

# Tuberculosis

## **Section IV.**

Evaluation and Treatment  
of Extrapulmonary Tuberculosis

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## Evaluation and Treatment of Extrapulmonary Tuberculosis

The basic principles that underlie the treatment of pulmonary tuberculosis (TB) also apply to extrapulmonary forms of the disease. As a general rule, regimens that are adequate for treating pulmonary TB in adults and children are also effective for treating extrapulmonary disease since, in most cases, the mycobacterial burden is considerably smaller in this form. However, for certain forms of extrapulmonary disease, such as central nervous system (CNS), disseminated and skeletal TB, the continuation phase of treatment is often prolonged.

This section covers special issues involved in diagnosing and managing certain extrapulmonary forms of TB. The topics herein are typical of those health care providers usually face when diagnosing TB and treating patients in the acute hospitalization phase, before they arrive in the chest center for follow-up care. Therefore, many of these procedures and decisions may not be those made by physicians in the Bureau of Tuberculosis Control (BTBC) chest centers.

About 25% of child and adult TB cases have extrapulmonary manifestations, but as many as 50% of adults who are HIV infected may have extrapulmonary TB. TB meningitis and miliary TB are more common in young children and are associated with high rates of death and disability, particularly if the diagnosis is delayed. It is therefore important to consider these diagnoses in young children as early as possible, especially in children who have a history of contact with an adult with infectious TB.

Table IV-I on p. 72 details the evaluation of extrapulmonary TB in children and adults with suggested appropriate diagnostic procedures, and also contains suggested treatment regimens for various extrapulmonary forms of TB, including follow-up specimens that should be obtained. However, these are only general guidelines. Use additional references for more detail on managing extrapulmonary TB.

Although there are multiple studies showing that clinically confirmed or culture-negative pulmonary TB can be treated successfully in only 4 months, there is little data to suggest this length of treatment can be extrapolated to extrapulmonary TB. Short-course chemotherapy has been shown to be more effective than 18- to 24-month conventional therapy since the 1970s, yet there are few studies exploring treatment of less than 6 months for extrapulmonary TB.

A study has shown that genitourinary TB can be treated in 4 months and posits that, compared to pulmonary TB, there are far fewer organisms in renal than in pulmonary lesions, the kidneys have a very good blood supply, there are high concentrations of the drugs in urine and that drugs penetrate closed cavities in lethal concentrations. This argument, however, cannot be extrapolated to other forms of extrapulmonary TB.

Another small prospective study showed 85% success in treating 68 patients with pleural TB with a 4-month regimen consisting of 2 months of isoniazid, rifampin and pyrazinamide and 2 months of isoniazid and rifampin. Despite this, the BTBC still recommends 6 months treatment for pleural TB.

A recent article reviewed the current trends in chemotherapy for all forms of TB and asserted that treatment of TB in 3 or 4 months would have some significant practical advantages. The article cited research by the Tuberculosis Research Centre in Chennai, India, that showed a 100% favorable response at the end of a 3-month regimen; however, a 20% relapse rate occurred in the subsequent 21 months for patients who had smear-positive pulmonary TB. The study contains comment that while there have been fewer studies focused on extrapulmonary TB, evidence from several trials has shown that all forms of extrapulmonary TB, except meningitis, can be successfully treated in 6 months. A larger, long-term study is needed,

Table IV-1

## Evaluation of Extrapulmonary Tuberculosis in Adults and Children

Suspected site	Approach to diagnosis
Bone and joint TB	X-ray, CT, magnetic resonance imaging (MRI), arthrocentesis, synovial or bone biopsy
Disseminated or miliary TB	CXR and lumbar puncture (to test for meningitis). Biopsy of affected sites if possible.
Meningeal TB	CT, MRI and lumbar puncture
Miliary pattern on CXR	Induced sputum, bronchoscopy with bronchial washing and transbronchial biopsy, and gastric aspirates
Pericardial TB	Echocardiogram; pericardiocentesis for biochemical analysis (LDH, protein, glucose concentration and pH), cell count, AFB-smear and culture; or pericardial biopsy
Peripheral lymph nodes (especially cervical)	Fine needle aspiration or lymph node biopsy
Peritoneal TB	Abdominal ultrasound or CT; paracentesis for biochemical analysis (LDH, protein, glucose concentration and pH), cell count, AFB-smear and culture; or peritoneal biopsy
Pleural effusion	CXR; thoracentesis for biochemical analysis (LDH, protein, glucose concentration and pH), cell count, AFB-smear and culture; or pleural biopsy

