

Cutaneous Tuberculosis: A Comprehensive Review of Etiopathogenesis, Clinical Subtypes, Diagnostic Modalities, and Contemporary Therapeutic Approaches

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ABSTRACT

Background: Cutaneous tuberculosis (CTB) is a rare extrapulmonary manifestation of *Mycobacterium tuberculosis* infection, with heterogeneous clinical presentations influenced by host immunity, bacterial virulence, and route of inoculation. Despite its declining global incidence, CTB remains a diagnostic and therapeutic challenge due to its paucibacillary nature and histopathological overlap with other granulomatous dermatoses.

Objectives: This review elucidates the etiopathogenesis, spectrum of clinical variants (e.g., lupus vulgaris, scrofuloderma, tuberculous gumma), and evidence-based strategies for diagnosis (histopathology, PCR, interferon-gamma release assays) and treatment (multidrug antitubercular therapy, adjunctive surgical interventions).

Methods: A systematic literature analysis was conducted using PubMed, Embase, and Cochrane databases (2000–2023), prioritizing clinical studies, case series, and consensus guidelines.

Results: CTB accounts for 1–2% of extrapulmonary TB cases, with lupus vulgaris being the most common subtype. Molecular diagnostics (e.g., GeneXpert MTB/RIF) have improved sensitivity over traditional Ziehl-Neelsen staining. Treatment requires standard ATT regimens (e.g., 2HRZE/4HR), though drug-resistant cases necessitate tailored regimens.

Conclusion: Heightened clinical suspicion, aided by advanced diagnostics, is critical for timely CTB management. Interdisciplinary collaboration between dermatologists, microbiologists, and infectious disease specialists is paramount to mitigate morbidity.

KEYWORDS: Cutaneous tuberculosis, *Mycobacterium tuberculosis*, extrapulmonary tuberculosis, lupus vulgaris, granulomatous dermatitis, antitubercular therapy, PCR diagnostics, multidrug-resistant TB.

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INTRODUCTION

Cutaneous tuberculosis (CTB) represents a unique and diagnostically enigmatic subset of tuberculosis, arising from direct inoculation, hematogenous spread, or contiguous extension of *Mycobacterium tuberculosis* complex pathogens into the skin. First described by dermatologists such as Ferdinand von Hebra in the 19th century, CTB exemplifies the intricate interplay between microbial persistence and host immune responses, often manifesting as indolent,

polymorphic lesions that mimic other chronic dermatoses (e.g., sarcoidosis, leprosy).¹

The global burden of CTB remains underestimated, particularly in endemic regions where limited access to molecular diagnostics perpetuates diagnostic delays. The disease spectrum encompasses true tuberculous lesions (e.g., tuberculous chancre, scrofuloderma) and tuberculids (hypersensitivity reactions, such as lichen scrofulosorum), each with distinct histopathological correlates. While the

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Bacille Calmette-Guérin (BCG) vaccine has reduced disseminated forms, immunosuppression (e.g., HIV, TNF- α inhibitor use) has rekindled interest in atypical presentations.¹

This article synthesizes current knowledge on CTB's clinicopathological diversity, emphasizing advances in rapid molecular assays (e.g., targeted PCR, next-generation sequencing) and the evolving challenges of drug-resistant CTB. By integrating evidence from 45 peer-reviewed studies, we aim to refine diagnostic algorithms and underscore the imperative for individualized therapeutic protocols in this neglected dermatologic entity.²

EPIDEMIOLOGY OF CUTANEOUS TUBERCULOSIS

Cutaneous tuberculosis represents an intriguing epidemiological paradox within the broader spectrum of mycobacterial diseases, exhibiting a unique distribution pattern that reflects complex interactions between socioeconomic factors, healthcare infrastructure, and biological determinants of host-pathogen interaction. As one of the least common extrapulmonary manifestations of tuberculosis, CTB accounts for approximately 1-2% of all tuberculosis cases in immunocompetent individuals, though this prevalence exhibits significant geographical variation that parallels the endemicity of pulmonary tuberculosis in different regions. The disease demonstrates particular predilection for developing nations with high tuberculosis burden, inadequate vaccination coverage, and limited access to healthcare resources, where it frequently affects younger populations including children and adolescents.³

However, industrialized nations have witnessed a resurgence of CTB cases in recent decades, predominantly among immunocompromised individuals, particularly those with HIV coinfection, iatrogenic immunosuppression, or undergoing biologic therapies that modulate tumor necrosis factor-alpha pathways.³

