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Pathogenesis and Therapeutic Advances in Spinal Tuberculosis: A Comprehensive Review

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Abstract: This review systematically explores the pathogenesis of spinal tuberculosis, emphasizing the interplay among Mycobacterium tuberculosis transmission routes, host immune responses, and anatomical and physiological characteristics of the spine. It also provides a comprehensive summary of current therapeutic advances, including optimized regimens of conventional anti-tuberculosis chemotherapy, surgical interventions, and emerging technologies such as local drug delivery systems, 3D printing, and targeted therapies. The aim is to offer clinicians an in-depth theoretical framework and therapeutic reference to further improve the diagnosis and treatment of spinal tuberculosis.

Keywords: Spinal Tuberculosis; Pathogenesis; Anti-tuberculosis Agents; Surgical Treatment; Therapeutic Advances.

1. Introduction

Spinal tuberculosis (TB), the most prevalent form of osteoarticular tuberculosis, accounts for approximately 50% of all skeletal TB cases. [1] Despite global advances in TB control, its incidence remains high, particularly in developing countries. [2] Spinal TB not only causes severe pain, spinal deformity, and neurological impairment, but if left untreated or improperly managed, it may lead to debilitating complications such as paraplegia, significantly compromising patients' quality of life and long-term prognosis. In recent years, the increasing mobility of populations, emergence of drug-resistant Mycobacterium tuberculosis strains, and the growing number of immunocompromised individuals have presented new challenges for the prevention and management of spinal TB. A thorough understanding of its pathogenesis and up-to-date knowledge of therapeutic strategies is crucial for improving early diagnostic accuracy and clinical outcomes. This review aims to elucidate the complex pathogenic mechanisms of spinal TB and to provide a comprehensive overview of conventional and emerging treatment modalities, offering valuable insights for clinicians and researchers.

2. Pathogenesis of Spinal Tuberculosis

2.1. Routes of Mycobacterium tuberculosis Dissemination

2.1.1. Hematogenous Spread

Hematogenous dissemination is the most common route of infection in spinal tuberculosis. [3] Following primary infection, Mycobacterium tuberculosis typically establishes a focus in the lungs. When host immunity declines, bacilli may escape alveolar macrophage containment, enter the pulmonary veins or capillaries, and spread systemically via the bloodstream. The vertebral bodies are particularly susceptible due to their rich vascularization by end arteries with sluggish blood flow and turbulence at arterial branches, allowing bacilli to localize and colonize within the metaphyseal capillary network. Clinical studies have shown that pulmonary TB is the primary source of infection in approximately 80% of spinal TB cases, and autopsy findings frequently reveal coexisting pulmonary lesions. [4] Moreover, Mycobacterium tuberculosis may disseminate through Batson's venous plexus, a valveless paravertebral venous network connected to thoracic, abdominal, pelvic, and cranial veins. Activities that increase intra-abdominal pressure, such as coughing or straining during defecation, can reverse venous flow and enable direct spread of bacilli to the spine, even in the absence of pulmonary TB.

2.1.2. Lymphatic Spread

The spine is surrounded by an extensive lymphatic network. When TB affects lymph nodes in the cervical, mediastinal, or abdominal regions, ruptured nodes may release bacilli into lymphatic channels, facilitating their spread to paravertebral nodes and eventually to the spine. [5] Although less common than hematogenous transmission, lymphatic spread is more prevalent in children due to their well-developed lymphatic systems.

2.1.3. Direct Contiguous Spread

Direct extension may occur when adjacent structures, such as the paraspinal soft tissue, ribs, or sternum, become infected with TB. For example, thoracic vertebral TB can originate from adjacent rib involvement, and lumbar TB may result from psoas abscess erosion into the vertebral body. Although limited in scope, direct spread may cause spinal infection in cases of severe or inadequately treated localized TB.

