

ABSTRACT

of the dissertation for the degree of Doctor of Philosophy
Topic: “Antibiotic resistance of secondary bacterial infection pathogens in hospitalized patients with drug-resistant tuberculosis”

Specialty: 6D110100 “Medicine”

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Relevance

Tuberculosis (TB) remains one of the leading causes of death worldwide, responsible for over a million deaths annually, and continues to be a major global public health concern [1].

High-priority pathogens, such as Gram-negative bacteria resistant to last-resort antibiotics and rifampicin-resistant *Mycobacterium tuberculosis*, pose a serious global threat due to the heavy disease burden they cause, their resistance to treatment, and their ability to transmit resistance to other bacteria. Antimicrobial resistance jeopardizes the effective treatment of socially significant infections such as tuberculosis, leading to severe disease progression and increased mortality rates [2].

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis are spreading globally. According to expert forecasts, the prevalence of MDR and XDR tuberculosis is expected to increase through 2040 [3]. The proportion of MDR-TB among new TB cases is projected to reach 12.4% (95% prediction interval: 9.4–16.2) in India, 8.9% (4.5–11.7) in the Philippines, 32.5% (27.0–35.8) in Russia, and 5.7% (3.0–7.6) in South Africa by 2040 [2].

Currently, the epidemiological situation regarding tuberculosis in Kazakhstan is improving, but TB remains a pressing issue.

The incidence rate of tuberculosis decreased from 81.7 in 2018 to 36.5 per 100,000 population in 2022, which is 55.3%, and mortality decreased from 7.4 in 2018 to 1.6 in 2022, which is 78.4%. However, the problem of drug-resistant tuberculosis remains relevant in the country [4]. According to WHO estimates, Kazakhstan is among the 30 countries with a high burden of drug-resistant tuberculosis (DR-TB). The level of primary MDR/XDR-TB in 2022 was 35.1%, meaning that drug-resistant tuberculosis poses a serious threat to the health of the population of Kazakhstan [5].

Translated with DeepL.com (free version) Despite these reported figures, the proportion of drug-resistant TB cases continues to rise. Resistance of *M. tuberculosis* to anti-TB drugs poses a significant threat to TB control efforts and remains under close public health surveillance [6, 7, 8, 9]. The steady increase in the spread of resistant *M. tuberculosis* strains is particularly alarming, with the greatest threats posed by extensively drug-resistant (XDR) and multidrug-resistant (MDR) strains. Today, drug-resistant TB is one of the main factors contributing to increased mortality and decreased treatment effectiveness worldwide [10, 11, 12, 13].

Pulmonary tuberculosis patients receive prolonged courses of antibiotic therapy (such as streptomycin, rifampicin, and others), which often leads to the development of resistant secondary microflora, particularly opportunistic microorganisms (OMs) [14].

The development of endogenous secondary infections caused by opportunistic pathogens (e.g., *Klebsiella pneumoniae*, *Escherichia coli*) largely depends on the patient's condition. The risk of nosocomial infections is significantly influenced by the patient's immune status as well as the quality of infection control measures in healthcare settings.

By causing pathological processes in the lungs, OMs aggravate the course of the primary disease. They damage pulmonary tissue and increase its susceptibility to *M. tuberculosis*. Lung tissue sensitized by bacterial allergens from *Staphylococcus*, *Streptococcus*, and other opportunistic microbes creates favorable conditions for the spread of mycobacteria and the formation of new lesions. When associated with *M. tuberculosis*, OMs accelerate the destruction of caseous lung areas, often giving tuberculous cavities an abscess-like character OMs are a contributing factor in the destabilization and reactivation of old tuberculous lesions, which may provoke bacterial shedding in patients with previously inactive tuberculosis.

The emergence of multidrug-resistant microorganisms necessitates not only rapid identification of pathogens but also immediate determination of their antimicrobial susceptibility [15, 16, 17].

Secondary infections, often presenting as nonspecific bronchitis, pneumonia, and complicating fibrocavitary tuberculosis, infiltrative TB, or tuberculomas, are diverse and not always attributable to a specific pathogen [18].

The incidence of tuberculosis combined with nonspecific respiratory diseases ranges from 7% to 49% [19, 20, 21]. Among patients with relapses of pulmonary tuberculosis, chronic nonspecific respiratory diseases are observed in 17.5% to 63.2% of cases [22].

The coexistence of tuberculosis and nonspecific lung diseases significantly complicates the course of TB, with increased multisymptomatology and predominance of destructive and exudative changes. In such combined processes, treatment outcomes are poorer, with lower rates of cavity closure and sputum decontamination, and prolonged recovery periods [23,24,25].