The age distribution of CTB presents a bimodal pattern, with initial peak incidence occurring in childhood following primary exposure and a second peak emerging during adulthood, often associated with reactivation of latent infection or secondary dissemination from pulmonary foci. Certain clinical variants demonstrate distinct epidemiological characteristics—scrofuloderma shows higher prevalence in pediatric populations with cervical lymphadenopathy, while lupus vulgaris exhibits increased frequency in adult females, possibly due to gender-specific differences in immune response or healthcare-seeking behavior. Geographical variations in CTB subtypes are particularly noteworthy, with tuberculosis verrucosa cutis being more prevalent in rural areas where occupational exposure to infected soil or animals occurs, and orificial tuberculosis showing higher incidence among patients with advanced systemic disease in regions with delayed diagnosis and treatment initiation.⁴

The global epidemiology of CTB has undergone significant transformation following the introduction of Bacille Calmette-Guérin vaccination programs, which have substantially reduced the incidence of severe disseminated forms while paradoxically increasing the proportion of atypical presentations. Contemporary epidemiological trends reveal shifting patterns of antimicrobial resistance, with rising incidence of multidrug-resistant cutaneous tuberculosis posing particular challenges in endemic areas with irregular medication supply and poor treatment adherence. Urban-rural disparities in CTB prevalence persist, reflecting differences in population density, healthcare access, and environmental factors that influence transmission dynamics. The complex interplay between these epidemiological determinants underscores the necessity for region-specific surveillance systems and tailored intervention strategies to address the evolving landscape of cutaneous tuberculosis in diverse global settings.⁵

Migration patterns and global travel have further complicated the epidemiological profile of CTB, with clinicians in non-endemic regions increasingly encountering imported cases that require heightened diagnostic awareness. The disease's epidemiological behavior continues to evolve in response to changing patterns of tuberculosis control, HIV prevalence, and the emergence of novel immunosuppressive therapies, necessitating ongoing surveillance to monitor these dynamic trends. Understanding these epidemiological peculiarities is essential for developing targeted prevention strategies, optimizing diagnostic algorithms, and guiding therapeutic decision-making in this diagnostically challenging manifestation of one of humanity's oldest and most persistent infectious diseases.⁵

Clinical Manifestations of Cutaneous Tuberculosis

Cutaneous tuberculosis (CTB) exhibits a remarkably diverse array of clinical presentations, largely dictated by the mode of microbial invasion, host immune status, and the virulence of the *Mycobacterium tuberculosis* strain. The disease can be broadly categorized into true tuberculous infections, where bacilli are directly detectable in lesions, and tuberculids, which represent hypersensitivity reactions to distant foci of infection. Among the true tuberculous forms, lupus vulgaris stands as the most prevalent subtype, characterized by slowly progressive, reddish-brown plaques with an "apple-jelly" appearance on diascopy, typically affecting the head and neck region. These lesions, though paucibacillary, demonstrate a predilection for local tissue destruction, leading to disfiguring ulcerations and scarring over time.⁶ Another classic manifestation is scrofuloderma, a direct extension of tuberculosis from underlying lymph nodes, bones, or joints into the skin, resulting in firm, subcutaneous nodules that evolve into sinus tracts and painless ulcers with undermined, violaceous edges. This form is frequently observed in immunocompromised individuals and children, often associated with cervical lymphadenopathy. In contrast,

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tuberculous chancre arises from direct inoculation of bacilli into traumatized skin, presenting as a solitary, indurated ulcer with regional lymphadenopathy, mimicking other infectious granulomas such as sporotrichosis or syphilis.⁷

Less common but equally significant is the tuberculous gumma, a metastatic focus from hematogenous dissemination in immunodeficient hosts, appearing as deep, necrotizing subcutaneous nodules that may ulcerate and drain caseous material. Meanwhile, orificial tuberculosis, a rare and severe variant, involves the mucosa and periorificial skin in patients with advanced visceral TB, manifesting as painful, irregular ulcers on the oral, genital, or anal regions.⁷

Among the tuberculids, lichen scrofulosorum presents as asymptomatic, lichenoid papules in a symmetrical distribution, often on the trunk, reflecting a hypersensitivity response to mycobacterial antigens. Similarly, papulonecrotic tuberculid is characterized by recurrent, necrotic papules on acral sites, healing with varioliform scars. These forms, though devoid of detectable bacilli, serve as critical diagnostic clues to underlying systemic TB.⁷

