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Multidrug-resistant Tuberculosis: The Contributing Roles of Nursing, Pharmacists, and Clinical Pathology in Diagnosis, Management, and Treatment-An Updated Review

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Abstract:

Background: Tuberculosis (TB), a major global health concern, continues to affect millions of individuals annually, with drug-resistant forms, especially multidrug-resistant TB (MDR-TB), escalating worldwide. MDR-TB, caused by Mycobacterium tuberculosis strains resistant to both rifampicin (RIF) and isoniazid (INH), poses significant treatment challenges. Its emergence stems from incomplete treatments, inadequate drug dosages, and transmission from infected individuals. Early and accurate diagnosis, as well as tailored treatment strategies, are vital for combating MDR-TB and preventing its spread.

Aim: This review aims to examine the critical roles of nursing professionals, pharmacists, and clinical pathology in the diagnosis, management, and treatment of MDR-TB, exploring the latest advancements in these areas.

Methods:A comprehensive literature review was conducted, focusing on recent studies that address the evolving methodologies in diagnosing MDR-TB, including molecular diagnostics, phenotypic drug susceptibility testing, and the contributions of healthcare professionals. The review also investigates therapeutic approaches and the involvement of different healthcare sectors in managing MDR-TB.

Results: The findings underscore the pivotal roles of nursing staff, pharmacists, and clinical pathologists in the fight against MDR-TB. Nurses are instrumental in ensuring patient adherence to treatment regimens, managing side effects, and educating patients on the importance of completing prescribed therapies. Pharmacists play a key role in the rational use of second-line drugs, optimizing drug regimens, and preventing resistance. Clinical pathologists are

crucial in improving diagnostic accuracy through advanced testing methods. The study also highlights the need for rapid, accurate diagnostics to facilitate early intervention.

Conclusion:MDR-TB remains a major threat to global health, but a collaborative approach involving nursing, pharmaceutical, and pathology professionals is essential to improving diagnosis, management, and patient outcomes. Continued advancements in molecular diagnostics and drug management strategies are critical for combating the rising prevalence of MDR-TB.

Keywords: Multidrug-resistant tuberculosis, nursing, pharmacists, clinical pathology, diagnosis, treatment, molecular diagnostics, drug resistance, TB management.

Introduction:

Tuberculosis (TB) affects over 10 million individuals annually, with its incidence continuing to escalate. It ranks as the second leading cause of mortality from infectious diseases globally, surpassed only by COVID-19, and accounts for nearly double the deaths attributed to HIV/AIDS [1]. TB is caused by an aerobic bacterium known as *Mycobacterium tuberculosis* (MTB), which predominantly infects oxygen-rich tissues [2], [3], [4], [5], [6]. The lungs are the primary site of infection, and the disease is transmitted through airborne droplets when an infected individual coughs, sneezes, or spits [1], [5].

Historically, rifampicin (RIF) and isoniazid (INH) have been regarded as the cornerstone drugs for TB treatment [7], [8]. However, the emergence of drug-resistant TB has posed a significant public health challenge. Multidrug-resistant tuberculosis (MDR-TB) is characterized by resistance to both RIF and INH, the two most potent first-line anti-TB drugs [5], [9], [10], [11], [12], [13]. Factors contributing to MDR-TB include incomplete treatment regimens, suboptimal drug dosages, inadequate treatment durations, poor-quality medications, and transmission from individuals with drug-resistant TB [5], [13], [14]. The growing prevalence of MDR-TB has exacerbated the global TB crisis. In 2022, approximately 73% of individuals undergoing bacteriological testing were confirmed to have developed resistance to RIF and INH, representing a significant increase over the past three years [1].MDR-TB arises due to spontaneous chromosomal mutations in the MTB bacterium. This phenotype is defined by resistance to at least INH and RIF, the two most efficacious anti-TB drugs recommended by the World Health Organization (WHO) for initial TB treatment [13], [15]. Resistance to these medications remains a critical concern for TB patients. At least ten gene variants have been linked to resistance against first-line anti-TB medications, with INH resistance associated with mutations in genes such as *katG*, *inhA*, *ahpC*, *kasA*, and *ndh*, while RIF resistance is primarily linked to mutations in the *rpoB* gene [16].

These mutations reduce the bacterium's susceptibility to specific antituberculosis drugs [2]. Drug resistance can manifest either primary or secondary resistance. Primary resistance occurs when a patient is exposed to a strain of MTB that is already drug-resistant. In contrast, secondary resistance develops due to poor adherence to prescribed treatment regimens [5], [17].The delayed and inaccurate diagnosis of MDR-TB remains a significant barrier to effective treatment. Consequently, the advancement of rapid and precise diagnostic techniques is vital for curbing the spread of MDR-TB. Confirming MDR-TB requires bacteriological evidence along with drug resistance testing. The phenotypic drug susceptibility testing (DST) is considered the gold standard for MDR-TB detection [18], [19], [20]. However, a deeper understanding of the relationship between specific mutations and diverse drug resistance profiles, coupled with the advantages of molecular diagnostics, can enable the development of rapid molecular diagnostic tests. These tests could significantly enhance the detection of mutated MTB strains, thereby improving the efficiency of MDR-TB management through molecular diagnostics [21].

