

Canadian Tuberculosis Standards

7th Edition

Chapter 7: Nonrespiratory Tuberculosis



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CHAPTER 7

NONRESPIRATORY TUBERCULOSIS

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KEY MESSAGES/POINTS

EPIDEMIOLOGY

- Nonrespiratory tuberculosis accounted for 25% of cases of tuberculosis (TB) in Canada in 2010.
- Isolated nonrespiratory TB is more commonly seen in females and foreign-born people.
- Disseminated disease (concurrent involvement of at least two non-contiguous organ sites of the body or the involvement of the blood or bone marrow) is associated with immune-deficiency.

DIAGNOSIS

- Diagnosis of nonrespiratory TB often requires biopsy of the affected organ, and samples must be sent for acid-fast bacteria (AFB) smear and culture.
- All suspected cases of nonrespiratory TB should be assessed for concomitant respiratory TB to determine whether the case is infectious and to assist with diagnosis.

TREATMENT

- In life-threatening nonrespiratory TB disease (meningitis, miliary, pericardial) it is suggested that empiric treatment be commenced while appropriate diagnostic samples are being obtained.
- Six months of standard anti-tuberculous medical therapy is considered adequate for most forms of nonrespiratory TB.
- Given the severity of disease in disseminated and meningeal TB, and the lack of randomized controlled studies comparing different treatment durations, treatment is commonly extended to 12 months.
- Adjuvant corticosteroids are recommended in meningeal TB and pericardial TB.

DEFINITION

The terms non-respiratory TB and extra-pulmonary TB are often used interchangeably. In Canada, extra-pulmonary TB refers to everything but pulmonary TB (TB of the lungs and conducting airways, and includes tuberculous fibrosis of the lung, tuberculous bronchiectasis, tuberculous pneumonia and tuberculous pneumothorax, isolated tracheal or bronchial TB and tuberculous laryngitis), whereas respiratory TB includes pulmonary TB, plus TB of the pleura, the intrathoracic or mediastinal lymph nodes, nasopharynx, nose or sinuses. Nonrespiratory TB, reviewed in this chapter, refers to all other disease sites not part of respiratory TB.¹

When comparing data among countries and reviewing the literature it is important to recognize the distinction between respiratory and nonrespiratory TB (as listed above), and pulmonary (disease limited to the lung parenchyma) and extrapulmonary TB.¹⁻⁴

This chapter will review the epidemiology, diagnosis and treatment of nonrespiratory TB disease as defined in Canada.

EPIDEMIOLOGY

Canadian data from the early 1970s indicated that approximately 17% of all TB cases involved primarily a nonrespiratory site.^{5,6} The genitourinary system and lymph nodes were the most common nonrespiratory sites of involvement. Both sites of disease were more common in the foreign-born: genitourinary TB was more common among those born in Europe and TB lymphadenitis among those born in Asia.⁷

More recent US data have shown young age and female sex to be independent risk factors for extrapulmonary TB.^{8,9} It is important to note that any cause of significant immune suppression (e.g. HIV, tumour necrosis factor (TNF) alpha inhibitors, end-stage renal disease) has been shown to predispose to disseminated TB.^{2,10-13}

In 2010, 25% of TB cases in Canada were nonrespiratory (Table 1), of which 50% were in the superficial lymph nodes.¹⁴

The number of reported cases of respiratory TB in Canada has decreased steadily since the 1980s, whereas the number of nonrespiratory cases decreased by a lesser extent. As a result, the proportion of total cases that were nonrespiratory rose.² Similar trends have been reported in the United States.¹¹ The smaller decline in nonrespiratory cases over recent years is not fully understood. Part of the explanation may be the increasing proportion of TB cases in Canada that are foreign-born, reflecting the shift in immigration from countries with low TB incidence (Western Europe) to those with high TB incidence (Africa, Asia, Central and South America, Eastern Europe).¹⁵ Foreign-born people are significantly more likely to have nonrespiratory than respiratory TB compared with Canadian-born people (Table 1).¹⁴ This may reflect the fact that respiratory, and not nonrespiratory, disease is actively screened for in new immigrants to Canada. Another possibility is the impact of HIV infection on TB morbidity. The incidence of HIV-TB coinfection is higher in certain foreign-born cohorts than among Canadian-born individuals.^{16,17} TB patients with HIV infection are more likely to have nonrespiratory TB alone or concurrent with respiratory TB.¹⁰⁻¹³

Table 1. Anatomic site of disease and population groups of patients with TB, Canada 2010

Disease site	Aboriginal*		Canadian-born (other)		Foreign-born		Unknown		Total	
	N	%	N	%	N	%	N	%	N	%
Respiratory [†]	270	81.8	144	78.7	660	63.6	14	53.7	1,088	69.0
Nonrespiratory	36	10.9	33	18.0	310	29.9	10	38.4	389	24.7
Both	24	7.3	6	3.3	68	6.6	2	7.7	100	6.3
TOTAL	330	100	183	100	1038	100	26	100	1,577	100

*Includes Status and Non-Status Indians, Métis and Inuit.

[†]Includes primary, pulmonary, pleural and "other" respiratory TB.

DIAGNOSTIC CONSIDERATIONS

A high index of suspicion is paramount to the rapid diagnosis of nonrespiratory TB. Any delay in diagnosis could increase the risk of morbidity and mortality for the at-risk patient.¹⁸ Delays in diagnosis of nonrespiratory TB are common, especially when it is present in unusual sites. Symptoms may be nonspecific (e.g. fever, night sweats, weight loss), or an organ-specific presentation may not be considered to be related to TB in the presence of a normal chest radiograph and negative sputum assessment for AFB. When evaluating at-risk patients with fever of unknown origin and site-specific signs and symptoms or patients with biopsy-proven granulomatous inflammation, appropriate steps should be taken to confirm the diagnosis of TB, including repeat sampling if mycobacterial cultures were not obtained.

Whenever practical, every effort should be made to obtain clinical samples for both mycobacteriologic (AFB smear and culture) and histopathologic tests.^{7,19,20} Drug susceptibility testing can only proceed with a viable culture, the results of which can have important treatment implications.^{7,19,20}

(Strong recommendation, based on strong evidence)

This point cannot be overemphasized: with the rising incidence of resistant *M. tuberculosis*, especially in the foreign-born, it is difficult to provide appropriate treatment when mycobacterial cultures and drug susceptibility test results are not available. A positive tuberculin skin test result supports the diagnosis, but its absence does not rule out the diagnosis and should never be relied on to exclude TB.

The clinical specimens obtained for diagnostic purposes will depend upon the suspected anatomic site of involvement. In general, tissue biopsy yields positive culture results more often than fluid aspiration; both are superior to swabs (please see Table 2 for diagnostic yield estimates). Biopsy material for mycobacterial culture should be submitted fresh or in a small amount of sterile saline.^{19,20} Histopathologic examination requires the specimen to be placed in formalin, which destroys the mycobacteria and prevents further culture confirmation.^{19,20} Common histopathologic findings include necrotizing and non-necrotizing granulomatous inflammation, giant cells or epithelioid cells and may rarely demonstrate AFB (see Table 2). Loss of host immune function can result in histopathologic findings demonstrating greater suppurative response and less well-formed granulomas.⁸⁸ The utility of nucleic acid amplification (NAA) in nonrespiratory specimens remains incompletely defined. Its major advantage is a rapid diagnosis, generally within 48 hours, and its greatest promise is the early diagnosis of life-threatening disease such as meningeal TB.³⁵⁻³⁷ The World Health Organization has not recommended the use of automated polymerase chain reaction (PCR) tests for the diagnosis of nonrespiratory TB to date, but this is an area of active research and thus the recommendation may change in the future.^{21,89,90}

Every presumed case of nonrespiratory TB should be assessed for pulmonary TB. How infectious the possible case is depends upon respiratory involvement. Pulmonary involvement in patients with nonrespiratory TB disease can range from 10% to 50%, thus it may be possible to secure a diagnosis of TB with sputum assessment and avoid the need for more invasive sampling.²⁰

(Strong recommendation, based on strong evidence)

A diagnosis of nonrespiratory TB, as with all cases of respiratory TB, should prompt an HIV test.

Table 2. Sensitivity and Specificity of Diagnostic Tests in Non-Respiratory Tuberculosis, Low HIV-prevalence

Site	Specimen-Type	Culture		Direct Stain (ZN)		GeneXpert		Histopathology and/or cytology		Fluid ADA		CXRAY	Percentage with Active Pulmonary TB	References
		SN	SP	SN	SP	SN	SP	SN	SP	SN	SP			
TB Lymphadenitis	Sputum	0.05-0.14	0.04			nsr						14-42	5.0-15%	26,35-40, 185-191
	FNA	0.62-0.79	0.26-0.35	0.60-0.77	0.92-0.96	0.53-0.83		n/a	n/a					
	Exisional biopsy	0.71-0.88	0.35-0.53	nr	nr	0.85-1.00		n/a	n/a					
CNS-Meningitis	Sputum	0.24-0.29	0.02	nsr		nsr		n/a	n/a			30-50	22-24%	22,24,26,155,161-163,189-191
	CSF	0.40-0.80	0.05-0.20	0.29-0.85	0.98	n/a		n/a	0.79	0.91				
CNS-Tuberculoma	FNA			nsr		nsr		0.85-0.92	n/a	n/a				
	Exisional biopsy	0.8	0.33			nsr		1	n/a	n/a				
Abdominal TB	Sputum	0.28-0.50	0.05	nsr		nsr								
	Feces	0.5	0	1	1	n/a								20,46,127,131-137
	Ascitic Fluid	0.20-0.80	0.0-0.06	0.05-0.57	0.99				0.95	0.93		50-64% in colonic; 38% in peritoneal	28-50% for colonic; 21% for peritoneal	
	Peritoneal Biopsy	0.38-0.92	0.05-0.20	nsr		0.9								
	Colon Biopsy	0.36-0.40	0.03-0.14			0.3								
	Urine	0.80-0.90	0.15-0.30	0.67-0.85	1	0.88								
GUTB - Renal	FNA/Biopsy	1	0.44	Nsr										
GUTB - Scrotal	Urine	0.63-0.93	0.24	0.67-0.85	1	0.95						32-45	13-53% for renal TB; 3% for female genital tract; 25% male genital tract	20,26,55,58,64-75,79-83,189-191
	Biopsy	0.8	0.25-0.75											
GUTB - Female Tract	Menstrual Fluid	0.06	0.05			Nsr								
	Endometrial Biopsy	0.08	0.05											
	Surgical Biopsy	0.08-0.11	0.05			0.05-0.12								
Bone TB	FNA/Bone	0.50-0.83	0.30-0.36	0.5	1	0.55-0.89						7	7%	20,46,107-109,114-116,189-191
	Synovial Fluid	0.64-0.79	0.19	0.71	1	n/a			n/a	n/a				
	FNA Paraspinal Fluid	0.9	nr	0.8	1	n/a								
Pericardial TB	Sputum	0.10-0.11							n/a	n/a				
	Pericardial Fluid	0.25-0.77	0.01	nsr	nsr				0.88-0.94	0.68-0.89		30	10-11%	20,170-174,192-194
	Pericardial Biopsy		0.04						0.34-0.70	n/a				
Disseminated TB	Sputum	0.53-0.90	0.31-0.37						n/a					
	Bronchial Wash	0.07-0.27	0.20-0.55											
	Lung biopsy	0.42-0.54	0.25-0.43											
	Liver biopsy	0.33-0.50	0.4	nsr	nsr	0.63			n/a	n/a		90%	n/a	20,90-94
	Bone Marrow	0.21-0.25	0.25			0.88								
Urine	0.33-0.67	0-0.18			0.67			n/a						

