

Mycobacterial Sepsis and Multiorgan Failure Syndrome

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*“Man is a creature composed of countless millions of cells:
a microbe is composed of only one, yet throughout the ages
the two have been in ceaseless conflict.”*
A.B. Christie

Introduction

Tuberculosis (TB) is a global disease with high prevalence in developing countries. According to the World Health Organization (WHO) fact sheet 2009, more than 2 billion (equal to one third of world's population) people are infected with TB bacilli. Of the cases detected, 5 % were cases of multi-drug resistant TB. Admission to a critical care unit is not required in the majority of cases. However, TB sepsis is a rapidly fatal disease that requires intensive care unit (ICU) admission and management and represents a big diagnostic and therapeutic challenge.

Mycobacterial sepsis was described first by Landouzy in the late 19th century and has been occasionally referred to as “sepsis tuberculosa gravissima” or “sepsis tuberculosa acutissima”. As a disease, TB sepsis is not due to a virulent pathogen, but is due to host issues like depressed cell-mediated immunity resulting in lympho-hematogenous dissemination of tubercle bacilli. Only a few cases of TB sepsis have been described in the literature and it is generally considered a rare disease [1].

Pathogenesis

The outcome from sepsis due to serious infection has a number of determinants. The most important of these factors are host defense mechanisms, the environment, and the specific bacteria involved. TB sepsis has the same basic pathogenesis with a few additional factors.

Predisposing Conditions

Age is one of the most significant risk factors for development of TB sepsis. In the post-antibiotic era, the growing population of elderly adults, with a relative waning of cellular immunity, has become the most common group to develop TB sepsis [2, 3]. However, the increase in human immunodeficiency virus (HIV) and the increasing proportion of other adults with conditions associated with natural or iatrogenic impairment in cellular immunity has led to an additional peak of TB sepsis among young adults. The percentage of patients with TB sepsis and some other identifiable medical condition ranges from 38 to 70 % in large studies. Predisposing medical conditions include HIV, depressed immunity, alcohol abuse, malignancy, corticosteroids, connective tissue disease, renal failure, diabetes mellitus and pregnancy.

Bacterial Factors

Catalase-peroxidase, which can resist oxidative stress, and lipoarabinomannan (LAM), which can induce cytokines and resist host oxidative stress, have been strongly implicated in the pathogenesis of TB sepsis [4]. Tumor necrosis factor (TNF)- α plays an important role in pathogenesis of tuberculosis. Increasing use of anti-TNF agents has led to an increase in reports of patient suffering from TB.

Immunology

Mycobacterium invasion triggers a cell-mediated immune response. Activated macrophages present the antigens to CD4+ T-helper cells and CD8+ T suppressor cells, which in turn release cytokines and lead ultimately to granuloma formation. Occasionally, dominance of Th-2 cytokines (interleukin [IL]-4, IL-5, IL-10) increases the risk of dissemination by inhibiting protective responses such as granuloma formation.

Clinical Features

TB sepsis occurs as a progressive primary infection, reactivation of latent infection and subsequent spread, or rarely as iatrogenic infection. The clinical manifestations are highly variable and non-specific. This can delay the diagnosis and account for the fact that diagnosis is missed, even in this era of rapid diagnostics. TB sepsis has been reported after extracorporeal shock wave lithotripsy [5], homograft valve replacement, and urethral catheterization [6]. In cases with various predisposing factors, the disease tends to have a more acute course and may lead to fulminant disease in the form of shock and potentially multiorgan system failure.

XII

Pulmonary Involvement

Clinically significant pulmonary disease is noted in over 50 % of patients in most series. Patients report dyspnea or cough and have râles or rhonchi on physical examination. Hypoxemia, when looked for, is common.

Gastrointestinal Involvement

Signs or symptoms referable to the gastrointestinal tract included diffuse abdominal pain or pain localizing to the right upper quadrant, nausea, vomiting and diarrhea [7]. Hepatomegaly may be appreciated on physical examination more frequently than splenomegaly. Liver function test abnormalities are common. Cholestatic jaundice and ascites may be detected in occasional patients.

Central Nervous System (CNS) Involvement

Meningitis or tuberculoma is suggested clinically in 15 to 20 % of patients.

Other Systems

Seeding of every organ system has been documented including bone, joints and eyes. Involvement of the adrenals was found in as many as 42 % of autopsies of fatal cases. Overt adrenal insufficiency is rare, occurring in less than 1 % of reported cases of disseminated TB [8].

Diagnosis

The biggest challenge in the diagnosis of TB as a cause of sepsis is thinking about it as a possibility. Previous reports of diagnosis of TB sepsis have been based only on autopsy findings. With the advent of newer diagnostic modalities, it is possible to identify such patients faster and hence start effective treatment to decrease mortality.

