, the dissociated steroid vamorolone, received marketing approval in 2024, confirming that altering the transrepression-transactivation profile is a valid strategy [87].

Targeted delivery systems: targeted delivery of a GRM payload via an immunology antibody–drug conjugate (iADC) may deliver significant efficacy at doses that do not lead to unwanted side effects. This approach could revolutionize TB treatment by providing localized antiinflammatory effects [88].

Key advantages of SGRMs in TB treatment:

- Preserved antiinflammatory efficacy with reduced metabolic side effects
- Maintained antimicrobial immunity through selective pathway modulation
- Reduced risk of opportunistic infections
- Potential for prolonged treatment courses with improved safety profiles

Host-directed therapies represent a complementary approach to conventional antimicrobial treatment, targeting host pathways that influence TB pathogenesis and treatment outcomes.

Autophagy modulators: autophagy is vital in clearing mycobacteria and supporting immune responses. Glucocorticoids suppress TBK1 kinase, hindering autophagosome maturation, prompting interest in autophagy boosters as adjunct therapy. Understanding the mechanisms and key players involved in modulating antibacterial autophagy will provide innovative improvements in anti-TB therapy via an autophagy-targeting approach [89].

MMP Inhibitors: MMPs drive tissue destruction in TB, particularly in pulmonary cavitation and CNS involvement. Research is focused on using selective MMP inhibitors, combining them with antiinflammatories for extra protection, and monitoring therapy through MMP biomarker levels [90].

Reduced systemic toxicity approaches: novel delivery systems and formulation strategies aim to maximize therapeutic benefits while minimizing systemic exposure [91, 92]:

- Inhaled corticosteroids for PTB
- Targeted nanoparticle delivery to infection sites
- Controlled-release formulations for sustained local effects

7.4 Biomarkers and personalized medicine

The integration of biomarkers and personalized medicine approaches represents a critical advancement in optimizing corticosteroid adjunct therapy for TB patients.

7.4.1 Circulating inflammatory markers

- CRP and erythrocyte sedimentation rate (ESR) for monitoring inflammatory responses
- Cytokine profiles (TNF- α , IL-6, IL-1 β , IFN- γ) for personalized antiinflammatory therapy
- MMP levels for tissue damage assessment
- Complement activation markers for severe inflammatory complications

Advanced biomarker approaches: recent advances in TB diagnosis include insights into blood-based biomarkers and emerging technologies. These developments are expanding beyond diagnosis to treatment monitoring and personalization [93]. Current research focuses on:

- Multibiomarker panels for treatment response prediction
- Point-of-care inflammatory marker testing
- Integration of biomarkers with clinical scoring systems
- Machine learning approaches for biomarker interpretation

7.4.2 Genetic factors influencing response

Pharmacogenomic research is revealing significant individual variations in corticosteroid response and the risk of toxicity.

GR polymorphisms: variants in the GR gene alter receptor sensitivity and expression, while polymorphisms in CYP3A4 and CYP3A5 affect how corticosteroids are metabolized. Furthermore, genetic factors can modify how patients experience drug-drug interactions with anti-TB treatments [94].

Immune response genetics: genetic variations affect inflammation and disease progression through mechanisms like HLA links to severe complications, cytokine gene polymorphisms influencing treatment response, and complement pathway variants increasing tissue damage risk [95].

Precision medicine approaches

TB precision medicine and personalized approaches through immune profiling are advancing the field toward individualized treatment strategies [96, 97].

8. Conclusion(s)

Corticosteroids have played a pivotal role in shaping adjunctive strategies for TB management, reflecting decades of evolving evidence and clinical practice. Their primary benefit lies in mitigating the harmful consequences of excessive host inflammation, which, while essential for infection control, is also responsible for significant tissue damage and poor clinical outcomes. Robust evidence supports their use in EPTB, particularly in TBM and pericarditis, where corticosteroids consistently reduce mortality and neurological or cardiac complications. Additional benefits are observed in pleural and lymph node TB, though with more variable evidence. In PTB, routine use is not supported; instead, corticosteroids may be selectively considered in severe or complicated cases, such as acute respiratory failure or ARDS.

Beyond organ-specific outcomes, corticosteroids can enhance quality of life by accelerating symptom relief, improving functional recovery, and reducing fibrotic complications. Their mechanisms – ranging from cytokine suppression and granuloma modulation to improved drug penetration – underscore their central role as host-directed therapy. However, risks remain significant: immunosuppression, delayed diagnosis, opportunistic infections, and drug–drug interactions, particularly with rifampin, demand careful monitoring and judicious application. These concerns are magnified in certain populations, including HIV-co-infected patients, children, the elderly, and those with drug-resistant TB, where evidence is still limited and individualized assessment is essential.

Looking ahead, the field is shifting toward precision medicine and targeted host-directed therapies. Advances such as selective GR modulators, biomarker-guided treatment, and nanoparticle-based delivery systems promise to maximize benefits while minimizing systemic toxicity. Thus, while corticosteroids remain a cornerstone of adjunctive TB therapy in defined contexts, their future role will likely be integrated into a broader framework of individualized, host-focused treatment strategies. Optimal outcomes will depend on tailoring therapy to the disease site, patient profile, and emerging scientific insights.

Appendices

Component	Type/ subtype	Protective role	Pathological role	Key mediators/ products	Clinical significance
Alveolar macrophages	M1 (Classical)	Reduce excessive proinflammatory cytokine produc- tion while main- taining some bacterial containment.	Suppress exces- sive inflamma- tion and tissue damage from prolonged M1 activation	↓ TNF- α , ↓ IL-1 β , ↓ IL-6, ↓ ROS, ↓ NO	Reduces sys- temic inflamma- tion and tissue destruction in severe TB cases
Neutrophils	Early responders	Reduce excessive tissue damage while maintaining some antimicrobial function	Prevent cavi- tation formation and lung par- enchymal destruction	↓ Elastase, ↓ MPO, ↓ NETs, ↓ ROS	Reduces severe disease progres- sion and poor outcomes
Toll-like receptors	TLR2, TLR4	Modulate excessive inflammatory responses while maintaining patho- gen recognition	Prevent cytokine storm and sep- sis-like responses	↓ MyD88 pathway, ↓ NF- κ B activation	Reduces sys- temic inflamma- tion and tissue injury in severe TB
Inflammasomes	NLRP3	Reduce excessive cell death while maintaining some bacterial clearance.	Prevent exces- sive tissue damage and bac- terial release/ spread.	↓ IL-1 β , ↓ IL-18, ↓ Pyroptosis	Balance is criti- cal for TB pathology control.
Antimicrobial Systems	Reactive oxygen species	Reduce oxidative tissue damage while maintaining some antimicrobial activity	Prevent collat- eral tissue damage from excessive ROS production	↓ H ₂ O ₂ , ↓ O ₂ ⁻ , ↓ OH•	Reduces inflam- matory lung injury
Complement system	Classical and Alternative pathways	Reduce comple- ment-mediated tis- sue damage	Prevent bystan- der injury and excessive inflammation amplification	↓ C3b, ↓ C5a, ↓ MAC formation	Controls sys- temic inflamma- tory responses

Table A1.
Effect of corticosteroids on innate immunity.

Component	Type/subtype	Protective role	Pathological role	Key cytokines produced	Clinical significance
cd4 + t cells	Th1	Modulate excessive Th1 responses while preserv- ing some pro- tective immunity	Reduce tissue damage from prolonged inflammation and granuloma necrosis	↓ IFN- γ , ↓ IL- 2, ↓ TNF- α	Critical in TB meningitis and pericarditis to prevent CNS damage and con- strictive pericarditis

Component	Type/subtype	Protective role	Pathological role	Key cytokines produced	Clinical significance
CD4 + T cells	Th17	Reduce excessive neutrophil recruitment and tissue destruction	Prevent cavitation formation and severe pulmonary damage	↓ IL-17A, ↓ IL-17 F, ↓ IL-22	May reduce cavitary disease and severe pulmonary TB complications
CD8 + T cells	Cytotoxic T cells	Reduce excessive cytotoxicity while maintaining some bacterial killing	Prevent tissue damage and lung parenchymal destruction	↓ IFN- γ , ↓ TNF- α , ↓ Granulysin, ↓ Perforin	Important in preventing excessive tissue destruction in severe TB
Key cytokines	Proinflammatory (TNF- α , IFN- γ , IL-17)	Reduce systemic inflammation and tissue damage	Prevent cachexia, fever, tissue necrosis, and cavitation	Direct suppression of cytokine production and signaling	Essential in TB meningitis, pericarditis, and severe pulmonary TB

Table B1.
Effect of corticosteroids on adaptive immunity.

Study	Year	Study type	TB form/population	Main finding	Recommendation
Diallo et al. [50]	2025	Systematic review and meta-analysis	TB-HIV co-infection	Corticosteroids reduce mortality in TB-HIV patients	Support use in HIV-TB co-infection
Mishra et al. [98]	2020	Systematic review and meta-analysis	Endobronchial TB	Corticosteroids beneficial as adjunct therapy	Recommend as adjunctive treatment
Hayford et al. [14]	2020	Systematic review and meta-analysis	General TB	Antiinflammatory agents show promise as adjuncts	Support host-directed therapy approach
Soni et al. [99]	2019	Systematic review and meta-analysis	Abdominal TB	Beneficial for abdominal tuberculosis	Support use in abdominal TB
Xie et al. [100]	2017	Systematic review and meta-analysis	Tuberculous pleurisy	Effective and safe in pleural TB	Recommend for tuberculous pleurisy
Ryan et al. [101]	2017	Systematic review and meta-analysis	Tuberculous pleurisy	Beneficial for pleural TB	Recommend for pleural involvement
Prasad et al. [45]	2016	Systematic review and meta-analysis	Tuberculous meningitis	Reduce mortality and severe disability	Strong recommendation for CNS TB
Critchley et al. [1]	2014	Systematic review and meta-analysis	Pulmonary TB	Limited evidence for routine use	Insufficient evidence for general recommendation

Study	Year	Study type	TB form/ population	Main finding	Recommendation
Wallis [60]	2014	Meta-regression analysis	Pulmonary TB	Effects on sputum culture conversion	Mixed effects on bacteriological outcomes
Critchley et al. [44]	2013	Systematic review and meta-analysis	General TB	Prevent mortality in TB patients	Support for mortality reduction
Siddiqui et al. [102]	2013	Evidence-based review	General TB	Role established in specific conditions	Evidence-based selective use
Kadhiravan & Deepanjali [2]	2010	Evidence-based review	General TB	Comprehensive evidence-based assessment	Evidence-based recommendations for TB treatment
Sang et al. [49]	2025	Review article	Pleural and pericardial TB	Current evidence for pleural/pericardial TB	Strong recommendation for serosal TB
Gundamraj & Hasbun [103]	2020	Review article	CNS infections including TB	Adjunctive steroids in CNS infections	Support use in CNS tuberculosis
Schutz et al. [6]	2018	Review article	General TB	Corticosteroids useful as adjunct therapy	Support selective use

Table C1.
Summary of relevant studies.

Conflict of interest

The author declares that there is no conflict of interest.

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Imaging and AI Techniques in Intrapulmonary Tuberculosis Diagnosis and Management

Victor Chigbundu Nwaiwu

Abstract

Pulmonary tuberculosis (PTB) remains a major health threat worldwide, resulting in millions of deaths yearly, despite ongoing global, regional, and national efforts to eradicate and control this highly infectious disease. The lungs are the primary organs affected, which can be permanently damaged or spread to other body parts if not treated early, making medical imaging crucial in diagnosis, assessment, staging, monitoring, and guidance. Chest X-ray (CXR) is the standard initial screening tool for suspected PTB, providing an overall view of structures within the chest. Computed tomography (CT) provides more insights into lymphadenopathy and early bronchogenic spread. Positron emission tomography–computed tomography (PET/CT) is being explored for determining treatment response. Radiological appearances of PTB alongside details from diverse research across these imaging modalities were evaluated. A targeted screening approach involving taking X-ray services down to the doorstep of many in TB-endemic countries, including strategies such as campaigning, mass screening, active case finding, and contact tracing, certainly yielded better results. AI introduction in imaging has surprisingly been instrumental to the recent success and giant strides made in addressing PTB. Empirical studies have demonstrated the remarkable performance of AI techniques such as machine learning (ML), deep learning (DL), natural language processing (NLP), expert systems (ES), robotics, and fuzzy logic (FL) in PTB imaging tasks – worklist management, triaging/prioritization, dose optimization, diagnosis/reporting, and treatment outcome prediction. However, while it is necessary for models to undergo robust training and validation, it is imperative to address growing ethical and regulatory concerns regarding responsible AI use.

Keywords: medical imaging, AI techniques, intrapulmonary tuberculosis, diagnosis, management

1. Introduction

Pulmonary tuberculosis (PTB) is a form of tuberculosis (TB) that affects the lungs, accounting for a large majority (85–90%) of reported TB cases worldwide.

It is the most frequent clinical manifestation of the disease and poses a globally significant health issue, with incidence rates varying significantly by region, from low rates in high-income countries to high rates in low- and middle-income countries, primarily in Asia (45%), Africa (23%), Western Pacific (18%), Eastern Mediterranean (8.1%), Americas (2.9%), and Europe (2.2%) [1, 2].

The prevalence of intrapulmonary TB in 2017 globally was 9.6 cases per 100,000 people, and this figure is projected to increase to 11.4 by 2030. In 2021, statistics reveal that 10.6 million people were affected, with a whopping 6.4 million newly diagnosed TB cases, of which 5.3 million are PTB [2, 3]. Recent figures from the World Health Organization (WHO) reveal a staggering 1.25 million deaths, making it currently the world's leading cause of death from a single infectious agent [4]. Several driving factors are responsible for these abysmal results. The fact that millions of people with intrapulmonary TB are missed by diagnostic systems each year is one factor. Multidrug-resistant TB (MDR-TB), a public health crisis characterized by resistance to at least two of the most effective first-line anti-TB drugs (isoniazid and rifampicin), is yet another factor (estimated 450,000 new cases annually), making standard TB treatments ineffective and resulting in longer, more complex, and expensive treatment courses (nearly 20 times greater than those associated with drug-sensitive TB). Also, the impact of HIV coinfection with TB has worsened treatment outcomes [5]. Despite global efforts that have resulted in saving about 79 million lives since 2000, its easy spread nature and late detection mean the world is unlikely to meet the WHO milestone of a 75% reduction in TB mortality between 2015 and 2025, reports the World Bank [6]. Early detection of intrapulmonary TB remains key to preventing transmission and improving health outcomes [7].

The following medical imaging techniques are proven modalities used to diagnose and manage intrapulmonary TB:

- *Chest radiography* (chest X-ray [CXR])
- *Computed tomography* (CT)
- *Positron emission tomography–computed tomography* (PET/CT)

Chest radiography, otherwise called CXR, remains the first-line imaging due to its ready availability, cost-effectiveness, and relatively low radiation dose [8]. Chest X-ray screening services have been very useful in intrapulmonary TB programs in TB-endemic countries (mostly rural areas) faced with a higher burden and greater barriers to accessing health services, which can affect outcomes. Computed tomography is usually resorted to in the detection and characterization of subtle lung lesions, lymphadenopathy, and bronchiectasis [9]. Positron emission tomography–computed tomography (PET/CT) is a hybrid technology that combines the anatomical information from CT with the metabolic information from PET, allowing for the visualization of metabolically active areas and distinguishing between active and inactive TB lesions [10].

The advent of artificial intelligence (AI), rooted in advanced algorithms and learning systems, and its integration with imaging modalities, is beginning to make waves in contemporary TB practice and research in a bid to further improve

intrapulmonary TB diagnosis and management strategies, cutting across aspects of worklist management, prioritization, dose reduction, image quality, and reporting tasks [11]. It is in these imaging and AI directions that this chapter looks to synthesize evidence.

2. Intrapulmonary TB

Intrapulmonary TB is an airborne infectious disease confined in the lungs and caused by the bacteria *Mycobacterium tuberculosis*. The International Consensus for Early TB (ICE-TB) framework distinguishes latent-active paradigm of TB, from disease to infection state that is symptomatic (chest pain, cough, weakness or fatigue, weight loss, night sweats, and loss of appetite) and highly contagious [12].

Latent intrapulmonary TB is commonly diagnosed using a TB skin test (Mantoux test) or a TB blood test (interferon gamma release assay [IGRA]), as imaging tests alone cannot accurately diagnose the latent TB state but help identify individuals at higher risk of progressing from latent to active [13]. Without treatment, latent intrapulmonary TB can develop into active intrapulmonary TB, although it is important to note that not all active cases begin as latent (see **Figure 1**). While some people infected with intrapulmonary TB develop a latent infection (one in four people globally are estimated to have a latent TB infection), it is possible for the infection to progress directly to active disease within weeks or months (see **Figure 2**). Its easy-to-spread nature when in the active state (via airborne droplets released when an infected person coughs or sneezes) makes it quite difficult and challenging to control, which is the reason imaging techniques are crucial for early diagnosis and effective management [14, 15]. Risk factors include exposure to infected persons, congregate settings (homeless shelters, correctional facilities),

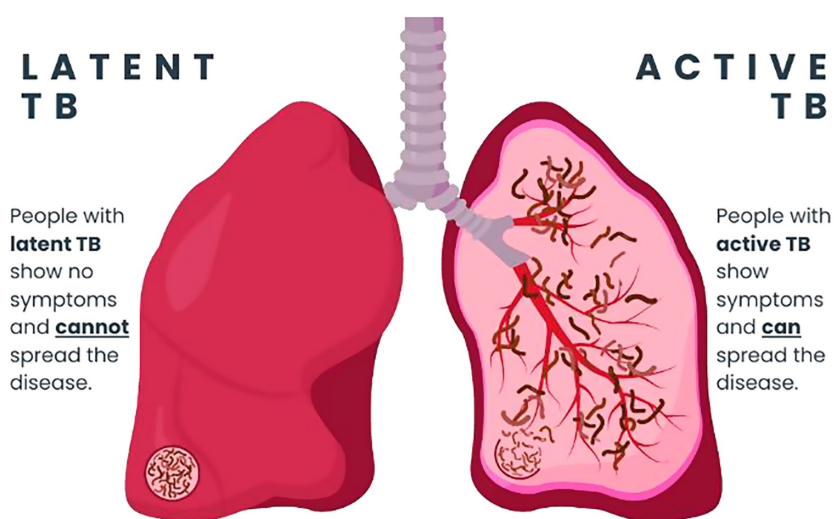


Figure 1.
Latent and active intrapulmonary tuberculosis.

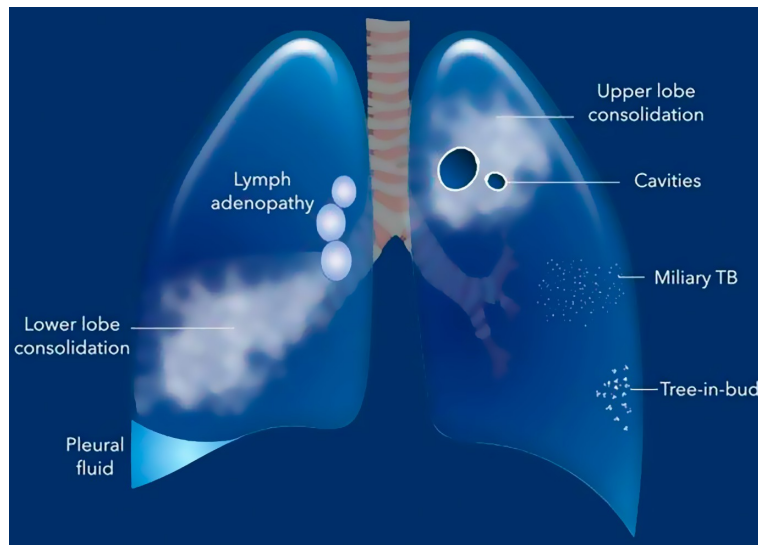


Figure 2.
Active intrapulmonary tuberculosis.

certain health conditions (e.g., diabetes, cancer, kidney disease), environment (being born in or frequently traveling to high TB burden countries), and lifestyle factors (malnutrition, smoking/tobacco use, excessive alcohol consumption) [16, 17]. Following recent studies [18], it has become imperative to disrupt the chain of transmission that sustains the TB epidemic by intensifying efforts in detecting and treating PTB, employing population-wide imaging approaches such as mass screening, targeted chest screening, contact tracing, and further imaging tests [19, 20].

3. Anatomy of the lung

The lungs are large, air-filled, spongy organs, both encased by membranes called the pleura, contained within and protected by the thoracic cage, also known as the rib cage (see **Figure 3**). The right and left main bronchi, which are a continuation of the trachea, alongside blood vessels, nerves, and lymphatic vessels, penetrate and enter each lung on the medial surface in a region called the hilum and thereafter branch extensively throughout the lung. Each lung (right and left lung) is divided anatomically into distinct lobes by fissures, with each lobe containing a portion of the bronchial tree leading into the alveoli [21].

The right lung (slightly shorter and wider than the left) has three lobes: superior, middle, and inferior, and two fissures: horizontal fissure and oblique fissure (the horizontal fissure separates the superior and middle lobes, while the oblique fissure separates the middle and inferior lobes). The left lung has two lobes: superior and inferior, and one fissure: oblique fissure (the oblique fissure separates the superior and inferior lobes) [22].

