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Editorial

Tuberculosis (TB) is an ongoing (chronic) infection caused by bacteria. It usually infects the lungs. But other organs such as the kidneys, spine, or brain may be affected. TB is most often spread through droplets breathed or coughed into the air. A child can be infected with the TB bacteria and not have active disease.

TB may be staged like this:

- **Exposed.** This is when a child has been in contact with a person who has TB, but the child still has a negative TB skin or blood test, a normal chest X-ray, and no symptoms.
- **Latent TB infection.** This is when a child has TB bacteria in their body, but does not have symptoms. The infected child's immune system causes the TB bacteria to be inactive. For most people who are infected, the TB will be latent for life. This child would have a positive TB skin or blood test but a normal chest X-ray and no TB symptoms. They can't spread the infection to others.
- **TB disease.** This is when a child has signs and symptoms of an active infection. This child would have a positive or negative TB skin or blood test, and testing showing active TB disease in the lungs or another site in the body. They can spread the disease if the infection is in the lungs and it is untreated.

This issue covers "PEDIATRIC TUBERCULOSIS" under the "**DISEASE DIAGNOSIS**" segment.

An important investigation while assessing tubercular effusions anywhere in the body is estimation of ADA. Hence, "**INTERPRETATION**" delves deep into all aspects related to this Tuberculosis specific analyte.

"**TROUBLESHOOTING**" highlights the workup process/ protocol of a case having Pleural Effusion.

"**BOUQUET**" exists within the covers too.

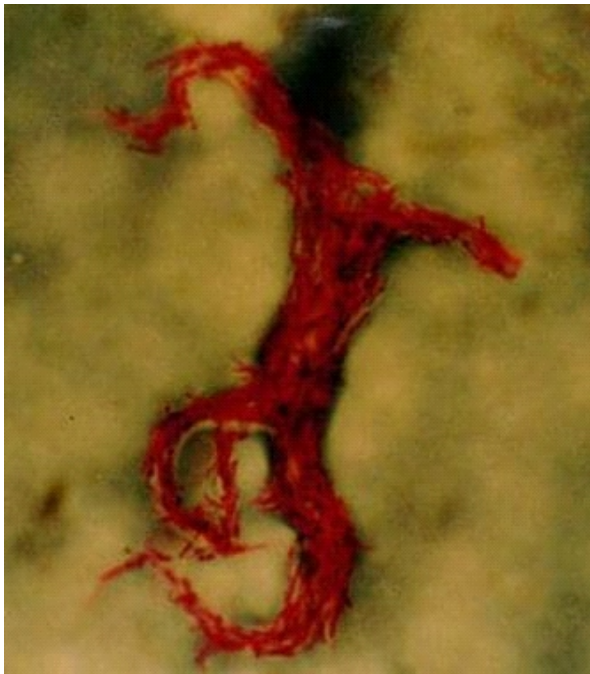


DISEASE DIAGNOSIS

Pediatric Tuberculosis

Overview of Tuberculosis

Tuberculosis (TB) is the most common cause of infection-related death worldwide. In 1993, the World Health Organization (WHO) declared TB to be a global public health emergency. The image below depicts typical radiographic findings on a patient with tuberculosis. This radiograph shows a patient with typical radiographic findings of tuberculosis. Tubercle bacilli belong to the order Actinomycetales and family Mycobacteriaceae. Mycobacterium tuberculosis is the most common cause of this disease, and it is seen in the image below. Other rare causes include *M bovis* and *M africanum*. The acid-fast characteristic of the mycobacteria is their unique feature. *M tuberculosis* is an aerobic, non-spore-forming, nonmotile, slow-growing bacillus with a curved and beaded rod-shaped morphology. It is a very hardy bacillus that can survive under adverse environmental conditions. Humans are the only known reservoirs for *M tuberculosis*.



Acid-fast bacillus smear showing characteristic cording in *Mycobacterium tuberculosis*.

Most persons infected with *M tuberculosis* do not develop active disease. In healthy individuals, the lifetime risk of developing disease is 5-10%. In certain instances, such as extremes of age or defects in cell-mediated immune (CMI) response (eg, human immunodeficiency virus [HIV] infection, malnutrition, administration of chemotherapy, prolonged steroid use), TB may develop. For patients with HIV infection, the risk of developing TB is 7-10% per year.

TB Risk Factors

Risk factors for the acquisition of tuberculosis (TB) are usually exogenous to the patient. Thus, likelihood of being infected depends on the environment and the features of the index case. However, the development of TB disease depends on inherent immunologic status of

the host. Tuberculosis has been reported in patients treated for arthritis, inflammatory bowel disease, and other conditions with tumor necrosis factor (TNF)-alpha blockers/antagonists.

Factors in acquiring TB infection

The number of bacilli in the inoculum and the relative virulence of the organism are the major factors determining transmission of the disease. TB is transmitted by inhaling the tubercle bacilli. The infectiousness of the source case is of vital importance in determining likelihood of transmission. Bacillary population of TB lesions varies and depends on the morphology of the lesion. Nodular lesions have 100-10,000 organisms, whereas cavitory lesions have 10 million to 1 billion bacilli. Thus, persons with cavitory lesions are highly infectious. Also, contacts of persons with sputum-positive smears have an increased prevalence of infection as opposed to contacts of those with sputum-negative smears. Persons who have received anti-TB drugs are much less infectious than those who have not received any treatment. This decline in infectiousness is due primarily to reduction in the bacillary population in the lungs. Environmental factors also contribute to the likelihood of acquiring the infection. The concentration of bacilli depends on the ventilation of the surroundings and exposure to ultraviolet light. Thus, overcrowding, congregation in prison settings, poor housing, and inadequate ventilation predispose individuals to the development of TB. Defects in cell-mediated immunity (CMI) and level of immunocompetence are major determinants for development of disease. In fact, infection with human immunodeficiency virus (HIV) is one of the most significant risk factors for TB infection. Case rates for persons who are dually infected with HIV and *M tuberculosis* exceed the lifetime risk of persons with TB infection who are not infected with HIV. Steroid therapy, cancer chemotherapy, and hematologic malignancies increase the risk of TB. In addition, malnutrition interferes with the CMI response and therefore accounts for much of the increased frequency of TB in impoverished patients. Non-TB infections, such as measles, varicella, and pertussis, may activate quiescent TB. Individuals with certain human leukocyte antigen (HLA) types have a predisposition to TB. Hereditary factors, including the presence of a Bcg gene, have been implicated in susceptibility to acquisition of this disease.

Mechanism of TB Infection

Tuberculosis (TB) occurs when individuals inhale bacteria aerosolized by infected persons. The organism is slow growing and tolerates the intracellular environment, where it may remain metabolically inert for years before reactivation and disease. The main determinant of the pathogenicity of TB is its ability to escape host defense mechanisms, including macrophages and delayed hypersensitivity responses.

Virulence factors and infective droplets

Among the several virulence factors in the mycobacterial cell wall are the cord factor, lipoarabinomannan (LAM), and a highly immunogenic 65-kd *M tuberculosis* heat shock protein. Cord factor is a surface glycolipid present only in virulent strains that causes *M tuberculosis* to grow in serpentine cords in vitro. LAM is a heteropolysaccharide that inhibits macrophage activation by interferon (IFN)-gamma and induces macrophages to secrete TNF-alpha, which causes fever, weight loss, and tissue damage. The infective droplet nucleus is very small, measuring 5 μm or less, and may contain approximately 1-10 bacilli. Although a single organism may cause disease, 5-200 inhaled bacilli are usually necessary for infection. The small size of the droplets allows them to remain suspended in the air for a prolonged time period. Primary infection of the respiratory tract occurs as a result of inhalation of these aerosols. The risk of infection is increased in small enclosed areas and in

areas with poor ventilation. Upon inhalation, the bacilli are deposited (usually in the midlung zone) into the distal respiratory bronchiole or alveoli, which are subpleural in location. Subsequently, the alveolar macrophages phagocytose the inhaled bacilli. However, these naïve macrophages are unable to kill the mycobacteria, and the bacilli continue to multiply unimpeded.

Seeding

Transportation of the infected macrophages to the regional lymph nodes then occurs. Lymphohematogenous dissemination of the mycobacteria travels to other lymph nodes, the kidney, epiphyses of long bones, vertebral bodies, juxtaependymal meninges adjacent to the subarachnoid space, and, occasionally, to the apical posterior areas of the lungs. In addition, chemotactic factors released by the macrophages attract circulating monocytes to the site of infection, leading to differentiation of the monocytes into macrophages and ingestion of free bacilli. Logarithmic multiplication of the mycobacteria occurs within the macrophage at the primary site of infection.

