Review of literature on disseminated tuberculosis with emphasis on the focused diagnostic workup

Fahmi Y. Khan

Abstract:

Disseminated tuberculosis (TB) is a life-threatening disease resulting from the hematogenous spread of *Mycobacterium tuberculosis.* The diagnosis is challenging owing to its subtle nonspecific clinical presentation, which usually reflects the underlying organ involved. Besides, tools for confirmatory laboratory diagnosis are limited. Therefore, a high index of suspicion is required for early diagnosis. Miliary pattern on chest radiography is a common finding that has an important role in the early detection of the disease. Nevertheless, approximately 10%–15% of patients have normal chest radiography. Although abnormalities are present, basic hematologic and biochemical tests as well as tuberculin skin test are nonspecific for the diagnosis. Imaging studies are helpful adjunct tools for disseminated TB as they can help determine the involved sites and guide technicians to obtain appropriate specimens for diagnosis. Clinical confirmation of the diagnosis of disseminated TB is usually based on bacteriological or histological evidence. Response to first-line anti-TB drugs is good as evidenced by many reports. This review aims to present a current update on disseminated TB with emphasis on the diagnostic workup of this devastating condition.

Keywords:

Bone marrow, bronchoscopy, disseminated tuberculosis, miliary pattern

Introduction

Disseminated tuberculosis (TB) is defined as the presence of two or more noncontiguous sites resulting from hematogenous dissemination of *Mycobacterium tuberculosis*, occurring as a result of progressive primary infection, reactivation of a latent focus with subsequent spread,[1] or rarely through iatrogenic origin.[2] Nowadays, the term miliary TB also refers to progressive and widely spread forms of TB. It entails a hematogenous spread of the disease to several organs, even if the classical pathologic or radiologic findings are absent.[1,3]

Disseminated TB is a life-threatening condition, especially if the diagnosis and treatment are delayed.[1] The diagnosis is difficult because of its nonspecific clinical picture and the paucity of tools available for confirmatory laboratory diagnosis, such as low sensitivity of acid-fast bacilli (AFB) smear, time-consuming cultures, and the inability to easily detect miliary changes in chest X-ray.

Epidemiology

The exact global incidence of disseminated TB is still unclear; however, among immunocompetent adults, it is estimated as accounting for <2% of all cases of TB and up to 20% of all extrapulmonary TB cases.[4] Several aspects of this disorder, including its subtle and nonspecific clinical presentation and the paucity of tools for confirmatory laboratory diagnosis, constitute barriers to accurate diagnosis. We, therefore, believe that the incidence of this disorder is probably underestimated.

Department of Medicine, Hamad General Hospital, Doha, Qatar

Address for correspondence:
Dr. Fahmi Y. Khan,
Department of Medicine,
Hamad General Hospital,
P.O. Box 3050, Doha,
Qatar.
E-mail: fakhanqal@
gmail.com

Disseminated TB is considered an important cause of morbidity and mortality in developing countries, especially in children under the age of 15 years. However, it has become more common in most technically advanced countries and in different age groups owing to several risk factors. These include human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS), and other causes of immunosuppression such as use of biologicals and immunosuppressive drugs for the treatment of various medical disorders, increasing prevalence of organ transplantation, alcoholism, chronic liver disease, chronic hemodialysis, diabetes mellitus, malignancies, and silicosis.[1-7]

Pathogenesis

Dissemination of *M. tuberculosis* may occur as a result of progressive primary infection or the reactivation of a latent focus with subsequent lymphohematogenous spread. However, the mechanism by which this occurs is not well understood.[8]

One proposed mechanism is that tuberculous infection in the lungs results in the erosion of the epithelial layer of alveolar cells and the spread of infection into a pulmonary vein.[8,9] Once the bacteria reach the left side of the heart and enter the systemic circulation, they multiply and infect extrapulmonary organs causing systemic disseminated TB. The bacilli could also attack the cells lining the alveoli and enter the lymph node(s). Through lymphatics, the bacilli enter the systemic venous blood in large numbers and circulate back to the lung through the right side of the heart, causing pulmonary disseminated TB with miliary appearance.[8,9] The two forms of dissemination can occur independently or together.