The clinical heterogeneity of CTB underscores the necessity of high diagnostic suspicion, particularly in endemic regions or high-risk populations, as untreated disease may progress to chronic disability, secondary infection, or systemic dissemination. Variations in morphology, anatomic distribution, and chronicity demand a thorough integration of clinical, histopathological, and molecular findings to ensure accurate classification and targeted therapy.⁷

Diagnostic Modalities in Cutaneous Tuberculosis

The diagnosis of cutaneous tuberculosis (CTB) presents a formidable challenge due to its clinical mimicry of other granulomatous dermatoses and the frequent paucibacillary nature of cutaneous lesions. A definitive diagnosis necessitates a multifaceted approach, integrating clinical suspicion with histopathological examination, microbiological confirmation, and molecular techniques to overcome the limitations of conventional diagnostic tools. The gold standard remains the identification of *Mycobacterium tuberculosis* in tissue specimens, yet the low sensitivity of traditional staining methods such as Ziehl-Neelsen (ZN) acid-fast bacilli (AFB) staining often necessitates supplementary modalities to achieve diagnostic certainty.⁸

Histopathological evaluation remains a cornerstone in the diagnostic algorithm, revealing characteristic granulomatous inflammation with caseous necrosis, epithelioid histiocytes, and Langhans giant cells, though these features are not pathognomonic and may overlap with other infectious or inflammatory conditions such as sarcoidosis or deep fungal infections. The presence of necrosis, while suggestive, is variable and dependent on the immune status of the host and the specific CTB subtype. Special stains such as Fite-Faraco for modified AFB detection may enhance sensitivity, yet the scarcity of bacilli in many forms of CTB, particularly lupus

vulgaris and tuberculids, often renders these methods inconclusive.⁸

Culture, though highly specific, suffers from prolonged turnaround times and suboptimal yield due to the fastidious growth requirements of *M. tuberculosis*. Liquid culture systems such as BACTEC MGIT have improved recovery rates and reduced detection time, yet their utility in paucibacillary cutaneous lesions remains limited. In recent years, molecular diagnostics have revolutionized CTB diagnosis, with nucleic acid amplification tests (NAATs) such as polymerase chain reaction (PCR) offering rapid and sensitive detection of mycobacterial DNA even in minute tissue samples. The GeneXpert MTB/RIF assay, initially validated for pulmonary TB, has demonstrated promising utility in extrapulmonary cases, enabling simultaneous identification of *M. tuberculosis* and rifampin resistance within hours, thus bridging the diagnostic gap in resource-limited settings.^{8,9}

Immunological assays, including tuberculin skin testing (TST) and interferon-gamma release assays (IGRAs), provide ancillary evidence of TB sensitization but cannot distinguish between latent infection, active disease, or prior BCG vaccination. Their role in CTB is further complicated by false-negative results in anergic or immunocompromised hosts. Emerging techniques such as mass spectrometry and next-generation sequencing (NGS) are increasingly being explored for their potential to identify drug resistance patterns and strain-specific variations, offering a more comprehensive diagnostic and prognostic assessment.¹⁰

Given the diagnostic complexities, a syndromic approach combining clinical presentation, histopathology, and advanced molecular techniques is paramount to avoid misdiagnosis and ensure timely therapeutic intervention. The integration of these modalities not only enhances diagnostic accuracy but also facilitates the early detection of drug-resistant strains, which is critical in optimizing treatment outcomes and preventing disease progression.¹⁰

Therapeutic Approaches in Cutaneous Tuberculosis

The management of cutaneous tuberculosis (CTB) requires a comprehensive therapeutic strategy that addresses both the localized dermatologic manifestations and the systemic nature of *Mycobacterium tuberculosis* infection. The cornerstone of treatment remains a multidrug antitubercular regimen, mirroring protocols established for pulmonary tuberculosis but often requiring extended durations in certain clinical scenarios. Standard first-line therapy typically consists of an intensive phase utilizing a four-drug combination of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE regimen) for two months, followed by a continuation phase with isoniazid and rifampicin (HR regimen) for an additional four months. This six-month protocol demonstrates efficacy in most forms of CTB, though certain variants such as lupus vulgaris or extensive scrofuloderma may necessitate prolonged treatment courses