Immune response

A cell-mediated immune (CMI) response terminates the unimpeded growth of the M tuberculosis 2-3 weeks after initial infection. CD4 helper T cells activate the macrophages to kill the intracellular bacteria with resultant epithelioid granuloma formation. CD8 suppressor T cells lyse the macrophages infected with the mycobacteria, resulting in the formation of caseating granulomas. Mycobacteria cannot continue to grow in the acidic extracellular environment, so most infections are controlled. [TNF is a potent inflammatory cytokine that plays an important role in immune defense against M tuberculosis.](#) TNF-mediated innate immune responses, including phagolysosomal maturation and cell-mediated responses (eg, IFN-gamma secretion by memory T cells, complement-mediated lysis of M tuberculosis –reactive CD8+ T cells) are important immune responses in M tuberculosis infection. [Evidence of infection includes a positive tuberculin skin test \(TST\) result](#) (see Tuberculin Skin Test) or a positive IFN-gamma release assay (IGRAs) finding. However, the initial pulmonary site of infection and its adjacent lymph nodes (ie, primary complex or Ghon focus) sometimes reach sufficient size to develop necrosis and subsequent radiographic calcification.

Disease progression

Progression of the primary complex may lead to enlargement of hilar and mediastinal nodes with resultant bronchial collapse. Progressive primary TB may develop when the primary focus cavitates and organisms spread through contiguous bronchi. [Lymphohematogenous dissemination, especially in young patients,](#) may lead to miliary TB when caseous material reaches the bloodstream from a primary focus or a caseating metastatic focus in the wall of a pulmonary vein (Weigert focus). TB meningitis may also result from hematogenous dissemination. Bacilli may remain dormant in the apical posterior areas of the lung for several months or years, with later progression of disease resulting in the development of reactivation-type TB (ie, endogenous reinfection TB).

TB Incidence and Prevalence

Globally, the World Health Organization (WHO) reports more than 9 million new cases of tuberculosis (TB) occur each year, and an estimated, 19-43.5% of the world's population is infected with M tuberculosis. This disease occurs disproportionately among disadvantaged populations, such as homeless individuals, malnourished individuals, and those living in crowded areas. Most cases of TB occur in the South-East Asia (35%), African (30%), and Western

Pacific (20%) regions. [In the United States, approximately 15 million people are infected with M tuberculosis.](#) The number of US cases reported annually dropped 74% between 1953 and 1985 (84,304 to 22,201), but there was a subsequent resurgence, peaking at 26,673 cases in 1992. Unfortunately, although the incidence of TB increased by approximately 13% in all ages from 1985-1994, the rate among children younger than 15 years increased by 33%. [This resurgence was attributed to the human immunodeficiency virus \(HIV\) epidemic,](#) which increased the risk of developing active TB among persons infected with HIV and those latent TB infection. Other contributory factors included emigration from developing countries and transmission in settings such as endemic hospitals and prisons. In addition, the development of multidrug-resistant (MDR) organisms and deterioration of the public health infrastructure for TB services further contributed to the rise in the number of cases. [Go to Tuberculosis, HIV Infection, and HIV Disease](#) for more information on these topics.

ATS Staging Criteria of Pediatric TB

Although the natural history of tuberculosis (TB) in children follows a continuum, the American Thoracic Society (ATS) definition of stages is useful.

Stage 1

Exposure has occurred, implying that the child has had recent contact with an adult who has contagious TB. The child has no physical signs or symptoms and has a negative tuberculin skin test (TST) result (see Tuberculin Skin Test). Chest radiography does not reveal any changes at this stage. [Not all patients who are exposed become infected,](#) and the TST result may not be positive for 3 months. Unfortunately, children younger than 5 years may develop disseminated TB in the form of miliary disease or TB meningitis before the TST result becomes positive. Thus, a very high index of suspicion is required when a young patient has a history of contact. [Go to Miliary Tuberculosis, and Tuberculous Meningitis](#) for more information on these topics.

Stage 2

This second stage is TB infection heralded by a positive TST result. No signs and symptoms occur, although an incidental chest radiograph may reveal the primary complex.

Stage 3

In stage 3, TB disease occurs and is characterized by the appearance of signs and symptoms depending on the location of the disease. Radiographic abnormalities may also be seen.

Stage 4

Stage 4 is defined as TB with no current disease. This implies that the patient has a history of previous episodes of TB or abnormal, stable radiographic findings with a significant reaction to the TST and negative bacteriologic studies. No clinical findings suggesting current disease are present.

Stage 5

TB is suspected, and the diagnosis is pending.

Overview of Pediatric TB Evaluation

Any patient with pneumonia, pleural effusion, or a cavitary or mass lesion in the lung that does not improve with standard antibacterial therapy should be evaluated for tuberculosis (TB). Also, patients with fever of unknown origin, failure to thrive, significant weight loss, or unexplained lymphadenopathy should be evaluated for TB.

Congenital TB

Congenital disease is rare. Symptoms typically develop during the second or third week of life and include poor feeding, poor weight gain,

cough, lethargy, and irritability. Other symptoms include fever, ear discharge, and skin lesions. [Signs of congenital TB include](#) failure to thrive, icterus, hepatosplenomegaly, tachypnea, and lymphadenopathy.

Asymptomatic infection

Patients with asymptomatic infection have a positive tuberculin skin test (TST) result, but they do not have any clinical or radiographic manifestations. Children with asymptomatic infection may be identified on a routine well-child physical examination, or they may be identified subsequent to TB diagnosis in household or other contacts (eg, children who recently have immigrated, adopted children). [Primary TB is characterized by the absence of any signs on clinical evaluation.](#) As discussed above, these patients are identified by a positive TST result. Tuberculin hypersensitivity may be associated with erythema nodosum and phlyctenular conjunctivitis.

Evaluation of Pediatric Pulmonary TB

Pulmonary tuberculosis (TB) may manifest itself in several forms, including endobronchial TB with focal lymphadenopathy, progressive pulmonary disease, pleural involvement, and reactivated pulmonary disease. Symptoms of primary pulmonary disease in the pediatric population are often meager. Fever, night sweats, anorexia, nonproductive cough, failure to thrive, and difficulty gaining weight may occur. Signs of disease depend on the site involved (pulmonary or extrapulmonary).

Endobronchial TB with lymphadenopathy

Endobronchial disease with enlargement of lymph nodes is the most common variety of pulmonary TB. Symptoms are the result of impingement on various structures by the enlarged lymph nodes. Enlargement of lymph nodes and persistent cough may result in signs suggestive of bronchial obstruction or hemidiaphragmatic paralysis, whereas difficulty swallowing may result from esophageal compression. Vocal cord paralysis may be suggested by hoarseness or difficulty breathing and may occur as a result of local nerve compression. Dysphagia due to esophageal compression may also be observed.

TB pleural effusion

Pleural effusions due to TB usually occur in older children and are rarely associated with miliary disease. The typical history reveals an acute onset of fever, chest pain that increases in intensity on deep inspiration, and shortness of breath. Fever usually persists for 14-21 days. [Signs include tachypnea, respiratory distress,](#) and dullness to percussion, decreased breath sounds, and, occasionally, features of mediastinal shift.

Progressive primary TB

Progression of the pulmonary parenchymal component leads to enlargement of the caseous area and may lead to pneumonia, atelectasis, and air trapping. This is more likely to occur in young children than in adolescents. The child usually appears ill with symptoms of fever, cough, malaise, and weight loss. [This condition presents with classic signs of pneumonia,](#) including tachypnea, nasal flaring, grunting, dullness to percussion, egophony, decreased breath sounds, and crackles.

Reactivation TB

Reactivation of TB disease usually has a subacute presentation with weight loss, fever, cough, and, rarely, hemoptysis. This condition typically occurs in older children and adolescent and is more common in patients who acquire TB at age 7 years and older. [Physical examination results](#) may be normal or may reveal posttussive crackles.

Evaluation of Pediatric Extrapulmonary TB

Extrapulmonary tuberculosis (TB) includes peripheral lymphadenopathy, TB meningitis, miliary TB, skeletal TB, and other organ involvement. Other unusual sites for TB include the middle ear, gastrointestinal (GI) tract, skin, kidneys, and ocular structures. [Go to Scrofula, Tuberculosis of the Genitourinary System, Miliary Tuberculosis, and Tuberculous Meningitis](#) for more information on these topics.