In 10.2% of cases, nonspecific respiratory diseases are the cause of death in patients with active tuberculosis [26].

Timely diagnosis and appropriate treatment of secondary lower respiratory tract infections (LRTIs) in patients with pulmonary tuberculosis is a critical issue in modern phthysiology [19].

Bacteriological analysis of sputum or bronchial secretions for the detection of opportunistic microorganisms (other than *Mycobacterium tuberculosis*) is performed in routine phthysiatric practice in no more than 10% of cases, usually only in severely ill patients [27].

In this regard, it is necessary to conduct a study aimed at investigating the etiological structure and antimicrobial susceptibility of nonspecific pathogens in patients with drug-resistant tuberculosis.

Study Objective

To investigate the etiological structure and antimicrobial susceptibility of secondary infection pathogens in hospitalized patients with drug-resistant tuberculosis.

Research Objectives.

1) To analyze clinical features of tuberculosis and treatment efficacy in hospitalized patients with drug-resistant TB co-infected with secondary pathogens

2) To identify the etiological structure of secondary infections in patients with drug-resistant tuberculosis.

3) To determine the antimicrobial susceptibility profiles of secondary pathogens in drug-resistant TB patients.

4) To evaluate the effectiveness of sub-species identification using MALDI-TOF mass spectrometry, with a focus on *K. pneumoniae* isolated from hospitalized pulmonary TB patients in Central Kazakhstan.

Scientific Novelty

- The clinical characteristics of tuberculosis and treatment outcomes were studied in hospitalized patients with drug-resistant tuberculosis co-infected with secondary infections.

- The etiological structure of secondary infection pathogens in hospitalized patients with drug-resistant tuberculosis was identified in Central Kazakhstan during the period of 2018–2019.

- The antimicrobial susceptibility profiles of secondary infection pathogens in hospitalized patients with drug-resistant tuberculosis were determined.

- For the first time, sub-species typing of *Klebsiella pneumoniae* isolates from hospitalized pulmonary tuberculosis patients in Central Kazakhstan was performed using MALDI-TOF technology (Certificate of copyright registration No. 23607 dated 15.02.2022).

- The results of this research were implemented in the practical work of the Regional Tuberculosis Dispensary under the Health Department of the Karaganda Region (2019), and in the research laboratory of the NJSC “KMU”.

Key Provisions for Defense:

1. The secondary microflora in patients with drug-resistant tuberculosis (DR-TB) was predominantly composed of Gram-negative microorganisms, particularly representatives of the *Enterobacterales* order (e.g., *E. coli*, *Klebsiella* spp.). Gram-positive bacteria were detected less frequently. No statistically significant differences in microflora composition were found between the DR-TB and drug-susceptible TB (DS-TB) groups.

2. Carbapenems and aminoglycosides demonstrated the highest activity against Gram-negative bacteria. A high rate of resistance to penicillins was observed, limiting their clinical applicability.

3. A significantly reduced *in vitro* susceptibility of *K. pneumoniae* secondary microflora to levofloxacin was detected in the DR-TB group. This finding is likely a consequence of selective pressure resulting from the use of this antibiotic in DR-TB treatment regimens..

4. Sub-species typing of *K. pneumoniae* strains revealed substantial genetic diversity, indicating a polyclonal nature of infection and suggesting predominantly different sources of infection..

5. The combination of drug-resistant tuberculosis and secondary non-specific infections was more frequently observed in patients with chronic and progressive forms, such as fibrocavitary pulmonary tuberculosis, as well as in those classified

under "Relapse" and "Treatment after interruption." The presence of resistant secondary microflora reduces the overall effectiveness of therapy.

Practical Significance

This study examined the etiological structure and antimicrobial susceptibility of secondary infection pathogens in hospitalized patients with drug-resistant tuberculosis (DR-TB)..

Identification of the causative agents of secondary infections and determination of their antimicrobial susceptibility enables timely and appropriate antibacterial therapy, which can enhance treatment effectiveness and reduce the length of hospital stay.

The results of the study highlight the necessity of conducting microbiological analysis of sputum for secondary infection in all tuberculosis patients.

Relation of the Dissertation to Other Research Projects

This dissertation was carried out at the State Enterprise with the Right of Economic Management "Regional Center of Phthisiopulmonology" under the Health Department of the Karaganda Region, within the Department of Infectious Diseases and Phthisiology, and the Shared Research Laboratory of the NJSC "Karaganda Medical University".

Author's Personal Contribution

The author took an active part in the analysis and synthesis of the literature, as well as in the organization of material collection. The author independently carried out the collection and processing of data, performed the analysis, summarized the research results, and prepared the full text of all chapters of the dissertation.

