REVIEW

http://dx.doi.org/10.4046/trd.2015.78.2.47
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2015;78:47-55

TRD
Tuberculosis and Respiratory Diseases

Diagnosis and Treatment of Extrapulmonary Tuberculosis

Ji Yeon Lee, M.D.
Department of Internal Medicine, National Medical Center, Seoul, Korea

Extrapulmonary tuberculosis (EPTB) constitutes about 20% of all cases of tuberculosis (TB) in Korea. Diagnosing EPTB remains challenging because clinical samples obtained from relatively inaccessible sites may be paucibacillary, thus decreasing the sensitivity of diagnostic tests. Whenever practical, every effort should be made to obtain appropriate specimens for both mycobacteriologic and histopathologic examinations. The measurement of biochemical markers in TB-affected serosal fluids (adenosine deaminase or gamma interferon) and molecular biology techniques such as polymerase chain reaction may be useful adjuncts in the diagnosis of EPTB. Although the disease usually responds to standard anti-TB drug therapy, the ideal regimen and duration of treatment have not yet been established. A paradoxical response frequently occurs during anti-TB therapy. It should be distinguished from other causes of clinical deterioration. Surgery is required mainly to obtain valid diagnostic specimens and to manage complications. Because smear microscopy or culture is not available to monitor patients with EPTB, clinical monitoring is the usual way to assess the response to treatment.

Keywords: Tuberculosis; Diagnosis; Therapeutics; Surgical Procedures, Operative

Introduction

The two types of clinical manifestation of tuberculosis (TB) are pulmonary TB (PTB) and extrapulmonary TB (EPTB). The former is most common. EPTB refers to TB involving organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, or meninges). A patient with both pulmonary and EPTB is classified as a case of PTB. For example, miliary TB is classified as PTB because there are lesions in the lungs. On the other hand, tuberculous intrathoracic lymphadenitis (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of EPTB[1].

Address for correspondence: Ji Yeon Lee, M.D.
Department of Internal Medicine, National Medical Center, 245 Eulji-ro, Jung-gu, Seoul 100-799, Korea
Phone: 82-2-2260-7536, **Fax:** 82-2-2260-7281
E-mail: jedidiah125@gmail.com
Received: Feb. 3, 2015
Revised: Feb. 12, 2015
Accepted: Mar. 3, 2015

Epidemiology

According to the TB notification data, there were 36,089 reported cases of TB (71.4 cases per 100,000 people) in Korea in 2013. Of these, 7,369 cases were EPTB (14.6 cases per 100,000) which comprised 20.4% of all cases of TB. The most commonly affected sites of EPTB in Korea were pleura, followed by lymph nodes, gastrointestinal organs, bones and joints, central nervous system (CNS), and genitourinary organs. The reported proportion of EPTB among total TB cases from 2005 to 2007 was about 14%, but increased to more than 20% from 2010 to 2013[2]. The reason for the increase remains unclear. Considering lower voluntary reporting, diagnostic difficulty of EPTB, and missed cases, it is likely that actual proportion of EPTB was much higher than reported. Various factors associated with EPTB have been reported in the literature. Young age, female gender, Asian and African origin, and human immunodeficiency virus (HIV) infection are independent risk factors for EPTB[3].

Diagnosis

1. Mycobacterial stain and culture

A definitive diagnosis of TB can only be made by culturing *Mycobacterium tuberculosis* organisms from a specimen obtained from the patient. However diagnosing EPTB remains challenging because clinical samples obtained from relatively inaccessible sites may be paucibacillary, decreasing the sensitivity of diagnostic tests. Since the conventional smear microscopy has a low sensitivity with a range of 0%–40%, negative results cannot exclude the presence of TB[4]. The reported yields of mycobacterial culture vary from 30% up to 80%, but it usually takes 2–8 weeks to receive the results, which is too slow to help treatment decisions[4].

About 10%–50% of EPTB patients have concomitant pulmonary involvement. Therefore, all suspected cases of EPTB should be assessed for concomitant PTB to determine whether the case is infectious and to assist with diagnosis. Some EPTB patients have positive sputum culture results despite normal chest radiography findings[5]. The sensitivity of sputum culture varied in previous studies by site of EPTB: 28%–50% for abdominal TB, 10%–11% for tuberculous pericarditis, 24%–29% for tuberculous meningitis, and 5%–14% for tuberculous lymphadenitis[4]. Bronchoscopic evaluation or sputum induction with nebulized hypertonic saline can increase diagnostic sensitivity[6,7]. In one prospective study of patients with suspected pleural TB, the yield of sputum culture in induced samples approached 52%[7].

If possible, repeating tests may improve diagnostic performance. In patients with urinary tract TB, three to six first-void morning urine specimens can improve the likelihood of a positive acid-fast bacilli (AFB) culture result with approximately 80%–90% (only 30%–40% of single specimens are positive)[4]. Repeated lumbar punctures and cerebrospinal fluid (CSF) examination also increase diagnostic yield. A previous study reported that AFB smears and culture positivity approached 87% and 83%, respectively, in four serial CSF samples[8]. Stool cultures for tubercle bacilli are not recommended for diagnosis of gastrointestinal TB because positive results are more likely to occur in patients with active pulmonary disease who are swallowing infected sputum[9].

Drug susceptibility testing (DST) should be performed on the first isolate of *M. tuberculosis* from all patients. A paradoxical reaction during anti-TB therapy occurs more frequently in EPTB patients as compared to those with PTB. Therefore, DST can have important treatment implications to distinguish the paradoxical reaction from the treatment failure due to drug resistance.

