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Review on the Pathogenesis and Treatment Progress of Spinal Tuberculosis

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Abstract

This review systematically elaborates on the pathogenesis of spinal tuberculosis, including the interaction of factors such as the transmission route of *Mycobacterium tuberculosis*, the body's immune response, and the anatomical and physiological characteristics of the spine. It comprehensively summarizes the current progress in the treatment of spinal tuberculosis, covering traditional anti-tuberculosis drug therapy, optimized surgical treatment plans, as well as the application achievements and development trends of cutting-edge technologies such as emerging local drug-loaded sustained-release systems, 3D printing technology, and targeted therapy. The review aims to provide clinicians with a comprehensive and in-depth theoretical basis and treatment reference, and to promote the further improvement of the diagnosis and treatment level of spinal tuberculosis.

Keywords

Spinal Tuberculosis, Pathogenesis, Anti-Tuberculosis Drugs, Surgical Treatment, Treatment Progress

1. Introduction

Spinal tuberculosis is the most common type of osteoarticular tuberculosis, accounting for approximately 50% of all osteoarticular tuberculosis cases [1]. Its incidence remains high globally, especially in developing countries. Spinal tuberculosis not only causes severe pain, deformity, and neurological dysfunction in patients [2], but also may lead to serious complications such as paraplegia if treated improperly or delayed, seriously affecting patients' quality of life and survival

prognosis. In recent years, with the increase in population mobility, the emergence of drug-resistant *Mycobacterium tuberculosis* strains, and the expansion of immunocompromised populations, the prevention and treatment of spinal tuberculosis face new challenges. In-depth understanding of its pathogenesis and mastery of the latest treatment progress is of great clinical significance for improving the early diagnosis rate and treatment effect of spinal tuberculosis.

2. Pathogenesis of Spinal Tuberculosis

2.1. Transmission Routes of *Mycobacterium tuberculosis*

2.1.1. Hematogenous Spread

Hematogenous spread is the most important infection route of spinal tuberculosis [3]. After the human body is initially infected with *Mycobacterium tuberculosis*, a primary infection focus is usually formed in the lungs. When the body's immunity declines, *Mycobacterium tuberculosis* in the primary focus breaks through the restriction of alveolar macrophages, enters the pulmonary veins or capillaries, and spreads to the whole body through the systemic circulation. Since the nutrient arteries of the spinal vertebrae are mostly end arteries, the blood flow velocity is slow, and eddies are easily formed at the branching of blood vessels, making it easy for *Mycobacterium tuberculosis* to stay and colonize in the capillary network of the vertebral metaphysis. Clinical studies have shown that the tubercle bacilli of approximately 80% of spinal tuberculosis patients originate from the lungs, and autopsy also confirms that most patients with spinal tuberculosis have pulmonary tuberculosis foci. In addition, *Mycobacterium tuberculosis* can also spread through the vertebral venous system (Batson's plexus) [4]. This venous plexus has no venous valves and is extensively connected with the thoracic, abdominal, pelvic, and intracranial veins. When the patient coughs, strains during defecation, or performs other actions that cause increased abdominal pressure, *Mycobacterium tuberculosis* can enter the spine directly through the vertebral venous system without passing through the pulmonary circulation, which explains the pathogenesis of some spinal tuberculosis patients without a history of pulmonary tuberculosis.

2.1.2. Lymphatic Spread

There is a rich lymphatic network around the spine. When lymphatic tuberculosis in the neck, mediastinum, abdomen, and other parts ruptures, *Mycobacterium tuberculosis* can spread to the lymph nodes around the spine through the lymphatic circulation, and then break through the lymph node barrier to invade the spinal tissue [5]. Although lymphatic spread is less common than hematogenous spread, the proportion of lymphatic spread is relatively higher in children with spinal tuberculosis due to the vigorous development of their lymphatic system.

2.1.3. Direct Invasion

When tissues around the spine (such as paravertebral soft tissues, ribs, and sternum) are infected with tuberculosis, *Mycobacterium tuberculosis* can directly invade the spine. For example, thoracic spinal tuberculosis may occur due to the

invasion of adjacent rib tuberculosis, and lumbar spinal tuberculosis may be caused by the direct erosion of the vertebral body by a psoas major abscess. This mode of spread is relatively localized, but it can also lead to spinal tuberculosis in cases of severe local infection and delayed treatment.

