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RESEARCH ARTICLE

Tuberculosis and Pulmonary Co-Infections: Clinical Profiles and Management Strategies

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ABSTRACT

Tuberculosis (TB) along with pulmonary co-infections in patients became a grave concern to public health complicating the disease diagnosis, treatment, and prognosis. It became a challenge to healthcare professionals urging to develop new diagnostic tools and treatment regimens. This paper reviews the complex interplay and management strategies for Tuberculosis patients with co-infections. It encompasses antimicrobial therapy tailored to particular pathogens, including their susceptibility profiles to antibiotics, and understanding the potential implications of drug interactions with anti-Tuberculosis medications. In cases of co-infection between Tuberculosis and Human Immuno-Deficiency Virus (HIV), a particular focus is placed on the significance of synergistic methods and treatment duration.

Moreover, immunomodulatory drugs, immunotherapies, cellular treatments, adjunct therapies, and immunomodulatory agents that are customised to the patient's immunological status and co-infecting pathogens emerge as a crucial component. Mitigating the transmission of pulmonary co-infections requires the implementation of infection control measures in both healthcare settings and communities. A strong barrier against the spread of tuberculosis and related illnesses is formed by administrative, engineering, and personal protective measures combined with screening, education, isolation, and contact tracking.

Prospective approaches underscore the necessity for enhanced diagnostic instruments, promoting cutting-edge technologies including molecular diagnostics, immunological tests, radiological imaging, biosensors, and point-of-care diagnostics. Comprehensive management is emphasised through multidisciplinary care comprising pulmonologists, infectious disease experts, microbiologists, and immunologists. Priorities for research include combination medications, new therapeutic approaches, personalised medicine, and developing diagnostic techniques to improve knowledge of and treatments for pulmonary co-infections.

Background

Tuberculosis (TB) and Pulmonary Co-Infections stands as a persistent global health threat, with its impact profoundly felt in regions burdened by a high prevalence of infectious diseases. It is estimated that over 10.6 million new cases of TB emerged globally in 2021, signifying the enduring challenges this disease poses.[1] While TB is a grave concern on its own, its intersection with concurrent pulmonary co-infections exacerbates the complexity of clinical management. Beyond individual clinical complexities, co-infections have broader implications for public health. These co-infections, which can involve bacterial, viral, or fungal pathogens, significantly impact the clinical profiles of TB patients, making timely and accurate diagnosis paramount.

The diagnostic process in the presence of co-infections, becomes more intricate as overlapping symptoms necessitate the use of advanced diagnostic tools such as molecular diagnostics, serological tests, and imaging techniques to differentiate between TB and co-infections. These diagnostic challenges are further exacerbated by symptoms and pronounced radiological findings, which call for comprehensive, multidisciplinary treatment plans.[2]

The co-occurrence of TB with other pulmonary infections further amplifies the clinical intricacies. Patients presenting with symptoms indicative of respiratory infections may challenge the differential diagnosis. Distinguishing between TB and concurrent pulmonary co-infections, such as bacterial, viral, or fungal pathogens, becomes a critical yet formidable task. The overlapping clinical manifestations often confound healthcare providers, delaying the initiation of appropriate treatment and potentially leading to suboptimal outcomes.[3] This clinical complexity underscores the need for improved diagnostic methods, timely interventions, and a high degree of vigilance on the part of healthcare professionals. It highlights the critical importance of accurate and rapid diagnostic tools that can distinguish between TB and co-infections to ensure that patients receive the most suitable and effective treatment promptly.

Additionally, co-infections can significantly influence the trajectory of TB. The presence of other pathogens may lead to exacerbated symptoms and altered response to standard anti-TB therapies. For instance, viral co-infections like influenza can exacerbate the immune-compromised state of TB patients, potentially leading to increased disease severity and mortality rates.[4] Furthermore, the presence of co-infecting pathogens can induce drug-drug interactions, necessitating careful medication management to ensure both TB and the co-infection are effectively treated.[5] Balancing multiple medications to target different pathogens while managing potential interactions becomes a critical aspect of the clinical care process, highlighting the complexity of treating individuals with co-occurring infections. In essence, the presence of co-infections not only exacerbates the clinical challenges of TB management but also underscores the need for a holistic and multidisciplinary approach to healthcare. Patients affected by both TB and co-infections often require a holistic approach that involves clinicians from various specialties collaborating to address all facets of patient care, including tailored anti-TB medications and co-infection treatments.[6] In particular, preventive measures, such as vaccination

against respiratory infections like influenza or pneumonia, are crucial, especially for immunocompromised individuals. For these patients, comprehensive management should include addressing the underlying causes of immunosuppression, like Human Immuno-Deficiency Virus (HIV) infection, with antiretroviral therapy and close monitoring of CD4 counts.