2. Biopsy

Conventional AFB smears have low sensitivity and it requires a long time for *M. tuberculosis* to become evident during culture. As a result, the diagnosis of EPTB mostly depends on histological evidence. For histopathological diagnosis, presence of granulomas, caseation, and demonstration of AFB have been commonly used to define a positive test. However, loss of host immune function can result in histopathologic findings demonstrating greater suppurative response and less well-formed granulomas[10]. Additionally, the granulomas can be seen also in nontuberculous mycobacteria disease, fungal infections, brucellosis, or syphilis, so cautious interpretation is required[11].

In general, tissue biopsy yields positive culture results more often than fluid aspiration. The diagnostic accuracy could increase further when the results of the biopsy histology and polymerase chain reaction (PCR) assays are combined with those of culture. In one study of tuberculous pleurisy patients, diagnostic success of 91% was achieved when the pleural biopsy and culture results were combined[12]. Likewise, both sensitivities (82.4%–100%) and specificities (94%–100%) were increased when fine needle aspiration (FNA) cytology and PCR were combined in the diagnosis of TB lymphadenitis[13,14].

The selection of the diagnostic procedures depends on the organ of involvement in EPTB. Various methods that include needle biopsy, excision, endoscopy, laparoscopy, and biopsies under guidance of ultrasound, computed tomography (CT), or endoscopic ultrasound have been employed to ascertain the diagnosis. The relative sensitivities of different procedures and the potential therapeutic benefits should be considered in making the choice of diagnostic approach. In superficial TB lymphadenitis, FNA biopsy of affected lymph nodes is the first-line diagnostic technique. Excisional biopsy has the highest sensitivity, whereas FNA is less invasive and may be useful[14]. Thus, if the FNA examination results are inconclusive, excision biopsy may need to be done. Laparoscopy with target peritoneal biopsy is the current investigation of choice in the diagnosis of peritoneal TB. Previous studies of peritoneal biopsy performed by laparoscopic guidance, minilaparotomy, or exploratory laparotomy reported a diagnostic yield of 85%–95% for TB peritonitis[15]. When bone TB is being considered, CT-guided needle biopsy is the recommended first approach to obtain tissue for assessment. If that assessment is non-diagnostic, a surgical biopsy should be performed for definitive diagnosis and to assess for etiologies other than TB.

Histopathologic examination requires the specimen to be placed in formalin, which destroys the mycobacteria and prevents further culture confirmation. Therefore, biopsy material for mycobacterial culture should be submitted fresh or in a small amount of sterile saline.

3. Body fluid examination

Although tissue biopsy is the most effective method of diagnosing EPTB, it is invasive and sometimes inaccessible. Con-

sequently, more easily accessible body fluids, such as pleural, peritoneal, and pericardial fluids, can often provide valuable diagnostic clues in EPTB patients.

As body fluid analysis can show atypical features, the absence of typical findings cannot rule out EPTB. Tuberculous pleural fluid is invariably an exudate, with lymphocytic predominance in about 90% of cases. However, polymorphonuclear cells may predominate in patients with symptoms of <2-week duration, though a shift towards lymphocytic predominance is observed at repeat thoracentesis[16]. The lymphocyte percentage in pleural fluid was negatively associated with the probability of a positive effusion culture[17,18]. Examination of the CSF typically reveals a leucocytosis (10-1000×10^3 cells/mL; mostly lymphocytes), raised protein (0.5–3.0 g/L), and CSF:plasma glucose <50%. However, atypical CSF findings are well described, particularly in immune-suppressed patients, and the CSF can be acellular or contain a predominance of neutrophils[19]. Pericardial fluid assessment typically demonstrates a bloody, exudative effusion that is often predominantly neutrophilic and not lymphocytic[4].

Measurement of adenosine deaminase (ADA) activity is one of the most studied and widely used biomarkers in body fluids for the diagnosis of EPTB. ADA is an enzyme involved in purin metabolism that is found in many tissues, particularly in T-lymphocytes from the lymphoid tissue. Activity of this enzyme increases in TB patients because of the stimulation of T-cell lymphocytes by mycobacterial antigens[20]. It has been proposed to be a useful surrogate marker for TB in body fluids, such as pleural, pericardial, and peritoneal fluid, although possible false-negative and false-positive results should be considered[21-23].

Different cut-off values for ADA activity have been suggested as being indicative of disease. For diagnosing TB pleurisy, sensitivity and specificity are reportedly 92% and 89%, respectively, using a cut-off value of 40 IU/L[20]. There is a wide range of CSF ADA activity in TB meningitis[24,25]. An ADA cut-off value of 8 IU/L showed a sensitivity of 59% and a specificity of 96% in the diagnosis of TB meningitis[25]. The sensitivity and specificity for diagnosing TB peritonitis have been reported to be 100% and 97%, respectively, using cut-off values from 36 to 40 IU/L, with the optimal cut-off point of 39 IU/L[26]. Liao et al.[23] suggested that lowering cut-off value to 27 IU/L could increase the sensitivity and specificity to 100% and 93.3%, respectively, in patients with liver cirrhosis, in whom false-negative results are a concern. In the diagnosis of TB pericarditis, the sensitivity was 88% and specificity was 83%, using an ADA cut-off value of 40 IU/L[27].