Lymphadenopathy

Patients with lymphadenopathy (ie, scrofula) may have a history of enlarged nodes. Fever, weight loss, fatigue, and malaise are usually absent or minimal. Lymph node involvement typically occurs 6-9 months following initial infection by the tubercle bacilli. More superficial lymph nodes commonly are involved. Frequent sites of involvement include the anterior cervical, submandibular, and supraclavicular nodes. TB of the skeletal system may lead to involvement of the inguinal, epitrochlear, or axillary lymph nodes. [Typically, infected lymph nodes are firm](#) and nontender with nonerythematous overlying skin. The nodes are initially nonfluctuant. Suppuration and spontaneous drainage of the lymph nodes may occur with caseation and the development of necrosis. [A study reported on the accuracy and safety of endobronchial ultrasound \(EBUS\) transbronchial needle aspiration \(TBNA\)](#) for the diagnosis of tuberculous mediastinal lymphadenitis. The study concluded that EBUS-TBNA is a safe and well tolerated procedure in the assessment of patients with suspected isolated mediastinal lymphadenitis. The authors add that EBUS-TBNA should be considered the procedure of choice for patients in whom TB is suspected.

TB meningitis

One of the most severe complications of TB is TB meningitis, which develops in 5-10% of children younger than 2 years; thereafter, the frequency drops to less than 1%. A very high index of suspicion is required to make a timely diagnosis because of the insidious onset of the disease. [A subacute presentation usually occurs within 3-6 months](#) after the initial infection. Nonspecific symptoms such as anorexia, weight loss, and fever may be present. After 1-2 weeks, patients may experience vomiting and seizures or alteration in the sensorium. Deterioration of mental status, coma, and death may occur despite prompt diagnosis and early intervention. [Three stages of TB meningitis have been identified.](#) Stage 1 is defined by the absence of focal or generalized neurologic signs. Possibly, only nonspecific behavioral abnormalities are found. [Stage 2 is characterized by the presence of nuchal rigidity,](#) altered deep tendon reflexes, lethargy, and/or cranial nerve palsies. TB meningitis most often affects the sixth cranial nerve due to the pressure of the thick basilar inflammatory exudates on the cranial nerves or to hydrocephalus; this results in lateral rectus palsy. The third, fourth, and seventh cranial nerves may also be affected. Funduscopic changes may include papilledema and the presence of choroid tubercles, which should be carefully sought. [Stage 3, the final stage, comprises major neurologic defects,](#) including coma, seizures, and abnormal movements (eg, choreoathetosis, paresis, paralysis of one or more extremities). In the terminal phase, decerebrate or decorticate posturing, opisthotonus, and/or death may occur. Patients with tuberculomas or TB brain abscesses may present with focal neurologic signs. Spinal cord disease may result in the acute development of spinal block or a transverse myelitis-like syndrome. A slowly ascending paralysis may develop over several months to years.

Miliary TB

This is a complication of primary TB in young children. Miliary TB may

manifest subacutely with low-grade fever, malaise, weight loss, and fatigue. A rapid onset of fever and associated symptoms may also be observed. History of cough and respiratory distress may be obtained. **Physical examination findings include** lymphadenopathy, hepatosplenomegaly, and systemic signs including fever. Respiratory signs may evolve to include tachypnea, cyanosis, and respiratory distress. Other signs, which are subtle and should be carefully sought in the physical examination, include papular, necrotic, or purpuric lesions on the skin or choroidal tubercles in the retina.

Bone or joint TB

Skeletal TB may present acutely or subacutely. Vertebral disease may go unrecognized for months to years because of its indolent nature. Common sites involved include the large weightbearing bones or joints, including the vertebrae (50%), hip (15%), and knee (15%). **Destruction of the bones with deformity is a late sign of TB.** Manifestations may include angulation of the spine (gibbus deformity) and/or Pott disease (severe kyphosis with destruction of the vertebral bodies). Cervical spine involvement may result in atlantoaxial subluxation, which may lead to paraplegia or quadriplegia.

Diagnostic Overview

Making the diagnosis of tuberculosis (TB) in children is extremely challenging because of the difficulty in isolating M tuberculosis. Definitive TB diagnosis depends on isolation of the organism from secretions or biopsy specimens. Despite innovations in rapid diagnosis, many of the classic diagnostic tools remain useful and continue to be used in the evaluation of patients with TB.

To make a diagnosis of congenital TB, the infant should have proven TB lesions and at least one of the following:

- Skin lesions during the first week of life, including papular lesions or petechiae
- Documentation of TB infection of the placenta or the maternal genital tract
- Presence of a primary complex in the liver
- Exclusion of the possibility of postnatal transmission

Differentials

The following conditions should also be considered in cases of suspected TB:

- Actinomycosis
- Aspergillosis
- Bronchiectasis
- Bronchopulmonary Dysplasia
- Brucellosis
- Chronic Granulomatous Disease
- Coccidioidomycosis
- Failure to Thrive
- Fever Without a Focus
- Histoplasmosis
- Legionella Infection
- Meningitis, Aseptic
- Meningitis, Bacterial
- Nocardiosis
- Pleural Effusion
- Pneumonia

Tuberculin Skin Test

The tuberculin skin test (TST) is a widely used diagnostic test for evaluation of patients who have symptoms of tuberculosis (TB) or in

whom infection with M tuberculosis is suspected. The TST is neither 100% sensitive nor 100% specific. Interferon gamma release assays (IGRA) are now replacing the TST as the preferred test for screening and testing for tuberculosis in children > 5 years old who have been vaccinated with Bacilli Calmette-Guerin (BCG).

AAP guidelines for pediatric testing

According to the American Academy of Pediatrics (AAP), immediate skin testing is indicated for the following children :

- Those who have been in contact with persons with active or suspected TB
- Immigrants from TB-endemic countries (eg, Asia, Middle East, Africa, Latin America) or children with travel histories to these countries
- Those who have radiographic or clinical findings suggestive of TB

An annual TST is indicated for the following children :

- Children who are infected with human immunodeficiency virus (HIV) or those living in a household with persons infected with HIV
- Incarcerated adolescents

Testing at 2-year to 3-year intervals is indicated if the child has been exposed to high-risk individuals including those who are homeless, institutionalized adults who are infected with HIV, users of illicit drugs, residents of nursing homes, and incarcerated adolescents or adults.

Testing when children are aged 4-6 years and 11-16 years is indicated for the following children :

- Children without risk factors residing in high-prevalence areas
- Children whose parents emigrated from regions of the world with a high prevalence of TB or who have continued potential exposure by travel to the endemic areas and/or household contact

Performing an initial TST before the initiation of immunosuppressive therapy is recommended in any patient.

Administration of TST

The recommended TST is the Mantoux test. The dosage of 0.1 mL or 5 tuberculin units [TU] of purified protein derivative (PPD) should be injected intradermally into the volar aspect of the forearm using a 27-gauge needle. A detergent called Tween 80 to prevent loss of efficacy on contact and adsorption by glass stabilizes the PPD. A wheal should be raised and should measure approximately 6-10 mm in diameter. **Skilled personnel should always read the test 48-72 hours after administration.** Measure the amount of induration and not erythema. This should be measured transverse to the long axis of the forearm. **Multiple puncture tests** (eg, tine test, Heaf test) lack sensitivity and specificity and hence are not recommended.

Interpretation of TST results

The Centers for Disease Control and Prevention (CDC) and the AAP provided recommendations regarding the size of the induration created by the TST that is considered a positive result and indicative of disease. The TST is interpreted on the basis of 3 "cut points": 5 mm, 10 mm, and 15 mm.

Induration of 5 mm or more is considered a positive TST result in the following children :

- Children having close contact with known or suspected contagious cases of the disease, including those with household contacts with active TB whose treatment cannot be verified before exposure
- Children with immunosuppressive conditions (eg, HIV) or children who are on immunosuppressive medications
- Children who have an abnormal chest radiograph finding consistent with active TB, previously active TB, or clinical evidence of the disease

Induration of 10 mm or more is considered a positive TST result in the

following children :

- Children who are at a higher risk of dissemination of TB disease, including those younger than 5 years or those who are immunosuppressed because of conditions such as lymphoma, Hodgkin disease, diabetes mellitus, and malnutrition
- Children with increased exposure to the disease, including those who are exposed to adults in high-risk categories (eg, homeless, HIV infected, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized persons); those who were born in or whose parents were born in high-prevalence areas of the world; and those with travel histories to high-prevalence areas of the world

Induration of 15 mm or more is considered a positive TST result in children aged 5 years or older without any risk factors for the disease.