In regions with a high burden of infectious diseases, socioeconomic determinants and healthcare infrastructure often create an environment conducive to the proliferation of TB.[7] Poverty, overcrowded living conditions, and limited access to quality healthcare are common factors contributing to the heightened prevalence of TB in these regions.[8] These areas become fertile ground for the persistence and transmission of TB, necessitating targeted and comprehensive interventions. To address these challenges, the World Health Organization's (WHO) TB control strategy focuses on effective diagnosis and treatment. However, the strategy has not fully considered preventive efforts. Additional interventions are needed to reduce vulnerability to TB, addressing risk factors like poor living conditions and factors that impair the host's defence against TB, such as HIV infection, malnutrition, smoking, diabetes, alcohol abuse, and indoor air pollution.[9] Co-infections further complicate contact tracing efforts. Identifying the source of infection becomes more complex, as individuals may have acquired various pathogens from different sources. This complexity can hinder timely isolation and prevention measures, potentially leading to the unintentional spread of diseases.

TB co-infections, in conjunction with socioeconomic factors, present multifaceted challenges in clinical management and public health. To achieve long-term epidemiological targets for global TB control, a comprehensive approach encompassing prevention and treatment is required, addressing both TB risk factors and social determinants. Further research is needed to assess the suitability, feasibility, and cost-effectiveness of these intervention options.

Rationale

Distinguishing TB from co-infections poses a significant diagnostic challenge. The overlapping clinical manifestations often lead to misdiagnoses or delays in initiating appropriate treatment.[3] A nuanced understanding of the distinct clinical profiles associated with TB and co-infections is therefore indispensable for accurate diagnosis.

Furthermore, the presence of co-infections significantly impacts the progression and management of TB. Co-infecting pathogens can exacerbate symptoms, alter radiological findings, and influence the response to standard anti-TB therapies. Additionally, co-infecting pathogens may introduce complexities in drug management due to potential interactions with anti-TB medications.

This paper addresses the complex interplay between TB and co-infections, shedding light on the intricate clinical scenarios and to provide a comprehensive overview of the clinical profiles and management strategies for TB patients with concurrent pulmonary co-infections. Through an extensive literature review and analysis of clinical case studies, this paper endeavours to equip healthcare providers with the knowledge needed to navigate these complex clinical scenarios. By elucidating the challenges and presenting evidence-based

management strategies, this paper contributes to the body of knowledge guiding clinical decision-making in the realm of TB and concurrent pulmonary co-infections.

Clinical Profiles of Tuberculosis Patients with Pulmonary Co-Infections

A. Bacterial Co-Infections

Co-infection of TB and bacteria, while common in immunocompromised individuals, can also occur in those with preserved immunity, making diagnosis and treatment challenging.[10] In pulmonary TB patients, atypical tubercular lesions can complicate diagnosis when only one pathogen is initially identified, leading to suboptimal treatment. *Streptococcus pneumoniae* is a common bacterial co-pathogen in TB patients, particularly in those with advanced disease or immunocompromised states. It can lead to pneumonia and exacerbate respiratory symptoms. *S. pneumoniae* and *Mycobacterium tuberculosis* (*Mtb*) are highly significant and dangerous bacterial pathogens that cause respiratory tract infections. Their co-occurrence, especially in immunosuppressed individuals, particularly those with HIV, has been well documented.[10] The prevalence of these co-infections varies based on geographic location and the CD4 cell count in HIV-infected patients.[11] Before the introduction of Highly Active Anti-Retroviral Therapy (HAART) and Co-trimoxazole prophylaxis, pneumonia was a leading cause of mortality in HIV patients in the United States of America (USA) and European countries. Prompt treatment and early detection of co-infection with *Mtb* and *S. pneumoniae* are essential to stop further depletion of CD4 cells and the quick development of Acquired ImmunoDeficiency Syndrome (AIDS) in HIV-positive individuals.

In a study by Attia et al. conducted in Cambodia, among patients with presumptive lower respiratory infections (LRI) who underwent mycobacterial and bacterial sputum testing, the findings revealed that 9% of all patients and 33% of TB patients had TB and other bacterial co-infections.[12] *Klebsiella* and *Pseudomonas* were identified as the dominant bacterial pathogens cultured, irrespective of TB co-infection in the study by Samson et al. Patients with cavitary lesions on chest radiography are at a higher risk of TB and bacterial co-infection.[11]

A study in Cambodian provincial hospitals involving patients with acute LRI revealed that those with chest radiographs showing pulmonary sequelae of prior infections, including TB, were more likely to have Gram-negative bacteria detected in their samples, in contrast to patients with normal chest radiographs.[13] This suggests a connection between radiographic evidence of past infections and an increased likelihood of bacterial infections, particularly of the Gram-negative variety. Specifically, the presence of *S. pneumoniae* can be identified as Gram-positive diplococci, while *Mtb* is detected as red-stained (acid-fast) slightly curved rods, either individually or in small clusters.[10] The exact relationship between pulmonary TB infection and the increased risk of bacterial super-infection, or whether the acute presentation of pulmonary TB is triggered by the development of bacterial pneumonia, remains unclear.[12] Nevertheless, it's important to emphasize that misdiagnosis of either TB or other bacterial pulmonary infections can have detrimental consequences, including elevated healthcare expenses, the emergence of antimicrobial resistance, and higher mortality rates.