ZN= Ziehl-Neelsen, ADA = adenosine deaminase, CXRAY = chest radiography, SN = sensitivity, SP = specificity, FNA = fine-needle aspiration, nsr = no significant results, CNS = central nervous system, CSF = cerebrospinal fluid, GU TB = genitourinary TB

CLINICAL PRESENTATIONS

PERIPHERAL TB LYMPHADENITIS

Almost all forms of TB involve regional lymphatics and nodes. Intrathoracic lymph nodes are commonly involved in primary disease, in advanced pulmonary disease and in patients with HIV/AIDS. Intrathoracic nodes may be the major site of TB lymphadenitis seen in TB patients, but this section will focus on extrathoracic lymph nodes and specifically peripheral TB lymphadenitis. Peripheral TB lymphadenitis accounted for 12% of all cases of TB in Canada in 2010 (Table 3), and cervical lymph node TB is the most commonly affected nonrespiratory site.¹⁴

Table 3. Number of TB cases and incidence per 100,000 population by main diagnostic site, Canada 2010

Disease site	Cases		Incidence per 100,000
	<i>n</i>	(%)	population
Respiratory	1,088	(70.0)	3.2
Nonrespiratory	389	(24.7)	1.1
Peripheral lymph nodes	196	(12.4)	0.50
Miliary/disseminated	16	(1.0)	0.04
Meninges/central nervous system	22	(1.4)	0.06
Abdominal	39	(2.5)	0.1
Bones and joints	39	(2.5)	0.1
Genitourinary	24	(1.5)	0.07
Other*	53	(3.4)	0.16
Both	100	(6.3)	0.19
Total	1,577	100	4.64

*Includes 8 cases with more than one nonrespiratory site identified.

Tuberculous involvement of the lymph glands can be secondary to infection from *M. tuberculosis* as well as other nontuberculous mycobacteria.⁹¹ Nontuberculous mycobacteria (NTM) are most commonly isolated from the cervical lymph nodes and submandibular glands of young (<5 years) Caucasian children.⁹² Peripheral TB lymphadenitis has been identified at the anterior and posterior triangles of the neck, supraclavicular and axillary regions, as well as a variety of other nodal sites (Table 2).^{10,14,93} Presentation can be at a single nodal site or in multiple sites. A study of TB lymphadenitis in Manitoba found that 18% of cases also had a concurrent diagnosis of TB elsewhere in the body.⁹³ In general, the disease is most often indolent, and the patient usually presents with an isolated, unilateral, nontender neck mass. The term “scrofula” has been used historically to describe tuberculous involvement of a cervical lymph node with sinus tract formation or ulceration of the overlying skin. Non-nodal symptoms are rare except in individuals infected with HIV/AIDS.^{11,12,17} Peripheral lymphadenitis is particularly common among immigrants to Canada from Asian countries such as China, Viet Nam and the Philippines.^{93,94} Among these immigrants, young women are especially prone to isolated lymph node involvement.^{93,95} High rates of tuberculous lymphadenitis in the foreign-born are well documented in high-income countries.^{17,95-97} In Manitoba, the highest incidence of peripheral lymphadenitis has been reported among older Aboriginal women.⁹³ The reasons for this age-, sex- and ethnicity-related organotropism are unknown.

Fine-needle aspiration (FNA) biopsy of affected lymph nodes is a useful initial procedure with a reported sensitivity of 77%, specificity of 93% and diagnostic accuracy of 62% (see Table 2).^{22-27,98,99} If it is non-diagnostic, the highest-yield procedure is an excisional lymph node biopsy, which has a sensitivity of 80%. Incisional biopsies are discouraged because of the risk of sinus tract formation at the biopsy site. Swabs are discouraged because of the limited material obtained and because the hydrophobic nature of the mycobacterial cell wall inhibits the transfer of organisms from the swab to the culture media.¹⁰⁰

As stressed earlier, specimens must be submitted for both mycobacteriologic and histopathologic analysis. Differentiation of *M. tuberculosis* from the *M. avium* complex (MAC) is important, as treatment of the two conditions is different. *M. tuberculosis* of the superficial lymph nodes should be treated with anti-tuberculous medication, whereas treatment of MAC lymphadenitis may be cured with surgery alone, medical therapy alone or a combination of both approaches, or it may undergo spontaneous resolution without intervention (please see Chapter 11, Nontuberculous Mycobacteria, for details).^{101,102}

Medical treatment of tuberculous lymphadenitis results in the uneventful resolution of the condition in up to 80% of patients.³⁰ The suggested duration of treatment is 6 months.¹⁰³⁻¹⁰⁸

(Strong recommendation, based on strong evidence)

It is important to note that in up to 30% of patients, nodes can appear afresh or enlarge during treatment, possibly as an immune response, but this usually resolves without change in regime or additional therapy and should not be considered evidence of treatment failure.¹⁰⁹ At the end of treatment, 10% of patients may be left with residual nodes, and if after treatment the nodes enlarge or reappear afresh this is usually transient.¹⁰⁹ Such events do not necessarily imply relapse, but repeat FNA for mycobacterial culture can be performed to assess this possibility.¹¹⁰

Surgical procedures, other than diagnostic, should be reserved for the relief of discomfort caused by enlarged nodes or tense, fluctuant nodes.¹¹¹

GENITOURINARY TB

Genitourinary TB accounted for 1.5% of all cases of TB in Canada in 2010 (Table 3).¹⁴ The incidence of genitourinary TB has been decreasing over the last two decades in Canada.^{7,14} Urinary tract disease is more commonly seen in men and those with end-stage renal disease requiring dialysis.⁵⁰

URINARY TRACT

At the time of primary infection, or in the case of dissemination associated with reactivation, *M. tuberculosis* seeds the vascular renal cortex. Healed granulomatous lesions in the glomeruli can rupture into the renal tubule and become mechanically caught up at the loop of Henle; here granulomatous progression, necrosis and cavitation is likely to ensue in the medullary portion, which has poor host defense. Although both kidneys are usually seeded, severe renal involvement is often asymmetric or unilateral (25%), so that renal failure is uncommon.^{51,112,113} Subsequently, through descending infection, the infundibulum, ureter, bladder, prostate, epididymis and testes may be involved.^{20,50} A combination of upper and lower tract disease is highly suggestive of TB. Granulomatous lesions, usually in the upper or lower third of the ureter, can cause narrowing of the collecting system and strictures that can progress despite treatment.⁵⁰

Most often, onset of the disease is insidious, and patients present with asymptomatic sterile pyuria, gross hematuria, frequency and dysuria.¹¹⁴ Back pain or flank pain resembling acute pyelonephritis often reflects calyceal or ureteral obstruction, though renal colic is uncommon. Bladder involvement (with resultant diminished bladder capacity) may present with complaints of an inability to empty the bladder and may be associated with the development of a secondary bacterial bladder infection. It is important to obtain historical information regarding the prior administration of intravesical BCG for the treatment of bladder cancer, as in 1% of patients receiving this treatment local genitourinary disease will develop and in 0.4% disseminated BCG disease.¹¹⁵

Ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) are useful diagnostic modalities for the assessment of genitourinary TB and are replacing an intravenous pyelogram as the primary method of radiologic investigation. Radiologic abnormalities associated with genitourinary TB are distorted or eroded calyces, overt papillary necrosis, renal parenchymal scarring and calcification (all of which can mimic the changes seen in chronic pyelonephritis).¹¹⁶⁻¹¹⁸

In patients with urinary tract disease, 80% to 90% will have positive urine cultures confirming the diagnosis. Three to six first-void morning urine specimens should be collected for AFB smear and culture to give the highest yield (only 30% to 40% of single specimens are positive).^{52-56,113} Antibiotics, such as fluoroquinolones, used to treat superimposed bacterial infection may compromise the laboratory's ability to recover *M. tuberculosis* in urine samples and therefore should be stopped more than 48 hours before urine specimens are collected for mycobacteriologic assessment.⁵⁵ Occasionally, FNA of the kidney under ultrasound guidance may be indicated if radiologic assessment is suggestive of renal TB and urine mycobacterial cultures are negative^{56,57} (see Table 2 for diagnostic yield).

GENITAL TRACT

Genital tract TB may follow from a renal focus, therefore the diagnosis of genital TB should lead to a search for urinary tract disease. However, disease involving the female genital tract or the seminal vesicles in males is most often due to hematogenous or direct spread from neighbouring organs.²⁰

Female

Any site in the female genital tract may be involved; however, for reasons that are unknown, 90% to 100% of patients with pelvic TB have fallopian tube infection, and both tubes are usually involved with resultant high rates of infertility.¹¹² Pelvic TB is most commonly diagnosed during a work-up for infertility or during evaluation of abnormal uterine bleeding, pelvic pain or adnexal masses. Other less common sites of involvement in the female genital tract include cervical or vulvovaginal, which frequently presents as abnormal vaginal bleeding or ulcers. The diagnosis of female genital TB requires a combination of microbiologic, histologic and radiologic techniques.⁵⁹⁻

⁶¹ Findings on hysterosalpingography may suggest TB, though, as with renal TB, imaging is often nonspecific and characteristic findings are typically seen only with more advanced disease. Cultures of *M. tuberculosis* can be obtained from several sources, including menstrual fluid, peritoneal fluid, endometrial biopsy or biopsy of abnormal tissue identified during laparoscopy.^{59-63,119,120} The sensitivity of these tests for the diagnosis of female genital tract TB is difficult to determine given the lack of a gold standard (see Table 2). Even with adequate treatment for genital TB, subsequent fertility rates range between 10% and 30%.^{61,119,121}

Male

As with the female genital tract, any site of the male genital tract can be involved. Epididymo-orchitis is the most common presentation.¹¹² Penile and prostatic involvements are rare. Male genital TB usually presents with scrotal swelling, sometimes with rectal or pelvic pain and less commonly with epididymitis, hydrocele or, in advanced cases, a discharging sinus (“watering can” perineum).¹¹² On examination, the epididymis can be rubbery or nodular, and the prostate can be thickened with hard nodules. Between 50% and 75% of patients have palpable thickening of the vas deferens. Urine and discharge from draining sinuses should be sent for AFB smear and culture.^{64,65,120,121} If this is non-diagnostic, biopsies (FNA or excisional) should be performed for diagnosis (see Table 2).