Dissemination of TB rarely occurs as iatrogenic infection. A few cases have been published, describing dissemination of TB after instrumentations of the renal system.[2,10-12] Other reports have described the disease after surgical intervention in a tuberculous epididymitis,[13] intraocular TB,[14] and following intravesical Bacillus Calmette–Guérin (BCG) immunotherapy for transitional cell cancer of the bladder.[15] Dissemination of TB was also described in the transplantation of organs with unrecognized TB such as infected cadaveric kidney[16] and homograft valve.[17]

Pathology

Disseminated TB may involve many organs such as the lung, liver, spleen, bone marrow, kidney, adrenals, eyes, and thyroid. On gross pathology of the involved organs, there are numerous small, gray-to-reddish brown, punctate rounded lesions of more or less uniform size similar to innumerable millet seeds and appearance.[4,18] Microscopically, the disseminated nodules reveal tuberculous granulomas with or without central caseation; with the possibility of finding AFB within the macrophages or epithelioid cell of the granulomas or in the areas of caseation[4,18]

Causative Agent

M. tuberculosis causes most of the cases. However, *Mycobacterium bovis* has been identified in one study[19] and in iatrogenic disseminated BCG infection.[15,20]

Clinical Features

The clinical presentation of disseminated TB is highly variable and usually includes subacute or chronic constitutional symptoms (such as fever, weight loss, and night sweats) as well as clinical pictures ranging from anorexia and pyrexia of unknown origin to even multiorgan failure that reflects the underlying organ involved.[1-4,21]

The duration of symptoms before the diagnosis is variable. Patients may experience progressive symptoms and signs over days to weeks or occasionally over several months. Therefore, the diagnosis of this disease is generally difficult and more than 50% of patients usually delay in seeking medical help for >1 month.[1] The diagnosis is more difficult in children because the clinical pictures are so vague that the diagnosis is often missed. Table 1 describes the clinical presentation of disseminated TB in adults and children. It shows a difference in presenting symptoms/signs between these two age groups.[1,7,22-25] Adults more commonly have symptoms and signs of anorexia, fatigue, dyspnea, night sweats, fever, abdominal pain, hemoptysis, headache, mental changes, pleural effusion, ascites, and lymphadenopathy than child patients, whereas diarrhea, vomiting, seizures, hepatomegaly, splenomegaly, jaundice, and meningism are more common in children.

Investigations

Abnormal results of several investigations have been described, most of which are diagnostically insignificant as they provide nonspecific results.

Laboratory workup
Hematological abnormalities include anemia of different types, pancytopenia, and leukopenia mainly lymphopenia, leukemoid reaction, high Erythrocyte sedimentation rate, dissemination intravascular coagulation, and rarely myelofibrosis.[1,26] Abnormal liver function tests usually with moderate elevations in transaminases, alkaline phosphatase, and bilirubin

Table 1: Reports of various clinical features (percentage) of disseminated tuberculosis by various studies

