

Mycobacterium tuberculosis - TB

Clinical Background

Mycobacterium tuberculosis, as well as other non-tuberculosis species, can be infectious agents in humans.

Mycobacterium tuberculosis

- Epidemiology
 - Incidence and prevalence
 - 4-6/1,000,000 (CDC 2006)
 - 8-9 million new cases occur per year
 - 3-4 million cases of infectious pulmonary disease (smear positive)
- Organism
 - Mycobacteria belong to the order Actinomycetales and the family Mycobacteriaceae
 - *Mycobacterium tuberculosis* – rod-shaped aerobic bacterium with acid-fast staining properties
 - *Mycobacterium tuberculosis* complex (MTB) – *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti* and others
 - Transmission is via inhalation of droplet nuclei
- Risk Factors
 - Once the patient has been infected, the risks for developing active tuberculosis (TB) include:
 - Comorbidity present (HIV, immunosuppression, fibrotic lung disease, chronic renal failure, diabetes mellitus)
 - Recent tuberculosis infection (<1 year)
 - Malnutrition, alcoholism
 - Fibrotic lesions on chest x-ray
- Clinical Presentation
 - Primary disease
 - Ranges from mild, self-limited illness to severe disseminated disease
 - Post primary disease
 - Reactivation of latent infection
 - Moderate to severe, progressive and often fatal disease
 - Extrapulmonary TB
 - Gastrointestinal disease
 - Genitourinary
 - Lymphadenitis
 - Meningitis, central nervous system tuberculoma
 - Miliary
 - Pericarditis
 - Pleural disease
 - Skeletal (Pott disease)
 - TB in patients with HIV
 - Extrapulmonary disease is common
 - Atypical chest x-ray findings
 - Delays in diagnosis and treatment are common
 - Increased risk of reactivation of latent disease and rapid progression of newly acquired infection

Nontuberculous (atypical) mycobacteria (NTM)

- Epidemiology

- Age – usually isolated
- Transmission via cutaneous, inhalation, or parenteral routes
 - Widely distributed in water, soil and animal species
 - Person-to-person transmission has not been reported
- Organisms
 - Free-living organisms; more than 125 species of NTM
 - Nontuberculous organisms
 - *M. avium* complex, *M. kansasii*, *M. fortuitum*, *M. abscessus*, *M. chelonae*, *M. marinum*, *M. haemophilum*
 - Rare new organisms
 - *M. nebraskerise*, *M. parmense*, *M. saskat-chewanense*, *M. arupense*, *M. caprae*, *M. colombiense*, *M. florentium*, *M. montefiorensis*
 - Pathogenicity and clinical significance vary with species and host
 - Asymptomatic infections are common
- Clinical Presentation
 - Cutaneous – *M. fortuitum*, *M. abscessus*, *M. chelonae*, *M. marinum*, *M. haemophilum*
 - Nodular or ulcerating chronic lesions that fail to respond to standard antimicrobial therapy
 - Lymphadenitis - *M. avium* complex, especially in children
 - Pulmonary – *M. avium* complex, *M. kansasii*, *M. abscessus*
 - Chronic cough usually present
 - Immunocompromised and immunocompetent hosts
 - Increased in elderly and patients with underlying pulmonary disease
 - Bronchiectatic, nodular or cavitory disease
 - Disseminated
 - Weight loss, fever, fatigue, lymphadenopathy, hepatosplenomegaly, gastrointestinal complaints
 - Usually immunocompromised patients (advanced HIV, transplant)
 - Other (catheter-related, skeletal)

Diagnosis

Mycobacterium tuberculosis

- Diagnosis
 - Indications for testing – cough, fever, weight loss in at-risk patients
 - Laboratory testing
 - Based on acid-fast bacilli (AFB) smear, culture and nucleic acid amplification testing
 - Culture provides the definitive diagnosis
 - Susceptibility testing is mandatory
 - Latent *M. tuberculosis* – Interferon alpha release assays (QuantiFERON®)
 - Adenosine deaminase (ADA)
 - Adjunctive test for use in the evaluation of suspected extrapulmonary tuberculosis involving body cavities (or cerebrospinal fluid [CSF])
 - Reported sensitivity and specificity vary
 - Meta-analysis derived summary receiver operator curves (ROC) from pleural fluid: sensitivity 92%; specificity 92%
 - Not specific for tuberculosis
 - AFB culture should always be performed
 - Imaging studies

- Chest x-ray confirmation is required (may have been performed prior to TB testing)