Abbreviations: AFB=acid-fast bacilli, CT=computed tomography, CXR=chest X-ray, LDH= lactate dehydrogenase test, MRI=magnetic resonance imaging, pH=acid loading test, TB=tuberculosis

however, before treatment recommendations can be changed.

When considering length of treatment for extrapulmonary TB, based on the lack of successful research on 4-month regimens, we cannot endorse the shortening of chemotherapy for extrapulmonary TB to anything less than 6 months. In several forms of TB, corticosteroids have been shown to be useful. (see Table IV-2)

### Lymphatic Tuberculosis

Lymphatic TB most commonly affects cervical or supraclavicular lymph nodes, although any lymph node can be involved. However, in children, cervical involvement is most commonly due to non-tuberculous mycobacteria.

#### Diagnosis

The diagnosis can be established by the culture of *Mycobacterium tuberculosis* (*M. tb*) from lymph node biopsy or aspirate. The presence of acid-fast bacilli (AFB) in tissue (seen in slightly over half

of cases) or aspirate, or pathologic evidence of caseating granuloma, is consistent with TB or non-tuberculous mycobacterial infection. Aspiration is also useful, especially if the node(s) demonstrate fluctuance. Individuals suspected of having tuberculous lymphadenitis should be referred for biopsy or aspiration.

#### Treatment

Lymphatic TB should be treated according to the regimens for pulmonary TB. Even if lymph node excision is complete, chemotherapy is indicated. The patient's clinical response should be carefully considered in determining the length of treatment; decisions about the duration of treatment should be individualized. Most patients respond well to the standard 6-month regimen.

### Pleural Tuberculosis

Small pleural effusions are common as part of primary pulmonary complex in children; larger TB pleural effusions usually occur in children older

than 2 years of age. The patient presents with fairly sudden onset of dyspnea, fever and chest pain, with dullness to percussion and decreased breath sounds (unilaterally or bilaterally) usually present on physical examination. The test for TB infection is often positive.

### Diagnosis

Thoracentesis should be done and the pleural fluid sent for white blood count and differential, and measures such as pH, LDH, protein and glucose. A lymphocytic exudate with low glucose typically occurs in TB. AFB stains of the pleural fluid sediment obtained by pleurocentesis are seldom positive (25% to 33% of cases).

A transthoracic needle pleural biopsy is used routinely to establish or support a diagnosis of TB pleuritis based on the presence of caseating granuloma with or without AFB on tissue stains. The combined yield of AFB stains of pleural fluid and biopsy tissue, coupled with mycobacterial culture of pleural fluid and biopsy tissue, is greater than 90%. In nearly 100% of cases, a small open pleural biopsy (usually achieved with video-assisted thoroscopic surgery) is diagnostic of pleural TB. Although a chest X-ray (CXR) may show no visible parenchymal lesions, cultures of sputum or gastric fluid are positive in 25% to 33% of cases. Therefore, 3 sputa for AFB smear and culture should be obtained on all patients with pleural TB.

An individual suspected of having TB pleuritis treated in a BTBC chest center must be referred to an appropriate provider for diagnostic evaluation.

### Treatment

Pleural TB should be treated according to a regimen for pulmonary TB. While steroids may decrease pain and hasten the resolution of pleural effusion, we do not recommend their use routinely. If used, a dose of 20 mg to 40 mg per day of prednisone, tapered over 4 to 8 weeks, may be appropriate.

## Pericardial Tuberculosis

Pericardial TB is much more common in persons infected with HIV. The onset may be subtle (characterized by cardiovascular consequences of constrictive effusion) or abrupt (fever and precordial pain).

