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CANADIAN TUBERCULOSIS STANDARDS—8TH EDITION

Chapter 7: Extra-pulmonary tuberculosis

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KEY POINTS

Diagnosis

- Samples (fluid and tissue) for extra-pulmonary tuberculosis (TB) should be sent for acid-fast bacilli smear, mycobacterial culture and nucleic acid amplification test. Tissue biopsy should be sent in sterile saline for these mycobacterial tests as well as in formalin for histopathologic assessment. Drug susceptibility testing should be requested for positive culture samples.
- If the specimen is insufficient for all testing, mycobacterial culture should be prioritized given it has the highest diagnostic yield and allows for gold-standard phenotypic drug testing.
- Every person with presumed extra-pulmonary TB should also be assessed for pulmonary TB to assess infectiousness and potentially assist with diagnosis.

Treatment

- A standard 6-month anti-TB treatment course for microbiologically confirmed, drug-susceptible disease is recommended for most forms of extra-pulmonary TB. In patients with meningitis or bone and joint TB, treatment may be extended to 12 months.
- In the absence of culture confirmation and drug susceptibility results, the continuation phase of empiric anti-TB treatment should include a third agent such as ethambutol.
- Empiric anti-TB therapy should be considered in suspected life-threatening extra-pulmonary TB while appropriate diagnostic samples are being obtained.

NEW AND UPDATED RECOMMENDATIONS

1. We conditionally recommend against routine adjunctive corticosteroid use for pleural TB.
2. We conditionally recommend against routine therapeutic thoracentesis/chest tube drainage for pleural TB-associated effusions.
3. We conditionally recommend using higher doses of rifampin (greater than 15 mg/kg/day orally up to maximum dose 35 mg/kg/day or 15 mg/kg/day intravenously [IV]) along with standard dose isoniazid, pyrazinamide, and ethambutol, during intensive phase of treatment for drug susceptible TB meningitis (TBM).
4. We conditionally recommend against using fluoroquinolone for TBM unless there is a concern regarding drug resistance.
5. We conditionally recommend initial adjunctive corticosteroid treatment in all human immunodeficiency virus (HIV)-negative patients with TB pericarditis. Routine use of adjunctive corticosteroids in people with HIV NOT on antiretroviral treatment is NOT recommended. Lack of data means we are unable to provide a specific recommendation on use of adjunctive corticosteroids in people with HIV ON antiretroviral treatment with TB pericarditis and suggest assessing on a case-by-case basis pending further study.

1. Introduction

Internationally, pulmonary TB is defined as disease involving the lung parenchyma or tracheobronchial tree. Extra-pulmonary TB (EPTB) is defined as disease involving any other organs and includes pleural and isolated intrathoracic lymph node TB.[1] This differs from the terminology for reporting in Canada, which classifies TB as either respiratory (lungs and the conducting airways, pleural, fibrosis of the lung, bronchiectasis, pneumonia, pneumothorax, primary, intrathoracic and mediastinal lymph nodes, isolated tracheal or bronchial, laryngitis, nasopharynx, nose and sinus TB) or nonrespiratory (all other disease sites not listed).[2] This chapter focuses on the diagnosis and treatment of EPTB.

Over the last 10 years in Canada, the incidence of EPTB has remained stable, similar to other low TB-incidence, and low HIV-TB co-infection countries.[3] Peripheral TB lymphadenitis, pleural TB and abdominal TB have remained the three most common types of EPTB (see Chapter 1: Epidemiology of Tuberculosis in Canada). Impaired host immune status is a risk factor for EPTB and increases associated mortality. Organ transplant recipients, persons with advanced HIV and those undergoing chemotherapy for malignancies are at particularly high risk of life-threatening disease.[4–9]

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Table 1. Sensitivity and specificity of diagnostic tests in extra-pulmonary tuberculosis compared to mycobacterial culture as gold standard unless otherwise stated.

		Direct stain (ZN)	Culture	GeneXpert[a]		GeneXpert Ultra[a]		Histopathology and/or cytology	
Site	**Specimen type**	**Sensitivity**	**Sensitivity**	**Sensitivity[b]**	**Specificity[b]**	**Sensitivity[b]**	**Specificity[b]**	**Sensitivity**	**References**
TB lymphadenitis	FNA	0.23-0.37	0.17-0.67	0.89	0.86		INS	0.62-0.80[d]	10–14
	Excisional biopsy	0.35-0.53	0.71-0.80	0.82[c]	0.80[c]			0.85-1.00[d]	
Pleural TB	Pleural Fluid	0-0.10	0.10-0.63	0.50	0.99	0.75	0.87	N/A	14–24
				0.19[d]	0.99[d]				
	Closed pleural biopsy	0.13-0.39	0.39-0.67	0.31	0.97		INS	0.69-0.97[d]	
	Thoracoscopic pleural biopsy	INS	0.41-0.76	0.52[e]	1.0[e]			1.0[d,f]	
CNS - meningitis	CSF	0.05-0.83[g]	0.40-0.87[g]	0.71	0.97	0.89[h]	0.91[h]	N/A	23,25–35
						0.63[d,h]	0.99[d,h]		
CNS - tuberculoma	FNA	INS	INS	INS			INS	0.85-0.92[d]	
	Biopsy (excisional/stereotactic)	0.17-0.38[f]	0.5-0.8[f]	0.87-1[f]	0.89-0.96[f]		INS	1[f]	
Abdominal TB	Feces	0-0.11[i]	0.44-0.5[i]	0.39[d]	0.86[d]		INS	INS	23,36–49
	Ascitic fluid	0.0-0.06	0.17-0.80	0.5	0.98		INS		
	Peritoneal biopsy	0.02-0.20	0.34-0.92	0.38-0.5[d,f]	0.92-1.0[d,f]		INS	0.76-1[d]	
	Intestinal biopsy	0.03-0.14	0.36-0.40	0.08-0.32[d,f]	1.0[d,f]		INS	0.16-0.7[d]	
GU TB - renal	Urine	0.15-0.30	0.80-0.90	0.83	0.98	1.00[j]	1.00[j]	N/A	23,25,50–71
	FNA/biopsy	0.29-0.44	0.95-1.0[b,j]	INS			INS	0.88-0.95[j]	
GU TB - scrotal	Urine	0.20-0.24	0.63-0.93[b]	0.83	0.98		INS	N/A	
	FNA/Biopsy	0.25-0.75	0.8[e]	INS			INS	0.95[d,e]	
GU TB - female tract	Menstrual fluid	0.03-0.05	0.06-0.19	INS			INS	N/A	
	Endometrial biopsy	0.05-0.57	0.06-0.46	INS			INS	0.07-0.71[d]	
Bone and Joint TB	FNA bone/synovial tissue	0.30-0.36	0.37-0.97	0.95	0.85	0.96[k]	0.97[k]	0.56-0.97	23,50–53,72–80
	Synovial fluid	0.08-0.26	0.50-0.86	0.97	0.90	0.96[k]	0.97[k]	n/a	
	Paraspinal fluid	0.52-0.59	0.9-0.93	0.97	0.90	0.96[k]	0.97[k]	n/a	
Pericardial TB	Pericardial fluid	0-0.42[j]	0.20-0.86	0.61	0.90		INS	N/A	13,14,23,81–88
	Pericardial biopsy	0.38-0.40[j]	0.22-1.0	0.71[e,j]	1.0[e,j]			0.34-0.87[d]	
Disseminated TB[l]	Sputum	0.31-0.37	0.32-0.90	INS			INS	INS	23,89–96
	Bronchial wash	0.20-0.55	0.07-0.71	INS			INS	INS	
	Lung biopsy	0.25-0.43	0.42-0.54	INS			INS	0.63-0.95	
	Liver biopsy	0.13-0.40	0.33-0.54	INS			INS	0.88-1.00	
	Bone marrow	0.16-0.25	0.21-0.67	INS			INS	0.56-0.67	
	Urine	0.00-0.18	0.33-0.67	INS			INS	INS	
	Blood	INS	0.20-0.65	0.07-0.56	0.94-1.0		INS	INS	

Abbreviations: TB, tuberculosis; ZN, Ziehl-Neelsen; SN, sensitivity; SP, specificity; FNA, fine-needle aspiration; INS, insufficient reported data; CNS, central nervous system; CSF, cerebrospinal fluid; GU, genitourinary; N/A, nonapplicable; HIV, human immunodeficiency virus.