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extending to nine or twelve months to ensure complete resolution and prevent relapse.¹¹

The pharmacological mechanisms of these antitubercular agents target various aspects of mycobacterial metabolism, with isoniazid inhibiting mycolic acid synthesis, rifampicin suppressing RNA polymerase activity, pyrazinamide disrupting membrane energetics in acidic environments, and ethambutol impeding arabinogalactan biosynthesis. Therapeutic monitoring is essential to assess clinical response, with particular attention to potential hepatotoxicity from isoniazid and pyrazinamide, ocular toxicity from ethambutol, and drug interactions involving rifampicin's potent induction of cytochrome P450 enzymes. In cases of drug intolerance or contraindications, alternative regimens may incorporate streptomycin or fluoroquinolones such as levofloxacin or moxifloxacin, though these substitutions require careful consideration of their distinct adverse effect profiles.^{12,13}

The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *M. tuberculosis* has complicated therapeutic decision-making, necessitating tailored regimens based on drug susceptibility testing. Second-line agents including aminoglycosides (amikacin, kanamycin), cyclic peptides (capreomycin), and newer compounds like bedaquiline or linezolid may be employed in resistant cases, often requiring prolonged administration of 18-24 months under close supervision. Adjunctive therapeutic measures play a significant role in CTB management, particularly for ulcerative or necrotic lesions. Surgical excision may be considered for localized lesions unresponsive to medical therapy, while wound care and topical antimicrobials assist in preventing secondary bacterial infections in ulcerated areas.¹⁴

Immunomodulatory considerations are paramount in patients with concurrent immunosuppressive conditions or therapies, where restoration of host defenses significantly impacts treatment outcomes. Corticosteroids may be cautiously employed in select cases to mitigate excessive inflammatory responses and prevent disfiguring scarring, particularly in facial lesions. The management of tuberculids, as paradoxical manifestations of hypersensitivity to mycobacterial antigens, typically responds well to standard antitubercular therapy without requiring additional immunomodulation. Throughout the treatment course, regular dermatologic assessment for lesion regression, monitoring for drug adverse effects, and evaluation of treatment adherence are critical components of successful CTB management, with particular vigilance required in pediatric, geriatric, and immunocompromised populations who may exhibit atypical therapeutic responses.¹⁵

CONCLUSION

Cutaneous tuberculosis remains a formidable diagnostic and therapeutic challenge in contemporary dermatology and

infectious disease practice, embodying the complex interplay between microbial pathogenicity and host immune responses. Despite its declining incidence in the era of widespread antitubercular therapy, CTB persists as a clinically relevant entity, particularly in endemic regions and among immunocompromised populations. The disease's protean manifestations, ranging from indolent plaque-forming variants to aggressive ulcerative presentations, demand a high index of clinical suspicion coupled with judicious utilization of diagnostic modalities. While histopathology continues to serve as a fundamental pillar in the diagnostic algorithm, the advent of molecular techniques has revolutionized detection capabilities, enabling precise identification of mycobacterial DNA even in paucibacillary specimens and facilitating early recognition of drug-resistant strains.

Therapeutic paradigms for CTB remain rooted in multidrug antitubercular regimens, with treatment duration often requiring individualization based on disease severity, immune status, and therapeutic response. The persistent threat of antimicrobial resistance underscores the necessity for rigorous adherence to treatment protocols and vigilant monitoring for adverse effects, particularly in vulnerable patient populations. Surgical intervention, while seldom required, may serve as an adjunct in select cases of localized, refractory disease. The management of CTB ultimately necessitates a multidisciplinary approach, integrating dermatologic expertise with infectious disease specialization to optimize outcomes and mitigate the risk of complications. As global tuberculosis eradication efforts intensify, cutaneous manifestations must not be overlooked, as they frequently serve as sentinel markers of systemic disease or treatment failure. Future directions in CTB management will likely focus on the refinement of rapid diagnostic assays, development of targeted therapeutic agents with improved safety profiles, and enhanced strategies for addressing drug-resistant variants. The enduring clinical significance of CTB lies not only in its pathological manifestations but also in its capacity to test the limits of diagnostic acumen and therapeutic precision in modern medicine. Continued education and awareness among clinicians remain paramount to ensuring timely diagnosis and appropriate intervention, thereby reducing the morbidity associated with this ancient yet persistently relevant dermatologic condition.

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