### Diagnosis

Fluid from pericardiocentesis is similar to fluid from tuberculous pleural effusion with low glucose and pleocytosis. Positive smears for AFB are not common, and cultures are positive in only 25% to 50% of cases. Some authorities do not advocate pericardiocentesis as part of the diagnostic work-up due to the risks of the procedure and the limited benefit in terms of immediate treatment. Some physicians advocate primary surgical intervention with a pericardial "window" and biopsy in every case of suspected TB pericarditis.

The BTBC recommends pericardiocentesis, or surgical biopsy, to obtain culture and susceptibility data unless there is a positive culture from another source, or the patient urgently requires surgical intervention.

### Treatment

Pericardial TB should be treated according to a regimen for pulmonary TB.

Corticosteroids are generally recommended as several studies have shown they improve prognosis. If used, begin prednisone at 60 mg daily and gradually decrease the dosage over a period of 6 to 12 weeks as the effusion subsides. The dose for children is 2 mg/kg of body weight per day to a maximum of 60 mg per day, or its equivalent for 4 to 6 weeks followed by tapering. The dose should be tapered as for adults, and the medication should only be given if the patient is on appropriate anti-tuberculosis therapy. Pericardiectomy is indicated if there is chronic constriction with adverse hemodynamic consequences.

## Central Nervous System Tuberculosis

### Diagnosis of Meningeal Tuberculosis

Meningeal TB in children and adults has an insidious presentation; it may present as personality changes, irritability and anorexia, then headache, neck stiffness, drowsiness and cranial nerve palsies, and may later progress to coma. Therefore, a detailed history of symptoms should be taken from the patient and family members as the patient may not be able to provide adequate details. The outcome

depends significantly on the stage of disease at presentation (Stage III has the worse outcome):

- Stage I: Isolated meningeal disease without focal neurologic abnormalities
- Stage II: Isolated parenchymal disease and neurologic abnormalities without altered consciousness
- Stage III: Parenchymal and meningeal disease with stupor or obtundation

The key diagnostic procedure is examination of the cerebral spinal fluid (CSF). Characteristic CSF findings are:

- Pleocytosis (65% of cases have white blood cell counts of 100 - 500) with lymphocytic predominance (in 73% of cases in one series)
- Predominance of polymorphonuclear cells is often seen
- Elevated protein and low glucose (common)

These measures may be consistent with TB meningitis but are non-specific. Diagnosis may be supported by positive microscopy (AFB smear) or nucleic acid amplification (NAA) tests, but may not be excluded if these measures are negative.

- AFB are seen in up to 37% of cases on initial examination, and in up to 87% of cases when the fluid from 4 serial spinal taps has been examined. In one recent study, bacteriological diagnosis was made in 107 of 132 (81%) of cases, based on AFB smear or positive culture from CSF collected during a single lumbar puncture. Large volume of CSF (greater than 5 ml) was associated with seeing or culturing *M. tb*.
  - NAA techniques such as polymerase chain reaction (PCR) are more sensitive than AFB smear but are not more sensitive than bacteriology in detecting cases prior to treatment; however, they may be positive and may be useful in cases where antituberculosis therapy has been initiated already.

The diagnosis of TB meningitis cannot be excluded by negative bacteriology and/or negative NAA if clinical criteria are highly suggestive.

## Treatment of Meningeal Tuberculosis

Empiric treatment should be started promptly while awaiting results of AFB smears and cultures. Drug-susceptible or culture-negative TB should be treated with isoniazid, rifampin, pyrazinamide and ethambutol in doses the same as those used for pulmonary TB for the first 2 months. This phase should be followed by a regimen of isoniazid and rifampin for 7 to 10 additional months in the continuation phase, as long as drug resistance is not suspected.

- Isoniazid, rifampin and pyrazinamide penetrate the blood-brain barrier efficiently. Ethambutol, the aminoglycosides and capreomycin penetrate only when meninges are inflamed. (For information on the penetration of anti-TB medications in the CNS, see p. 211, Appendix I-C.)