B. Viral Co-Infections

Human Immunodeficiency Virus

Mtb and HIV-1 co-infection is a significant factor in mortality in afflicted individuals; in fact, 17% of HIV-positive individuals also have tuberculosis co-infection.[14] HIV-1 infection has a major effect on *Mtb* infection progression and increases the likelihood of developing active TB. HIV-1 replication, transmission, and genetic variability are all made worse by TB concurrently. Both pathogens gain from this dual infection, resulting in a mutually beneficial relationship. Reduced immunopathology in the case of TB co-infection is associated with advanced HIV-1 infection. Antiretroviral therapy (ART) initiation, however, has the potential to exacerbate immunopathology related to TB and result in the immune reconstitution inflammatory syndrome (IRIS). This happens as a result of *M. tuberculosis*-induced innate immune inflammatory responses recovering. The recirculation of T cells reactive to *Mtb* and the breakdown of regular mechanisms regulating inflammatory responses could exacerbate the situation.[14,15]

The heightened pro-inflammatory response to *Mtb* could contribute to the progression of HIV-1/AIDS by promoting increased virus replication through enhanced transcription and cell-to-cell transmission. In patients with HIV-TB co-infection, their weakened immune system and lower bacterial load in sputum make clinical and imaging manifestations appear more atypical. Conventional TB diagnostic methods, like sputum smear, sputum culture, tuberculin skin tests, and interferon-gamma release tests, have low detection rates in these individuals, potentially leading to underdiagnosis.[16] Autopsy research in South Africa indicates that a significant proportion of HIV-infected patients remain undiagnosed for TB before death.[17]

To address these challenges, various screening and diagnostic tools have been proposed for TB in HIV-infected individuals. These include:

1. Interferon-Gamma Release Assay: This test detects IFN-γ released by specific T lymphocytes in response to TB antigens, helping to screen for latent TB infection. It can be more accurate than traditional methods like the TB skin test.[18,19] C-Reactive Protein (CRP): CRP is an inexpensive and immediate screening test for TB with high sensitivity and specificity, making it suitable for resource-constrained settings.[20–22]
2. Lipoarabinomannan (LAM): LAM is a low-cost point-of-care test that can be performed on urine within a short time. Its use has been recommended by the WHO in HIV-positive patients.[23,24]
3. Case Finding (ICF) Algorithm: This WHO-recommended algorithm combines symptom-based screening with confirmatory testing (e.g., Xpert MTB/Rifampicin (RIF)) for those who screen positive. However, it can be expensive and may not be suitable for areas with high TB incidence.[25,26]

In addition to screening, the development of accurate diagnostic tools are essential:

1. Xpert Ultra: This advanced kit is more sensitive than standard Xpert MTB/RIF kits, especially in HIV-positive individuals, and can detect rifampicin resistance[27]
2. High-Throughput Nucleic Acid Amplification Testing (NAAT) Platforms:

These platforms can handle multiple samples simultaneously, making them suitable for reference laboratories. Some platforms can detect different pathogens on a single platform, allowing for the integration of TB and HIV testing services[28–30]

DNA Sequencing: DNA sequencing of *Mtb* provides comprehensive genetic information about strains, aiding in drug susceptibility testing and treatment selection. The WHO is working on building a sequencing database to standardize genotyping and phenotypic drug sensitivity testing.[31,32]

Improving the diagnosis of TB in HIV-infected individuals is crucial, given their unique challenges and the potential for underdiagnosis. Screening tests and diagnostic tools that are rapid, sensitive, and cost-effective are being developed to address these concerns and enhance TB detection and management in this vulnerable population