Advances in MDR-TB Diagnosis and Treatment: A Review of Literature

Jang and Chung [17] conducted a comprehensive review of multidrug-resistant tuberculosis (MDR-TB) diagnosis, emphasizing the importance of rapid and accurate drug sensitivity tests (DSTs) for selecting effective treatment regimens. The study highlighted various DST methodologies, including solid culture, liquid culture, and molecular culture techniques. Furthermore, the authors discussed the therapeutic strategies for managing MDR-TB, which focus not only on curing the individual patient but also on preventing the transmission of MDR-TB within the community.Fisher [22] addressed the global challenge of MDR-TB diagnosis in a 2002 study, emphasizing diagnostic limitations due to the high costs and inadequate infrastructure for testing in many regions. The review also explored the mutational variability of MDR-TB and examined several culture-based and molecular-based anti-TB susceptibility testing methods reported between 1995 and 2001.A thorough review by Migliori et al. [23] provided insights into the diagnostic methods for both MDR-TB and extensive drug-resistant tuberculosis (XDR-TB), ranging from traditional culture-based procedures to newer, rapid molecular techniques. The study further elaborated on the challenges involved in developing effective control measures for these resistant strains, acknowledging that such challenges are not only technical but also involve ensuring that the developed diagnostic tools and methods are accessible to the populations that are most affected.In 2009, Ahmad and Mokaddas [24]

explored the advancements in MDR-TB diagnosis and treatment, with a focus on the mechanisms of anti-TB drug resistance. The article reviewed both traditional (phenotypic) and rapid (genotypic) molecular approaches for identifying resistance and noted the relevance of these approaches in resource-limited settings, particularly in developing countries, where affordability and speed are key considerations.

Lemos and Matos [25] investigated the mechanisms behind anti-TB resistance and the various diagnostic methods used to detect such resistance, including phenotypic methods, which involve culture growth in the presence of drugs, and genotypic methods, which identify mutations responsible for resistance. The article further discussed the critical need for rapid and specific methods for detecting anti-TB resistance, a need that led to the development of several genotyping techniques by 2013.Saravanan et al. [26] examined the significant global health burden of TB, particularly in developing countries like Ethiopia, where inadequate laboratory diagnostic quality control and a lack of molecular diagnostic facilities contribute to the growing issue of TB resistance. The review focused on molecular diagnostic methods for detecting anti-TB resistance, such as real-time PCR, line probe assays, array-based technologies, oligonucleotide or DNA microarray development, and microRNA. The authors provided a forward-looking perspective, suggesting that microRNA expression methods hold significant potential for improving the diagnosis and prognosis of MDR-TB.

Anti-tuberculosis (Anti-TB) Drugs

The treatment of tuberculosis (TB) commonly involves a multidrug regimen that typically lasts from 6 to 8 months. Anti-TB medications are classified based on their clinical effectiveness and tolerability. The first-line drugs most frequently used to treat tuberculosis include rifampicin, isoniazid, ethambutol, and pyrazinamide. When bacterial strains exhibit resistance to one or more of these drugs, second-line drugs are employed, though they tend to be less effective and more toxic than first-line options [27], [28]. This reduced efficacy and increased toxicity of second-line drugs stem from their complex chemical structures, which complicate absorption and increase the potential for cellular damage. These drugs primarily target bacterial strains that have developed resistance to first-line agents [29], [30].

Classification of Drug-resistant TB

Drug-resistant TB is classified into several categories based on the extent and nature of resistance to anti-TB drugs. Mono-resistant TB refers to resistance against only one first-line anti-TB drug. Poly-resistant TB denotes resistance to more than one first-line anti-TB drug, excluding both isoniazid and rifampicin. Multidrug-resistant TB (MDR-TB) involves resistance to at least isoniazid and rifampicin, the two most critical first-line drugs. Extensively drug-resistant TB (XDR-TB) is characterized by resistance to any fluoroquinolone and at least one of three second-line injectable drugs—capreomycin, kanamycin, or amikacin—along with resistance to both isoniazid and rifampicin. Rifampicin-resistant TB (RR-TB) is defined by resistance to rifampicin, identified through either phenotypic or genotypic methods, and may or may not also involve resistance to other anti-TB drugs. This category encompasses all forms of rifampicin resistance, including mono-resistance, poly-resistance, MDR, or XDR. Isoniazid-resistant TB involves resistance to isoniazid, but the bacteria remain susceptible to rifampicin. Pre-extensively drug-resistant TB is characterized by resistance to rifampicin, isoniazid, and either fluoroquinolones or injectable drugs like amikacin or kanamycin. This classification is adapted from the World Health Organization and [17].

First-line Anti-TB Drugs

First-line anti-TB drugs are essential in the management of TB. These medications are highly effective in inhibiting the growth and replication of Mycobacterium tuberculosis (MTB). Some of the primary drugs used to treat drug-susceptible TB with optimal efficacy and minimal toxicity include isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) [28].

Rifampicin (RIF)

Rifampicin is a lipophilic antibiotic that functions by inhibiting bacterial RNA synthesis. It binds to the β-subunit of DNA-dependent RNA polymerase, thereby preventing RNA transcription [31]. The β-subunit, encoded by the rpoB gene, is crucial for RNA polymerase function. Rifampicin obstructs the transition from short oligoribonucleotides to longer transcripts through a steric occlusion mechanism. Known side effects of rifampicin include hepatotoxicity, which may result in liver disease, and immunological allergies, such as skin reactions, gastrointestinal disturbances, influenza-like symptoms, hemolytic anemia, shock, and acute renal failure. The hepatotoxicity is exacerbated by the drug's induction of cytochrome P450 enzymes in the liver, with patients possessing a history of liver disease being particularly vulnerable. Mutations in the rpoB gene can reduce rifampicin's binding affinity to RNA polymerase, contributing to drug resistance. Resistance to rifampicin in MTB is a major indicator of MDR-TB, with over 90% of rifampicin-resistant strains also resistant to isoniazid [33]. The most frequent mutations leading to rifampicin resistance occur at codons 526 and 531, while mutations at codons 511, 516, 518, 522, and 533 are less common [34].