Reported data from single studies and meta-analyses included a minimum of 50 patients unless otherwise noted.

Reported data from single studies come from HIV-negative cohorts or studies with a TB-HIV coinfection rate of less than 5% (where reported and if available). Data from meta-analyses that included studies with HIV prevalence greater than 5% and that reported a difference in diagnostics based on HIV status are noted.

[a]GeneXpert and GeneXpert Ultra data provided as data from individual NAAT available in single site small studies.

[b]Point estimates used for data provided from meta-analyses.

[c]Data from Cochrane review does not define method of obtaining biopsy sample.[14]

[d]Composite reference standard definition: Positive result as the presence of granulomatous inflammation or a positive microbiologic result +/- clinical diagnosis of TB and/or improvement on TB treatment.

[e]Single study data.

[f]Data limited to two studies (combined n > 50).

[g]Higher range sensitivity with larger volume (10 cc, 3 samples) concentrated samples (centrifuged at 3000 g).

[h]Majority of people with HIV and from single study.[32]

[i]Majority of studies do not explicitly state if abdominal TB or intestinal TB present (many state disseminated disease). Presence of stool AFB and positive culture/Xpert documented in isolated pulmonary disease (primarily in children and HIV/AIDS studies).

[j]Less than 50 patients.

[k]Biopsy and fluid samples combined.

[l]Disseminated TB includes miliary TB, as some included autopsy data did not allow differentiation.

2. General diagnostic considerations

A high index of suspicion is paramount to the diagnosis of EPTB. Any delay in diagnosis could increase the risk of morbidity and mortality.[18] In 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.

Gold-standard phenotypic drug susceptibility testing can only proceed with a viable culture, the results of which can have important treatment implications.[7,19,20] This point cannot be overemphasized: with the rising incidence of drug-resistant TB, especially in foreign-born residents of Canada, it is difficult to provide appropriate treatment when mycobacterial cultures and drug susceptibility test results are not available.

The clinical specimens obtained for diagnostic purposes will depend upon the suspected anatomic site of involvement. In general, tissue biopsy yields positive nucleic acid amplification test (NAAT) and culture results more often than fluid aspiration; both are superior to swabs (see Table 1 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 kills the mycobacteria and prevents further culture confirmation.[19,20] Common histopathologic findings include necrotizing and non-necrotizing granulomas (Table 1). Loss of host immune function can result in histopathologic findings demonstrating greater suppurative response and less well-formed granulomas.[88]

Good practice statement

- **Every effort should be made to obtain clinical samples for both mycobacteriologic (acid-fast bacilli smear, culture, nucleic acid amplification test) and histopathologic tests. If the specimen is insufficient for all testing, mycobacterial culture should be prioritized given it has the highest diagnostic yield and allows for gold-standard phenotypic drug testing.**

Anywhere from 10 to 50% of patients with EPTB also have pulmonary involvement; it may, therefore, be possible to confirm a diagnosis of TB (and obtain drug susceptibility testing) with sputa assessments, averting the need for more invasive sampling.[20]

Good practice statement

- **Every person with presumed extra-pulmonary TB should be assessed for pulmonary TB to assess infectiousness and potentially assist with diagnosis.**

3. Clinical presentations by organ-specific site

Clinical presentation, investigations and management by organ specific site are reviewed in the following sections. Evidence for treatment duration and other adjunct measures for each organ site is summarized in Table 3. Examples of published corticosteroid regimens for relevant organ sites are described in Table 2.

3.1. Peripheral TB lymphadenitis

Almost all forms of TB involve regional lymphatics and nodes. This section will focus on extrathoracic lymph nodes and, specifically, peripheral TB lymphadenitis.

Mycobacterial involvement of the lymph glands can be secondary to infection from Mycobacterium tuberculosis (*M. tuberculosis*) as well as other non-TB mycobacteria (NTM).[97] Unilateral cervical chain involvement is the most common site of TB lymphadenitis (45 to 80%) but lymphadenitis can occur in the supraclavicular and axillary regions, as well as a variety of other nodal sites.[98–100] Presentation can be at a single nodal site or in multiple sites.

In general, the disease is most often indolent, and the patient usually presents with an isolated, unilateral, nontender neck mass.[98] The term "scrofula" has been used historically to describe TB involvement of a cervical lymph node with sinus tract formation or ulceration of the overlying skin. Non-nodal symptoms are rare, except in people with HIV.[101,102]

Fine-needle aspiration (FNA) biopsy of affected lymph nodes is a useful initial procedure (see Table 1). If FNA is nondiagnostic, the highest-yield procedure is an excisional lymph node biopsy. If there is high suspicion for an alternate diagnosis (eg, lymphoma), clinicians may choose to pursue excisional biopsy as the initial diagnostic test. Incisional biopsies are discouraged for initial testing because of the risk of sinus tract formation at the biopsy site in mycobacterial disease.[103] 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.[104] Specimens should be submitted for both mycobacteriologic (smear, culture and NAAT) and histopathologic analysis. Differentiation of *M. tuberculosis* from *M. avium complex* is important, as treatment of the 2 conditions is different.

3.1.1. TB lymphadenitis treatment

Two small randomized controls trials that compared 6- versus 9-month treatment courses did not report any difference in treatment completion or relapse rates.[105,106] Three systematic reviews that also included observational studies reported the same findings.[107–109]

Recommendation

- **We conditionally recommend six months of standard anti-TB therapy for treating drug-susceptible TB lymphadenitis** (*poor evidence*).

In up to 23% of patients, nodes can appear afresh or enlarge during treatment, possibly as an immune response.

This usually will resolve without change in regime or additional therapy and should not be considered evidence of treatment failure.[110] At the end of treatment, up to 34% of patients may be left with residual nodes and, if after treatment, the nodes enlarge or reappear, this is usually transient.[107] Such events do not necessarily imply relapse, but repeat FNA for mycobacterial culture should be considered to assess this possibility if the nodes are persistent.[111,112]

Good practice statement

- **In TB lymphadenitis, surgical/drainage procedures, other than diagnostic, should be reserved for the relief of discomfort caused by enlarged nodes or tense, fluctuant nodes.**

3.2. Pleural TB

TB pleural-space disease can range from simple TB pleural effusion to TB empyema. Fever, unilateral pleuritic chest pain and cough are the most frequent presenting symptoms in TB pleural effusion. Dyspnea, night sweats and weight loss are also common.[113] TB pleural effusion is typically paucibacillary and often culture negative.[113] In some patients, TB pleural effusion may spontaneously resolve within 2 to 4 months without treatment; however, up to 65% will subsequently develop active TB within the following 5 years.[114]

TB empyema is less common than TB pleural effusion and characterized by purulent pleural space and presence of acid-fast bacilli on fluid microscopy.[115]