Laboratory Evaluation

There is no specific hematological pattern found in TB [8]. Patients may have various degrees of normochromic normocytic anemia. Total white cell count may be normal or may show leukopenia. In some cases, thrombocytopenia may also be observed. Patients may present with pancytopenia, which may suggest bone marrow infiltration by granulomas or may suggest triggering of hemophagocytic reaction [10]. These findings are neither sensitive, nor specific for TB. However, in appropriate epidemiological and clinical conditions it should alert us to the possibility. The erythrocyte sedimentation rate (ESR) is elevated in the majority of patients with disseminated TB along with other acute phase reactants. Isolated hyponatremia is a frequent biochemical finding in patients with TB. No other biochemical marker is available for diagnosis of TB [8].

Testing for Latent TB

Newer *in vitro* assays are now available that can detect latent TB infection based on measurement of interferon gamma (IFN- γ), which is released by T cells in response to specific mycobacterial antigens. The QuantiFERON-TB Gold In-Tube (QFT-GIT) assay (Cellestis, Carnegie, Australia) and the T-SPOT.TB assay (Oxford Immunotec, Marlborough, USA) are the IFN- γ release assays that are approved by the US Food and Drug Administration (FDA). However, it is still not clear how these tests would perform in detecting latent infections in cases of TB sepsis [11].

Imaging

Imaging is useful for evaluating symptomatic patients with appropriate epidemiologic risk factors for TB. Presence of cavitation, upper lobe infiltrates or fibrosis, intra-thoracic lymphadenopathy, pleural effusion, pneumothorax may all suggest tuberculosis. The classic miliary pattern described with disseminated TB (as seen in Fig. 1) may not be apparent on presentation or until after a few weeks as the immune system is overwhelmingly suppressed. Computed tomography (CT) scan especially high resolution CT is more sensitive than chest radiography for detecting subtle parenchymal and nodular changes. However, its specificity for TB is

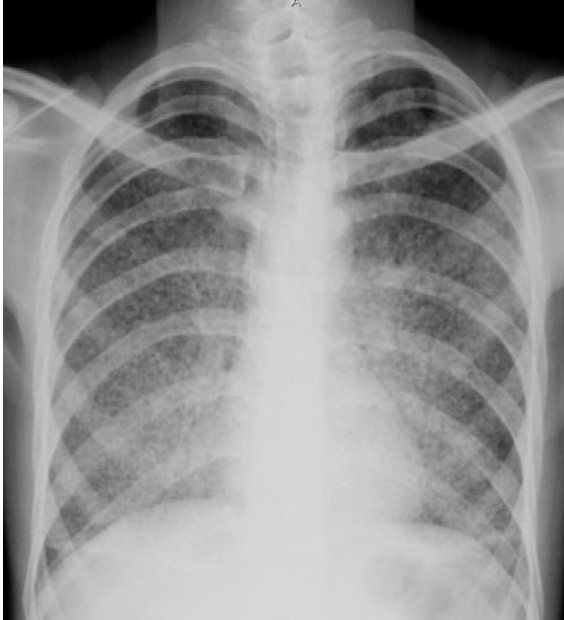


Fig. 1. Classic miliary shadows in lung fields in a case of tuberculosis with multiorgan dysfunction syndrome.

still not established. When any lesion amenable to CT-guided biopsy is present, it may help in establishing diagnosis. But there are no data on whether these can be helpful.

Microbiological Evaluation

Acid-fast bacillus smear

AFB smears of expectorated or induced sputum, bronchoalveolar lavage (BAL) fluid, gastric lavage, stool, pleural, pericardial and peritoneal fluid, cerebrospinal fluid (CSF), urine, blood, bone marrow aspirate, lymph node biopsy, liver biopsy and transbronchial biopsy have shown various degrees of sensitivity ranging from 30 % to 80 %. The probability of a positive smear increases with the number of sites sampled. CSF should only be examined in cases where neurological symptoms or signs are present. If the chest radiograph does not suggest pulmonary involvement, bronchoscopy may be less useful. Bronchoscopy with BAL did not add significantly to the diagnostic yield, if all the other sites were also sampled [12]. Further concentration of samples prior to processing for smear may help to increase sensitivity. Fluorochrome dye-based stains are more sensitive than the routine Ziehl-Neelsen stain [13]. However, neither of these staining methods helps differentiate between tuberculous and non-tuberculous mycobacteria; further testing with nucleic acid amplification is required to achieve this [14].