Isoniazid (INH)

Isoniazid is an anti-TB drug that requires activation by mycobacterial catalase-peroxidase (katG), which is encoded by the katG gene. This activation occurs after INH enters the bacterial cell via passive diffusion [35], [36], [37]. Once activated, isoniazid targets the enoyl-acyl enzyme (inhA) and β-ketoacyl-acyl carrier proteins involved in the synthesis of mycolic acid, a crucial component of the bacterial cell wall. Mycolic acid plays a key role in protecting MTB against chemical damage and dehydration, and it facilitates the bacterium's survival within macrophages, enabling it to evade the host immune system. Isoniazid is considered highly effective during the initial phase of treatment, as it targets rapidly dividing bacteria, acting as a bacteriostatic agent against slow-growing strains. However, the drug may cause toxic, idiosyncratic, and hypersensitivity reactions, with peripheral neuropathy being a common toxicity at normal doses, and seizures occurring due to overdose. Idiosyncratic reactions include lupus erythematosus and rheumatoid-like syndrome, while hypersensitivity reactions may present as hepatitis, dermatitis, fever, and hemolytic anemia. Mutations in the katG gene can lead to a loss of catalase activity, reducing INH activation. Additionally, mutations in the inhA gene can alter the drug's binding site or increase inhA production, resulting in INH resistance. Resistance due to mutations in the katG gene typically leads to a high level of resistance, while mutations in the inhA gene cause lower levels of resistance and cross-resistance to ethionamide [33].

Ethambutol (EMB)

Ethambutol is a specialized anti-TB drug that is often used in combination with other drugs like isoniazid, rifampicin, streptomycin, and pyrazinamide [38]. Discovered by Wilkinson and colleagues in 1961, EMB was noted for its ability to effectively kill nearly all strains of Mycobacterium species [39]. The drug's biological activity is attributed to its inhibition of mycobacterial arabinosyltransferase, an enzyme involved in the biosynthesis of essential components of the bacterial cell wall, such as lipoarabinomannan (LAM) and arabinogalactan (AG). This inhibition disrupts the glycosylation process during the biosynthesis of these cell wall components. EMB is thought to work by mimicking arabinofuranosyl, which impedes the normal transfer of glucose into D-arabinose residues, leading to the accumulation of mycolic acid within the bacterial cell. This results in bacterial aggregation and morphological changes. EMB resistance may occur due to mutations in the genes coding for arabinosyltransferase, including embC, embA, and embB, particularly at the embB 306 codon. Resistance to EMB has been observed in MTB strains harboring these mutations [38].

Pyrazinamide (PZA):

Pyrazinamide (pyrazine-2-carboxamide) is a specialized anti-tuberculosis agent with a distinct sterilizing effect against drug-susceptible tuberculosis forms. According to Sarkar and colleagues, PZA acts as a prodrug that requires enzymatic activation into its active form, pyrazinoic acid (POA), by the bacterial enzyme pyrazinamidase/nicotinamidase in *Mycobacterium tuberculosis* (MTB). This enzyme is particularly active in an acidic pH environment [27]. The active POA disrupts bacterial fatty acid synthesis. PZA is often used in combination with isoniazid (INH) and rifampicin (RIF) as part of a modern regimen for treating drug-susceptible tuberculosis, typically within a six-month period [41]. Recent investigations suggest that PZA could be integrated into drug regimens alongside bedaquiline (TMC207), the bicyclic nitroimidazole PA-824, and moxifloxacin, aiming to reduce the treatment duration for drug-susceptible TB, multidrug-resistant TB (MDR-TB), and extensively drug-resistant TB (XDR-TB) [42]. Resistance to PZA in MTB is frequently linked to mutations in the pncA gene [43], with additional mutations observed in the rpsA and panD genes [44]. The pncA mutation is most prevalent across various MTB complexes in different geographic regions [41], [45], [46], [47].

Second-line anti-TB Drugs

Second-line anti-TB drugs are primarily utilized when multidrug-resistant tuberculosis (MDR-TB) is diagnosed. These drugs include Amikacin, Fluoroquinolones (FQs), Para Aminosalicylic Acid (PAS), Ethionamide (ETA), and D-Cycloserine (CYS), among others.

Amikacin

Amikacin, a semi-synthetic aminoglycoside derived from kanamycin, exhibits broad-spectrum antibacterial activity against both gram-positive and gram-negative bacteria. It exerts its therapeutic effect by inducing errors in the translation of MTB tRNA, thereby inhibiting bacterial protein synthesis, a crucial process for bacterial growth. Amikacin binds to the 30S subunit of the bacterial ribosome, which disrupts the interaction between mRNA and the tRNA acceptor site [48].

Fluoroquinolones (FQs)

Fluoroquinolones, a class of third-generation quinolone antibiotics, include Moxifloxacin (MOXI), Gatifloxacin (GATI), Levofloxacin (LEV), Ciprofloxacin (CIP), and Ofloxacin (OFL). These drugs target the bacterial enzymes topoisomerase II and IV. Topoisomerase II, also referred to as DNA gyrase, is crucial for unwinding DNA into two strands, a necessary step for DNA replication. In contrast, topoisomerase IV plays a

critical role in the decatenation of chromosomal DNA during cell division. DNA gyrase is a tetrameric protein composed of two subunits encoded by the gyrA and gyrB genes [49]. Mutations in the gyrA gene at codons 90, 91, and 94 are commonly associated with fluoroquinolone resistance [50].

Para Aminosalicylic Acid (PAS)

Para-aminosalicylic acid is a bacteriostatic anti-mycobacterial agent that is often administered in combination with INH to prevent the development of bacterial resistance. PAS functions through two primary mechanisms: it inhibits folate synthesis by binding to pteridine synthetase and prevents iron uptake by MTB by interfering with the biosynthesis of cell wall components. Mutations in the thyA gene are associated with PAS resistance in clinical isolates of MTB [51]. Additionally, PAS resistance has been linked to mutations in several genes, including R127L, L143P, C146R, L172P, A182P, and V261G. Moreover, mutations in the promoter region of the methionine transporter gene (metM, Rv3253c) are implicated in PAS resistance in MTB [52], [53].