2.2. Host Immune Response

2.2.1. Innate Immunity

Innate immunity constitutes the first line of defense against Mycobacterium tuberculosis. Upon invasion, bacilli are recognized by innate immune cells, such as macrophages and dendritic cells, via pattern recognition receptors (e.g., Toll-like receptors) that identify pathogen-associated molecular patterns (PAMPs) like lipoarabinomannan and peptidoglycan. Macrophages engulf the bacilli to form phagosomes, which typically fuse with lysosomes to create phagolysosomes that destroy pathogens using enzymes and reactive oxygen species. [6] However, the lipid-rich cell wall of M. tuberculosis—

containing arabinogalactan, mycolic acids, and phospholipids—can inhibit phagosome-lysosome fusion or resist degradation within phagolysosomes, allowing intracellular survival and replication.

Activated macrophages release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which recruit additional immune cells to the infection site. While beneficial for pathogen containment, excessive inflammation may result in local tissue damage, facilitating bacterial dissemination.

2.2.2. Cell-Mediated Immunity

Cell-mediated immunity plays a pivotal role in controlling M. tuberculosis infection. Antigen-presenting cells (APCs), such as macrophages and dendritic cells, process and present mycobacterial antigens to naive T lymphocytes, promoting their differentiation into helper T (Th) cells and cytotoxic T lymphocytes (CTLs). Th1 cells secrete interferon-gamma (IFN-γ), which enhances macrophage activation, increases intracellular killing of bacilli, and promotes positive feedback on Th1 differentiation. [7] CTLs directly recognize and eliminate infected host cells. In immunocompetent individuals, this response typically controls the infection, maintaining it in a latent state. However, in immunocompromised populations—such as those with HIV/AIDS, organ transplant recipients on immunosuppressants, or poorly controlled diabetes—T-cell dysfunction leads to uncontrolled bacillary proliferation and progression to active spinal TB.

2.2.3. Immune Evasion by M. tuberculosis

M. tuberculosis employs multiple immune evasion strategies. Its cell wall component, lipoarabinomannan, downregulates co-stimulatory molecules (e.g., B7-1, B7-2) on macrophages, impairing T-cell activation.[8] Secreted proteins such as ESAT-6 and CFP-10 interfere with antigen processing and presentation by APCs, reducing recognition by T cells. The bacillus also induces regulatory T cells (Tregs), which release inhibitory cytokines like interleukin-10 (IL-10), suppressing Th1 responses and weakening host immunity. These mechanisms contribute to the persistence and dissemination of infection.[9]

2.3. Anatomical and Physiological Features of the Spine

2.3.1. Structural Characteristics of Vertebral Bodies

Vertebral bodies are predominantly composed of cancellous bone, which contains abundant marrow that provides a favorable microenvironment for the proliferation of Mycobacterium tuberculosis. Compared to cortical bone, cancellous bone has richer vascularization but slower blood flow, facilitating bacterial colonization and growth. The nutrient arteries of vertebrae are terminal in nature, making local circulation vulnerable to disruption during infection. This impairs immune clearance and hinders the drainage of inflammatory exudate and necrotic tissue, exacerbating disease severity. Additionally, the trabecular structure of cancellous bone allows the bacilli to spread easily within the vertebrae, leading to extensive bone destruction.

2.3.2. Avascular Nature of Intervertebral Discs

Intervertebral discs, composed of the nucleus pulposus, annulus fibrosus, and cartilaginous endplates, lack direct blood supply and rely on diffusion through the vertebral endplates for nutrient exchange. This unique avascularity results in low metabolic activity and limited immune surveillance. Once infected, discs have a diminished ability to clear bacilli. Furthermore, the cartilaginous endplates are prone to destruction by M. tuberculosis, disrupting nutrient diffusion and accelerating disc degeneration and necrosis. This facilitates spread of infection to adjacent vertebral bodies.

2.3.3. Biomechanical Load of the Spine

The spine serves as the central structural axis of the human body, bearing axial loads and absorbing mechanical stress during movement. The lumbar and lower thoracic vertebrae, in particular, endure substantial compression and shear forces. When infected, the integrity of the vertebral body is compromised, leading to mechanical instability. [10] This may result in vertebral collapse and kyphotic or scoliotic deformities. Such deformities further alter biomechanical load distribution, aggravating vertebral damage and increasing the risk of spinal cord or nerve compression, forming a vicious cycle.