Because penetration of some drugs (e.g., rifampin and streptomycin) into the cerebrospinal fluid is poor, treatment regimens for TB meningitis and miliary TB will most likely benefit from the higher end of the recommended dose ranges. Some experts advocate the addition of pyrazinamide during the continuation phase as CSF concentrations of rifampin are low and pyrazinamide readily penetrates the CNS; however, there are no clinical trials to support this.

- Due to different degrees of drug penetration into the CNS, some experts recommend modifying the standard anti-TB treatment regimen for children. The World Health Organization recommended regimen in children is 2 months of isoniazid, rifampin, pyrazinamide and streptomycin rather than ethambutol. The American Academy of Pediatrics recommends ethionamide as the fourth drug, rather than ethambutol, as it crosses both healthy and inflamed meninges, and is well-tolerated by children.
- Corticosteroids improve survival in children with severe disease and probably reduce neurologic morbidity as well. Many experts advocate the use of corticosteroids in all patients with CNS TB, particularly those with a decreased level of consciousness. Corticosteroids should only be given if the patient is on appropriate antituberculosis therapy. Dexamethasone or prednisone can be given in the following manner:

- **Dexamethasone.** The recommended regimen is an initial dose of 8 mg/day for children weighing less than 25 kg and 12 mg/day for children weighing 25 kg or more and for adults. The initial dose is given for 3 weeks and then decreased gradually during the following 3 weeks.
- **Prednisone.** In children, 2 mg/kg daily for 4 weeks and the dose should be gradually tapered over 1 to 2 weeks before stopping. The dosage of prednisone can be increased to 4 mg/kg daily (maximum 60 mg/day) in the case of seriously ill children, as rifampin decreases corticosteroid concentration. In adults, depending on the site, corticosteroid dosages equivalent to 40-60 mg/day of prednisone are recommended with gradual tapering over 4 to 6 weeks.
- Based on clinical experience, some individuals require a prolonged course of treatment with corticosteroids.
- All children with suspected or confirmed TB meningitis or miliary TB should be hospitalized until their clinical status has stabilized. These patients are at high risk of long-term disability and therefore benefit from specialist care.
- Treatment of drug-resistant TB meningitis is complicated by the pharmacokinetics of antituberculous drugs in the CNS, and intrinsic activity of the drugs. Multidrug-resistant TB meningitis confers a dismal outcome in most cases. In one series, it was associated with an in-hospital case fatality rate of 57% and in another, overall mortality of 100%. Treatment of drug-resistant TB meningitis should be guided by the CNS penetration of first- and second-line agents listed on p. 211, Appendix I-C. Expert consultation should be sought.
- Patients already on appropriate therapy for meningeal, pulmonary or miliary TB may paradoxically develop intracranial tuberculomas on therapy, likely related to immune reconstitution. Tapering of steroids in patients on antituberculous therapy has been associated with the development of intracranial tuberculomas. A recent review described more than 50 cases since 1974 of intracranial tuberculomas progressing or developing while on therapy, most occurring within the first 3 months. Another case series described 22 cases of adult tuberculomas, 8 coexisting with TB meningitis on admission and 14 that developed it while on therapy, mostly within the first 6 weeks. This paradoxical response is generally believed to be due to a recovery of immune function as active TB is controlled, and may be related to a local hypersensitivity response to mycobacterial proteins (see p. 56).
- Usually tuberculomas appear as ring-enhancing lesions on imaging studies. When tuberculomas are identified during the course of treatment, antituberculous therapy generally does not need to be changed, as the lesions reflect enhanced immune response rather than treatment failure. Most authorities recommend treating intracranial tuberculomas for a minimum of 12 months, or longer if they have developed during therapy.
- Most experts use corticosteroids in all symptomatic cases, though there are no randomized trials assessing treatment of tuberculomas with steroids. If corticosteroids are used, dosage and tapering are as above for TB meningitis in preceding section.