Cytomegalovirus

Cytomegalovirus (CMV) is an opportunistic virus commonly found in TB patients with advanced immunosuppression. It can cause severe respiratory complications, contributing to increased morbidity and mortality. Co-infection involving CMV, a widespread herpes virus, can influence how the host responds to *Mtb* infection. This co-infection has the potential to affect the likelihood of disease progression, the specific type of TB disease, the accuracy of TB diagnostic tests, and the ultimate disease outcome.[33] In 2018, an association between CMV infection and TB was observed in both adults and children. This connection is of particular interest because CMV is widespread in Low- and Middle-Income Countries (LMICs), with a high percentage of people becoming CMV-seropositive by age 56, most acquiring the infection by age 1, and nearly all women of childbearing age being seropositive.[34] The overlapping epidemiology of CMV and TB in these regions underscores the significance of this association. Moreover, it is probable that *Mtb* infection can also have an impact on how CMV causes disease.[33] There is supporting epidemiological and immunological evidence that suggests an interaction between TB and CMV. The frequency of *Cytomegalovirus* infection (CMVI) in patients with lung TB is relatively high, and interestingly, this occurrence doesn't seem to be linked to the presence of HIV infection. Furthermore, elevated levels of markers associated with CMVI may serve as predictive indicators of mortality, particularly among TB patients who are not co-infected with HIV.[34]

C. Fungal Co-Infections

Aspergillus spp

Molds known as *Aspergillus* species are common and can cause invasive aspergillosis in TB patients, particularly in those with advanced disease or immunosuppression.[35] Undoubtedly, one of the main risk factors for pleural aspergillosis is the existence of an existing lung cavity, frequently brought on by previous TB infection. This condition usually arises from prior damage to the lung or pleura caused by active TB. *Aspergillus* infections can cause a range of complications, with radiological and pathological features resembling those of TB. These infections are mainly seen in immunocompromised individuals.[35,36]

The prevalence of *Aspergillus* co-infection with TB varied, ranging from 3.7% to 33.3%,

according to a 2020 systematic review. It was discovered that 15.4% of patients with pulmonary TB also had *Aspergillus* co-infection.[36]

Cryptococcus neoformans

Immune system-compromised TB patients are more likely to co-infect with *C. neoformans.* A high index of suspicion is necessary for a correct diagnosis because this encapsulated yeast can cause meningoencephalitis and pulmonary symptoms. Approximately 14% of patients with cryptococcal meningitis are also diagnosed with TB at the time of the diagnosis, and 9% more develop TB after receiving treatment for two weeks.[37]

Co-infection with *Mtb* and *C. neoformans* (the causative agent of cryptococcal meningitis) increases the risk of death in people living with HIV considerably when compared to people who only have one infection or neither infection. The co-occurrence of TB with bacterial, viral, and fungal pathogens poses complex clinical challenges. Early recognition and management of these co-infections are crucial to improve patient outcomes. Furthermore, the presence of co-infections necessitates a tailored treatment approach, considering potential drug interactions and overlapping toxicities.

3. Impact on Disease Progression: Analysis of how co-infections may influence the course of TB, including exacerbations of symptoms, altered treatment response, and potential for drug interactions.

Pulmonary co-infections, especially in the context of TB, can significantly influence the course of the disease. Understanding the interplay between co-infections and TB is essential for optimizing treatment strategies and improving patient outcomes.

A. Exacerbations of Symptoms:

i. Increased Disease Severity: Co-infections often lead to heightened disease severity in TB patients. For instance, bacterial co-infections like *S. pneumoniae* can exacerbate respiratory symptoms, leading to more pronounced clinical manifestations.

ii. Delayed Recovery: The presence of a co-infection may prolong the recovery period for TB patients. Viral co-infections, such as influenza or respiratory syncytial virus, can lead to prolonged respiratory symptoms and increased morbidity.[4]

B. Altered Treatment Response:

i. Impaired Immune Function: Co-infections can compromise the immune system, affecting the body's ability to mount an effective response to TB treatment. This may result in slower or inadequate resolution of TB lesions.

ii. Resistance Development: The presence of co-infections, particularly in immunocompromised individuals, may lead to altered antimicrobial susceptibility patterns. This can necessitate adjustments in TB treatment regimens to ensure efficacy.

C. Potential for Drug Interactions:

i. Pharmacokinetic Interactions: Co-infections may alter the pharmacokinetics of TB medications, affecting absorption, distribution, metabolism, and excretion. This can lead to suboptimal drug levels, potentially compromising treatment efficacy.[38]

ii. Toxicity and Side Effects: Some co-infections and their respective treatments may overlap with TB medications, increasing the risk of drug-drug interactions and potential toxicity. Clinicians must carefully consider the potential for adverse effects when managing co-infected individuals.

The impact of co-infections on TB progression underscores the complexity of managing these dual infections. Clinicians must carefully assess and monitor patients for signs of exacerbations, altered treatment responses, and potential drug interactions.

