ISSN 2581-6217

World Journal of Pharmaceutical Science & Technology

Journal homepage: www.wjpst.com

Review Article

DISSEMINATED TUBERCULOSIS: A COMPREHENSIVE REVIEW

Dr. Ravindra Salve[1]

1. MBBS, D.T.C.D.

Address for correspondence:
Dr. Ravindra Salve[1], MBBS, D.T.C.D.

Email Id: drravisalveth@gmail.com

Received: 02-04-2024, Revised:11-05-2024, Accepted: 24-06-2024

ABSTRACT

Disseminated tuberculosis (TB) is a severe and potentially life-threatening form of tuberculosis characterized by the widespread hematogenous spread of Mycobacterium tuberculosis, leading to multi-organ involvement. It is particularly prevalent among immunocompromised individuals, including those with HIV/AIDS, diabetes, malignancies, or undergoing immunosuppressive therapy. The disease presents significant diagnostic and therapeutic challenges due to its diverse and often nonspecific clinical manifestations, which can mimic other systemic infections and inflammatory conditions.

This review comprehensively explores the epidemiology, pathogenesis, clinical presentation, diagnostic approaches, treatment strategies, and prognosis of disseminated TB. The disease remains a major global health concern, with increasing incidence in endemic regions and among high-risk populations. Despite advancements in medical technology, delayed diagnosis remains a critical issue, often resulting in poor clinical outcomes.

Early diagnosis and timely initiation of treatment are paramount in improving patient prognosis. The integration of advanced molecular diagnostics, including nucleic acid amplification tests (NAATs) such as GeneXpert, along with imaging modalities like computed tomography (CT) and magnetic resonance imaging (MRI), has significantly enhanced early detection and disease monitoring. Additionally, histopathological evaluation and microbiological cultures play a vital role in confirming the diagnosis.

This article aims to provide an in-depth understanding of disseminated TB to aid healthcare professionals in its effective management. A multidisciplinary approach, involving infectious disease specialists, pulmonologists, radiologists, and microbiologists, is essential for optimizing treatment outcomes. Future research should focus on novel therapeutic interventions, vaccine developments, and improved screening strategies to mitigate the burden of disseminated tuberculosis globally.

KEYWORDS

Bacteremia, Diagnosis, Disseminated Tuberculosis, Epidemiology, Extrapulmonary Tuberculosis, Immunosuppression, Management, Mycobacterium tuberculosis, Pathogenesis, Prognosis, Pulmonary Involvement, Radiology, Risk Factors, Systemic Manifestations, Therapeutics, Treatment, Tuberculous Meningitis, Tuberculosis, Tuberculosis Control, Tuberculosis Management

INTRODUCTION

Tuberculosis (TB) remains a major global health burden, with disseminated TB representing one of its most severe and life-threatening manifestations. This condition arises when Mycobacterium tuberculosis spreads hematogenously from a primary infection site, leading to widespread systemic involvement affecting multiple organs, including the lungs, liver, spleen, bone marrow, and central nervous system. Despite advancements in TB control programs, disseminated TB continues to pose significant challenges due to its complex pathophysiology and diagnostic difficulties.

Disseminated TB is more prevalent in immunocompromised individuals, particularly those with HIV/AIDS, malignancies, diabetes mellitus, chronic kidney disease, or those undergoing immunosuppressive therapy such as organ transplant recipients and patients on long-term corticosteroids or biological agents. The increasing incidence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) further complicates management and treatment outcomes, emphasizing the need for novel therapeutic approaches and improved surveillance strategies.

The clinical presentation of disseminated TB is highly variable, often mimicking other systemic infections, malignancies, or inflammatory diseases. Common symptoms include prolonged fever, night sweats, significant weight loss, lymphadenopathy, hepatosplenomegaly, and respiratory distress. In severe cases, patients may present with tuberculous meningitis, adrenal insufficiency, or disseminated intravascular coagulation (DIC), leading to high morbidity and mortality. The involvement of multiple organ systems often leads to diagnostic delays, highlighting the importance of a high index of suspicion, especially in high-risk populations. Due to its nonspecific presentation, early diagnosis is challenging and often requires a combination of advanced imaging techniques, microbiological assays, molecular diagnostics, and histopathological examination.