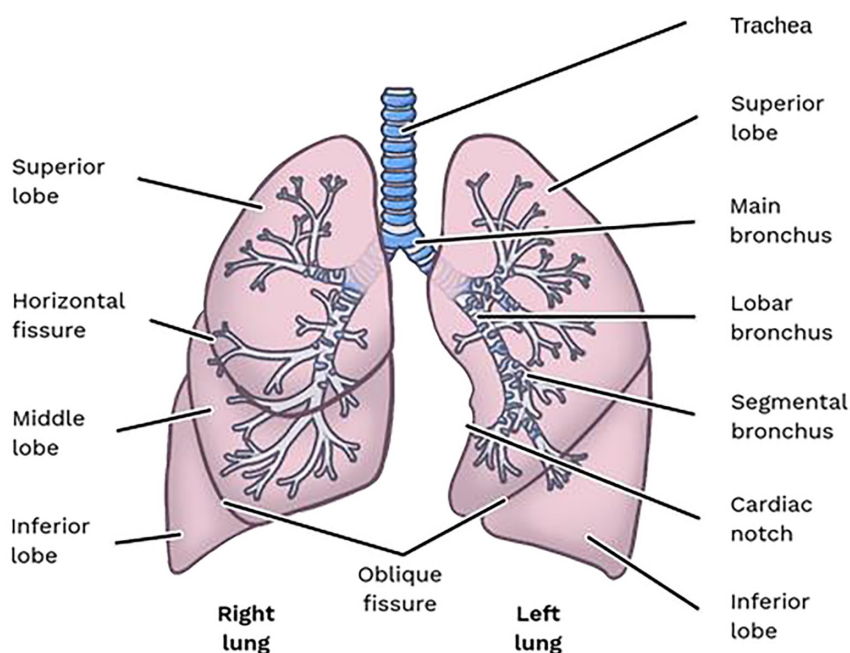


Figure 3.
Anatomy of the lungs.

4. Imaging of intrapulmonary TB (modalities, diagnosis, and assessment)

4.1 Chest X-ray

Conventional chest X-ray is the initial modality employed for screening and diagnosis and remains the standard for detecting and monitoring intrapulmonary TB. It makes use of a small dose of ionizing radiation (approximately 0.1mSv) to produce pictures of the internal structures of the thoracic region (lungs, ribs, heart, airways, blood vessels, bones, and diaphragm), capturing the resulting image on an image receptor system. The image produced depicts different levels of absorption that occur in the various tissues, creating contrast. A standard posteroanterior (PA) and lateral view is the typical initial screening projection, although an anteroposterior (AP) lordotic view may be used as a supplementary projection to better visualize lung apices if obscured [8].

X-ray systems are large, stationary units typically found in hospitals. Nonetheless, due to the need to bring diagnostic services directly to hard-to-reach communities, mobile vans equipped with digital X-ray machines gained traction for rapid and efficient on-site intrapulmonary TB screening to identify and manage cases. The mobile van facility comprises an inbuilt X-ray room, battery/capacitor-assisted X-ray unit and generator, operator/computer room, uninterrupted power supplies (UPS), and lead protective walls/shields (see **Figure 4a**). The use of mobile vans in mass screening campaigns was successful in detecting a large pool of prevalent intrapulmonary TB cases among hard-to-reach populations, and surveys of

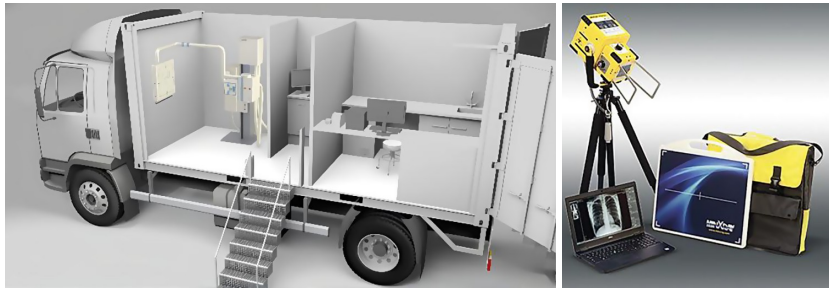


Figure 4.

(a) Mobile van housing compact digital X-ray machine and (b) portable X-ray system.

follow-up campaigns showed significant reductions in the burden of this disease, overcoming socioeconomic barriers and improving access to high-quality TB treatment [23]. A similar mobile van equipped with a digital X-ray machine was again useful in detecting 236 (3.4%) TB cases out of 6,899 screened in a cross-sectional descriptive study [24]. Elsewhere, mobile chest X-ray screening events (in camps) that screened a total of 1,214,289 individuals (from 2017 to 2021) detected 7,625 cases of intrapulmonary TB and patients successfully treated [25]. These findings agree with an epidemiological analysis of historical data on mass chest X-ray screening conducted in 2024, demonstrating a major and sustained reduction in TB case notifications [26]. In the studies of [27], mobile X-ray targeted screening for TB resulted in an overall yield of 200 per 100,000 persons screened, with a focus at homeless persons and problem drug users. This proves that targeted active case finding using X-rays has the potential to deliver a major contribution to intrapulmonary TB. Despite several positives, this approach has been reported to suffer logistics and funding challenges, impacting successful TB program implementation across the globe especially in low resource settings [24, 28].

Contemporary practice in chest radiography has witnessed the creation of portable systems that prioritize convenience and accessibility, now being deployed for diagnostic and/or screening activities located far from health structures, for example, outreach interventions (see **Figure 4b**). This battery-powered and completely wireless transportable technology (weighing less than 30 kg, including all accessories) allows rapid and accurate chest X-ray services for intrapulmonary TB to be brought directly to communities and can be performed in remote locations, resource-constrained or other non-clinical settings. It possesses an energy-efficient high-frequency generator that produces image quality comparable to stationary X-ray systems and an integrated digital detector and precise collimation system; but since it is mostly not performed in a dedicated room, it will demand adequate radiation protection measures put in place, such as distance, time, and shielding [29].

Community-based screening efforts with these portable digital X-ray units, as illustrated, have shown the potential to identify people with intrapulmonary TB at a very early stage in their disease course and to substantially increase notification rates. Its emerging use in combination with AI systems is rapidly reshaping the landscape of imaging practice.

Artificial intelligence is concerned with replicating human intelligence in machines, trained to perform knowledge-intensive tasks, accomplish advanced

functions, solve problems, and make decisions. The roots of AI can be traced back to the 1940s, when the “Turing test” – a test to check the ability of a machine to exhibit intelligent behavior equivalent to human intelligence – sparked the first AI conference held at Dartmouth College. McCarthy’s AI programming language (LISP), Weizenbaum’s interactive natural language processing (NLP) computer program (ELIZA), and Shakey, the mobile robot, were notable achievements between the 1940s and 1970s, which laid the foundation for the discovery of expert systems (ES) (knowledge-based systems MYCIN and EMYCIN), algorithms, machine learning (ML), and deep learning (DL) from the 1970s to the 2020s. Later advances have seen AI systems being able to process vast amounts of data to make accurate predictions and generate images, texts, videos, and 3D designs in response to prompts. This is known as generative AI (GenAI), rooted in the GPT (generative pre-trained transformer) architectural foundation and built into different language models such as GPT-1, GPT-2, GPT-3, and GPT-4. GenAI continues to learn and evolve, using neural networks to identify patterns and undergoing training on large unlabeled datasets to predict outcomes in the same ways humans act [30].

In the field of medical imaging, the ability of these computer systems to learn to identify complex patterns and trends in radiographic images and reports (via feature learning techniques, artificial neural networks [ANNs], NLP, etc.) without constant guidance from humans is the reason behind AI’s successful integration with imaging technologies. They are able to extract features from images, identify abnormalities, and generate reports. Chest X-ray-compatible AI-powered computer-aided detection (CAD) software solutions (such as CAD4TB [Delft Imaging], INSIGHT CXR [Lunit], and qXR [Qure.ai]) have been able to solve intra and inter-reader variability of CXR reporting and the challenging nature of precise adherence of human readers to guidelines on CXR interpretation by providing reports in a few seconds/minutes that are consistent, adaptable, and unaffected by fatigue, stress, or lapses of concentration. AI-powered portable X-ray systems could be deployed either in the form of cloud-based solutions or offline systems. The cloud-based option is cheaper, quicker to troubleshoot, and easier to upgrade to new services/software versions, and it can be accessed by a central expert radiologist for quality control, although it is dependent on stable internet connections with high upload bandwidth and may experience downtime, resulting in major delays in screening practices, particularly when not used in conjunction with an on-site human reader. The offline category does not need an internet connection and can be very useful for screening in remote areas that lack stable internet, but it requires expensive laptops with high-end computing and graphical processing power; also, installation and maintenance can be cumbersome. Nevertheless, a key consideration will be the availability of information technology (IT)/human resources for support as well as skilled personnel to conduct CXR examinations, maintain the equipment, and read the results [31–33].

This AI feature has significantly increased the diagnostic capacities of the system, its efficacy and efficiency, and its appropriateness and advantages of use, as seen in the latest studies. Abiola, in 2025, with the aim of bringing pulmonary TB screening innovations to hard-to-reach communities and strengthening the active case-finding interventions for TB, demonstrated an average presumptive TB proportion of $10.84 \pm 5.42\%$ and 10% confirmed TB cases from 94,694 subjects screened using ultra-portable digital X-ray with CAD4TB [34]. Similarly, a Delft-light backpack portable digital X-ray CAD4TB unit identified 1,140 (13.9%)

presumptive TB cases out of a total of 8,230 participants screened for PTB, with the proportion of confirmed TB cases given as 12.0% and 5.6% for men and women, respectively ($P < 0.001$) [35]. The evaluation of the ultra-portable X-ray system revealed its significant potential to improve PTB case detection and equitable access to high-quality TB care, producing a mean image quality rating of 3.71 (compared to a reference of 3.99, $P < 0.001$) with no significant differences in TB abnormality scores, nor in any of the steps along the TB care cascade during campaigning [36]. In a comparative study of ultra-portable CXR screening to TB symptom screening in campaigns, it was found to provide more efficient TB screening in hard-to-reach areas, with the AI feature able to improve triaging when human readers are unavailable and save expensive diagnostic testing costs [37]. According to a recent formative assessment in 2024, the implementation of a portable digital chest X-ray machine at the community level is the best means for PTB screening/contact tracing, allowing for more TB contacts living with the index patient to be screened without proximity and transportation constraints [38]. In a further literature review, the heterogeneity of active TB risk among population groups was noted, indicating that systematic chest X-ray-led screenings should be targeted at specific high-risk groups rather than universally applied to optimize PTB yield [39].

Chest radiography contains a large amount of information about a patient's health and has great clinical value in the diagnosis of a range of chest anomalies. Radiographic findings associated with active intrapulmonary TB (**Figure 5a–d**) are [40–42]:

- (1) *Airspace disease*: Infiltration, consolidation, or opacification of lung parenchyma involving any lung segment or lobe (Ghon focus) and silhouetting adjacent structures, including caseating granuloma (also known as a tuberculoma, representing a pulmonary nodule), which typically calcifies, becoming a Ghon lesion.
- (2) *Lymphadenopathy*: Chest X-ray is usually unremarkable during the incubation stage (CT preferred) but typically presents with lobulated hilar/paratracheal opacity. There is potential for airway attenuation or deviation. A doughnut sign may be observed on a lateral radiograph. Airway compression or displacement is the most reliable finding. Attenuation can result in distal ipsilateral hyperinflation, atelectasis, or consolidation.

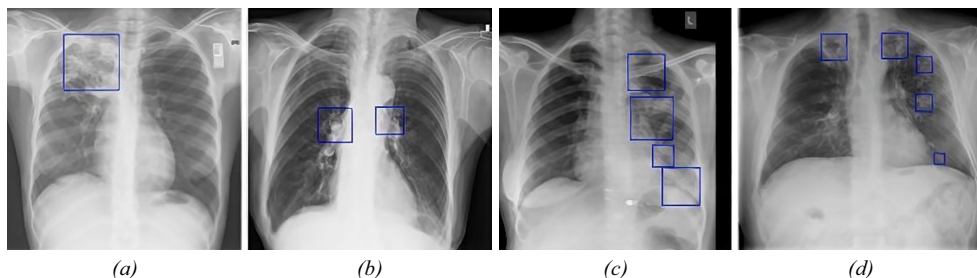


Figure 5.
Primary and post-intrapulmonary tuberculosis appearance on a chest X-ray.

- (3) *Cavitation*: Cavity formation is the hallmark of postprimary TB. Small cavities are easily missed on CXR, as it is often difficult to distinguish a small cavity from consolidation. Airspace opacification surrounding an area of cavitation represents central caseous necrosis and liquefaction. An air-fluid level may represent secondary infection.
- (4) *Miliary TB*: Chest X-ray is usually unremarkable at the onset but manifests as diffuse small non-calcified/sarcoid nodules (1–3 mm to 5 mm in diameter, randomly distributed throughout both lungs with a “snow-storm” appearance) with intra and interlobular septal thickening. Computed tomography is able to demonstrate miliary disease before it becomes radiographically apparent. This miliary pattern, well-defined, uniformly distributed, and representing hematogenous dissemination, is different from the tree-in-bud nodules seen under bronchiectasis below, which have a patchy distribution and are poorly defined.
- (5) *Pleural effusion*: Increased homogeneous density superimposed over the lung fields, more commonly seen in 30–40% of adult cases and 5–10% of pediatric cases.

Chest X-ray is a vital and preferred imaging technique employed to monitor intrapulmonary TB treatment and clinical outcomes, such as response to characteristic features like infiltrates, cavitation, effusion, lymphadenopathy, and miliary pattern (see **Figures 6, 7** and **Table 1**). Repeated tissue damage and repair often result in pulmonary fibrotic scarring, linear opacity, calcifications, or volume loss on CXR even after treatment [43].

4.2 Computed Tomography

Computed tomography is the method of choice to reveal early bronchogenic spread in postprimary intrapulmonary TB and is more sensitive than CXRs in detecting lymphadenopathy and characterizing the infection as active or not. A CT scan combines a series of X-rays to create cross-sectional, detailed gray-scale images of internal structures in the chest region that represent the distribution of X-ray attenuation coefficients. Images obtained through 360 degrees then undergo reconstruction into three primary planes – axial, coronal, and sagittal – from a single 3D dataset, allowing for detailed multiplanar views of the anatomy [44].

A CT machine is very bulky and expensive and requires on-site installation. Most importantly, it involves a much higher dose of radiation (5–7mSv) compared to a standard CXR (0.1mSv), which poses a greater health risk, especially for routine screening, making it impractical for widespread screening. Again, CT alone lacks the sensitivity and specificity required for accurate intrapulmonary TB diagnosis due to overlapping imaging features with other conditions like lung cancer, leading to misdiagnosis, and is therefore not recommended for routine use [45, 46].

It is, therefore, not recommended for initial mass screening but is useful in certain clinical situations (see **Figures 8–10** and **Table 2**) [42, 47, 48]:

- (1) *Lymphadenopathy*: Right paratracheal and hilar lymph nodes are the most common sites of nodal enlargement (>2 cm), with a “rim sign,” consisting of

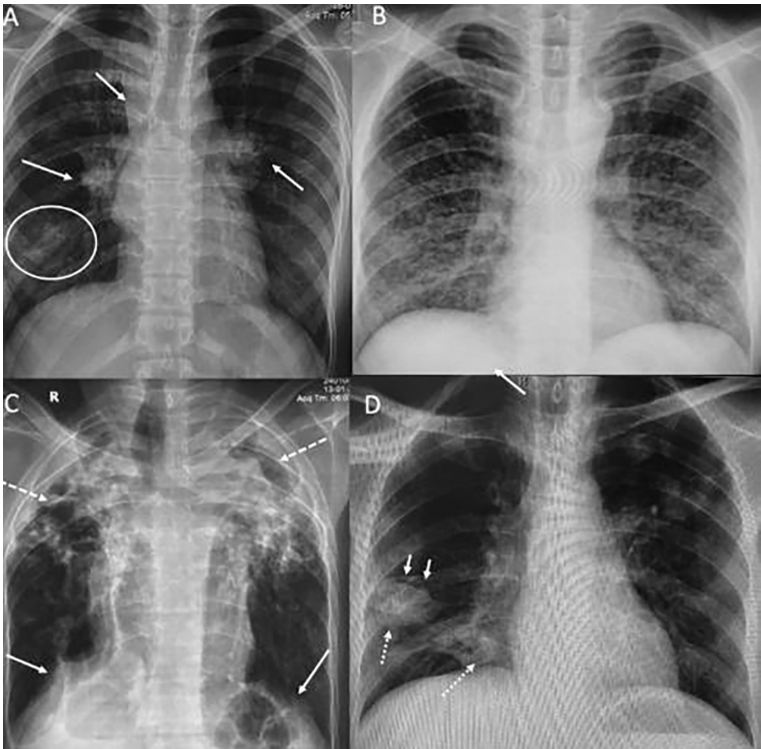


Figure 6.
Chest X-ray in PTB.

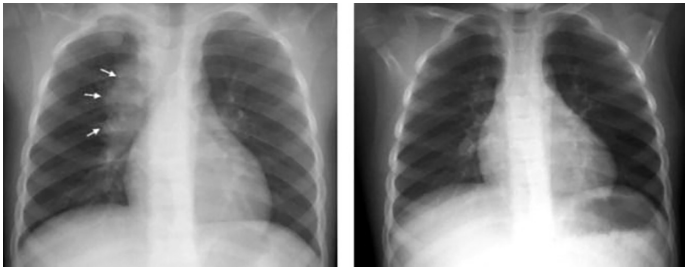


Figure 7.
Right paratracheal and hilar lymphadenopathy before and after treatment.

1	Patches of consolidation
2	Centrilobular nodules (tree-in-bud appearance)
3	Miliary nodules
4	Cavitation
5	Lymphadenopathy
6	Fibro-cavitary changes and pleural effusion

Table 1.
Summary of CXR findings.

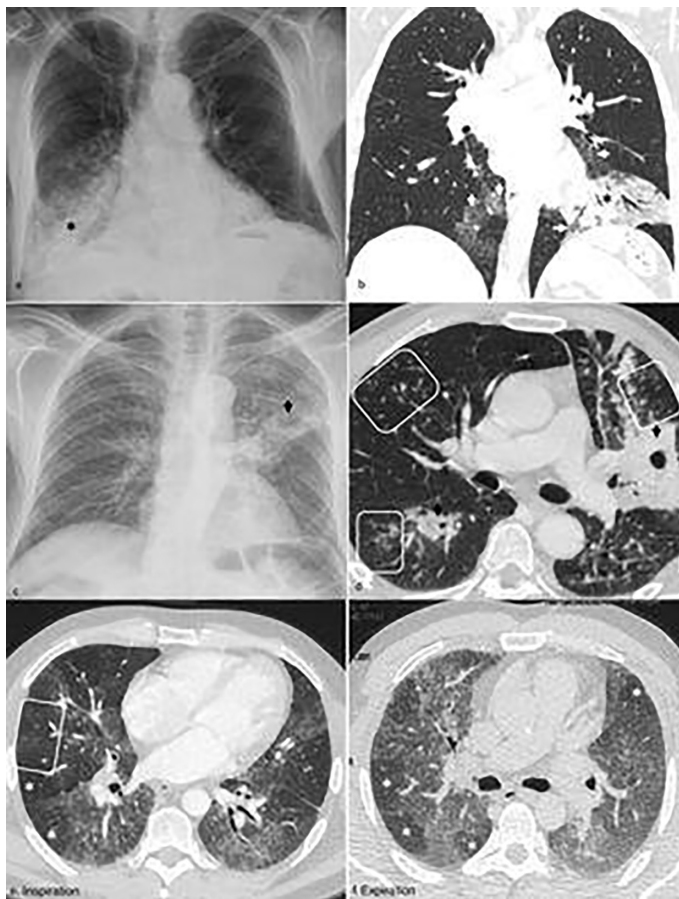


Figure 8.
Multifocal pulmonary opacities.

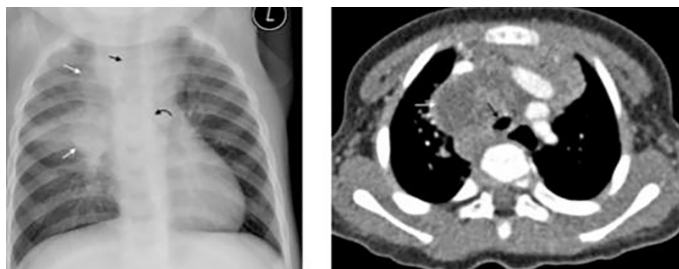


Figure 9.
Imaging comparison on CXR and CT of same patient.

a low-density center representing caseous necrosis, surrounded by a peripheral enhancing rim due to granulomatous inflammatory tissue. Contrast-enhanced CT delineates lymph nodes and shows central necrosis well, along with peripheral rim enhancement. It allows accurate assessment of

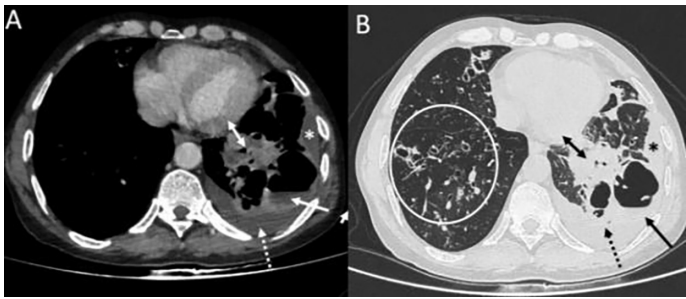


Figure 10. PTB CT chest windowing alt- text: (a) Axial mediastinal and (b) lung window sections denoting cavities with air-fluid levels in left lower lobe, consolidation, associated pleural effusion and bronchiectatic changes encircled in right lower lobe.

1	Location	Upper lobes, superior segments of the lower lobes, subpleural consolidation
2	Nodules	Centrilobular (tree-in-bud), miliary, peri-lymphatic
3	Lymph nodes	Hilar and mediastinal, calcified, central necrosis (rim sign), enhancing
4	Pleural involvement	Pleural effusion, empyema, bronchopleural fistula

Table 2. Summary of CT findings.

