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MODERN APPROACHES TO DIAGNOSING AND DIFFERENTIATING DRUG-RESISTANT TUBERCULOSIS

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Abstract: Drug-resistant tuberculosis (DR-TB), including multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) forms, is a critical global health challenge. The field of diagnostics is rapidly evolving, moving away from slow, traditional culture methods toward fast, molecular techniques that can identify resistance within hours or days. This review explores the main diagnostic methods for DR-TB, highlighting their strengths, weaknesses, and role in clinical practice. It pays special attention to automated molecular platforms and next-generation sequencing (NGS), assessing their potential for widespread use.

Introduction

Tuberculosis remains a leading cause of infectious disease mortality worldwide. The problem of drug resistance is escalating. In 2022, the WHO reported approximately 410,000 new cases of rifampicin-resistant TB (the most effective first-line drug), with 78% being multidrug-resistant.

The Shift to Rapid Diagnostics

Delayed or inaccurate diagnosis of DR-TB leads to ineffective treatment, disease progression, transmission of resistant strains, and increased mortality. Therefore, rapid and precise diagnosis is the foundation of an effective DR-TB response.

1. Traditional Diagnostic Methods

Smear Microscopy & Culture: While microscopy is quick and widely available, it cannot test for drug resistance. For decades, culturing bacteria on solid or liquid media was the gold standard for drug susceptibility testing (DST). Liquid culture reduced the wait time to 10-14 days but is still too slow for making urgent treatment decisions.

2. Modern Molecular Genetic Methods

These techniques detect genetic mutations associated with drug resistance directly from patient samples, bypassing the need for time-consuming culture.

Automated PCR Tests (e.g., Xpert MTB/RIF Ultra): These cartridge-based systems can detect TB and rifampicin resistance (a proxy for MDR-TB) in about two hours. They are the WHO-recommended first test for TB diagnosis and MDR-TB risk assessment.

Line Probe Assays (LPA): These tests use DNA hybridization to identify resistance mutations.

First-line LPAs check for resistance to rifampicin and isoniazid, with results in 1-2 days.

Second-line LPAs are used to diagnose XDR-TB by detecting resistance to fluoroquinolones and injectable drugs.

3. Advanced Technologies and Future Directions

Next-Generation Sequencing (NGS): NGS can sequence the entire TB genome, ushering in an era of personalized treatment.

Advantages: Identifies resistance to a wide array of drugs in a single test, detects complex mutation patterns, and aids in tracking outbreaks.

Limitations: High cost, requires specialized data analysis, and can be complex to interpret.

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A Modern Diagnostic Pathway
Current best practice uses a combined, step-by-step approach:
Initial Screening: Use a rapid test like Xpert MTB/RIF Ultra for any patient with TB symptoms.
Confirmation of MDR-TB: If rifampicin resistance is detected, this is a strong indicator of MDR-TB, and treatment should be initiated.
Differentiating Between Types of Tuberculosis
Accurate differentiation is crucial for determining the correct treatment strategy.
Ruling Out XDR-TB: For patients with MDR-TB, a second-line LPA is performed to quickly check for additional resistance that defines XDR-TB.
Comprehensive Profiling: In complex cases, NGS is used to get a complete resistance profile, guiding personalized therapy.

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	Xpert MTB/RIF:	Xpert MTB/RIF: MTB+, RIF-R.	2nd-line LPA or phenotypic LC:	High-level resistance

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

Conclusion

Molecular genetic technologies have revolutionized DR-TB diagnostics, replacing slower culture methods and enabling the timely start of appropriate treatment. Tools like Xpert MTB/RIF and LPAs have dramatically improved DR-TB control. In the future, the broader adoption of NGS will provide unparalleled insights into resistance patterns, driving progress toward the global goal of eliminating tuberculosis. Ultimately, successfully diagnosing and differentiating DR-TB relies on a combination of clinical suspicion, monitoring treatment response, and the mandatory use of these advanced molecular tools.

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