False-positive and false-negative results

False-positive reactions and false-negative results can have various causes. False-positive reactions are often attributed to asymptomatic infection by environmental non-TB mycobacteria (due to cross-reactivity). **False-negative results may be due to vaccination** with live-attenuated virus, anergy, immunosuppression, immune deficiency, or malnutrition. Other factors that may cause a false-negative result include improper administration (eg, subcutaneous injection, injection of too little antigen), improper storage, and contamination. PPD has been recognized to have an initial false-negative rate of 29%.

Previous BCG vaccination

Some important points regarding administering the TST to previous recipients of the bacille Calmette-Guérin (BCG) are briefly discussed. **Immunization with BCG is not a contraindication to the TST.** BCG vaccination is used in many parts of the world, especially in developing countries. **Differentiating tuberculin reactions caused by vaccination with BCG** versus reactions caused by infection with M tuberculosis is difficult. History of contact with a person with contagious TB or emigration from a country with a high prevalence of TB suggests that the positive results are due to infection with M tuberculosis. However, multiple BCG vaccinations may increase the likelihood that the positive TST result is due to the BCG vaccination. The positive reactivity caused by BCG vaccination generally wanes with the passage of time. With the administration of TST, this positive tuberculin reactivity may be boosted. **A previous BCG vaccination does not affect interpretation of a TST result** for a person who is symptomatic or in whom TB is strongly suspected.

Specimen Collection for Analysis

The initial step in detection and isolation of the mycobacterium is to obtain appropriate specimens for bacteriologic examination. Examination of sputum, gastric lavage, bronchoalveolar lavage, lung tissue, lymph node tissue, bone marrow, blood, liver, cerebrospinal fluid (CSF), urine, and stool may be useful, depending on the location of the disease. **Decontamination of other microorganisms in the specimens obtained** may be performed by the addition of sodium hydroxide, usually in combination with N -acetyl-L -cysteine. Other body fluids (eg, CSF, pleural fluid, peritoneal fluid) can also be centrifuged; the sediment can be stained and evaluated for presence of acid-fast bacilli (AFB). CSF smear results are positive in fewer than 10% of patients in some series. Enhancement of the yield may be possible by staining any clot that may have formed in standing CSF specimens, as well as using the sediment of a centrifuged specimen. Increased yield may also be obtained from cisternal or ventricular fluid.

Sputum specimens

Sputum specimens may be used in older children, but not in very young children (< 6 y), who usually do not have a cough deep enough to

produce sputum for analysis. In those younger than 6 years, gastric aspirates are used. **Nasopharyngeal secretions and saliva are not acceptable.** In older children, bronchial secretions may be obtained by the stimulation of cough by an aerosol solution of propylene glycol in 10% sodium chloride (see Bronchial secretions).

Gastric aspirates

Gastric aspirates are used in lieu of sputum in children younger than 6 years. **Using the correct technique for obtaining the gastric lavage is important** because of the scarcity of the organisms in children compared with adults. An early morning sample should be obtained before the child has had a chance to eat or ambulate, because these activities dilute the bronchial secretions accumulated during the night. **Initially, the stomach contents should be aspirated**, and then a small amount of sterile water is injected through the orogastric tube. This aspirate should also be added to the specimen. **Because gastric acidity is poorly tolerated by the tubercle bacilli**, neutralization of the specimen should be performed immediately with 10% sodium carbonate or 40% anhydrous sodium phosphate. Even with careful attention to detail and meticulous technique, the tubercle bacilli can be detected in only 70% of infants and in 30-40% of children with disease.

Bronchial secretions

Bronchoalveolar lavage may be used in older children (6 y or older). Bronchial secretions may be obtained by the stimulation of cough by an aerosol solution of propylene glycol in 10% sodium chloride. This technique may also be used to provide bronchial secretions for detection of tubercle bacilli.

Urine specimens

Obtain overnight urine specimens in the early morning. Send immediately for analysis, because the tubercle bacilli poorly tolerate the acidic pH of urine.

AFB Staining

Because M tuberculosis is an acid-fast bacilli (AFB), AFB staining provides preliminary confirmation of the diagnosis. Conventional methods include the Ziehl-Neelsen staining method. The Kinyoun stain is modified to make heating unnecessary. Fluorochrome stains, such as auramine and rhodamine, are variations of the traditional stains. The major advantage of these methods is that slides can be screened faster, because the acid-fast material stands out against the dark, nonfluorescent background. However, fluorochrome-positive smears must be confirmed by Ziehl-Neelsen staining. **Staining can also give a quantitative assessment of the number of bacilli being excreted (eg, 1+, 2+, 3+).** This can be of clinical and epidemiologic importance in estimating the infectiousness of the patient and in determining the discontinuation of respiratory isolation. However, for reliably producing a positive result, smears require approximately 10,000 organisms/mL. Therefore, in early stages of the disease or in children in whom the bacilli in the respiratory secretions are sparse, the results may be negative. A single organism on a slide is highly suggestive and warrants further investigation. **A significant drawback of AFB smears is that they cannot be used** to differentiate M tuberculosis from other acid-fast organisms such as other mycobacterial organisms or Nocardia species.

Mycobacterium Cultures

Culture of mycobacterium is the definitive method to detect bacilli. It is also more sensitive than examination of the smear. Approximately 10 acid-fast bacilli (AFB) per millimeter of a digested concentrated specimen are sufficient to detect the organisms by culture. **Another advantage of culture is that it allows specific species identification** and

testing for recognition of drug susceptibility patterns. However, because *M tuberculosis* is a slow-growing organism, a period of 6-8 weeks is required for colonies to appear on conventional culture media.

Conventional growth techniques

Conventional solid media include the Löwenstein-Jensen medium, which is an egg-based medium, and the Middlebrook 7H10 and the 7H11 media, which are agar-based media. Liquid media (eg, Dubos oleic-albumin media) are also available, and they require incubation in 5-10% carbon dioxide for 3-8 weeks. These media usually have antibacterial antibiotics, which are slightly inhibitory for tubercle bacilli.

Rapid growth techniques

Because mycobacteria require 6-8 weeks for isolation from conventional media, automated radiometric culture methods (eg, BACTEC) are increasingly used for the rapid growth of mycobacteria. The methodology uses a liquid Middlebrook 7H12 medium that contains radiometric palmitic acid labeled with radioactive carbon-14 (^{14}C). Several antimicrobial agents are added to this medium to prevent the growth of nonmycobacterial contaminants. Production of CO_2 by the metabolizing organisms provides a growth index for the mycobacteria. Growth is generally detected within 9-16 days. [Another rapid method for isolation of mycobacteria is SEPTICHEK](#). This nonradiometric approach has a biphasic broth-based system that decreases the mean recovery time versus conventional methods. [Mycobacterial growth indicator tubes \(MGITs\)](#), which presently are used as a research tool, have round-bottom tubes with oxygen-sensitive sensors at the bottom. MGITs indicate microbial growth and provide a quantitative index of *M tuberculosis* growth.

Species Identification

M tuberculosis can be reliably differentiated from other species on the basis of culture characteristics, growth parameters, and other empiric tests. *M tuberculosis* produces heat-sensitive catalase, reduces nitrates, produces niacin, and grows slowly. Serpentine cording is demonstrated on smears prepared from the BACTEC system. [Addition of p -nitro-acetyl-amino-hydroxy-propiofenone \(NAP\)](#) inhibits the growth of *M tuberculosis* complex (including *M bovis* and *M africanum*) but does not inhibit growth of other mycobacteria. This provides the basis for the NAP differentiation test. [Chromatographic analysis of mycobacterial cell wall lipids can provide further speciation](#). The most useful approaches include gas-liquid chromatography and high-performance liquid chromatography (HPLC). The unique mycolic acid pattern associated with the species can be detected by the chromatographic separation of the ester. [A significant drawback of these chromatographic methods](#) is the requirement of bacterial colonies grown in conventional solid media, a process that takes at least 3 weeks. However, the recent combination of HPLC with fluorescence detection has made the method more sensitive; thus, BACTEC broth culture can be used instead of conventional solid media. This may make the method comparable to the NAP and AccuProbe tests (see Nucleic Acid Probes). The expense of the initial equipment limits the availability of HPLC.

Nucleic Acid Probes

Because biochemical methods are time-consuming and laborious, nucleic acid hybridization using molecular probes has become widely accepted. The basic principle is the use of a chemiluminescent, ester-labeled, single-strand DNA probe. A luminometer is used to assess the chemiluminescence. [Commercially available probes, including the AccuProbe technology](#), help advance identification of the *M tuberculosis* complex. Sensitivity and specificity approach 100% when at least

100,000 organisms are present. [Positive test results should be reported as *M tuberculosis* complex](#), because the probe does not reliably differentiate between *M tuberculosis* and other members of the complex (eg, *M bovis*). In addition, final identification to species level is required, because pyrazinamide should not be included in the treatment regimen if the isolate is *M bovis*. [Niacin production, nitrate reduction, pyrazinamidase](#), and susceptibility to thiophene-2-carboxylic acid hydrazide can help differentiate between *M bovis* and *M tuberculosis*.