Treatment with standard 6-month therapy is usually adequate in genitourinary TB (*conditional recommendation, based on moderate evidence*). Surgery is not indicated except for symptom relief, complications or failure to respond to appropriate antituberculous therapy.^{50,68}

There are high rates of associated pulmonary disease described in renal TB and male genital TB, thus assessment for associated pulmonary disease is recommended.^{7,20,50,51,66-68,112,113}

MILIARY/DISSEMINATED TB

The term miliary TB was originally a pathologic and then radiologic description of the clinical disease caused by the widespread hematogenous dissemination of bacteria to most organs of the body.¹²² Bacteria enter the bloodstream at the time of primary infection before the host’s immune system has fully responded, or later, during reactivation of latent infection.¹²³ The disease may be manifest as a miliary pattern on the chest radiograph, which is characterized by 1-5 mm nodules, or, among those without a miliary pattern on chest radiograph, as a bone marrow aspirate/biopsy or a blood culture positive for *M. tuberculosis*, or as generalized TB at postmortem examination.^{20,122} For this discussion, the terms miliary and disseminated are interchangeable.

Only 16 cases of miliary TB were reported in Canada in 2010 (Table 3). While the incidence in Canada has remained relatively stable for the last decade it has risen in the United States, largely because of HIV/AIDS. When the incidence of TB is high, disseminated TB occurs most commonly in childhood (especially <1 year of age). When the incidence of TB is low, it is mainly a disease of adults, especially people who are elderly, malnourished or HIV-infected or who have other conditions associated with impaired cell-mediated immunity, such as solid organ transplantation, renal failure, TNF alpha inhibitor use and steroid use. Fever, night sweats, anorexia, weight loss and weakness are common, respiratory or other organ-specific symptoms less so. A significant proportion present with fever of unknown origin, and the findings on chest radiography and tuberculin testing may be negative.¹²³ Choroidal tubercles seen on fundoscopy are very suggestive of the diagnosis. Most often, the presentation is subacute or chronic, though acute fulminant presentations can occur, with shock and acute respiratory distress syndrome.¹²⁴ The nonspecific and often variable presentation frequently leads to a delay or lack of diagnosis and a high mortality rate.¹²⁵

Diagnosis of miliary TB is difficult, and a high index of suspicion with institution of therapy before a diagnosis is confirmed is recommended to prevent morbidity and death.¹²⁶

(Strong recommendation, based on moderate evidence)

Laboratory findings are nonspecific, though hematologic abnormalities are common. Up to one-third of cases do not have the classic discrete micronodular or “miliary” pattern on chest radiograph. High-resolution CT is more sensitive though not necessarily specific for miliary TB.¹²⁷ Prompt examination by AFB smear and culture of clinical specimens from multiple sites increases the probability of a positive result and may obviate the need for more invasive testing.^{20,83-87} Biopsy of lung if the imaging is abnormal (transbronchial, thoracoscopic or surgical), biopsy of liver (highest yield >90%) and biopsy of bone marrow will frequently demonstrate caseating granulomas or AFB on special stains, justifying the early commencement of anti-tuberculous therapy^{20,83-87} (see Table 2). In children, gastric washings may be positive. Blood cultures may be positive (especially in those with HIV coinfection), however the mean time to culture positivity is 24.7 days, once again highlighting the importance of empiric treatment in these patients pending confirmation of TB diagnosis.¹²⁸ The yield of mycobacterial blood cultures increases in inverse proportion to the absolute CD4 count, and cultures may be positive in up to 50% of HIV-positive patients with CD4 counts less than 100 x 10⁶/L. Liquid culture media specifically designed for the growth of *M. tuberculosis* should be used; these are different from the blood culture bottles used for the isolation of other bacteria.¹²⁸

Standard anti-tuberculous treatment regimens should achieve microbiologic and clinical cure, but longer therapy (i.e. 12 months) can be considered for children and the immune compromised (e.g. those with HIV/AIDS), as well as patients with a slow response to treatment or with drug-resistant disease.^{20,129}

(Conditional recommendation, based on weak evidence)

Despite appropriate treatment, mortality from miliary TB remain as high as 20%.^{84,86} Negative prognostic indicators include meningeal disease, hematologic abnormalities, late presentation, concomitant diseases, cachexia and anergy.^{84,86}

BONE AND JOINT (OSTEOARTICULAR) TB

Bone and joint TB made up approximately 2.5% of all reported cases of TB in Canada in 2010 (Table 3), a proportion that has not changed significantly for decades.

SPINAL/VERTEBRAL DISEASE

Spinal or vertebral TB (Pott's disease) involvement is noted in approximately 50% of bone and joint TB cases.²⁰ Vertebral bodies remain highly vascular into adulthood, which explains the propensity for bone and joint TB to develop at this site. Infection often starts in the anterior-inferior aspect of a vertebral body, spreads beneath the anterior longitudinal ligament and can lead to disease in adjacent vertebral bodies. The lower thoracic and upper lumbar vertebrae are most often affected in spinal tuberculosis. Thoracic disease is more commonly seen in children, and lumbar disease is more commonly seen in adults.^{20,130-132}

Most patients present with slowly progressive back pain. Fever and constitutional symptoms are not common unless in conjunction with extraspinal or disseminated disease. Complications include paraspinal fluid collections that have a typical fusiform appearance on imaging and that can progress to psoas muscle abscesses. Advanced disease may lead to spinal cord or nerve root compression with resulting neurologic deficits.¹³⁰⁻¹³²

Radiographic findings can be helpful in suggesting the diagnosis but are nonspecific and should not be used to make a definitive diagnosis.²⁰ White blood cell scans and bone scans will be positive in osteoarticular TB, suggesting infection and activity. CT and MRI findings suggestive of vertebral TB include anterior vertebral involvement of thoracic or lumbar vertebrae adjacent to the endplate with evidence of marrow edema with minimal sclerosis; discitis of intervening discs with preservation of the disc until late in disease; and large paraspinal abscesses (calcification being very suggestive of TB). MRI is very helpful in investigating spinal cord involvement or damage.¹³³⁻¹³⁹

As in all other forms of nonrespiratory TB, it is best to confirm the diagnosis microbiologically with AFB smear microscopy and TB culture. Culture and specifically sensitivity data are very important to obtain, given the difficulty in following and documenting cure in bone and joint TB. A CT-guided needle biopsy is the recommended first approach to obtain tissue for assessment when bone TB is being considered. The specimen should be sent for histopathologic assessment, microbiologic assessment (to assess for pyogenic infections) and AFB smear and culture.^{69,70} If that assessment is non-diagnostic, a surgical biopsy should be performed for definitive diagnosis and to assess for etiologies other than tuberculosis osteomyelitis. It is important to review the patient for other manifestations of TB disease, as a recent study demonstrated that one-third of patients with spinal TB had evidence of TB elsewhere, and the diagnosis of TB disease was made in one-quarter of patients by obtaining extraspinal specimens (see Table 2).^{69,70}

A recent Cochrane review has suggested that early surgical intervention for all cases of spinal TB is not required, and this is consistent with previous literature.^{145,146} Surgical treatment of spinal TB should be considered in those with neurologic deterioration and in those less than 15 years of age with significant kyphosis.^{145,146}

(Strong recommendation, based on strong evidence)

JOINT/ARTHRITIS TB

Tuberculous arthritis is usually a mono-arthritis affecting large, weight-bearing joints such as the hip or knee. Symptoms can include swelling, pain and loss of function. Focal signs typically associated with septic arthritis, such as local erythema and warmth, are invariably missing, as are constitutional symptoms. Cartilage erosion, deformity and draining sinuses have been associated with late presentation. *M. tuberculosis* has also been associated with prosthetic joint infections. Osteomyelitis affecting other sites in the skeleton is uncommon but has been described. Multifocal presentations can occur in 15%-20% of patients, often in immune-suppressed individuals, and can be misinterpreted as metastases.^{71,140}

Radiologic findings suggestive of TB in joints primarily demonstrate the signs of synovial disease with thickening of the synovium and effusions, usually affecting only one joint. Differentiation of tuberculous arthritis from other arthritic conditions can be difficult. MRI changes suggestive of TB include moderate but uniform thickening of the synovium, as compared with the larger and more irregular synovial thickening seen in rheumatoid arthritis. Adjacent soft-tissue abscesses and bony erosions can be seen in tuberculous, pyogenic or rheumatoid arthritis, but the more numerous the abscesses (two or more) the more likely the arthritis is due to TB. Adjacent fasciitis and cellulitis can be seen in both TB and pyogenic arthritis but are more indicative of a pyogenic arthritis.^{133,141-143}

Synovial fluid assessment is a reasonable first step in obtaining a diagnosis of tuberculous arthritis. Synovial fluid microscopy for AFB has a low yield (19%), but mycobacterial cultures have been reported as positive in 79% of cases.^{70,140,142,143} Synovial biopsy with mycobacterial culture has a reported sensitivity of 94% and may be required if synovial fluid assessment is non-diagnostic (see Table 2).^{72-74,134,140,143}

Standard anti-tuberculous treatment regimens will frequently achieve microbiologic and clinical cure. Six months of treatment is recommended when using isoniazid- and rifampin-based regimens.¹⁴⁴

(Conditional recommendation, based on moderate evidence)

A recent literature review demonstrated the risk of relapse with these regimens in osteoarticular TB of 1.35% with 6 months of treatment, 0.86% with 6-12 months of treatment and 0.5% with treatment regimens longer than 12 months.¹⁴⁴ Increased risk of failure has been associated with extensive disease at the outset of treatment and evidence of sclerotic bony disease.¹⁴⁴ The definition of cure is difficult in bone and joint TB, and follow-up samples are not routinely obtained to demonstrate lack of mycobacterial growth. Alternative definitions of cure have used radiologic markers; however, plain x-rays may never return to baseline, and recent studies in spinal TB have shown that 50% of patients will have MRI evidence of tuberculous activity even at the end of 12 months of treatment.^{136,137} Further research into osteoarticular TB may help determine the optimum treatment duration and cure definition. With these concerns, some physicians may extend treatment to 9 to 12 months in complicated patients with osteoarticular TB.