Clinical picture	Mert et al.[7]	Hussain et al.[22]	Khan et al.[1]	Hussey et al.[23]	Tanrıkulu et al.[24]	Gurkan et al.[25]
Symptoms						
Fever	100	81.0	95.0	61.0	17.9	73.9
Fatigue/weakness	90.5	34.0	52.0	13.0	21.4	-
Anorexia	84.8	29.0	73.0	40.0	35.7	4.3
Weight loss	66.2	49.0	57.0	40.0	51.9	4.3
Night sweats	65.0	7.0	56.0	-	28.6	4.3
Cough	60.5	41.0	80.0	72.0	35.7	17.4
Headache	43.3	-	32.0	2.0	3.5	-
Dyspnea	30.0	25.0	21.0	12.0	12.5	-
Abdominal pain	14.4	19.0	24.0	3.0	7.1	-
Hemoptysis	6.1	2.0	9.0	1.0	1.8	-
Diarrhea/vomiting	-	-	12.0	33.0	12.5	8.7
Signs						
Fever	100	81.0	95.0	39.0	17.9	73.9
Lymphadenopathy	21.3	18.0	15.0	16.0	12.5	8.7
Hepatomegaly	20.0	27.0	23.0	82.0	-	39.1
Splenomegaly	19.4	14.0	23.0	54.0	17.9	39.1
Mental changes	18.3	26.0	12.0	-	-	-
Pleural effusion	18.0	-	10.0	-	-	-
Ascites	-	16.0	10.0	-	-	-
Meningism	17.5	9.0	16.0	19.0	17.9	17.4
Choroid tubercles	7.6	-	-	-	-	-
Skin involvement	1.5	2.0	-	-	-	4.3
Delirium, psychosis	5.0	-	-	-	-	-
Jaundice	-	-	-	6.0	-	-
Convulsion	-	-	1.0	3.0	7.1	-

occur in half of the patients.[27] Hypercalcemia has been described in 13.4% of patients with disseminated TB.[28]

Purified protein derivative tuberculin skin test
This test has no diagnostic value as it often yields negative results in a patient with confirmed disseminated TB.[1]

Interferon-gamma releasing assays
Interferon-gamma (IFN-γ) releasing assays such as T-SPOT. TB assay and QuantiFERON-TB In-Tube (QFT-GIT) are more specific than the tuberculin skin test because they tend to give fewer false-positive test results in patients with prior BCG vaccination or during exposure to environmental mycobacteria. However, neither test can accurately distinguish between latent TB infection and active TB disease and little is known about the usefulness of these assays for diagnosing disseminated TB.[29] Available data show that the sensitivity of the T-SPOT. TB in patients with disseminated TB is 93%–95%, while the sensitivity of QFT-GIT is 67%–68%.[29,30] In view of the scarcity of reported data, it is too early to make a definitive conclusion on the usefulness of these assays for the diagnosis of disseminated TB, as more studies are needed.

Imaging modalities
Imaging studies alone are insufficient for the making of a conclusive diagnosis as they lack sensitivity and specificity. However, they are important adjuncts in the diagnostic evaluation of disseminated TB as they can help determine the sites involved and guide technicians to obtain appropriate specimens for diagnosis.[31] The roles of several imaging modalities for the diagnosis of this disorder are reviewed here.

Chest radiograph
Chest radiography is usually the initial and most cost-effective tool, which plays an important role in the early diagnosis of disseminated TB. The classic miliary pattern is seen in 85%–90% of cases. However, these findings are not specific for disseminated TB as they can be mimicked by histoplasmosis, sarcoidosis, pneumoconiosis, metastasis, bronchoalveolar carcinoma, and pulmonary siderosis.[32,33] Less common findings on chest X-rays are consolidation, cavities, calcification, granulomas, and pleural effusion.[1,32,33]

High-resolution computed tomography
High-resolution computed tomography (CT) may show findings not visible on chest X-rays such as miliary nodules, ground-glass opacities, and interlobular septal thickening.[33]

Abdominal ultrasonography
This imaging modality may reveal diffuse liver disease, focal splenic or hepatic lesions, hepatosplenomegaly,

peritoneal thickening, multiple thin septae, and visible debris of different densities within ascitic fluid. Other findings include para-aortic, mesenteric, or omental nodes. However, these abnormalities are not specific and can be mimicked by other nontuberculous conditions.[34]

Abdominal computed tomography

Abdomen CT may reveal para-aortic lymph nodes, hepatosplenomegaly, peritoneal thickening, free and loculated ascites, mesenteric or omental thickening, mesenteric or omental strand, and mesenteric or omental nodes. The nodes are usually matted, appearing in groups, with mild fat stranding and a hypoattenuating center, with or without calcification.[31,34]