- lymph node compression, measurement of stenosis length, and prediction of whether the offending node is endobronchial, submucosal, or peri-bronchial.
- (2) *Bronchiectasis*: Early bronchogenic spread in CT appears as 2–4-mm centrilobular nodules (inflammatory lesions in the bronchioles and peri-bronchial alveoli) and sharply margined linear branching opacities around terminal and respiratory bronchioles (tree-in-bud sign). This sign mimics the branching pattern of a budding tree, and an increased broncho-arterial ratio (severely dilated bronchial lumens or bronchial wall thickening, leading to increased broncho vascular markings) is indicative of bronchiectasis.
- (3) *Differentiation between active and latent PTB*: While chest radiographs may show mild or nonspecific findings in patients with active PTB, studies reveal that CT scans can correctly diagnose 91% of cases of PTB and correctly characterize 80% of patients with active disease and 89% with inactive disease. Features include cavitation/cavity lesions, clusters of nodules, presence of centrilobular nodules, and consolidation involving the apex, the superior segment of the right or left lower lobe, or the posterior segment of the right upper lobe or left upper lobe.

Computed tomography provides insights into postprimary intrapulmonary TB/treatment, such as the response to parenchymal, airway, pleural, mediastinal, and vascular sequelae of intrapulmonary TB (although CXR, to some extent, can reveal

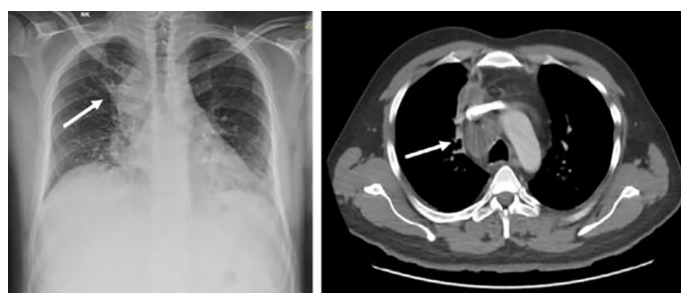


Figure 11.
Imaging comparison on CXR and CT of same patient presenting with PTB.

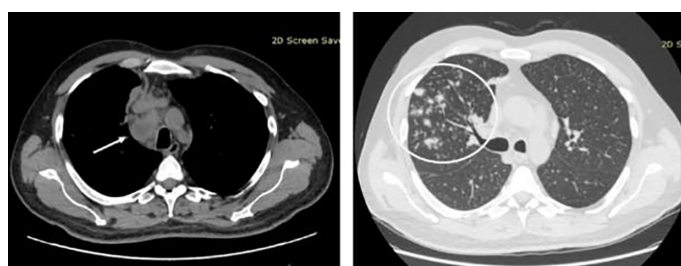


Figure 12.
Follow-up CT after eight weeks of treatment.

some of these features) (see **Figures 11** and **12**). These include calcified mediastinal or hilar masses with central airway narrowing, mediastinal lymphadenopathies, early bronchogenic spread, bronchial obstruction secondary to fibrosis (which may result in obstructive pneumonia or atelectasis), pulmonary vessel encasement, and compression of the superior vena cava [49].

4.3 Positron emission tomography–computed tomography

Is a hybrid form of imaging in nuclear medicine that involves the injection of a radioactive compound such as F-18 Choline, Ga68 PSMA, F-18 Choline, F-18 PSMA, C11 Methionine, ^{18}F -FDG (18F-fluorodeoxyglucose, most common) into the body, which undergoes decay to produce two 511 KeV gamma photons following annihilation, detected externally with a PET scanner. This imaging method provides both anatomic and metabolic information and is widely used for the differentiation of malignant from benign lesions, including identifying patients at high risk of relapse. It works by the accumulation of ^{18}F -FDG in inflammatory cells such as neutrophils, activated macrophages, and lymphocytes at the site of inflammation or infection; these signals are detected as ^{18}F -FDG uptake, usually seen in intrapulmonary TB, in tuberculoma, and in other TB-related lesions [50].

Several studies have demonstrated the relevance of PET/CT in assessing the response to intrapulmonary TB treatment (although it can mimic lung cancer), owing to its high sensitivity in detecting and assessing disease activity,

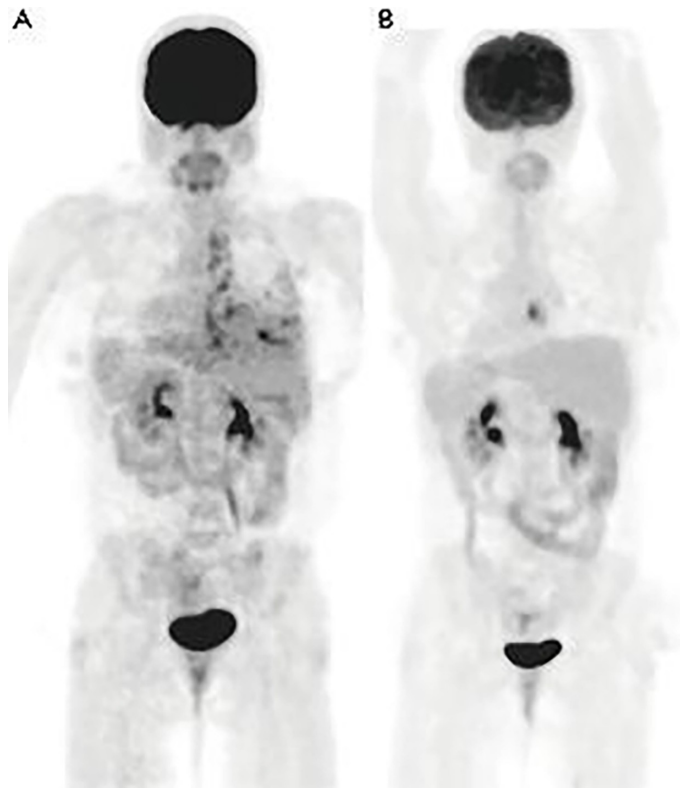


Figure 13.
Whole-body PET scan.

inflammation, response to therapy, and malignancy (see **Figures 13 and 14**). However, it is not for routine use and involves high radiation exposure.

Chen [51], in a prospective study, discovered bronchial spread of PTB, primarily from cavities but occasionally from consolidations, with PET/CT displaying 17% new or expanding lesions linked to cavities via bronchial inflammation that were not present at baseline.

Active PTB shows increased ^{18}F -FDG uptake with high standardized uptake values (although it may mimic cancer). Evaluating FDG/PET-CT studies assessing response to treatment in a recent review in 2024 [52, 53] showed a decrease of 31% in ^{18}F -FDG standardized uptake value after one month of treatment. This finding seems consistent with [54], where a reduction in the total glycolytic activity index by 30–62% at four weeks of treatment in cured patients was observed. With treatment, this translates to a reduction in standardized uptake value max as noted in [55]. On the contrary, the standardized uptake value in nonresponders to TB treatment was higher after four months, outperforming lymph node size in predicting nonresponders ($P < 0.01$) [56], which agrees with studies where baseline standardized uptake value and the number of lymph node regions involved were higher in treatment nonresponders [52].

Predicting unfavorable outcomes or recurrent infections is another aspect. Treatment failure was reflected by the failure to reduce the total glycolytic activity

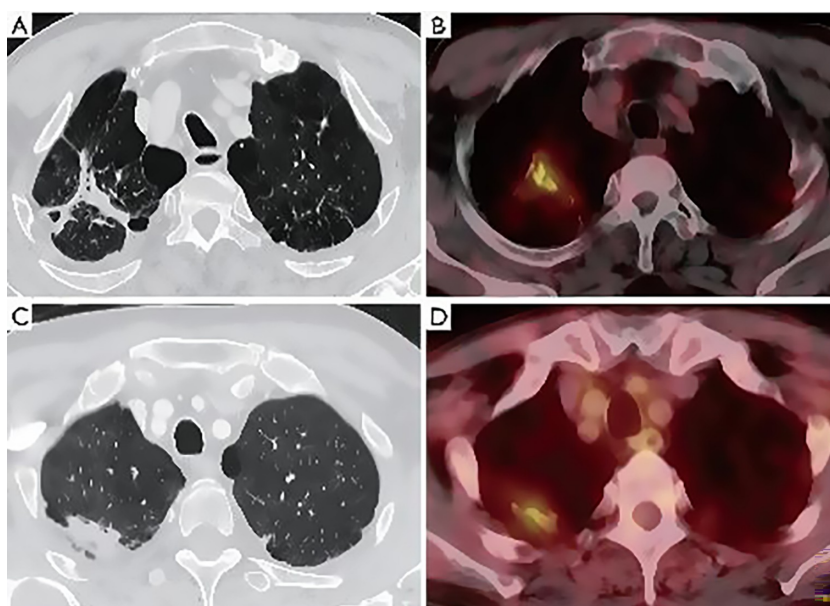


Figure 14.
 Previously healed PTB: CT and 18F-FDG-PET/CT imaging comparison among two subjects.

index by $< 80\%$ at the end of treatment (EoT) in 2020 [57]. In cases requiring a longer duration of treatment and higher chances of mortality, nonresponse at 12 weeks following PET/CT imaging was observed [58]. Persistent metabolic activity at EoT may signal metabolically active old lesions (not active); thus, correlation with clinical data is essential when assessing EoT [59].

4.4 Ultrasound

Ultrasound, though portable, cost-effective, and radiation-free, lacks sufficient evidence regarding its appropriateness as a diagnostic imaging method for intrapulmonary TB. Nevertheless, studies have reported its useful role in identifying pleural effusions and guiding minimally invasive interventional procedures, such as the placement of chest tubes, drainage of loculated collections, thoracentesis, and percutaneous biopsy of subpleural pulmonary consolidations or pleural plaques [60].

5. AI techniques in imaging of intrapulmonary TB (workflow, triaging, prioritization, diagnosis, dose reduction, image quality, reporting, and treatment outcome prediction) and concerns

Artificial intelligence is a set of technologies that empowers intelligent computers to learn, reason, and perform a variety of advanced tasks in ways that used to require human intelligence, utilizing certain techniques, methods, and algorithms to successfully carry out knowledge-intensive tasks. Artificial intelligence use in intrapulmonary TB diagnosis/management is rapidly

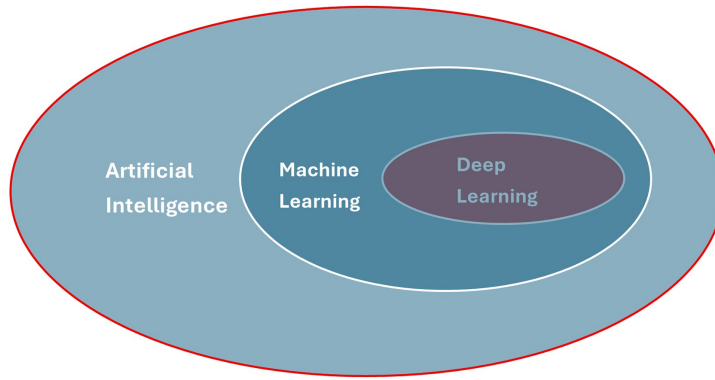


Figure 15.
Artificial intelligence and major domains.

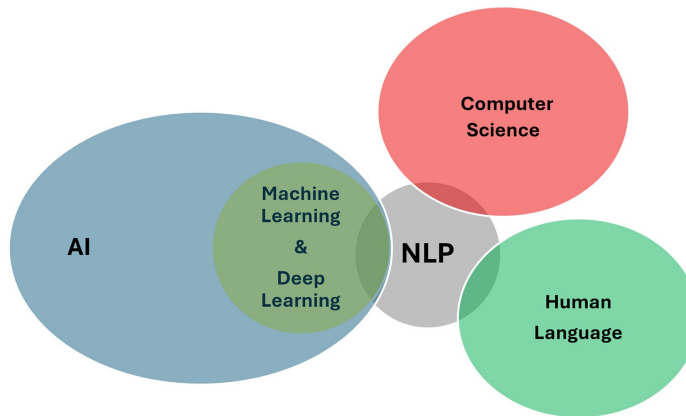


Figure 16.
Natural language processing and components.

evolving, employing techniques such as ML, DL, NLP, ES, fuzzy logic (FL), and robotics. However, ML and DL appear to be the most used due to their robust performance (see **Figures 15** and **16**).

5.1 Machine learning

Machine learning is powered by “algorithms,” which inform the computer how to learn to operate on its own. These algorithms are the step-by-step instructions that enable an intelligent system to complete a task and are divided into three major types (supervised, unsupervised, and reinforcement learning) based on the learning process involved to make predictions. Supervised learning entails humans acting as a guide, training the model on a labeled dataset on predefined tasks, for example, classification (predicting distinct class labels) and regression (predicting a continuous quantity). In unsupervised learning, the computer learns from an unlabeled dataset with no defined output to identify complex processes and patterns

in the absence of constant guidance from humans, for example, cluster analysis and feature learning tasks (feature extraction and feature selection). Reinforcement learning, on the other hand, is characterized by the absence of both human intervention and a training dataset, as the system learns from its experience through repeated trial and error [30].

In imaging and management of PTB, ML algorithms (supervised and unsupervised), as seen in studies, play vital roles in workflow, diagnosis, prediction, and dose reduction. Popular ML models that carry out these tasks include k-nearest neighbors (KNN), support vector machine (SVM), decision tree (DT), hierarchical clustering, random forest (RF), k-means clustering, logistic regression, and naive Bayes (NB) [61–63]. A brief description of these models is given in **Table 3**.

As seen in a practical case study on PTB screening [64], an AI-integrated queue management system driven by advanced algorithms was extremely useful in workflow, worklist management, and crowd control, promoting orderliness, accuracy, communication, and maintaining privacy. These parameters are vital in

ML model	Type and function	Role in PTB imaging
K-nearest neighbors (KNN)	Supervised; classification and regression	Classifies a pixel or region (e.g., a lung nodule) based on the majority class of its “k” closest neighbors (already labeled images) in the feature space and averages values for regression
Support vector machine (SVM)	Supervised; classification and regression	Robust classification by finding the best “hyperplane” (decision boundary) to separate TB-positive features from healthy lung features, also extended to regression
Decision tree (DT)	Supervised; classification and regression	Tree-like model of decisions (e.g., “Is the nodule solid? Is it calcified?”) to classify regions/discrete classes and continuous values (regression) by choosing different splitting criteria; also useful for interpretability
K-means clustering	Unsupervised; clustering and feature learning	Partitions data points into a predefined number of clusters (k), where each data point belongs to the cluster with the nearest mean (centroid); useful in CXR image segmentation, feature analysis, and as a component in CAD automated diagnostic systems
Hierarchical clustering (HCA)	Unsupervised; clustering and feature learning	Builds a hierarchy of clusters and does not require the number of clusters to be specified beforehand, offers natural groupings within complex image data (e.g., various subgroups of radiographic presentations of PTB), correlates severe pulmonary radiological manifestations with clinician data, facilitates feature extraction, and enhances advanced deep learning models
Random forest (RF)	Supervised; classification and regression	Ensemble of many decision trees by averaging predictions from individual trees for regression and taking the majority vote for classification, thus improving robustness and accuracy, making it strong at handling noisy PTB CXR image data
Logistic regression	Supervised; classification and regression	Classifier that extracts image features to predict the probability of PTB presence and odds ratios
Naïve Bayes (NB)	Supervised; classification and regression	Uses probability (Bayes’ theorem) to predict disease and classification and is good for text-based or feature-rich PTB data

Table 3.
Description of popular ML models.

improving the quality of care and clinical outcomes, owing to the highly infectious and widespread nature of the disease. Elsewhere [65], an ML algorithm (XmarTB tool) reportedly yielded a sensitivity of 98.1% and specificity of 99.7% in detecting PTB cases among abnormal CXRs, as well as a sensitivity of 96.7% and specificity of 98.7% in detecting PTB cases among all CXRs, proving to be an accurate diagnostic tool in automatically detecting abnormal CXRs and satisfactorily differentiating PTB from other thoracic diseases. This is consistent with the studies of [66], where a similar CAD software (comprising image preprocessing, extracting region of interest [ROI] regions, extracting ROI features, and classifying disease according to the features) enhanced CXR interpretation and resulted in the discovery of more PTB patients during community screening initiatives. In addition, the use of noise reduction algorithms has achieved dose reductions of approximately half (47.8%) in CXR without compromising image quality for abnormal lung findings [11]. Furthermore, ML models (DT) were useful in predicting PTB treatment success and adverse effects (accuracy – 92.72%, AUC – 0.909, precision – 95.90%, recall – 95.60%, and F1-score – 95.75%), thus improving PTB management [67]. However, as radiological data continues to increase disproportionately in comparison with trained readers, determining in a robust way features for PTB as well as other chest abnormalities has opened up opportunities for advancing traditional CAD systems in imaging, leading to deep learning.

5.2 Deep learning

Deep learning entails the use of “artificial neural networks”, which comprise several processing layers to learn from data, mimicking the way the brain processes information. Examples of common DL algorithms are multilayer perceptron (MLP), convolutional neural networks (CNNs), long short-term memory networks (LSTMs), recurrent neural networks (RNNs), generative adversarial networks (GANs), and Autoencoder. Convolutional neural network is the most widely used DL algorithm, consisting of a convolutional layer (feature extraction), pooling layer (feature selection), and connected layer (integrates extracted features), which has been excellent in diagnosis, triaging/prioritization, and dose reduction in PTB imaging (see **Figure 17**) [60]. **Table 4** describes these algorithms [68–70].

As demonstrated in the experimental studies of [71], an AI system based on CNNs (incorporating NLP) successfully automated real-time triaging of adult CXR on the



Figure 17.
DL model- PTB in CXR.

DL algorithms	Description	Role in PT imaging
Multilayer perceptron (MLP)	Fully connected network consisting of an input layer, one or more hidden layers, and an output layer, utilizing the backpropagation technique	Basic detection and classification tasks in PTB struggle with complex spatial patterns compared to CNNs
Convolutional neural networks (CNNs)	Comprise convolutional layers (feature detection and extraction), pooling layers (feature aggregation), and connected layers (feature integration)	Excel at spatial feature extraction (lesions, opacities) in PTB diagnosis, segmenting lung fields, classifying disease severity, and dose reduction
Recurrent neural networks (RNNs) and Long short-term memory networks (LSTMs)	Consist of a generator (creates content) and a discriminator (checks for accuracy) in processing sequential data and capturing temporal patterns	Sequential data, like changes over time or time-series scans, crucial for tracking PTB disease progression and treatment response in follow-up scans (with LSTMs handling longer dependencies better) and predicting future disease states
Generative adversarial network (GAN)	Comprises of input, hidden layers (for remembering information), and output	Data augmentation and image enhancement, for example, generating synthetic PTB X-rays to balance datasets and creating high-quality images for better model training
Autoencoder	Feedforward neural network, made up of the encoder, the code, and the decoder trained to repeat data from the input to the output layer	Feature extraction/compression, capturing essential features with minimal data loss, dose reduction, image enhancement, and PTB anomaly detection

Table 4.
Description of popular DL models.

basis of the urgency of imaging appearances (critical, urgent, nonurgent, or normal), recording sensitivity, specificity, positive predictive value, and negative predictive value of 71%, 95%, 73%, and 94%, respectively. A feature that can be incorporated during mass screening programs further reduced the average reporting delay time from 11.2 to 2.7 days for critical imaging findings ($P < 0.001$) and from 7.6 to 4.1 days for urgent imaging findings ($P < 0.001$). A similar deep neural network was found to be non-inferior to radiologists for active pulmonary TB triaging in a population with a high TB burden ($P < 0.001$) [72].

The use of recent DL-based models for accurate and precise detection of PTB in CXR achieved classification accuracy, precision, recall, F1-score, and AUC values of 99.29%, 99.30%, 99.29%, 99.29%, and 0.999, respectively, asserting the system's efficacy and superiority to clinicians' precision in PTB diagnosis [73].

Evaluation of three popular DL systems (CAD4TB, Lunit INSIGHT, and qXR) for PTB detection in CXR TB programs achieved similar AUC values (CAD4TB [0.92, 95% CI: 0.90–0.95], Lunit [0.94, 95% CI: 0.93–0.96], qXR [0.94, 95% CI: 0.92–0.97]) with significantly higher sensitivity than radiologists (except one), further reducing by 66% the number of Xpert MTB/RIF confirmation tests for PTB, which is the gold standard, while also maintaining sensitivity at 95% or better [74]. The findings of [75] noted a nearly perfect AUC (0.99) for PTB in CXR.

An integrated DL model, upon evaluation in PET/CT, yielded hugely promising results (AUC 0.84 [0.82–0.88], sensitivity 0.85 [0.80–0.88], and specificity 0.84

[0.83–0.87]) in distinguishing PTB nodules from lung cancer based on DL features, radiomic features, and clinical information [76].

In chest CT, there was no statistically significant difference between the deep learning CNN model and the physicians in detecting PTB [77]. Interestingly, another study proved that the mean effective radiation dose of ultra-low-dose CT following DL algorithm use (CycleGAN) was 0.12 mSv, with a mean 93.9% reduction compared to standard-dose CT, still producing quality images [78].

5.3 Natural language processing

Natural language processing (NLP) is an AI technique that understands and processes human language development in the form of texts or spoken words (historically focused on English due to larger datasets, but significant advances are now happening with multilingual tools such as translation and chatbots). Natural language processing comprises natural language understanding (NLU), which understands the arrangement of words and sounds, and natural language generation (NLG), which produces sentences. NLP in PTB imaging has applications across dataset creation, report generation, diagnosis, and assistance in clinical decision-making [60].

Natural language processing has been used to generate captions for abnormal CXR (pulmonary diseases such as PTB) in 283 seconds (consistent with the radiologist's report), which provides prior information for writing reports and making CXR interpretation more efficient [79]. Natural language processing (embedded into deep CNN) also generated reports of lung diseases (TB) from CXR, achieving an accuracy of 94% [80]. In addition, an NLP model discovered PTB in an incidental lung nodule (ILN) follow-up program on a CT scan, which produced positive acid-fast bacilli (AFB) testing and a positive culture for pan-susceptible *Mycobacterium tuberculosis*, prompting initiation of treatment [81].