The materials of the dissertation were processed and analyzed by the author personally, accounting for 95% of the total work.

Thesis Approval and Dissemination

The main findings and results of the dissertation were presented at the following scientific events:

- In the journal *Problems of Medical Mycology* and at the Russian-Chinese Congress on Medical Microbiology, Epidemiology, Clinical Mycology, and Immunology — XXII Kashkin Readings (poster presentation: "Lower Respiratory Tract Pathogens in Pulmonary Tuberculosis Patients in Karaganda", 2019).

- At the International Scientific and Practical Conference "New Approaches to Ending the Tuberculosis Epidemic", dedicated to the 85th anniversary of the National Scientific Center of Phthisiopulmonology, Ministry of Health of the Republic of Kazakhstan, Almaty, 2018.

- A thesis published in the *International Journal of Infectious Diseases*, Volume 73S (2018).

- At the extended meeting of the Institute of Life Sciences, NJSC "Medical University of Karaganda" (September 20, 2024, Karaganda, Republic of Kazakhstan).

Publications

Three articles in journals recommended by the Committee for Quality Assurance in the Sphere of Science and Higher Education of the Ministry of Science

and Higher Education of the Republic of Kazakhstan (MSHE RK); wo articles in international journals indexed in the Scopus database (with Scopus CiteScores of 54% and 60% at the time of publication), Three abstracts in Russian, Kazakh, and English, including one abstract published in a journal with a non-zero Impact Factor. The dissertation was presented and approved at the extended meeting of the Institute of Life Sciences, NJSC "Medical University of Karaganda".

Additionally, the author holds one certificate of state registration of copyright (entered into the official register of copyright-protected works).

Structure and Volume of the Dissertation

The dissertation comprises 92 pages of typed text and includes the following sections: Introduction, Literature Review, and the Main Part (consisting of chapters on Materials and Methods, and chapters presenting the Author's Original Research), Conclusion, Findings, Practical Recommendations, References (including 169 sources), and 3 Appendices. The dissertation materials are illustrated with 6 tables and 13 figures.

Materials and Methods.

The study included all patients hospitalized in the inpatient departments of the Regional Phthisiopulmonology Center (RPC) during the specified observation period.

Inclusion Criteria:

- ✓ Verified diagnosis of drug-resistant pulmonary tuberculosis
- ✓ Confirmed drug-sensitive forms of pulmonary tuberculosis
- ✓ Patients aged over 18 years

Exclusion Criteria:

- ✓ **Minors (patients under 18 years of age)**

The sample was formed by consecutive inclusion of patients meeting the criteria, ensuring the representativeness of the study groups for subsequent comparative analysis.

The sample was formed by continuous inclusion of patients meeting the criteria, which ensured the representativeness of the study groups for subsequent comparative analysis.

The study design allowed for a comparative analysis of clinical and laboratory parameters between patient groups with different drug susceptibility profiles of the causative agents.

The study material consisted of microorganisms isolated from the sputum of patients with a verified diagnosis of tuberculosis. Identification of *M. tuberculosis* and cultivation of accompanying microflora were performed at the laboratory of the Regional Phthisiopulmonology Center.

Upon detection of secondary microflora growth, culture plates were transported to the shared-use laboratory of the NJSC "Karaganda Medical University" in

accordance with established procedures [28] for species identification of microorganisms and determination of their antibiotic susceptibility.

During the study, 994 samples of nonspecific microflora were analyzed, obtained from patients with tuberculosis hospitalized in the inpatient departments of the Regional Phthisiopulmonology Center in Karaganda in 2018–2019.

To address the research objectives, patients were divided into two groups: Group I (n=103) — with drug-resistant forms of pulmonary tuberculosis; Group II (n=122) — with drug-sensitive forms.

Further analysis was conducted at the shared-use laboratory of the NJSC "Karaganda Medical University" (KMU).

Species identification of the isolated microbial strains was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). The analysis was carried out on a Microflex LT mass spectrometer (Bruker Daltonics, Germany) using the standard sample preparation protocol recommended by the manufacturer.

To preserve the strain collection and for further subtyping, the isolated microorganisms were frozen at -70°C .

Antimicrobial susceptibility of the isolated microorganisms was determined by two methods: the standard disk diffusion method on Mueller-Hinton agar and the broth microdilution method in Mueller-Hinton broth. All testing steps, including incubation conditions, measurement of inhibition zones (for the disk diffusion method), determination of minimum inhibitory concentration (MIC, for the microdilution method), and interpretation of the results were carried out strictly in accordance with the current Clinical and Laboratory Standards Institute (CLSI) guidelines [29].