TB pleural effusions are usually unilateral and can occur on either side of the chest.[15,115,116] Effusions are usually small to moderate in size but in some cases can occupy over two-thirds of the hemithorax.[15,116] Co-existing parenchymal abnormalities on chest x-ray are reported in 19 to 67% of patients.[17,116,117] Chest computed tomography (CT) imaging usually demonstrates smooth pleural thickening with an associated effusion. Parenchymal abnormalities on chest CT are reported in up to 86% of cases.[117,118] Pleural ultrasound can assist in diagnostic procedures for pleural TB, but imaging findings are nonspecific.[119]

Even in patients without parenchymal abnormalities on chest x-ray, the yield of induced sputum culture for *M. tuberculosis* is over 50%.[15,120] TB pleural fluid is exudative and typically straw colored. Pleural fluid glucose may be low or normal. Pleural fluid pH is usually above 7.3. The majority of TB pleural effusions are lymphocyte predominant. However, a neutrophil predominance may be seen in the very early stages of infection or if TB empyema develops.[113,121] Pleural fluid adenosine deaminase (ADA) testing is not used in Canada (see Chapter 3: Diagnosis of Tuberculosis Disease and Drug-resistant Tuberculosis). Diagnosis is based on bacteriologic confirmation (positive acid-fast bacilli [AFB] smear and/or positive culture and/or NAAT), histologic confirmation (granulomas with or without necrosis, and with or without positive AFB smears on pleural biopsy) or typical radiological features with confirmed TB in other sites. The diagnostic yield(s) for pleural TB microbiologic investigations are summarized in Table 1.

Good practice statement

- **In patients with suspected TB pleural effusion, pleural fluid should be sent for cell count and differential, protein, glucose, pH, lactate dehydrogenase, acid-fast bacilli smear and culture, Gram stain and culture, nucleic acid amplification test and cytology.**

If pleural and sputum samples are nondiagnostic, pleural biopsy should be considered for definitive diagnosis, given higher diagnostic yield from tissue samples. Timing of pleural biopsy (waiting for final pleural/sputa mycobacterial culture results versus expedited biopsy if NAAT and smears are negative) should be determined on a case-by-case basis, based on patient's clinical scenario.

Biopsy samples should be sent for AFB smear, NAAT and culture (in saline) and for histopathology in cytolyte/formalin. Either image-guided closed or thoracoscopic pleural biopsy can be performed, dependent on local resources and expertise.

3.2.1. Pleural TB treatment

Data from multiple observational studies has demonstrated high rates of treatment completion with low relapse rate with 6 months of therapy. Medical treatment of TB pleural effusion results in successful outcomes in more than 85% of patients.[122–125]

Based on data from a Cochrane review, adjunctive corticosteroids may accelerate the resolution of pleural fluid and reduce pleural thickening. However, there is no evidence that steroids impact lung function and steroids are associated with adverse effects.[126]

Two small randomized trials have compared therapeutic drainage (thoracentesis or chest tube) and found conflicting results.[123,127] In one study, chest tube drainage did not reduce residual pleural thickening or improve end-of-treatment forced vital capacity (FVC).[133] In the second study, thoracentesis was associated with less residual fluid and a higher FVC at the end of treatment, though the difference was minimal and likely not clinically significant.[137]

Recommendations

- **We conditionally recommend six months of standard anti-TB therapy for treating drug susceptible pleural TB** (*poor evidence*).
- **We conditionally recommend against routine adjunctive corticosteroid use for pleural TB** (*poor evidence*).
- **We conditionally recommend against routine therapeutic thoracentesis/chest tube drainage for pleural TB-associated effusions** (*poor evidence*).

Good practice statement

- **In patients with significant dyspnea, therapeutic thoracentesis may be considered on a case-by-case basis to relieve symptoms.**

Fevers usually resolve within 2 weeks of treatment initiation but may take up to 2 months for full resolution in some cases.[113,128] Paradoxical radiologic worsening may occur early after initiation of therapy in up to 26% of patients.[118] In most cases, pleural fluid resolves after 6 weeks but may last up to 3 months.[128]

TB empyema is diagnosed based on the presence of purulent fluid in a patient with TB pleural space infection.[115] Based on expert opinion, drainage and/or decortication is recommended in addition to standard anti-TB therapy.[113,129] There are limited data to guide the optimal composition/duration of therapy or the use of adjunctive treatments such as intrapleural thrombolytics.[129,130] Consultation with a TB expert is recommended in this setting.

3.3. Abdominal TB

Abdominal TB can be subdivided into clinically distinct or overlapping presentations, comprising gastrointestinal disease (luminal), peritoneal, visceral, and abdominal lymph node disease. Gastrointestinal and peritoneal forms of TB disease occur most frequently and are the focus of this section. Isolated visceral and abdominal lymph node disease are uncommon forms of abdominal TB.[131,132]

3.3.1. Gastrointestinal TB

TB may affect any part of the gastrointestinal tract. Ileocecal and jejunoileal involvement are most common (up to 75% of cases), followed by colorectal disease (majority on right side).[131–134] Gastrointestinal TB, particularly ileocecal disease, may present with clinical and radiographic features that are indistinguishable from Crohn's disease, such as chronic abdominal pain, constitutional symptoms and a right lower quadrant mass.[135,136] Mesenteric lymph node enlargement is more commonly found on diagnostic imaging in patients with gastrointestinal TB than in patients with inflammatory bowel disease.[137–140]

Diagnostic testing for gastrointestinal TB includes stool studies for *M. tuberculosis* and, where available, endoscopy for biopsies with multiple dedicated samples sent for both culture/NAAT in saline and histopathology to maximize diagnostic yield. Collectively, these tests may support or confirm diagnosis of TB in up to 70% of cases (see Table 1).[133,141–143]

If endoscopy is nondiagnostic, laparoscopy/laparotomy can be considered for definitive diagnosis. An empiric trial of anti-TB therapy may be required in some cases. However, in addition to the usual concerns regarding empiric therapy, partial short-term clinical response of Crohn's disease to anti-TB therapy is well described and may confound diagnosis.[144] Such delays in Crohn's disease treatment have been shown to worsen long-term outcomes (increased rates of stricture and future surgery).[135,144,145] When empiric TB therapy is pursued, end-of-treatment endoscopy may be helpful in differentiating TB disease as significant or complete mucosal healing is reported in more than 75% of cases.[133,143]

3.3.2. Peritoneal TB

TB involving the peritoneum presents most commonly (in more than 60% of cases) with abdominal swelling secondary to ascites, often concurrent with abdominal pain, fevers and/or weight loss.[38,40] Individuals with chronic liver disease (particularly alcoholic liver disease), chronic renal disease and HIV are at increased risk.[7,18,146]

Radiologic assessment can be helpful but is not diagnostic in peritoneal TB.[137,140,147] Diagnosis of peritoneal TB typically starts with percutaneous sampling of ascites for fluid analysis, microscopy and culture. Assessment of ascitic fluid classically demonstrates a proteinaceous exudative pattern (protein greater than 30 grams per L) with a predominance of lymphocytes (greater than 70%) and a low (less than 11 grams per L) serum ascites albumin gradient (SAAG). However, when TB peritonitis complicates chronic peritoneal dialysis or decompensated cirrhosis, it may not have this typical ascites profile. Ascitic fluid is rarely AFB-smear positive but may culture *M. Tuberculosis* in up to 80% of cases. Larger volume (greater than 1 liter) and concentration of samples are reported to increase culture yield.[38,148] If ascitic fluid sampling is nondiagnostic, peritoneal biopsy (diagnostic image-guided or laparoscopic) for AFB smear, culture, NAAT and histopathology should be considered, as diagnostic yield for peritoneal tissues is significantly higher than ascitic fluid alone (See Table 1).[38,41,149] ADA testing is not used in Canada (see Chapter 3: Diagnosis of Tuberculosis Disease and Drug-resistant Tuberculosis).