Nucleic Acid Amplification Tests

Nucleic acid amplification techniques (eg, polymerase chain reaction [PCR]) allows the direct identification of *M tuberculosis* in clinical specimens, unlike the nucleic acid probes, which require substantial time for bacterial accumulation in broth culture. [The US Food and Drug Administration \(FDA\) has approved at least 2 tests](#), the amplified *M tuberculosis* direct test and the AMPLICOR *M tuberculosis* test. The amplified *M tuberculosis* direct test is an isothermal transcription-mediated amplification that targets RNA. The AMPLICOR test targets the DNA. The most commonly used target sequence for the detection of *M tuberculosis* has been the insertion sequence IS6110. [Although amplification techniques are promising tools for the rapid diagnosis of tuberculosis \(TB\)](#), several caveats remain. Contamination of samples by products of previous amplification and the presence of inhibitors in the sample may lead to false-positive or false-negative results. [Although the sensitivity and specificity of the nucleic acid techniques](#) in smear-positive cases exceed 95%, the sensitivity of smear-negative cases varies from 40% to 70%. Thus, discordance between the acid-fast smear result and the nucleic acid amplification techniques requires careful clinical appraisal and judgment.

Immunoassays

IFN-gamma plays a critical role in regulating cell-mediated immune responses to *M tuberculosis* infection. This resulted in the development of IGRAs to aid clinicians in diagnosing *M tuberculosis* infection (latent infection and active infection). [IGRAs detect sensitization to *M tuberculosis* by measuring IFN-gamma release](#) in response to antigens that represent *M tuberculosis*. Available assays include the QuantiFERON-TB test (QFT), the QuantiFERON-TB Gold test (QFT-G), the QuantiFERON-TB Gold In-Tube test (QFT-GIT), and the T-SPOT.TB test (T-Spot).

The use of IGRAs in children is subject to the following limitations:

- Studies evaluating IGRAs performance in children are scant.
- Indeterminate results for children are a potential limitation to implementing IGRAs into clinical practice. The frequencies of indeterminate IGRA results in children vary (range, 0-17%) and most are attributable to a low mitogen response as a result of a lack of immunologic maturity. A study of 761 children by Critselis et al confirmed that indeterminate results from the QFT-IT assay occur more frequently among younger children.
- Difficulties in collecting blood for these tests and the need for a relatively large volume of blood from small children (especially for infants) are also limitations.

Because of the above limitations, a TST is preferred for testing children younger than 5 years. Regardless, sensitivity of IGRAs in children is expected to be comparable to TST. Specificity of IGRAs in children is expected to be high. However, additional studies are needed to evaluate the performance of IGRAs in children.

Situations in which an IGRA is preferred but a TST is acceptable include the following:

- Children > 5 years of age
- Testing patients who have low rates of returning for TST
- Testing persons who have received BCG as a vaccine or for cancer therapy to increase diagnostic specificity and improve acceptance of treatment for latent infection

M tuberculosis Drug Susceptibility

Because of the emergence of multidrug-resistant (MDR) organisms, determination of the drug susceptibility panel of an isolate is important so that appropriate treatment can be ensured. Numerous chromosomal mutations are associated with drug resistance. Genotypic methods now being evaluated to identify these mutations include DNA sequencing, solid phase hybridization, and polymerase chain reaction (PCR)-single-strand combination polymorphism analysis. Mutations of the catalase peroxidase gene *katG*, the *inhA* gene involved in fatty acid biosynthesis, the *ahpC* gene, and the *oxyR* gene have been identified as major determinants for isoniazid (INH) resistance. Resistance to rifampin is determined by mutations in the *rpoB* gene encoding the beta subunit of the RNA polymerase. Phenotypic susceptibility assays, which are still under investigation, use mycobacteriophages to type the mycobacteria grown in the presence of antituberculous agents. Rapid molecular detection of TB and drug resistance using an automated molecular test for M tuberculosis and resistance to rifampin (Xpert MTB/RIF), by PCR assay to amplify an M tuberculosis–specific sequence within the rifampin resistance–determining region has been studied in countries with a high TB burden. Overall, the findings suggest use of MTB/RIF test in low-resource countries may be feasible to allow to early diagnosis and treatment. This test can be performed using nasopharyngeal specimens in settings where induced sputum and culture are not practical.

Serology

M tuberculosis increases the levels of antibody titers in the serum. However, there is no available serodiagnostic test for tuberculosis (TB) that has an adequate sensitivity and specificity for routine use in diagnosing TB in children.

Management Overview

The American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) have provided standard guidelines for the treatment of tuberculosis (TB). The ultimate goal of treatment is to achieve sterilization of the TB lesion in the shortest possible time. The general rule is strict adherence to TB treatment regimens for a sufficient time period. To prevent the emergence of resistance, the regimens for the treatment of TB always should consist of multiple drugs.

Pharmacotherapy considerations

Anti-TB medications kill mycobacteria, thereby preventing further complications of early primary disease and progression of disease. However, disappearance of caseous or granulomatous lesions does not occur even with therapy. These drugs are classified as first-line and second-line drugs. First-line drugs have less toxicity with greater efficacy than second-line drugs. All first-line agents are bactericidal with the exception of ethambutol. First-line agents include rifampin, isoniazid (INH), pyrazinamide, ethambutol, and streptomycin. Second-line agents are capreomycin, ciprofloxacin, cycloserine, ethionamide, kanamycin, ofloxacin, levofloxacin, and para-aminosalicylic acid. INH and rifampin are effective against bacilli in necrotic foci and intracellular populations of mycobacteria. Streptomycin, aminoglycosides, and capreomycin have poor intracellular penetration. Multidrug-resistant (MDR) TB is defined as resistance to at least INH and rifampin (see Multidrug-Resistant TB). The emergence of drug-resistant strains has necessitated the use of second-line agents. Naturally drug-resistant organisms occur with a frequency of approximately 10⁻⁶; however, individual resistances may vary. The resistance to streptomycin is 10⁻⁶, to INH is 10⁻⁶, and to rifampin is 10⁻⁶. The chance that an organism is naturally resistant to both INH and rifampin is on the order of 10⁻¹². Because populations of this size do not occur in patients, organisms naturally resistant to 2 drugs are essentially nonexistent. If only a single medication is administered to a patient with TB, the subpopulations susceptible to that medication are destroyed, but the other categories continue to multiply. Thus, the use of multiple agents in the treatment of TB is essential.

Adverse drug effects

Adverse effects of isoniazid (INH) (eg, hepatitis) are rare in children; therefore, routine determination of serum aminotransferase levels is not necessary. Consider monthly monitoring of hepatic function tests in the following patients: (1) those with severe or disseminated TB; (2) those with concurrent or recent hepatic disease; (3) those receiving high daily doses of INH (10 mg/kg/d) in combination with rifampin, pyrazinamide, or both; (4) women who are pregnant or within the first 6 weeks postpartum; (5) those with clinical evidence of hepatotoxic effects; and (6) those with hepatobiliary tract disease from other causes.

Bed rest

The advisability of bed rest varies with the type and severity of the disease. No limitation of activity is required in patients with TB infection or asymptomatic primary pulmonary TB. Severely ill patients with miliary TB, TB meningitis, or disseminated TB may require complete bed rest; these individuals may also need transfer to the intensive care unit until their condition is stabilized.

INTERPRETATION

Adenosine Deaminase

ADA

Formal Name

Adenosine Deaminase, fluid.

At a Glance

Why Get Tested?

To help detect or rule out a *Mycobacterium tuberculosis* infection in pleural fluid in order to assist in the diagnosis of tuberculosis; rarely to detect the infection in other body fluids such as peritoneal fluid or cerebrospinal fluid (CSF).

When To Get Tested?

When a healthcare practitioner suspects that someone with chest pain, coughing, and/or difficulty breathing has tuberculosis that has spread to their pleurae (lining around the lungs).

Sample Required?

A volume of pleural fluid is collected by a healthcare practitioner using a procedure called thoracentesis; other body fluids are collected using other procedures.

Test Preparation Needed?

None.

What is being tested?