Ethionamide (ETA)

Ethionamide is an essential drug in the treatment of MDR-TB. The activation of ETA occurs through a mechanism involving the katG gene, which leads to the formation of a sulfur-containing metabolite. This metabolite inhibits the synthesis of mycolic acids, a key component of the bacterial cell wall, by blocking the activity of the inhA gene. Resistance to both ETA and INH is often due to mutations in the inhA gene. Naturally occurring ETA resistance can also arise from alterations in the enzyme responsible for the drug's activation [51], [54], [55], [56].

D-Cycloserine (CYS)

D-Cycloserine is a bactericidal drug that interferes with bacterial cell wall synthesis by inhibiting two enzymes—L-alanine racemase and D-alanine ligase—that are involved in the synthesis of the core pentapeptide from D-alanine. These enzymes are essential for peptidoglycan synthesis and the formation of the bacterial cell wall [51], [57].

Tuberculosis Biomarker

Biomarkers are biological indicators utilized to reflect normal biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions [58], [59]. These markers can be measured at various levels, including molecular, cellular, and whole organism scales [60]. The utilization of biomarkers plays a crucial role in the early detection of diseases. Biomarkers can be classified into different categories depending on their specific application in disease contexts. These categories include antecedent biomarkers, which help in identifying disease risks, screening biomarkers used for identifying subclinical disorders, diagnostic biomarkers that aid in the recognition of overt disorders, staging biomarkers for categorizing disease severity, and prognostic biomarkers that predict disease outcomes [61], [62]. Various types of biomarkers serve as diagnostic tools, such as protein antibodies, microbial indicators, DNA, RNA, lipid-based agents, metabolic compounds, and proteinaceous components derived from biological materials like blood, serum, urine, and other biological samples. Numerous reviews have discussed the potential biomarkers for tuberculosis (TB) detection [13], [27], highlighting markers based on bacterial culture, cellular components, DNA compounds, and proteins from different sample types.

Biomarkers for Tuberculosis Diagnosis

The pathogen perspective focuses on identifying MTB bacteria in bodily samples, whereas the host perspective looks at abnormal immune responses indicative of MTB infection. Under thepathogen category, biomarkers like Mycobacterium tuberculosis (MTB) DNA,Lipoarabinomannan (LAM), and antigen 85, ESAT-6, and MPT64 complex are used, primarily from sputum or urine samples. From the host's immune system perspective, markers such as RV0310c-E and RV1255c-E antigens, MTB P12037, and Proline-Proline Glutamic Acid Protein 17 (PPE17) are analyzed from blood samples. The integration of pathogen and host biomarkers provides a comprehensive approach to TB diagnosis, examining both the presence of the bacteria and the immune system's reaction to infection [63].Despite significant advancements in diagnostic methods, challenges remain, particularly in diagnosing TB cases involving drug-resistant strains [65], [66]. Many of the biomarkers listed for TB detection face limitations when used to identify drug-resistant strains of TB, as they cannot effectively differentiate between resistant and susceptible MTB strains [67], [68]. Recently, novel biomarkers have been identified that may help distinguish multi-drug resistant TB (MDR-TB) from drug-sensitive TB (DS-TB) using validated techniques like high-performance liquid chromatography-mass spectrometry (HPLC-MS) and mass spectrometry (MS).

Novel Biomarkers for MDR-TB Detection

These biomarkers have been validated using various methods such as HPLC-MS and mass spectrometry. For example, IDO, an enzyme that catalyzes the conversion of tryptophan to kynurenine, has shown potential as a diagnostic marker for MDR-TB. Studies have demonstrated that IDO activity is elevated in MDR-TB patients compared to DS-TB patients, with sensitivity and specificity values of 87.50% and 72.22%, respectively, suggesting its promise as an early detection tool for MDR-TB [65]. Further studies have focused on sCD14, a protein associated with monocyte activation, which has been found to be less specific for MDR-TB detection due to its responsiveness

to other infections and lung diseases [66]. PGLYRP2, an enzyme implicated in bacterial peptidoglycan hydrolysis and macrophage activation, is found to be significantly increased in MDR-TB patients, suggesting its role in the immune response to TB infection [66]. Additionally, FGA, a component of the fibrinolytic plasminogen system, has been linked to the increased invasiveness of MTB and is more abundant in MDR-TB patients compared to healthy individuals [66]. These biomarkers are part of ongoing research efforts to improve MDR-TB diagnostics, with sensitivity and specificity rates reaching 81.2% and 90%, respectively.

Existing Studies on Biomarkers for MDR-TB

Research by Shi et al. [65] highlighted the potential of plasma IDO levels as an indicator of TB, specifically for distinguishing between MDR-TB and DS-TB. The study showed that plasma IDO activity was higher in MDR-TB patients compared to those with DS-TB or lung cancer, reinforcing its potential as an early biomarker for MDR-TB diagnosis. Similarly, studies by Tan et al. [71], [72] identified significant immune system differences in MDR-TB patients, including reduced CD4+ T cell responsiveness, decreased Th1 frequency, low IFN-γ levels, and elevated pro-inflammatory cytokine levels before treatment. This information guided subsequent research measuring Trp, Kyn, and IDO activity using HPLC-MS, which further confirmed the diagnostic utility of IDO in differentiating MDR-TB from other conditions.Chen et al. [73] utilized mass spectrometry techniques such as data-independent acquisition (DIA) and parallel reaction monitoring (PRM) to identify differential proteins in the serum of MDR-TB patients. Through bioinformatics, proteins like sCD14, PGLYRP2, and FGA were selected as candidate biomarkers. sCD14, although useful in chronic infections, was found to have limited specificity for MDR-TB, as it can also respond to other lung infections. PGLYRP2, however, demonstrated increased abundance in MDR-TB patients and is associated with a heightened immune response. FGA, which participates in the fibrinolytic pathway, also showed elevated levels in MDR-TB patients, suggesting its role in TB pathogenesis and its potential as a diagnostic biomarker.