ABDOMINAL TB

Abdominal TB made up approximately 2.5% of all reported cases of TB in Canada in 2010 (Table 3). It was the second most frequent site of nonrespiratory TB involvement in 2010.¹⁴ Abdominal TB includes disease of the intestines, peritoneum and mesenteric glands. The intestines and peritoneum are involved with similar frequency. The pathogenesis of abdominal TB has been attributed to direct infection through swallowing of infected sputum, ingestion of contaminated milk, hematogenous spread from initial primary foci in the lung or later dissemination of reactivated disease, and/or contiguous spread from adjacent organs. Both intestinal and peritoneal TB often present in association with enlarged mesenteric lymph nodes, but occasionally mesenteric adenitis is the only finding.^{147,148}

GASTROINTESTINAL

Gastrointestinal involvement usually occurs in the ileocecal, jejunoileal or anorectal area but has been described in the esophagus, stomach and duodenum. Hepatosplenic, biliary tract and pancreatic TB are described but are comparatively rare. Patients with ileocecal TB may present with clinical and radiographic features that are indistinguishable from those of Crohn's disease, such as chronic abdominal pain (up to 90%), constitutional symptoms and a right lower quadrant mass (25% to 50%).^{147,148}

Radiologic investigations for enteric TB can include barium assessment, CT scan and abdominal MRI studies. Radiographic features of enteric TB are nonspecific and difficult to differentiate from inflammatory bowel disease. Associated involvement of the peritoneum and mesenteric lymph nodes is more commonly seen in TB than in inflammatory bowel disease. It is important to assess for pulmonary involvement when considering the diagnosis of enteric TB, as up to 50% of patients with intestinal TB have evidence of active or inactive pulmonary TB on chest radiography.¹⁴⁹⁻¹⁵²

The diagnosis of enteric TB should include stool assessments for AFB smear and culture (up to 50% yield). This should be specifically considered in HIV-positive individuals who are also at risk of gastrointestinal involvement with *Mycobacterium avium/ intracellulare*. Given that the main differential diagnosis of ileocecal TB is that of Crohn's disease, the next investigative step in diagnosis should be colonoscopy with biopsy for histopathology, as well as AFB smear and culture (up to 80% diagnostic yield) (see Table 2).^{42,152-156}

Histopathology findings on colonic biopsy suggestive of TB include the findings of multiple, confluent granulomas with caseous necrosis and ulcers lined with epithelioid histiocytes.^{42,153,154} TB PCR assessments of colonoscopy biopsy specimens have been troubled by poor sensitivity and lack of gold standard comparison.¹⁵⁵ If colonoscopy is non-diagnostic, laparoscopy/laparotomy can be considered for definitive diagnosis, as can an empiric trial of anti-TB treatment with the usual concerns regarding empiric therapy.^{20,154,155}

PERITONEAL

In those with primarily peritoneal involvement, common presenting symptoms are abdominal swelling, abdominal pain, fever, weight loss and diarrhea.^{43,156} Patients with cirrhosis and those undergoing continuous ambulatory peritoneal dialysis are at increased risk. The peritoneum becomes studded with tubercles that leak proteinaceous fluid, clinically identified as ascites. Late presentations of TB peritonitis can be “dry” with predominant fibro-adhesive features (“doughy abdomen”) and minimal ascitic fluid.^{20,43,156}

Radiologic assessment can be helpful but is not diagnostic. An abnormal chest radiograph can be seen in 38% of patients with peritoneal TB. Ultrasound assessment often demonstrates peritoneal fluid with fine mobile strands. CT scan assessment demonstrates ascites fluid with high attenuation values (20-45 HU) with a thickened and nodular peritoneum. “Dry” TB peritonitis is characterized by omental masses and a hypervascular peritoneum. The commonly associated mesenteric adenopathy can be seen with both modalities.^{150,151}

Assessment of ascitic fluid demonstrates an exudative pattern with a predominance of lymphocytes, although when TB peritonitis complicates chronic peritoneal dialysis, neutrophils may predominate.^{44,45} Ascitic fluid is rarely smear positive (3%) but can demonstrate positive cultures in up to 80% of samples.⁴⁴⁻⁴⁶ If ascitic fluid sampling is non-diagnostic, peritoneal biopsy (diagnostic image-guided or laparoscopic) for definitive diagnosis should be considered as its diagnostic yield is higher than that of ascitic fluid sampling (see Table 2).^{20,44-49}

Ascitic fluid adenosine deaminase (ADA) has shown reasonable sensitivity and specificity for the diagnosis of peritoneal TB in a recent meta-analysis;¹⁵⁷ however, with the low prevalence of tuberculous peritonitis in Canada this test is more helpful in ruling out the disease (negative predictive value) than ruling in the disease (positive predictive value). In addition, a diagnosis based on ADA does not yield the organism or the drug susceptibility profile of the organism, potentially affecting treatment. It is also important to recognize that tuberculosis peritonitis is associated with an elevation in serum CA 125 level, and there are multiple case reports of incorrect diagnosis of metastatic ovarian cancer in the setting of tuberculosis peritonitis when this tumour marker is relied on for a diagnosis of ovarian cancer.⁴⁵

Treatment of abdominal TB follows the standard approach.

(Conditional recommendation, based on moderate evidence)

Surgery is generally advised only in the face of serious complications, such as perforation, bleeding or obstruction.¹⁵⁸

CENTRAL NERVOUS SYSTEM TB

Central nervous system (CNS) TB includes tuberculous meningitis, tuberculous myelitis and tuberculomas, as well as tuberculous abscesses and cerebritis. In Canada, CNS TB made up 1.4% of all reported cases of TB in Canada in 2010 (Table 3).¹⁴ Meningitis, with or without tuberculoma, occurs in approximately 75% of cases and tuberculoma alone in 25% of patients with CNS TB.¹⁵⁹ Cerebral tuberculomas are thought to be more common in patients with HIV/AIDS and people from low-income countries.¹⁶⁰ CNS involvement is seen in up to 15% to 20% of miliary TB cases, and in up to 50% of these cases it is fatal.²⁰

MENINGITIS

TB meningitis should be treated as a medical emergency; time is of the essence in achieving a good outcome, as the condition is frequently associated with devastating consequences: 25% morbidity (i.e. permanent neurologic deficit) and 15% to 40% mortality despite available treatment.^{159,161,162} It is believed that the initial lesion is a tubercle in the superficial cortex (subependymal area) or meninges that ruptures into the subarachnoid space (Rich focus). Brain and cranial nerve damage results from the effects of a granulomatous basal exudate (proliferative arachnoiditis). The proliferative arachnoiditis may cause both an obstructive hydrocephalus (with subsequent elevation in intracranial pressure) as well as a periarteritis with subsequent thrombosis of blood vessels and brain infarction most commonly in the vessels supplying the basal ganglia and brainstem.^{162,163}

The clinical course is characterized by a prodromal headache, malaise, fever and personality changes, followed by meningismus, cranial nerve palsies and confusion, which, if left untreated, can lead to seizures, coma and death within weeks.¹⁶¹ Outcomes are known to be affected by the following: age, whether hydrocephalus is present at diagnosis, cerebrospinal fluid (CSF) protein levels and, most important, the clinical stage of disease at diagnosis.¹⁶⁴⁻¹⁶⁶ Clinical staging is done at the time of presentation, stage 1 indicating patients who are conscious and rational with no focal neurologic signs, stage 2 patients presenting with lethargy and confusion with focal signs, and stage 3 patients exhibiting stupor, coma and seizures.

Neurologic imaging can suggest the diagnosis. A CT scan or MRI of the brain showing basilar meningeal enhancement, hydrocephalus and infarctions in the supratentorial brain parenchyma and brain stem is highly suggestive of TB meningitis.¹⁶⁷⁻¹⁷⁰

Lumbar puncture is the usual first diagnostic test to consider in meningitis. At presentation, the CSF measurements are often normal, but subsequent abnormal results include low glucose levels (<45 mg/dL or <2.5 mmol/L [normal 50-80 mg/dL]), elevated protein (100-500 mg/dL or 0.5-5 g/L [normal 15-45 mg/dL]) and a moderate pleocytosis with lymphocyte predominance (cell count 100-500 cells/ μ L [normal 0-5 white blood cells/ μ L]).^{20,171} The opening pressure is usually elevated.^{20,171} Although regularly performed, bacteriologic methods are generally considered inadequate for early diagnosis of TB meningitis because there are too few organisms in the CSF for consistent demonstration by smear, and cultural identification may take several weeks.¹⁶⁴ Serial sampling of CSF for AFB smear and culture may increase the diagnostic yield (up to 87% with daily lumbar puncture for 3 days), and empiric treatment should not be delayed for fear of influencing smear or culture results. The sensitivity of AFB smears may be improved by using the last tube collected, as well as obtaining a large volume sample (10 to 15 mL).^{165,166} NAAs are commercially available to identify mycobacteria directly from CSF.

The availability and reliability should be discussed with local laboratories. The major advantage of NAA is a rapid diagnosis, generally within 48 hours, and it is most useful in diagnosing meningeal TB.^{21,37,90,172} A positive NAA assay result from the CSF of a patient with a high clinical probability of TB meningitis can be considered a presumptive case, whereas a negative NAA assay in these circumstances cannot be relied upon to exclude the diagnosis.¹⁷⁰ Newer PCR tests amplifying several target gene sites are likely to improve sensitivity in the future.

In meningitis, empiric therapy with standard quadruple therapy should be initiated immediately on suspicion of the diagnosis to prevent complications.

(Strong recommendation, based on moderate evidence)

Isoniazid, rifampin and pyrazinamide all penetrate the CSF well. A meta-analysis has suggested that 6 months of therapy is adequate, although treatment extension to 12 months has been promoted given the severity of disease in tuberculous meningitis and lack of comparative trials.^{38,173,174} Given the ability of pyrazinamide to penetrate the CSF well, some physicians promote the use of this medication beyond 2 months; however, specific trials have not confirmed the benefit of this approach to date.³⁸ Consultation with a TB specialist is recommended in resistant CNS tuberculosis disease given issues of CSF penetration of several second-line agents.¹⁷⁴

Adjuvant steroid use has been shown to decrease mortality in HIV-negative children and adults with tuberculous meningitis (no evidence of harm with the use of adjuvant steroids in HIV-positive individuals with tuberculous meningitis).

It is therefore recommended that all patients presenting with tuberculous meningitis receive a course of steroids (dose of dexamethasone 0.4 mg/kg IV every 24 hours in adults [2 weeks] and 0.6 mg/kg IV every 24 hours in children [4 weeks], subsequently tapered over a total of 8 weeks).¹⁷⁵⁻¹⁷⁷

(Strong recommendation, based on strong evidence)

Neurosurgical intervention may be indicated for complications such as hydrocephalus or, less likely, large local collections.^{164,175,176}

A recent study has addressed the optimal timing for the initiation of antiretroviral (ARV) therapy in HIV-positive patients with tuberculosis meningitis and has found that early initiation of ARV (within the first 8 weeks of anti-tuberculous treatment) increased morbidity without a mortality benefit.¹⁷⁸ Thus, it is currently recommended that ARV initiation be delayed to 8 weeks in this cohort of patients (*strong recommendation, based on moderate evidence*). See Chapter 10, Tuberculosis and Human Immunodeficiency Virus.

TUBERCULOMAS

Patients with tuberculoma are usually asymptomatic but may present with headache, seizures (focal or generalized) or focal neurologic signs, depending upon the location of the lesion(s).²⁰

Diagnosis of tuberculoma can be suggested by neurologic imaging (CT or MRI) with evidence of ring enhancing lesion(s) with surrounding edema.¹⁶⁷⁻¹⁶⁹ The primary competing diagnosis on CNS imaging is that of cysticercosis. Diagnosis may be obtained with stereotactic biopsy or excisional biopsy (yields provided in Table 2), or an empiric trial of therapy with clinical monitoring can be attempted with radiographic follow-up.^{38-41,170-178}

Standard anti-tuberculous therapy for 6 months is recommended, although there are no randomized controlled trials to confirm outcomes in tuberculoma. Adjuvant steroid use in all cases of tuberculoma is not recommended given the lack of randomized controlled trials assessing its effectiveness. Its use can be considered in patients with vasogenic edema and neurologic symptoms, as some case studies have reported decreased neurologic symptoms with the use of adjuvant steroid therapy.³⁸

(Conditional recommendation, based on weak evidence)

OCULAR TB

The epidemiology of ocular TB has not been well described in Canada, and there is wide variation reported from around the world. The diagnosis is often problematic given the difficulty in obtaining clinical specimens for mycobacteriologic and histopathologic testing.¹⁷⁹⁻¹⁸¹ Cases are usually referred to a TB centre by an ophthalmologist for consideration of empiric treatment.