5.4 Expert system

Expert system refers to a computer program that learns by accumulating knowledge and integrates it with a set of rules (inference rules engine) to make decisions; the main components are the knowledge base, inference engine, and user interface. It is mostly used in conjunction with ML/DL systems to improve accuracy. In the research of Zulkifli et al. [82], they developed InceptionV3, a lung disease diagnosis expert system (built on CNN and SVM architecture), which uses human knowledge to diagnose lung TB (including other lung diseases) in CXR. It produced one of the best results – classification accuracy, precision, recall, and F1-score were 0.86, 0.91, and 0.91, respectively.

5.5 Robotics

It is a system in which robots are conditioned to carry out certain tasks without any further human intervention. Excellent results in robotic-assisted lung resection surgery on patients with advanced intrapulmonary TB have been observed, demonstrating the efficacy and safety of using robots in standard lobectomy with pulmonary TB [83]. Elsewhere, robot-assisted thoracoscopic (RATS) bi-lobectomy

for PTB yielded very impressive results with a one-year follow-up, reducing some limitations of video-assisted thoracoscopic surgery (VATS) [84].

5.6 Fuzzy logic

Fuzzy logic is rooted in approximate reasoning and decision-making, applied in situations where true or false cannot be ascertained. It comprises four parts as follows:

- (1) *Rule base*: It contains all rules and conditions to control decision-making.
- (2) *Fuzzification*: It converts crisp input into fuzzy sets.
- (3) *Inference engine*: It checks for the degree of match between fuzzy inputs and rules
- (4) *Defuzzification*: It converts fuzzy sets to crisp output.

Recently, in 2024, a novel fuzzy lattice (formed using X-ray image pixels and lattice kinetic energy (K.E.) assisted EJAYA Q-Learning, utilizing a classifier for the automatic detection of pulmonary TB (presence or absence)) remarkably achieved accuracy, sensitivity, specificity, precision, and F-score of 95.50%, 96.39%, 94.40%, 95.52%, and 95.95%, respectively. When compared with contemporary classification techniques, it showed superiority in terms of accuracy (96.928% and 95.905% for presence and absence of PTB, respectively) and speed of classification (39.98 seconds) [85].

The use of AI effectively and safely in PTB imaging requires a thoughtful and cautious approach, acknowledging that while AI offers immense potential, it also presents significant risks, ranging from data privacy issues, security concerns, cost/hardware limitations, algorithmic biases, information accuracy and reliability challenges, and ethical and regulatory ambiguities. It is important to anonymize data where possible, adjust privacy settings (e.g., access, deletion, restrict data processing), educate patients on informed consent for data sharing, and implement strong cybersecurity measures. Again, training models on large, quality, and diverse datasets will boost accuracy, robustness, and generalizability. Issues regarding transparency, explainability, accountability, human oversight, and regulatory frameworks need to be addressed. Above all, interdisciplinary collaboration, stakeholder engagement, AI literacy, external funding for AI research, and continuous professional development training are required to effectively integrate AI into imaging practice, understanding its capabilities and limitations [11, 30].

6. Conclusion

Medical imaging plays a critical role in the screening, diagnosis, treatment, and management of intrapulmonary TB; AI applications are rapidly gaining momentum and enthusiasm for their utilization due to impressive results. However, rigorous validation of AI models, as well as ethical considerations, must be in check to guarantee responsible AI use.

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Section 2

Challenges of Extrapulmonary Tuberculosis Treatment

Progress in the Diagnosis and Treatment of Tuberculous Meningitis

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Abstract

Tuberculous meningitis (TBM) is the most severe form of tuberculosis, with high mortality and neurological disability in survivors. Recent advances include improved nucleic-acid diagnostics for cerebrospinal fluid (CSF), refined pediatric regimens, and emerging intensified/adjunctive treatments. Narrative synthesis of current guidelines and peer-reviewed articles (priority on 2019–2025), with an emphasis on pathophysiology, diagnostics, treatment (drug-susceptible and drug-resistant TBM), and age-specific issues. Xpert MTB/RIF or Xpert Ultra should be the first-line CSF tests in adults and children with suspected TBM; the latter has greater sensitivity in paucibacillary syndrome. The use of adjunctive corticosteroids (mortality benefit) remains supported, and trials of high-dose rifampicin and fluoroquinolone add-on have shown mixed clinical outcome improvements, even with improved pharmacokinetics. A 6-month intensive regimen of HRZE-ethionamide has been added as an alternative to the usual 12-month course of treatment for carefully selected, drug-susceptible TBM. With MDR-TB, linezolid and fluoroquinolones have desirable CNS penetration; bedaquiline demonstrates a quantifiable CSF exposure and is being increasingly used as part of MDR-TBM regimens. Early empiric therapy and steroids remain the cornerstone. Quick molecular diagnosis, individualized therapy with CNS-penetrant agents, and adjuncts (e.g., aspirin to decrease infarcts) are transforming care, and large trials are being conducted to clarify the best intensified therapy, particularly in children and in HIV co-infection.

Keywords: tuberculous meningitis, Xpert Ultra, pediatrics, high-dose rifampicin, linezolid, bedaquiline, corticosteroids, aspirin, hydrocephalus

1. Introduction

Tuberculous meningitis (TBM) is the most pernicious type of tuberculosis, with high death and neurologic disability rates [1]. It is a consequence of the hematogenous diffusion of *Mycobacterium tuberculosis* (*M. tuberculosis*) to the meninges and subarachnoid space, resulting in a subacute meningitis that is usually hard to detect and difficult to treat. Tuberculous meningitis constitutes a smaller

percentage of tuberculosis (TB), with an estimated global prevalence of 1–5% (around 129,000–199,000 cases per year), although its prevalence is much higher in regions with a significant burden of TB [2]. Modeling studies show that there is a worldwide TBM mortality rate of approximately 27%, and approximately 50% of survivors experience permanent neurologic sequelae [3, 4]. Young children (less than 5 years old, in particular) and immunocompromised adults are especially susceptible: TBM manifests in children under 5 years old at a rate of about 4% of TB cases, and one out of every three to five adults who have TBM also has HIV co-infection [5]. In fact, TBM patients with HIV have a significantly increased mortality rate (~57% versus 16% when HIV-negative) [6]. Additional risk groups include infancy (poor immunity), old age, diabetes, and close contact with untreated TB patients [7]. Despite being curable with prompt therapy, TBM frequently causes delayed diagnosis and poor outcomes, underscoring the need for improved diagnostic tools and therapeutic strategies [8, 9].

2. Diagnostic approaches

Timely diagnosis of TBM is challenging due to its nonspecific early symptoms and the paucibacillary nature of CSF infection [10]. A high index of suspicion is required, particularly in endemic regions or at-risk populations (young children, HIV-positive patients). The diagnosis rests on a combination of clinical assessment, characteristic neuroimaging, and laboratory confirmation (via CSF analysis, microbiology, or molecular tests) [11].

2.1 Clinical presentation and staging

Tuberculous meningitis is generally a subacute meningitic disease that develops progressively over days to weeks, in contrast to pyogenic bacterial meningitis [12]. There is a tendency for nonspecific early symptoms: low-grade fever, malaise, night sweats, and anorexia, with headache being a typical prodromal symptom [13]. During the prodrome, patients may also complain of unspecified gastrointestinal symptoms (e.g., vomiting or constipation) [8]. The more pronounced the inflammation in the CNS, the more certain symptoms of meningitis are revealed: stiffening of the neck, photophobia, intense headache, vomiting, and changes in mental status [14]. Neurological symptoms (cranial nerve palsies, seizures, or focal weakness) are likely indicators of advanced disease complications, such as hydrocephalus or infarcts [8]. Tuberculous meningitis severity is frequently determined by the British Medical Research Council (BMRC) staging at presentation: Stage I (alert, minimal deficits), Stage II (confusion or mild focal deficits), and Stage III (coma or severe neurologic deficit) [15]. The majority of patients are in Stage II or III because their cases were not identified in a timely manner [16]. It is important to note that children also present at higher stages than adults. In a comparative series, at admission, 73% of children were in Stage III (coma) compared to approximately 41% of adults [17]. There are also more intense symptoms of elevated intracranial pressure (such as bulging fontanel in newborns and projectile vomiting) and seizures in children, with less clear symptoms of confusion or stroke-like local impairment in adults [18–20]. Important diagnostic clues may include a history of chronic cough, known TB exposure, or concomitant

pulmonary TB on the chest X-ray (present in approximately 16–90% of cases in children and 22–83% of cases in adults) [21, 22]. In any chronic meningitic disease, particularly when there are risk factors or a lymphocytic CSF profile, TBM should be considered, and urgent investigations should be sought [21].

2.2 Neuroimaging findings

Neuroimaging forms part of TBM diagnosis and usually reveals typical abnormalities. The modality of choice is magnetic resonance imaging (MRI) using gadolinium contrast, as it has better sensitivity to meningeal inflammation and parenchymal lesions [23, 24]. Computed tomography (CT) may help identify gross alterations (hydrocephalus, infarcts) and is indicated in the absence of or contraindication to MRI [25]. Tuberculous meningitis has classic neuroimaging characteristics that include the following (see **Table 1**):

- **Basal cistern leptomeningeal enhancement:** Contrast MRI typically shows thick enhancement of the meninges at the skull base (interpeduncular, prepontine, suprasellar cisterns) due to the gelatinous exudate [26]. This observation is highly indicative of TBM (though not a pathogen) and is observed in as many as about 90% of cases. Leptomeningeal enhancement can spread across the cerebral convexities and along cranial nerves [27]. Basal hyperintensities may also signify exudates on FLAIR sequences [28].
- **Hydrocephalus:** Obstructed CSF pathways caused by basal exudates result in ventricular enlargement, which is apparent on imaging in most pediatric TBM patients and a significant proportion of adults [29]. The most common communication is that of hydrocephalus (dilation of the 3rd and lateral ventricles) [30]. Hydrocephalus on initial CT/MRI is reported in approximately 40–88% of

Finding	Description and significance	Frequency in TBM (Approx.)
Basal meningeal enhancement	Contrast uptake in basal cisterns due to tuberculous exudates; a hallmark of TBM.	Seen in the majority of cases (up to ~90%).
Hydrocephalus	Enlargement of ventricles (usually communicating type) due to CSF blockage at the base, leading to raised intracranial pressure.	Very common in children (~50–80%); ~20–50% in adults.
Infarcts (stroke)	Ischemic lesions (often in the basal ganglia or cortex) due to TB vasculitis may cause focal deficits or stroke syndrome.	Occur in approximately 20–40% of cases (range: 4–60%).
Tuberculomas	Intracranial tuberculous granulomas: ring-enhancing mass lesions that may accompany meningitis. They can cause seizures or focal signs if sizable.	Present in a subset (10–30% overall; up to ~50% in pediatrics).
Cranial nerve enhancement	Enhancement or thickening of cranial nerves (III, VI, VII, VIII commonly) due to basal arachnoiditis manifests as cranial neuropathies (e.g., diplopia, deafness, facial palsy).	Common; specific cranial nerve palsies in ~20–30% (III nerve palsy is the most frequent).

Table 1.
Common neuroimaging features in tuberculous meningitis.

children and ~4–62% of adults in series [24]. This complication requires emergency neurosurgical examination, as an extraventricular drain or shunt may be necessary.

- **Infarcts:** Cerebral TB vasculitis infarctions appear on MRI as regions of limited diffusion or on CT as hypodense foci, commonly in the basal ganglia, thalamus, or frontal lobes [31]. Ischemic strokes are seen in up to 20–40% of TBM patients on imaging (range reported as 4–65%) [32]. These are normally caused by obliterative arteritis of small perforating arteries and are associated with local neurologic impairments (e.g., hemiplegia).
- **Tuberculomas:** Coexisting tuberculous granulomas are ring-enhanced or nodular lesions, solitary or multiple. MRI is more sensitive than CT when it comes to detecting tuberculomas and related edema [33]. In adults with TBM, tuberculomas are detected in an estimated range of 10–30% (3–89% in other series) and slightly higher in children (12–50%) [34]. They can be found at baseline or may develop in the course of therapy (paradoxical reaction). Tuberculomas may cause mass effect or seizures due to the edema around them.
- **Other findings:** MRI can reveal ependymitis (a linear problem of the lining of the ventricles) in serious cases of inflammatory dissemination into the ventricular system [35]. In cases of spinal subarachnoid involvement (particularly chronic cases), spinal imaging in TBM may disclose the presence of spinal arachnoiditis or tuberculous radiculomyelitis [36]. More modern MR imaging, including MR angiography, can show the presence of vessel narrowing or occlusion due to vasculitis, and further suggestive evidence may be obtained using perfusion MRI or MR spectroscopy, which are not standard practice [31, 34].

Neuroimaging is useful not only in assisting with diagnosis but also in aiding management (e.g., the presence of hydrocephalus or tuberculomas may require brain surgery or steroids). It should be noted that normal imaging does not rule out TBM, particularly in its early stages. However, basal meningeal enhancement and hydrocephalus on MRI in a patient with subacute meningitic disease are excellent indications of TBM rather than other etiologies [37].

2.3 Laboratory and CSF diagnostic biomarkers

CSF analysis: Tuberculous meningitis is associated with a classic lymphocytic pleocytosis in the cerebrospinal fluid, raised protein, and low glucose. A typical CSF is: white cell count 100 to 500 cells/microliter (usually more than 80% lymphocytes), protein 100 to 500 mg/dL, and glucose less than 45 mg/dL (usually less than half the glucose in parallel blood circulation) [38]. Nonetheless, none of these findings is unique to TBM and may be shared with fungal or neoplastic meningitis. The CSF can be abnormal in very young patients with TBM or in HIV co-infected patients (e.g., neutrophil-predominant, normal glucose) [39]. Therefore, despite the support of the diagnosis by CSF chemistry and cytology, the ultimate determination of *M. tuberculosis* or its elements is necessary. The main diagnostic tests and their performance are highlighted in **Table 2**.

Test/method	Typical sensitivity	Specificity	Notes and utility
CSF AFB smear	<20% (often ~10%) [43]	~99% (high)	Rapid (minutes), but very low yield in TBM due to paucibacillary CSF. Multiple large-volume taps modestly increase yield.
Mycobacterial culture (CSF)	~30% (range 4–60%) [43]	~100%	Gold standard for confirmation and drug-susceptibility testing; slow (2–6 weeks) and low sensitivity, even with centrifugation.
Xpert MTB/RIF (PCR)	~60–70% vs. culture (up to 80% with large volume) [44]	>95%	Rapid (~2 hours). Detects <i>Mycobacterium tuberculosis</i> DNA and rifampin resistance. WHO-recommended first-line test for TBM (especially in HIV).
Xpert MTB/RIF Ultra	~70–90% [45]	>90%	Improved sensitivity due to a lower detection threshold. Particularly useful in paucibacillary cases (children, early TBM).
TB-LAMP (Loop AMP)	~76–88% [49]	~99%	Isothermal NAAT, featuring faster and simpler equipment than PCR, could be deployed in resource-limited laboratories.
CSF adenosine deaminase (ADA)	~89% [52]	~91%	An ADA level > ~10 U/L in CSF is suggestive of TBM. It is a useful adjunct in smear-negative cases, but beware of overlap with other meningitides.
CSF Xpert Ultra LFA (LAM)	~50–70% (in HIV*) [48]	~95% (in HIV*)	Lateral flow assay for mycobacterial LAM antigen (usually performed on urine; CSF use is off-label) is helpful in HIV co-infected patients with disseminated TB.
CSF T-SPOT.TB (IGRA)	~70–80% [53]	~85–90%	Measures T-cell IFN- γ release in response to TB antigens in CSF. Requires a large sample volume; not routinely available.
mNGS (metagenomic sequencing)	~60–70% [57]	~98%	Unbiased sequencing that detects <i>M. tuberculosis</i> DNA (and others) is valuable in culture-negative cases; however, it requires high cost and technical expertise.

AFB – acid-fast bacilli; NAAT – nucleic acid amplification test; LAM – lipoarabinomannan; IGRA – interferon-gamma release assay; mNGS – metagenomic next-generation sequencing.

Table 2.
Diagnostic tests for tuberculous meningitis – performance characteristics.

Microscopy and culture: In TBM, microscopy and culture have a low yield because of the low bacillary load. A positive CSF acid-fast bacilli (AFB) smear occurs in less than 20% of cases (usually less than 10% in most series) [40]. Smear sensitivity (large-volume lumbar puncture with centrifugation) can be modestly improved by concentration techniques, achieving a sensitivity for detecting TBM of about 30–40%, although a negative smear is still expected in TBM. Mycobacterial culture (on Löwenstein-Jensen or liquid media) is the gold standard for diagnosis and drug susceptibility testing, but it is agonizingly slow (up to 4–6 weeks) and insensitive in TBM. Even with culture in liquid media (e.g., BACTEC MGIT 960), CSF cultures become positive in only 30–60% of TBM cases [41]. Therefore, a negative culture does not exclude the disease, and clinicians are frequently forced to initiate treatment on an empirical basis.

Nucleic acid amplification tests: Within the last few years, rapid molecular tests have revolutionized the diagnosis of TBM. The Xpert MTB/RIF assay (GeneXpert) is a cartridge-form PCR capable of identifying *M. tuberculosis* and rifampicin resistance in 2 hours [42]. In TBM, Xpert has moderate sensitivity (~63% compared to culture) but much higher sensitivity if larger CSF volumes (≥ 6 mL) are used or if centrifuged deposits are tested (up to ~80% sensitivity) [43]. Its specificity exceeds 95% [44]. The newer Xpert MTB/RIF Ultra has a lower detection limit (identifies bacilli some 10-fold less frequently) and is more sensitive, in the 70–90% range, in TBM [45, 46]. A multicenter study reported Ultra detecting ~90% of culture-positive TBM cases [47]. In line with its velocity and sensitivity, WHO currently suggests Xpert Ultra as the initial diagnostic test in suspected TB meningitis [48]. A moderately accurate (approximately 76–88% sensitivity) alternative PCR technique is loop-mediated isothermal amplification (TB-LAMP), which can be of value in low-resource environments [49]. Finally, NAATs can significantly assist in early diagnosis, but a negative result does not rule out TBM (empirical treatment should be continued when the clinical suspicion is high) [50]. Rifampin resistance can be identified quickly by molecular tests, which is extremely important to manage therapy at the initial stage of the course [51].

CSF biochemical markers: When microbiologic tests are not positive, several CSF biomarkers may be used to help make a diagnosis of TBM. TBM is associated with an increase in the levels of adenosine deaminase (ADA) in CSF, which is a result of T-lymphocyte activation; ADA above 10 U/L is a suggestive level of TBM, with a reported sensitivity of about 89% and specificity of about 91% [52]. ADA, however, may also be slightly raised in bacterial or fungal meningitis; hence, it is an adjunct marker. Interferon- γ release assays (IGRAs) on CSF (e.g., TB Gold in-tube or T-SPOT.TB applied to CSF cells) have shown ~70–80% sensitivity for TBM, but they require large CSF volumes and are not widely available [53, 54]. Lipoarabinomannan (LAM) is an immunoassay-detectable mycobacterial cell wall antigen; LAM CSF in TBM has moderate sensitivity (50–70%) but may prove more valuable in HIV-infected patients [55]. The lateral-flow urine LAM test is WHO-approved to diagnose TB in HIV-infected patients but has low sensitivity to detect disseminated TB by urine in the absence of co-infection with HIV [56].

New high-throughput technologies should enhance TBM diagnosis. Next-Generation Sequencing (mNGS) of CSF is capable of unbiasedly identifying *M. tuberculosis* DNA and other pathogens. Research indicates that mNGS is able to detect TB where other tests have failed to detect it; the sensitivity of mNGS is in the range of 60–70%, and the specificity is very high [57]. Currently, mNGS is restricted to research environments because of cost and the necessary knowledge, but it has the potential to resolve indeterminate cases [58]. Biomarkers in CSF (which include particular mRNA or protein signatures of TBM) are being studied using transcriptomic and proteomic techniques [59]. Some proposed markers include elevated CSF cytokine profiles (IL-6, IFN- γ , etc.) and unique protein panels (e.g., fragments of neural proteins reflecting injury) [60–62]. Although none of them are currently in everyday use, these markers may become useful as an additive to the diagnostic arsenal in the future to differentiate between TBM and other meningitides. To determine proteins or mRNAs unique to TBM patients versus those with other forms of meningitis, researchers are examining the total protein and gene expression profile in the CSF. Research has found patterns of various differentially expressed CSF-based proteins that are linked to TBM, such as

anti-thrombin III, haptoglobin, APOAI, APOB, APOE, S100A8, and transthyretin [59, 63]. Interest also exists in applying the tools of transcriptomics and proteomics to comprehend the role of mycobacterial genes and proteins in the pathogenesis of TBM. It is possible that these biomarkers would result in a more precise and expedited identification of TBM, particularly distinguishing between the disease and other types of meningitis. Through host response analysis and bacterial factors, researchers are able to gain more insight into the disease by understanding the development of TBM. The discovery of particular molecular signatures can contribute to the development of new vaccines, new antibiotics, and host-directed treatments. Initial mass spectrometric analyses have been able to detect possible TBM-specific protein signatures in the CSF [64]. The next critical step is to confirm the existence of these biomarkers in separate groups of patients to ascertain the reproducibility and accuracy of the findings before clinical application. These forms of comprehensive analyses have become feasible with advances in proteomics and transcriptomics, overcoming technological barriers from the past to detect low-concentration biomarkers.