### Tuberculoma

- Patients with intracranial tuberculoma(s) may present with cranial nerve deficits, altered mental status, hemiparesis, seizures or headache; concomitant meningitis may be present.
- Diagnosis depends on computed tomography (CT) or magnetic resonance imaging (MRI) findings and biopsy of the lesion unless there is a contraindication.

## Disseminated Tuberculosis

Disseminated TB is a result of the hematogenous spread of *M. tb* with clinical manifestation of active disease at 2 or more non-contiguous sites and can manifest as discrete involvement of affected sites or as miliary tuberculosis (i.e., when the appearance of tissue within affected organs is similar to millet seeds). If a miliary pattern is noted on the CXR, the radiograph can be described as miliary in the patient's medical record and the patient should be designated as having miliary or disseminated disease. However, miliary should NOT be used to

describe TB involving 2 or more discrete sites, despite the use of these 2 terms interchangeably in the literature.

### Diagnosis

Disseminated TB is usually suspected because of the presence of miliary infiltrates on a CXR or involvement of 2 or more sites. Transbronchial biopsy is the highest-yielding procedure for obtaining tissue in miliary TB. In other instances, tissue biopsy of other organs, such as the lymph nodes, liver or bone marrow can confirm the diagnosis.

In children, disseminated TB disease is more common under the age of 5 and affects many organs, including the brain and bone marrow. Enlargement of the spleen and liver is common and the test for TB infection is often negative. Sputum smears and culture are also usually negative, despite the extensive miliary appearance on CXR. CSF should be evaluated if miliary TB is suspected (see p. 72, Table IV-1 for further directed evaluation). Disseminated TB has a high risk (60%–70%) of meningeal involvement and should therefore be managed similarly to TB meningitis; many experts recommend that all children with disseminated TB (or suspected of having disseminated TB) undergo a lumbar puncture to test for the presence of meningitis.

In many patients with AIDS with hematogenous dissemination, urine or blood cultures obtained by appropriate techniques yield *M. tb*. These patients should be assumed to have disseminated TB, even in the absence of radiologically or pathologically demonstrated TB lesions in other organs.

### Treatment

A 6-month regimen with standard anti-tuberculosis therapy is recommended for treatment of tuberculosis at multiple sites and for miliary tuberculosis in adults. The American Academy of Pediatrics recommends 9 months of treatment for children with disseminated TB. Corticosteroids may be useful for treating respiratory failure due to disseminated tuberculosis and meningitis. (See p. 79, Table IV-2.)

## Skeletal Tuberculosis

Skeletal TB (TB of the bones and joints) usually occurs in the weight-bearing joints; Pott's disease (TB of the spine) is the most common form, followed by TB of the hip and knee. The typical presenting symptoms are pain and difficulty with locomotion. In children, it usually develops in the first year after infection.

### Diagnosis

Skeletal TB is diagnosed by X-ray or CT scan of the involved joint, followed by specimen collection and culture. A tissue biopsy is necessary to confirm the diagnosis and obtain cultures for susceptibility testing. All individuals suspected of having bone or joint TB should be referred for appropriate radiologic studies and biopsy or aspiration.

### Treatment

Skeletal TB should be treated according to the regimen for pulmonary TB, although some authorities advise 6 to 9 months of treatment for all individuals, regardless of immune status. Most patients with skeletal TB who are treated in a BTBC chest center should also be followed by an orthopedist.

## Genitourinary Tuberculosis

### Diagnosis

Approximately 90% of patients with genitourinary TB have abnormal urinalysis results (usually gross or microscopic hematuria and/or pyuria). Also, in 90% of patients, *M. tb* can be cultured from 1 of 3 morning urine specimens. Diagnosis of male or female genital tract TB is usually based on biopsies and cultures of affected sites.

### Treatment

In general, regimens for treating pulmonary TB are highly successful for treating renal TB. Surgery is indicated only for intractable pain, persistent non-tuberculous infection from obstruction, serious, persistent hematuria or a nonfunctioning or poorly functioning kidney. All patients with renal TB who are treated in a BTBC chest center should be followed by a urologist.