Mutation in MTB as DNA Biomarker for MDR-TB Detection

Another important aspect of MDR-TB detection lies in identifying specific mutations in MTB genes. Resistance to rifampicin (RIF), a key drug in TB treatment, is a hallmark of MDR-TB. Mutations in the rpoB gene, which reduce the binding affinity of RIF to RNA polymerase, are commonly associated with resistance to RIF and, by extension, MDR-TB. Over 90% of rifampicin-resistant isolates are also resistant to isoniazid (INH) [33]. Notably, mutations at codons 526 and 531 of the rpoB gene account for 65% to 86% of RIF resistance cases, while mutations at codons 511, 516, 518, and 522 are associated with low-level resistance [74]. DNA sequencing remains the gold standard for detecting such mutations, with the rifampicin resistance-determining region (RRDR) within the rpoB gene being a critical target for identifying RIF resistance [32], [77]. In addition, mutations at codon 315 of the katG gene are particularly prevalent in resistant TB strains, with frequencies ranging from 46% to 85% across various studies [2], [78]. These mutations serve as crucial biomarkers for detecting MDR-TB and monitoring treatment efficacy.

Detection Methods of MDR-TB

The identification of Multidrug-resistant Tuberculosis (MDR-TB) through drug susceptibility testing (DST) provides essential insights for selecting effective treatment regimens for various forms of tuberculosis (TB) [79]. Two primary techniques are employed to detect MDR-TB: phenotypic and genotypic methods.Phenotypic testing is a culture-dependent approach that observes the growth or inhibition of *Mycobacterium tuberculosis* (MTB) in media that have been supplemented with anti-TB drugs, allowing the identification of drug-resistant genes. This method can be conducted using either solid media, such as Lowenstein-Jensen (LJ) medium, or liquid media, such as the Mycobacterium Growth Indicator Tube (MGIT) [79], [80]. However, phenotypic testing requires a considerable period, typically 2–3 months, to yield confirmed results [79]. On the other hand, genotypic testing is a molecular-based method that detects specific genetic mutations responsible for resistance to anti-TB drugs. Compared to phenotypic testing, genotypic testing has a shorter turnaround time. This method employs nucleic acid amplification techniques to identify genetic mutations in specific genes. Genotypic testing encompasses two main types of molecular DSTs: probe-based assays and sequence-based assays [81]. Various detection methods for MDR-TB are outlined below.

Bacterial Culture Method

Bacterial culture is a key method for detecting MTB, especially when patients present with BTA-positive results or treatment failure, which raises the suspicion of MDR-TB. Fluorescein diacetate (FDA) staining for bacterial cultures, using sputum smear microscopy, has been documented in studies such as that by Salim et al. [82]. This staining technique relies on the principle of intracellular FDA hydrolysis, which is facilitated by enzymes abundant in living MTB cells. These cells convert non-fluorescein FDA compounds into fluorescein green compounds through enzymatic activity. The presence of fluorescent bacilli is indicative of MDR-TB strains that exhibit resistance to anti-TB drugs. The FDA staining method has demonstrated sensitivity, specificity, and accuracy

ranging from 33% to 100%, 82% to 98%, and 67% to 97%, respectively [83].Another notable method for detecting MTB strains resistant to anti-TB drugs is the nitrate reductase assay (NRA), also known as the Griess method. This technique exploits MTB's ability to reduce nitrate to nitrite, which is detected upon the addition of 1 mg/mL potassium nitrate (KNO3) and Griess reagent to LJ medium, resulting in a color change. A red color signifies resistance to either Rifampicin (RIF) or Isoniazid (INH) at specified concentrations, while a lack of color change indicates susceptibility. The NRA method has proven to be highly sensitive and specific, offering accurate and rapid results for detecting resistance to RIF and INH [84], [85].

Traditional culture-based drug susceptibility tests conducted on solid media require approximately 2 to 3 months for results to be available, based on the commencement of anti-TB treatment [88], [89]. In 2007, the World Health Organization (WHO) recommended the adoption of liquid culture techniques to detect growth-dependent changes in MTB more efficiently, with a reduced turnaround time of about one month. The BACTEC MGIT 960 system, which involves the inoculation of sputum samples into 7 mL of Middlebrook 7H9 broth containing an O2-sensitive fluorescent indicator, enables the detection of oxygen consumption and bacterial growth in liquid media exposed to anti-TB drugs, such as INH and RIF, at defined concentrations [79], [90].However, there are notable limitations to culture-based MDR-TB detection methods. Mekonnen et al. [91] identified shortcomings, such as the inability of acid-fast staining to detect drug resistance, the extended timeline required for results from solid culture DST, and the relatively high cost of liquid culture systems, which restricts their accessibility. As a result, the MDR ColorTest (TB-CX), utilizing a thin-layer agar (TLA) culture method, has emerged as a promising alternative for detecting TB strains resistant to RIF, INH, and Pyrazinamide (PZA), which is known as MDR-TB plus PZA. This method displays excellent performance in differentiating between susceptible and resistant TB strains by using quadrants in the culture medium: one quadrant for growth detection (colorless) and the other three for DST, incorporating 0.2 µg/mL INH (green), 1.0 µg/mL RIF (yellow), and 100 µg/mL PZA (blue). This system provides rapid and accurate results, aiding in the timely identification of resistant strains.