2.2. The Body's Immune Response

2.2.1. Innate Immune Response

Innate immunity is the first line of defense for the body against *Mycobacterium tuberculosis* infection. After *Mycobacterium tuberculosis* enters the body, it is first recognized by innate immune cells such as macrophages and dendritic cells. Macrophages recognize the pathogen-associated molecular patterns (PAMPs) of *Mycobacterium tuberculosis* (such as lipoarabinomannan and peptidoglycan) through surface pattern recognition receptors (PRRs, e.g., Toll-like receptors), and then phagocytose *Mycobacterium tuberculosis* to form phagosomes. Under normal circumstances, phagosomes fuse with lysosomes to form phagolysosomes, which kill *Mycobacterium tuberculosis* using enzymes and reactive oxygen species in lysosomes [6]. However, the cell wall of *Mycobacterium tuberculosis* contains a large number of lipid components, such as arabinogalactan and phospholipids, which can inhibit the fusion of phagosomes and lysosomes or resist the killing of enzymes and reactive oxygen species in phagolysosomes, thereby surviving and reproducing in macrophages. At the same time, activated macrophages release pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) to recruit more immune cells to the infection site. However, an excessive inflammatory response can also cause local tissue damage, creating conditions for the spread of *Mycobacterium tuberculosis*.

2.2.2. Cellular Immune Response

Cellular immunity plays a key role in controlling *Mycobacterium tuberculosis* infection. Antigen-presenting cells (such as macrophages and dendritic cells) present the processed *Mycobacterium tuberculosis* antigens to naive T lymphocytes, which are then activated and differentiated into helper T cells (Th cells) and cytotoxic T cells (CTLs). Th1 cells secrete interferon-γ (IFN-γ), which can activate macrophages, enhance their bactericidal ability, and promote the phagocytosis and killing of *Mycobacterium tuberculosis* by macrophages; at the same time, IFN-γ can also promote the differentiation of Th1 cells, forming a positive feedback regulation to enhance the cellular immune response [7]. CTLs can directly recognize and kill target cells infected with *Mycobacterium tuberculosis*, thereby eliminating infected cells in the body. In individuals with normal immune function, the cellular immune response can effectively control the growth and spread of *Mycobacterium tuberculosis*, keeping the infection in a latent state. However, in immunocompromised populations (such as AIDS patients, organ transplant patients taking long-term immunosuppressants, and patients with poorly controlled diabetes), the function of T lymphocytes is inhibited, and the cellular immune response cannot play an effective role, leading to the massive reproduction

of *Mycobacterium tuberculosis* and the occurrence of spinal tuberculosis.

2.2.3. Immune Escape Mechanisms

Mycobacterium tuberculosis has a variety of immune escape mechanisms. Its cell wall components (such as lipoarabinomannan) can inhibit the expression of co-stimulatory molecules (e.g., B7-1, B7-2) on the surface of macrophages, hindering the activation and proliferation of T lymphocytes [8]; proteins secreted by *Mycobacterium tuberculosis* (such as ESAT-6 and Cfp10) can interfere with the processing and presentation of *Mycobacterium tuberculosis* antigens by antigen-presenting cells, making it impossible for T lymphocytes to effectively recognize infected cells. In addition, *Mycobacterium tuberculosis* can induce the production of regulatory T cells (Treg cells), which secrete inhibitory cytokines such as interleukin-10 (IL-10) [9] to inhibit the function of Th1 cells and weaken the cellular immune response, thereby achieving immune escape.

2.3. Anatomical and Physiological Characteristics of the Spine

2.3.1. Structural Characteristics of the Vertebral Body

The vertebral body is mainly composed of cancellous bone, and the bone marrow tissue in cancellous bone provides rich nutrients for the growth of *Mycobacterium tuberculosis*. Compared with cortical bone, cancellous bone has an abundant blood supply but slow blood flow, making it easier for *Mycobacterium tuberculosis* to colonize and reproduce. The nutrient arteries of the vertebral body are mostly end arteries. Once infection occurs, the local blood circulation is easily affected, the anti-infection ability decreases, and inflammatory exudates and necrotic tissues are difficult to discharge, further aggravating the condition. At the same time, the trabecular structure of the vertebral body is loose, so *Mycobacterium tuberculosis* can easily spread in the trabecular space, causing extensive bone destruction.