TB of the male or female genitourinary tract responds well to standard chemotherapy, and surgery is necessary only for residual large tubo-ovarian abscesses. Infertility is one of the complications of tuberculosis of the female genital tract. The patient should be referred to a gynecologist if necessary.

## Gastrointestinal Tuberculosis

TB can affect any part of the gastrointestinal tract, from the tongue or oropharynx to the anus. The cecum is the most common gastrointestinal site. Evidence of coexistent pulmonary TB is present in about 25% to 50% of cases. The most common symptoms are anorexia, early satiety, abdominal pain or symptoms of intestinal obstruction.

### Diagnosis

Many patients with gastrointestinal TB have a stool culture that is positive for *M. tb*; it is important to determine whether the positive culture represents organisms from a gastrointestinal source or organisms that were swallowed from a pulmonary source.

In individuals with confirmed pulmonary TB and no evidence of intestinal obstruction, further evaluation is usually unnecessary to seek the gastrointestinal source since treatment is the same for pulmonary and gastrointestinal TB.

If there is no evidence of pulmonary TB, an upper gastrointestinal series with small-bowel follow-through can detect ulcerative lesions. If there are no lesions in the upper gastrointestinal tract, the lower gastrointestinal tract can be evaluated by air-contrast barium enema. Alternatively, endoscopy and/or colonoscopy can be used to visualize the lumen and obtain specimens for AFB and other cultures.

Most patients will have had a CT scan of the abdomen and pelvis. Common, but not specific, findings are lymphadenopathy, especially in the retroperitoneum, and thickening of the bowel wall with associated lymphadenopathy. The presence of enlarged lymph nodes with hypodense centers is suggestive of necrosis, especially common in patients with HIV.

AFB in stool specimens has no diagnostic significance since water and certain foods are often contaminated by environmental saprophytic mycobacteria that transverse the gastrointestinal tract and are excreted.

Carbolfuchsin, the standard stain for cyclospora in stool specimens, is also a basic stain for mycobacteria. Reports of stool specimens examined for cyclospora and positive for AFB should be assumed to be saprophytes unless a stool culture yields *M. tb*.

### Treatment

Gastrointestinal TB should be treated according to a regimen for pulmonary TB. Many patients with gastrointestinal TB treated in a BTBC chest center should have follow-up with a gastroenterologist or surgeon as appropriate.

## Peritoneal Tuberculosis

### Diagnosis

Peritoneal TB usually presents with 1 of 2 manifestations (1) the presence of ascites, which leads to abdominal pain and distention, with or without gastrointestinal symptoms; or (2) abdominal pain, with or without symptoms suggesting intestinal obstruction. There may be associated systemic symptoms, such as fever, night sweats, fatigue and weight loss. Paracentesis may reveal ascitic fluid with a lymphocytic pleocytosis and elevated protein and low glucose. The diagnosis of tuberculous ascites is made usually by culture of the ascitic fluid or peritoneal or open biopsy; the diagnosis of "dry" tuberculous peritonitis is usually made by laparotomy and biopsy that reveals caseating granulomas, with or without tissue stains positive for AFB.

### Treatment

Peritoneal TB should be treated with the same regimen as pulmonary TB. Anyone suspected of having peritoneal TB should be referred to an appropriate gastrointestinal center or hospital for further evaluation; if possible, treatment should not be initiated without such an evaluation.

## Cutaneous Tuberculosis

Cutaneous tuberculosis is rare and can be divided into 2 broad categories: (1) cutaneous TB and (2) tuberculids.

Cutaneous TB is *M. tb* infection of the skin that causes disease, and tuberculids are cutaneous manifestations of extracutaneous TB. Cutaneous tuberculosis can be exogenous, with chancres and warty tuberculosis caused by infections of



the skin from outside sources, or endogenous, due to hematogenous or lymphatic spread that may be confused with the cutaneous lesions seen in systemic diseases such as sarcoidosis. Autoinoculation from underlying infected tissues or secretions can also occur. If there is aerosolization of secretions from a skin lesion, the patient should be isolated as per protocol (see p. 122).