Interferon-gamma (IFN-γ) is a major macrophage-activating cytokine during *M. tuberculosis* infection. Many studies have investigated the usefulness of IFN-γ measurements in pleural or pericardial fluid for the early diagnosis of TB. A meta-analysis of 22 studies that included 782 patients with TB and 1,319 patients with nontuberculous pleural effusion reported a mean sensitivity and specificity of the IFN-γ assay of 89% and 97%, respectively[28]. A study of 30 consecutive patients with diverse causes of pericardial effusion demonstrated a sensitivity and a specificity of 100%, using a cut-off level of >200 pg/L of IFN-γ for the diagnosis of TB pericarditis[29]. However, INF-γ is not commonly used in clinical practice compared with ADA, because it is expensive to acquire and complicated to use, and because there is lack of evidence that INF-γ is more useful than ADA.

4. Nucleic acid amplification test

The major advantage of nucleic acid amplification test (NAAT), such as PCR, is rapid diagnosis. The greatest promise is the early diagnosis of life-threatening disease such as TB meningitis. Because EPTB is a paucibacillary disease, the sensitivity could be improved by PCR, as it can detect as few as 10 mycobacteria[30]. A systematic review suggested that the NAAT has a relatively high specificity in EPTB, while sensitivity is generally lower and highly variable among sample types and test methods[31-33]. Therefore, a positive NAAT result can be considered a presumptive case, whereas a negative NAAT cannot be relied upon to exclude the diagnosis[31].

Xpert MTB/RIF assay, a novel, automated, cartridge-based NAAT, is considered useful for rapid molecular diagnosis of EPTB[34,35]. A recent meta-analysis reported that Xpert MTB/RIF has an overall sensitivity of 83.1% and a pooled specificity of 98.7% for the diagnosis of EPTB[35]. Xpert sensitivity differed substantially between sample types. While Xpert was highly sensitive for TB detection in lymph node samples and moderately sensitive for the detection of TB meningitis (80.5% and 83.1%, respectively), lower sensitivity was shown (46.4%) for testing pleural fluid[35]. Based on this systematic review, the World Health Organization now recommends Xpert over conventional tests for diagnosis of TB in lymph nodes and other tissues, and as the preferred initial test for diagnosis of TB meningitis[36]. The consequences of TB meningitis may be life-threatening. Thus timely diagnosis and initiation of appropriate therapy are crucial. Given this urgency for rapid diagnosis, Xpert is recommended as the initial diagnostic test for CSF specimens from patients suspected of having TB meningitis, in preference to conventional microscopy and culture. Also, Xpert is conditionally recommended as a replacement test for usual practice in specific non-respiratory specimens (lymph nodes and other tissues) for EPTB. Though Xpert has a low sensitivity in pleural fluid, a positive Xpert result in pleural fluid can be treated as TB. However, a negative result should be followed by other tests, as it cannot rule out the disease. The data on the utility of Xpert MTB/RIF for ascitic fluid, pericardial fluid, urine, blood, or stool are limited.

http://dx.doi.org/10.4046/trd.2015.78.2.47

5. Immunological tests

Tuberculin skin test (TST) and IFN-γ releasing assay (IGRA) may be the supportive method for diagnosing EPTB, but it has a limited diagnostic value.

Interpretation of TST reactivity can be complicated by cross-reactivity with previous bacille Calmette–Guerin vaccination or latent TB infection in countries where TB is prevalent. Factors like HIV infection, poor nutritional status, recent viral or bacterial infections, or vaccination with live virus can reduce response to the TST.

Like the TST, IGRA cannot distinguish between latent infection and active pulmonary TB or EPTB, and negative results cannot entirely exclude the disease. A recent meta-analysis evaluating the accuracy of commercially available IGRAs on blood reported that pooled sensitivity and specificity for the diagnosis of EPTB was 72% and 82%, respectively, for QuantiFERON-TB Gold or QuantiFERON-TB Gold in-tube assay and 90% and 68%, respectively, for T-SPOT.TB[37]. The diagnostic performance of IGRA on blood samples varies according to the site of infection. In a prospective study, the T-SPOT.TB was more sensitive in patients with chronic forms of EPTB, such as lymph node or osteoarticular TB (89% and 100%), than in patients with acute forms of EPTB, such as TB meningitis (74%)[38]. In another retrospective study, the sensitivity and specificity of QuantiFERON-TB Gold in-tube in patients with TB lymphadenitis was 81.8% and 80.0%, but 38.5% and 50.0% in patients with TB pleurisy[39]. In patients with suspected lymph node or osteoarticular TB, the negative result of blood IGRA may be useful to exclude EPTB. However, the diagnostic value of blood IGRA is more limited in TB meningitis or TB pleurisy, given the relatively low sensitivities of the tests.

Several studies have investigated the diagnostic value of IGRA on body fluid from infected site for the diagnosis of EPTB. In a prospective study including 74 patients with TB serositis, both the sensitivity and specificity of T-SPOT.TB on serous effusion (91.9% and 87.1%) were significantly higher than the test on peripheral blood (73.0% and 73.1%)[40]. Previously, the sensitivities of IGRAs using pleural fluid as test samples were inconsistent, ranging from 86.4%–100% for T-SPOT.TB, and 44.4%–96.4% for QuantiFERON-TB Gold[40]. In a meta-analysis of 7 publications, the sensitivity and specificity of pleural fluid IGRAs for diagnosing TB pleurisy were 75% and 82%, respectively[41]. Based on the evidence so far, the IGRAs are not recommended to diagnose TB pleurisy. The CSF IGRAs show comparatively high specificity (70%–90%) to make a useful rule-in test, but have low sensitivity (50%–70%) for the diagnosis of TB meningitis[42,43]. Because indeterminate results are common unless CSF volumes of 5–10 mL are tested, the advantage of IGRAs compared with NAATs is unclear[44]. Limited studies suggest the diagnostic potential of IGRA for TB peritonitis and pericarditis[45-47]. Overall, the diagnostic utility of IGRAs according to each site of infection is difficult to generalize due to lack of data.

