JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205
Volume 15 Issue 11, November 2025
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

DIAGNOSTICS AND DIFFERENTIAL DIAGNOSIS OF DRUG-RESISTANT PULMONARY TUBERCULOSIS AT THE PRESENT STAGE

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Abstract: Drug-resistant tuberculosis (DR-TB), particularly multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), poses a global public health threat and is a key factor hindering the success of tuberculosis control programs . Current DR-TB diagnostics are characterized by a transition from lengthy and insensitive culture methods to rapid molecular genetic technologies that allow resistance detection within hours or days. This review examines the main methods for DR-TB diagnostics, their advantages, limitations, and place in the diagnostic algorithm. Particular attention is paid to automated molecular platforms, next-generation sequencing (NGS) methods, and the prospects for their implementation in routine practice.

Key words: Tuberculosis, drug resistance, diagnostics

Introduction . Tuberculosis (TB) remains one of the leading causes of infectious disease mortality worldwide. According to the World Health Organization (WHO), the problem of drug-resistant TB is worsening: in 2022, approximately 410,000 people developed TB resistant to rifampicin , the most effective first-line anti-TB drug, of whom 78% had multidrug-resistant TB [1].

Results . Late and inaccurate diagnosis of DR-TB leads to inappropriate treatment, disease progression, the spread of resistant strains, and, ultimately, high mortality. Therefore, rapid and accurate diagnosis is the cornerstone of the fight against DR-TB.

1. Classical methods of diagnosing DR-TB

1.1 Microscopy and cultural method

Sputum smear microscopy, while widely available and rapid, does not allow for drug susceptibility testing (DS). For a long time, the gold standard for DS determination was culture on solid (Loewenstein-Jensen medium) and liquid (e.g., BACTEC™ MGIT™ 960) media. Liquid systems have reduced the time to results to 10-14 days (compared to 3-4 weeks on solid media) and are highly sensitive. However, the main drawback of these methods is their time-consuming nature, which is unacceptable for prompt initiation of appropriate therapy for DR-TB.

1.2. Methods for determining drug susceptibility in in vitro .

Tuberculosis resistance is determined by culturing Mycobacterium tuberculosis (MBT) in the presence of critical concentrations of anti-TB drugs. Despite their high accuracy, these methods require culture isolation, which prolongs the diagnostic process to 6-8 weeks or more. This limits their use for initial clinical decision-making.

2. Rapid molecular genetic methods

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Modern diagnostics of DR-TB is based on the identification of mutations in MBT genes associated with drug resistance.

2.1. PCR-based nucleic acid amplification tests (NAATs)

These methods allow direct detection of MBT DNA and resistance mutations in a clinical sample, bypassing the cultivation stage.

Xpert MTB/RIF and Xpert MTB/RIF Ultra (Cepheid): These automated cartridge systems simultaneously detect MTB and resistance to rifampicin (a marker of MDR-TB) in 2 hours by analyzing mutations in the rpoB gene . They are the WHO-recommended method for the initial diagnosis of TB and MDR-TB risk assessment [2]. The high sensitivity of Ultra allows for the effective detection of TB in patients with HIV infection and in extrapulmonary forms.

Line Probe Assays (LPA) – tests on basis hybridization (Hain Lifescience):

- First-line tests: Determine resistance to rifampin (rpoB) and isoniazid (katG , inhA). Results are available in 1-2 days.
- Second-line tests: Detect resistance to fluoroquinolones (gyrA , gyrB) and second-line injectable drugs (amikacin , kanamycin , capreomycin – " rrs " and " eis "). These are key for diagnosing XDR-TB. They are used on culture material or a direct specimen in patients with confirmed MDR-TB.

3. High-tech methods and prospects

3.1 Next-generation sequencing (NGS)

NGS is a technology that determines the complete genome sequence of MBT. It opens a new era of personalized medicine in phthisiology.

Advantages:

- Completeness of information: Allows detection of resistance to a wide range of drugs (first and second line, as well as new drugs such as bedaquiline , delamanid) in a single study.
- Detection of complex resistance patterns: Detects rare and accumulating mutations that may be missed by targeted TANKs.
- Epidemiological monitoring: Allows tracking of transmission routes and the emergence of local outbreaks of resistant strains.

Limitations: High cost of equipment and reagents, need for bioinformatics data processing, difficulty in interpreting results.

3.2. Automated systems based on microfluidic technologies and microchips

Platforms such as GenoType are being developed MTBDRplus and MTBDRsl , which perform hybridization and detection automatically . Microarrays, which allow for the simultaneous testing of hundreds of mutations, are also promising.