Virtually any part of the eye can be involved. Ocular TB can be characterized by direct infection of external and internal eye structures or an inflammatory hypersensitivity response to mycobacterial antigens, which can lead to retinal vasculitis.¹⁷⁹⁻¹⁸¹ Direct infection can occur from hematologic dissemination at the time of primary infection or reactivation or, less commonly, direct extension from a site external to the eye.¹⁷⁹⁻¹⁸¹ Intraocular disease, specifically choroidal TB, is the most common form of ocular tuberculosis.^{20,179-181} Choroidal TB can be unilateral or bilateral, and can lead to retinal disease. Patients usually present with decreased visual acuity and often have signs of disseminated TB.

Clinical specimens are easily obtained from external eye structures. Intraocular disease is often a clinical diagnosis, based on ophthalmological findings consistent with TB, evidence of TB infection and response to a clinical trial of anti-tuberculous medications.¹⁷⁹⁻¹⁸² Some studies have suggested that sampling of the anterior chamber fluid for TB PCR may be helpful in confirming the diagnosis.¹⁸³

Standard 6-month TB treatment is suggested for ocular TB.¹⁸¹

(Conditional recommendation, based on weak evidence)

However, given the lack of randomized controlled trials there is disagreement in the literature as to the optimal length of treatment in this disease. Some authors recommend discontinuation of therapy if there has been no response after 2 months.¹⁸¹ Other authors recommend that a minimum of 9 months of therapy is required to achieve cure.¹⁸⁴

TUBERCULOUS PERICARDITIS

In developed countries the incidence of TB pericarditis has declined alongside the decline in TB incidence, whereas in countries with a high prevalence of HIV and TB coinfection the incidence of TB pericarditis has been steadily increasing.⁷⁵

The pathogenesis of pericardial TB has been attributed to hematogenous spread from initial primary infection or later dissemination of reactivated disease, or contiguous spread from adjacent organs, such as mediastinal lymph nodes. It is often accompanied by tuberculous disease at another site, commonly pulmonary, pleural, mediastinal lymph node and/or peripheral lymph node locations.²⁰

The earliest clinical presentation of TB pericarditis is of a serosanguinous exudative effusion that may resolve spontaneously over a few weeks but may progress to cardiac tamponade or pericardial constriction. Common symptoms are nonspecific and are those of the underlying infectious process (fever, night sweats), cardiac compromise (dyspnea, orthopnea) or of disease elsewhere (cough). Physical signs vary depending upon the degree of cardiac compromise.^{76,77}

Imaging modalities can include chest radiography, echocardiography, cardiac MRI (helpful in identifying myocardial involvement seen more commonly in HIV-positive individuals) or CT assessment (helpful in identifying mediastinal lymph node involvement).^{76,77}

Pericardial fluid assessment typically demonstrates a bloody, exudative effusion that is often predominantly neutrophilic and not lymphocytic. Diagnosis can be made with sampling of pericardial fluid and/or pericardial tissue for AFB smear (4%), culture (25%-75 %) and histopathologic analysis (71%).⁷⁶⁻⁷⁸ Pericardial fluid ADA and interferon gamma assays have demonstrated reasonable sensitivity and specificity in a recent meta-analysis;⁷⁸ however, with the low prevalence of tuberculous pericarditis in Canada these tests are more helpful in ruling out the disease (negative predictive value) than ruling in the disease (positive predictive value).

It is important to remember that pericardial TB is often associated with disease elsewhere, and microbiologic assessment of sputum, pleural effusion, mediastinal lymph node and/or other involved sites can increase the yield of diagnosis significantly. However, given the difficulties in diagnosis and the high morbidity and mortality associated with this condition, empiric treatment may need to be considered (especially in the immunocompromised, as typical histopathology findings may not be present).^{78,79}

Six-month anti-tuberculous treatment is recommended and has been shown to reduce the incidence of constrictive pericarditis (10%-20%) and mortality associated with tuberculous pericarditis.¹⁸⁵

(Strong recommendation, based on moderate evidence)

Adjunctive corticosteroid treatment has been shown in small studies to reduce the mortality and morbidity associated with pericarditis in both HIV-negative and HIV-positive individuals^{185,186}

(Strong recommendation, based on moderate evidence)

The recommended adult steroid (prednisone) dosage is 1 mg/kg per day for 4 weeks, tapered slowly over the following 8 weeks (the use of corticosteroids in TB is discussed in Chapter 5, Treatment of Tuberculosis Disease). In patients with recurrent effusions or persistently elevated central venous pressures despite removal of pericardial fluid and use of anti-tuberculous drugs, early pericardiectomy is advised.^{185,187}

OTHER TYPES OF NONRESPIRATORY TB

TB can affect any organ or organ system of the body, including the skin, non-nodal glandular tissue (i.e. breast), great vessels and bone marrow.^{20,188} It is important to consider TB in the differential diagnosis and submit the appropriate specimens to the laboratory.

TB affecting the skin includes both cutaneous TB (infection of the skin by direct inoculation, contiguous spread from underlying structures or hematogenous spread) and tuberculids (cutaneous hypersensitivity/autoimmune reactions to noncutaneous TB infection).¹⁸⁹ Cutaneous TB disease is not common, as the organism prefers temperatures that are higher than those at the surface of the body. Examples of cutaneous TB are lupus vulgaris, scrofuloderma and tuberculous gumma. Examples of tuberculids are papulonecrotic tuberculid, erythema induratum and erythema nodosum. Erythema nodosum usually implies recent infection and possibly infection that may be more likely to progress to disease. However, it does not necessarily mean underlying active disease.¹⁹⁰

Diagnosis of cutaneous TB depends on biopsy for histopathology and mycobacterial smear and culture. Diagnosis of tuberculids depends on biopsy specimens demonstrating the typical histopathology of the underlying autoimmune/hypersensitivity reaction and demonstration of TB infection with response to empiric anti-tuberculous therapy.

Standard 6 months of therapy is likely adequate for treatment, and small studies suggest that shorter courses of treatment may be effective¹⁹⁰

(Conditional recommendation, based on weak evidence)

IMMEDIATELY LIFE-THREATENING FORMS OF TB

Nonrespiratory TB (other than lymph node TB) is more likely to cause a life-threatening complication than is respiratory TB.^{14,20} Together, bone and joint, disseminated, CNS, pericardial and adrenal TB account for a relatively small fraction of all reported TB cases, yet they are responsible for a large share of the morbidity and mortality associated with the disease.^{14,20} Adrenal insufficiency should be considered in all patients with active or remote TB who are doing poorly, particularly if hypotension, hyponatremia or hyperkalemia is present.¹⁹¹

In certain life-threatening forms of nonrespiratory TB, such as CNS, disseminated or pericardial TB, empiric treatment should be instituted with a presumptive diagnosis while confirmation is pending. Successful outcomes of these and other forms of nonrespiratory TB are critically dependent upon the rapidity with which the diagnosis is made and appropriate treatment introduced.²⁰ Depending upon what drugs remain available for treatment and upon host immune status, multidrug-resistant TB at any site may also be immediately life-threatening.¹²⁹

RECOMMENDED TREATMENT

As a general rule, nonrespiratory TB responds to the same regimens used to treat respiratory TB (see Chapter 5, Treatment of Tuberculosis Disease).^{192,193} For example, a 6-month regimen of isoniazid and rifampin supplemented with pyrazinamide for the initial 2 months is as efficacious as a 9-month course of isoniazid and rifampin therapy supplemented for the first 2 months with either pyrazinamide or ethambutol in the treatment of tuberculous lymphadenitis.¹⁹⁴

The data for the recommendation of a 6-month treatment course for most other forms of nonrespiratory disease is not based on studies as robust as those for pulmonary TB nor is treatment cure as easy to define, thus treatment extension to 9 or 12 months is often considered in patients with complicated conditions.

(Conditional recommendation, based on weak to moderate evidence)

CNS TB and disseminated TB are notable exceptions, in that a longer course of therapy is advised.¹⁹³ Unfortunately, in the case of TB meningitis there are no randomized controlled trials to provide guidance as to optimal regimens and length of treatment. As discussed elsewhere, adjunctive therapy with corticosteroids may reduce the inflammatory response and improve outcomes of some forms of nonrespiratory TB, specifically CNS TB and pericardial TB. In contrast to respiratory TB, the management of nonrespiratory TB not uncommonly requires surgical intervention, initially for the purpose of obtaining diagnostic specimens and later in the management of local complications of the disease.

■ ■ ■

REFERENCES

1. Public Health Agency of Canada. Canadian Tuberculosis Reporting System. Reporting form completion guidelines version 1.9: Appendix B. Code table listing by ICD-9 code for diagnosis. Available at: <http://www.phac-aspc.gc.ca/tbpc-latb/pdf/guidelinesform-eng.pdf>
2. Peto HM, Pratt RH, Harrington TA, LoBue PA, Armstrong LR. Epidemiology of extrapulmonary tuberculosis in the United States 1993-2006. *Clin Infect Dis* 2009;49(9):1350-57.
3. World Health Organization. Global tuberculosis report. Geneva: WHO, 2012;31.
4. Marais BJ, Gie RP, Schaaf HS, Hesselning AC, Enarson DA, Beyers N. The spectrum of disease in children treated for tuberculosis in a highly endemic area. *Int J Tuberc Lung Dis* 2006;10(7):732-38.
5. Long R, Njoo H, Hershfield E. Tuberculosis: 3. Epidemiology of the disease in Canada. *Can Med Assoc J* 1999;160:1185-90.
6. Enarson DA, Ashley MJ, Grzybowski S, et al. Non-respiratory tuberculosis in Canada: epidemiologic and bacteriologic features. *Am J Epidemiol* 1980;112:341-51.
7. Fanning A. Tuberculosis: 6. Extrapulmonary disease. *Can Med Assoc J* 1999;160:1597-603.
8. Rieder HL, Snider DE, Cauthen GM. Extrapulmonary tuberculosis in the United States. *Am Rev Respir Dis* 1990;141:347-51.
9. Ong A, Creasman J, Hopewell PC, et al. A molecular epidemiological assessment of extrapulmonary tuberculosis in San Francisco. *Clin Infect Dis* 2004;38:25-31.
10. Shriner KA, Mathisen GE, Goetz MB. Comparison of mycobacterial lymphadenitis among persons infected with human immunodeficiency virus and seronegative controls. *Clin Infect Dis* 1992;15:601-5.
11. Atomyia AN, Uip DE, Leite OH. Evaluation of disease patterns, treatment and prognosis of tuberculosis in AIDS patients. *Braz J Infect Dis* 2002;6:29.
12. Lee MP, Chan JW, Ng KK, et al. Clinical manifestations of tuberculosis in HIV-infected patients. *Respirology* 2000;5:423.
13. Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of effective anti-retroviral therapy. *Am J Respir Crit Care Med* 2001;164:7-12.
14. Public Health Agency of Canada. Tuberculosis in Canada 2010: pre-release. Ottawa: PHAC, 2012. Available at: http://publications.gc.ca/collections/collection_2012/aspc-phac/HP37-5-1-2010-eng.pdf
15. Statistics Canada. 2006 Census. Immigration in Canada: a portrait of the foreign-born population, 2006 Census: findings.
16. Public Health Agency of Canada. Summary: estimates of HIV prevalence and incidence in Canada, 2008.
17. Long R, Boffa J. High HIV-TB co-infection rates in marginalized populations: evidence from Alberta in support of screening TB patients for HIV. *Can J Public Health* 2010;101(3):202-4.