Treatment

1. Anti-TB drugs

Anti-TB treatment is the mainstay in the management of EPTB. However, the treatment regimen is one of the controversial aspects of the management of EPTB. Most current guidelines recommend the same regimen for both EPTB and PTB, but the data for the recommendation for most other forms of EPTB is not based on studies as robust as those for PTB.

In addition, the ability of the blood-brain barrier to limit intracerebral concentrations of anti-TB drugs is an important consideration in the treatment of TB meningitis. While isoniazid, pyrazinamide, protionamide, and cycloserine penetrate well into CSF, ethambutol and p-aminosalicylic acid have poor or no penetration. Rifampicin, streptomycin, and kanamycin penetrate the CSF well only in the presence of meningeal inflammation. The fluoroquinolones have variable CSF penetration, with excellent penetration seen in later generation drugs, such as levofloxacin and moxifloxacin[48]. In a recent phase 2 clinical trial, treatment incorporating high-dose intravenous rifampicin with the addition of moxifloxacin led to a three-times increase in the plasma and CSF area under the concentration-time curve and was associated with a survival benefit in TB meningitis patients[49].

The optimal duration of therapy is debatable. Although 6 months of standard anti-TB medical therapy is generally considered adequate for most forms of EPTB, longer treatment is suggested for TB meningitis and for bone and joint TB. In case of bone and joint TB, some guidelines recommend 6 months regimens, because these frequently achieve microbiologic and clinical cure[4]. However, many experts still prefer a duration of more than 12 months or until radiological or pathological evidence of regression of disease occurs, due to the difficulties of both assessing treatment response and defining the cure. In this respect, Korean guidelines also recommend 9–12 months of treatment for bone or joint TB. In TB meningitis, treatment extension to 12 months has been promoted given the serious risk of disability and mortality and the lack of randomized controlled studies comparing different treatment durations. Korean guidelines recommend the regimen consisting of 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by 7–10 months of isonazid and rifampin[50].

On the one hand, 6-month regimens are recommended for both lymphatic and intestinal TB, because previous randomized controlled studies on these forms of EPTB showed no significant difference in treatment outcome between the 6-month and the 9-month regimens[51,52].

There is scant information regarding drug-resistant EPTB

in the medical literature. A recent study of EPTB in Korea reported that the overall resistance rate to at least one anti-TB drug was 8.9%, and multidrug resistance rate was 1.8%, which were similar to or slightly lower than those in the entire TB patients[53]. EPTB that is drug-resistant is treated with the same strategy and duration as drug-resistant PTB. If the patient has symptoms suggestive of CNS involvement and is infected with drug-resistant TB, the regimen should use drugs that have adequate penetration into the CNS[48].

2. Paradoxical reaction

A paradoxical reaction is generally defined as the clinical or radiological worsening of preexisting TB lesions or the development of new lesions in a patient who initially improves with anti-TB therapy. A paradoxical reaction occurs more frequently in EPTB than in PTB. It is rarely reported in <3% of HIV-negative PTB patients, whereas in about 16%–50% of those patients with EPTB[54,55]. The diagnosis is made by exclusion. Investigations should be performed to rule out other causes of clinical deterioration such as secondary infections, treatment failure, multidrug-resistance, poor compliance, or drug toxicity. DST is important to distinguish between a paradoxical reaction and treatment failure due to drug resistance. In patients with a paradoxical reaction, an anti-TB regimen can be administered without any alteration[56].

The most common sites involved in paradoxical reactions are lymph nodes, pleura, and CNS[54]. In a retrospective study of 459 patients with isolated TB pleurisy, paradoxical reaction developed in 16% of the patients approximately 2 months after initiation of anti-TB treatment, mostly presenting with aggravation of preexisting pleural effusion[57]. A number of different paradoxical reactions have been reported in patients with TB meningitis including expansion of existing cerebral tuberculomas and appearance of new tuberculomas, hydrocephalus, vasculitic infarcts, and optochiasmatic and spinal arachnoiditis. Although corticosteroids are routinely used in all patients with TB meningitis, there are conflicting reports about the role of corticosteroids in preventing the development of paradoxical worsening[58]. Reported outcomes were not generally different between the patients with and without paradoxical reaction[58]. However, for some severe forms of paradoxical reaction, like optochiasmatic and spinal arachnoiditis presenting as vision loss and paraplegia, more aggressive forms of treatment, like immuno-modulatory drugs and surgery could be required. In TB lymphadenitis, paradoxical reaction has been observed in 20%–30% of the patients, usually within 3 months after therapy[59]. Moreover, the worsening of lymph node lesion has also been observed after the completion of anti-TB therapy, that is post-therapy paradoxical response, as well as during the therapy. According to a recent prospective study, re-biopsy performed in 23 of the 36 patients with post-treatment lymphadenopathy revealed granuloma in 52.2%, positive AFB stain in 17.4%, and positive TB-PCR in 47.8%, but all samples were sterile (no microbiological recurrence) and most of the patients with lymphadenopathy improved spontaneously without further TB medication[60]. It is complicated to differentiate post-therapy paradoxical response from post-chemotherapy relapse. Comprehensive assessment considering the clinical findings, previous TB treatment history and DST results is needed.