2.3.2. Special Physiological State of the Intervertebral Disc

The intervertebral disc is composed of the nucleus pulposus, annulus fibrosus, and cartilaginous endplate. It lacks a direct blood supply, and nutrients are mainly obtained through the vertebral body-endplate-intervertebral disc penetration pathway. This special nutrient supply mode results in slow metabolism of the intervertebral disc and difficulty for immune cells to reach it. Once the intervertebral disc is infected with *Mycobacterium tuberculosis*, its self-immune defense ability is weak, and it is difficult to eliminate *Mycobacterium tuberculosis*. Moreover, the cartilaginous endplate of the intervertebral disc is easily damaged under the erosion of *Mycobacterium tuberculosis*, leading to the obstruction of nutrient supply to the intervertebral disc, accelerating the degeneration and necrosis of the intervertebral disc, and at the same time providing conditions for the spread of *Mycobacterium tuberculosis* to adjacent vertebral bodies.

2.3.3. Mechanical Load of the Spine

The spine is the axial skeleton of the human body, bearing the weight of the body

and the stress generated by various movements. During daily activities, the vertebral bodies of the spine need to bear large pressure and shear force, especially in the lumbar and lower thoracic regions. After the vertebral body is infected with tuberculosis, the bone is damaged and its mechanical strength decreases significantly, making it difficult to bear the normal mechanical load, which easily leads to vertebral body collapse and deformation, and then causes kyphosis or scoliosis deformity of the spine [4]. In turn, spinal deformity further changes the biomechanical distribution of the spine, aggravates the damage to the diseased vertebral body, forms a vicious cycle, and increases the risk of compression of the spinal cord and nerves.

2.4. Pathological Progression

2.4.1. Exudative Phase

In the early exudative phase of spinal tuberculosis, after *Mycobacterium tuberculosis* invades the vertebral body or paravertebral tissues, the body's immune system immediately initiates an inflammatory response. Local blood vessels dilate, permeability increases, and a large number of inflammatory cells (such as neutrophils and macrophages) migrate to the infection site, leading to local hyperemia and edema. At this time, a small amount of *Mycobacterium tuberculosis* can be seen in the lesion tissue, and the surrounding tissue is mainly characterized by exudative changes, showing serous or fibrinous exudate in the tissue space. Patients may have systemic and local symptoms such as low fever, night sweats, fatigue, and local pain. Imaging examinations show slight changes such as blurred vertebral body edges and a narrowed intervertebral space.

2.4.2. Proliferative Phase

As the disease progresses to the proliferative phase, macrophages phagocytose *Mycobacterium tuberculosis* and gradually differentiate into epithelioid cells under the action of cytokines. Multiple epithelioid cells fuse with each other to form Langhans giant cells. At the same time, lymphocytes, fibroblasts, and other cells gather around epithelioid cells and Langhans giant cells to form tuberculous nodules. Tuberculous nodules are specific immune responses of the body to *Mycobacterium tuberculosis* infection, which can restrict the spread of *Mycobacterium tuberculosis* to a certain extent. In this phase, the number of *Mycobacterium tuberculosis* in the lesion tissue is relatively stable, the inflammatory response is alleviated, but tissue destruction continues. Imaging shows an expanded range of vertebral bone destruction, bone defects, and more obvious swelling of paravertebral soft tissues.

2.4.3. Caseous Necrosis Phase

When the body's immunity further declines or *Mycobacterium tuberculosis* reproduces in large quantities, the lesion enters the caseous necrosis phase [10]. Epithelioid cells and Langhans giant cells in the center of tuberculous nodules undergo necrosis, forming yellowish-white, soft, cheese-like necrotic material, *i.e.*, caseous necrosis. The caseous necrotic material contains a large number of *Mycobacterium tuberculosis* and lacks blood supply, making it difficult for the body

to absorb and eliminate it. With the increase in caseous necrotic material, the pressure in the lesion increases, which can break through the periosteum of the vertebral body and accumulate in the paravertebral soft tissues to form cold abscesses. Cold abscesses can spread to distant places along the tissue space to form migratory abscesses. For example, cold abscesses caused by lumbar spinal tuberculosis can spread downward along the psoas major muscle to the iliac fossa and inguinal region. Abscesses compress surrounding nerves, blood vessels, and tissues, leading to aggravated pain, limb numbness, weakness, and other symptoms. In severe cases, they can compress the spinal cord and cause paraplegia. Imaging examinations show severe vertebral destruction and collapse, significantly narrowed intervertebral space, and formation of paravertebral or migratory abscesses.