Integration of diagnostic methods enhances output. Practically, an urgent contrast-enhanced neuroimaging examination and lumbar puncture (barring any contraindication indicated by increased intracranial pressure) should be performed on any suspected patient of TBM. Preferably, a minimum of 5–10 mL of CSF is collected to carry out a series of tests: cell count/chemistry, AFB smear, cultures, and an Xpert Ultra PCR [65]. When initial tests are negative but there is a high level of suspicion, repeat lumbar puncture to culture or refer to send CSF for more advanced tests [66] (where available), such as mNGS. Early diagnosis is also essential because the delay in treatment is one of the major contributors to the high morbidity of TBM.

3. Treatment and management

Tuberculous meningitis requires an aggressive, multi-pronged treatment approach to eradicate the infection and manage CNS complications. The cornerstone is the prompt initiation of anti-tuberculosis therapy, combined with adjunctive corticosteroids and supportive care. Treatment is prolonged and often needs to be tailored to drug susceptibility results, especially in regions with drug-resistant TB.

3.1 Antituberculous therapy: Standard regimen

Tuberculous meningitis standard chemotherapy is similar to that of pulmonary TB but with a longer duration. Existing guidelines (e.g., WHO) suggest a minimum duration of therapy for drug-susceptible TBM of 9–12 months [67]. The standard regimen is defined by 2 months of intensive therapy with four first-line drugs, that is, isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB), followed by a prolonged period of INH and RIF [68]. Streptomycin may be used instead of ethambutol in the intensive phase of some programs (particularly in young children or in cases of suspected drug resistance), although EMB is likely to be preferred because it is easier to administer and equally effective [68]. This longer duration (compared to 6 months for pulmonary TB) is necessary to guarantee sterilization of the CNS, as this is not easily accomplished with large drug levels in

the CSF and because relapse in the brain is a significant concern [69]. Of all first-line medications, INH and RIF play the most important roles in TBM because of their superior CSF penetration and bactericidal action [70]. INH crosses the blood–brain barrier quite well, even without inflammation. Rifampin also achieves therapeutic CSF concentrations, though inflammation increases its absorption; in particular, experimental results reveal that the prognosis in TBM is closely correlated to rifampin susceptibility – rifampin-resistant TBM has a very poor prognosis [71]. Pyrazinamide is active in the acidic environment of the CSF and is moderately penetrative. Ethambutol is not predictably penetrative of the CSF and is mainly used to prevent the emergence of resistance; instead, some authorities replace ethambutol with moxifloxacin in TBM because moxifloxacin achieves better CNS levels [72, 73]. In fact, some experts recommend moxifloxacin as an adjunct to the first-line TBM treatment, and some studies have shown its efficacy in the treatment of TBM [74]. The optimum dosage of drugs used in TBM is an active area of research. To address the problem of penetration, high-dose rifampicin (up to 30 mg/kg IV or oral, compared with the standard of around 10 mg/kg) has been studied, with some reports of improved survival in advanced TBM [75]. Intensified regimens (e.g., the INTENSE-TBM study) are undergoing trials, which involve high-dose RIF and other agents such as linezolid in the intensive stage [76]. Until results are definitive, standard dosing with careful adherence remains the practice, but clinicians should be aware of these emerging data. During therapy, drug interactions and comorbidities should be addressed. The timing of antiretroviral therapy (ART) initiation in co-infected patients is challenging: while prompt ART may cause immune reconstitution inflammatory syndrome (IRIS) in the brain, delayed ART may result in uncontrolled HIV [77]. Recent recommendations do not rule out the possibility of initiating ART during 2–8 weeks of TBM treatment, and close observation is advised [78]. TBM-IRIS will develop in approximately 10% of HIV-positive patients and may lead to paradoxical clinical deterioration (new or progressive tuberculomas, hydrocephalus) [79]. It is treated with corticosteroids and, in more severe cases, with anti-TNF therapy [80].

3.2 Adjunctive corticosteroids

The use of adjunctive corticosteroid treatment is a proven, highly supported practice in TBM management [81]. The rationale is that dexamethasone or prednisone would partly suppress the acute inflammatory process in the subarachnoid space, which would help minimize cerebral edema, intracranial pressure, and inflammatory tissue damage [82]. In a landmark randomized trial and follow-up meta-analyses, the addition of corticosteroids decreased mortality by approximately 30% in HIV-negative TBM patients [83]. Based on this, the WHO and others advise initiating corticosteroids with anti-TB medications in all TBM patients (except in cases of contraindications) [84]. The common course of action is a course of several weeks of dexamethasone IV with tapering over 6–8 weeks [85]. A sample dosing regimen in adults is 0.4 mg/kg/day IV dexamethasone during the first week, followed by gradual tapering of the drug to oral intake over a period of 6 weeks. A similar regimen of prednisone (e.g., 2 mg/kg/day) is frequently used in children [86, 87].

Steroids are demonstrated to have a significant beneficial effect on acute complications, such as infarcts and hydrocephalus, and on short-term neurological

outcomes [85, 88]. However, their impact on long-term disability is less clear, and in HIV-positive patients, a large trial (Donovan et al.) found no clear survival benefit of dexamethasone [86]. Nonetheless, the majority of specialists continue to recommend steroid use despite HIV co-infection (with close supervision) due to possible advantages in the context of CNS inflammation subsidence [88]. The steroid immunosuppression effect should be weighed against the risk of infection, and therefore, opportunistic infection prevention and close attention to other infections (fungal and so on) is justified in the face of steroid therapy.

3.3 Other adjunct and supportive therapies

Management of Raised Intracranial Pressure: A significant number of patients with TBM develop raised intracranial pressure (ICP) due to either the presence of hydrocephalus or cerebral edema. Vigilant treatment is essential to avoid herniation and additional ischemia. Treatment of persistent or high-grade hydrocephalus includes repeated therapeutic lumbar punctures (to relieve the pressure), osmotic therapy (mannitol), and permanent CSF drainage by an external ventricular drain or ventriculoperitoneal (VP) shunt [89]. Neurosurgical consultation is suggested in the early stages when imaging reveals the presence of hydrocephalus; a VP shunt may be life-saving and may significantly reduce headaches and sensorium in affected patients.

Anticonvulsants: Seizures are a major cause of TBM, occurring either because of cortical tuberculomas, infarcts, or acute inflammation. Anti-epileptic drugs to prevent recurrent seizures should be initiated in patients with seizures or severe encephalopathy [90]. The importance of seizure control lies in both patient safety and the fact that seizures may cause an increase in ICP and secondary brain injury.

Aspirin: There is now some evidence on the application of antiplatelet therapy to vascular complications of TBM. A randomized trial in Vietnam established that aspirin (at 1,000 mg/day) in combination with standard therapy was not associated with a decrease in overall mortality, though it significantly decreased the incidence of stroke and new infarcts on MRI [91, 92]. It is believed that the effect of aspirin is due to the inhibition of thrombosis in inflamed arteries in the brain. There is ongoing investigation into the role of aspirin (in various doses) in TBM, and some specialists already use low-dose aspirin (300–500 mg daily) in TBM patients without contraindications, particularly when vasculitic infarcts are suspected [93].

Immunomodulators: Since steroids alone are only partially effective in modulating the immune response, other immunotherapies are under investigation in severe TBM, including steroid-refractory situations [94]. One target is TNF- α , a cytokine heavily involved in TB inflammation [93]. Thalidomide, a TNF- α inhibitor, has been demonstrated to decrease brain inflammation in pediatric TBM in a small series; however, due to its toxicity (peripheral neuropathy), it is not widely used [95, 96]. Tuberculous meningitis, in desperate cases of severe paradoxical reaction or vasculitis, has also been treated with infliximab and adalimumab (anti-TNF monoclonal antibodies); case reports show some success in lowering inflammation with steroids combined with one of these agents [97, 98]. Anti-TNF therapy does, however, involve a risk of uncontrolled infection and is not routine. Immunosuppressants are another option: small case series have experimented with cyclophosphamide or azathioprine in TBM IRIS or refractory inflammation [99, 100]. There is extremely little evidence, and this treatment

should be used only in a specialized facility. Finally, neuroprotective activity has been demonstrated in statins (with their anti-inflammatory and adjunctive host-directed effects) and melatonin (a free-radical scavenger) in experimental models and initial clinical trials, but additional information is required before they can be used routinely [101, 102].

Nutritional and supportive care: Tuberculous meningitis requires proper nutrition and rehabilitation. A significant portion of TBM patients, particularly children, are malnourished at baseline, which is related to poor outcomes [103]. Inpatient care and follow-up should include nutritional support. Long-term function is highly enhanced by neurological rehabilitation (physiotherapy to address motor deficits, and occupational and speech therapy to address mental and speech deficits, respectively) in patients as they regain normal functioning [104]. Involved cranial neuropathies (e.g., optic nerve) may need special treatment (special visual aids or hearing rehabilitation in cases of VIII nerve damage). Patients and families may also require psychological support, as the outcome of TBM can result in life-changing neurological impairments.

3.4 Treatment of drug-resistant TBM

The development of drug-resistant tuberculosis (DR-TB) is a serious problem in the management of TBM [105]. Multidrug-resistant TBM (resistant to at least INH and RIF) is, fortunately, rare, but when it does occur, it is associated with very high mortality, with reported fatality rates of 50–100% in some series [106]. Monoresistance to rifampicin or isoniazid can also have a negative impact [107]. Thus, culture and drug susceptibility outcomes should be obtained by any available means, and in cases where drug resistance is found (or there is high epidemiological suspicion thereof), the regimen should be changed immediately. No standard regimen exists for MDR-TBM; however, treatment typically includes at least 5–6 drugs, including second-line agents, administered over 12–18 months or longer [108]. A standard MDR-TBM treatment regimen may include: a fluoroquinolone (high-dose levofloxacin or moxifloxacin), an aminoglycoside (e.g., amikacin, which has some penetration into the CSF, or streptomycin, which can be used as an alternative), ethionamide or prothionamide, cycloserine, and linezolid, along with other first-line agents that may still be effective [109–111]. Anti-TB drugs have also proven effective in TBM: bedaquiline, an anti-MDR-TB bactericidal agent, crosses the blood–brain barrier and has been used in MDR-TBM [112]. Linezolid achieves high CSF levels and has good sterilizing activity; it is often included in MDR-TBM regimens despite long-term toxicity concerns (e.g., peripheral neuropathy, bone marrow suppression) [113, 114]. A recent Phase 2 trial (LASER-TBM) examined adding linezolid to high-dose RIF regimens. While it did not show a mortality benefit and highlighted linezolid's side effects, linezolid remains a key drug for resistant TBM when the benefits outweigh the risks [115]. Meropenem with clavulanate has activity against TB and has been used in XDR-TB cases. Meropenem penetrates the meninges when inflamed. Although there is limited experience, it is an option for fluoroquinolone-resistant TBM when combined with other drugs [115]. Treatment of drug-resistant TBM should involve expert advice (e.g., TB specialists) and customized treatment based on susceptibility outcomes. Even more critical in DR-TBM is the use of adjunctive therapies (e.g., steroids, surgery) to allow time for second-line drugs to take effect. Sadly, XDR-TBM (extensively drug-resistant

TBM) is frequently fatal despite the best efforts. Newer agents such as pretomanid or delamanid do not have much data in TBM but could be used on a compassionate basis in XDR cases. Directly observed therapy and intensive supportive care should be applied to all cases of DR-TBM [116, 117]. Reducing delays in diagnosis and applying molecular tests (such as Xpert to investigate rifampin resistance) may aid in initiating the correct therapy as early as possible, which is the single hope for a cure in MDR-TBM [118].

There have been several landmark clinical trials undertaken in the last two years (2022–2025):

- **ZeNiX (2022):** BPaL regimen (bedaquiline, pretomanid, linezolid) optimized by modulating linezolid exposure. A 600-mg course of linezolid after 6 months had 84–91% cure rates, with lower neuropathy and myelosuppression [119].
- **TB-PRACTECAL (2022–2024):** Demonstrated that a 6-month BPaLM regimen (BPaL plus moxifloxacin) achieved ~89% favorable outcomes, far superior to the ~52% success rate of the standard 9–20 month therapy [120]. This led the WHO (2022) to recommend BPaL/BPaLM as the preferred regimen for most MDR/RR-TB patients [121, 122].
- **endTB (2025):** Assessed five combinations of all-oral medications (9 months) combining bedaquiline, delamanid, linezolid, and clofazimine. Three regimens showed 85–90% treatment success, noninferior to standard care. These offer alternative short-course treatment, enhancing flexibility for tailored treatment [123].
- **endTB-Q (2025):** Focused on pre-XDR-TB (MDR-TB with fluoroquinolone resistance). A 69 month regimen of bedaquiline, delamanid, linezolid, and clofazimine (BDLC) was 87% successful, almost the same as the 24-month standard, with reduced adverse events [124].

Taken together, these trials determined that MDR-TB is now essentially treatable in 6–9 months with oral regimens, without injectables, and with a significant increase in adherence, tolerability, and cure rates [125].

3.5 Emerging and adjunctive therapies

In addition to antibiotic courses, a number of host-directed therapies (HDTs) and immunomodulatory approaches are under investigation to induce better bacterial clearance and reduce lung destruction.

- Metformin and statins have demonstrated potential to promote better immune responses and decrease inflammatory processes related to TB [101, 102].
- Immune enhancers are under investigation, using vitamin D supplementation and interferon-gamma therapy [126].
- There is some preliminary evidence of therapeutic vaccines in the form of *Mycobacterium vaccae* (Vaccae™), RUTI, and MIP (*Mycobacterium indicus*

pranii), which have been shown to provide benefits as adjuncts, such as greater sputum conversion and reduced relapse rates, in some MDR-TB cohorts [127].

3.5.1 Innovations in drug delivery and diagnostics

Long-acting injectables (e.g., bedaquiline nanoformulations) and inhaled nanoparticle systems are being preclinically tested to ensure sustained drug exposure and lung targeting [105].

- New diagnostic technologies, such as Xpert MTB/XDR and whole-genome sequencing (WGS), can now be used to rapidly profile resistance and select individualized regimens.
- Such tools facilitate the early introduction of optimized regimens, such as BPaL/BPaLM, and minimize delays and treatment failures.

MDR-TB treatment has taken a new turn with shorter, effective, and easier treatment regimens. Regimens like BPaL and BPaLM now achieve cure rates in the 90% range and are safer and easier to tolerate. The combination of host-directed treatment, novel drug delivery, and new diagnostics will further improve treatment outcomes [128]. To ensure the consolidation of these gains and the success of global TB elimination activities, sustained drug-resistance surveillance, equitable access to new drugs, and further clinical research are critical.

4. Pediatric versus adult differences in TBM

Although the pathophysiology of TB meningitis in children and adults is similar, the epidemiology, presentation, and outcomes vary significantly between children and adults [129]. In the past, however, children and adults have been approached with equal methods, and studies tend to use all ages together, which may not be able to capture age-related differences [130].

Epidemiology and risk: Young children (especially below the age of 5 years) have the greatest risk of TBM in relation to primary TB infection due to an incomplete immune response [131]. TBM among children is usually secondary to an acute primary infection that spreads (typically within 3–6 months of the incident pulmonary TB). By contrast, adult TBM is more commonly an example of reactivation of latent TB or progression of untreated pulmonary TB; it occurs more frequently in adults with some susceptibility factors, especially HIV/AIDS, which significantly increases the risk of TBM, but also diabetes, alcoholism, or old age (immunosenescence) [132]. The highest incidence of TBM occurs in the early childhood stage, followed by older adults (e.g., >60 years) [132].

Clinical presentation: A prodrome of fever and headache is common in both children and adults, although the former may have a more nonspecific initial presentation (irritability, poor feeding, vomiting) that can be confused with other common viral infections [18, 21, 133]. Young children are unable to complain of headache or stiffness in the neck, and these symptoms usually become noticeable later in the disease process. Accordingly, children are more often found at an advanced stage with lethargy or coma (Stage III) [134]. Among children, vomiting

and seizures are especially frequent early symptoms [135]. However, adults can also present with classic signs of meningitis (severe headache, photophobia, neck stiffness) and are more likely to have confusion or focal motor activity at presentation [136]. Palsies of the cranial nerves (e.g., sixth nerve leading to diplopia) are present in both but are commonly observed in older children and in adults who can cooperate during cranial nerve examination. Another distinction: a history of known TB contact or TB (e.g., pulmonary TB symptoms, abnormal chest X-ray) is often elicited in children, as in pediatric TBM the disease often occurs after recent household exposure [137]. Adults may have a history of TB more often or have other comorbidities.

Diagnostic issues: TBM is hard to diagnose in young children. Smear and even Xpert tests are less sensitive in children with lower bacillary load in CSF (paucibacillary disease) [138–140]. In addition, it may be hard to obtain sufficient volumes of CSF in infants and toddlers, which may limit diagnostic tests. In infants, clinical evidence of irritation of the meninges (stiffness of the neck, Kernig sign) is less reliable. Consequently, clinicians are frequently forced to use indirect evidence (e.g., positive TB skin test or IGRA, suggestive chest X-ray, history of exposure) along with CSF results in order to diagnose TBM in pediatrics [141]. In adults, diagnostic lumbar puncture is usually easier, and larger volumes can be tested, with Xpert Ultra showing high yield. However, in adults, the differential diagnosis is broader (e.g., chronic meningitis due to fungi, carcinomatous meningitis, etc.), and it may be difficult to rule out other etiologies [142]. Particularly, HIV-infected adults can become infected with multiple pathogens (TBM can be detected alongside or mimicked by cryptococcal meningitis, etc.). Therefore, diagnostic algorithms should prioritize identifying co-infections in adults, while in children the primary consideration should be initiating TB treatment without microbiologic evidence, provided the clinical picture fits.

Neuroimaging: The typical MRI findings (basal enhancement, hydrocephalus, infarcts) are present in both groups, but hydrocephalus is particularly noticeable in children (70–80% of TBM patients in children develop hydrocephalus, frequently necessitating shunting) [145, 146]. In adults, the incidence of significant hydrocephalus is less (~20–50%) [143]. The distribution of tuberculomas on radiography also may vary: in children, miliary brain tubercles may occur in response to miliary TB, and in adults (particularly immunocompetent), fewer tuberculomas may be evident at presentation but may develop as a paradoxical response to treatment [144, 145].

Therapeutic differences: There are no differences in the necessary drugs; only the doses vary. Children more actively break down TB drugs and often have to take in more mg/kg. As an illustration, WHO recommends pediatric doses of rifampicin at approximately 20–30 mg/kg (as opposed to 10 mg/kg in adults) and isoniazid at approximately 10–20 mg/kg (as opposed to 5 mg/kg in adults) [146]. These weight-adjusted higher doses take into account that many drugs vary in their pharmacokinetics (children have a greater volume of distribution and quicker clearance) [147, 148]. TBM cases in children also consistently undergo steroid therapy, as in adults, but the exact tapering may be modified according to weight [149]. Managing raised ICP is a greater focus in children (with earlier use of shunts), whereas in adults, careful monitoring for drug hepatotoxicity or interactions (e.g., with antiretrovirals) is a bigger issue [150]. Early physical therapy will help both

children and adults, although children will also require developmental tests and support because of the effects on the developing brain [151].

Outcomes: Children, paradoxically, are equally or even more likely to survive TBM, but with more neurological disability. Meta-analyses show that the all-cause mortality of pediatric TBM is approximately 19% (range 12–58%), comparable to adults at approximately 23% (range 2–36%) [152]. Nevertheless, children have higher rates of serious neurologic sequelae among survivors (more than half of child survivors have long-term neurological impairments, such as cognitive impairment, motor deficits, and vision/hearing loss, etc.) [153]. This may be due to the fact that the infection and inflammation destroy the developing brain at key stages, resulting in permanent developmental problems [154]. Adults are also capable of having sequelae (around a third of adult survivors have cognitive or functional impairments); however, adults may have subtle deficits (e.g., memory or executive function) that do not get reported [155, 156]. Extremes in age do not fare as well in both categories: children under the age of 2 years and adults older than 60 have the highest percentage of poor outcomes [157].

In summary, pediatric TBM tends to be an acute, fulminant disease occurring soon after infection, with a high risk of hydrocephalus and long-term developmental consequences. Adult TBM often involves reactivation, intersects with other health issues like HIV, and can present more heterogeneously. These differences highlight the need for age-tailored approaches – for instance, aggressive neurosurgical management of hydrocephalus in children versus vigilant management of comorbid conditions in adults. Importantly, both groups require early therapy and supportive care; delays in diagnosis are devastating regardless of age.

5. Evolving guidelines and best practices

Guidelines and best practices on TBM have undergone immense changes in recent years, in line with new research findings. Some international professional organizations have tried to develop standard care for TBM in adults and children, and organizations such as the WHO has revised TB treatment guidelines to include TBM-specific guidelines. The evolution of TBM management can be pointed out as follows:

- **Diagnostic strategies:** Rapid molecular diagnostics are now at the center stage. WHO guidance (2017/2019) endorsed GeneXpert as the initial test for suspected TBM, and with the improved Xpert Ultra, this is reinforced in current practice [139]. Clinicians are advised to obtain large-volume CSF and use NAATs early, rather than relying on culture, which is too slow for initial decision-making [158]. There is also an increasing focus on the importance of early neuroimaging; any patient with unexplained subacute meningitis should now receive an MRI (or CT where MRI is not available) to seek clues of TBM or other diagnoses [158, 159]. Emerging imaging methods (such as MRI perfusion or vessel wall imaging) are under investigation in order to further identify vascular alterations due to TB but are not included in current guidelines [32, 160]. It is suggested that the incorporation of clinical scoring systems (e.g., Marais diagnostic score of TBM) with contemporary tests would enhance diagnostic confidence in resource-limited settings [161].