Polymerase Chain Reaction (PCR) Method

Molecular techniques hold significant potential for the direct detection of *Mycobacterium tuberculosis* (MTB) in clinical specimens. Among these techniques, PCR has emerged as a widely utilized method for tuberculosis (TB) diagnosis in clinical laboratories, employing various DNA isolation protocols [93]. PCR functions as a DNA amplification technique, enabling the selective amplification of DNA fragments from a given source [94]. When applied to MTB detection, PCR technologies are integrated into systems such as the GeneXpert platform, which automates the process for enhanced efficiency in detecting target genetic material. The incorporation of PCR into the GeneXpert platform has revolutionized molecular diagnostics, offering rapid and precise results for a range of infectious diseases.

The GeneXpert test utilizes a cartridge-based nucleic acid amplification test (NAAT) to identify TB and Rifampicin (RIF) resistance within approximately two hours. The core mechanism behind the GeneXpert test involves multiplexed, semi-nested quantitative real-time PCR, targeting the rpoB gene and utilizing molecular beacons to increase sensitivity. This test employs a heminested real-time PCR assay to detect mutations in the rpoB hotspot region, followed by the detection of these mutations through molecular beacons as probes. The test cartridge is preloaded with all necessary reagents for bacterial lysis, nucleic acid extraction, amplification, and subsequent detection of the amplified gene [95]. A variety of molecular assays available on the GeneXpert platform are marketed under the Xpert/MTB-RIF trade name. In 2013, the Xpert MTB/RIF assay was approved by the United States Food and Drug Administration (FDA) for the detection of RIF resistance. Additionally, PCR and line probe assay (LPA)-based tests have been endorsed by the World Health Organization (WHO) for detecting resistance to RIF and Isoniazid (INH) by amplifying bacterial DNA and utilizing oligonucleotide probe techniques [81].

The Xpert MTB/RIF assay represents a rapid diagnostic test for TB and RIF resistance, leveraging simultaneous quantitative reverse transcription PCR (qRT-PCR) analysis with molecular beacon probe technology to measure the quantity of MTB DNA. However, the sensitivity of the Xpert MTB/RIF test is reduced in sputum specimens negative for acid-fast bacilli (AFB), leading to false results for RIF resistance. To address this issue, Chakravoty et al. developed the Xpert MTB/RIF Ultra (Ultra) test, which includes improvements in cartridge design, thermal parameters, and mutation detection. Sensitivity and Limit of Detection (LOD) tests comparing Xpert MTB/RIF Ultra and Xpert MTB/RIF demonstrated that the Ultra version exhibited higher sensitivity and a lower LOD of 15.6 CFU/mL and 105.4 CFU/mL, respectively. Consequently, the Ultra test produces more accurate results for RIF resistance detection than the standard Xpert test.

PCR-Enzyme-Linked Immunoassay (ELISA)

PCR-enzyme-linked immunoassay (ELISA) is an immunological technique used to directly measure PCR products by immobilizing biotinylated DNA onto a microplate, involving three main stages: amplification, immobilization, and detection. The primary aim of integrating PCR with ELISA is to enhance detection sensitivity

and diagnostic precision. While PCR detects genetic material, ELISA identifies bacterial antigens or antibodies, thereby improving both sensitivity and specificity [97]. Sue et al. compared various PCR-based detection methods, including conventional PCR (with agarose gel electrophoresis) and PCR-ELISA. The PCR-ELISA method serves as a semi-quantitative tool due to its use of specialized probe genes for detection. In comparison with conventional PCR, PCR-ELISA testing can increase the detection limit to 0.01 ng/L from a range of 1-10 ng/L and allows for large-scale screening using standard laboratory equipment. Additionally, PCR-ELISA testing offers faster analysis than conventional PCR [98], [99], [100], [101].

Zhou et al. [102] employed PCR-ELISA microplate hybridization techniques to identify mutations in the rpoB and katG genes responsible for resistance to RIF and INH, comparing these results with DNA sequencing and conventional drug susceptibility testing (DST). The study demonstrated that the PCR-ELISA microplate hybridization assay achieved sensitivities and specificities of 93.7% for RIF, 87.5% for INH, and 100% for phenotypic DST. Furthermore, a concordance test between the PCR-ELISA results and DNA sequencing to identify RIF-resistant and INH-resistant mutations in multidrug-resistant tuberculosis (MDR-TB) isolates revealed a concordance rate of 96.9%.In recent years, PCR methods for detecting MDR-TB have seen significant advancement. The improvements in sensitivity and selectivity can be attributed to innovations such as the design of super-selective primers targeting heteroresistant mutations [103], the development of DNA primers for rpoB and katG genes, plasmids, and specific probes [104], and the application of DeepMelt analysis to selectively detect mutated DNA in MTB, as confirmed by DNA sequencing and digital PCR [105].

Nursing Interventions:

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis*, primarily affecting the lungs, though it can also involve other organs. The disease spreads through airborne droplets when an infected individual coughs, sneezes, or talks. Effective nursing care is critical in managing TB to prevent complications, ensure optimal health outcomes, and reduce transmission. This involves not only addressing the patient's medical needs but also providing education and psychosocial support to facilitate adherence to treatment.

Nursing Diagnoses for Tuberculosis (TB)

Several nursing diagnoses are pertinent in the care of TB patients, reflecting the complex nature of the disease. One of the primary diagnoses is Ineffective Airway Clearance related to excessive mucus production and inflammatory response. TB often results in coughing and the production of thick, viscous sputum, which can obstruct the airway. The inflammation in the lungs further exacerbates this issue, requiring active nursing interventions. Another critical diagnosis is Imbalanced Nutrition: Less than Body Requirements related to decreased appetite, fatigue, and systemic infection. Due to the catabolic nature of the disease and side effects of treatment, TB patients frequently experience weight loss, anorexia, and fatigue, all contributing to insufficient nutritional intake. Risk for Infection related to compromised immune system and the infectious nature of TB is another common diagnosis. The airborne transmission of TB, coupled with the patient's potential immunocompromised status, presents a risk of spreading the infection to others and developing secondary infections. Additionally, Fatigue related to fever, infection, and inadequate sleep is a common diagnosis due to the systemic effects of TB, including persistent fever, night sweats, and overall exhaustion. Lastly, Knowledge Deficit related to the nature of TB, treatment regimen, and preventive measures is often observed, as patients may lack awareness about TB, the importance of completing their treatment regimen, and the measures needed to prevent disease transmission.