Treatment of paradoxical reaction remains controversial. The usefulness of corticosteroids is not well established. Nevertheless, in selected patients who continue to have severe systemic symptoms, the use of corticosteroids may be beneficial. Occasionally, additional treatment, such as aspiration of lymph nodes, surgery, or drainage of pleural fluid, may be helpful despite the lack of data.

3. Corticosteroids

Despite the availability of effective antimycobacterial treatment, adverse outcomes are common in patients with EPTB, such as death and neurological disability, and fibrotic sequelae like pleural fibrosis/loculations and constrictive pericarditis, and strictures of hollow viscera, such as the intestine and ureter. Corticosteroids often have been used as an adjunctive in the treatment of EPTB for the prevention of these complications. However, there is uncertainty regarding the role of adjunctive corticosteroids for EPTB. Currently, the available evidence indicates meaningful clinical benefits only in patients with TB meningitis or TB pericarditis.

In TB meningitis, recent randomized controlled trials and meta-analysis revealed that corticosteroids significantly decrease the mortality and improve the disability-free survival. Thus adjunctive corticosteroids (either dexamethasone or prednisolone) are recommended to all patients, regardless of disease severity[61,62]. The recommended dosage regimens of corticosteroids are dexamethaxone 12 mg/day or 0.4 mg/kg/day for the first 3 weeks in adults, with tapering over the next 3–5 weeks with monitoring of the improvement[19,50].

The effectiveness of treatment with corticosteroids in TB pericarditis remains controversial. Previous randomized controlled trials showed that corticosteroids increase the rate of clinical improvement and reduce the need for repeated pericardiocentesis. In addition, there tends to be lower mortality and progression to constrictive pericarditis in patients receiving steroids, but the trials and the meta-analysis did not reach statistical significance[63,64]. Although published trials are inconclusive, it seems that corticosteroids show a potentially large beneficial effect on the mortality and morbidity associated with pericarditis. Therefore, most guidelines recommend corticosteroids as adjunctive therapy for TB pericarditis during the initial weeks of anti-TB therapy. The recommended adult steroid (prednisone) dosage is 1 mg/kg/day (60 mg/day) for 4 weeks, tapered slowly over the following 8 weeks (30 mg/day

for 4 weeks, 15 mg/day for 2 weeks, and finally 5 mg/day for 2 weeks)[50,56].

In pleural TB, corticosteroids hasten the resolution of pleural effusion as well as clinical symptoms, but there is no beneficial influence on the development of pleural thickening, or residual lung function[65]. There are insufficient data to recommend adjunctive corticosteroid therapy in the treatment of peritoneal TB or genitourinary TB. For those forms of TB, the use of corticosteriods does not significantly reduce the development fibrotic complications like intestinal obstruction or ureteric stenosis[56].

4. Surgery

With the advent of effective chemotherapeutic agents, the need for surgical treatment in TB patients has largely revolved. Nevertheless, surgery is often required in EPTB patients, mainly to obtain valid diagnostic specimens (biopsies) and as a therapeutic option under certain circumstances to deal with complications or sequelae arising from the disease.

Therapeutic lymph node excision is not indicated except in unusual circumstances. For patients who have discomfort from tense, large lymph nodes that are fluctuant and appear to be about to drain spontaneously, aspiration or incision and drainage appears to be beneficial, although this approach has not been examined systematically[14].

Although most spinal TB with or without functional impairment often responds to chemotherapy, surgery appears to be beneficial and may be indicated in some circumstances. Such situations include severe kyphosis, persistence or recurrence of neurological deficit, instability of the spine or clinical deterioration while on anti-TB therapy[56].

In TB pleurisy, routine complete drainage of pleural fluid at the time of diagnosis is not needed because it does not appear to decrease the amount of residual pleural thickening[66]. However, if the patient is dyspneic from a large pleural effusion, a therapeutic thoracentesis should be performed. The administration of a fibrinolytic may decrease the degree of residual pleural thickening in patients with loculated tuberculous pleural effusions[67].

Pericardiectomy is advised in the setting of persistent constrictive pericarditis despite anti-TB therapy for TB pericarditis. However, the timing is controversial, and data are limited[68].

Placement of a ventriculo-peritoneal shunt for treatment of hydrocephalus is the most frequent surgical intervention performed in patients with TB meningitis. Also, urgent surgical decompression should be considered in patients with tuberculomas producing obstructive hydrocephalus or compressing the brainstem, and extra-dural lesions causing paraparesis[19].

In urinary system TB, surgery is more frequently required than in other organs. Although chemotherapy is the mainstay of treatment, ablative surgery as a first-line management may be unavoidable for sepsis or abscesses. Nephrectomy is not routinely required in those patients without complications, but is indicated for a non-functioning kidney or extensive disease involving the whole kidney, together with hypertension and ureteropelvic junction obstruction. Reconstructive surgery, mainly the repair of ureteral strictures, and bladder augmentation for a small fibrotic bladder, is frequently required. Early ureteral stenting or percutaneous nephrostomy in patients with tuberculous ureteral strictures may increase the opportunity for later reconstructive surgery and decrease the likelihood of renal loss[69].