2.4. Pathological Progression of Spinal Tuberculosis

2.4.1. Exudative Phase

In the early exudative phase, the invasion of M. tuberculosis activates an acute inflammatory response. Local vasodilation and increased vascular permeability facilitate the migration of neutrophils, macrophages, and other immune cells to the infection site, leading to congestion and edema. Histologically, the lesion is dominated by serous or fibrinous exudate in the interstitial space, with sparse bacilli presence. Clinically, patients may exhibit low-grade fever, night sweats, fatigue, and localized pain. Imaging may reveal mild vertebral edge blurring and intervertebral disc space narrowing.

2.4.2. Granulomatous Phase

As the disease progresses, macrophages ingest bacilli and transform into epithelioid cells under the influence of cytokines. These cells may fuse into multinucleated Langhans giant cells, and are surrounded by lymphocytes and fibroblasts, forming characteristic tuberculous granulomas. Granuloma formation reflects a specific immune response that helps limit bacterial spread. Although inflammation may subside, tissue destruction continues. Radiologically, there is evidence of expanding bone loss and increasing paravertebral soft tissue swelling.

2.4.3. Caseous Necrosis Phase

With further immune compromise or unchecked bacillary replication, lesions enter the caseous necrosis phase. [11] The central area of granulomas undergoes necrosis, forming yellow-white, soft, cheese-like material known as caseous necrosis. These necrotic zones contain high concentrations of bacilli, lack vascular supply, and are resistant to resorption or clearance. Progressive accumulation increases intralesional pressure, leading to rupture of cortical bone and subperiosteal spread. Cold abscesses form within adjacent soft tissue and may track along anatomical planes, such as the psoas muscle, reaching the iliac fossa or inguinal region. These abscesses can compress surrounding nerves, vessels, and tissues, causing worsening pain, numbness, or motor deficits. In severe cases, spinal cord compression may result in paralysis. Imaging studies typically reveal extensive vertebral destruction, collapse, marked disc space narrowing, and the presence of paravertebral or tracking abscesses.

3. Therapeutic Advances in Spinal Tuberculosis

3.1. Anti-Tuberculosis Pharmacotherapy

3.1.1. Standard Chemotherapeutic Regimens

Pharmacotherapy remains the cornerstone of spinal tuberculosis management and follows the principles of early initiation, combination therapy, appropriate dosing, treatment regularity, and completion of the full course. First-line anti-tuberculosis drugs include isoniazid (INH), rifampicin (RFP), pyrazinamide (PZA), ethambutol (EMB), and streptomycin (SM).[12] Isoniazid disrupts mycolic acid synthesis, compromising cell wall integrity; rifampicin binds to bacterial RNA polymerase, inhibiting RNA synthesis; pyrazinamide exerts bactericidal effects under acidic conditions, such as within macrophages; ethambutol impairs the synthesis of arabinogalactan in the cell wall; and streptomycin targets bacterial ribosomes to inhibit protein synthesis. For newly diagnosed patients, a standard regimen involves a 2–3-month intensive phase using a four-drug combination (INH, RFP, PZA, EMB), followed by a 4–6-month continuation phase with two drugs (INH and RFP), totaling 6–9 months. In patients with severe disease, complications (e.g., abscesses, neurological deficits), or relapse, treatment duration may be extended to 12–18 months. Routine monitoring of liver and renal function, complete blood counts, and ocular status is essential due to potential adverse effects, including hepatotoxicity, gastrointestinal disturbances, and optic neuritis. If serious side effects occur, treatment plans must be adjusted promptly.