Nursing Interventions for Tuberculosis (TB)

The management of TB requires a multi-faceted approach. To improve airway clearance, one essential intervention is proper positioning. Placing the patient in an upright or semi-Fowler's position facilitates easier breathing and promotes the drainage of secretions. Encouraging deep breathing and coughing exercises also helps the patient expel mucus and clear the airways effectively. In addition, administering prescribed expectorants or mucolytics, such as acetylcysteine, can help thin mucus and make it easier to expectorate. In more severe cases, suctioning may be necessary to remove thick sputum that the patient is unable to clear independently. These interventions aim to reduce respiratory complications and maintain effective airway function.To address nutritional deficiencies, a critical intervention involves offering high-calorie, protein-rich meals that meet the increased metabolic demands associated with the infection. Due to the anorexia and gastrointestinal side effects of TB medications, it is essential to monitor the patient's dietary intake and weight closely. If necessary, a dietitian can be consulted to develop a tailored nutrition plan. Antiemetic medications may be prescribed to alleviate nausea caused by TB medications. By ensuring that the patient maintains adequate nutrition, nurses can help mitigate the effects of the disease and improve the patient's overall strength and immunity.

Preventing the spread of TB is another central nursing intervention. The patient should be placed under airborne precautions in a negative pressure room to reduce the risk of transmission to others. Nurses must also provide education to the patient and their family about infection control practices. This includes the importance of

covering the mouth when coughing, wearing a mask in public, and maintaining good hand hygiene. Directly Observed Therapy (DOT) should be implemented to ensure that the patient adheres to the full course of treatment. Adherence to medication is crucial in preventing drug resistance and relapse, making it an essential component of TB management.To manage fatigue, nurses should encourage frequent rest periods throughout the day to allow the patient to conserve energy. It is important to create an environment that promotes rest, ensuring the patient's comfort and minimizing distractions. Nurses can also promote sleep hygiene by addressing any disturbances caused by night sweats or coughing, helping the patient establish a regular sleep routine, and providing a cool, dark environment for rest. Monitoring vital signs, particularly for signs of increasing fatigue or infection, allows for timely adjustments in care and treatment.Lastly, providing education is a critical nursing intervention. Patients often have many questions about TB, its treatment, and the prevention of transmission. Nurses should provide clear, accessible information about the disease, emphasizing the importance of completing the prescribed treatment regimen and adhering to preventive measures. Nurses should address any misconceptions or fears about TB and its treatment, reinforcing that adherence to therapy is necessary to prevent relapse or drug-resistant TB.

Care Plans for Tuberculosis (TB)

A comprehensive care plan for a patient with TB should focus on addressing the patient's immediate medical needs while promoting long-term health outcomes. One key aspect is the Airway Clearance Plan, which aims to maintain effective airway function. The goal of this plan is for the patient to demonstrate effective airway clearance through the expulsion of mucus and the maintenance of a clear airway. Interventions such as positioning, deep breathing exercises, and the administration of mucolytic agents are essential. The plan's effectiveness can be evaluated by monitoring the patient's ability to clear secretions, assessing lung sounds, and noting a reduction in sputum production.For Nutritional Support, the care plan's goal is for the patient to maintain or regain adequate nutritional intake. Interventions include offering calorie-dense, protein-rich foods, monitoring weight and intake, and addressing any gastrointestinal side effects of medication. This plan can be evaluated by tracking weight gain, improvements in appetite, and the patient's ability to engage in daily activities without excessive fatigue.The Infection Control Plan focuses on preventing the spread of TB to others. The goal is for the patient to understand and practice TB prevention measures effectively. Interventions involve educating the patient and their family on infection control practices, ensuring the patient adheres to airborne precautions, and implementing DOT for treatment adherence. Evaluation is based on the patient's understanding of the preventive measures and their ability to implement them in daily life.

The Fatigue Management Plan aims to help the patient manage fatigue by balancing activity with rest. The goal is for the patient to experience increased energy levels and improved capacity to engage in activities. Interventions include scheduling rest periods, promoting sleep hygiene, and monitoring vital signs. Evaluation of this plan is based on the patient's reported energy levels and ability to participate in activities without undue fatigue.Finally, the Educational Plan aims to ensure that the patient fully understands TB, its treatment, and prevention strategies. The goal is for the patient to demonstrate an understanding of the disease, its transmission, and the importance of adhering to the prescribed treatment regimen. Interventions include providing written and verbal instructions, addressing any concerns, and reinforcing the importance of infection control. Evaluation is based on the patient's ability to articulate the disease process, treatment adherence, and preventive practices.Nursing interventions for tuberculosis are essential in promoting recovery, preventing the spread of infection, and managing symptoms. Effective care requires a multi-dimensional approach that includes airway management, nutritional support, infection control, fatigue management, and education. Through a comprehensive care plan, nurses can ensure that TB patients receive the necessary care to improve their health outcomes and minimize the risk of complications. The role of nurses in the management of TB is critical in ensuring adherence to treatment and providing the support needed to overcome the challenges of this chronic infectious disease.