It is important to recognize that peritoneal and other forms of TB can cause an elevation in serum tumor marker CA 125 levels. Given shared radiographic findings with peritoneal carcinomatosis of metastatic ovarian cancer, there are numerous case reports of misdiagnosis of malignancy, underscoring the importance of pursuing tissue and/or culture diagnosis of peritoneal TB.[39,150]

3.3.3. Abdominal TB treatment

Three clinical trials evaluating treatment of abdominal TB consistently found that 6 months of standard anti-TB treatment is adequate in individuals with drug-susceptible abdominal TB and extension of treatment does not significantly improve clinical cure or relapse risk. The available evidence is limited to HIV-negative individuals and strongest for gastrointestinal forms of abdominal TB.[151]

Surgery should generally be reserved for abdominal TB cases with serious complications, such as perforation, bleeding or obstruction.[152]

Recommendation

- **We conditionally recommend six months of standard anti-TB therapy for all forms of drug-susceptible abdominal TB** (*poor evidence*).

3.4. Bone and joint TB

3.4.1. Spinal/vertebral disease

Spinal or vertebral TB (Pott's disease) involvement is noted in approximately 50% of bone and joint TB cases.[52,153–155]

Most patients present with slowly progressive back pain.[156–157] Fever and constitutional symptoms are not common unless there is concurrent extraspinal or disseminated disease. Given nonspecific complaints, the diagnosis of spinal TB usually is not made until several months after the beginning of symptoms.[72,73,80,154,155,156–162] Radiographic findings include loss of vertebral body height and scalloping of vertebral bodies by paraspinous fluid collections; however, these findings are insensitive.[163] CT and magnetic resonance imaging (MRI) imaging are more sensitive for detection of vertebral and soft-tissue abnormalities associated with spinal TB.[163] Findings include anterior vertebral involvement of thoracic or lumbar vertebrae adjacent to the endplate with evidence of marrow edema with minimal sclerosis; discitis of intervening disks with preservation of the disk until late in disease; and large paraspinal abscesses (calcification being suggestive of TB). MRI is the modality of choice for assessing spinal cord involvement or damage.[80,159,160,163–168]

CT-guided needle biopsy of vertebrae and/or aspiration of paraspinal fluid collections have the highest diagnostic yield, outside of surgery, and are the recommended initial diagnostic sampling method (Table 1).[23,72,73,77] If CT guided sampling cannot be performed or is nondiagnostic, a surgical biopsy can be obtained for definitive diagnosis and to assess for etiologies other than TB osteomyelitis.[23,50,72,78,169–174] It is important to assess the patient for other manifestations of TB disease, as studies have 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 nonspinal specimens.[73]

3.4.2. Joint TB (TB arthritis)

Joint TB 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 often 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.[52,175–178] Multifocal presentations can occur in 15% to 20% of cases, often in immune-suppressed individuals, and can be misinterpreted as metastases or inflammatory arthritis.[74,179]

Radiologic findings suggestive of joint TB include synovial thickening and joint effusion, however differentiation from other arthritic conditions can be difficult. MRI changes suggestive of joint TB include moderate but uniform thickening of the synovium, as compared with the larger and irregular thickening seen in rheumatoid arthritis. Adjacent fasciitis and cellulitis can be seen in both TB and pyogenic arthritis but are more indicative of a pyogenic arthritis.[153,164,177–181]

Synovial fluid aspirate is a reasonable first step in obtaining a diagnosis of joint TB.[79,153,178,182] Typical synovial fluid findings are that of an elevated white blood cell count (WBC) (10,000 to 20,000 WBC per ml with neutrophil predominance), decreased glucose (less than 2.2 mmol per L) and elevated protein (greater than 25 g per L).[79,153,157,178] The yield of synovial-fluid AFB smear is low (19%); however, NAAT and mycobacterial culture synovial-fluid sensitivity is relatively high at 75 to 85%.[23,50,51,74,75,79,153,178,182] Synovial biopsy with sampling for NAAT, mycobacterial smear and culture, as well as histopathology, has high diagnostic yield (94%) and should be obtained if joint TB is still a diagnostic consideration and synovial fluid mycobacteriology assessment is negative (Table 1).[23,50,51,74,75,79,153,178,182]

3.4.3. Bone and joint TB treatment

In a review of bone and joint TB treatment with isoniazid (INH) and rifampin (RMP) anti-TB therapy for individuals with drug-susceptible TB (majority of studies were observational cohort in adults and children), a risk of relapse was 1.35% with 6 months of anti-TB therapy (539 individuals studied), 0.86% with 6-12 months of anti-TB therapy (437 individuals studied) and 0.51% with greater than 12 months of anti-TB therapy (1,386 individuals studied).[183] Similar outcomes were identified in 2 small randomized controlled trials.[184–186]

Increased risk of failure/relapse has been associated with extensive disease at the outset of treatment (radiographically defined or with evidence of smear positivity at beginning of therapy), evidence of sclerotic bony disease on imaging, and Erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) (both measures of inflammatory response) elevation at end of treatment.[162,183] The definition of cure is difficult in bone and joint TB, and follow-up samples are infrequently obtained to demonstrate lack of mycobacterial growth. Alternative definitions of cure have utilized radiologic markers; however, vertebral x-rays may never return to baseline and studies in spinal TB have shown that 50% of patients will have MRI evidence of TB activity even at the end of 12 months of treatment.[165,168,187] Studies utilizing vertebral CT positron emission tomography (PET) imaging have suggested decrease in PET activity may predict when TB treatment for spinal TB can be safely discontinued, but there is not enough evidence to recommend currently.[188] Routine surgery for bone and joint TB is not required to achieve cure, but should be considered to treat complications of vertebral TB (neurologic compromise) and joint disease (pain and immobility).[161,185,189]

Recommendations

- **We conditionally recommend 6 months of standard anti-TB therapy for individuals with drug-susceptible bone and joint TB with extension to 9-12 months in individuals with markers of increased risk of failure/relapse; diagnostic biopsy sample smear positive for acid-fast bacilli and/or elevated erythrocyte sedimentation rate/C-reactive protein (ESR/CRP) at planned end of treatment** (*poor evidence*).
- **We conditionally recommend against routine surgical intervention as part of treatment in spinal TB. Surgical treatment of spinal TB should be considered in those with progressive neurologic deterioration and in those less than 15 years of age with significant kyphosis** (*poor evidence*).

- **We conditionally recommend against routine surgical intervention as part of treatment in joint TB. Surgical treatment should be considered to prevent extension of disease and to provide relief of pain and immobility after control of infection is established** (*poor evidence*).