Management Strategies for Tuberculosis Patients with Co-Infections

Antimicrobial Therapy

TB becomes very fatal when combined with diseases such as HIV and Hepatitis B and Hepatitis C, especially in resource constraint settings or LMICs leading to delays in therapy initiation.[39] Moreover, substantial financial burdens on health services of the country is imposed due to necessity of more complex prevention/treatment especially for immune compromising co-infections and co-morbidities.[40] In co-infections, antimicrobial therapy should be tailored keeping in consideration the co-infecting pathogens of different co-infecting diseases, their susceptibility, as well as potential interactions with anti-TB drugs for successful management.[41]

A. Specific Co-Infecting Pathogens

i. Bacterial Co-Infections: Co-infection with TB and bacterial pathogens has been documented, especially in populations with a high TB prevalence. Moreover, wrong diagnosis of either TB or other bacterial pulmonary infection can lead to worse health outcomes such as catastrophic healthcare costs, antimicrobial resistance, and death.[12] In such cases, targeted antibiotics should be used based on the pathogen. For an instance in case of *S. pneumoniae,* beta-lactam agents can be used,[42] whereas beta-lactamase-stable antibiotics are the best choice in case of *Haemophilus influenzae*.[43]

ii. Viral Co-Infections: Antiviral therapy is critical for managing viral co-infections. For severe influenza associated disease, antiviral treatment improves health outcomes.[44] Specific antiviral agents such as oseltamivir or ganciclovir should be considered in cases of concurrent influenza[45] or CMV infections.[46]

iii. Fungal Co-Infections: Pulmonary fungal infections may possibly be wrongly diagnosed as TB easily as it has clinical and radiological characteristics quite similar to TB[47]. This often demands treatment antifungal therapy, based on determined pathogen. Drugs like voriconazole or amphotericin B may be indicated in pathogen like *Aspergillus spp*. and or *C. neoformans.*[48]

B. Susceptibility Profiles

i. Microbiological Testing: In order to guide for the appropriate antimicrobial therapy, obtaining susceptibility profiles through culture and sensitivity testing is crucial. This will help in understanding whether the chosen agents are effective against the detected pathogens.[49]

ii. Empirical Treatment: In the absence of data on susceptibility profile, the patient is started on empirical treatment based on all the factors that contribute to a patient's likelihood of having TB and/or having a poor outcome assessed against the threshold for starting anti-TB treatment; these factors are TB prevalence in that particular geographical area, clinical picture indicative of TB, comorbidities like TB-HIV coinfection and the outcomes of other diagnostic approaches (for e.g., chest radiography).[50]

C. Interactions with Anti-TB Drugs

i. Pharmacokinetic Interactions: Pharmacokinetics is defined as the time period until which a drug stays in different body parts like plasma, blood, brain, lungs and other tissues.[51] Various antimicrobial agents and anti-TB drugs have similar pathways which could result in pharmacokinetic interactions. Some serious consequences of such interaction include therapeutic failure or toxicity.[52] Thus, to avoid adverse events, prescribing and monitoring of each dosage should be done cautiously.

ii. Drug-Drug Interactions: Certain antimicrobials and anti-TB drugs such as rifampicin and isoniazid may reflect direct interactions by affecting serum levels and efficacy. For instance, rifampicin can induce cytochrome P450 enzymes (responsible for drug metabolism in liver and/or intestine), influencing the metabolism of various co-administered drugs such as anticoagulants, anti-infectives, contraceptives, and psychotropics, etc, while Isoniazid, which is an inhibitor in drug metabolism, interacts with anticonvulsants, theophylline, benzodiazepines, paracetamol, and some kinds of food.[52]

D. Combination Therapy and Duration

i. Synergistic Approaches: Due to increase in multiple drug resistance pathogens, co-infections and co-morbidities in some cases, combination therapy warrantees promising results.[53] Combining antibiotics with various mechanisms of action can boost efficacy of the therapy. With new drugs addition or repurposed drugs and host-directed treatment, various treatment regimens are in 2nd or 3rd phase of trials.[54]

ii. Duration of Treatment: For co-infections, factors like pathogen characteristics, response and immunity influence the duration of antimicrobial therapy. Prolonged treatment courses may be required for certain co-infecting organisms.[55] For an instance, current standard treatment regimen for TB-HIV co-infection in drug susceptible TB is isoniazid, rifampicin, pyrazinamide, and ethambutol are given for 2-months (initial intensive phase), followed by isoniazid and rifampicin for 4 months (continuation phase) along with ART to be started in all HIV-infected patients with TB, regardless of the status of CD4 cell count.[56]

Immune Modulation

Due to overlapping epidemiological characteristics of co-infections like HIV and

malaria, a clear understanding of immune response dynamics to TB with co-infection is necessary.[57] Effectively modulating the host immune response is critical in managing pulmonary co-infections. Strategies such as include adjunctive therapies and immunomodulatory agents is explored to optimize the host immune response TB and co-infections.