4. Integrated diagnostic algorithms

At the present stage, a combined approach (diagnostic algorithm) is used in clinical practice:

1. Primary screening: Patient with TB symptoms or at risk.
2. Rapid testing for MDR-TB: Using Xpert MTB/RIF Ultra as an initial test. A positive result for MTB and rifampin is a direct indication for initiating MDR-TB therapy.
3. Advanced testing: For a patient with detected rifampicin resistance , second-line LPA or phenotypic determination of DL-serotonin to second-line drugs is performed to confirm/exclude XDR-TB.

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4. Clarifying diagnostics: In complex cases, in case of treatment failure or for epidemiological analysis, NGS is used.
Differential diagnosis within the tuberculosis group. This is the most important step, determining treatment strategy.

Sign	Sensitive tuberculosis	MDR-TB (Resistant to Rif and INH)	XDR-TB (MDR + resistance to fluoroquinolones and second-line injectable drugs)	TB (resistant to almost all drugs)
Anamnesis and risk groups	Primary infection	Contact with MDR-TB, previous treatment failure, self-interruption of therapy, migration from regions with high prevalence of MDR-TB	Same as for MDR-TB + ineffective therapy with second-line drugs, repeated courses of treatment	Long history, multiple unsuccessful courses of therapy, use of reserve drugs
Clinical picture	Often responds to standard therapy, improvement within the first 2-3 months	Lack of improvement or worsening of disease during first-line therapy (HRZE). More severe and progressive course	Extremely severe course, severe intoxication, cachexia, high mortality rate. Often extensive destructive lung damage.	Cachexia, multiple organ failure, chronic fluctuating course with rare periods of improvement
X-ray picture	It can be any, but positive dynamics are often observed (resorption of infiltrates, closure of cavities)	Rapid progression: the appearance of new lesions and cavities, an increase in the volume of the lesion during treatment. Often extensive destructive forms	Massive lesion, "destroyed lung", multiple giant cavities, fibrocavernous tuberculosis	Picture of the "end stage": massive fibrosis, bullous -dystrophic changes, residual cavities

Laboratory diagnostics (key method)	Xpert MTB/RIF: MTB+, RIF-S. 1st-line LPA: No resistance. DST culture: Sensitive to all drugs.	Xpert MTB/RIF: MTB+, RIF-R. 1st-line LPA: Resistance to Rif (rpoB) and INH (katG / inhA). DL culture: Confirms the MDR profile.	2nd-line LPA or phenotypic LC: Resistance to fluoroquinolones and at least one 2nd-line injectable drug is confirmed	High-level resistance determined by phenotypic LC or NGS. Resistance to most first- and second-line drugs, as well as bedaquiline and linezolid.

Diagnostic algorithm for suspected DR-TB
Clinical and anamnestic suspicion: Lack of positive dynamics (persistent bacterial excretion , deterioration of the radiographic picture) after 2-3 months of adequate chemotherapy + presence of risk factors for MDR/XDR-TB.
Rapid testing: Immediate Xpert MTB/RIF (Ultra) or first-line LPA to detect rifampicin resistance (a marker of MDR-TB).
In-depth diagnostics: If resistance to rifampicin is confirmed :
Implementation of second-line LPA for rapid screening for XDR-TB.
Submitting the material for sowing with an extended determination of the LC for 1st and 2nd line drugs.
Final verification: In complex cases, if there is a suspicion of XDR-TB or for personalization of therapy, a whole genome sequencing is performed. sequencing (NGS) to detect mutations of resistance to all known drugs.

Conclusion

culture methods have been replaced by rapid, accurate molecular genetic technologies, allowing for rapid identification of resistance patterns and timely initiation of appropriate therapy. The introduction of methods such as Xpert MTB/RIF and LPA has significantly improved the situation with DR-TB control . In the future, the widespread use of whole-genome sequencing technologies NGS sequencing will not only allow for the fastest and most complete identification of resistance, but also a deeper understanding of the mechanisms of its development and spread, which is key to achieving the goals of eliminating tuberculosis as a global threat.
Differential diagnosis of DR-TB is a dynamic process based on a triad: physician alertness (based on the patient's medical history), assessment of progression during treatment, and the mandatory use of modern molecular genetic methods. Early detection of resistance and accurate differentiation of the DR-TB type are critical for the establishment of an effective chemotherapy regimen, without which successful treatment of patients with these forms of tuberculosis is impossible.

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