Magnetic resonance imaging of abdomen

Magnetic resonance imaging (MRI) is a useful tool for identifying miliary lesions at occult extrapulmonary sites because of its superior soft-tissue resolution and multiplanar acquisition. Ultrasonography and MRI are the imaging techniques of choice for the pregnant patient.[31]

Brain computed tomography scanning with contrast and/or magnetic resonance imaging

These techniques can be used to assess suspected TB lesions such as meningeal enhancement, tuberculoma, tuberculous abscess, and cerebritis.[35]

Echocardiography

This diagnostic tool is helpful in detecting tuberculous lesions such as pericardial effusion and cardiac masses.[36]

Positron emission tomographic computed tomography

This has recently been used for the detection of extrapulmonary TB.[37] 18F-FDG PET–CT may show peripheral uptake and central hypometabolism, depending on the amount of caseation allowing the selection of the organ or site most suitable for biopsy.[31]

Specimens Examination

To confirm the diagnosis in patients with suspected disseminated TB, a selection of appropriate specimens is needed for AFB smear, polymerase chain reaction (PCR), mycobacterial culture, and histology.[1]

Microbiological studies of specimens

Similar to other forms of TB, identification of AFB by both smears and cultures of specimens remains the useful means of diagnosing disseminated TB. Although AFB smear is a rapid, inexpensive, and highly specific tool for diagnosing TB, its sensitivity on different specimens is low and variable and cannot identify drug-resistant strains.[38,39] Culture is considered the golden standard for the diagnosis, but conventional mycobacterial culture

takes up to 4–6 weeks to yield results, while the process of liquid culture requires at least 2 weeks, which is still rather long and may increase mortality and morbidity. For this reason, application of new rapid diagnostic tools such as PCR and some biomarkers has been tried.[34,38,39]

Polymerase chain reaction study on specimens

Nucleic acid amplification (NAA) tests using PCR have recently been used as a rapid diagnostic tool for TB, which is able to detect *M. tuberculosis* complex (MTBC) directly from patient samples in just 2 h.[39] This procedure consists of DNA extraction, DNA amplification, and DNA detection. The target sequence for PCR amplification is IS6110, which is a specific gene segment from MTBC that has not been detected in other mycobacteria organisms.

The Xpert MTB/RIF test is an example of NAA tests that have been approved by the Food and Drug Administration for the direct detection of MTBC from respiratory specimens. In addition to detecting MTBC, it has the additional benefit of providing information on potential rifampin resistance, by detecting mutations in an 81-base pair region of the *rpoB* gene that is responsible for conferring approximately 96% of rifampin resistance in MTBC.[40]

Despite this specificity, the diagnostic yield shows variability in different studies owing to the lack of uniformity in the methodology in processing the sample, the amplified target of *M. tuberculosis,* and the method of detecting the amplified DNA.[39,40] On the other hand, physicians should keep in mind that negative results cannot exclude TB because of its low sensitivity. Therefore, samples must be cultured for mycobacterial growth in case of false-negative results through NAA testing to detect nontuberculous mycobacteria species and to facilitate antimicrobial susceptibility testing.[40]

Biomarker

Other rapid and noninvasive tests that rely on various nonsputum samples in the diagnosis of TB have been used recently. The measurement of biomarkers such as adenosine deaminase (ADA) and IFN-γ in the supernatant of fluid specimens (pleural fluid, ascites, pericardial fluid, and cerebrospinal fluid [CSF]) has been used to diagnose TB.[34,41-45] Although there are numerous reports on these biomarkers, their validation and confirmatory role are inconclusive.[34,41-45]

Histologic study of specimens

Histopathology remains one of the most important methods of diagnosing TB. Histopathologic study of a tissue sample usually shows caseating granulomas and sometimes noncaseating granulomas with or without AFB positivity.[46]