- **Therapeutic regimens:** Current recommendations (e.g., the 2022 WHO consolidated TB guidelines) still support a long course of TBM, usually 12 months of treatment for drug-sensitive cases [66]. Nevertheless, shorter regimens are actively being studied. Trials such as SHINE (in children with minimal TB) and TBM-specific trials (such as studies of the INSTRuCT consortium) are investigating whether 6- or 9-month regimens may be adequate in some groups of TBM [162, 163]. Until then, the advice remains conservative on TBM duration due to the stakes involved in relapse in the CNS. Motion on the intensive phase side: some authorities recommend the regular use of a fluoroquinolone (moxifloxacin) during the original TBM regimen to improve bactericidal effectiveness in the brain [164]. The current trial INTENSE-TBM is comparing conventional therapy with more intensive therapy using high-dose rifampicin, moxifloxacin, and linezolid (with adjunctive aspirin) [74]. Findings from such research might guide future practices; for instance, if high-dose rifampicin proves to have a substantial positive effect, guidelines could change their suggested dose for TBM. Likewise, in severe cases, linezolid or other new drugs that are shown to be useful may be employed [165]. Guidelines on drug-resistant TBM are also evolving: a recent consensus emphasized the use of at least five effective drugs in MDR-TBM, including newer drugs and longer durations (12–18 months), although the quality of evidence was low [166]. Individualized MDR-TBM regimens are encouraged, and clinicians are advised to consult experts or WHO DR-TB guidelines.
- **Adjunctive therapy:** There is consensus on corticosteroids in the management of TBM. In TBM specifically, the 2018 WHO TB guidelines state that an initial adjunctive corticosteroid (dexamethasone or prednisolone), tapered over 6–8 weeks, should be used [167]. This has become the standard of care all over the world. In the case of aspirin, this is not formally recommended by WHO guidelines, although some national guidelines (such as that of Vietnam) have introduced low-dose aspirin as an adjunct in TBM in light of the evidence of stroke reduction [91]. It is only natural that once the current trials prove beneficial, aspirin can be included in the standard recommendations on TBM (at least in adults). Close, supportive care and monitoring are now regarded as a priority in best practice: guidelines stress the importance of serial clinical and radiologic evaluations during treatment, addressing complications such as hyponatremia (frequent in TBM because of SIADH or cerebral salt wasting) and the importance of rehabilitation services early [168].
- **HIV co-management:** Any section in best practice guidelines (e.g., ATS/CDC/IDSA TB guidelines) covering the management of TBM in the context of HIV. It is agreed that TB treatment should be initiated, and after a period of 2–8 weeks, ART should be initiated with close observation of IRIS [169]. In the case of TBM-IRIS, temporary steroid doses can be increased. These guidelines also advise that co-trimoxazole prophylaxis be regularly administered to HIV/TBM patients to prevent other infections during immune reconstitution.
- **Surgery and critical care:** The team involved in modern TBM management usually includes a neurosurgeon and an intensivist. Any patient with TBM who has hydrocephalus or a reduced level of consciousness is recommended to

undergo early neurosurgical evaluation. In the case of a VP shunt, it is better to place it before the damage becomes irreversible [170]. External ventricular drains are increasingly used to control elevated ICP in ICU settings, and ICP is monitored (although this is resource-dependent) in severe cases, similar to cases of traumatic brain injury. These measures are included in the overall care guidelines of specialized centers [171].

- **Follow-up and outcome measurement:** Understanding the long-term effect, today the guidelines emphasize post-treatment follow-up, such as neurodevelopmental assessment in children and neurocognitive testing in adults, for as long as possible [172]. The standardization of outcome definitions in TBM trials (death, disability scales, cognitive scores) is being pursued to improve comparisons between interventions [173]. This result-oriented focus ensures that, in addition to survival, the quality of survival is also considered during the course of therapy.

Lastly, one of the most important elements of best practice is early suspicion and treatment, so most national TB programs are educating health workers to consider TBM whenever meningitis is not responding promptly to standard antibiotics, particularly in regions with TB or in children. Even before a confirmed diagnosis can be made, rapid referral and empiric treatment can save lives. The consequence of late diagnosis and treatment of TB meningitis, as one review briefly stated, is immediate death or significant permanent neurological disability [174]. This is why changing practice is not only about strengthening the healthcare system (e.g., ensuring access to GeneXpert and MRI, enhanced referral pathways) but also about new drugs. As research continues, with many clinical trials ongoing, there is hope that the next generation of evidence will be used to guide shorter and more effective regimens and adjuncts that can make a significant contribution to the prognosis of TBM in adults and children [175].

6. Conclusions and future directions

For both adults and children, rapid CSF molecular testing (Xpert Ultra), immediate empiric HRZE-based therapy, and adjunctive corticosteroids remain the pillars of care. Pediatric options now include a 6-month intensive HRZE-ethionamide regimen in selected drug-susceptible cases. Research priorities include definitive trials of intensified bactericidal regimens (high-dose rifampicin, linezolid/fluoroquinolones), optimal use of bedaquiline in MDR-TBM, and host-directed strategies (e.g., aspirin) to reduce vasculitic strokes and long-term disability.

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Female Extrapulmonary Tuberculosis: Integrating Advances in Targeted Drug Delivery for Neglected Forms of Tuberculosis

Daniëlle van Staden

Abstract

The cyclical nature of female hormones during the menstrual cycle significantly impacts pharmacological activity. This highlights the need for personalized therapy aimed at developing drug delivery systems for women, whether for systemic or localized treatment. This chapter addresses two challenging conditions: tuberculosis of the female genital tract, which is the second most common manifestation of extrapulmonary tuberculosis, and breast tuberculosis, a rare form of cutaneous tuberculosis. Both present difficulties regarding diagnosis and treatment for female patients. The aim of this work is to bridge the gap in targeted drug delivery advances for anti-tubercular treatments in order to develop tailored therapies for female patients facing under-reported and complex-to-diagnose extrapulmonary tuberculosis conditions.

Keywords: cutaneous tuberculosis, extrapulmonary tuberculosis, genital tuberculosis, infertility, new treatments, tuberculosis, targeted drug delivery, tubercular mastitis, skin

1. Introduction

In 2023, tuberculosis (TB) resulted in 1.25 million fatalities, with 161,000 cases linked to human immunodeficiency virus (HIV) co-infection [1]. This resurgence positions TB as the global leading cause of death from a single infectious agent. According to the literature, TB remains a global health concern as it continues to be the primary cause of death in HIV-infected individuals and a significant contributor to the global antimicrobial resistance burden [1]. Moreover, it is reported that during 2022, approximately 7.5 million cases of TB were diagnosed, indicating that 17% of global TB cases were extrapulmonary compared to the 83% related to pulmonary TB involvement [2]. Extrapulmonary TB (EPTB) refers to TB infection of any organ or body system other than the lungs and mainly involves the lymph nodes ($\pm 39\%$ of cases), pleura ($\pm 23.6\%$ of cases), peritoneum ($\pm 9.9\%$ of cases), and bones ($\pm 7.4\%$ of cases) [3]. EPTB can also be classified as a primary or secondary infection. Primary

infection refers to TB entry from an exogenous source, leading to EPTB affecting a single organ without pulmonary involvement. In contrast, secondary EPTB infection can originate from lymphatic or hematological dissemination from pulmonary TB infection or can be a consequence of dormant TB reactivation [3, 4].

Early and accurate diagnosis of EPTB is imperative to improve therapeutic outcomes and to avoid the development of antimicrobial resistance [5]. However, due to TB's reputation as the "great disease mimicker," other diseases often resemble EPTB by presenting with unusual, non-specific symptoms [6]. This implies that EPTB is often not suspected, leading to delayed diagnosis and disease progression before patients receive anti-tubercular treatment. Additionally, sites affected by EPTB are challenging to access, necessitating invasive procedures and specialized equipment, which are not always readily available at facilities in developing countries, where an increased incidence of EPTB is reported compared to developed countries [2].

Apart from the complexities associated with accurate and timely diagnosis of EPTB manifestation, a growing concern is the global antimicrobial drug resistance burden [5, 7, 8]. Antimicrobial drug resistance is a common phenomenon in anti-tubercular treatment regimens, as first-line oral, multiple-drug combination therapy is also employed to aid in the treatment of EPTB manifestations, despite the localized nature of certain forms of EPTB. The literature reports that the TB directly observed treatment short-course (TB-DOTS) regimen can be effectively used to treat female genital TB (FGTB) [9, 10]. The six-month TB-DOTS refers to two months of isoniazid, rifampicin, pyrazinamide, and ethambutol administration as the initiation treatment phase, followed by four months of isoniazid and rifampicin co-administration as maintenance therapy in an individual who is HIV-negative [11]. The cure rate is reported to be as high as 95% for this short-course treatment in clinical trials, while poor performance is reported in clinical settings due to poor patient adherence, leading to high relapse rates and drug resistance. TB therapy is also complex due to the ability of TB disease to present either as active or latent, with infection resurgence occurring upon immunocompromised situations [12]. Anti-tubercular regimens can be described as torturous due to the extended treatment times required while simultaneously administering multiple drugs known for unpleasant side-effect profiles. This leads to poor patient adherence, which can render resistance to first-line anti-tubercular agents, necessitating the introduction of second-line anti-tubercular agents with even more disruptive side-effect profiles. Moreover, treatment options for both FGTB and tubercular mastitis (neglected forms of EPTB considered in this chapter) should also carefully balance the potential impact on female reproductive health and the health of offspring while optimizing targeted treatment strategies [13].

Numerous innovative strategies have been proposed during decades of anti-tubercular drug delivery research to optimize targeting of this devastating disease [12, 14–17]. Direct targeting of infected macrophages has been proposed as a highly promising approach to alternative therapy optimization by incorporating known drugs into tailored systems, such as targeted nanocarriers. This targeting is achieved by ligand inclusion, mediating specialized engagement with specific macrophage receptors to combat drug resistance and, in some cases, even enable dose reduction with superior therapeutic efficacy to reduce the incidence of side effects [18]. Human studies on nanocarriers specifically for anti-tubercular treatment are currently limited, except for the clinical success of the United States Food and Drug

Administration (FDA)-approved amikacin liposomal inhalable nanocarrier targeting alveolar macrophages, which provides a strong precedent for the future potential of macrophage-targeted nanotherapeutics in human TB treatment [19].

Another targeting approach reported in the literature is delivering therapeutic agents via different administration routes to optimize drug delivery [20]. This is considered a specialized field, as each physiological environment presents its own unique barriers to drug delivery. Most alternative drug delivery routes involve crossing barriers designed to protect the body against the entry of pathogens and xenobiotic substances [21]. However, mediating drug delivery via non-oral routes of administration holds advantages such as superior onset of action at the target site, bypassing the liver's first-pass metabolism, and avoiding gastrointestinal side effects. For example, research reports that parenteral and pulmonary administration of anti-tubercular therapy can render elevated bioavailability when compared to oral anti-tubercular drug administration, thereby revealing that inhaled dosage forms of anti-tubercular drugs can enhance therapeutic efficacy and potentially also improve patient compliance, as side effects and toxicity risks known to accompany systemic therapies can be avoided [12].

Therefore, this chapter presents the development of tailored vaginal and dermal drug delivery vehicles as a potential solution to TB infections of the female genital tract and breasts. Both of these forms of female EPTB are considered under-reported and even neglected due to limited advances in the literature reporting their targeting via localized drug delivery. However, vaginal and dermal drug delivery are vastly expanding pharmaceutical fields, utilizing similar excipients and dosage forms to preserve the vaginal microbiome and avoid dermal irritation upon long-term dosage form application.

2. The female genital tract: A site for EPTB infection

FGTB refers to chronic TB infection affecting structures of the female reproductive system. FGTB is reported as the second most prevalent EPTB manifestation, with estimates suggesting that FGTB accounts for 8 to 10 million cases on a global scale [13]. Of these cases, approximately 5% to 30% comprise isolated primary FGTB infection that does not affect any other organs or bodily systems. The clinical presentation of FGTB involves gynecological abnormalities such as chronic pelvic pain and irregular menstrual cycles. Moreover, it impacts fertility in the short term by recurrently obstructing implantation due to fallopian tube blockage, or endometrial involvement via Asherman's syndrome, which is described as an acquired condition involving intrauterine adhesions that inflict symptoms such as abnormal menstruation, pelvic pain, recurrent miscarriage, infertility, abnormal placentation, as well as attendant psychological distress [22], or by impacting ovarian function [11]. Unfortunately, due to the asymptomatic nature of FGTB, this condition is mostly diagnosed after disease progression has led to infertility caused by irreversible damage to female genital tract structures. In general, the fallopian tubes are the predominant site for FGTB, followed by structures such as the endometrium, ovaries, and cervix [13]. It is important to consider that FGTB can be sexually transmitted, thereby infecting the vulva, cervix, and/or vagina. However, fallopian tube infections almost without exception accompany all forms of FGTB infection. According to the literature, approximately

50% of tubal FGTB infections also spread to the endometrium [23]. Additionally, ovarian involvement is observed as a consequence of tubo-ovarian mass formation or by TB dissemination from the bowel, peritoneum, or hematogenous TB distribution. It is important to consider that any immune suppression drastically increases the risk of FGTB infection. This specifically refers to T-cell-mediated conditions, leaving patients more vulnerable, such as individuals who are receiving steroid therapy, malnourished women, those experiencing high levels of stress, and patients suffering from Hodgkin lymphoma or acquired immunodeficiency syndrome (AIDS) [24].

Limited data exist to confirm the suspicion that FGTB can primarily be sexually transmitted, with the exception of the literature reporting genital TB in an elderly couple, where the male partner presented with testicular TB and the female partner with TB infection of the endometrium [25]. Moreover, case reports reveal the identification of genetically identical *Mycobacterium tuberculosis* (Mtb) isolates via whole genome sequencing following culture analyses of a vaginal test of a spouse after her male partner was diagnosed with epididymal TB [26]. In contrast, another study reported the identification of two different genotypes of Mtb via genome sequencing in one individual suffering from pulmonary TB as well as testicular TB [27], thereby implying that two different modes of TB transmission can be possible due to the different Mtb genotypes affecting different anatomical regions of a single individual.

In terms of treatment guidelines, no official international treatment regimen is recommended for female genital TB infection. According to the literature, similar treatment regimens are followed as prescribed for pulmonary TB [11]. This regimen comprises a six-month or longer treatment period, dependent on therapeutic efficacy and factors such as co-infection with HIV. Interestingly, results obtained from a randomized controlled trial published in 2016 concluded that the cure rate of female genital tract TB was unaffected by extending the six-month DOTS regimen to nine months [11]. However, limited progress has been made to target female genital tract TB at the infection site as an alternative to generalized oral anti-tubercular treatment regimens. This can be attributed to the fact that, in the past, female-centered drug delivery approaches may not have garnered as much scientific attention due to their only applying to females, whereas oral therapies can benefit and treat both male and female patients [28, 29]. Despite this reasoning, a drastic scientific upsurge has been reported in the development of vaginal drug delivery systems to mediate targeted drug delivery, improve patient compliance, reduce the incidence of side effects, and optimize therapeutic outcomes [30–34].

2.1 Female genital tract barriers to drug delivery

The female genital tract refers to a collection of organs that actively participate in reproduction via gamete production, egg fertilization, and the *in utero* development and delivery of offspring [35]. An overview of these structures is presented in **Figure 1**.

As is evident from the intricate and dynamic physiological environment of the female genital tract, there are numerous obstacles to targeted drug delivery, which can alter the metabolism, absorption, distribution, and excretion of vaginally administered drugs. Therefore, it is understandable that drug administration via the female genital tract structures can be challenging in terms of establishing therapeutic efficacy and safety during development to transition to regulatory approval. This can

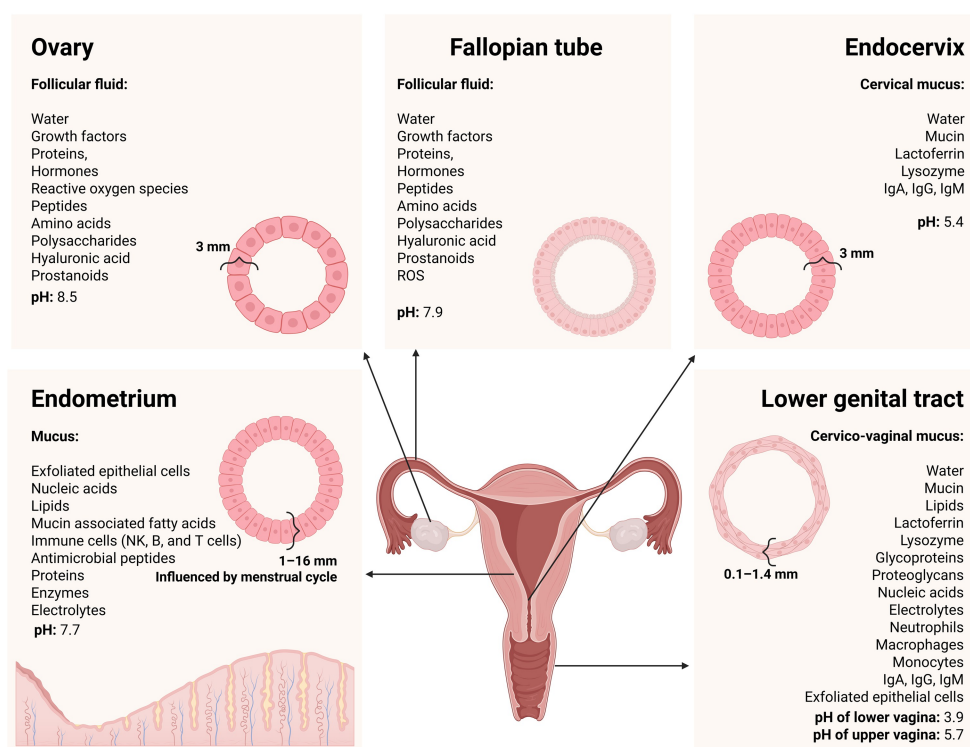


Figure 1.
Overview of the female genital tract organs [29]. Reprinted with permission from the publisher Multidisciplinary Digital Publishing Institute ©2024.

be attributed to the intricate anatomy of different organs forming part of the female reproductive tract, the cyclic hormonal changes influencing endometrial thickness throughout the menstrual cycle, and the inherent self-cleaning capacity of the female reproductive tract [29, 36]. Concerns involving direct drug administration via the female genital tract include cultural acceptability of these dosage forms, impact on the vaginal microbiome that can lead to the development of infections, and potential consequences involving the development of offspring *in utero* [37–39].

Importantly, the fact that TB can impact more than one organ simultaneously while often only manifesting in one form makes it understandable for the literature to report that female TB patients suffer from negative pregnancy outcomes compared to control groups [40]. This can be attributed to a vicious cycle where the TB infection can inflict undetected and irreversible fibrosis on other organs, such as the female reproductive structures, leading to infertility challenges, abnormal menstruation, and poor pregnancy outcomes if patients are able to conceive [40]. The impact of TB on female sex hormones is often overlooked. A study by Garg et al. [40] performed a cross-sectional, non-interventional study evaluating 100 female subjects of childbearing age. Twenty-five subjects were diagnosed with pulmonary TB, 25 were confirmed cases of non-genital EPTB, 25 were known cases of FG TB, and 25 healthy females served as the control group [40]. Their findings revealed that female TB patients present with a significant increase in testosterone compared to the control group. Moreover, TB patients had drastically lower prolactin levels,

whereas follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels were reported as lower in pulmonary TB patients compared to healthy individuals. In contrast, some studies report elevated levels of FSH and LH in TB-infected individuals, while other studies also documented lower LH and FSH levels [41–44]. Therefore, despite inconclusive literature, the disrupted hormone profiles of female TB patients may impact long-term reproductive function and result in altered menstrual cycles [40]. Importantly, despite scientific evidence reporting that hormonal changes during the menstrual cycle impact numerous systems of the body and evidence suggesting that dose adjustments of medication can benefit therapeutic efficacy in women, dosing is still standardized for male and female users [29]. Hence, localized administration of drugs at therapeutic target sites, such as the vagina, can benefit women by avoiding the effect of multiple body systems on drug metabolism, viewing vaginal drug administration as a type of personalized medication. Additionally, personalized medication for vaginal drug delivery systems would be ideal, as the vaginal environment changes with aging, birthing methods, contraceptive use, nutritional intake, and the chronic use of vaginal dosage forms [45–49].

Additional considerations include accurately measuring drug concentrations at the site of therapeutic action, as the complex anatomy and invasiveness of sample collection from these therapeutic sites can hinder confirmation of accurate dosing following localized drug delivery compared to the accuracy of evaluating plasma drug concentrations following oral drug administration [35]. Moreover, the development of *in vitro* and *ex vivo* models that accurately resemble the complexity of the female genital tract is not, at this stage, considered to optimally prioritize time or cost in experimental evaluations [35], thereby contributing to further delays in the optimized development of female genital tract-administered dosage forms.

Despite these challenges, there is a scientific upsurge in the development of dosage forms (i.e., nanocarriers, mucoadhesive vehicles, dosage forms transitioning from solution to gel at 37°C), facilitating drug administration via the female genital tract to achieve both local and systemic drug delivery, as this route presents certain advantages [30–32, 50–52]. These advantages include bypassing the hepatic first-pass metabolism and the degrading conditions of the gastrointestinal tract. Moreover, direct female reproductive tract drug administration can establish targeted drug delivery by limiting off-target effects and ensuring sustained drug release by facilitating prolonged contact time between mucosal surfaces and dosage forms [21, 29]. The female reproductive tract also offers a large surface area and superior blood perfusion to mediate local and even systemic uptake of drugs. According to a recent study, more than 30 products are marketed as reference drug products, including rings, gels, intrauterine devices, and creams, with 27 products marketed for intravaginal drug administration, at least 7 products for intrauterine drug administration, and one product for endocervical drug administration. These products can aid in numerous female reproductive health-related issues, including female cancers, hormone replacement, contraception, avoiding premature birth, inflammation, and infections [35].