Adenosine deaminase (ADA) is a protein that is produced by cells throughout the body and is associated with the activation of lymphocytes, a type of white blood cell that plays a role in the immune response to infections. Conditions that trigger the immune system, such as an infection by *Mycobacterium tuberculosis*, the bacteria that causes tuberculosis (TB), may cause increased amounts of ADA to be produced in the areas where the bacteria are present. This test measures the amount of adenosine deaminase present in pleural fluid in order to help diagnose a tuberculosis infection of the pleurae. **Pleurae are membranes that cover the chest cavity and the outside of each lung.** Small amounts of pleural fluid are continuously produced to lubricate the movement of the lungs against these membranes and the membranes against each other during inhalation and exhalation. A variety of conditions and diseases, including infection, can cause inflammation of the pleurae (pleurisy or pleuritis) and can lead to excessive pleural fluid accumulation (pleural effusion). **Tuberculosis can spread into the lungs and pleurae, causing symptoms such as chest pain, chronic cough, and shortness of breath.** Since these symptoms may also be seen with a variety of other conditions, it is important to determine the cause as rapidly as possible in order to properly treat the affected person. Detecting mycobacteria in pleural fluid can be difficult because there may be a large volume of fluid and very low numbers of bacteria present. Though the ADA test is not specific and does not replace the culture for diagnosing TB, it may be positive even when numbers of bacteria are very low and can be used as an adjunct test to help determine whether tuberculosis is the likely source of a person's symptoms.

How is the sample collected for testing?

A sample of pleural fluid is collected by a healthcare practitioner with a syringe and needle using a procedure called thoracentesis. Rarely, other body fluid samples, such as peritoneal or cerebrospinal fluid (CSF), are collected using procedures specific to the fluid type.

How is it used?

The adenosine deaminase (ADA) test is not a diagnostic test, but it may be used along with other tests such as pleural fluid analysis, acid-fast bacillus (AFB) smear and culture, and/or tuberculosis molecular testing to help determine whether a person has a *Mycobacterium tuberculosis* infection (tuberculosis or TB) of the lining of the lungs (pleurae). **A culture is considered the "gold standard" for diagnosing tuberculosis and guiding treatment,** but it may take several days to weeks to complete. Molecular testing and the AFB smear are rapid tests, but they require that a sufficient number of microorganisms be present in the fluid to detect them. Pleural fluid presents a unique problem with detecting *M. tuberculosis* because there may be a large volume of fluid with a very low number of bacteria present. Though the ADA test is not definitive, it is a rapid test and may be elevated even when there are few bacteria present. ADA results may be used to help guide treatment until results from a culture are available. **The ADA test is used as an adjunct test to help rule in or rule out tuberculosis in pleural fluid.** Rarely, it may be ordered to detect tuberculosis in other body fluids, such as peritoneal fluid or cerebrospinal fluid (CSF).

When is it ordered?

An ADA test may be ordered when a person has an accumulation of fluid in the chest cavity (pleural fluid) and has signs or symptoms that suggest TB, such as:

- Chronic cough, sometimes with bloody sputum
- Fever, chills
- Night sweats
- Unexplained weight loss
- Chest pain

This test may be ordered as one of several tests to help rule in or rule out TB as the cause of a person's symptoms, especially if the individual falls into a high-risk group, such as:

- People with close contact with someone who has active infectious TB
- Immigrants from areas of the world where the incidence of TB is high
- Children younger than 5 years old who have a positive TB screening test
- People who work with or are part of groups with high rates of infection, such as the homeless, IV drug users or confined populations, such as hospitalized patients, prisoners, and residents of nursing homes
- People with weakened immune systems such as:
 - Those with HIV/AIDS
 - Those with chronic underlying conditions, including diabetes and kidney disease
 - Organ transplant recipients and others on immunosuppressant drugs
 - Pregnant women
 - The elderly

Testing may be ordered when a healthcare practitioner wants to determine whether a person likely has tuberculosis, in advance of other test results, in order to initiate treatment.

What does the test result mean?

If adenosine deaminase (ADA) is markedly elevated in pleural fluid in a person with signs and symptoms that suggest tuberculosis, then it is likely that the person tested has a *M. tuberculosis* infection in their pleurae. This is especially true when there is a high prevalence of tuberculosis in the geographic region where a person lives. **When there is a low prevalence of tuberculosis in a region**, then a person may have tuberculosis or may have an ADA result that is elevated for another reason, such as cancer (particularly lymphomas), pulmonary embolus, sarcoidosis, or lupus. These other diagnoses are more likely if the ADA result is only mildly or moderately elevated. **A person with a low ADA level is unlikely to have tuberculosis** in their pleurae. This does not rule out having the infection in other parts of their body. **If ADA is markedly elevated in fluid from another part of the body**, such as peritoneal fluid or CSF, then there is an increased likelihood that tuberculosis is present in this area.

Is there anything else I should know?

The ADA test cannot positively identify *M. tuberculosis* as the cause of a person's symptoms, and the test results cannot be used to determine if the person has drug-resistant tuberculosis.

Can my doctor diagnose tuberculosis without testing my pleural fluid?

A healthcare practitioner cannot diagnose tuberculosis in the pleural space without testing the pleural fluid. If the infection is present in your lungs, then sputum may be collected or, if meningitis is suspected, cerebrospinal fluid (CSF) would be tested.

Should everyone with suspected tuberculosis have an ADA test performed?

The ADA test is primarily performed when tuberculosis is suspected in the pleurae, and it is not routinely available in all laboratories. It will be performed when a healthcare practitioner determines that it will be useful and timely in helping to diagnose or rule out tuberculosis.

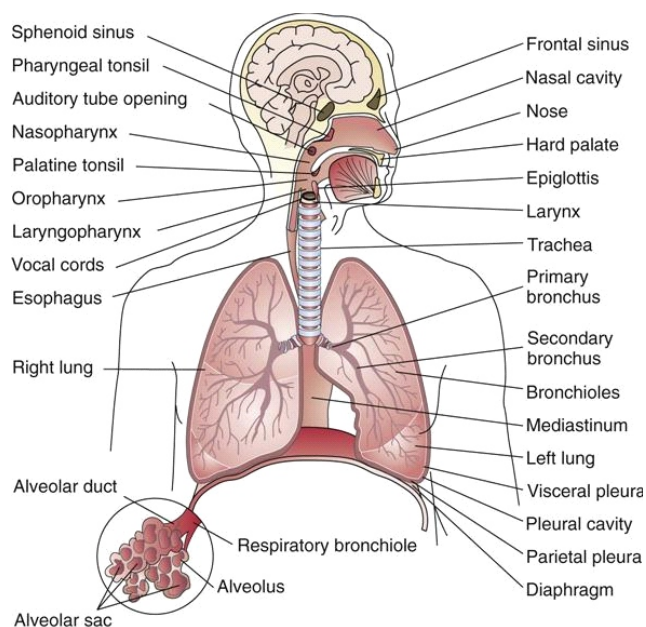
Can my blood be tested for ADA?

Yes, and it sometimes is, but it is done for another purpose and not to detect tuberculosis. The blood may be tested to help identify ADA deficiency.

What is ADA deficiency?

ADA is an enzyme that converts one byproduct into another byproduct. The first substance is toxic to lymphocytes and must be inactivated by ADA. With ADA deficiency, a rare inherited condition, the body makes insufficient ADA. This leads to the buildup of the toxic byproduct and can cause severe combined immunodeficiency disease (SCID). Infants with this condition have seriously compromised immune systems and may not survive without bone marrow transplantation.

Related Images



TROUBLESHOOTING

Pleural Effusion Workup

Pleural Fluid Culture and Cytology

Cultures of infected pleural fluids yield positive results in approximately 60% of cases. This occurs even less often for anaerobic organisms. Diagnostic yields, particularly for anaerobic pathogens, may be increased by directly culturing pleural fluid into blood culture bottles.

Malignancy is suspected in patients with known cancer or with lymphocytic, exudative effusions, especially when bloody. Direct tumor involvement of the pleura is diagnosed most easily by performing pleural fluid cytology. **Heparinized samples (1 mL of 1:1000 heparin per 50 mL of pleural fluid) should be submitted for analysis** if the pleural fluid is bloody and they should be refrigerate if samples will not be processed within one hour. **The reported diagnostic yields in cytology vary from 60-90%**, depending on the extent of pleural involvement and the type of primary malignancy. Cytology findings are positive in 58% of effusions related to mesothelioma. **The sensitivity of cytology is not highly related to the volume of pleural fluid tested.** Sending more than 50-60 mL of pleural fluid for cytology does not increase the yield of direct cytospin analysis, and volumes of approximately 150 mL are sufficient when both cytospin and cell block preparations are analyzed. **Tumor markers, such as carcinoembryonic antigen, Leu-1, and mucin, are suggestive of malignant effusions** (especially adenocarcinoma) when pleural fluid values are very high. However, because of low sensitivity, they are not helpful if the values are normal or only modestly increased.