Diagnostic Criteria

Clinical confirmation of disseminated TB should be established by bacteriological (AFB smear and culture in both liquid and solid media), PCR, and/or histological evidence. Therefore, disseminated TB is confirmed if a patient has any of the following conditions:[1,4,28] isolation of *M. tuberculosis*, positive PCR, or histologic demonstration of caseating granulomatous inflammation from bone marrow, blood, liver biopsy specimen, or at least two noncontiguous organs with or without miliary lung lesions and isolation of *M. tuberculosis*, positive PCR, or histopathological identification of caseating granulomas from one organ and radiographic finding of miliary lung lesions.

Focused Diagnostic Workup

Due to its subtle and nonspecific clinical presentation and limited tools for confirmatory laboratory diagnosis, the development of efficient diagnostic tools and strategies for the diagnosis of disseminated TB represents areas of priority in public health research, especially in countries with limited resources. However, no well-validated studies and no consensus on a framework for the diagnostic workup of disseminated TB are found in the literature reviewed. In general, we believe that the aim of any diagnostic workup for disseminated TB is to increase workers' awareness of this clinical entity and identify the involved site to obtain appropriate specimens to send for AFB smear, PCR, mycobacterial culture, and histology test.

We describe, in this study, a stepwise approach to diagnostic workup based on chest radiograph appearance. Accordingly, disseminated TB is divided into two groups: disseminated TB with pulmonary involvement and without pulmonary involvement.

Disseminated tuberculosis with pulmonary involvement

Patients with disseminated TB may present with typical miliary pattern or atypical radiographic findings. In this section, we focus on the diagnostic workup of miliary pattern disseminated TB.

Sputum

In these patients, spontaneously expectorated or induced sputum should be sent for the study to confirm the diagnosis. Two sputum samples must be subjected to smear, PCR, and mycobacterial culture examination. For a positive AFB sputum test, at least 5000–10,000 bacilli/mm of specimens are required, while *M. tuberculosis* culture needs 10–100 microorganisms/mm.[27,28] The diagnostic performance of the sputum smear is low in patients with miliary pattern because of the very low *Bacillus*

concentration compared to those with pulmonary TB; it ranges from 6% to 36%,[27,28,47-49] while the frequency of a positive sputum culture for *M. tuberculosis* is 27%–97%.[1] In children, sputum study is usually inefficient as they develop paucibacilar forms of the disease and do not expectorate sputum easily.[49] Little is known about the performance of PCR on the sputum of patients with disseminated TB, as most evidence is based on descriptive studies of pulmonary TB, which describes the sensitivity of the PCR from 42% to 93%.[50]

Endotracheal secretions and gastric lavage

If the patient cannot give sputum as is usually the case with comatose patients or children, endotracheal secretions and gastric lavage can also be used to confirm the diagnosis. However, identification of AFB on gastric aspirates of children is positive in <15% of samples, and only 25%–50% are positive on culture.[33,35] Recent data have shown that the yield of PCR is much higher than that of smear and culture, as it provides a rapid test in a child with suspected TB, with a sensitivity varying between 40% and 83%.[40] Among adults, the sensitivities of AFB smear and mycobacterial culture on gastric aspirate are 12%–23% and 24%–32%, respectively.[51]

Fiber-optic bronchoscopy

In patients with suspected disseminated TB who have smear-negative or PCR-negative sputum or nonproductive cough or who cannot expectorate, fiber-optic bronchoscopy can provide alternative respiratory specimens for diagnosis, through procedures such as bronchoalveolar lavage, bronchoscopic aspirate (BA), brushings, washings, and transbronchial biopsy (TBB).[52-54] To maximize the chance of confirming the diagnosis, specimens should be taken from as many sites as possible. Collected specimens must be subjected to AFB smear, PCR and mycobacterial culture examination, and additional histopathological examination is required for tissue samples. Alone, each of these diagnostic methods (direct examination of various bronchoscopy samples for AFB, PCR, mycobacterial culture, and histopathological examination of TBB specimens) has relatively low diagnostic sensitivity; however, the diagnostic sensitivity significantly increases to a range between 84% and 92% when used in combination.[52-54]

Other diagnostic tools

If diagnosis cannot be established by the above diagnostic modalities, coexisting conditions such as lymphadenopathy, pleural, pericardia, and joint effusions and ascites should be looked for.[1] Therefore, careful physical examination and meticulous utilization of imaging studies are crucial in identifying the involved organs or sites to obtain specimens for diagnosis.