3. Treatment Progress of Spinal Tuberculosis

3.1. Modern Diagnostic Tools and Early Detection

Early diagnosis of spinal tuberculosis is crucial for improving prognosis. In recent years, advancements in molecular biology and imaging technologies have provided new tools for the early and accurate diagnosis of spinal tuberculosis.

Rapid Molecular Detection Techniques: Rapid molecular detection (such as GeneXpert MTB/RIF, TB-LAMP) can identify specific nucleic acid sequences of *Mycobacterium tuberculosis*, completing diagnosis and simultaneously detecting rifampicin resistance within hours. These techniques, based on a deep understanding of the pathogen's genetic material, significantly shorten diagnostic time and improve sensitivity and specificity, especially in cases where traditional culture methods are time-consuming or smear-negative. Early molecular diagnosis facilitates the timely initiation of precise anti-tuberculosis treatment, allowing intervention before significant bone destruction and vertebral collapse occur.

Advanced MRI Protocols: Magnetic Resonance Imaging (MRI) plays an indispensable role in the diagnosis of spinal tuberculosis. In addition to conventional MRI sequences, advanced MRI protocols such as Diffusion-Weighted Imaging (DWI), perfusion imaging, and Susceptibility-Weighted Imaging (SWI) can identify vertebral inflammation, bone marrow edema, abscess formation, and microscopic structural changes in bones earlier and more accurately. DWI reflects restricted water molecule diffusion, aiding in the early detection of inflammatory infiltration; perfusion imaging assesses lesion blood flow, helping to differentiate active from chronic lesions; and SWI is sensitive to hemorrhage and calcification. These advanced techniques reflect early changes in the pathogenesis of spinal tuberculosis at a microscopic level, providing clinicians with richer diagnostic information for early detection and intervention.

3.2. Anti-Tuberculosis Drug Therapy

3.2.1. Traditional Anti-Tuberculosis Drug Treatment Regimens

Anti-tuberculosis drug therapy is the cornerstone of spinal tuberculosis treat-

ment, following the principles of "early, combined, appropriate, regular, and full-course" medication. First-line anti-tuberculosis drugs include isoniazid (INH), rifampicin (RFP), pyrazinamide (PZA), ethambutol (EMB), and streptomycin (SM) [11]. INH destroys the integrity of the cell wall by inhibiting the synthesis of mycolic acid in the cell wall of *Mycobacterium tuberculosis*; RFP binds to the RNA polymerase of *Mycobacterium tuberculosis* to inhibit RNA synthesis; PZA has a bactericidal effect in an acidic environment (e.g., in macrophages); EMB inhibits the synthesis of arabinose-arabinan in the cell wall of *Mycobacterium tuberculosis*; SM acts on the ribosome of *Mycobacterium tuberculosis* to affect protein synthesis.

For newly treated spinal tuberculosis patients, the commonly used standardized chemotherapy regimen includes an intensive phase of 2 - 3 months with quadruple medication (INH, RFP, PZA, and EMB) and a consolidation phase of 4 - 6 months with dual medication (INH and RFP), with a total course of 6 - 9 months. For patients with severe conditions, complications (such as abscess formation and neurological dysfunction), or recurrent disease, the course of treatment can be appropriately extended to 12 - 18 months. During treatment, it is necessary to closely monitor the patient's liver and kidney function, blood routine, and other indicators because anti-tuberculosis drugs may cause adverse reactions such as liver function damage, gastrointestinal reactions, and optic neuritis. Once severe adverse reactions occur, the treatment plan should be adjusted in a timely manner.

3.2.2. Treatment of Drug-Resistant Spinal Tuberculosis

In recent years, the incidence of drug-resistant spinal tuberculosis has been on the rise. Especially, the emergence of multidrug-resistant tuberculosis (MDR-TB, resistant to both INH and RFP) and extensively drug-resistant tuberculosis (XDR-TB, resistant to at least four anti-tuberculosis drugs including INH and RFP) has brought great challenges to treatment [12]. The treatment of drug-resistant spinal tuberculosis requires the selection of second-line anti-tuberculosis drugs based on drug sensitivity test results, such as aminoglycosides (kanamycin, amikacin, capreomycin), fluoroquinolones (levofloxacin, moxifloxacin), thioamides (ethionamide, prothionamide), cycloserine, and linezolid. The antibacterial mechanism of second-line anti-tuberculosis drugs is different from that of first-line drugs. For example, fluoroquinolones hinder DNA replication and transcription by inhibiting the activity of DNA gyrase and topoisomerase IV of *Mycobacterium tuberculosis*.