A. Adjunct Therapies

i. Corticosteroids: Corticosteroids are known to have various applications such as mitigating inflammation and repair immune-mediated tissue damage in severe infections.[58] In the context of co-infections, they may help reduce excessive inflammatory responses. In case of TB-HIV coinfection, TB-immune reconstitution inflammatory syndrome (IRIS), steroids are preferred as a choice of adjunctive therapy.[59] Moreover, corticosteroids are also beneficial in preventing paradoxical relapse of HIV-TB IRIS.[60]

ii. Intravenous Immunoglobulin (IVIg): IVIg is a source of pooled antibodies derived from multiple donors. IVIg is beneficial for treating primary antibody deficiencies, a spectrum of autoimmune disorders and inflammatory diseases[61] It can provide passive immunity and augment the host's immune response by shortening the current treatment period especially in patients with co-infections as well as MDR-TB.[62,63]

B. Immunomodulatory Agents:

i. Interleukin-1 (IL-1) Antagonists: IL-1 is responsible for controlling immune response to infections whereas IL-1 antagonist like anakinra may lead to increased risk of infections like TB.[51] However, anti-IL-1 therapy like anakinra could be used as a first line adjunct therapy in order to control paradoxical inflammatory reactions due to cytokine storms occurring in rheumatic diseases.[64]

ii. Tumor Necrosis Factor (TNF) Inhibitors: TNF-α is a crucial element in controlling the *Mtb* infection, however paradoxically, it is equally responsible in causing severe tissue damage due to its pro-inflammatory cytokinetic potency, especially in the case of MDR-TB.[65] TNF inhibitors like infliximab are responsible for development of disease from TB infection.[66,67] However, in carefully selected cases, they may be considered to temper inflammatory reactions, particularly in conditions with dysregulated cytokine profiles.[65]

C. Immunotherapies

i. Monoclonal Antibodies: Monoclonal antibodies directed against specific pathogens, or their toxins can enhance the host's ability to clear infections. For example, in people living with HIV or people with multidrug-resistant TB who illustrate faster progression of disease as well as toxicity from TB-HIV co-infection, passive antibody treatment could be beneficial to shorten treatment of TB.[68]

ii. Vaccination Strategies: Vaccination against preventable co-infecting pathogens is a cornerstone of immune modulation. For an instance a higher incidence of influenza A (H1N1) is noted

in patients with TB than the general population. In such case, annual influenza vaccination and pneumococcal vaccination are vital in reducing the risk of viral co-infections like influenza.[69]

D. Cellular Therapies:

i. T-Cell Therapies: T-cell transfer involves culturing, expanding, and infusing ex vivo expanded, pathogen-specific T-cells back into the TB patients.[70] This strategy may be a feasible choice for T-cells identifying wild-type and/or mutant epitopes TB *as well as other infectious diseases.*[71]

ii. Stem Cell Therapies: Hematopoietic stem cell transplantation (HSCT) is commonly used therapy can restore immune function in severely immunocompromised individuals with co-infections such as HIV, *Ebstein-Barr virus* and CMV.[71,72] Careful patient selection and tailored conditioning regimens are crucial in optimizing outcomes since HSCT can increase the risk of morbidity and mortality in viral infections.[72,73]

Infection Control Measures

Tubercular bacilli are resistant to various adverse environmental conditions due to its aerobic, slow growing and non-sporous nature. Therefore, implementing robust infection control measures is essential in managing pulmonary co-infections, especially involving TB and co-infecting pathogens.[74] Infection control can be done in following ways-

A. Healthcare Setting Infection Control:

i. Administrative Controls

1. Risk Assessment: Early diagnosis, isolation of airborne infection and prompt treatment are crucial and are often missed especially in non-endemic areas.[74] Therefore, conducting regular assessments to identify individuals at high risk of TB or co-infection and implementing appropriate control measures is primary and critical to infection control.[75]

2. Policies and Procedures: Promoting integration of services of screening, diagnosis and management of TB and other pulmonary infections can give a scope of early diagnosis and prompt treatment[76] However, integrated services are only available for HIV and for other potential pulmonary infection is not known. Management strategies including respiratory hygiene should also be a mandate.[77]

ii. Engineering Controls

Airborne Precautions: It is well known since the origin of treatment of TB- putting TB patients in a sanatorium (open, well-ventilated area), that a poorly ventilated environment and crowded area with a potential source will have more spread of TB infection than the counterparts[75]. Thus, it is important to ensure that healthcare facilities have appropriate ventilation systems and negative pressure rooms for isolating and managing patients with potentially infectious respiratory diseases. Ventilation can be mechanical (created using exhaust fans or air supply or both- negative and positive pressure mechanical ventilation system); building or choosing a naturally ventilated area; or both are a few practices commonly used.[77]

iii. Personal Protective Equipment (PPE):

1. Respiratory Protection: Staff must wear N95 (FP2) masks or equivalent when

entering the room with a TB patient whereas while handling respiratory waste of a critically ill in intensive care unit, N98 (FP3) masks should be worn.[74,77]