18. Sen P, Kapila R, Salaki J, et al. The diagnostic enigma of extra-pulmonary tuberculosis. *J Chron Dis* 1977;30:331-50.
19. Laszlo A. Tuberculosis: 7. Laboratory aspects of diagnosis. *Can Med Assoc J* 1999;160:1725-29.
20. Iseman MD. *A Clinician's Guide to Tuberculosis*. Lippincott, Williams & Wilkins, 2000.
21. Tortoli E, Russo C, Piersimoni C, et al. Clinical validation of Xpert MTB/RIF for the diagnosis of extrapulmonary tuberculosis. *Eur Respir J* 2012;40(2):442-7.
22. Lau SK, Wei WI, Hsu C, et al. Efficacy of fine needle aspiration cytology in the diagnosis of tuberculous cervical lymphadenopathy. *J Laryngol Otol* 1990;104:24.
23. Parimon T, Spitters CE, Muangman N, Euathrongchit J, Oren E, Narita M. Unexpected pulmonary involvement in extrapulmonary tuberculosis patients. *Chest* 2008;134(3):589-94.
24. Roberts DS, Dowdall JR, Winter L, Sulis CA, Grillone GA, Grundfast, KM. Cervical tuberculosis: a decision tree for protecting healthcare workers. *Laryngoscope* 2008;118:1345-49.
25. Dandapat MC, Mishra BM, Dash SP, Kar PK. Peripheral lymph node tuberculosis: a review of 80 cases. *Br J Surg* 1990;77:911-12.
26. Polesky A, Grove W, Bhatia G. Peripheral tuberculous lymphadenitis: epidemiology, diagnosis, treatment, and outcome. *Medicine* 2005;84(6):350-62.
27. Pithie AD, Chicksen B. Fine-needle extrathoracic lymph-node aspiration in HIV-associated sputum-negative tuberculosis. *Lancet* 1992;340:1504.
28. Artenstein, AW, Kim JH, William SWJ, Chung RL. Isolated tuberculosis lymphadenitis in adults. Current clinical and diagnostic issues. *Clin Infect Dis* 1995;20(4):876-82.
29. Ligthelm LJ, Nicol MP, Hoek KG, et al. Xpert MTB/RIF for rapid diagnosis of tuberculous lymphadenitis from fine-needle-aspiration biopsy specimens. *J Clin Microbiol* 2011;49(11):3967-70.
30. Tokuda Y, Kishaba Y, Kato J, Nakazato N. Assessing the validity of a model to identify patients for lymph node biopsy. *Medicine* 2003;82(6):414-18.
31. Vassilakopoulos TP, Pangalis GA. Application of a prediction rule to select which patients presenting with lymphadenopathy should undergo a lymph node biopsy. *Medicine* 2000;79(5):338-347.
32. Zeka AN, Tasbakan S, Cavusoglu C. Evaluation of the Gene Xpert MTB/RIF assay for rapid diagnosis of tuberculosis and detection of rifampin resistance in pulmonary and extra pulmonary specimens. *J Clin Microbiol* 2011;49(12):4138-41.
33. Armand S, Vanhuls P, Delcroix G, Gourcol R, Lemaitre N. Comparison of the Xpert MTB/RIF test with an IS6110-TaqMan real-time PCR assay for direct detection of *Mycobacterium tuberculosis* in respiratory and nonrespiratory specimens. *J Clin Microbiol* 2011;49(5):1772-76.
34. Hilleman D. Rapid molecular detection of extrapulmonary tuberculosis by the automated GeneXpert MTB/RIF system. *J Clin Microbiol* 2011;49(4):1202-1205.
35. Lang AM, Feris-Iglesias J, Pena C, et al. Clinical evaluation of the Gen-Probe Amplified Direct Test for detection of *Mycobacterium tuberculosis* complex organisms in cerebrospinal fluid. *J Clin Microbiol* 1998;36(8):2191-94.

36. Pai M, Flores LL, Pai N et al. Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2003;3(10):633-43.
37. Bonington A, Strang JI, Klapper PE, et al. Use of Roche AMPLICOR *Mycobacterium tuberculosis* PCR in early diagnosis of tuberculous meningitis. *J Clin Microbiol* 1998;36:1251.
38. Thwaites G, Fisher M, Hemingway, Scott G, Solomon T, Innes J. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *J Infect* 2009;59:167-87.
39. Bouchama A, al-Kawi MZ, Kanaan I, et al. Brain biopsy in tuberculoma: the risks and benefits. *Neurosurgery* 1991;28(3):405-9.
40. Rajshekhar V, Chandy MJ. CT-guided stereotactic surgery in the management of intracranial tuberculomas. *Br J NeuroSurg* 1993;7:665-71.
41. Mohanty A, Santosh V, Anandh B, et al. Diagnostic efficacy of stereotactic biopsy in intracranial tuberculomas. *Surg Neurol* 1999;52(3):252-57.
42. Guiouleme O, Paschos P, Katsaros M, et al. Intestinal tuberculosis: a diagnostic challenge – case report and review of the literature. *Eur J Gastroenterol Hepatol* 2011;23(11):1074-77.
43. Singh MM, Bhargava AN, Jain KP. Tuberculous peritonitis. *N Engl J Med* 1969;281:1091-94.
44. Sanai FM, Bzeizi KI. Systematic review: tuberculous peritonitis – presenting features, diagnostic strategies and treatment. *Aliment Pharmacol Ther* 2005;22(8):685-700.
45. Chau TN, Leung VK, Wong S, et al. Diagnostic challenges of tuberculosis peritonitis in patients with and without end-stage renal failure. *Clin Infect Dis* 2007;45(12):e141-146.
46. Yeh HG, Chiu TF, Chen JC, Ng CJ. Tuberculous peritonitis: analysis of 211 cases in Taiwan. *Dig Liver Dis* 2012;44(2):111-17.
47. Que Y, Wang X, Liu Y, Li P, Ou G, Zhao W. Ultrasound-guided biopsy of greater omentum: an effective method to trace the origin of unclear ascites. *Eur J Radiol* 2009;70(2):331-35.
48. Vadareli E, Kebapci M, Saricam T, Pasaoglu O, Acikalin M. Tuberculous peritonitis of the wet ascetic type: clinical features and diagnostic value of image-guided peritoneal biopsy. *Dig Liver Dis* 2004;36(3):199-204.
49. Chow KM, Chow VC, Szeto CC. Indication for peritoneal biopsy in tuberculous peritonitis. *Am J Surg* 2009;185(6):567-73.
50. Abbara A, Davidson RN. Etiology and management of genitourinary tuberculosis. *Nat Rev Urol* 2011;8(12):678-88.
51. Christensen WI. Genitourinary tuberculosis: review of 102 cases. *Medicine* 1974;53(5):377-90.
52. Bentz RR, Dimcheff DG, Nemiroff MJ, et al. The incidence of urine cultures positive for *Mycobacterium tuberculosis* in a general tuberculosis patient population. *Am Rev Respir Dis* 1975;111:647-50.
53. Lattimer JK, Reilly RJ, Segawa A. The significance of the isolated positive urine culture in genitourinary tuberculosis. *J Urol* 1969;102:610.

54. Hsu HL, Lai CC, Yu MC, et al. Clinical and microbiologic characteristics of urine culture-confirmed genitourinary tuberculosis at medical centers in Taiwan from 1995 to 2007. *Eur J Clin Microbiol Infect Dis* 2011;30(3):319-26.
55. Webster D, Long R, Shandro C, et al. Fluoroquinolone resistance in renal isolates of *Mycobacterium tuberculosis*. *Int J Tuberc Lung Dis* 2010;14(2):217-22.
56. Baniel J, Manning A, Leiman G. Fine needle cytodiagnosis of renal tuberculosis. *J Urol* 1991;146(3):689-91.
57. Das KM, Vaidyanathan S, Rajwanshi A, Indudhara R. Renal tuberculosis: diagnosis with sonographically guided aspiration cytology. *Am J Roentgenol* 1992;158(3):571-73.
58. Neonakis IK, Spandidos DA, Petinaki E. Female genital tuberculosis: a review. *Scand J Infect Dis* 2011;43(8):564-72.
59. Turkmen IC, Bassullu N, Comunoglu C, et al. Female genital system tuberculosis: a retrospective clinicopathological study of 1,548 cases in Turkish women. *Arch Gynecol Obstet* 2012; epub ahead of print.
60. Khanna A, Agrawal A. Markers of genital tuberculosis in infertility. *Singapore Med J* 2011;52(12):864-7.
61. Margolis K, Wranz PA, Kruger TF, Joubert JJ, Odendall HJ. Genital tuberculosis at Tygerberg Hospital – prevalence, clinical presentation and diagnosis. *S Afr Med J* 1992;81(1):12-15.
62. Sharma JB, Roy KK, Pushparaj M, Kumar S, Malhotra N, Mittal S. Laparoscopic findings in female genital tuberculosis. *Arch Gynecol Obstet* 2008;278(4):359-64.
63. Thangappah RB, Paramasivan CN, Narayanan S. Evaluating PCR, culture, and histopathology in the diagnosis of female genital tuberculosis. *Indian J Med Res* 2011;134:40-6.
64. Gomez-Garcia IG, Mampaso EG, Revilla JB, et al. Tuberculous orchiepididymitis during 1978-2003 period: review of 34 cases and role of 16SrRNA amplification. *Urology* 2010;76:776-81.
65. Lee, I, Yan W, Liu J. Scrotal tuberculosis in adults patients: a 10 year experience. *Am J Trop Med Hyg* 2007;77(4):714-18.
66. Gorse GJ, Belshe RB. Male genital tuberculosis: a review of the literature with instructive case reports. *Rev Infect Dis* 1985;7(4):511-24.
67. Madeb R, Marshall J, Nativ O, Erturk E. Epididymal tuberculosis: case report and review of the literature. *Urology* 2005;65(4):798.
68. Cek M, Lenk S, Naber KG, et al.; members of the Urinary Tract Infection (UTI) Working Group of the European Association of Urology (EAU) Guidelines Office. EAU guidelines for the management of genitourinary tuberculosis. *Eur Urol* 2005;48(3):353-62
69. Colmenero JD, Ruiz-Mesa JD, Sanjuan-Jimenez R, Sobrino B, Morata P. Establishing the diagnosis of tuberculous vertebral osteomyelitis. *Eur Spine J* 2012; May 2012 epub ahead of print.
70. Cormican L, Hammal R, Messenger J, Milburn HJ. Current difficulties in the diagnosis and management of spinal tuberculosis. *Postgrad Med* 2006;82:46-51.
71. Wallace R, Cohen AS. Tuberculous arthritis. A report of two cases with review of biopsy and synovial fluid findings. *Am J Med* 1976;61:277-82.