Cultures

Cultures are the gold standard for definitive diagnosis of TB. Mycobacterial blood cultures, preferably using lysis centrifugation techniques, are a rapid and non-invasive method of diagnosis. The conventional Lowenstein-Jensen medium used takes 4–6 weeks to detect growth. With evolution of diagnostic microbiology,

newer mediums are now available which can detect growth within 2–4 weeks. All specimens should be inoculated in a commercial automated radiometric detection system, which is more rapid and more sensitive than standard techniques.

Rapid Diagnostic Tests

Adenosine deaminase levels

Adenosine deaminase (ADA) levels represent a faster and cheaper way to establish diagnosis especially in resource-limited areas with a high prevalence of TB. Elevated concentrations of pleural fluid or peritoneal fluid ADA has been described in the setting of TB. Peritoneal and pleural fluid ADA values greater than 40 IU had a very high sensitivity and specificity for TB peritonitis and TB pleural effusions, respectively [15, 16]. The utility of ADA levels for diagnosis in areas of low prevalence and peritoneal fluid levels in cases of cirrhosis is still debatable. In pleural effusions, ADA was also found to be raised in empyema and rheumatoid disease. However, further studies have revealed that the increased ADA in TB effusion was mainly due to an increase in ADA2 levels, which was not the case with empyema and rheumatoid disease; measurement of ADA2 may thus improve sensitivity [17]. The sensitivity of ADA for TB is higher than a polymerase chain-reaction (PCR) based test, which has greater specificity in a high prevalence setting [18]. The role of ADA in the diagnosis of TB meningitis is still not well established [19].

Interferon gamma assay

Determination of IFN- γ levels in pleural fluid has good sensitivity (90 %) and specificity (97 %), and may be useful to differentiate tuberculous from non-tuberculous effusions [20].

Nucleic acid amplification test

Nucleic acid amplification testing is useful for rapid identification of *Mycobacterium tuberculosis* in respiratory samples; results can be available within two to seven hours. Currently two tests, enhanced MTD (enhanced *M. tuberculosis* direct test) and enhanced amplicor *M. tuberculosis* test 2 (AMTD2), are approved for nucleic acid amplification testing in smear-positive and smear-negative respiratory specimens. According to FDA data, the sensitivity of the tests for tuberculosis (compared with culture) is approximately 95 % in patients with a positive AFB smear, but only about 50 % in smear-negative cases. Specificity is greater than 95 % in smear-negative and smear-positive samples. Although the FDA has not yet approved the use of nucleic acid amplification testing on non-respiratory samples, research has shown that nucleic acid amplification testing can be very useful in these samples, especially gastric fluid, lymph node biopsies, and skin biopsies [21]. However, nucleic acid amplification tests do not perform well with pleural fluid samples because pleural fluid has many inhibitors which affect the test, resulting in poor sensitivity. When TB meningitis is suspected without extrameningeal disease, nucleic acid amplification tests give a better yield than any other test, but experience with these specimens is minimal and they require special handling [22]. Nucleic acid amplification tests have poor sensitivity in smear-negative cases. A negative result does not rule out a diagnosis of TB. Most published data regarding the performance of nucleic acid amplification tests are based upon laboratory trials. These studies do not completely address their clini-

cal applicability. It remains to be seen whether the routine use of nucleic acid amplification tests in non-research settings by less experienced and less trained technicians will result in a deterioration in performance.

Histopathology of tissue specimens

Histopathology continues to play an important role in the rapid diagnosis of TB. Liver biopsies have the highest yield. In case of disseminated disease? granulomas were demonstrable in nearly 100 % of liver biopsies (Fig. 2), 82 % of bone marrow biopsies and 72 % of transbronchial biopsies [8]. If biopsies are targeted based on involvement of specific organ systems, then the diagnostic yield is increased.