The treatment course of drug-resistant spinal tuberculosis is usually long, generally 18 - 24 months or even longer. Since second-line anti-tuberculosis drugs have relatively more adverse reactions (e.g., aminoglycosides can cause hearing damage and renal function damage; fluoroquinolones may cause tendinitis and arrhythmia), it is necessary to more closely monitor the patient's adverse reactions during treatment and conduct regular examinations of hearing, renal function, and electrocardiogram. At the same time, to improve the treatment effect, immunomodulators such as γ-interferon and interleukin-2 can be used in combination to enhance the body's immune function. In addition, new anti-tuberculosis

drugs such as bedaquiline and delamanid provide new options for the treatment of drug-resistant spinal tuberculosis, but their application still needs further accumulation of clinical experience.

3.3. Surgical Treatment

3.3.1. Surgical Indications

The main purposes of surgical treatment are to clear the lesion, relieve nerve compression, correct deformity, and reconstruct spinal stability [13]-[16]. Specific surgical indications include: 1) obvious sequestrum, caseous necrotic tissue, and cold abscess that are unresponsive to standardized anti-tuberculosis drug treatment, or abscesses with the risk of rupture and infection; 2) spinal cord or nerve root compression caused by spinal tuberculosis, resulting in neurological dysfunction (such as limb numbness, weakness, hypoalgesia, and urinary and fecal dysfunction) that does not improve with conservative treatment; 3) severe kyphosis or scoliosis deformity caused by spinal tuberculosis (Cobb angle exceeding 30˚), which affects the patient's cardiopulmonary function or appearance, or has the risk of further aggravation of the deformity; 4) continuous progression of the disease after standardized anti-tuberculosis drug treatment, with severe vertebral destruction and risk of pathological fracture; 5) spinal tuberculosis combined with other diseases (such as pyogenic infection and tumor) that require surgical treatment.

3.3.2. Surgical Methods

Debridement: Debridement is the basic surgical method for spinal tuberculosis treatment. It directly exposes the lesion through a surgical incision and thoroughly removes sequestrum, caseous necrotic tissue, granulation tissue, and cold abscess. According to the location and scope of the lesion, anterior, posterior, or combined anterior-posterior approaches can be selected. Anterior debridement is suitable for patients with lesions mainly located in the anterior part of the vertebral body, which can directly clear the lesion and restore the height of the vertebral body; posterior debridement is suitable for patients with lesions involving the posterior structures of the vertebral body (such as pedicles and laminae), and posterior internal fixation can be performed while clearing the lesion; for patients with extensive lesions involving both anterior and posterior structures of the vertebral body, combined anterior-posterior debridement can be used to ensure thorough lesion clearance. After debridement, bone graft fusion is usually required to promote the restoration of spinal stability.

Bone Graft Fusion: Bone graft fusion is a key link in the surgical treatment of spinal tuberculosis, aiming to restore the height and stability of the vertebral body and promote osseous healing of the lesion site. Commonly used bone graft materials include autologous bone, allogeneic bone, and artificial bone [17] [18]. Autologous bone (such as iliac bone and rib bone) has good osteoconductivity, osteoinductivity, and osseointegration ability, and is the first choice for bone graft fusion, but it has disadvantages such as donor site pain and limited bone harvest. Allogeneic bone can reduce immune rejection after treatment, but its bone healing

speed is relatively slow and there is a potential risk of disease transmission. Artificial bone materials (such as calcium phosphate cement and hydroxyapatite) have good biocompatibility and plasticity, and can be filled according to the shape of the lesion, but they lack osteoinductive activity and need to be used in combination with autologous bone or bone growth factors. Bone graft fusion methods include intervertebral bone graft and interpedicular bone graft, and the specific method is selected according to the lesion location and surgical approach.

Internal Fixation: The application of internal fixation technology has significantly improved the effectiveness of surgical treatment for spinal tuberculosis. It can further enhance spinal stability on the basis of debridement and bone graft fusion, reduce the displacement and collapse of bone grafts, and promote early ambulation of patients. Commonly used internal fixation materials include titanium alloy screw-rod systems and plate-screw systems. Posterior pedicle screw internal fixation is currently the most widely used internal fixation method. By inserting pedicle screws into the vertebral body, adjacent vertebral bodies are fixed together using connecting rods and cross-links to provide three-dimensional stability. The anterior internal fixation system is suitable for post-anterior debridement, which can directly support the vertebral body and restore the stability of the anterior spinal column. The timing of internal fixation needs to be comprehensively determined based on the patient's condition, general condition, and surgical method, and is generally performed after debridement and bone graft fusion.