72. Garrido G, Gomez-Reino JJ, Fernandez-Dapica P, Palenque E, Prieto S. A review of peripheral tuberculous arthritis. *Semin Arthritis Rheum* 1998;18(2):142-49.
73. Ellis ME, el-Ramahi KM, al-Dalaan AN. Tuberculosis of peripheral joints: a dilemma in diagnosis. *Tuber Lung Dis* 1993;74(6):399-404.
74. Sant M, Bajaj H. Role of histopathology in the diagnosis of tuberculous synovitis. *J Indian Med Assoc* 1992;90(10):263-64.
75. Mayosi BM, Burgess LJ, Doubell AF. Tuberculous pericarditis. *Circulation* 2005;112:3608-16.
76. Trautner BW, Darouiche RO. Tuberculous pericarditis: optimal diagnosis and management. *Clin Infect Dis* 2001;33:954.
77. Syed FF, Mayosi BM. A modern approach to tuberculous pericarditis. *Prog Cardiovasc Dis*;2007;50(3):218-36.
78. Reuter H, Burgess LJ, Van Vuren W, Doubell AF. The role of histopathology in establishing the diagnosis of tuberculous pericardial effusions in the presence of HIV. *Histopathology* 2006;48:295-302.
79. Tuon F, Litvo M, Lopes M. Adenosine deaminase and tuberculous pericarditis – a systematic review with meta-analysis. *Acta Tropica* 2006;99:67-74.
80. Tuon FF, Silva VI, Almeida GM, Antonangelo LD, Ho YL. The usefulness of adenosine deaminase in the diagnosis of tuberculous pericarditis. *Rev Inst Med Trop Sao Paulo* 2007;49(3):165-70.
81. Burgess LJ, Reuter H, Carstens ME, Taljaard JJ, Doubell AF. The use of adenosine deaminase and interferon-gamma as diagnostic tools for tuberculous pericarditis. *Chest* 2002;122(3):900-5.
82. Reuter H, Burgess LJ, Carstens ME, Doubell AF. Adenosine deaminase activity – more than a diagnostic tool in tuberculous pericarditis. *Cardiovasc J S Afr* 2005;16(3):143-47.
83. Prout S, Benatar SR. Disseminated tuberculosis. A study of 62 cases. *S Afr Med J* 1980;58(21):835-42.
84. Kim JH, Langston AA, Gallis HA. Miliary tuberculosis: epidemiology, clinical manifestation, diagnosis, and outcome. *Rev Infect Dis* 1990;12(4):583-90.
85. Mert A, Bilir M, Tabak F, et al. Miliary tuberculosis: clinical manifestations, diagnosis and outcome in 38 adults. *Respirology* 2001;6(3):217-24.
86. Maartens G, Willcox PA, Benatar SR. Miliary tuberculosis: rapid diagnosis, hematologic abnormalities, and outcome in 109 treated adults. *Am J Med* 1990;89(3):291-96.
87. Hussain SF, Irfan M, Abbasi M, et al. Clinical characteristics of 110 miliary tuberculosis patients from a low HIV prevalence country. *Int J Tuberc Lung Dis* 2004; 8(4):493-99.
88. Jagirdar J, Zagzag D. Pathology and insights into pathogenesis of tuberculosis. In: Rom WN, Garay S, eds. *Tuberculosis*. Toronto: Little, Brown and Company, 1996;330.
89. World Health Organization. Rapid implementation of the Xpert MTB/RIF diagnostic test. Geneva: WHO, 2011.
90. Vadwai V, Boehme C, Nabeta P, Shetty A, Alland D, Rodrigues C. Xpert MTB/RIF: a new pillar in diagnosis of extrapulmonary tuberculosis? *J Clin Microbiol* 2011;49(7):2540-5.

91. Dankner WM, Davis CE. *Mycobacterium bovis* as a significant cause of tuberculosis in children residing along the United States-Mexico border in the Baja California region. *Pediatrics* 2000;105:115.
92. Martin T, Hoepfner V, Ring ED. Superficial mycobacterial lymphadenitis in Saskatchewan. *Can Med Assoc J* 1988;138:431-4.
93. Cook VJ, Manfreda J, Hershfield ES. Tuberculous lymphadenitis in Manitoba: incidence, clinical characteristics and treatment. *Can Respir J* 2004;11(4): 279-86.
94. Cowie RL, Sharpe JW. Extrapulmonary tuberculosis: a high proportion in the absence of HIV infection. *Int J Tuberc Lung Dis* 1997;1:159-62.
95. Geldmacher H, Taube C, Kroeger C, et al. Assessment of lymph node tuberculosis in Northern Germany. *Chest* 2002;121(4):1177-82.
96. Fain O, Lortholary O, Djouab M, et al. Lymph node tuberculosis in the suburbs of Paris: 59 cases in adults not infected by the human immunodeficiency virus. *Int J Tuberc Lung Dis* 1999;3:162.
97. Wark P, Goldberg H, Ferson M, et al. Mycobacterial lymphadenitis in eastern Sydney. *Aust N Z J Med* 1998;28(4):453-58.
98. Jha BC, Dass A, Nagarkar NM, et al. Cervical tuberculous lymphadenopathy: changing clinical pattern and concepts in management. *Postgrad Med J* 2001;77:185.
99. Perenboom RM, Richter C, Swai AB, et al. Diagnosis of tuberculous lymphadenitis in an area of HIV infection and limited diagnostic facilities. *Trop Geogr Med* 1994;46(5):288-92.
100. Metchock BG, Nolte FS, Wallace RJ. Mycobacterium. In: Murray P, Baron EJ, Pfaller MA, et al., eds. *Manual of Clinical Microbiology* (7th edition). Washington, D.C., 1999;399-437.
101. Pham-Huy A, Robinson JL, Tapiero B, et al. Current trends in nontuberculous mycobacteria infections in Canadian children: a Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study. *Paediatr Child Health* 2010;15(5):276-82.
102. Pilkington EF, MacArthur CJ, Beekmann SE, Polgreen PM, Winthrop KL. Treatment patterns of pediatric nontuberculous mycobacterial (NTM) cervical lymphadenitis reported by nationwide surveys of pediatric otolaryngology and infectious disease societies. *Int J Pediatr Otolaryngol* 2010;74(4):343-46.
103. Yuen AP, Wong SH, Tam CM, et al. Prospective randomized study of thrice weekly six-month and nine-month chemotherapy for cervical tuberculous lymphadenopathy. *Otolaryngol Head Neck Surg* 1997;116:189.
104. Van Loenhout-Rooyackers JH, Laheij RJ, Richter C, et al. Shortening the duration of treatment for cervical tuberculous lymphadenitis. *Eur Respir J* 2000;15:192.
105. McMaster P, Isaacs D. Critical review of evidence for short course therapy for tuberculous adenitis in children. *Pediatr Infect Dis J* 2000;19:401.
106. Campbell IA, Ormerod LP, Friend JAR, et al. Six months versus nine months chemotherapy for tuberculosis of lymph nodes: final results. *Respir Med* 1993;87:621-3.
107. Jawahar MS, Rajaram K, Sivasubramanian S, et al. Treatment of lymph node tuberculosis – a randomized clinical trial of two 6-month regimens. *Trop Med Int Health* 2005;10(11):1090-98.

108. Donald PR. The chemotherapy of tuberculous lymphadenopathy in children. *Tuberculosis* 2010;90(4):213-24.
109. Hawkey CR, Yap T, Pereira J, et al. Characterization and management of paradoxical upgrading reactions in HIV-uninfected patients with lymph node tuberculosis. *Clin Infect Dis* 2005;40:1368-71.
110. Blaikley JF, Khalid S, Ormerod LP. Management of peripheral lymph node tuberculosis in routine practice: an unselected 10-year cohort. *Int J Tuberc Lung Dis*. 2011;15(3):375-8.
111. Campbell IA. The treatment of superficial tuberculous lymphadenitis. *Tubercle* 1990;71:1-3.
112. Goldfarb DS, Saiman L. Tuberculosis of the genitourinary tract. In: Rom WN, Garay S, eds. *Tuberculosis*. Toronto: Little, Brown and Company, 1996;609-22.
113. Simon, HB, Weinstein, AJ, Pasternak, MS, et al. Genitourinary tuberculosis. Clinical features in a general hospital population. *Am J Med* 1977;63:410.
114. Eastwood JB, Corbishley CM, Grange JM. Tuberculosis and the kidney. *J Am Soc Nephrol* 2001;12:1307.
115. Lamm DL. Efficacy and safety of Bacille Calmette Guerin immunotherapy in superficial bladder cancer. *Clin Infect Disease* 2000;31:S86-S93.
116. Tonkin AK, Witten DM. Genitourinary tuberculosis. *Semin Roentgenol* 1979;1:305-18.
117. Kollins SA, Hartman GW, Carr DT, et al. Roentgenographic findings in urinary tract tuberculosis. *Am J Roentgenol Radium Ther Nucl Med* 1974;121:487.
118. Becker JA. Renal tuberculosis. *Urol Radiol* 1988;10:25.
119. Kumar P, Shah NP, Singhal A, et al. Association of tuberculous endometritis with infertility and other gynecological complaints of women in India. *J Clin Microbiol* 2008;46(12):4068-70.
120. Rana T, Sing UB, Kulshrestha V, et al. Utility of reverse transcriptase PCR and DNA-PCR in the diagnosis of female genital tuberculosis. *J Med Microbiol* 2011;60:486-91.
121. Neelam B, Mohanlal S, Namita K. Genital tuberculosis and its consequences on subsequent fertility. *J Obstet Gynecol India* 2005;55(6):534-37.
122. Slavin RE, Walsh TJ, Pollack AD. Late generalized tuberculosis. *Medicine* 1980;59:352-66.
123. Long R, O'Connor R, Palayew M, et al. Disseminated tuberculosis with and without a miliary pattern on chest radiograph. *Int J Tuberc Lung Dis* 1997;1:52-8.
124. Mohan A, Sharma SK, Pande JN. Acute respiratory distress syndrome (ARDS) in miliary tuberculosis: a twelve year experience. *Indian J Chest Dis Allied Sci* 1996;38:157.
125. Rieder HL, Kelly GD, Bloch AB, et al. Tuberculosis diagnosed at death in the United States. *Chest* 1991;100:678.
126. Sharma SK, Mohan A, Sharma A, et al. Miliary TB: new insights into an old disease. *Lancet Infect Dis* 2005;5:415-30.
127. Optican RJ, Ost A, Ravin CE. High-resolution computed tomography in the diagnosis of miliary tuberculosis. *Chest* 1992;102:941.