Lymphadenopathy

It is present in 25%–93% of cases of disseminated TB with abdominal involvement. The diagnostic yield of lymph node biopsy or fine-needle aspiration is high. The yield of caseating granulomas is close to 100%.[1,55]

Ascitic fluid and pleural effusion

Acid-fast smear of ascitic fluid has a low yield with a reported sensitivity of 0%–6%, while the frequency of a positive culture for *M. tuberculosis* is 2%–50%.[34] Similarly, pleural fluid mycobacterial culture had a higher sensitivity than direct smear for AFB.[56] Peritoneal and pleural biopsies give better diagnostic value than ascitic and pleural fluid alone.[34,56] Although reports on their validation and confirmatory role are inconclusive, fluid PCR and measurement of ADA and IFN-γ, in the supernatant of fluid samples, could potentially help improve the diagnosis.

Brain imaging and cerebrospinal fluid study

If disseminated TB is still suspected, clinical assessment for the presence of meningitis is essential since tuberculous meningitis (TBM) is found in 10%–30% of adult patients[4,47,57] and 20%–70% of children with disseminated TB.[58,59]

Imaging studies should be performed, and an examination of the CSF should be strongly considered, even with normal brain MRI findings. Detection of AFB on CSF smear, which varies considerably from study to study, depends on the quality and volume of the sample sent, the skill of the technician, and their persistence in examining for AFB. The repeated study of CSF for AFB is positive in 5%–85% of adults and 0%–6% of children, while culture for *M. tuberculosis* is positive in 40%–85% and 35%–85% of adults and children, respectively.[60] CSF PCR has a sensitivity of 50% and specificity close to 100%.[61] The use of ADA and IFN-γ to improve the diagnosis warrants further investigation as the current data to support their utility in TBM diagnosis are inconclusive.[60,61]

In circumstances where it is difficult to establish the sites involved with disease or the failure of the above-mentioned diagnostic workup, samples from systemic sites such as the bone marrow, liver, and blood should be obtained to support the diagnosis of disseminated TB.[62]

Bone marrow aspiration and biopsy

Bone marrow aspiration and biopsy have been found useful for the diagnosis of disseminated TB if subjected to smear, PCR, and mycobacterial culture and histopathology examination. The combined tests increased the diagnostic yield to between 50% and 93%.[28,47,62]

Liver biopsy

It is believed that the liver is affected in most cases of disseminated TB, being found in 80%–100% of the cases in autopsy series.[63] Therefore, the diagnosis of disseminated TB can be confirmed by the histopathology of a tissue sample from the liver. Several studies have shown that the sensitivity of AFB and PCR on liver tissue is inconclusive; conversely, the sensitivity of liver biopsy to caseating granulomas is 91%–100%.[1,49,63-65]

Blood culture

PCR testing of blood yields positive results in most cases of HIV-related disseminated TB. Mycobacterial blood culture is also found to be positive in 14%–30% of cases with advanced HIV.[66-69] Therefore, performing mycobacterial blood culture in HIV patients with suspected disseminated TB is recommended by some authors, as a useful adjunct, especially when the yield from other tissues is poor.[62,66,67,69]