3.5. Central nervous system (CNS) TB

CNS TB refers to the clinical and pathological spectrum of TBM, spinal TB arachnoiditis and tuberculoma. The epidemiology of CNS TB varies by regional TB prevalence. In areas of high TB prevalence, CNS TB occurs more commonly among children and young adults, whereas TBM predominates and occurs more commonly in adults as reactivation disease in low-prevalence settings. In one retrospective Canadian series, 75% of CNS TB disease was adult TBM.[190–192]

3.5.1. TBM

TBM is the most severe and rapidly progressive form of TB, meaning suspected cases must be treated as a medical emergency. Young children (less than 5 years) and people with HIV are at greatest risk of TBM. Although classically, TBM is described as a slow progressive meningitis syndrome, 50% of people with TBM are ill for less than 2 weeks before diagnosis.[193] TBM may have a prodrome of headache, malaise, fever and personality changes, followed by meningismus, cranial nerve palsies and confusion.[194]

Prior to the development of anti-TB therapy, TBM was universally fatal. Despite major advances in diagnosis and treatment, global mortality estimates for TBM remain high (20-40%), with up to 50% of survivors suffering permanent neurologic deficits and long-term disability.[194–197] Unfavorable outcomes in TBM correlate with older age, immunosuppression, presence of hydrocephalus and/or vasculitis and more advanced clinical stage at time of presentation.[193,198,199] Prognostic models have been developed for the prediction of unfavorable outcomes among adults (greater than 14 years of age) with TBM.[198,200]

Neurologic imaging in TBM can support the diagnosis; inform prognosis; and identify a need for neurosurgical intervention. Basal meningeal enhancement on contrast-enhanced CT has high specificity for TBM (greater than 90% in adults and children), further increased by additional findings of infarcts and hydrocephalus that may become more apparent in later-stage disease.[194,201] Gadolinium-enhanced MRI of the brain provides improved identification of early disease by visualization of localized leptomeningeal disease, characterization of ischemia and early infarction and superior evaluation of cranial nerve and brain stem involvement, compared with CT. However, both CT and MRI lack diagnostic sensitivity. Typical findings may be less prominent or absent in 15-30% of children, those with early disease, and those with advanced HIV.[202,203]

Lumbar puncture should be performed when feasible as the preferred diagnostic test for TBM. Early in the disease, cerebrospinal fluid (CSF) measurements are often normal. With disease progression, opening pressure becomes elevated, with low glucose levels (less than 2.5 mmol per L), elevated protein (greater than or equal to 0.5 g per L) and a moderate pleocytosis with lymphocyte/mononuclear cell predominance (100-500 total white cells per mL).[204] Identification of *M. tuberculosis* in CSF is the standard for definite diagnosis of TBM (Table 1). However, the paucibacillary nature of TBM limits the diagnostic yield of microbial tests. Large volume sampling (7 to 15 mL, 3 serial samples), concentration of samples, experienced laboratory-technician review and the inclusion of more gene targets in NAATs can maximize diagnostic yield.[23,205–207] Based on the insensitivity of CSF microscopy and diagnostic delay of culture-based methods, NAAT testing should be performed if adequate volume of CSF is available to assist with rapid diagnosis.[208,209] Among commercially available NAATs, GeneXpert ULTRA has the best-available evidence supporting high sensitivity and should be used when possible.[32]

3.5.2. TBM treatment

Clinical suspicion of TBM should be based upon presence of epidemiological risk factors and clinical features for TB, as well as relative suspicion of alternate diagnosis. Treatment started during early-stage TBM disease may decrease mortality to less than 10%.[206,210–212]

Good practice statement

- **In cases with high suspicion of TB meningitis, we suggest initiating empiric therapy immediately while awaiting diagnostic results, to reduce mortality and prevent complications.**

An optimal anti-TB therapy regimen for TBM remains uncertain. Current guidelines from the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America, National Institute for Health and Care Excellence, American Academy of Pediatrics and World Health Organization (WHO) recommend standard dose RMP and INH with pyrazinamide (PZA) during initial two-month intensive phase, with lack of consensus on the best fourth agent.[213–218]

Based on relatively low CNS penetration of RMP, a series of clinical trials have evaluated the clinical and pharmacokinetic outcomes of higher dose ("intensified") RMP as part of intensive-phase regimens for TBM (in these studies high dose RMP was not given throughout full duration of treatment). Although published studies have not identified an optimal dose or conclusively demonstrated clinical benefit, there are now compelling and consistent findings for both RMP CNS-concentration response correlation and safety studies supporting use of higher-dose RMP regimens.[219–226]

Recommendation

- **We conditionally recommend using higher doses of rifampin (greater than 15 mg/kg/day orally, up to a**

maximum dose of 35 mg/kg/day orally or 20 mg/kg/day IV) along with standard dose isoniazid, pyrazinamide and ethambutol during the intensive phase treatment for drug-susceptible TB meningitis (*poor evidence*).

In the absence of clinical trial data regarding the optimal fourth drug in a TBM regimen, the American Pediatric Association and the WHO advise the use of streptomycin or ethionamide in place of ethambutol (EMB), based on low CNS penetration of EMB and difficulty monitoring EMB toxicity in children.[227] Although fluoroquinolones have a favorable CNS-penetration profile, clinical trials evaluating their use as a fourth agent for TBM in adults and children have not shown benefit outside of drug-resistant disease and raise concern about adverse effects.[228–231] Second-line drugs with favorable CNS-penetration profiles (linezolid, ethionamide) lack adequate quality clinical data to support standard use at this time.[232,233,234,235,219]

Recommendation

- **We conditionally recommend against using fluoroquinolone for TB meningitis unless there is a concern about drug resistance** (*poor evidence*).

No clinical trials have directly assessed duration of anti-TB treatment for CNS TB. A review of TBM observational studies did not find increased relapse among those treated for 6 months.[236] However, given concerns about variable CNS drug penetration and potential for significant harm from relapsed disease if undertreated, current American, British and WHO guidelines continue to recommend a minimum of nine months and up to 12 months of anti-TB therapy for all forms of drug-susceptible CNS-TB.[190,214,217,237,238] Based on poor evidence for extended duration of therapy, if issues with anti-TB therapy tolerance occur, then continuation beyond 6 months should be reevaluated in consultation with an expert in TB.

Recommendation

- **We conditionally recommend, given the severity of disease and risk of morbidity with inadequate treatment of central nervous system TB, extending treatment to 9-12 months for drug-susceptible disease** (*poor evidence*).

In addition to anti-TB therapy, measures to mitigate elevated intracranial pressure and prevent hydrocephalus and infarction are important. Adjunctive steroids have been shown to reduce short-term mortality of TBM but have not been demonstrated to reduce disabling neurologic defects or longer-term survival.[194,197,239,240] (Table 2 Corticosteroid Dosing).

Recommendation

- **We strongly recommend that all individuals presenting with TB meningitis receive a course of corticosteroids guided by disease severity** (*good evidence*).

Several small controlled trials using aspirin (ASA), in addition to anti-TB therapy and corticosteroids, for TBM in both adults and children have suggested potential benefit (reduction of new infarctions and decrease in 60-day mortality) without added harm. Studied ASA regimens ranged from 81 to 1000 mg per day for the initial 1-2 months of treatment.[241,242] Given the preliminary nature of these findings, recommendation for the addition of ASA to TBM treatment cannot be made at this time but may change with results from pending studies in both adults and children.[243,244]

Several large clinical studies evaluating TBM treatment are currently underway (INTENSE-TBM, HARVEST, and TBM-KIDS) and guideline recommendations will be refined as data from the trials become available.[219–221]

3.5.3. Tuberculoma and spinal TB arachnoiditis

Both tuberculoma and spinal TB arachnoiditis may occur with TBM. Spinal disease (often clinically occult) has been reported in up to 76% of TBM cases and brain tuberculomas in approximately 10% of TBM cases, with even higher prevalence in people with HIV.[195,242,245] When presenting in isolation, symptoms are more typically subacute and neurologic in nature relating to mass effect (headache and/or focal neurologic signs of hemiplegia, nerve root compression and spinal cord syndromes), in contrast to the more acute infectious and inflammatory presentation of TBM.[191,212]