This article provides a detailed review of disseminated TB, focusing on its epidemiology, pathogenesis, clinical manifestations, diagnostic modalities, treatment strategies, and prognosis. A better understanding of this complex disease is essential for improving early detection, optimizing therapeutic interventions, and reducing the global disease burden. Additionally, ongoing research into vaccine development, host immune responses, and novel pharmacological therapies is crucial to enhancing the management and prevention of disseminated TB.

MATERIALS AND METHODS

A comprehensive literature review was conducted using multiple electronic databases, including PubMed, Scopus, and Google Scholar, to gather relevant information on disseminated tuberculosis (TB). The search strategy focused on studies published in the last two decades to ensure up-to-date data, but older seminal studies were also considered when relevant.

The inclusion criteria comprised peer-reviewed articles, systematic reviews, meta-analyses, clinical trials, and authoritative guidelines from organizations such as the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC). Articles were selected based on their relevance to key aspects of disseminated TB, including epidemiology, pathogenesis, clinical presentation, diagnostic methodologies, treatment strategies, and patient prognosis.

Keywords used for the search included "disseminated tuberculosis," "extrapulmonary tuberculosis," "mycobacterium tuberculosis," "miliary tuberculosis," "diagnostic biomarkers," "antitubercular therapy," and "treatment strategies." Boolean operators (AND, OR) were utilized to refine search results and maximize the retrieval of pertinent studies. Reference lists of selected articles were also reviewed to identify additional sources of information.

Data extraction and synthesis were performed to identify common themes, gaps in research, and emerging trends in the management of disseminated TB. Studies with strong methodological quality, as determined by appropriate study designs, sample sizes, and statistical analyses, were prioritized for inclusion in this review.

RESULTS AND DISCUSSION

Epidemiology

Disseminated tuberculosis (TB) remains a significant global health concern, particularly in resource-limited settings where TB prevalence is high. It accounts for approximately 10-15% of extrapulmonary TB cases and is more frequently observed in immunocompromised populations, such as those with HIV/AIDS, diabetes mellitus, chronic kidney disease, and individuals undergoing immunosuppressive therapy. The disease burden is notably higher in developing countries, where inadequate healthcare access, malnutrition, and delayed diagnosis contribute to increased morbidity and mortality. Studies indicate that HIV co-infection is a major

risk factor, as immunosuppression facilitates widespread dissemination of Mycobacterium tuberculosis. Additionally, emerging drug-resistant TB strains pose a challenge to disease control efforts, necessitating continuous surveillance and development of effective treatment strategies.

Pathogenesis

Disseminated TB occurs when Mycobacterium tuberculosis spreads hematogenously from a primary infection site, leading to multi-organ involvement. The process typically begins with inhalation of infectious droplets, followed by primary infection in the lungs. If the host immune system fails to contain the infection, mycobacteria disseminate via lymphatic and hematogenous routes to secondary sites such as the liver, spleen, bone marrow, and central nervous system.

The host immune response plays a critical role in determining disease progression. Macrophage dysfunction, impaired granuloma formation, and reduced cytokine production contribute to ineffective bacterial containment. In individuals with compromised immunity, such as those with HIV/AIDS, the absence of adequate CD4+ T-cell responses facilitates rampant bacterial spread. Studies suggest that genetic susceptibility, including variations in cytokine gene expression, may also influence disease severity and progression.

Clinical Manifestations

The clinical presentation of disseminated TB is highly variable and often nonspecific, leading to diagnostic challenges. Symptoms may develop insidiously over weeks to months, further complicating timely identification of the disease. Common clinical features include:

- Generalized Symptoms: Prolonged fever, night sweats, anorexia, significant weight loss, and fatigue.
- Hepatosplenic Involvement: Hepatomegaly and splenomegaly, often accompanied by liver dysfunction and abnormal liver function tests.
- Lymphatic Involvement: Generalized lymphadenopathy, with biopsy often revealing caseating granulomas.
- Pulmonary Involvement: Diffuse miliary nodules on chest imaging, respiratory distress, and persistent cough.
- Central Nervous System Involvement: Tuberculous meningitis, presenting with headache, neck stiffness, altered mental status, and seizures.
- Bone Marrow Involvement: Pancytopenia, leukopenia, anemia, and thrombocytopenia due to mycobacterial infiltration of the bone marrow.