5. Monitoring during treatment

For patients with EPTB, bacteriological evaluation of the response to treatment is often limited by the difficulty in obtaining follow-up specimens. Response often must be judged on the basis of clinical and radiographic findings. The frequency and kinds of evaluations will depend on the sites involved, severity of disease, and the ease with which specimens can be obtained. In contrast with PTB treatment, cure for EPTB is difficult to define. Moreover, there are no established criteria for the end of treatment.

In case of studies on TB lymphadenitis, residual lymph nodes at the end of treatment have usually been used for assessing treatment outcomes. However, residual nodes do not always mean an unfavourable outcome. The size of the nodes during follow-up could decrease more after completion of treatment. Furthermore, 11%–13% of patients may be left with residual nodes in the long term[51,70]. In bone and joint TB, radiologic markers have been used to assess the cure. However, plain X-rays may never return to baseline, and recent studies in spinal TB have shown that 50% of patients had magnetic resonance imaging evidence of tuberculous activity even at the end of 12 months of treatment[71,72]. In intestinal TB, most patients seem to improve within 2 months after therapy initiation. Youn et al.[73] reported that considerable colonoscopic improvement was noted in 93% of patients with intestinal TB at 3 months of therapy. Based on these results, Korean guidelines recommend the follow-up colonoscopy after 2–3 months of anti-TB therapy[74]. However, prolongation of therapy may be considered in patients with complicated conditions because of the difficulty in defining a cure.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

1. World Health Organization. Definitions and reporting framework for tuberculosis: 2013 revision (updated December 2014). Geneva: World Health Organization; 2013.
2. Korea Centers for Disease Control and Prevention. Annual report on the notified tuberculosis in Korea, 2013. Cheongwon: Korea Centers for Disease Control and Prevention; 2014.
3. Kruijshaar ME, Abubakar I. Increase in extrapulmonary tuberculosis in England and Wales 1999-2006. Thorax 2009;64:1090-5.
4. Canadian Thoracic Society and The Public Health Agency of Canada and Licensors. Canadian tuberculosis standards. 7th ed. Ottawa: Public Health Agency of Canada; 2013.
5. Parimon T, Spitters CE, Muangman N, Euathrongchit J, Oren E, Narita M. Unexpected pulmonary involvement in extrapulmonary tuberculosis patients. Chest 2008;134:589-94.
6. Lee J, Lee SY, Choi KJ, Lim JK, Yoo SS, Lee SY, et al. Clinical Utility of CT-based bronchial aspirate TB-PCR for the rapid diagnosis of pleural tuberculosis. Tuberc Respir Dis 2013;75:150-6.
7. Conde MB, Loivos AC, Rezende VM, Soares SL, Mello FC, Reingold AL, et al. Yield of sputum induction in the diagnosis of pleural tuberculosis. Am J Respir Crit Care Med 2003;167:723-5.
8. Kennedy DH, Fallon RJ. Tuberculous meningitis. JAMA 1979;241:264-8.
9. Marshall JB. Tuberculosis of the gastrointestinal tract and peritoneum. Am J Gastroenterol 1993;88:989-99.
10. de Noronha AL, Bafica A, Nogueira L, Barral A, Barral-Netto M. Lung granulomas from *Mycobacterium tuberculosis*/HIV-1 co-infected patients display decreased in situ TNF production. Pathol Res Pract 2008;204:155-61.
11. Zumla A, James DG. Granulomatous infections: etiology and classification. Clin Infect Dis 1996;23:146-58.
12. Valdes L, Alvarez D, San Jose E, Penela P, Valle JM, Garcia-Pazos JM, et al. Tuberculous pleurisy: a study of 254 patients. Arch Intern Med 1998;158:2017-21.
13. Kim DW, Jung SJ, Ha TK, Park HK. Individual and combined diagnostic accuracy of ultrasound diagnosis, ultrasound-guided fine-needle aspiration and polymerase chain reaction in identifying tuberculous lymph nodes in the neck. Ultrasound Med Biol 2013;39:2308-14.
14. Fontanilla JM, Barnes A, von Reyn CF. Current diagnosis and management of peripheral tuberculous lymphadenitis. Clin Infect Dis 2011;53:555-62.
15. Chow KM, Chow VC, Hung LC, Wong SM, Szeto CC. Tuberculous peritonitis-associated mortality is high among patients waiting for the results of mycobacterial cultures of ascitic fluid samples. Clin Infect Dis 2002;35:409-13.
16. Jeon D. Tuberculous pleurisy: an update. Tuberc Respir Dis 2014;76:153-9.
17. Ruan SY, Chuang YC, Wang JY, Lin JW, Chien JY, Huang CT, et al. Revisiting tuberculous pleurisy: pleural fluid characteristics and diagnostic yield of mycobacterial culture in an endemic area. Thorax 2012;67:822-7.
18. Bielsa S, Palma R, Pardina M, Esquerda A, Light RW, Porcel JM. Comparison of polymorphonuclear- and lymphocyte-rich tuberculous pleural effusions. Int J Tuberc Lung Dis 2013;17:85-9.
19. Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J, et al. 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.
20. Greco S, Girardi E, Masciangelo R, Capoccetta GB, Saltini C. Adenosine deaminase and interferon gamma measurements for the diagnosis of tuberculous pleurisy: a meta-analysis. Int J Tuberc Lung Dis 2003;7:777-86.
21. Lee SJ, Kim HS, Lee SH, Lee TW, Lee HR, Cho YJ, et al. Factors influencing pleural adenosine deaminase level in patients with tuberculous pleurisy. Am J Med Sci 2014;348:362-5.
22. Abrao FC, de Abreu IR, Miyake DH, Busico MA, Younes RN. Role of adenosine deaminase and the influence of age on the diagnosis of pleural tuberculosis. Int J Tuberc Lung Dis 2014;18:1363-9.
23. Liao YJ, Wu CY, Lee SW, Lee CL, Yang SS, Chang CS, et al. Adenosine deaminase activity in tuberculous peritonitis among patients with underlying liver cirrhosis. World J Gastroenterol 2012;18:5260-5.
24. Cho BH, Kim BC, Yoon GJ, Choi SM, Chang J, Lee SH, et al. Adenosine deaminase activity in cerebrospinal fluid and serum for the diagnosis of tuberculous meningitis. Clin Neurol Neurosurg 2013;115:1831-6.
25. Tuon FF, Higashino HR, Lopes MI, Litvoc MN, Atomiya AN, Antonangelo L, et al. Adenosine deaminase and tuberculous meningitis: a systematic review with meta-analysis. Scand J Infect Dis 2010;42:198-207.
26. Riquelme A, Calvo M, Salech F, Valderrama S, Pattillo A, Arellano M, 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.
27. Tuon FF, Litvoc MN, Lopes MI. Adenosine deaminase and tuberculous pericarditis: a systematic review with meta-analysis. Acta Trop 2006;99:67-74.
28. Jiang J, Shi HZ, Liang QL, Qin SM, Qin XJ. Diagnostic value of interferon-gamma in tuberculous pleurisy: a metaanalysis. Chest 2007;131:1133-41.
29. 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;122:900-5.
30. Manjunath N, Shankar P, Rajan L, Bhargava A, Saluja S, Shriniwas. Evaluation of a polymerase chain reaction for the diagnosis of tuberculosis. Tubercle 1991;72:21-7.
31. Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh

N, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technol Assess 2007;11:1-196.
32. Linasmita P, Srisangkaew S, Wongsuk T, Bhongmakapat T, Watcharananan SP. Evaluation of real-time polymerase chain reaction for detection of the 16S ribosomal RNA gene of *Mycobacterium tuberculosis* and the diagnosis of cervical tuberculous lymphadenitis in a country with a high tuberculosis incidence. Clin Infect Dis 2012;55:313-21.
33. Trajman A, da Silva Santos Kleiz de Oliveira EF, Bastos ML, Belo Neto E, Silva EM, da Silva Lourenco MC, et al. Accuracy of polimerase chain reaction for the diagnosis of pleural tuberculosis. Respir Med 2014;108:918-23.
34. Kim YW, Kwak N, Seong MW, Kim EC, Yoo CG, Kim YW, et al. Accuracy of the Xpert(R) MTB/RIF assay for the diagnosis of extra-pulmonary tuberculosis in South Korea. Int J Tuberc Lung Dis 2015;19:81-6.
35. Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. Eur Respir J 2014;44:435-46.
36. World Health Organization. Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children: policy update. Geneva: World Health Organization; 2013.
37. Fan L, Chen Z, Hao XH, Hu ZY, Xiao HP. Interferon-gamma release assays for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. FEMS Immunol Med Microbiol 2012;65:456-66.
38. Cho OH, Park KH, Kim SM, Park SJ, Moon SM, Chong YP, et al. Diagnostic performance of T-SPOT.TB for extrapulmonary tuberculosis according to the site of infection. J Infect 2011;63:362-9.
39. Shin JA, Chang YS, Kim HJ, Ahn CM, Byun MK. Diagnostic utility of interferon-gamma release assay in extrapulmonary tuberculosis. Diagn Microbiol Infect Dis 2015 Feb 14 [Epub]. http://dx.doi.org/10.1016/j.diagmicrobio.2015.02.002.
40. Zhang L, Zhang Y, Shi X, Zhang Y, Deng G, Lalvani A, et al. Utility of T-cell interferon-gamma release assays for diagnosing tuberculous serositis: a prospective study in Beijing, China. PLoS One 2014;9:e85030.
41. Zhou Q, Chen YQ, Qin SM, Tao XN, Xin JB, Shi HZ. Diagnostic accuracy of T-cell interferon-gamma release assays in tuberculous pleurisy: a meta-analysis. Respirology 2011;16:473-80.
42. Park KH, Cho OH, Lee EM, Lee SO, Choi SH, Kim YS, et al. T-cell-based assays on cerebrospinal fluid and PBMCs for rapid diagnosis of TB meningitis in non-HIV patients. Eur Respir J 2012;39:768-70.
43. Kim SH, Cho OH, Park SJ, Lee EM, Kim MN, Lee SO, et al. Rapid diagnosis of tuberculous meningitis by T cell-based assays on peripheral blood and cerebrospinal fluid mononuclear cells. Clin Infect Dis 2010;50:1349-58.
44. Thwaites GE, van Toorn R, Schoeman J. Tuberculous meningitis: more questions, still too few answers. Lancet Neurol 2013;12:999-1010.
45. Lee JY, Kim SM, Park SJ, Lee SO, Choi SH, Kim YS, et al. A rapid and non-invasive 2-step algorithm for diagnosing tuberculous peritonitis using a T cell-based assay on peripheral blood and peritoneal fluid mononuclear cells together with peritoneal fluid adenosine deaminase. J Infect 2015;70:356-66.
46. Biglino A, Crivelli P, Concialdi E, Bolla C, Montrucchio G. Clinical usefulness of ELISPOT assay on pericardial fluid in a case of suspected tuberculous pericarditis. Infection 2008;36:601-4.
47. Bathoorn E, Limburg A, Bouwman JJ, Bossink AW, Thijsen SF. Diagnostic potential of an enzyme-linked immunospot assay in tuberculous pericarditis. Clin Vaccine Immunol 2011;18:874-7.
48. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2008.
49. Ruslami R, Ganiem AR, Dian S, Apriani L, Achmad TH, van der Ven AJ, et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. Lancet Infect Dis 2013;13:27-35.
50. Joint Committee for the Revision of Korean Guidelines for Tuberculosis, Korea Centers for Disease Control and Prevention. Korean guidelines for tuberculosis. 2nd ed. Seoul and Cheongwon: Joint Committee for the Revision of Korean Guidelines for Tuberculosis, Korea Centers for Disease Control and Prevention; 2014.
51. Campbell IA, Ormerod LP, Friend JA, Jenkins PA, Prescott RJ. Six months versus nine months chemotherapy for tuberculosis of lymph nodes: final results. Respir Med 1993;87:621-3.
52. Park SH, Yang SK, Yang DH, Kim KJ, Yoon SM, Choe JW, et al. Prospective randomized trial of six-month versus nine-month therapy for intestinal tuberculosis. Antimicrob Agents Chemother 2009;53:4167-71.
53. Cho OH, Park KH, Park SY, Moon SM, Chong YP, Kim MN, et al. Drug-resistant extrapulmonary tuberculosis. Infect Chemother 2011;43:258-61.
54. Cheng VC, Ho PL, Lee RA, Chan KS, Chan KK, Woo PC, et al. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. Eur J Clin Microbiol Infect Dis 2002;21:803-9.
55. Geri G, Passeron A, Heym B, Arlet JB, Pouchot J, Capron L, et al. Paradoxical reactions during treatment of tuberculosis with extrapulmonary manifestations in HIV-negative patients. Infection 2013;41:537-43.
56. American Thoracic Society; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep 2003;52:1-77.
57. Jeon K, Choi WI, An JS, Lim SY, Kim WJ, Park GM, et al. Paradoxical response in HIV-negative patients with pleural tuber-