Contrast-enhanced CT and gadolinium-enhanced MRI can demonstrate solitary or multiple ring-enhancing lesions suggestive of tuberculoma in the brain and spinal cord. MRI offers improved visualization of spinal TB arachnoiditis and associated epidural space infection, myelitis, spondylitis and nerve root involvement.[201] When possible, a tissue/microbiologic diagnosis should be pursued prior to treatment initiation (Table 1). If empiric therapy is commenced, it is important to note that paradoxical clinical (30%) and radiographic (65%) worsening during the first 6 months of effective therapy is common and confounds assessment of treatment response. Follow-up neuroimaging should be used primarily to evaluate for alternate diagnoses and complications, and be interpreted in concert with clinical and microbiological information.[246]

3.5.4. Tuberculoma treatment

There are no controlled trials evaluating optimal management of either tuberculoma or TB arachnoiditis. Recommendations for treatment duration and adjunctive corticosteroids are extrapolated from observational and clinical trial data for TBM.[246]

Good practice statement

- **In cases of drug-susceptible tuberculoma and spinal arachnoiditis, 9-12 months of standard anti-TB therapy is suggested, given the severity of disease and risk of morbidity with inadequate treatment.**

Extrapolating from other inflammatory parenchymal CNS diseases (ie, cancer) and limited observational data,

corticosteroids may have a limited role for symptom relief in the context of tuberculomas with vasogenic edema-associated neurologic symptoms.[190]

Recommendation

- **We conditionally recommend against universal use of adjunctive corticosteroids in cases of central nervous system tuberculoma without meningitis** (*poor evidence*).

The Tuberculosis Meningitis International Research Consortium has compiled a collection of peer-reviewed, open-access expert reviews to address the rapidly evolving field of CNS-TB diagnosis and management (https://wellcomeopenresearch.org/collections/tbmeningitis). A comprehensive review of the management of complications associated with CNS-TB has also recently been by published by Donovan et al.[247]

3.6. Disseminated TB

Disseminated TB is defined as disease occurring in two or more noncontiguous organs or the isolation of *M. tuberculosis* in blood, bone marrow or liver biopsy.[21] Miliary TB is a distinct subset of disseminated TB, one that comes with increased mortality.[248] Hematogenous dissemination of TB in miliary disease causes formation of minute tubercles throughout multiple organs, often resulting in characteristic uniform micronodular (1-5 mm) changes on lung imaging and life-threatening systemic illness.[95]

The clinical presentation of disseminated TB is often nonspecific. Fever, night sweats, anorexia, weight loss and weakness are commonly reported, while respiratory or other organ-specific symptoms occur less frequently.[94,96,249,250] Clinical presentation is often subacute or chronic, although acute fulminant deterioration (including shock and acute respiratory distress syndrome) has been described.[251,252] In elderly patients, disseminated TB may mimic metastatic carcinoma, being characterized by progressive wasting alone. The absence of fever and chest radiograph changes in this setting can confound TB diagnostic work-up.[253,254] Funduscopic exam demonstrating choroidal tubercles is a specific finding and occurs in up to 20% of cases among people with HIV.[255,256] The nonspecific and often variable presentation of disseminated TB frequently leads to a delay or lack of diagnosis and a high mortality rate.[96,257]

Good practice statement

- **In severely ill cases, or in those with significant immunocompromising conditions, empiric anti-TB treatment should be considered to prevent morbidity and death while waiting for mycobacterial culture confirmation.**

Laboratory findings in disseminated TB are nonspecific, though hematologic abnormalities are common, and hypoalbuminemia, hypercalcemia and elevated ferritin portend a worse prognosis.[95,96] Between 30 and 50% of cases do not have the classic discrete micronodular or "miliary" pattern on chest radiograph.[95] High-resolution CT is more sensitive than chest radiograph, though not necessarily specific for miliary TB.[258] Prompt examination of AFB smear, NAAT and culture of sputum and urine, along with clinical specimens from multiple sites where disease may be clinically or radiographically apparent (pleural, pericardial, peritoneal, CSF, liver, bone marrow, blood) increases the probability of a positive result and may obviate the need for more invasive tissue biopsy testing (Table 1).[93,94,96,248] Positron emission tomography-computed tomography (PET-CT) scan may aid in the work-up of disseminated TB by accurately mapping involved lymph nodes to improve diagnostic yield of minimally invasive sampling.[259] However, limited accessibility may make routine use of PET-CT impractical and delayed access should not delay other investigations or treatment. CNS involvement in disseminated TB may occur in 10-30% of cases, with increased prevalence among people with HIV. Thorough clinical assessment and a low threshold for neuroimaging and lumbar puncture, among those with objective neurologic findings, is advised when disseminated TB is suspected or confirmed.

3.6.1. Disseminated TB treatment

There are no clinical trials specifically evaluating optimal therapy for disseminated TB and observational studies are confounded by variable definitions. Existing guideline recommendations are largely expert opinion based on extrapolation from evidence on treatment of other forms of organ-specific EPTB.[95,96,213,214]

Recommendation

- **For drug-susceptible disseminated TB without central nervous system involvement, we conditionally recommend treatment with six months of standard anti-TB therapy. Extension to 9-12 months can be considered in immune-compromised patients if the predisposing condition is not modified (eg, people with human immunodeficiency virus not receiving antiretroviral therapy, or continuation of immunosuppressive therapy)** (*poor evidence*).

3.7. Genitourinary TB

3.7.1. Urinary tract

Urinary tract disease is more commonly seen in men and those with end-stage renal disease requiring dialysis.[56,260] Most often, onset of the disease is insidious, and patients present with asymptomatic sterile pyuria, gross hematuria, frequency and dysuria.[261–264] 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.

Ultrasonography, CT and MRI are useful diagnostic modalities for the assessment of genitourinary TB.[265,266] Radiologic abnormalities associated with urinary tract TB are distorted or eroded calyces, hydronephrosis, renal parenchymal scarring and calcification (all of which can mimic the changes seen in chronic pyelonephritis).[265,267]

In patients with urinary tract disease, urine samples sent for AFB smear, NAAT and culture will confirm the diagnosis in more than 90% of cases. (Table 1 and Chapter 3: Diagnosis of Tuberculosis Disease and Drug-resistant Tuberculosis for details).[23,54–57,268] Antibiotic therapy with 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.[268] Occasionally, fine needle aspiration (FNA) of the kidney under ultrasound guidance may be indicated if radiologic assessment is suggestive of renal TB and urine mycobacterial cultures are negative.[57,58]

3.7.2. Genital tract

Genital tract TB may follow from a renal focus; the diagnosis of genital TB, therefore, 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 neighboring organs; as such a lack of confirmation of urinary TB should not preclude further investigation in genital tract TB.