For quality control of antimicrobial susceptibility testing, the following control strains were used: *E. coli* ATCC®25922, *E. coli* ATCC®35218, *Pseudomonas aeruginosa* ATCC®27853, and *S. aureus* ATCC®25923.

Antimicrobial susceptibility data analysis was performed using WHONET 2022 software (World Health Organization) and the AMRcloud cloud platform [30].

For subspecies typing by MALDI-TOF MS, a representative collection of *Klebsiella pneumoniae* isolates (n = 47) was formed. This pathogen was isolated in 41.25% of patients with tuberculosis, which is consistent with current epidemiological data on the high frequency of bacterial coinfections in tuberculosis [31].

The obtained bacterial spectrum data files were imported into FlexAnalysis software version 2.4 (Bruker Daltonics, Germany) [32] for automated peak detection.

Discriminatory peaks identified after outlier removal were further analyzed using MALDI Biotyper SW software (Bruker Daltonics).

This data processing approach allowed for high-precision characterization of the genetic diversity of *K. pneumoniae* isolates and provided a reliable basis for subsequent subspecies typing and epidemiological analysis.

Analysis of antimicrobial susceptibility and group comparisons were performed using the specialized online platform AMRcloud (<http://amrcloud.net>) [30]. This unique Russian platform is a web application for analyzing and sharing antibiotic resistance monitoring data, developed by the Institute of Antimicrobial Chemotherapy at Smolensk State Medical University [33-35].

The statistical approach implemented in AMRcloud ensures accurate estimation of resistance prevalence with confidence intervals, statistically valid comparisons between patient groups, control for multiple testing errors, and reproducibility of results according to international standards.

This comprehensive statistical methodology, combined with the capabilities of the AMRcloud platform, ensured a high level of reliability in the antimicrobial resistance study results for the isolated microorganisms.

CONCLUSIONS:

1. It was established that the combination of multidrug-resistant tuberculosis (MDR-TB) with secondary nonspecific infection occurs significantly more often in patients with chronic and progressive forms, such as fibrocavernous pulmonary tuberculosis (16.5%, $p < 0.05$), as well as in patients with tuberculosis types "Relapse" (30.1%, $p = 0.017$) and "Treatment after interruption" (12.62%, $p < 0.001$). The presence of resistant secondary microflora reduces the effectiveness of therapy: the proportion of successful treatment outcomes ("cured" and "treatment completed") in the MDR-TB group was 58.22% compared to 79.51% in the control group ($p < 0.05$).
2. The structure of secondary microflora in MDR-TB patients was dominated by Gram-negative microorganisms, particularly representatives of the order *Enterobacterales* (*E. coli* – 27.2%, *Klebsiella spp.* – 24.3%). The proportion of non-fermenting bacteria was 12.7% (*A. baumannii* – 4.9%, *P. aeruginosa* – 7.8%). Gram-positive bacteria (*S. aureus* – 13.6%, *S. pneumoniae* – 5.8%) were less frequent. No statistically significant differences in the microflora structure were found between the MDR-TB and drug-sensitive TB groups.
3. Carbapenems (with susceptibility $> 80\%$ among *Enterobacterales* (and $> 50\%$ among non-fermenting bacteria) and aminoglycosides (susceptibility to gentamicin $> 80\%$, amikacin $> 90\%$) showed the highest activity against Gram-negative bacteria. A high frequency of resistance to penicillins (over 50%) was registered, which limits their clinical use..
4. A significantly decreased in vitro susceptibility of secondary microflora *K. pneumoniae* to levofloxacin was found in the MDR-TB group (resistance rate 40%, $p < 0.05$). This is likely due to selective pressure from the use of this antibiotic in MDR-TB treatment regimens.

5. Subspecies typing of *K. pneumoniae* strains revealed considerable genetic diversity, indicating a polyclonal nature of the infection and suggesting predominantly different sources of infection.

Practical Recommendations

- Patients with multidrug-resistant tuberculosis (MDR-TB) should undergo microbiological examination for early detection and management of secondary infections.
- When prescribing empirical therapy for secondary infections in MDR-TB patients, emphasis should be placed on agents active against Gram-negative bacteria, especially Enterobacterales and non-fermenting pathogens.
- Carbapenems and aminoglycosides (in particular, amikacin) can be considered drugs of choice for empirical treatment of severe infections caused by Gram-negative microflora. The use of penicillins is not recommended without sensitivity testing results.
- Levofloxacin should be used cautiously for treating secondary infections in MDR-TB patients. Sensitivity testing is advisable prior to its prescription.

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