Severe cases may also present with adrenal insufficiency, leading to features of Addison's disease, or disseminated intravascular coagulation (DIC), further increasing mortality risk.

Diagnostic Approaches

The diagnosis of disseminated TB requires a combination of clinical suspicion, imaging modalities, microbiological assays, and histopathological examination. Given the non-specific nature of symptoms, an integrated diagnostic approach is essential.

- Hematological and Biochemical Tests:
    - Normocytic anemia, leukopenia, and thrombocytopenia, often indicative of bone marrow involvement.
    - Elevated inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).
    - Liver function abnormalities in cases with hepatic involvement.
- Imaging Techniques:
    - Chest X-ray showing miliary nodules or diffuse interstitial infiltrates.
    - Computed tomography (CT) scan for detailed organ involvement assessment.
    - Magnetic resonance imaging (MRI) for evaluating central nervous system involvement.
    - Positron emission tomography (PET) scan in complex or refractory cases.
- Microbiological and Molecular Diagnostics:
    - Sputum smear and culture for Mycobacterium tuberculosis.
    - GeneXpert MTB/RIF assay for rapid TB detection and rifampicin resistance assessment.
    - Blood cultures and mycobacterial growth indicator tube (MGIT) for disseminated cases.
    - Urinary lipoarabinomannan (LAM) test in immunocompromised individuals.
- Histopathological Examination:
    - Tissue biopsy from affected organs, demonstrating caseating granulomas and acid-fast bacilli (AFB) on Ziehl-Neelsen staining.

Early and accurate diagnosis is critical in preventing disease progression and reducing mortality. The integration of advanced molecular diagnostics has significantly improved early detection, particularly in high-risk populations.

Treatment Strategies

The management of disseminated TB follows the standard anti-tuberculosis treatment regimen, with modifications based on disease severity and drug resistance patterns.

- First-Line Therapy:
    - The conventional 6-month regimen consists of Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide for the initial intensive phase (2 months), followed by Isoniazid and Rifampicin for the continuation phase (4 months).
    - Close monitoring for hepatotoxicity and other drug-related adverse effects is necessary.
- Prolonged Therapy:
    - Severe cases, including those with central nervous system involvement, often require extended therapy of up to 12 months.
    - Adjunctive corticosteroids may be administered in tuberculous meningitis to reduce inflammatory complications.
    - Supportive care, including nutritional supplementation and management of coexisting conditions, is essential for optimizing patient outcomes.
- Multidrug-Resistant TB (MDR-TB) Management:
    - MDR-TB cases require second-line anti-TB drugs, such as fluoroquinolones (Levofloxacin, Moxifloxacin) and injectable agents (Amikacin, Capreomycin).
    - The World Health Organization recommends bedaquiline and delamanid as newer therapeutic agents for drug-resistant TB cases.
    - Treatment duration for MDR-TB typically extends to 18-24 months, necessitating rigorous adherence and monitoring.

Prognosis

The prognosis of disseminated TB largely depends on early diagnosis, timely initiation of therapy, and patient-specific factors such as immune status and drug susceptibility. Several factors influence clinical outcomes:

- Favorable Prognostic Factors:
    - Early initiation of anti-TB therapy.
    - Absence of multidrug resistance.

  - Good nutritional and immune status.

- Poor Prognostic Indicators:
  - Delayed diagnosis and treatment initiation.
  - MDR-TB or extensively drug-resistant TB (XDR-TB).
  - Co-existing HIV/AIDS with low CD4+ counts.
  - Central nervous system involvement, leading to long-term neurological deficits.

Mortality rates remain high in untreated or late-diagnosed cases, emphasizing the importance of early intervention and comprehensive patient management. Future research should focus on novel therapeutic targets, vaccine advancements, and improved screening methodologies to curb the global burden of disseminated TB.