128. von Gottberg A, Sacks L, Machala S, et al. Utility of blood cultures and incidence of mycobacteremia in patients with suspected tuberculosis in a South African infectious disease referral hospital. *Int J Tuberc Lung Dis* 2001;5:80-6.
129. Iseman MD. Treatment of multidrug-resistant tuberculosis. *N Engl J Med* 1993;329:784-91.
130. Boachie-Adjei O, Squillante RG. Tuberculosis of the spine. *Ortho Clin North Am* 1996;27:95-103.
131. Pertuiset E, Beaudreuil J, Lioté F, et al. Spinal tuberculosis in adults. *Medicine* 1999;78:309-20.
132. Rezai AR, Lee M, Cooper PR, et al. Modern management of spinal tuberculosis. *Neurosurgery* 1995;36:87-97.
133. Burrill J, Williams CJ, Bain G, Conder G, Hine AL, Misra RR. Tuberculosis: a radiologic review. *RadioGraphics* 2007;27:1255-77.
134. Boxer DI, Pratt C, Hine AL, et al. Radiological features during and following treatment of spinal tuberculosis. *Br J Radiol* 1992;65:476.
135. Joseffer SS, Cooper PR. Modern imaging of spinal tuberculosis. *J Neurosurg Spine* 2005;2(2):145-50.
136. Jain AK, Sreenivasan R, Saini NS, Kumar S, Jain S, Chammi IK. Magnetic resonance evaluation of tubercular lesion in spine. *Int Orthop* 2012;36(2):261-69.
137. Shikhare SN, Singh DR, Shimpi TR, Peh WC. Tuberculous osteomyelitis and spondylodiscitis. *Semin Musculoskelet Radiol* 2011;15(5):446-58.
138. Chang MC, Wu HT, Lee CH, Liu CL, Chen TH. Tuberculous spondylitis and pyogenic spondylitis: comparative magnetic resonance imaging features. *Spine* 2006;31(7):782-88.
139. Evangelista E, Itti E, Malek Z, et al. Diagnostic value of 99mTc-HMDP bone scan in atypical osseous tuberculosis mimicking multiple secondary metastases. *Spine* 2004;29(5):E85-87.
140. Watts HG, Lifeso RM. Tuberculosis of bones and joints. *J Bone Joint Surg Am* 1996;78:288-98.
141. Sanghvi DA, Iyer VR, Deshmukh T, Hoskote SS. MRI features of tuberculosis of the knee. *Skeletal Radiol* 2009;38(3):267-73.
142. Sawlani V, Chandra T, Mishra RN, Aggarwal A, Jain UK, Gujral RB. MRI features of tuberculosis of peripheral joints. *Clin Radiol* 2003;58(10):755-62.
143. Choi JA, Koh SH, Hong SH, Koh YH, Choi JY, Kang HS. Rheumatoid arthritis and tuberculous arthritis: differentiating MRI features. *AJR Am J Roentgenol* 2009;193(5):1347-53.
144. Donald PR. The chemotherapy of osteo-articular tuberculosis with recommendations for treatment of children. *J Infect* 2011;62:411-39.
145. Thirteenth report of the Medical Research Council Working Party on Tuberculosis of the Spine: a 15-year assessment of controlled trials of the management of tuberculosis of the spine in Korea and Hong Kong. *J Bone Joint Surg (Br)* 1998;80(3):456-62.
146. Jutte PC, Van Loenhout-Rooyackers JH. Routine surgery in addition to chemotherapy for treating spinal tuberculosis. *Cochrane Database Syst Rev* 2006;Jan 25;(1):CD004532.

147. Jakubowski A, Elwood RK, Enarson DA. Clinical features of abdominal tuberculosis. *J Infect Dis* 1988;158:687-92.
148. Marshall JB. Tuberculosis of the gastrointestinal tract and peritoneum. *Am J Gastroenterol* 1993;88:989-99.
149. Balthazar EJ, Gordon R, Hulnick D. Ileocecal tuberculosis: CT and radiologic evaluation. *Am J Roentgenol* 1990;154:499.
150. Pereira JM, Madureira AJ, Vieira A, Ramos I. Abdominal tuberculosis: imaging features. *Eur J Radiol* 2005;55(2):173-80.
151. Lee WK, Van Tonder F, Tartaglia CJ, et al. CT appearances of abdominal tuberculosis. *Clin Radiol* 2012;67(6):596-604.
152. Pulimood AB, Ramakrishna BS, Kurian G, et al. Endoscopic mucosal biopsies are useful in distinguishing granulomatous colitis due to Crohn's disease from tuberculosis. *Gut* 1999;45:537.
153. Ye BD, Yang SK, Kim D, et al. Diagnostic sensitivity of culture and drug resistance patterns in Korean patients with intestinal tuberculosis. *Int J Tuberc Lung Dis* 2012;16(6):799-804.
154. Lin PY, Wang JY, Hsueh PR, et al. Lower gastrointestinal tract tuberculosis: an important but neglected disease. *Int J Colorectal Disease* 2009;24:1175-80.
155. Almadi MA, Chosh S, Aljebreen AM. Differentiating intestinal tuberculosis from Crohn's disease: a diagnostic challenge. *Am J Gastroenterol* 2009;104(4):1003-12.
156. Marrie TJ, Hershfield ES. Tuberculous peritonitis in Manitoba. *Can J Surg* 1978;21:533-6.
157. Riquelme A, Calvo M, Salech F, et al. Value of adenosine deaminase (ADA) in ascitic fluid for the diagnosis of tuberculous peritonitis: a meta-analysis. *J Clin Gastroenterol* 2006;40:705-10.
158. Park SH, Yang SK, Yang DH, et al. Prospective randomized trial of six-month versus nine-month therapy for intestinal tuberculosis. *Antimicrob Agents Chemother* 2009;53(10):4167-71.
159. Arvanitakis Z, Long R, Hershfield E, et al. *M. tuberculosis* molecular variation in CNS infection: evidence of strain dependent neurovirulence. *Neurology* 1998;50:1827-32.
160. Dube MP, Holtom PD, Larsen RA. Tuberculous meningitis in patients with and without human immunodeficiency virus infection. *Am J Med* 1992;93:520.
161. CDC. Tuberculosis morbidity – United States, 1997. *MMWR* 1998;47:253.
162. Thwaites GE, Tran TH. TB meningitis: many questions, too few answers. *Lancet Neurol* 2005;4:160-70.
163. Dastur DK, Lalitha VS. The many facets of neuro-tuberculosis: an epitome of neuropathology. In: Zimmerman HM, ed. *Progress in Neuropathology*. New York, NY: Grune and Stratton, 1973;351-408.
164. Schoeman JF, Van Zyl LE, Laubscher JA, et al. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. *Pediatrics* 1997;99:226-31.
165. Kennedy DH, Fallon RJ. Tuberculous meningitis. *JAMA* 1979;241:264.

166. Hsu PC, Yang CC, Ye JJ, Huang PY, Chiang PC, Lee MH. Prognostic factors of tuberculous meningitis in adults: a 6 year retrospective study at a tertiary hospital in northern Taiwan. *J Microbiol Immunol Infect* 2010;43(2):111-18.
167. Morgado C, Ruivo N. Imaging meningo-encephalic tuberculosis. *Eur J Radiol* 2005;55(2):188-92.
168. Gupta R, Kumar S, Central nervous system tuberculosis. *Neuroimaging Clin N Am* 2001;21(4):795-814.
169. Bernaerts A, Vanhoenacker FM, Parizel PM, et al. Tuberculosis of the central nervous system: overview of neuroradiological findings. *Eur Radiol* 2003;13(8):1876-90.
170. Zuger A, Lowy AD. Tuberculosis of the brain, meninges and spinal cord. In: Rom WN, Garay S, eds. *Tuberculosis*. Toronto: Little, Brown and Company, 1996;541-56.
171. Yechool VK, Shandera WX, Rodrigues P, Cate TR. Tuberculous meningitis among adults with and without HIV infection. Experience in an urban public hospital. *Arch Intern Med* 1996;156(15):1710-16.
172. Shankar P, Manjunath N, Mohan KK, et al. Rapid diagnosis of tuberculous meningitis by polymerase chain reaction. *Lancet* 1991;337:5-7.
173. van Loenhout-Rooyackers JH, Keyer A, Laheij RJ, Verbeek AL, van der Meer JW. Tuberculous meningitis: Is 6 month treatment regimen sufficient? *Int J Tuberc Lung Dis* 2011;5(11):1028-35.
174. Humphries M. The management of tuberculous meningitis. *Thorax* 1992;47:577.
175. Girgis NI, Farid Z, Kilpatrick ME, et al. Dexamethasone adjunctive treatment for tuberculous meningitis. *Pediatr Infect Dis J* 1991;10:179.
176. Thwaites GE, Nguyen DB, Dung NG, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004;351:1741-45.
177. Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev* 2008;Jan 23;(1):CD002244.
178. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of ART in (HIV)-associated tuberculous meningitis. *Clin Infect Dis* 2011;52(11):1374-83.
179. Helm CJ, Holland GN. Ocular tuberculosis. *Surv Ophthalmol* 1993;38:229.
180. Bodaghi B, LeHoang P. Ocular tuberculosis. *Curr Opin Ophthalmol* 2000;11:443-48.
181. Alvarez GG, Roth VR, Hodge W. Ocular tuberculosis: diagnostic and treatment challenges. *Int J Infect Dis* 2009;13(4):432-35.
182. Gupta A, Bansal R, Gupta V, Sharma A, Bambery P. Ocular signs predictive of tubercular uveitis. *Am J Ophthalmol* 2010;149(4):562-70.
183. Ortega-Larrocea G, Bobadilla-del-Valle M, Ponce-de-Leon A, et al. Nested polymerase chain reaction for *Mycobacterium tuberculosis* DNA detection in aqueous and vitreous of patients with uveitis. *Arch Med Res* 2003;34(2):116-9.
184. Ang M, Hedayatfar A, Wong W, Chee SP. Duration of anti-tubercular therapy in uveitis associated latent tuberculosis: a case-control study. *Br J Ophthalmol* 2012;96(3):332-36.
185. Strang JIG, Gibson DG, Mitchison DA, et al. Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. *Lancet* 1988;2:759-64.

186. Mayosi BM, Ntsekhe M, Volmink JA, et al. Interventions for treating tuberculous pericarditis. *Cochrane Database Syst Rev* 2002:CD000526.
187. Long R, Younes M, Patton N, et al. Tuberculous pericarditis: long term outcome in patients who received medical therapy alone. *Am Heart J* 1989;117:1133-39.
188. Long R, Guzman R, Greenberg H, et al. Tuberculous mycotic aneurysm of the aorta. Review of published medical and surgical experience. *Chest* 1999;155:522-31.
189. Burgin S, Pomeranz MK, Orbuch P, et al. Mycobacteria and the skin. In: Rom WN, Garay S, eds. *Tuberculosis*. Toronto: Little, Brown and Company, 2004;593-608.
190. Barbagallo J, Tager P, Ingleton R, Hirsch RJ, Weinberg JM. Cutaneous tuberculosis: diagnosis and treatment. *Am J Clin Dermatol* 2002;3(5):319-28.
191. Lowy J. Endocrine and metabolic manifestations of tuberculosis. In: Rom WN, Garay S, eds. *Tuberculosis*. Toronto: Little, Brown and Company, 1996;669-74.
192. Dutt AK, Moers D, Stead WW. Short course chemotherapy for extrapulmonary tuberculosis. *Ann Intern Med* 1986;104:7-12.
193. Blumberg HM, Burman WJ, Chaisson RE, et al. ATS/CDC and Prevention/Infectious Diseases Society of America. Treatment of tuberculosis. *Am J Respir Crit Care Med* 2003;167:603.
194. Caminero JA, Fuentes ZM, Martin TY, et al. A 6-month regime for EPTB with intermittent treatment in the continuation phase: a study of 679 cases. *Int J Tuberc Lung Dis* 2005;9(8): 890-95.