Minimally Invasive Surgery: In recent years, minimally invasive surgery has been increasingly used in the treatment of spinal tuberculosis [19]-[22], including percutaneous puncture drainage, percutaneous vertebroplasty, and endoscope-assisted debridement. Percutaneous puncture drainage is suitable for patients with paravertebral abscess formation. Under image guidance, the abscess is punctured percutaneously, and a drainage tube is inserted to drain the pus, which can reduce the compression of the abscess on surrounding tissues, relieve symptoms, and reduce the trauma of open drainage. Percutaneous vertebroplasty is mainly used for patients with spinal tuberculosis with mild vertebral destruction and no nerve compression symptoms. By injecting bone cement into the vertebral body, the strength of the vertebral body is enhanced, vertebral collapse is prevented, and pain is relieved. Endoscope-assisted debridement combines endoscopic technology with surgical operation. An endoscope is inserted through a small incision or natural cavity to clear the lesion under direct vision, which has the advantages of small trauma, less bleeding, and fast recovery, and is especially suitable for spinal tuberculosis in anatomically complex areas such as the cervical and thoracic spine.

3.3.3. Selection of Surgical Timing

Appropriate surgical timing is crucial for improving the success rate of surgery and reducing complications. It is generally recommended to perform surgery after 2 - 4 weeks of anti-tuberculosis drug treatment, when the patient's systemic toxic symptoms are controlled (such as normal body temperature, decreased erythrocyte sedimentation rate, and reduced local pain). At this time, the vitality of *My-*

cobacterium tuberculosis is inhibited, and the risk of *Mycobacterium tuberculosis* spread during surgery is reduced. However, for patients with emergency conditions (such as severe spinal cord compression caused by spinal tuberculosis and progressive neurological dysfunction), surgical decompression should be performed as soon as possible while actively conducting anti-tuberculosis treatment to save neurological function [23] [24].

3.4. Emerging Treatment Technologies and Concepts

3.4.1. Local Drug-Loaded Sustained-Release Systems

Local drug-loaded sustained-release systems are a new type of treatment technology. By combining anti-tuberculosis drugs with carrier materials, drugs are slowly released locally at the lesion site, improving the local drug concentration while reducing the systemic drug dosage and adverse drug reactions. Commonly used carrier materials include polylactic-co-glycolic acid (PLGA), calcium phosphate cement, and nano-hydroxyapatite.

Taking calcium phosphate cement as an example, it has good biocompatibility and osteoconductivity and can form a tight combination with bone tissue. When anti-tuberculosis drugs (such as INH and RFP) are mixed with calcium phosphate cement and implanted into the lesion site, the drugs can be continuously released for several weeks or even months, maintaining an effective bactericidal concentration locally. Studies have shown that local drug-loaded sustained-release systems can significantly increase the local drug concentration at the lesion site in the treatment of spinal tuberculosis, enhance the bactericidal effect, and reduce adverse reactions such as liver and kidney function damage caused by systemic medication. They are especially suitable for patients with drug-resistant spinal tuberculosis and for postoperative recurrence prevention. In addition, nanoparticle carriers can achieve targeted drug delivery by relying on their high specific surface area and unique physicochemical properties, further improving the treatment effect.

3.4.2. 3D Printing Technology

3D printing technology shows great potential in the treatment of spinal tuberculosis [2] [25]-[27]. Through high-precision CT or MRI scanning of the patient's spine, three-dimensional image data are obtained, and a spinal model is reconstructed using computer-aided design (CAD) software. Then, a 1:1 physical model is produced using a 3D printer [27]. This model can clearly show the location, size, and shape of the lesion, as well as its relationship with important surrounding structures such as nerves and blood vessels, helping doctors more intuitively understand the condition before surgery and formulate a precise surgical plan, including the selection of the surgical approach, determination of the lesion resection range, and planning of the internal fixation implantation position.

In terms of personalized implant manufacturing, 3D printing technology can customize artificial vertebral bodies, pedicle screws, and other implants according to the patient's anatomical structure. For example, for patients with spinal tuber-

culosis and severe vertebral destruction, traditional implants are difficult to perfectly match the lesion site, while 3D-printed personalized artificial vertebral bodies can highly match the patient's spinal shape, which not only improves the accuracy and stability of the surgery, but also better restores the biomechanical properties of the spine and promotes postoperative rehabilitation. At present, the application of 3D printing technology in the treatment of spinal tuberculosis is still in the development stage, but it has achieved good preliminary results in clinical practice and is expected to become an important auxiliary treatment method in the future.