3.1.2. Management of Drug-Resistant Spinal Tuberculosis

The incidence of drug-resistant spinal TB has risen in recent years, posing significant therapeutic challenges—especially with the emergence of multidrug-resistant TB (MDR-TB, resistant to at least INH and RFP) and extensively drug-resistant TB (XDR-TB, resistant to at least INH, RFP, and two or more second-line drugs). [13] Treatment should be guided by drug susceptibility testing and typically involves second-line agents such as aminoglycosides (kanamycin, amikacin, capreomycin), fluoroquinolones (levofloxacin, moxifloxacin), thioamides (ethionamide, prothionamide), cycloserine, and linezolid. These drugs differ mechanistically from first-line agents; for example, fluoroquinolones inhibit DNA gyrase and topoisomerase IV, preventing bacterial replication and transcription. Therapy duration for drug-resistant TB is considerably longer—typically 18–24 months or more. Second-line drugs are associated with increased toxicity: aminoglycosides can cause ototoxicity and nephrotoxicity; fluoroquinolones may induce tendonitis or cardiac arrhythmias. Therefore, patients require closer surveillance, including audiometry, renal function tests, and ECG monitoring. Adjunctive use of immunomodulators such as interferon-gamma or interleukin-2 may enhance host defense mechanisms. Additionally, newer drugs like bedaquiline and delamanid show promise for MDR/XDR-TB, although further clinical experience is needed to optimize their use in spinal TB.

3.2. Surgical Management

3.2.1. Indications for Surgery

The primary goals of surgical intervention in spinal tuberculosis are to debride infected tissues, decompress neural elements, correct spinal deformity, and restore mechanical stability. [14.15.16.17] Indications include:

- Presence of extensive necrotic bone, caseous material, or cold abscess unresponsive to adequate chemotherapy, or lesions at risk of rupture and secondary infection;
- Neurological deficits caused by spinal cord or nerve root compression, such as limb numbness, weakness, sensory loss, or bladder/bowel dysfunction, with no improvement under conservative treatment;
- Severe kyphotic or scoliotic deformity (Cobb angle >30°) that impairs cardiopulmonary function or aesthetics, or carries a risk of progression;
- Persistent disease progression and vertebral destruction despite standardized chemotherapy, with a high risk of pathological fracture;
- Coexisting conditions requiring surgical management, such as pyogenic infection, tumors, or suspected malignancy.

3.2.2. Surgical Techniques

Debridement:

Debridement is a fundamental surgical procedure that involves direct exposure and thorough removal of necrotic bone, caseous tissue, granulation tissue, and abscesses. Approaches include anterior, posterior, or combined anterior–posterior depending on lesion location and extent.

Anterior debridement is optimal for lesions confined to the anterior vertebral column, allowing direct access and height restoration. Posterior debridement is suitable for lesions involving posterior structures like pedicles and laminae, and can be combined with posterior instrumentation. Combined approaches are reserved for extensive or complex lesions to ensure complete clearance. Bone grafting is usually performed post-debridement to promote structural reconstruction.

Bone Grafting and Fusion:

Bone grafting is essential for reconstructing vertebral height and stability. Options include autografts (e.g., iliac crest, ribs), allografts, and synthetic materials. Autografts provide excellent osteoconduction, osteoinduction, and integration but are limited by donor-site morbidity and quantity. [18.19] Allografts reduce donor site trauma but have slower incorporation and risk of disease transmission. Synthetic grafts like calcium phosphate cement or hydroxyapatite are biocompatible and moldable but lack osteoinductive properties, often requiring combination with autografts or growth factors. Techniques include interbody fusion and transpedicular fusion, selected based on lesion site and surgical access.

Instrumentation and Internal Fixation:

Spinal instrumentation enhances stability, prevents graft migration or collapse, and facilitates early mobilization. Common systems include titanium rods, pedicle screws, and anterior plating.

Posterior pedicle screw fixation is widely used for three-dimensional stabilization. Anterior instrumentation may be employed post-anterior debridement to reinforce the anterior column. Timing of fixation is based on the extent of debridement and systemic condition, typically performed after lesion clearance and bone grafting.