Conclusion:

Multidrug-resistant tuberculosis (MDR-TB) presents a serious and growing challenge to global health systems. Its resistance to the primary anti-TB drugs, rifampicin and isoniazid, complicates both diagnosis and treatment, contributing to prolonged illness, increased mortality, and further spread of the disease. The emergence of MDR-TB is largely due to inadequate treatment regimens, insufficient drug dosages, and incomplete therapies, which result in the development of resistant strains of Mycobacterium tuberculosis (MTB). Given the gravity of this problem, a multifaceted approach is required to tackle the diagnosis, management, and treatment of MDR-TB.Nurses play an essential role in ensuring that patients adhere to complex treatment regimens, which often involve multiple second-line drugs. By providing education on proper medication use and addressing concerns about potential side effects, nurses contribute significantly to preventing further drug resistance and improving patient outcomes. Furthermore, nurses must be equipped to monitor the health status of patients undergoing long-term TB therapy, managing adverse reactions, and ensuring optimal support throughout the treatment period.Pharmacists are

equally vital in the management of MDR-TB. They assist in the proper selection and administration of second-line medications, optimize drug dosages, and reduce the likelihood of interactions or complications caused by polypharmacy. Pharmacists also serve as a valuable resource for educating patients about the potential risks of non-compliance with treatment and ensuring the safe, effective use of anti-TB medications.Clinical pathologists are instrumental in diagnosing MDR-TB through advanced molecular techniques, such as PCR and next-generation sequencing, which provide faster, and more accurate results compared to traditional culture-based methods. These technologies enable the early detection of resistant strains, allowing for the initiation of appropriate therapies before resistance spreads further. Moreover, the implementation of rapid diagnostic methods is crucial in areas with limited resources, where delays in diagnosis can result in increased morbidity and mortality.In conclusion, the management of MDR-TB requires the concerted efforts of a diverse healthcare team, including nurses, pharmacists, and clinical pathologists. Each plays a distinct and vital role in ensuring that patients receive timely, effective treatment and support. The development and widespread implementation of rapid diagnostic tools and effective drug regimens are essential in curbing the spread of MDR-TB and achieving global health goals.

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السل المقاوم للأدوية المتعددة: الأدوار المساهمة للتمريض والصيادلة وعلم الأمراض الإكلينيكي في التشخيص والإدارة والعلاج - مراجعة محدثة

الملخص:
الخلفية: يُعد السل (TB) من القضايا الصحية العالمية الرئيسية، ويستمر في التأثير على ملايين الأفراد سنويًا، مع تصاعد الأشكال المقاومة للأدوية، وخاصة السل المقاوم للأدوية المتعددة(MDR-TB) ، في جميع أنحاء العالم. يسبب السل المقاوم للأدوية المتعددة سلالات من *المتفطرة السلية* المقاومة لكل من الريفامبيسين (RIF) الإيزونيازيد(INH) ، مما يشكل تحديات كبيرة في العلاج. ينشأ هذا المرض بسبب العلاجات غير المكتملة، والجرعات غير الكافية من الأدوية، وانتقال العدوى من الأفراد المصابين. يُعد التشخيص المبكر والدقيق، بالإضافة إلى استراتيجيات العلاج المصممة خصيصًا، أمرًا بالغ الأهمية في مكافحة السل المقاوم للأدوية المتعددة ومنع انتشاره.
الهدف: تهدف هذه المراجعة إلى دراسة الأدوار الحيوية التي يلعبها المتخصصون في التمريض والصيادلة وعلماء الأمراض الإكلينيكية في التشخيص والإدارة والعلاج للسل المقاوم للأدوية المتعددة، مع استكشاف أحدث التطورات في هذه المجالات.
الطرق: تم إجراء مراجعة شاملة للأدبيات، مع التركيز على الدراسات الحديثة التي تتناول المنهجيات المتطورة في تشخيص السل المقاوم للأدوية المتعددة، بما في ذلك التشخيصات الجزيئية، واختبارات حساسية الأدوية الظاهرية، ومساهمات المتخصصين في الرعاية الصحية. كما تحقق المراجعة في الأساليب العلاجية ودور القطاعات الصحية المختلفة في إدارة السل المقاوم للأدوية المتعددة.
النتائج: تؤكد النتائج على الأدوار المحورية التي يلعبها العاملون في التمريض والصيادلة وعلماء الأمراض الإكلينيكية في مكافحة السل المقاوم للأدوية المتعددة. يعد الممرضون عنصرًا أساسيًا في ضمان التزام المرضى بأنظمة العلاج، وإدارة الآثار الجانبية، وتعليم المرضى حول أهمية إتمام العلاجات الموصوفة. يلعب الصيادلة دورًا رئيسيًا في الاستخدام العقلاني للأدوية من الخط الثاني، وتحسين أنظمة الأدوية، ومنع المقاومة. يُعد علماء الأمراض الإكلينيكية أساسيين في تحسين دقة التشخيص من خلال الأساليب المتقدمة للاختبار. كما تبرز الدراسة الحاجة إلى تشخيص سريع ودقيق لتسهيل التدخل المبكر.
الخاتمة: لا يزال السل المقاوم للأدوية المتعددة تهديدًا كبيرًا للصحة العالمية، لكن النهج التعاوني الذي يشمل المتخصصين في التمريض والصيدلة وعلم الأمراض أمر ضروري لتحسين التشخيص والإدارة ونتائج المرضى. إن التقدم المستمر في التشخيصات الجزيئية واستراتيجيات إدارة الأدوية أمر بالغ الأهمية لمكافحة الانتشار المتزايد للسل المقاوم للأدوية المتعددة.
الكلمات المفتاحية: السل المقاوم للأدوية المتعددة، التمريض، الصيادلة، علم الأمراض الإكلينيكي، التشخيص، العلاج، التشخيص الجزيئي، مقاومة الأدوية، إدارة السل.