Tuberculous pleuritis

Suspect tuberculous pleuritis in patients with a history of exposure or a positive PPD finding and in patients with lymphocytic exudative effusions, especially if less than 5% mesothelial cells are detected on differential cell counts. **Because most tuberculous pleural effusions probably result from a hypersensitivity reaction** to the Mycobacterium rather than from microbial invasion of the pleura, acid-fast bacillus stains of pleural fluid are rarely diagnostic (< 10% of cases). Pleural fluid cultures grow M tuberculosis in less than 65% of cases. **In contrast, the combination of histology and culture of pleural tissue** obtained by pleural biopsy increases the diagnostic yield for TB to 90%. **Adenosine deaminase (ADA) activity of greater than 43 U/mL in pleural fluid supports** the diagnosis of tuberculous pleuritis. However, the test has a sensitivity of only 78%. Therefore, pleural ADA values of less than 43-50 U/mL do not exclude the diagnosis of TB pleuritis. **Interferon-gamma concentrations of greater than 140 pg/mL in pleural fluid also support** the diagnosis of tuberculous pleuritis. Unfortunately, this test is not routinely available.

Additional Laboratory Tests

Additional specialized tests are warranted when specific etiologies are suspected. Measure pleural fluid amylase levels if a pancreatic origin or ruptured esophagus is suspected or if a unilateral, left-sided pleural effusion remains undiagnosed after initial testing. Of note, increased pleural fluid amylase can also be seen with malignancy. An additional assay of amylase isoenzymes can help distinguish a pancreatic source (diagnosed by elevated pleural fluid pancreatic isoenzymes) from other etiologies. **Measure triglyceride and cholesterol levels in milky pleural fluids** when chylothorax or pseudochylothorax is suspected. **Consider immunologic studies, including pleural fluid antinuclear antibody and**

rheumatoid factor, when collagen-vascular diseases are suspected.

CT Scanning and Ultrasonography

A study involving 41 consecutive patients with hepatic hydrothorax indicated that hepatic hydrothorax virtually always presents with ascites that can be revealed by ultrasonography or computed tomography (CT) scanning. Point of care bedside ultrasonography has become the standard of care in many facilities. **Chest CT scanning with contrast should be performed in all patients with an undiagnosed pleural effusion**, if it has not previously been performed, to detect thickened pleura or signs of invasion of underlying or adjacent structures. The two diagnostic imperatives in this situation are pulmonary embolism and tuberculous pleuritis. In both cases, the pleural effusion is a harbinger of potential future morbidity. In contrast, a short delay in diagnosing metastatic malignancy to the pleural space has less impact on future clinical outcomes. CT angiography should be ordered if pulmonary embolism is strongly suggested.

Chest Radiography

Effusions of more than 175 mL are usually apparent as blunting of the costophrenic angle on upright posteroanterior chest radiographs. On supine chest radiographs, which are commonly used in the intensive care setting, moderate to large pleural effusions may appear as a homogenous increase in density spread over the lower lung fields. Apparent elevation of the hemidiaphragm, lateral displacement of the dome of the diaphragm, or increased distance between the apparent left hemidiaphragm and the gastric air bubble suggests subpulmonic effusions. **Lateral decubitus films more reliably detect smaller pleural effusions.** Layering of an effusion on lateral decubitus films defines a freely flowing effusion and, if the layering fluid is 1 cm thick, indicates an effusion of greater than 200 mL that is amenable to thoracentesis. Failure of an effusion to layer on lateral decubitus films indicates the presence of loculated pleural fluid or some other etiology causing the increased pleural density. Note that decubitus films are almost never performed in those institutions with bedside ultrasonography

Diagnostic Thoracentesis

A diagnostic thoracentesis should be performed if the etiology of the effusion is unclear or if the presumed cause of the effusion does not respond to therapy as expected. Pleural effusions do not require thoracentesis if they are too small to safely aspirate or, in clinically stable patients, if their presence can be explained by underlying congestive heart failure (especially bilateral effusions) or by recent thoracic or abdominal surgery. **Depending on the clinician's experience**, a pulmonologist or interventional radiologist can be consulted for assistance with high-risk diagnostic thoracentesis.

Contraindications

Relative contraindications to diagnostic thoracentesis include a small volume of fluid (< 1 cm thickness on a lateral decubitus film), bleeding diathesis or systemic anticoagulation, mechanical ventilation, and cutaneous disease over the proposed puncture site. Reversal of coagulopathy or thrombocytopenia may not be necessary as long as the procedure is performed under ultrasound guidance by an experienced operator. Mechanical ventilation with positive end-expiratory pressure does not increase the risk of pneumothorax after thoracentesis, but it increases the likelihood of severe complications (tension pneumothorax or persistent bronchopleural fistula) if the lung is punctured. An uncooperative patient is an absolute contraindication for this procedure.

Complications

Complications of diagnostic thoracentesis include pain at the puncture site, cutaneous or internal bleeding from laceration of an intercostal artery or spleen/liver puncture, pneumothorax, empyema, reexpansion pulmonary edema, malignant seeding of the thoracentesis tract, and adverse reactions to anesthetics used in the procedure. Pneumothorax complicates approximately 6% of thoracenteses but requires treatment with a chest tube drainage of the pleural space in less than 2% of cases. The use of needles larger than 20 gauge increases the risk of a pneumothorax complicating the thoracentesis. In addition, significant chronic obstructive or fibrotic lung disease increases the risk of a symptomatic pneumothorax complicating the thoracentesis.

Procedure

In patients with large, freely flowing effusions and no relative contraindications to thoracentesis, diagnostic thoracentesis can usually be performed safely, with the puncture site initially chosen based on the chest radiograph and located 1-2 rib interspaces below the level of dullness to percussion on physical examination. In other situations, ultrasonography or chest CT scanning should be used to guide thoracentesis. **Ultrasonography guidance at bedside significantly increases** the likelihood of obtaining pleural fluid and reduces the risk of pneumothorax. A postprocedure chest film may not be needed, but it is always a good practice to look for ultrasonic evidence of a pneumothorax. The presence of lung sliding would confirm the absence of a pneumothorax. **After the site is disinfected with chlorhexidine** (preferred) or povidone/iodine (no longer recommended) solution and sterile drapes are placed, anesthetize the skin, periosteum, and parietal pleura with 1% lidocaine through a 25-gauge needle. If pleural fluid is not obtained with the shorter 25-gauge needle, continue anesthetizing with a 1.5-inch, 22-gauge needle. For patients with larger amounts of subcutaneous tissue, a 3.5-inch, 22-gauge spinal needle with inner stylet removed can be used to anesthetize the deeper tissues and to aspirate pleural fluid. **Confirm the correct location for thoracentesis by aspirating pleural fluid** through the 25- or 22-gauge needle before introducing larger-bore thoracentesis needles or catheters. If pleural fluid is not easily aspirated, stop the procedure and use ultrasonography or chest CT scanning to guide thoracentesis. **While there is no consensus amount for a diagnostic thoracentesis**, a minimum of 20 mL would be enough for basic analysis and culture. Most of these procedures remove less than 100 mL of fluid. **When possible, patients should sit upright for thoracentesis**. Patients should not lean forward, because this causes pleural fluid to move to the anterior costophrenic space and increases the risk of puncture of the liver or spleen. For debilitated and ventilated patients who cannot sit upright, obtain pleural fluid by puncturing over the eighth rib at the midaxillary to posterior axillary line. To avoid puncturing liver or spleen, the needle should not be inserted below the ninth rib. In such patients, imaging may be required to guide thoracentesis. **Supplemental oxygen is often administered during thoracentesis** to offset hypoxemia produced by changes in ventilation-perfusion relationships as fluid is removed and to facilitate reabsorption of pleural air if pneumothorax complicates the procedure. **The frequency of complications from thoracentesis may be lower** when a more experienced clinician performs the procedure and when ultrasonographic guidance is used. Consequently, a skilled and experienced clinician should perform thoracentesis in patients who have a higher risk of complications or relative contraindications for thoracentesis and in patients who cannot sit upright. **Postprocedure expiratory chest radiographs to exclude pneumothorax** are not needed in asymptomatic patients after uncomplicated procedures (single needle

pass without aspiration of air). However, postprocedure inspiratory chest radiographs are recommended to establish a new baseline for patients likely to have recurrent symptomatic effusions.