Minimally Invasive Procedures:

Minimally invasive techniques are increasingly adopted for selected spinal TB cases, including percutaneous drainage, vertebroplasty, and endoscopic debridement. [20, 21] Percutaneous drainage, guided by imaging, is effective for cold abscesses, alleviating compression while minimizing trauma. Vertebroplasty is suitable for patients with mild vertebral destruction and no neural involvement, offering pain relief and structural support via bone cement injection. Endoscopic-assisted debridement combines minimal access with direct visualization and is particularly valuable in anatomically complex regions like the cervical or upper thoracic spine. It offers reduced bleeding, shorter recovery, and less postoperative pain. [22, 23]

3.2.3. Timing of Surgery

Optimal surgical timing is critical for maximizing outcomes and minimizing complications. Elective surgery is generally recommended after 2–4 weeks of anti-tuberculosis chemotherapy, when systemic symptoms (e.g., fever, elevated ESR) are controlled and inflammation is reduced. This minimizes intraoperative dissemination of bacilli and enhances recovery. However, emergency surgery is warranted in cases of rapidly progressing neurological deterioration due to spinal cord compression. In such scenarios, decompression must proceed concurrently with active anti-tuberculosis therapy to prevent permanent neurological damage. [24.25]

3.3. Emerging Therapies and Technologies

3.3.1. Local Drug Delivery and Sustained-Release Systems

Local drug delivery systems represent a novel therapeutic strategy in spinal tuberculosis. By incorporating anti-tuberculosis drugs into biocompatible carriers, these systems enable sustained, high-concentration drug release directly at the lesion site while minimizing systemic exposure and adverse effects. Common carriers include poly (lactic-co-glycolic acid) (PLGA), calcium phosphate cement (CPC), and nano-hydroxyapatite. For instance, CPC offers excellent biocompatibility and osteoconductivity, allowing it to bond tightly with host bone. When mixed with isoniazid or rifampicin and implanted into the infected site, the cement can release drugs over weeks or months, maintaining bactericidal levels locally. Studies have shown that such systems significantly enhance local drug efficacy and reduce systemic toxicity, especially useful for drug-resistant TB and for preventing postoperative recurrence. Nanoparticle-based systems further enable targeted delivery, leveraging their high surface area and tunable physicochemical properties to improve drug penetration and precision.

3.3.2. 3D Printing Technology

Three-dimensional (3D) printing has shown considerable promise in spinal TB treatment. [26.27.28] Through high-resolution CT or MRI imaging, a 3D digital model of the patient's spine is reconstructed using computer-aided design (CAD) software. A 1:1 physical model is then printed using additive manufacturing. [29] These models provide detailed visualization of lesion size, extent, and proximity to vital structures, aiding in preoperative planning, surgical approach selection, and instrumentation placement.Moreover,3D printing enables the fabrication of patient-specific implants—such as customized vertebral bodies and pedicle screws—that precisely conform to the patient's anatomy. In cases with extensive vertebral destruction, conventional implants often fail to provide an optimal fit. Customized implants improve surgical precision, biomechanical restoration, and fusion outcomes. Although still in the developmental phase, early clinical results suggest that 3D printing enhances surgical accuracy and efficiency, and is poised to become a valuable adjunct in spinal TB management.

3.3.3. Targeted Therapy

Targeted therapy has emerged from the expanding understanding of mycobacterial pathogenesis and host immune responses. This approach focuses on specifically interfering with key bacterial or host pathways involved in disease progression. [30.31.32] On the bacterial side, drug development targets vital processes such as cell wall synthesis and energy metabolism. For example, inhibitors of arabinogalactan synthesis disrupt cell wall integrity, rendering bacilli more susceptible to immune clearance and pharmacological attack. On the host side, immune modulation has gained attention. Tumor necrosis factor-alpha (TNF-α) plays a central role in TB-related inflammation and bone destruction. TNF-α inhibitors, originally used in autoimmune diseases like rheumatoid arthritis, are being explored in spinal TB to control excessive inflammation and prevent structural damage. However, immunosuppression-associated risks—especially reactivation of latent TB—require careful consideration. Some targeted therapies are currently in clinical trials, offering hope for a more precise and individualized approach to spinal TB management.

3.3.4. Gene Therapy

Gene therapy represents a frontier in spinal TB treatment, aiming to modify host genetic responses to enhance bacterial clearance or inhibit immune evasion.[33] Two main strategies are under investigation:

- Introducing genes encoding antimicrobial peptides or immune-enhancing cytokines into host cells. For example, delivering a lysozyme-encoding gene to macrophages enhances their mycobactericidal activity.