3.7.2.1 Female genital tract TB. Any site in the female genital tract may be involved; however, for reasons that are unknown, 90-100% of patients with female genital tract TB have fallopian tube infection, and both tubes are usually involved, with resultant high rates of infertility.[269–271] Female genital tract 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.[272] The diagnosis of female genital tract TB requires a combination of microbiologic, histologic and radiologic techniques.[59,60,270,271,273] Findings on hysterosalpingography may suggest TB, although, as with renal TB, imaging is often nonspecific and characteristic findings are typically seen only with more advanced disease.[274] 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.[59,60,62,273,275] Small studies have examined the role of NAAT testing in diagnosis of female genital tract TB, with high sensitivity in tissue samples.[61] Even with adequate treatment for female genital tract TB, subsequent fertility rates range between 10% and 30%.[60,276,277] The importance of confirming a diagnosis of TB-related infertility has been highlighted by cases of congenital TB in those in whom the diagnosis has not been identified prior to in-vitro fertilization.[278]

3.7.2.2 Male genital tract TB. As with the female genital tract, any site of the male genital tract can be involved. Epididymitis/orchitis is the most common presentation.[269] Penile and prostatic involvement are rare.[269,279,280] Male genital tract TB usually presents with scrotal swelling, sometimes with rectal or pelvic pain and less commonly with hydrocele or, in advanced cases, a discharging sinus ("watering can" perineum).[269,279] 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, NAAT and culture.[63–66] If this is nondiagnostic, biopsies (FNA or excisional) should be performed for diagnosis.[63–66]

3.7.3. Bacillus Calmette-Guérin (BCG) disease

Individuals who have received intravesical administration of BCG for treatment of bladder cancer are at risk of developing localized genitourinary TB (1% of patients) or spinal or disseminated disease (0.4% of patients).[281–287] Men are more likely to develop BCG disease, with a median time to diagnosis of 170 days post-installation.[284] Diagnosis can be made with urine mycobacterial sampling for genitourinary disease, and with biopsy sampling of affected organ(s) for disseminated disease.

3.7.4. Genitourinary TB treatment

Standard 6-month anti-TB treatment for drug-susceptible genitourinary TB has demonstrated adequate mycobacterial cure rates in observational studies in male genital TB and urinary TB, and is the suggested regime.[21,288–290] There has been one randomized controlled trial in female genital TB comparing 6 months and 9 months of treatment that demonstrated similar treatment outcomes; therefore 6 months is the suggested treatment duration.[291] Given the drug-susceptibility profile of BCG mycobacterium (with sensitivity to INH and RMP and resistance to pyrazinamide), individuals with disease caused by BCG are usually treated with 9 months of INH and RMP.[281,282,285–287]

Recommendations

- **We conditionally recommend six months of standard anti-TB therapy for treatment of drug-susceptible genitourinary TB** (*poor evidence*).
- **We conditionally recommend a minimum of nine months of treatment with isoniazid and rifampin for BCG disease, given inherent pyrazinamide resistance** (*poor evidence*).

3.8. TB pericarditis

Common presenting symptoms are nonspecific and result from the underlying infectious process (fever, night sweats),

cardiac compromise (dyspnea, orthopnea) or disease elsewhere (eg, cough). Physical signs vary depending upon the degree of cardiac compromise.[86,292] Early presentation is associated with a serosanguinous exudative pericardial effusion that may resolve spontaneously over a few weeks or may progress to cardiac tamponade or pericardial constriction.

Imaging modalities for TB pericarditis can include chest radiography, echocardiography, cardiac MRI or CT chest imaging.[86,292] TB pericardial effusion is more likely than viral/idiopathic pericardial effusion if there is mediastinal lymphadenopathy on CT imaging; however, this does not assist with differentiation from malignant pericardial effusions.[293,294]

TB pericardial fluid is typically a bloody exudative effusion and often lymphocyte-predominant.[84] However, similar findings can be found in chronic idiopathic and malignant pericardial effusions.[295]

Diagnosis of TB pericarditis can be confirmed with sampling of pericardial fluid (60% sensitivity) and/or pericardial tissue (90% sensitivity) for AFB smear, NAAT, culture and histopathologic analysis (Table 1). Given the difficulties in diagnosis and the high morbidity and mortality associated with this condition (80-90% mortality in the pre-antibiotic era), empiric treatment may need to be considered while awaiting the results of microbiologic/histologic testing (especially in the immunocompromised, as typical histopathology findings may not be present).[296–298]

3.8.1. TB pericarditis treatment

Treatment regimen/duration recommendations are based on observational data that has demonstrated a reduction in incidence of constrictive pericarditis and mortality compared to the pre-antibiotic era.[82,84,296,299–301]

In a Cochrane review that analyzed HIV-negative and people with HIV separately, corticosteroids significantly reduced the risk of death from pericarditis. In people with HIV, steroids did not significantly improve any clinical outcome. Of note, only 20% of the participants with HIV were taking antiretroviral medications. There was not a significant increase in opportunistic infections or malignancy among either People with HIV or HIV-negative participants, although the data are limited. There are minimal data for people with HIV on established antiretroviral treatment. In patients with good antiretroviral drug viral suppression, the data from HIV negative patients may be considered more applicable.[296] An initial dose of prednisolone 120 mg PO daily with a taper over six weeks was prescribed in the largest and most recent study included in the 2017 Cochrane meta-analysis (Table 2).[296,301]

Recommendations

- **We conditionally recommend six months of standard anti-TB therapy for treatment of drug-susceptible TB pericarditis** (*poor evidence*).
- **We conditionally recommend initial adjunctive corticosteroid treatment in all HIV negative patients with TB pericarditis** (*poor evidence*).
- **We conditionally recommend against routine use of adjunctive corticosteroids in people with HIV not on antiretroviral treatment** (*poor evidence*).

Good practice statements

- **We are unable to provide a specific recommendation on use of adjunctive corticosteroids in people with HIV who are on antiretroviral treatment with TB pericarditis given lack of data. We suggest assessing on a case-by-case basis pending further study.**
- **In patients with recurrent pericardial effusions or persistently elevated central venous pressures despite removal of pericardial fluid and use of anti-TB drugs, we suggest referral for consideration of early pericardiectomy.**

3.9. Ocular TB

Ocular involvement is a rare manifestation of EPTB. Although commonly encountered in the context of disseminated disease, ocular TB more typically occurs without clinically apparent systemic disease.[255,302] In low TB-incidence settings such as Canada, ophthalmologist evaluation of uveitis of unknown etiology with positive immune markers for TB infection (identified through a tuberculin skin test (TST) or interferon-gamma release assay (IGRA)) often leads to a TB center referral for consideration of empiric anti-TB therapy.[303,304]

TB can affect all parts of the eye and may result from hematogenous spread or adjacent structure extension. Ocular TB can be subcategorized by involvement of the peri-ocular, superficial and intra-ocular structures of the eye, which may occur in isolation or overlap. Intra-ocular TB (IOTB) is the most common form of ocular TB and predominantly manifests as uveitis, primarily involving the vascular posterior portion of the eye (choroid). IOTB may occur in one or both eyes, with variable symptoms ranging from blurred vision to ophthalmalgia, conjunctivitis and vision loss.[302] The pathophysiology of IOTB remains incompletely characterized but is posited to involve direct infection of the eye or immune-mediated hypersensitivity reaction triggered by TB infection elsewhere in the body.[305]

The clinical overlap between IOTB and other, more common infectious and noninfectious causes of uveitis pose a significant diagnostic challenge. Whereas ophthalmic exam findings of choroidal granulomas, occlusive retinal vasculitis and multifocal serpiginoid choroiditis have been proposed as specific to IOTB in high TB-incidence settings, the transferability of these findings to low-incidence setting has been questioned.[302,306] Confirmation of IOTB (culture, molecular or pathologic) is rarely achieved, given the risks associated with ocular sampling and generally low diagnostic yield of such samples when obtained.[307,308] Therefore, a presumptive diagnosis of IOTB is often made based upon ophthalmic exam findings, epidemiologic risk factors for TB exposure and

positive immune markers of TB infection (TST and/or IGRA) in the absence of alternate cause.[309,310] This approach will over-estimate those with IOTB compared with those diagnosed based on polymerase chain reaction (PCR) ocular sampling (46.9% vs 37.7%) or TB culture confirmation at another site (3.8%).[310–313]

3.9.1. Ocular TB treatment

Consensus guidance has recently been published summarizing clinical evaluation and treatment of ocular TB.[311] Given the treatable nature of ocular TB and risk of vision loss with treatment delay, initiation of anti-TB therapy should not be delayed once adequate work-up is complete.[304,312] Given that IOTB diagnosis is typically indirect and highly dependent on eye exam findings, clear communication with the TB care provider regarding ophthalmic findings and degree of clinical suspicion for IOTB is essential to ensuring timely and appropriate management.