For the purposes of this chapter, we will only focus on advances made in localized drug delivery routes such as intrauterine, intraperitoneal, intraovarian, and mainly vaginal administration. Localized drug delivery can support sustained drug release of high drug dosages at a target organ where a pharmacological action is desired while reducing the risk of side effects [36]. For example, a study reported superior

therapeutic efficacy of metformin in a rat model of polycystic ovary syndrome following intraovarian injection of the drug incorporated into nanoparticles [53]. This localized treatment was compared to oral metformin therapy, and results concluded that the localized administration of metformin in a vehicle of high targeting capacity demonstrated enhanced therapeutic efficacy regarding histopathological and immunohistochemical observations, as well as superior hormone amelioration profiles. Intraovarian injection of drugs such as metformin holds vast promise to improve patient adherence and achieve superior treatment outcomes, as significant side effects like pernicious anemia, hepatotoxicity, coagulation alterations, acute pancreatitis, and unpleasant, chronic gastrointestinal discomfort that accompany metformin treatment can be avoided via localized drug administration [29, 53]. Similarly, this localized method of drug administration might also benefit patients suffering from FGTB as an alternative to torturous anti-tubercular treatment regimens demanding long-term drug administration to achieve sufficient bactericidal activity.

However, injections intended for localized drug administration to specific female organs can still seem invasive and traumatic to patients. Moreover, only a skilled professional should attempt administering these injections, which can be a limiting factor in the clinical settings of developing countries where FGTB manifestation is more prevalent. Importantly, the literature reports intrauterine administration of streptomycin as a potential treatment for FGTB. However, this treatment was discontinued due to the occurrence of systemic side-effects and questionable therapeutic effectiveness, since systemic anti-tubercular therapy is considered effective while also having systemic side effects [54]. Therefore, capitalizing on the advances made in vaginal drug administration can be considered more beneficial and clinically sustainable, as patients can administer these dosage forms themselves while benefiting from a reduced risk of side effects due to localized, targeted drug delivery to the female genital tract [29, 31, 36, 55–57].

Vaginal absorption of drugs can be impacted by drug physicochemical properties such as molecular weight, ionization, lipophilicity, and drug surface charge [58]. Generally, lipophilic drugs with low molecular weights demonstrate a superior capacity to cross mucosal barriers to vaginal drug administration [58]. Moreover, during the development of innovative vaginal dosage forms, it is highly important to consider that the pharmacokinetic behavior of drugs can differ in divergent physiological environments. For instance, the solubility of a drug in plasma compared to vaginal mucus may differ [59], or the microbiome of the administration site can also interact with drugs, causing a different treatment response [58]. However, instead of viewing the vaginal microbiome as a therapeutic obstacle, it can also be leveraged as an opportunity to mediate targeted drug delivery via interactions between a drug and the *lactobacillus*-dominated microbiome of the vagina by approaches such as indirect modification of the female host metabolism, thereby creating competing metabolites and superior therapeutic efficacy [58].

Another important barrier to vaginal drug delivery is pathogenic biofilm formation, which may restrict drug delivery. This biofilm formation can occur as an attempt to adapt to changes within the vaginal channel caused by environmental and nutritional factors [58]. Here, it is also essential to consider the impact that excipients can have on the naturally occurring vaginal flora, as physiologically compatible excipients, and ideally excipients that contribute to normal vaginal flora composition, should be used to create drug delivery vehicles [58].

Vaginal drug administration can also facilitate localized targeting of other female genital tract tissues, such as the cervix and uterus [31]. This refers to cumulative drug diffusion to the lining of the endometrium and a phenomenon referred to as the uterine first-pass effect. The uterine first-pass effect provides a pathway for drug transport from the lower genital tract to the upper genital tract following vaginal drug administration, as attributed to counter currents involving the lymphatic, venous, and arterial systems, thereby providing localized access to the uterus [31]. Theoretically, this pathway for drug transport is mediated by the molecular exchange facilitated by the dense venous network found in the upper vagina and its connection to the uterine artery, serving as a gateway for drug transport from vaginal blood vessels to the uterine artery [29]. Therefore, correct placement of vaginal dosage forms is essential to therapeutic efficacy, as drugs could unintentionally be transported to the uterus, rendering sub-therapeutic drug concentrations at target sites such as the cervix. However, this obstacle can be overcome by locally administering higher drug dosages to compensate for the uterine first-pass effect. On the other hand, higher drug dosages can lead to drug accumulation in the uterus, potentially inflicting unexpected toxicity and side effects [34]. Therefore, a good understanding of the uterine first-pass effect (as presented in **Figure 2**) and optimization of vaginal dosage forms targeting specific areas of the female genital tract is imperative.

As indicated by **Figure 2**, the dynamic vaginal environment also provides access to the uterus via different routes of drug absorption. Another route of drug absorption after vaginal drug administration is transport to draining lymph nodes, which can also benefit anti-tubercular drug delivery as TB often disseminates via the lymphatic system [60]. Development of lymphatic targeting following vaginal drug administration is, at this stage, scarcely reported, hence identifying an opportunity for the future of innovative vaginal dosage form development.

3. The breasts: A site for EPTB

Female breasts are described as exocrine glands located in the anterior chest, forming part of the pectoral region. Due to the minimal protection provided by the fascia and skin covering the breasts, it is expected that breast injuries can occur easily despite the under-reporting thereof [61]. Apart from the exocrine function of the breast, the female breast is also an area known for rich blood perfusion, lymphatic drainage, exceptional innervation, and physiology impacted by hormonal changes across the lifespan of a woman, including puberty, pregnancy, lactation, and menopause [62]. Considering the dynamic physiology of breast tissue, it is imperative to note that women of reproductive age are at higher risk of developing tubercular mastitis compared to prepubertal and elderly females [63]. This can be attributed to the increased risk of injury or infection during the hormonal changes and physical use of the breast during lactation and childbearing years. Factors that enhance the risk of developing tubercular mastitis include trauma to the breast, lactation, multiparity, AIDS, and previous incidence of suppurative mastitis [64]. Fortunately, tubercular mastitis accounts for less than 1% of breast-associated diseases in modern medicine. However, TB-endemic countries can report up to a 4% incidence of tubercular mastitis compared to the 1% or less in non-endemic countries [6, 65].

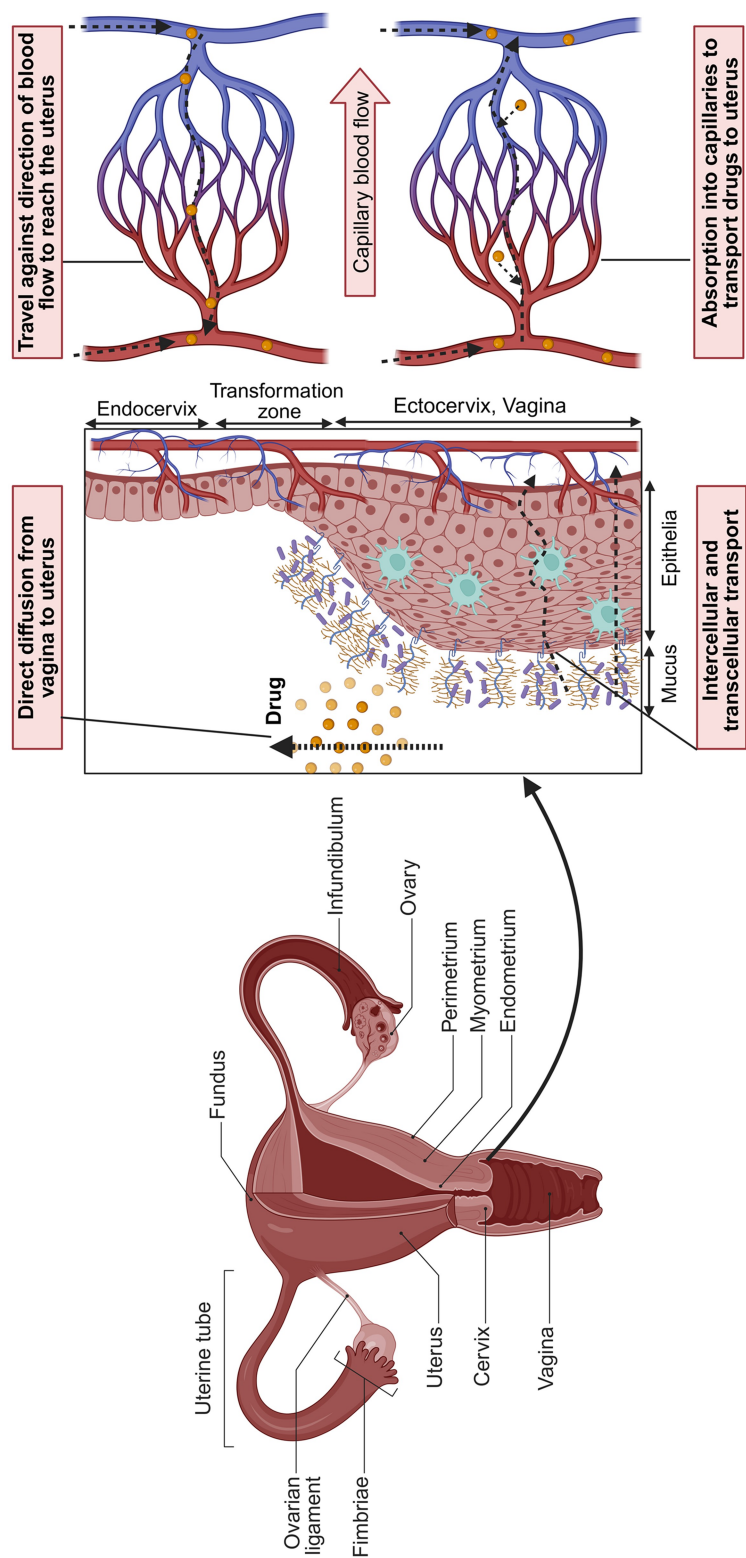


Figure 2.
Schematic illustration of the uterine first-pass effect. Created with BioRender.

3.1 Tubercular mastitis

The lymphatic, hematogenous, and contagious propagation of pulmonary TB infection is considered the most probable source of breast TB infections [6]. The literature supports this claim by stating that up to 75% of tubercular mastitis cases report lymphatic involvement of the axillary and ipsilateral nodes [6, 66, 67]. In contrast, hematogenous spreading is linked to disseminated tubercular mastitis, with this route of disease spreading being less common [6]. Whereas contiguous seeding is linked to TB infection spreading from the pleural space, ribs, or rectus sheath related to an intra-abdominal source of TB infection. On the contrary, tubercular mastitis can also be caused by direct *Bacillus* inoculation via nipple abrasions. However, direct inoculation is less frequently reported compared to lymphatic seeding of the *Bacillus*, indicating the rarity of direct inoculation [6].

Generally, the clinical presentation of tubercular mastitis includes the reporting of a unilateral, poorly-defined hard lump located in the upper outer quadrant or central area of the breast. Tubercular mastitis can easily be confused with breast carcinoma due to its presentation of hard, irregular borders and, sometimes, fixation to muscles, skin, and/or the wall of the chest [6, 66]. Importantly, tubercular mastitis can co-exist with breast carcinoma, which further complicates the correct diagnosis and treatment of tubercular mastitis [6]. Often, patients experience symptoms for a few months before being correctly diagnosed. Therefore, tubercular mastitis lesions can progress to form a tubercular ulcer covering the skin of the breast. Disease progression can also involve tubercular breast abscess formation, accompanied or unaccompanied by discharging sinuses in the skin covering the breast [68].

The work of McKeown et al. [69] reported the classification of five pathological tubercular mastitis varieties. The nodular form is considered the most frequently reported manifestation of tubercular mastitis, characterized by a localized, slow-growing mass presentation that may potentially progress to skin involvement, ulceration, and sinus formation [6]. Disseminated tubercular mastitis is considered the second most prevalent form, involving the full breast due to multiple intercommunicating tubercular masses invading the breast tissue, rendering caseation followed by ulceration, fluid secretion from discharging sinuses, and thickening of the overlying skin due to multiple ulcer formations. Disseminated tubercular mastitis is also associated with enlarged and matted ipsilateral axillary lymph nodes, which can easily be confused with malignancy. Interestingly, this is also the form of EPTB that is most frequently observed in older females [6]. The third variety of tubercular mastitis, the sclerosing form, is described as extensive fibrosis instead of caseation, inflicting an overall hardness of the breast with a retracted nipple appearance. Sclerosing tubercular mastitis can easily be misdiagnosed as carcinoma of the breast and is also more prevalently observed in the involuting breasts of older women [6].

The fourth and fifth forms of tubercular mastitis are rarely reported in recent publications and are only mentioned due to their historical importance in the reporting of cutaneous TB breast infections. The fourth form of tubercular mastitis refers to tubercular mastitis obliterans, known for duct infection leading to epithelial lining proliferation and fibrosis of the epithelial and periductal structures [6]. Due to the occlusion of the ducts, cystic spaces bearing a resemblance to cystic mastitis are formed. As the fifth and final form of tubercular mastitis, the rarely

reported acute miliary tubercular mastitis refers to breast involvement related to generalized miliary TB [6].

In terms of the modern classification of tubercular mastitis, the simplified classification of tubercular mastitis, as described by Tewari and Shukla [71], reduced the classification to three classes: nodulo-caseous tubercular mastitis, the disseminated form of tubercular mastitis, and tubercular breast abscess [70, 71]. The classification of the different varieties of tubercular mastitis is displayed in **Figure 3**.

When considering the anatomical impact of tubercular mastitis as presented in **Figure 3**, surgical interventions are required in approximately 14% of cases, depending on factors such as the extent of lesions affecting the breast or if chemotherapy fails due to poor patient adherence or drug resistance [6, 71–73]. Drainage of tubercular breast abscesses is imperative to reduce the risk of sinus formation. Modern studies rarely report using simple mastectomy as an alternative surgical treatment option; however, it is reserved for individual cases of extensive disease progression where the entire breast is affected by large, painful ulcerations and drainage into the axillary lymph nodes [6].

Specific antimycobacterial chemotherapy regimens are not established for the treatment of tubercular mastitis. Therefore, the literature reports following the general antitubercular treatment regimens involving multiple drug administration for extensive treatment periods. A success rate of approximately 95% is associated with the six-month anti-tubercular treatment regimen, referring to an intensive phase of two months while administering isoniazid, rifampicin, pyrazinamide, and ethambutol simultaneously, followed by a four-month maintenance treatment phase of isoniazid and rifampicin co-administration [6]. Successful treatment outcomes have also been reported by following a nine-month treatment regimen, starting with two months of the initiation phase comprising isoniazid, pyrazinamide, rifampicin, and ethambutol administration, followed by extended co-administration of isoniazid and rifampicin for a period of seven months, as a reduced relapse rate has been

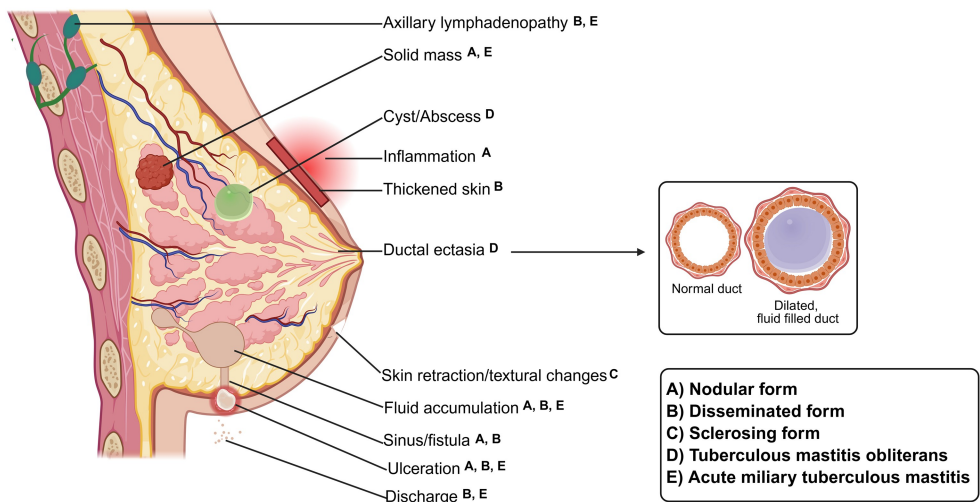


Figure 3.
Visual presentation of the different tubercular mastitis varieties as classified by McKeown et al. [69], created with BioRender.

reported for extending the maintenance phase of the anti-tubercular treatment regimen [6]. However, other sources report up to an 18-month extension of the anti-tubercular treatment regimen to ensure the bactericidal efficacy of these torturous drug regimens [70]. Moreover, in the case of multidrug-resistant TB, successful treatment has been reported by combining first- and second-line anti-tubercular agents, introducing drugs such as ofloxacin, kanamycin, and para-aminosalicylic acid to a pyrazinamide and isoniazid-based first-line agent regimen [6, 74].

3.2 Barriers to dermal drug delivery

Skin-mediated drug delivery in breast tissue has been receiving increasing scientific attention in clinical conditions such as breast cancer [75]. The reasoning behind utilizing targeted drug delivery to the breast tissue, as mediated by dermal application, can be highly beneficial in leveraging advantages such as bypassing hepatic first-pass metabolism, avoiding drug-drug interactions with orally administered anti-tubercular agents and antiretroviral drugs, and eliminating the occurrence of side effects known to accompany systemic drug administration [4, 75, 76]. Similar to anticancer therapy, anti-tubercular treatment regimens are extensive in terms of treatment time and side-effect profiles. Therefore, inspiration for the development of innovative skin-mediated anti-tubercular dosage forms can be taken from the advances made in breast tissue targeting following dermal application due to the superior and localized targeting capacity of these vehicles.

However, crossing the skin barrier provides a formidable challenge to formulators, as the barrier function of the skin must be overcome without causing dermal irritation or irreversible damage to the skin [4]. Moreover, the outer layer of the skin, known as the stratum corneum (SC), provides a lipophilic barrier while covering the two underlying hydrophilic layers (i.e., epidermis and dermis) [77]. Therefore, a dermal drug delivery vehicle should be able to cross both lipophilic and hydrophilic skin layers prior to reaching the breast tissue as a therapeutic target. The literature reports that drugs with low molecular weights (<500 Da) and a Log *p*-value ranging between 1 and 3 should theoretically be able to cross the lipophilic SC when incorporated into a first-generation topical dosage form, such as a cream [78]. However, the crossing of larger, more lipophilic molecules is deemed possible due to the development of advanced dosage forms [79–81]. Examples of such dosage forms are schematically represented in **Figure 4**, while considering the unique structure of the different skin layers, the dermal drug penetration pathways, and the specific advantages of dermal drug delivery vehicles.

As seen in **Figure 4**, different formulations have been developed to optimize drug delivery via the divergent dermal drug delivery pathways, offering unique advantages for long-term, localized anti-tubercular treatment of breast tissue. Considering the dermal permeation pathways, the transappendageal pathway, also referred to as the shunt pathway, involves the uptake of drugs via sweat glands, sebaceous glands, and hair follicles, which is generally favored by ions and certain hydrophilic molecules to gain dermal entry [78]. Second, hydrophilic and small molecular weight drug entities tend to diffuse via the intercellular spaces of the brick-and-mortar SC lipid structure, whereas lipophilic drugs tend to choose diffusion into the lipids of the SC, thereby utilizing the transcellular route to reach the underlying epidermis [4]. The literature reports active and passive approaches to enable crossing of the formidable SC [82]. Active approaches require the application

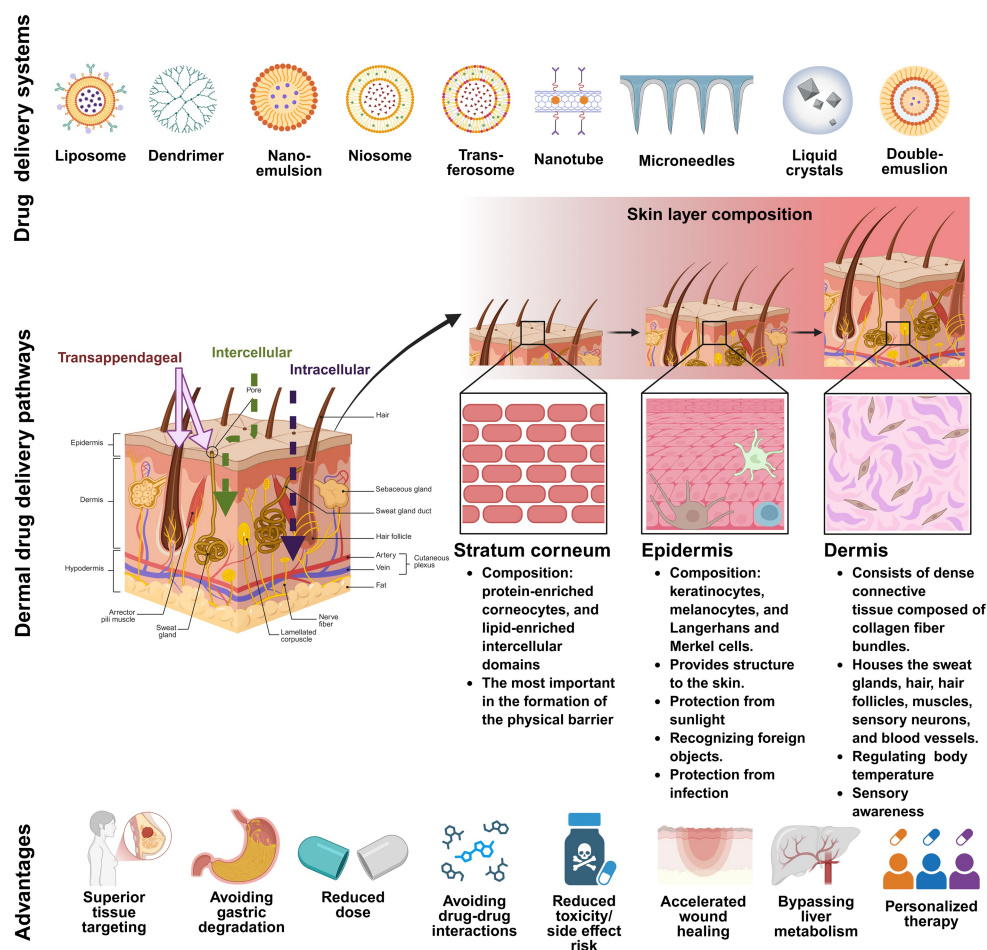


Figure 4. Summary of the advantages and drug penetration pathways of advanced dermal drug delivery vehicles. Created with BioRender.

of an external energy source to allow microchannel formation through the SC lipids or temporary SC lipid rearrangement, enabling entry into the underlying skin layers. These active approaches are restricted by complex procedures and cost implications [83–85]. On the contrary, passive approaches consider the inclusion of either natural or synthetic skin permeation enhancers (i.e., ionic liquids, surfactants, and fatty acids) to establish reversible SC lipid disruption as a means to achieve permeation into the epidermis, offering a simpler and more cost-effective alternative [78]. The literature reports successful delivery of anti-tubercular drugs into the different skin layers for clofazimine, as well as a combination of isoniazid and rifampicin incorporated into self-emulsifying drug delivery systems via the inclusion of natural oils as skin penetration enhancers [81, 86]. Moreover, the development of dermal self-double emulsifying drug delivery systems incorporating four anti-tubercular drugs (i.e., clofazimine, isoniazid, pyrazinamide, and rifampicin) and natural skin penetration enhancers has been reported by van Staden et al. [87].