Staff who work in mycobacteria labs or who work with autopsy specimens occasionally receive an inoculum of tuberculosis, which can lead to a condition called “Prosecutor’s Wart.” If the individual already has a positive test for TB infection (TTBI) prior to exposure, the individual should be given isoniazid prophylaxis for 9 months; if TTBI negative before exposure, a repeat TTBI should be performed and isoniazid prophylaxis started. If the repeat TTBI at 8 weeks is negative, isoniazid can be discontinued and if positive, isoniazid should be continued for 9 months total.

If active disease develops at the site, it should be treated according to a regimen for pulmonary TB. If the inoculum is known to be due to drug-resistant organisms, treatment should be tailored to the resistance pattern of the organism.

### Diagnosis

Diagnosis of skin lesions is usually made by biopsy of the lesion, which is sent for AFB smear and culture, and pathologic analysis.

### Treatment

Treatment of cutaneous TB is the same as for pulmonary TB.

## Disease Due to Intravesical Bacille Calmette-Guérin for Bladder Cancer

Bacille Calmette-Guérin (BCG) is a live attenuated strain of *Mycobacterium bovis* (*M. bovis*) which is used as immunotherapy for superficial transitional cell carcinoma of the bladder. The mechanism of action appears to be modulation of the immune response in the bladder, with localized inflammation induced by BCG leading to destruction of cancer cells. Occasionally, treatment for bladder cancer is complicated by disseminated or localized BCG-related disease.

A case of *M. bovis* BCG is not counted as a case of TB by CDC criteria.

### Diagnosis

BCG-related disease may present early (usually within 12 weeks) or late (usually more than 1 year) following initiation of intravesical therapy.

- Two mechanisms of disease have been postulated—hematogenous dissemination of infection and hypersensitivity reaction. It is likely that both play a role in pathogenesis.
- Early disease may be associated with fever, malaise, chills, sweats, weight loss, shortness of breath and arthralgias. The clinical picture is often consistent with disseminated disease with pneumonitis and/or hepatitis; however, disease may be localized. The diagnosis is supported by the finding of noncaseating granulomas on biopsy of affected organs, and while culture may be positive for *M. bovis* BCG, negative culture does not exclude the diagnosis.
- Late disease is more likely to present locally in the genitourinary tract without associated generalized symptoms of fever, malaise and weight loss, and is the result of reactivation following initial immunologic control. Biopsy uniformly yields noncaseating granulomas. Culture may or may not be positive for *M. bovis*.
- The individual should be tested for TB infection and sputa obtained for AFB smear and culture, as the patient will have an abnormal CXR. Bronchoscopy with biopsy may be indicated. Molecular techniques (genotyping) distinguish *M. bovis* BCG from *M. tb*.

### Treatment

No clinical trials have assessed treatment for disease related to intravesical BCG, but most experts recommend treatment for early- and late-presenting disease with isoniazid and rifampin for 9 months (all *M. bovis* strains, including *M. bovis* BCG, are uniformly resistant to pyrazinamide). Some BCG strains are also resistant to isoniazid. Therefore, susceptibility testing should still be done to guide treatment.

Corticosteroids have been used to treat pneumonitis associated with BCG disease; some experts think these drugs contribute to rapid resolution of symptoms.

Table IV-2

## Guidelines for Adjunctive Use of Corticosteroids for Extrapulmonary Tuberculosis\*§

Type	Length of TB Therapy (mo.)	Corticosteroid Use
Lymphatic	6	Not recommended
Pericardial	6	Strongly recommended
Pleural	6	Not recommended
CNS (including meningitis)	9-12	Strongly recommended
Disseminated	6	Not recommended (unless meningeal or pericardial involvement, or respiratory failure present)
Skeletal	6-9	Not recommended
Genitourinary	6	Not recommended
Abdominal	6	Not recommended
Peritoneal	6	Not recommended

\* Adapted from: American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Treatment of Tuberculosis. *Am J Respir Crit Care Med.* 2003; 167: 603-662.

§ See text for recommendation of steroid dosage and treatment.

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