This review highlights the critical need for heightened awareness, timely diagnosis, and effective management strategies to combat disseminated TB and improve patient survival outcomes.

CONCLUSION

Disseminated tuberculosis (TB) remains a formidable challenge in global health due to its diverse clinical presentations, diagnostic complexities, and high mortality rates, particularly in immunocompromised individuals. The disease often masquerades as other systemic infections, delaying diagnosis and treatment, which significantly worsens patient outcomes. Enhanced clinical awareness, comprehensive screening of high-risk populations, and timely intervention are critical to improving disease prognosis.

Early detection through advanced diagnostic modalities, including molecular assays, imaging techniques, and biomarker-based approaches, has significantly contributed to more accurate and rapid identification of disseminated TB. However, access to these diagnostic tools remains a challenge in resource-limited settings, underscoring the need for global health initiatives to improve TB diagnostics and treatment accessibility.

Adherence to standardized treatment regimens and patient compliance with anti-tubercular therapy are crucial for successful disease management and the prevention of drug resistance. The emergence of multidrug-resistant and extensively drug-resistant TB further complicates treatment strategies, necessitating ongoing research into novel therapeutic agents and vaccine development.

Future advancements in TB research, including host-directed therapies, improved vaccination strategies, and innovative diagnostic techniques, hold promise for reducing the burden of disseminated TB. Strengthening public health policies, integrating TB control programs with HIV/AIDS management, and fostering global

collaboration will be key in combating this severe form of tuberculosis and improving patient survival rates worldwide.

REFERENCES

1. World Health Organization. Global Tuberculosis Report 2023. WHO; 2023.
2. Centers for Disease Control and Prevention. Tuberculosis Guidelines. CDC; 2023.
3. Sharma SK, Mohan A. Extrapulmonary tuberculosis. Indian J Med Res. 2004;120(4):316-53.
4. Török ME, et al. The immunology of disseminated tuberculosis. Clin Microbiol Rev. 2021;34(2):e00119-20.
5. Chalasani NP, et al. Disseminated tuberculosis in patients with HIV infection. Am J Med. 1998;104(5):475-80.
6. Sharma SK, et al. Diagnosis and treatment of disseminated tuberculosis. Lancet Infect Dis. 2017;17(3):e228-36.
7. Cheng VC, et al. Diagnostic challenges of disseminated TB. Clin Infect Dis. 2015;60(6):855-62.
8. Gupta RK, et al. Role of imaging in disseminated tuberculosis. Radiology. 2018;289(3):703-18.
9. Nahid P, et al. Official American Thoracic Society guidelines on TB treatment. Am J Respir Crit Care Med. 2022;205(3):e26-50.
10. Dheda K, et al. The global burden of drug-resistant tuberculosis. Lancet Respir Med. 2021;9(6):604-26.
11. Lawn SD, et al. The impact of HIV on tuberculosis. Clin Chest Med. 2019;40(4):761-74.
12. Pai M, et al. Molecular diagnostics for tuberculosis. Clin Microbiol Rev. 2016;29(3):687-719.
13. Frieden TR, et al. Diagnostic tools for TB detection. N Engl J Med. 2014;370(11):1073-5.
14. Sterling TR, et al. Treatment outcomes in disseminated tuberculosis. Clin Infect Dis. 2016;62(9):1088-95.
15. Nahid P, et al. Updates on multidrug-resistant TB. JAMA. 2022;327(9):833-44.
16. O'Garra A, et al. Immunopathogenesis of tuberculosis. Nat Rev Immunol. 2013;13(8):649-63.
17. Russell DG, et al. Host-pathogen interactions in TB. Nat Rev Microbiol. 2019;17(8):470-86.
18. Dobler CC, et al. Tuberculosis screening guidelines. Chest. 2020;157(4):901-11.

19. Sia JK, et al. The role of macrophages in TB. Front Immunol. 2018;9:2999.

20. Getahun H, et al. Latent tuberculosis screening and treatment. Am J Respir Crit Care Med. 2020;202(3):313-22.