2. Gloves, Gowns, and Eye Protection: Ensuring availability and proper use of PPE to prevent direct contact with respiratory secretions.

iv. Environmental Controls:

1. Cleaning and Disinfection: Ensuring quality control through thorough and regular cleaning protocols, especially in high-risk areas where co-infected patients are taken care for.
2. Ventilation systems – natural, mechanical, mixed and recirculated ait with high efficiency particulate air (HEPA) filtration can be assessed based on their effectiveness and chosen according to the setting.[77]
3. Upper Room ultraviolet germicidal irradiation (UVGI): Very poorly understood, but very effective, both cost as well as action wise, this intervention is fixating a germicidal lamp in the wall or hung over the heads of the patient. It is beneficial for mitigating the risk of viral infections.[75]

B. Community Infection Control:

i. Education and Awareness:

Public Health Campaigns: Conduct educational campaigns to raise awareness about the risks of TB and co-infections and promote preventive measures within the community. Promoting hand hygiene, cough etiquette, personal protection can help in mitigating the risk of spread of co-infections.[74]

ii. Screening and Testing:

Targeted Screening: Identifying high-risk populations, such as individuals with known TB contacts through active contact tracing or immunocompromised individuals through regular reporting, and performing regular screening and testing.[74] For individuals with other pulmonary co-infections, the same strategy can be adopted.

iii. Isolation and Quarantine:

Isolation Facilities: Establish designated isolation facilities for individuals diagnosed with TB or co-infections to prevent further transmission in the community. For an instance, using negative pressure isolation rooms with HEPA filtration or via changing air per hour (APH) four to six times a day.[77]

iv. Contact Tracing:

Identification and Monitoring: It is an effective public health intervention. Contact tracing via provider is directly related to better control outcomes of communicable diseases. Thus, tracing and monitoring individuals who have had close contact with confirmed cases is important to ensure early detection and intervention if infection occurs.[78]

Adhering to established infection control guidelines is crucial in mitigating the transmission of pulmonary co-infections. Rigorous implementation of these measures in healthcare facilities and within communities plays a pivotal role in safeguarding public health.

Future Directions and Recommendations

1. Improved Diagnostic Tools: Discussion of the need for advanced diagnostic technologies to facilitate prompt and accurate identification of

TB and co-infections. Accurate and timely diagnosis of pulmonary co-infections, particularly involving TB and co-infecting pathogens, is crucial for effective management. The adoption of advanced diagnostic technologies plays a pivotal role in enhancing diagnostic accuracy and expediting appropriate treatment[79]

A. Molecular Diagnostics:

i. Nucleic Acid Amplification Tests (NAATs): NAATs, such as GeneXpert MTB/RIF, have revolutionized TB diagnosis by detecting TB-specific DNA or RNA, enabling rapid and sensitive identification of *M. tuberculosis*.[80]

ii. Next-Generation Sequencing (NGS): NGS technologies provide high-throughput sequencing of genetic material, offering valuable insights into the genetic diversity and interactions of co-infecting pathogens.[81]

B. Immunological Assays:

i. Interferon-Gamma Release Assays (IGRAs): IGRAs measure the release of interferon-gamma in response to TB-specific antigens, aiding in the detection of latent TB infection.[82]

ii. Multiplex Immunoassays: Multiplex immunoassays simultaneously detect multiple antibodies or antigens, enabling the identification of co-infecting pathogens.[83]

C. Radiological Imaging:

i. Computed Tomography (CT): High-resolution CT scans provide detailed images of pulmonary structures, aiding in the differentiation of TB lesions from those caused by co-infecting pathogens.

ii. Positron Emission Tomography-Computed Tomography (PET-CT): PET-CT combines metabolic and anatomical imaging, allowing for improved localization and characterization of lesions associated with co-infections.[84]

D. Biosensors and Point-of-Care Tests:

i. Biosensors: Biosensors can detect specific molecular targets, offering rapid and portable diagnostic capabilities for identifying co-infecting pathogens.[85]

ii. Point-of-Care Tests (POCT): POCT platforms, like lateral flow assays, provide rapid results at the patient's location, facilitating timely initiation of appropriate treatment.[86]

Advanced diagnostic technologies offer significant advantages in identifying pulmonary co-infections. Molecular diagnostics and immunological assays provide high sensitivity and specificity, while radiological imaging enhances anatomical visualization. Biosensors and point-of-care tests further streamline diagnostic processes.