- Using gene editing tools like CRISPR-Cas9 to silence host genes critical for M. tuberculosis survival inside macrophages, thereby weakening bacterial immune escape mechanisms.

Although gene therapy for TB remains in the preclinical stage, with challenges in delivery vectors, transduction efficiency, and long-term safety, ongoing advances hold promise for future clinical translation.

4. Challenges and Countermeasures in the Treatment of Spinal Tuberculosis

4.1. Drug Resistance

The increasing prevalence of drug-resistant spinal tuberculosis poses a major therapeutic challenge. The development of resistance is primarily attributed to irregular medication use, inadequate treatment duration, and poor patient compliance. Drug-resistant TB is associated with prolonged therapy, high costs, low success rates, and increased risk of disease recurrence and transmission.

Effective countermeasures include:

- Strengthening national and regional drug resistance surveillance systems to monitor epidemiological trends;

- Strict adherence to standardized treatment protocols to minimize misuse and monotherapy;
- Enhancing patient education and follow-up to improve medication adherence;
- Accelerating the development of new anti-tuberculosis drugs, particularly agents targeting resistant strains;
- Exploring combination therapies integrating second-line drugs with immunomodulators or novel delivery systems to improve outcomes.

4.2. Surgical Risk and Postoperative Complications

Spinal TB surgery involves high technical demands due to the proximity of the spinal cord and nerve roots. Common complications include neurological injury, infection recurrence, instrumentation failure, and nonunion of bone grafts.

To reduce surgical risk:

- Comprehensive preoperative assessment is essential, including evaluation of general health status, neurological function, and lesion extent;
- Intraoperative precision should be improved using microsurgical techniques and intraoperative neuromonitoring to avoid nerve damage;
- Postoperative management should emphasize infection control, early mobilization, and rehabilitation;
- A multidisciplinary team (MDT) approach—integrating orthopedics, infectious disease specialists, neurosurgeons, and radiologists—can optimize surgical planning and reduce complications.

4.3. Patient Compliance

The long duration of anti-tuberculosis treatment and associated adverse effects often lead to poor patient adherence, which in turn compromises treatment effectiveness and increases the risk of relapse and drug resistance.

Strategies to improve compliance include:

- Strenghening patient education regarding disease nature, treatment goals, drug effects, and potential side effects to build trust and motivation;
- Simplifying regimens where feasible by reducing the number or frequency of medications without compromising efficacy;
- Establishing robust follow-up systems to monitor treatment progress and address barriers in real time;
- Utilizing digital health tools, such as mobile apps, SMS reminders, and electronic medication monitors, to support medication adherence and timely follow-up.

5. Conclusion

The pathogenesis of spinal tuberculosis is a multifactorial process involving complex interactions among Mycobacterium tuberculosis dissemination, host immune responses, and the anatomical and physiological features of the spine. With continuous advances in biomedical research and clinical technologies, the treatment paradigm for spinal TB has evolved from conventional chemotherapy and surgery toward more precise, individualized strategies. Pharmacotherapy remains the foundation of treatment, but drug resistance continues to pose a significant clinical challenge. Surgical techniques have been refined, with the integration of minimally invasive approaches and 3D printing significantly improving clinical outcomes. Emerging modalities—such as local sustained-release drug systems, targeted molecular therapies, and gene-based interventions—demonstrate promising potential for enhancing efficacy, especially in refractory or drug-resistant cases. Future efforts should prioritize basic research to elucidate the molecular mechanisms of spinal TB pathogenesis and drug resistance. Continued development of novel anti-tuberculosis agents and advanced therapeutic platforms will be essential for overcoming current limitations. Meanwhile, broader implementation of multidisciplinary care models, improved patient education, and optimized treatment compliance strategies will collectively elevate the standard of clinical care. Through these concerted efforts, it is hoped that the cure rate of spinal tuberculosis will be further increased, the disability rate reduced, and the overall quality of life for affected patients significantly improved.

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