culosis: a retrospective multicentre study. Int J Tuberc Lung Dis 2012;16:846-51.
58. Garg RK, Malhotra HS, Kumar N. Paradoxical reaction in HIV negative tuberculous meningitis. J Neurol Sci 2014;340:26-36.
59. Cho OH, Park KH, Kim T, Song EH, Jang EY, Lee EJ, et al. Paradoxical responses in non-HIV-infected patients with peripheral lymph node tuberculosis. J Infect 2009;59:56-61.
60. Park KH, Lee MS, Lee SO, Choi SH, Kim YS, Woo JH, et al. Incidence and outcomes of paradoxical lymph node enlargement after anti-tuberculosis therapy in non-HIV patients. J Infect 2013;67:408-15.
61. Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 2004;351:1741-51.
62. Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev 2008;(1):CD002244.
63. Mayosi BM, Ntsekhe M, Volmink JA, Commerford PJ. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev 2002;(4):CD000526.
64. Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumedze F, et al. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. N Engl J Med 2014;371:1121-30.
65. Engel ME, Matchaba PT, Volmink J. Corticosteroids for tuberculous pleurisy. Cochrane Database Syst Rev 2007;(4):CD001876.
66. Lai YF, Chao TY, Wang YH, Lin AS. Pigtail drainage in the treatment of tuberculous pleural effusions: a randomised study. Thorax 2003;58:149-51.
67. Chung CL, Chen CH, Yeh CY, Sheu JR, Chang SC. Early effective drainage in the treatment of loculated tuberculous pleurisy. Eur Respir J 2008;31:1261-7.
68. Mayosi BM, Burgess LJ, Doubell AF. Tuberculous pericarditis. Circulation 2005;112:3608-16.
69. Cek M, Lenk S, Naber KG, Bishop MC, Johansen TE, Botto H, et al. EAU guidelines for the management of genitourinary tuberculosis. Eur Urol 2005;48:353-62.
70. van Loenhout-Rooyackers JH, Laheij RJ, Richter C, Verbeek AL. Shortening the duration of treatment for cervical tuberculous lymphadenitis. Eur Respir J 2000;15:192-5.
71. Jain AK, Sreenivasan R, Saini NS, Kumar S, Jain S, Dhammi IK. Magnetic resonance evaluation of tubercular lesion in spine. Int Orthop 2012;36:261-9.
72. Joseffer SS, Cooper PR. Modern imaging of spinal tuberculosis. J Neurosurg Spine 2005;2:145-50.
73. Youn JE, Park IB, Kwon SY, Kim JS, Byun KS, Bak YT, et al. Follow-up colonoscopy at 3 months of therapy in patients with tentative diagnosis of intestinal tuberculosis. Korean J Med 1996;50:227-33.
74. Kim YS, Kim YH, Lee KM, Kim JS, Park YS; IBD Study Group of the Korean Association of the Study of Intestinal Diseases. Diagnostic guideline of intestinal tuberculosis. Korean J Gastroenterol 2009;53:177-86.