Nontuberculous (atypical) mycobacteria

- Diagnosis
 - Indications for testing – clinical setting suspicious for disease
- Laboratory testing
 - Concentrated AFB smear
 - Traditional standard screening method (sputum)
 - Not as sensitive as culture (requires approximately 10^4 bacilli/mL sputum for detection)
 - Not specific for *Mycobacterium tuberculosis* complex
 - Mycobacterial culture
 - Most sensitive test for detection of mycobacteria (gold standard)
 - Slow (2-8 weeks)
 - Should be performed on any specimen for which mycobacteria are a consideration
 - Required to make the diagnosis of disseminated disease
 - Positive culture from a normally sterile site
 - Nucleic acid amplified testing (NAAT)
 - Emerging recommended method for rapid, sensitive and specific detection of MTB complex
 - Less sensitive than culture
- Imaging studies
 - Chest x-ray – cavities, frank parenchymal infiltrates, bronchiectasis, pulmonary nodules
 - Does not distinguish between TB and NTM
 - CT – may give better global picture of disease present

Screening

(*Mycobacterium tuberculosis*)

- Targeted tuberculin testing for latent TB infection for foreign-born persons entering the U.S. within the past 5 years

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
<p>AFB Culture (Includes AFB Stain 0060151) 0060152</p> <p>Method: Standard reference procedures for stain and culture. Identification of AFB is ordered and billed separately. DNA probes are available for <i>M. tuberculosis</i> complex and <i>M. avium-intracellulare</i> complex as indicated. DNA sequencing and other molecular techniques are used for identification. For drug susceptibilities, refer to Antimicrobial Susceptibility - AFB Mycobacteria (0060217).</p>	<p>Gold standard, most sensitive test for diagnosing mycobacteria</p> <p>Use for detection in sputum, tissues, urine and other body fluids</p>	<p>Time to detection (mycobacteria are slow growing organisms)</p>	<p>DNA probes are available for <i>M. tuberculosis</i> complex and <i>M. avium-intracellulare</i> complex as indicated. DNA sequencing and other molecular techniques are used for identification of other mycobacteria species. For drug susceptibilities, refer to Antimicrobial Susceptibility - AFB Mycobacteria (0060217)</p>
<p><i>Mycobacterium tuberculosis</i> Amplified Direct Detection 0060095</p> <p>Method: Transcription Mediated Amplification (Gen-Probe®)</p>	<p>Order as adjunct to AFB culture in untreated patients with smear-positive and smear-negative respiratory samples</p> <p>Rapid, sensitive and specific detection of MTB complex from respiratory specimens</p>	<p>AFB culture should always be ordered with this test</p> <p>Low level false-positive results can occur in specimens with high concentration of mycobacteria other than <i>M. tuberculosis</i></p> <p>A negative result does not exclude <i>M. tuberculosis</i> infection</p>	

<p>QuantiFERON®-TB Gold In Tube 0051729</p> <p>Method: Cell Culture/Enzyme-Linked Immunosorbent Assay</p>	<p>Detect latent TB infections among persons who are at increased risk for TB</p> <p>Specific for <i>M. tuberculosis</i>, not nontuberculous mycobacteria or the BCG vaccine</p>	<p>Diagnosing or excluding tuberculosis disease and assessing the probability of latent tuberculosis infection require a combination of epidemiological, historical, medical, and diagnostic findings that should be taken into account when interpreting the results of this test</p>	
<p>QuantiFERON®-TB Gold In Tube & <i>Mycobacterium tuberculosis</i> Antibody, IgG 2001627</p> <p>Method: Cell Culture/Enzyme-Linked Immunosorbent Assay</p>	<p>Detect latent TB infections among persons at increased risk for TB</p> <p>Components include QuantiFERON®-TB Gold in Tube and <i>Mycobacterium tuberculosis</i> Antibody, IgG by ELISA</p>		
<p><i>Mycobacterium tuberculosis</i> Complex Speciation 0060771</p> <p>Method: Polymerase Chain Reaction</p>	<p>Identify species of the <i>M. tuberculosis</i> complex (<i>M. tuberculosis</i>, <i>M. bovis</i>, <i>M. bovis</i> BCG-vaccine strain, <i>M. africanum</i>, <i>M. microti</i>, <i>M. caprae</i>) to species level by comparing genomic deletion patterns</p>	<p>Non-tuberculous mycobacteria may have indeterminate patterns of the genomic deletions used as targets in this assay</p> <p>Changes in DNA sequence at the primer annealing sites may affect genomic deletion pattern determination and speciation</p>	
<p><i>Mycobacterium tuberculosis</i> Antibody, IgG by ELISA 0051698</p> <p>Method: Enzyme-Linked Immunosorbent Assay</p>	<p>Order this rapid serologic assay when clinical symptoms and the possibility of exposure indicate MTB infection</p> <p>Detect IgG antibodies against MTB in patients with active infection</p> <p>Monitor the success of therapeutic intervention</p> <p>Differentiate active and latent cases of TB</p> <p>Can also be used in previously BCG vaccinated individuals since the antigens utilized are not present in <i>Mycobacterium bovis</i></p>	<p>Not intended for use as a screening assay</p> <p>Results should be interpreted in conjunction with PPD or QuantiFERON® testing as well as the complete history of the patient</p> <p>Assay has not been validated for use on patients with HIV/TB co-infection and is not recommended for this population</p>	