While 9 or more months of therapy has been proposed to reduce relapse, particularly with evidence of persistent inflammatory changes, intra-ocular inflammatory response to effective therapy may be delayed and ongoing infection indistinguishable from hypersensitivity-associated inflammation.[303,304,310,312–317]

The role of ocular or systemic anti-inflammatories remains controversial and, when used, should be under the guidance and follow-up of an ophthalmologist.[304,318] TB preventative therapy should only be used when alternate etiology of ocular disease has been confirmed and is otherwise indicated.[311] EMB can be safely used as part of standard anti-TB therapy for intra-ocular TB, assuming close follow-up to monitor for signs of optic neuropathy, particularly in those with risk factors.[311,319]

Recommendation

- **We conditionally recommend 6 months of standard anti-TB therapy for drug-susceptible (suspected or confirmed) intra-ocular TB** (*poor evidence*).

3.10. Dermatologic and other rare manifestations of extra-pulmonary TB

TB involving skin is estimated to occur in 1%-2% of EPTB cases. This may be from direct infection (cutaneous TB) or immune-mediated reactions to TB infection elsewhere in the body (tuberculids).[320] Cutaneous TB typically results from endogenous spread (direct contiguous or lympho-hematogenous) and rarely from exogenous inoculation (TB chancre or verrucosa cutis).[321] More common forms of cutaneous TB include scrofuladerma (ulcerative erosions), lupus vulgaris (patches or plaques) and orificialis disease (anal and perianal localizing). Tuberculids are often papulo-nodular in character, ranging from superficial and minimally symptomatic (lichen scrofulosorum) to deeper, painful and, at times, ulcerating panniculitis (erythema induratum of Bazin and papulonecrotic disease).[320–322]

Diagnosis of cutaneous TB is made by biopsy, with histopathologic assessment and mycobacterial smear and culture. Non-TB mycobacteria and leprosy may also manifest as skin disease, underscoring the diagnostic importance of appropriate tissue-sample testing.

Tuberculid diagnosis can be challenging, often entailing a combination of consistent biopsy histopathology, exclusion of alternate diagnoses, demonstration of TB infection/disease (culture confirmed at another site or supported by chest x-ray, TST and/or IGRA) and response to TB treatment.

Recommendation

- **We conditionally recommend 6 months of standard anti-TB therapy for treatment of drug-susceptible TB of the skin, including tuberculids** (*poor evidence*).

In addition to more common extra-pulmonary sites previously described, TB may also involve non-nodal glandular tissue (eg, breast), great vessels, endocardium and bone marrow.[321,323–326] Although rare, life-threatening immune-mediated responses to *M. tuberculosis* may also occur more frequently with EPTB. These include, but are not limited to, hemophagocytic lymphohistiocytosis, acute

Table 2. Examples of published corticosteroid regimens for extra-pulmonary TB.[a]

	TBM				Pericardial TB
	Children[329,330] (≤14 years)		Adults/Adolescents[196] (>14 years)		Adults[301] (≥18 years)
Clinical Status	All	Alert (GCS 15)	Altered LOC (GCS <15) +/- focal neurologic deficits (8 wk course)	Alert (GCS 15), no focal neurologic deficits (6 wk course)	HIV-negative
Week 1	DEXA 0.6 mg/kg/d IV	Prednisolone[a] 4 mg/kg/d PO (max 60 mg/d)	DEXA 0.4 mg/kg/d IV	DEXA 0.3 mg/kg/d IV	Prednisolone PO 120 mg PO
Week 2	"	"	0.3 mg/kg/d IV	0.2 mg/kg/d IV	90 mg PO
Week 3	"	"	0.2 mg/kg/d IV	0.1 mg/d PO[b]	60 mg PO
Week 4	"	"	0.1 mg/kg/d IV	3 mg/d PO[b]	30 mg PO
Week 5+	Tapered through Week 8	Tapered through Week 8	4 mg/d PO[b] decrease by 1 mg/wk	2 mg/d PO[b] decrease by 1 mg/wk	Week 5 = 15 mg PO Week 6 = 5 mg PO

Abbreviations: TB, tuberculosis; TBM, tuberculosis meningitis; LOC, level of consciousness; GCS, Glascow Coma Scale; DEXA, dexamethasone; IV, intravenous; PO, by mouth; BMRC, modified British Medical Research Council TBM severity grading; GI, gastrointestinal.[199]

[a]All corticosteroid doses assume concurrent use of rifampin. If rifampin is not part of TB regimen, then dose adjustment advised.

[b]continue as IV if significant GI intolerance or compromise, early switch to PO may be considered in those with prompt improvement and GI tolerance.

Table 3. Summary of evidence for duration of treatment in extra-pulmonary TB with adjunct measures.

Site	Duration TB treatment	Level of guidance	Evidence[a]				Adjunct measures	
			Type of Studies	Number Studies (refs)	Number Participants	Consistency	Corticosteroids (ref)	Other Measures (ref)
Pleural	6 months	Conditional	OBS	4[122–125]	454	Good	Do not use[126]	Drainage not necessary[123,127]
Lymph Node	6 months	Conditional	RCT	2[105,106]	290	Good	-[b]	Surgery not necessary[98]
Abdominal (all forms)	6 months	Conditional	SRMA	3[151]	328	Good		
Bone and Joint	6 months, consider 9-12 months with markers of severe disease	Conditional	RCT/OBS/Review RCT thoracic/ lumbar	Review 77 studies[183] 2 RCTs[184,186]	2,889 293	Good, two studies with higher relapse rates Dutt et al.[331] twice weekly self-administered therapy for 9 months and Ramachandran et al.[332] primarily based on lack of radiograph response		Surgical intervention is not routinely recommended as part of treatment in spinal tuberculosis. 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[161,185,189]
Central Nervous System	TBM 9-12 months	Conditional	OBS/SR	18[c(236)]	2,098	Good	Use for all individuals, dosing guided by age group and disease severity.[239] See Table 2 for dosing guidance	Higher dose rifampin (IV or oral up to maximum dose 35 mg/kg/day) advised during intensive phase of therapy[223–225,229,333,334] Routine use fluoroquinolone not advised unless concern about drug resistant TBM[228,231]
	Tuberculoma/ archnoiditis 9-12 months	Conditional	OBS	20[246]	742	Poor	Do not use unless clinical significant mass effect[28,246]	
Disseminated	6 months	Conditional	Expert opinion					
Genitourinary	6 months	urinary female genital	OBS RCT	2[289,335] 1[291]	200 175	Good N/A – one study		
Pericardial	6 months		OBS	4[82,299–301]	660	Good	Use for HIV negative populations. People with HIV not on ARV-do not use.[296] Limited data for People with HIV on ARV	
Ocular	6 months	Conditional	OBS	4[303,314,316,317]	426	Poor		
Cutaneous	6 months	Conditional	OBS	Case reports and reviews				

Abbreviations: ARV, anti-retrovirals; TB, tuberculosis; OBS, observational study; RCT, randomized clinical trial; SR, systematic review; SRMA, systematic review meta-analysis.
[a](-) Insufficient data.
[b]One cohort in SR was unpublished.

respiratory distress syndrome and severe hypersensitivity reaction to BCG therapy.[251,281,327,328]

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