However, these studies did not evaluate efficacy against Mtb. Another study by the same research group evaluated the efficacy of dermal vesicles (i.e., niosomes, liposomes, and transfersomes) containing anti-tubercular drugs, clofazimine, artemisone, and decoquinatone against an Mtb H37RV strain, finding anti-tubercular activity of the vesicles themselves without incorporating anti-tubercular drugs, with the highest percentage inhibition (52%) of Mtb reported for niosomes comprising 1% clofazimine [88].

The skin poses unique barriers to drug delivery but can also be seen as an innovative site for advancing drug targeting by noninvasively delivering drugs to the lymphatic system via dermal dosage form application. The literature reports that interstitial administration is favored to establish lymphatic drug delivery as molecules enter the lymphatic system via interendothelial tight junctions, mediated by fluid flow [88]. This signifies that carrier size can impact successful lymphatic drug delivery due to the size-dependent permeability of the lymphatics. It is documented that nanocarriers smaller than 150 nm can deposit in the skin and later enter the lymphatic system [88], whereas nanocarriers smaller than 100 nm are effectively absorbed by the lymphatic system [88]. Reaching the lymphatic system in a noninvasive manner can benefit targeted anti-tubercular drug delivery to the breast due to the lymphatic system branching into the breast tissue as an integral part of lactation physiology [4, 12, 17, 89]. Targeting the dissemination of pulmonary TB infection via the lymphatic system can also aid in impeding different forms of EPTB infection, emphasizing its advanced application beyond breast tissue targeting [12].

3.3 Drug delivery advances in anti-tubercular therapy

Optimizing anti-tubercular drug delivery of existing drugs is considered a beneficial approach to improve drug bioavailability, establish superior patient compliance, and might even shorten treatment times [12]. Therefore, the literature reports the development of localized, targeted drug delivery via innovative drug delivery systems, such as nanoparticles, at infection sites to avoid systemic side effects while optimizing antibacterial efficacy [90]. Moreover, some publications report investigating drug delivery systems that are simple to administer, relatively inexpensive, and dosage forms that provide extended release to reduce dosing intervals [12]. Advances also aim to develop dosage forms suitable for personalized therapy [87]. Personalized therapy is particularly impactful when treating a disease such as TB, since drug resistance is quite common, and the option to combine different drugs into an already developed dosage form intended to optimize targeted anti-tubercular drug delivery would provide an ideal and tailorable solution [87, 91].

This chapter emphasizes the potential of optimizing drug delivery at infection target sites, such as vaginal dosage forms to aid in FG TB, and dermal drug administration to provide localized treatment of breast TB. This approach focuses on optimizing drug absorption at dynamic physiological target sites, minimizing off-target effects, safeguarding drugs against gastric degradation, and avoiding hepatic first-pass metabolism, all of which can contribute to dose reduction and improved adherence to anti-tubercular therapy [12]. However, the main challenges involve the clinical translation of academic innovations, as scalability, reproducibility, safety, and environmental impact are not always considered during laboratory optimization of dosage form development [92, 93].

This is of particular importance regarding nanodrug delivery systems, as minor changes to production procedures can impact upscaling and safety, leading to costly and unsafe development of nanodrug delivery systems [29, 94]. Despite these challenges, nanocarriers continue to advance anti-tubercular drug delivery by modulating physical drug carrier properties such as particle charge, shape, size, surface composition, and hydrophobicity [12].

Moreover, despite the limited knowledge regarding the long-term safety of nano-based formulations, some academic innovations have reached the pre-clinical and clinical trial phases, as reported by Nongkhlaw et al. [95]. This work describes the progress of innovations incorporating isoniazid, a cornerstone agent of successful first-line anti-tubercular therapy, into nano-based formulations to optimize therapeutic targeting, reduce side-effects, and avoid the development of antimicrobial resistance [95]. Preclinical evaluation of polyethylene glycol (PEG)-ylated liposome nanoparticles incorporating isoniazid and rifampicin was reported by Garhyan et al. [96]. This work aimed to target Mtb residing in bone marrow utilizing a mice model. Results revealed superior clearance of Mtb from macrophages. Additionally, the PEG-modified liposomes bypassed hepatic metabolism due to selectively targeting macrophages to mediate transport to the bone marrow, where Mtb resided. Upon liposome uptake by the macrophages, nanoparticles were gradually broken down via lysosomal enzyme exposure, which established controlled release of TB drugs into the surrounding tissue upon escaping from macrophages, thereby increasing intracellular isoniazid and rifampicin concentrations. Importantly, these *in vivo* findings can be beneficial when intending to clear dormant Mtb residing in the bone marrow of patients [96].

However, for preclinical findings to progress to clinical trials, it is crucial to validate the safety of drug delivery innovations in terms of efficacy and tolerability in human subjects. This refers to a four-phase process where Phase I trials aim to generate a drug safety profile and optimize the dosage of the drug candidate by involving healthy human volunteers. Phase II trials consider the efficacy of drugs in disease-burdened patients, for example, to explore adverse effects. Phase III trials are performed in larger cohorts of patients to establish drug comparative effectiveness and long-term effects of drug candidates. Finally, Phase IV trials refer to post-marketing surveillance by following up on drug safety and pharmacovigilance [95]. Therefore, it is understandable that, despite excellent academic innovations, clinical trials can be described as time-consuming, thus hindering swift bench-to-bedside transitions [97].

Nonetheless, the literature reports findings from clinical trials considering the effects of isoniazid-encapsulated liposomes in TB patients [95, 98]. Promising results were reported, as tolerability and pharmacokinetics were considered favorable. Specifically, regarding the ability of liposomal formulations to enhance the penetration capacity of isoniazid, mediating prolonged drug release while effectively minimizing isoniazid toxicity due to reduced systemic exposure when compared to conventional isoniazid therapy [98].

Apart from the beneficial size reduction of nanodrug delivery systems, ligand inclusion on the surface of nanocarriers can also facilitate targeted interactions with pre-selected receptors located on macrophages, thereby establishing ligand-mediated or active targeting of mycobacteria [99]. On the contrary, passive targeting techniques can include utilizing dosage forms such as solid lipid nanoparticles, liposomes, and golden nanorods for the simultaneous delivery of multiple anti-tubercular drugs [12].

Here, the superior biocompatibility of polysaccharides and related excipients such as inulin, alginate, and chitosan is increasingly investigated, as it is attributed to their superior muco-adhesion, biocompatibility, surface charge-altering capacity, optimizing target specificity, favorable biodegradability, and hydrophilicity [12, 100].

In terms of targeting, anti-tubercular drug delivery strategies can also involve targeting the lymphatic system, as lymphatic TB dissemination is well-reported in the literature [17]. The lymph nodes fulfill a filtering capacity to evacuate pathogens from the body by traversing through efferent lymphatic vessels. A pathogen such as TB travels through numerous lymph nodes prior to entering one of the two lymphatic ducts (i.e., the right lymphatic duct and thoracic duct). Next, pathogens such as TB can also enter the systemic circulation to further disseminate throughout the body by draining into the subclavian veins [101]. Apart from viewing the lymphatic system as a transport mechanism for infectious disease, this system can additionally provide the ideal conditions for the survival and reproduction of pathogens. The *Mtb* infection is known for disruptive granuloma formation that can ultimately replace normal lymph node structure, thereby impeding lymph node function. Additionally, reactivation of latent TB infection can be initiated in the lymph nodes, leading to an increased risk of bacterial dissemination to non-pulmonary organs [17]. Exposure to lower mechanical forces in the lymphatic system compared to that of the bloodstream impacts lymphatic clearance of pathogens, since some pathogens can more easily adhere to the endothelium of the lymphatic system [102]. Moreover, pathogenic impairment of lymphatic muscle cells inflicts inferior lymphatic vessel contractility, which further impedes the velocity of lymphatics and clearance of pathogens [101]. Importantly, lymphatic vessels are present throughout the body. This signifies that TB transmission can occur from various routes via the lymphatic system, such as the vagina or skin. However, lymphatic targeting of TB following dermal drug administration holds vast potential to target lymphatic dissemination of TB from any bodily site, as the skin is a highly accessible drug administration organ linked to the lymphatic system. Direct lymphatic targeting via dermal administration can be described as challenging, since the lymphatics are only accessible after reaching the dermis at a deeper level compared to blood vessels [101]. This can be achieved by utilizing microneedles that can accurately govern the depth of dermal penetration [103]. In terms of anti-tubercular drug delivery, a study by Anjani et al. reported the successful formation of hydrogel microneedle-forming arrays delivering ethambutol (40%), isoniazid (79%), pyrazinamide (20%), and rifampicin (75%) into the systemic circulation after dermal application [104]. Interestingly, different drug reservoirs were optimized, namely lyophilized tablets, PEG tablets, and directly compressed tablets, which were then integrated with hydrogel microneedle-forming arrays to optimize targeted delivery of high drug dosages [104].

The dermal lymphatic system follows a similar organization throughout the body, with the exception of the palms, fingers, soles of the feet, and scrotum, where more lymphatic vessels are concentrated [101], thereby potentially providing superior access to the lymphatic system. However, indirect access to the dermal lymphatic system can be gained via targeting uptake into macrophages, dendritic cells, and neutrophils guarding the injured dermal surface, which also provides an opportunity for the development of innovative anti-tubercular drug delivery systems by targeting these immunological cells via dermal application [101].

Apart from optimizing the targeting of either lymphatic, systemic, or localized anti-tubercular therapies, the literature also reports advances regarding long-acting anti-tubercular dosage forms. Examples include administering prodrugs with low aqueous solubility to impede swift dissolution and erratic drug release, combined with mediating slow bodily clearance and capitalizing on the high potency of drugs when injecting low dosages of specific anti-tubercular agents fitting this description, such as bedaquiline [15, 105, 106]. Long-acting dosage forms, such as sustained release from vaginal rings, polymeric films, and *in situ* gelling systems, are also attracting significant scientific interest in the field of vaginal drug delivery by improving mucoadhesion properties, as dosage form leakage drastically reduces drug absorption [107]. Moreover, less frequent dose administration within the vagina can also benefit patient adherence, as patients can perceive vaginal drug administration as unpleasant despite the benefits provided by its localized action [108]. Long-acting dosage forms, such as dermal patches, are also favorable candidates for optimizing anti-tubercular drug delivery if one considers the possibilities of combining drug delivery advances reported in the field of dermal drug delivery and advanced anti-tubercular therapies, as dermal application is less invasive than injections [12, 109].

Moreover, the literature also reports microneedle-mediated vaccine delivery, which can provide a foundation for the development of less invasive vaccination techniques via dermal microneedle, vaccine-embedded application [110]. As an example, a study by Lee and co-workers reports the development of a potential heterologous prime booster vaccine for TB, comprising a live *Mycobacterium paragordoniae* strain, intending to increase the efficacy of the Bacillus Calmette-Guérin (BCG) vaccine [111]. This vaccine was administered by microneedles loaded with the nontuberculous mycobacteria, and its efficacy was confirmed by reduced bacterial pulmonary burden and Ag85B-specific T-cell activation in a mouse model [111]. This also creates an opportunity for vaccine adjuvant therapies at mucosal sites, like the vagina, to avoid obtaining FGTB in TB-endemic areas [110, 112–115]

4. Integrating advances in targeted anti-tubercular drug delivery for neglected forms of female EPTB

After considering the advances made in targeted anti-tubercular drug delivery, it is important to compare the approaches used to enhance the targeting of anti-tubercular drugs with advances reported in vaginal and dermal drug delivery to establish whether research can unite in creating innovative drug delivery vehicles to aid in the treatment of neglected forms of female EPTB. **Table 1** provides a summary of advanced targeted drug delivery systems and directs readers to studies developing similar delivery systems intended for vaginal and dermal administration to identify uninvestigated areas for targeted drug delivery of anti-tubercular drugs for localized, targeted drug delivery at the vaginal and breast tissues.

As seen in **Table 1**, the literature reporting advances in targeted anti-tubercular drug delivery, as well as advances in targeted vaginal and dermal drug delivery, is successfully evolving toward developing solutions to overcome challenges associated with successful, localized EPTB treatment. Existing challenges in anti-tubercular therapy involve barriers to translating academic innovations into impactful clinical applications due to practical and ethical dilemmas [150].

Delivery system	Description	Key findings in anti-tubercular research	Potential for vaginal administration	Potential for dermal administration	Examples of anti-tubercular drug delivery
Liposomes	Spherical vesicles stabilized by phospholipids providing a spontaneous bilayer structure, which allows the inclusion of lipophilic and hydrophilic drugs.	Superior biocompatibility. Similarity to lung surfactants. Quickly absorbed by macrophages. Regulated and sustained drug release. pH-sensitive liposomes: prevent deactivation and guarantee the intended biological action. Inclusion of hydrophilic and lipophilic drugs.	[116]	[117]	[12, 118–124]
Niosomes	Similar in structure to liposomes, bilayer composition consists of mixtures of non-ionic surfactants and hydrated cholesterol.	Superior chemical stability. Less expensive. Superior penetrating capacity compared to traditional liposomes. Promising immunopotentiators and delivery systems for vaccines. Controlling sizes of niosomes: a major portion of the drug can be concentrated in the lungs. Effective drug compartmentalization in the lymphatic system. Prolonged and sustained drug release (over 30 hours). Multidrug-loaded formulations that complement existing treatment plans, with superior targetability of the drug at a low dose. Optimum drug entrapment efficiency, reducing the dose, dosing frequency, and toxicity in J744A.1 mouse macrophages.	[125]	[117]	[12, 118, 126, 127]

Delivery system	Description	Key findings in anti-tubercular research	Potential for vaginal administration	Potential for dermal administration	Examples of anti-tubercular drug delivery
Transferosomes	Ultra-deformable vesicular carriers, comprising phospholipids and edge activators (e.g., surfactants), which provide superior elasticity to the vesicles.	Tape-stripping data from human skin diffusion studies indicated that transferosomes delivered the highest average concentrations of clofazimine and decoquinone compared to niosomes and liposomes.	[128]	[117]	[117, 129]
Spontaneous emulsions	Isotropic mixtures of oil, water, surfactant, and co-surfactant give rise to self-emulsification under mild agitation without the application of heat...	Improving solubility of lipophilic drugs. Including lipophilic and hydrophilic drugs simultaneously. Potential for personalized therapy. Easy upscaling. Successful dermal delivery of anti-tubercular drugs.	[130, 131]	[4, 81, 86, 87]	[4, 81, 86, 87]
Liquid crystals	An intermediate state of matter exists between that of an isotropic liquid and a crystalline solid. Liquid crystals possess many liquid properties, such as high fluidity, droplet formation and coalescence, and an inability to support shear, while also exhibiting anisotropy in electric, magnetic, and optical properties, similar to crystals.	Sustained release and 93% loading frequency.	[132]	[133, 134]	[135, 136]
Nanoemulsion	Kinetically stable, clear dispersion of two immiscible phases (oil phase and water phase) in combination with surfactant molecules (droplet sizes ranging from 5 to 200 nm).	Effective ophthalmic anti-tubercular drug delivery. Electrostatic interaction with mucin, facilitating increased residence time. Superior potency and thermostability due to adjuvant addition.	[137, 138]	[139]	[140, 141]

Delivery system	Description	Key findings in anti-tubercular research	Potential for vaginal administration	Potential for dermal administration	Examples of anti-tubercular drug delivery
Dendrimers	A synthetic, polymeric macromolecule exhibiting nanometer dimensions, with multiple highly branched monomers that emerge radially from the central core. It improves drug delivery due to its monodisperse size, modifiable surface functionality, multivalency, and water solubility.	Superior bioavailability. Establishing sustained release.	[142]	[143]	[144, 145]
Microneedles	Inserting large pathways of microscopic dimensions to assist in the crossing of drug delivery barriers using an array of microscopic needles (solid or dissolvable) attached to a metal or polymer base.	Development of a safe and painless BCG booster vaccine by fabricating <i>Mycobacterium parafortis</i> <i>nae: microneedle</i> patch (Mpg:MNP), revealing enhanced protective efficacy of Mpg:MNP in a virulent Mtb infection model.	[146]	[147]	[111]
Nanotubes	Nanotubes are defined as nanometer-scale, tube-like structures providing high surface areas, high electrical conductivities, and hollow geometry for superior drug loading.	Increased lethality against Mtb. Biocompatible. High drug loading. Stable release. Significant distribution throughout the body.	[29]	[148]	[14, 149]

Table 1.
Summarizes similar advances in targeted anti-tubercular, vaginal, and dermal drug delivery.

This is better understood if the seven steps of clinical translation are considered to describe the complex factors involved in the successful clinical translation of innovative dosage forms. These seven steps include: (1) upscaling capacity, (2) procedures considering standardized characterization of products, (3) reliable and repeatable stability analysis, (4) establishing the mode of action, (5) confirming the effectiveness and safety of the administered drug dose, (6) applying Good Laboratory Practices (GLP) during toxicity evaluations, and (7) clinical evidence in human subjects [150]. These seven steps are provided to ensure that a product is safe before reaching the bedside of users, as the extent of potential side-effects and co-morbidities is then well-known and can be avoided where possible. However, these seven steps severely constrain the clinical translation of academic innovations, thereby implying that despite academic breakthroughs, these advances seldom reach patients, especially patients suffering from neglected diseases such as FGTB and tubercular mastitis.

5. Conclusion

TB remains a global health concern due to its ranking as the leading cause of death in HIV-infected patients and its continuous contribution to global antimicrobial drug resistance. Forming part of the global TB burden, EPTB manifestations such as FGTB and TB of the breasts are often misdiagnosed, leading to delayed treatment of progressed disease. Despite instances where these neglected conditions are localized infections restricted to affecting specific non-pulmonary areas, the TB-DOTS regimen involving at least six months of multiple anti-tubercular oral drug administration is recommended in HIV-negative patients due to the absence of official international treatment guidelines. Therefore, this chapter presents advances made in vaginal drug delivery as a potential foundation for the development of targeted therapies in FGTB. Additionally, dermal drug delivery strategies are considered to aid in the targeted treatment of tubercular mastitis. Both FGTB and tubercular mastitis can be described as neglected forms of EPTB, necessitating innovative drug delivery approaches to maximize drug absorption via localized drug administration while bypassing drug-drug interactions, avoiding hepatic metabolism, reducing the risk of side effects, and potentially even shortening treatment times. Despite the advances and potential demonstrated by the considered dosage forms, these remain academic innovations, with the literature reporting slow bench-to-bedside translation to make these advances available to patients. Therefore, this chapter emphasizes the importance of balancing academic innovation with practical implications, such as developing scalable, cost-effective, and safe targeted dosage forms to lighten the global EPTB burden.

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Conflict of Interest

The author declares no conflict of interest.

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Tuberculosis remains one of the deadliest infectious diseases worldwide. Despite saving an estimated 83 million lives since 2000, it claimed 1.23 million deaths in 2024 and a similar or higher number in previous years, while continuing to cause over 10 million new cases annually, including 10.4 million in 2024, according to the World Health Organization. Progress toward eradicating TB is multisectoral and depends both on the development of new tools in treatment and diagnostics and of effective advocacy to ensure rapid access to diagnostics and treatment while also addressing the stigma that remains associated with the disease in vulnerable communities. In this book, an international community of authors presents chapters on advances in the diagnosis and treatment of tuberculosis and challenges of extrapulmonary tuberculosis treatment. Collectively, these contributions summarise recent advances that help us stay at the forefront of the fight with the disease, now claimed a major cause of deaths related to antimicrobial resistance, and gradually edge closer to achieving the WHO targets of reducing TB incidence by 80%, TB deaths by 90%, and eliminating catastrophic costs for TB-affected households by 2030. The topics covered range from new all-oral regimens and the use of steroids in TB to AI-driven innovations in diagnostic imaging. They also include discussions of central nervous system-penetrating agents and novel mucosal delivery systems for neglected forms such as genital tract TB. The book, published by IntechOpen, attempts to broaden access to publishing for a diverse range of authors and is united by a shared commitment to fighting this difficult-to-eradicate and recurring disease.

*Alfonso J. Rodriguez-Morales,
Infectious Diseases Series Editor*

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