Disseminated TB without pulmonary involvement

Disseminated TB with normal chest radiograph is labeled by some authors as "cryptic tuberculosis."[68] Its presentation is insidious and mainly affects middle aged and the elderly. Diagnosing disseminated TB in such patients is still a dilemma, from both a clinical and laboratory perspective, because of the lack of localizing signs, absence of choroidal tubercles, normal chest X-rays, and negative tuberculin test.[70] Therefore, disseminated TB should be suspected in immunocompromised patients and in those from endemic areas who have prolonged pyrexia of unknown origin, weight loss, lassitude, hepatomegaly, splenomegaly, liver function abnormalities, and abnormal hematological indices. Relentless efforts should be made to identify the organ or site involved in these patients in order to obtain adequate samples for diagnosis. Imaging modalities such as ultrasonography, CT, and MRI are useful in identifying miliary lesions at occult extrapulmonary sites. Recently, PET-CT scan has been used successfully as an investigating tool for the evaluation of suspected disseminated TB.[70,71]

In circumstances where it is difficult to establish the sites involved with disease, samples from systemic sites such as bone marrow, liver, and blood should be obtained to support the diagnosis of disseminated TB. In countries with limited resources, this approach may be hampered by the lack of facilities. Therefore, empirical antituberculous therapy (ATT) is usually commenced on the bases of presentation and systemic evaluation without diagnostic intervention, and dramatic response to treatment is used to confirm the diagnosis.

Treatment, Outcome, and Complications

In fact, no randomized controlled trials of disseminated TB treatment have been conducted, and most evidence is based on randomized controlled trials of pulmonary TB.[72] Although there is no consensus regarding the optimum duration of treatment in patients with disseminated TB,[47] early initiation of therapy is associated with a significant improvement in outcomes.[1,73,74]

In general, the duration of ATT for disseminated TB is the same as for pulmonary TB; however, individualization of regimens may be warranted. For example, patients with high organism burden, slow clinical response, immune suppression, CNS infection and certain patients with bone and joint involvement and longer duration of therapy may be needed.[72,75] For susceptible organisms, treatment of disseminated TB includes the administration of the "four-drug regimen," which consists of two phases, rifampicin, isoniazid (INH), pyrazinamide, and ethambutol/streptomycin given daily for the first 2 months. The treatment is then continued with rifampicin and isoniazid for a further 4 months, with the possibility of being extended to 7 months in some cases.[72,73] Response to first-line anti-TB drugs is good as evidenced by many reports.[1,47] For multidrug resistance TB, treatment with a minimum of 1 susceptible injectable and at least 3 additional susceptible drugs, to prevent the development of additional resistance, is required.[76]

The impact of corticosteroid treatment on the outcome of disseminated TB is not clear as much of the evidence is derived from randomized controlled trials of TB infection rather than specific trials of patients with disseminated TB. In general, adjunct corticosteroid treatment can be given in disseminated TB with meningitis, pericarditis, and adrenal insufficiency and in disseminated TB with refractory hypoxemia.[47,74,77]

In-hospital Mortality Predictors

Despite advances in the supportive care and therapy of patients with disseminated TB, mortality is still high, ranging from 25% to 30%. Many predictors of mortality associated with disseminated TB are mentioned in the literature. Examples are meningismus, liver cirrhosis, leukopenia, leukocytosis, advancing age, presence of underlying disease, altered mental status, and night sweats.[1,4,72]

Conclusions

Disseminated TB is an important health problem worldwide associated with a significant burden of morbidity and mortality. Diagnosis is difficult owing to its nonspecific clinical picture and the limited tools for confirmatory laboratory diagnosis. Improved awareness of this disorder and associated trends might improve a clinician's index of suspicion and lead to a better diagnostic approach. Therefore, patients with immunosuppression (i.e., HIV patients and patients with organ transplantation and chronic liver diseases) and patients from endemic areas, who present with prolonged pyrexia of unknown origin, weight loss, lassitude, hepatomegaly, splenomegaly, liver function abnormalities, and abnormal hematological indices should be targeted with resolute efforts to diagnose and treat the disease promptly.

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Conflicts of interest
There are no conflicts of interest.

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