<p>AFB Culture (Includes AFB Stain 0060151) with Reflex to <i>Mycobacterium tuberculosis</i> Amplified Direct Detection (0060095) 0060738</p> <p>Method: Standard reference procedures for stain and culture. Identification of AFB is ordered and billed separately. DNA probes are available for <i>M. tuberculosis</i> complex and <i>M. avium-intracellulare</i> complex as indicated. DNA sequencing and other molecular techniques are used for identification. For drug susceptibilities, refer to Antimicrobial Susceptibility - AFB Mycobacteria (0060217). For AFB stain positive respiratory specimens, <i>Mycobacterium tuberculosis</i> Amplified Direct Detection (0060095) will be added at an additional charge.</p>	<p>Single order test incorporating culture and stain with reflex to amplified testing for MTB complex when smear positive</p>	<p>Available for respiratory specimens only</p> <p>Low-level false-positive results can occur in specimens with high concentration of mycobacteria other than <i>M. tuberculosis</i></p> <p>A negative result does not exclude <i>M. tuberculosis</i></p>	
<p>Blood Culture, AFB 0060060</p> <p>Method: Bactec® 9240, continuous monitoring systems. Standard reference procedures for identification of positive cultures.</p>	<p>Order for AFB culture of blood or bone marrow specimen</p>		

<p><i>Mycobacterium tuberculosis</i> Amplified Detection , CSF 0060063</p> <p>Method: Transcription Mediated Amplification (Gen-Probe®)</p>	<p>Amplified test offers rapid and specific detection of MTB complex from CSF</p>	<p>AFB culture should always be ordered with test</p> <p>The <i>Mycobacterium tuberculosis</i> Amplified Direct test does not differentiate among members of the MTB complex</p> <p>Low level false-positive results can occur in specimens with high concentration of mycobacteria other than <i>M. tuberculosis</i> (rare in CSF)</p> <p>Limited sensitivity</p> <p>A negative result does not exclude the possibility of isolating MTB from the specimen (eg culture)</p>	
<p>AFB Identification with Reflex to Susceptibility 0060997</p> <p>Method: Standard reference procedures for identification and susceptibility testing of AFB. DNA probes available for <i>M. tuberculosis</i> complex and <i>M. avium-intracellulare</i> complex. DNA sequencing and other molecular techniques are used for other mycobacteria species.</p>	<p>Identification of AFB isolated in pure culture with reflex susceptibility testing if indicated</p>	<p>Susceptibility testing may not be performed on all isolates (varies by species)</p>	

Antimicrobial Susceptibility - AFB/ Mycobacteria 0060217 Method: Varies with organism identification	Availability: a. <i>M. tuberculosis</i> primary and secondary panel b. <i>M. avium-intracellulare</i> complex (MAC) c. Rapid-growing mycobacteria d. Other slowly growing non-tuberculosis mycobacteria (NTM)		
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Additional Tests Available

Test Name and Number	Comments
AFB Stain Only 0060151 Method: Auramine O Stain	Monitor respiratory specimens on previously diagnosed patients Should not be ordered without culture in previously undiagnosed patients
AFB Identification 0060999 Method: Standard reference procedures for identification of AFB. DNA probes available for <i>M. tuberculosis</i> complex and <i>M. avium-intracellulare</i> complex. DNA sequencing and other molecular techniques are used for other mycobacteria species.	Identification of acid-fast organisms (AFB) isolated in pure culture
Blood Culture, AFB & Fungal 0060024 Method: Bactec® 9240, continuous monitoring systems. Standard reference procedures for identification of positive cultures.	
Adenosine Deaminase, Body Fluid 0098115 Method: Spectrophotometry	
Chylomicron Screen, Body Fluid 0098457 Method: Electrophoresis	

Additional Information

The laboratory should be notified when the presence of *Mycobacterium genavense* is suspected as this organism will not grow on media routinely used for Mycobacterial isolation.

Guidelines

Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. American Thoracic Society - Medical Specialty Society. Centers for Disease Control and Prevention - Federal Government Agency [U.S.]. Infectious Diseases Society of America - Medical Specialty Society. 2005 November 4.

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