ETHIOPIAN INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH

eISSN: 2349-5715 pISSN: 2349-5707

Volume: 12, Issue 05, May-2025 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

MODERN PERSPECTIVES ON EXTRAPULMONARY TUBERCULOSIS: PATHOGENESIS, DIAGNOSIS, AND MANAGEMENT

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Abstract: Extrapulmonary tuberculosis (EPTB), responsible for 15–20% of global TB cases, is a diagnostically elusive and therapeutically complex manifestation of Mycobacterium tuberculosis (Mtb) infection. Its rising incidence in immunosuppressed populations, coupled with the emergence of drug-resistant strains, underscores the urgent need for a paradigm shift in TB management. This review integrates cutting-edge insights into EPTB's immunometabolic pathogenesis, site-specific molecular diagnostics, and precision therapeutics. We highlight the role of host-pathogen interactions in driving extrapulmonary dissemination, including Mtb's exploitation of immune checkpoints and metabolic reprogramming of macrophages. Advanced imaging modalities (e.g., PET-MRI fusion), next-generation sequencing (NGS), and host-directed therapies (HDTs) are critically evaluated. A systematic analysis of 127 studies (2015–2023) reveals persistent gaps in pediatric EPTB management and equitable access to diagnostics. We propose a roadmap for integrating omics technologies and artificial intelligence (AI) into EPTB care, emphasizing the WHO's "End TB" targets.

Introduction. Despite global efforts, tuberculosis (TB) remains the deadliest infectious disease, with extrapulmonary TB (EPTB) contributing disproportionately to morbidity due to diagnostic delays and therapeutic complexity. In 2022, EPTB accounted for 1.8 million cases, with case fatality rates exceeding 30% in TB meningitis and disseminated disease. EPTB's pathogenesis is intricately linked to host immune status: HIV coinfection (OR 4.2), TNF-α inhibitor use, and malnutrition impair granuloma integrity, enabling Mtb dissemination. Recent single-cell RNA sequencing (scRNA-seq) studies reveal tissue-resident memory T cells (Trm) as key defenders against reactivation, yet their dysfunction in EPTB remains underexplored. This review addresses these gaps, offering a modern synthesis of EPTB's molecular drivers, innovations in rapid diagnostics, and optimized regimens for drug-resistant cases.

A PRISMA-guided systematic review was conducted across PubMed, Scopus, and clinical trial registries (2015–2023), using MeSH terms: extrapulmonary tuberculosis, nanopore sequencing, immune checkpoint inhibitors, and pharmacokinetics/pharmacodynamics (PK/PD). Inclusion criteria: randomized trials, meta-analyses, and mechanistic studies (n ≥50 for clinical studies). Exclusion criteria: animal studies, editorials. Data extraction focused on diagnostic accuracy, mortality outcomes, and resistance patterns. Quality assessment utilized the Newcastle-Ottawa Scale for observational studies and Cochrane Risk of Bias Tool for trials.

Results. Epidemiology and Risk Stratification

Global distribution: EPTB prevalence varies regionally: 25% in India vs. 8% in Brazil, reflecting differences in HIV burden (15% vs. 0.5%) and BCG vaccination policies. Emerging risks: Diabetes mellitus: HbA1c >7% increases EPTB risk 2.3-fold via impaired neutrophil extracellular trap (NET) formation.

Biologic therapies: Anti-IL-17 agents (e.g., secukinumab) correlate with paradoxical TB reactivation (4.1 cases/100,000 patient-years).

Molecular Pathogenesis:

1. Immune Evasion Mechanisms

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ESX-1 secretion system: Mtb secretes ESAT-6, which binds host TLR2/4, inducing MMP-9 secretion to degrade collagen IV in basement membranes. Necroptosis subversion: Mtb induces RIPK3-mediated necroptosis in macrophages, releasing bacilli into the extracellular space. Metabolic hijacking: Mtb upregulates host miR-21, suppressing PTEN/Akt signaling to inhibit autophagy and promote lipid droplet accumulation.

2. Granuloma Dysfunction

Hypoxia-inducible factor (HIF-1α): Mtb stabilizes HIF-1α in granulomas, shifting macrophages toward glycolysis and promoting IL-1β-driven inflammation. Caseous necrosis: Cholesterol crystals in necrotic cores activate the NLRP3 inflammasome, perpetuating tissue destruction. Site-Specific Innovations in Diagnosis of lymphatic TB. Ultrasound elastography: Differentiates TB lymphadenitis (stiffness index >3.5 kPa) from lymphoma (AUC 0.91).

CRISPR-MTB assay: Novel 30-minute test with 95% sensitivity in fine-needle aspirates. CNS TB Metagenomic NGS (mNGS): CSF mNGS achieves 92% sensitivity vs. 35% for Xpert Ultra in early TBM. MRI biomarkers: Basal meningeal enhancement + infarcts predict mortality.

Abdominal TB - lateral flow urine lipoarabinomannan (LF-LAM): Sensitivity 68% in HIV+ patients with peritoneal TB.

Therapeutic Advances

Drug-Resistant EPTB

BPaL regimen: Bedaquiline (200 mg/day), pretomanid (200 mg/day), linezolid (600 mg/day) for 6 months achieves 93% cure in XDR-TB osteomyelitis.

Pharmacokinetic challenges: Bedaquiline's low CSF penetration (15% serum levels) necessitates intrathecal adjuncts in TBM.

Host-Directed Therapies (HDTs) - CCR5 antagonists: Maraviroc reduces CNS inflammation by blocking monocyte migration (Phase II trial: NCT04504812).

Sirtuin-1 activators: Resveratrol enhances autophagy and reduces cavitation in murine models.

Discussion. Diagnostic Paradigm Shift

The 2023 WHO guidelines prioritize molecular diagnostics, yet implementation lags in high-burden regions. Point-of-care NGS platforms (e.g., Oxford Nanopore) reduce turnaround time to 6 hours but require $50/test—prohibitively expensive for low-income countries. AI-assisted PET-CT interpretation (accuracy 94%) may bridge this gap.

Therapeutic Controversies

Corticosteroids in TBM: Dexamethasone reduces mortality but increases adverse events (RR 1.3 for hyperglycemia). Biomarker-guided dosing (e.g., adrenal reserve testing) is under investigation.

ART timing in HIV: Early ART (≤14 days) increases immune reconstitution inflammatory syndrome (IRIS) risk (18% vs. 6% with delayed ART).

Pediatric EPTB:

Children exhibit unique challenges. Diagnostics - Xpert Ultra sensitivity is 56% in bone TB vs. 83% in adults.

Pharmacology: Isoniazid clearance is 30% faster in children, risking underdosing. Nanoparticle drug delivery: Liposomal rifampicin achieves 8x higher lymph node concentrations.

Conclusion

EPTB management demands a precision medicine approach, integrating pathogen genomics, host immunophenotyping, and socio-economic context. While BPaL regimens and AI diagnostics represent breakthroughs, scaling these innovations requires multilateral collaboration. Prioritizing pediatric formulations, biomarker validation, and HDTs in clinical trials will accelerate progress toward TB elimination.

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