3.4.3. Targeted Therapy

Targeted therapy is an emerging treatment strategy developed based on an in-depth understanding of the pathogenic mechanism of *Mycobacterium tuberculosis* and the host immune response. Its core is to design specific drugs to act on key targets for the growth and reproduction of *Mycobacterium tuberculosis* or host cell signaling pathways involved in the pathogenesis of spinal tuberculosis [28] [29].

On the one hand, the research and development of targeted drugs against *Mycobacterium tuberculosis* focus on key processes such as cell wall synthesis and energy metabolism. For example, drugs that specifically inhibit the arabinogalactan synthase in the cell wall of *Mycobacterium tuberculosis* can destroy the integrity of the cell wall and enhance the sensitivity of bacteria to drugs. On the other hand, targeted therapy for host immune regulation aims to correct immune imbalance. TNF-α plays an important role in the inflammatory response and bone destruction of spinal tuberculosis. Anti-TNF-α monoclonal antibodies have achieved good efficacy in autoimmune diseases such as rheumatoid arthritis and have been gradually applied in the research of spinal tuberculosis treatment in recent years. By blocking the activity of TNF-α, excessive inflammatory response can be reduced, and bone destruction can be alleviated, but potential problems such as increased infection risk need to be considered. At present, some targeted therapy drugs have entered the clinical trial stage, bringing new hope for the precise treatment of spinal tuberculosis.

3.4.4. Gene Therapy

Gene therapy achieves the purpose of treating diseases by introducing specific genes into host cells to correct or compensate for gene defects [30]. In the field of spinal tuberculosis treatment, gene therapy mainly has two strategies: one is to introduce genes encoding antimicrobial peptides or immunomodulatory factors into cells infected with *Mycobacterium tuberculosis*, so that they express substances with bactericidal or immune-enhancing effects. For example, introducing the gene encoding lysozyme into macrophages can enhance the killing ability of macrophages against *Mycobacterium tuberculosis*; the other is to knock out or regulate host genes related to *Mycobacterium tuberculosis* infection and immune escape through gene editing technology. For example, using CRISPR-Cas9 technology to knock out host genes that *Mycobacterium tuberculosis* depends on for

survival in macrophages can weaken the immune escape ability of *Mycobacterium tuberculosis*. Although the application of gene therapy in spinal tuberculosis is still in the stage of laboratory research and preclinical trials, and faces many challenges such as the safety of gene carriers, transfection efficiency, and long-term stability, it is expected to become an important method for the treatment of spinal tuberculosis in the future with the continuous advancement of technology.

4. Challenges and Countermeasures in Treatment

4.1. Drug Resistance Issue

The treatment of drug-resistant spinal tuberculosis is a major challenge currently faced. The emergence of drug-resistant strains is mainly related to factors such as irregular medication use, insufficient treatment course, and poor patient adherence [31] [32]. Patients with drug-resistant tuberculosis not only have a long treatment cycle and high cost but also have a low treatment success rate, which easily leads to disease recurrence and spread. Countermeasures include: strengthening the construction of drug resistance monitoring networks to timely grasp the epidemic trend of drug-resistant strains; strictly standardizing the use of anti-tuberculosis drugs to improve patient treatment adherence; accelerating the research and development of new anti-tuberculosis drugs, especially specific drugs for drug-resistant *Mycobacterium tuberculosis*; and exploring new treatment plans, such as combining multiple second-line drugs and integrating immunotherapy.

4.2. Surgical Risks and Complications

Spinal tuberculosis surgery involves important structures such as the spinal cord and nerves, resulting in high surgical risks and many postoperative complications. Common complications include nerve injury, infection recurrence, internal fixation failure, and nonunion of bone grafts. To reduce surgical risks, a comprehensive assessment of the patient's general condition, neurological function, and lesion scope should be conducted before surgery; delicate surgical techniques should be adopted during surgery, and neuroelectrophysiological monitoring should be used to reduce nerve injury; after surgery, anti-infection treatment and rehabilitation care should be strengthened, and the patient's condition changes should be closely observed. In addition, the multidisciplinary team (MDT) model, which integrates the advantages of orthopedics, infectious diseases, neurosurgery, radiology, and other disciplines, helps to formulate a more scientific and reasonable surgical plan, improve the success rate of surgery, and reduce the occurrence of complications.