2. **Multidisciplinary Care:** Pulmonary co-infections, particularly those involving TB and co-infecting pathogens, require comprehensive and integrated management. Multidisciplinary care, involving pulmonologists, infectious disease specialists, microbiologists, and immunologists, is essential for optimizing patient outcomes.[87]

A. Roles of Multidisciplinary Team Members:

i. Pulmonologists: Expertise in Respiratory Medicine: Pulmonologists are crucial in diagnosing and managing respiratory conditions, including TB. Their proficiency in pulmonary function and imaging interpretation is invaluable in co-infection cases.

ii. Infectious Disease Specialists: Expertise in Infectious Diseases: Infectious disease specialists have specialized knowledge in the diagnosis and treatment of a wide range of infections, making them pivotal in managing co-infecting pathogens alongside TB.

iii. Microbiologists: Laboratory Diagnosis and Surveillance: Microbiologists play a vital role in providing accurate and timely diagnostic information through microbiological testing. Their expertise ensures accurate identification of co-infecting pathogens and susceptibility testing.

iv. Immunologists: Immune System Assessment and Modulation: Immunologists assess the patient's immune status, particularly relevant in cases of immunosuppression. They may recommend immunomodulatory strategies to optimize the host's response.[88]

B. Collaborative Care Strategies:

i. Case Conferencing: Regular case conferences facilitate open communication and exchange of expertise among team members. This ensures a unified and coordinated approach to patient care.

ii. Treatment Planning and Coordination: Multidisciplinary teams collaborate to develop individualized treatment plans, considering the specific co-infecting pathogens, patient comorbidities, and potential drug interactions.

iii. Monitoring and Follow-Up: Regular follow-up assessments and monitoring of treatment response are essential. This ensures timely adjustments to the therapeutic regimen based on clinical, radiological, and microbiological outcomes.

Multidisciplinary care for pulmonary co-infections ensures a holistic approach, leveraging the specialized knowledge and skills of each team member. Collaboration enables a comprehensive assessment of the patient's condition and facilitates optimal treatment planning and coordination.[89]

3. **Research Priorities:** Identification of areas requiring further research, including the development of novel therapies and the evaluation of emerging diagnostic modalities.

Advancements in research are pivotal for improving the diagnosis and treatment of pulmonary co-infections, particularly those involving TB and co-infecting pathogens. This recommendation highlights critical areas requiring further exploration, with a focus on the development of innovative therapies and the evaluation of emerging diagnostic modalities.

A. Novel Therapies:

i. Host-Directed Therapies: Investigate interventions that modulate the host immune response to enhance its ability

to control co-infections. This may involve targeting specific host pathways or immune cell subsets to optimize treatment outcomes.[90]

ii. Antibody-Based Therapies: Explore the potential of monoclonal antibodies and passive immunization strategies to target co-infecting pathogens. Investigate the effectiveness of specific antibodies in preventing and treating pulmonary co-infections.[91]

B. Emerging Diagnostic Modalities:

i. Advanced Imaging Techniques: Evaluate the utility of emerging imaging technologies, such as artificial intelligence-enhanced radiology and functional imaging modalities, in improving the accuracy and efficiency of pulmonary co-infection diagnosis.[92]

ii. Biomarker Discovery and Validation: Identify and validate specific biomarkers associated with pulmonary co-infections. This could involve the use of proteomics, genomics, and metabolomics approaches to enhance diagnostic precision.[93]

C. Combination Therapies:

Optimizing Drug Combinations: Investigate synergistic effects of combination therapies involving antimicrobials, immunomodulators, and host-directed therapies to enhance treatment outcomes and reduce the risk of drug resistance.[94]

D. Patient Stratification and Personalized Medicine:

Genetic and Immunological Profiling: Explore the potential of genetic and immunological profiling to stratify patients based on their susceptibility to specific co-infections and response to therapy. This may lead to more tailored treatment regimens.[95]

Prioritizing research in these areas will significantly advance our understanding and management of pulmonary co-infections. By focusing on novel therapies, emerging diagnostic modalities, combination therapies, and personalized medicine approaches, we can work towards more effective and targeted interventions for co-infected individuals.

Conclusion

Managing the complexities of TB and pulmonary coinfections demands a multifaced and integrated approach using precise diagnostic tools, multidisciplinary collaborations, and ongoing research. The clinical studies reflecting the challenges in diagnosing and treating patients with TB along with the co-infections, underscoring the need of tailored approaches to increase their surveillance. Molecular and immunological discoveries are driving the rapid progress of diagnostic technology, which could lead to more precise pathogen identification and individualised treatment regimens in the future. The multidisciplinary care approach is a shining example of good cooperation across many specialisations and thorough patient comprehension. Approaches of research towards effective interventions include those that centre on innovative treatments, state-of-the-art diagnostics, optimal drug combinations, and customised care based on immunological and genetic profiles. By tackling these frontiers, we jointly advance the field towards a future in which TB and co-infections are

addressed with precise, effective, and understanding therapies, improving the standard of care and results for individuals coping with these intricate pulmonary issues. Our progress towards improved management is evidence of our dedication to improving respiratory health worldwide.

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