Idiopathic Exudative Effusions

Despite evaluations with repeated diagnostic thoracenteses, approximately 20% of exudative effusions remain undiagnosed. Clues to the diagnosis that may have been overlooked include (1) occupational exposure to asbestos 10-20 years earlier, which may suggest benign asbestos effusion; (2) medication exposure to nitrofurantoin, amiodarone, or medications associated with a drug-induced lupus syndrome; and (3) hepatic hydrothorax unrecognized in a patient with minimal or undetectable ascites. **Among patients with undiagnosed pleural effusions after the primary evaluation**, those who meet all 6 of the following clinical parameters are predicted to have a benign course, and no further evaluation is necessary:

- Patients are clinically stable
- Patients do not have weight loss
- The results of the purified protein derivative (PPD) test, used in detecting tuberculous pleural effusion, are negative and the pleural adenosine deaminase (ADA) value, also used in diagnosing tuberculous pleural effusion, is less than 43 U/mL
- The patient does not have a fever
- The pleural fluid differential blood cell count has less than 95% lymphocytes
- The effusion occupies less than 50% of the hemithorax

For other patients with undiagnosed exudative effusions, approximately 20% have a specific etiology determined, including malignancy. For such patients, weigh the benefits and risks of pursuing a diagnostic strategy that will involve using progressively more invasive procedures, given the low likelihood of finding a curable etiology. Note the following:

- Bronchoscopy - Consider only if a patient has parenchymal abnormalities or hemoptysis
- Surgical approaches to the diagnosis of pleural effusions - Includes video-assisted thoracoscopy (pleuroscopy) and open thoracotomy, allows direct visualization and biopsy of the pleura for diagnosis of exudative effusions, which reveals an etiology in 92% of effusions that remain undiagnosed after a medical evaluation, with an operative mortality of less than 0.5%
- Medical thoracoscopy - Where available, may be diagnostic and therapeutic; complete drainage of the effusion and talc sclerosis can be performed at the time of the procedure

Note that in most medical centers, surgical exploration using thoracoscopy or thoracotomy entails the risks of general anesthesia and is probably warranted only in patients who are symptomatic and anxious for a (potentially incurable) diagnosis.

Biopsy

Pleural biopsy should be considered, only if TB or malignancy is suggested. Medical thoracoscopy with the patient under conscious sedation and local anesthesia has emerged as a diagnostic tool to directly visualize and take a biopsy specimen from the parietal pleura in cases of undiagnosed exudative effusions. As an alternative, closed-needle pleural biopsy is a blind technique that can be performed at the patient's bedside. **Medical thoracoscopy has a higher diagnostic yield for malignancy**. Closed-needle pleural biopsy findings aid in diagnosis of only 7-12% of malignant effusions when cytology findings alone are negative. However, the yield of closed-needle pleural biopsy (histology plus culture) is as high as thoracoscopy for tuberculous pleuritis and is a

useful alternative procedure for this diagnosis when available. A randomized comparison of medical thoracoscopy with CT scan-guided cutting-needle pleural biopsy (CT-CNPB), found no statistically significant difference in diagnostic sensitivity between these two approaches. The study included 124 patients with exudative pleural effusion who could not be diagnosed by cytologic analysis. These researchers recommended using CT-ANPB as the primary diagnostic procedure in patients with pleural thickening or lesions observed on CT scans, and using medical thoracoscopy in patients whose CT scans demonstrate only pleural fluid, as well as in those who may have benign pleural pathologies other than TB.

Pleural Effusion Treatment & Management

Approach Considerations

Transudative effusions are managed by treating the underlying medical disorder. However, regardless of whether transudative or exudative, large, refractory pleural effusions causing severe respiratory symptoms can be drained to provide symptomatic relief. The management of exudative effusions depends on the underlying etiology of the effusion. Pneumonia, malignancy, and TB cause most exudative pleural effusions, with the remainder typically deemed idiopathic. Complicated parapneumonic effusions and empyemas should be drained to prevent development of fibrosing pleuritis. Malignant effusions are usually drained to palliate symptoms and may require pleurodesis to prevent recurrence. Medications cause only a small proportion of all pleural effusions and are associated with exudative pleural effusions. However, early recognition of this iatrogenic cause of pleural effusion avoids

unnecessary additional diagnostic procedures and leads to definitive therapy, which is discontinuation of the medication. Implicated drugs include medications that cause drug-induced lupus syndrome (eg, procainamide, hydralazine, and quinidine), nitrofurantoin, dantrolene, methysergide, procarbazine, and methotrexate. A meta-analysis and systemic review of 19 observational studies determined that pleural effusion drainage in patients on mechanical ventilation is safe and appears to improve oxygenation. No data supported or refuted claims of beneficial effects on clinical outcomes, such as duration of ventilation or length of stay.

Parapneumonic effusions

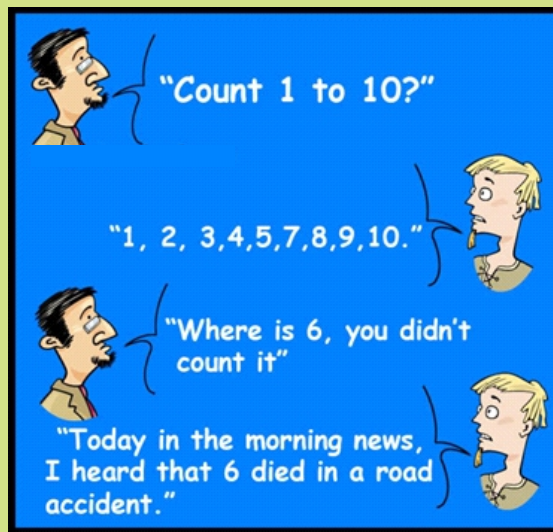
Of the common causes for exudative pleural effusions, parapneumonic effusions have the highest diagnostic priority. Even in the face of antibiotic therapy, infected pleural effusions can rapidly coagulate and organize to form fibrous peels that might require surgical decortication. Therefore, quickly assess pleural fluid characteristics predictive of a complicated course to identify parapneumonic effusions that require urgent tube drainage. These are observed more commonly in indolent anaerobic pneumonias than in typical community-acquired pneumonia. Indications for urgent drainage of parapneumonic effusions include (1) frankly purulent fluid, (2) a pleural fluid pH of less than 7.0-7.1, (3) loculated effusions, and (4) bacteria on Gram stain or culture. Patients with parapneumonic effusions who do not meet the criteria for immediate tube drainage should improve clinically within one week with appropriate antibiotic treatment.

BOUQUET

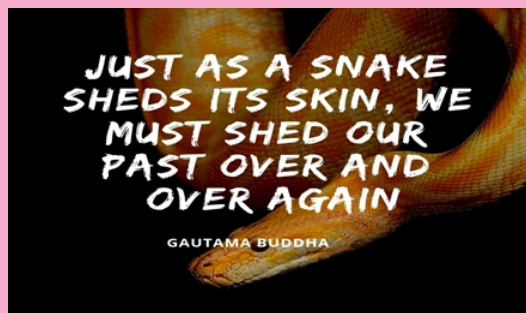
In Lighter Vein



If they had just called it "the stay at home challenge" and posted it on Facebook, the virus would be gone by now.



Wisdom Whispers



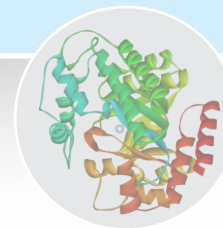
Brain Teasers

- ADA is also known as _____.
 - Adenosine Aminohydrolase
 - Adenosine Hydrolase
 - Adenosine Transaminase
 - Adenosine Catalase
- In how many forms does ADA exist?
 - Monomer
 - Dimer
 - Both of the above
 - None of the above
- In which forms does ADA exist?
 - Monomer
 - Dimer
 - Polymer
 - A & B
- How many Isoforms of ADA exist?
 - ADA 1
 - ADA 2
 - Both of the above
 - None of the above
- ADA is involved in Metabolism of _____.
 - Carbohydrates
 - Lipids
 - Purines
 - Proteins

ANSWER: 1: A: 2: C: 3: D: 4: C: 5: C

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ADENOSINE DEAMINASE



Serum

Pleural Fluid

Pericardial Fluid

Ascitic Fluid

CSF

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SURROGATE MARKER OF TUBERCULOSIS

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- Interprets ADA results in Serum, Plasma, CSF, Ascitic fluid, Pleural & Pericardial fluids.

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- Excellent reproducibility.

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