4.3. Patient Adherence

The treatment course of spinal tuberculosis is long, and there are many drug adverse reactions, leading to poor adherence in some patients, which affects the treatment effect. Measures to improve patient adherence include strengthening patient education, explaining the treatment process, drug effects, and adverse reactions to patients in detail to enhance their confidence in and understanding of

treatment; optimizing the treatment plan by minimizing the types and dosage of drugs to reduce adverse reactions; establishing a sound follow-up mechanism to track the patient's treatment status regularly and solve problems encountered by patients in the treatment process in a timely manner; and using informational tools such as mobile phone applications and SMS reminders to help patients take medication and return for reexamination on time.

4.4. Bone Remodeling Mechanisms and Vertebral Collapse

Chronic inflammation caused by *Mycobacterium tuberculosis* infection is a key factor leading to vertebral bone destruction and collapse. Although the immune response aims to clear the pathogen, it can also exacerbate bone destruction through an imbalance in bone remodeling mechanisms.

Inflammation-Mediated Bone Resorption: Macrophages and T lymphocytes activated by *Mycobacterium tuberculosis* infection secrete a large number of pro-inflammatory cytokines, such as Tumor Necrosis Factor-α (TNF-α), Interleukin-1 (IL-1), and Interleukin-6 (IL-6). These cytokines directly or indirectly stimulate the recruitment, differentiation, and activation of osteoclast precursors, enhancing osteoclastic bone resorption.

Vertebral Bone Destruction and Collapse: After vertebral infection with tuberculosis, the bone is damaged, and its mechanical strength significantly decreases, making it difficult to withstand normal mechanical loads, which easily leads to vertebral collapse and deformity, and further causes kyphosis or scoliosis [4].

5. Limitations of the Review

This review aims to comprehensively summarize the pathogenesis and treatment progress of spinal tuberculosis, but it still has some limitations.

Heterogeneity of Source Studies: Research on spinal tuberculosis involves diverse study designs, patient populations, diagnostic criteria, and treatment regimens. This leads to considerable heterogeneity in methodology and results among the included original studies, which may affect the generalizability and comparability of the conclusions of this review.

Lack of High-Level Evidence for New Technologies: For emerging technologies such as local drug-loaded sustained-release systems, 3D printing technology, targeted therapy, and gene therapy, most current research is still in in vitro, animal model, or small-scale clinical trial stages. There is a lack of large-scale, multi-center, randomized controlled trials to provide high-level clinical evidence to fully evaluate their long-term efficacy, safety, and cost-effectiveness, which limits a comprehensive assessment of their clinical translation prospects.

Potential Publication Bias: Publication bias is common in academia, meaning that studies with positive results are more likely to be published, while studies with negative or non-significant results may be overlooked. This bias may lead to an overly optimistic assessment of certain treatment effects in this review.

Scope Limitations of the Review: This review primarily focuses on the patho-

genesis and treatment progress of spinal tuberculosis. Other related aspects, such as rehabilitation therapy, complication management, and socioeconomic impact, have not been discussed in depth, which may limit its comprehensiveness.

6. Conclusions

The occurrence of spinal tuberculosis is a complex process involving the interaction of multiple factors such as the spread of *Mycobacterium tuberculosis*, the body's immune response, and the anatomical and physiological characteristics of the spine. With the in-depth development of medical research and the continuous advancement of technology, the treatment of spinal tuberculosis has gradually developed from traditional drug and surgical treatment to a precision and personalized emerging treatment model. Anti-tuberculosis drug therapy remains the basis, but the issue of drug resistance needs to be solved urgently; surgical treatment is constantly optimized, and the application of minimally invasive surgery and 3D printing technology has improved the treatment effect; emerging technologies such as local drug-loaded sustained-release systems, targeted therapy, and gene therapy show good application prospects.

In the future, it is necessary to further strengthen basic research, to explore in depth the pathogenesis and drug resistance mechanism of spinal tuberculosis, and to provide theoretical support for the development of more effective treatment methods; accelerate the research and development of new anti-tuberculosis drugs and treatment technologies to improve the treatment effect of drug-resistant tuberculosis; promote the MDT model to enhance the level of clinical diagnosis and treatment; and strengthen patient education and management to improve treatment adherence. Through multi-faceted efforts, it is expected to further improve the cure rate of spinal tuberculosis, reduce the disability rate, and improve the quality of life of patients.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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