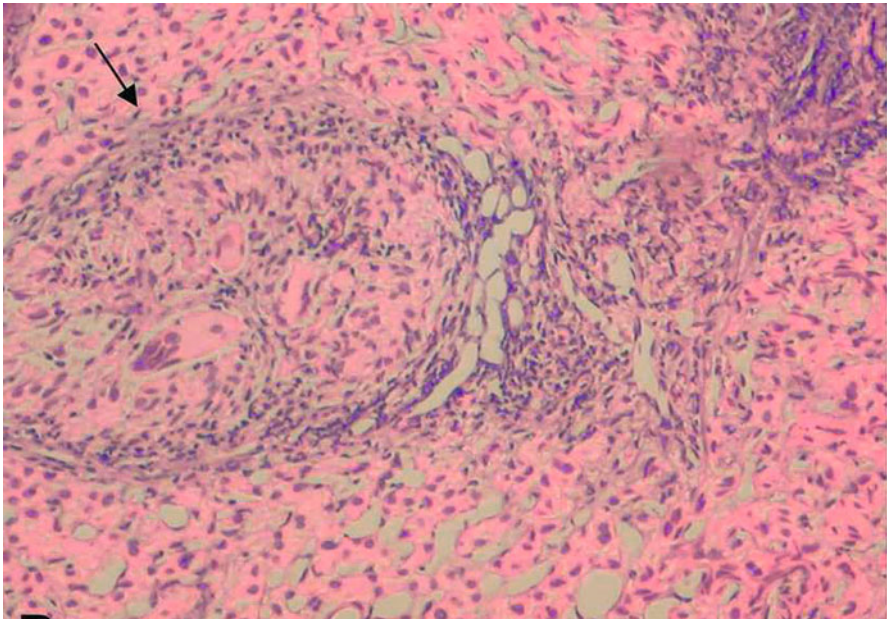


Fig. 2. Photomicrograph showing classic hepatic tubercular granuloma.

XII

Drug susceptibility testing

Drug susceptibility testing for isoniazid, rifampin and ethambutol should be performed on initial isolates from each site of disease. The agar proportion and liquid radiometric methods are used mainly to detect mycobacterial drug resistance. The agar proportion method requires around 1 month for susceptibility testing after visible growth appears. This translates into presumptive treatment until susceptibility reports are available. Liquid radiometric methods reduce this time to 15–20 days. However, with the increasing number of cases of drug-resistant tuberculosis, it is imperative to reduce this time to as short as possible. Several rapid molecular or genotypic tests for tuberculosis drug susceptibility testing have emerged:

- A) The microscopic-observation drug-susceptibility assay: This test combines organism detection and susceptibility testing using a single technique, by comparing mycobacterial growth in 24-well plates with liquid culture

medium in the presence and absence of antimycobacterial drugs [23]. The sensitivity of this assay compared to automated mycobacterial culture and Lowenstein-Jensen culture was 98 %. Median time to culture positivity was 7 days.

- B) Phage-based assays: Despite good agreement of phage-based assays for detecting rifampin resistance compared to conventional testing, significant concerns have been raised regarding rates of contamination. Furthermore, with development of line probe assays, the exact scope and role of phage-based assays needs to be determined.
- C) Line probe assays: These are automated molecular tests for diagnosis of *M. tuberculosis* and resistance to rifampin. They use real time PCR to amplify the specific *M. tuberculosis* sequence of the *rpoB* gene, which is then probed for mutations in the rifampin resistance determining region. Line probe assays provide sensitive detection of *M. tuberculosis* (97 %) and rifampin resistance (98 %) directly from untreated sputum in less than 2 hours [24].
- D) Molecular beacons: These are labeled oligonucleotides that fluoresce when hybridized to a target sequence encoding genes for drug resistance. About 95 % of rifampin-resistant strains contain mutations within a single locus (*rpoB*), and rifampin resistance may be considered a surrogate marker for multidrug-resistant TB (MDR-TB); approximately 90 % of rifampin-resistant strains are also resistant to isoniazid [25].

Drug susceptibility testing is less reproducible when testing susceptibilities of second-line drugs, which are integral to the treatment of any patient with XDR-TB (extensively drug resistant TB). Furthermore, all marketed rapid technologies (i.e., PCR-based techniques) and the Microscopic Observation and Drug Susceptibility assay detect resistance only to first-line medications [23–25].

Treatment

Tuberculosis sepsis is uniformly fatal if not diagnosed and treated in time. Even with treatment, mortality is as high as 40–50 %. Delay in diagnosis and initiation of treatment is responsible for this high mortality. Currently there are no randomized trials that have evaluated the efficacy of different regimens in the treatment of TB sepsis and multi-organ dysfunction syndrome.

Anti-tuberculous Therapy

The American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) have issued joint guidelines for the treatment of TB [26]. The initial regimen is for two months followed by a continuation phase of either 4 or 7 months. The choice of treatment in the initial phase is empiric and is based on likely susceptibility. Four drugs are used in the initial phase: isoniazid, rifampin, pyrazinamide, and ethambutol. In drug susceptible cases, rifampin and isoniazid are used in the continuation phase for 4 or 7 months. Directly observed therapy is the best way to ensure completion [26]. The recommendations for disseminated disease are the same as for pulmonary disease. A longer duration of therapy is required for miliary TB, bone disease, and in the immunocompromised. In the presence of TB meningitis, the

duration needs to be extended to at least 12 month. Patients who show slow microbiologic or clinical response have high relapse rates and may benefit from extended therapy. The biggest challenge in patients with TB sepsis and multi-organ dysfunction is which drugs to give.

Isoniazid, rifampin, and pyrazinamide have significant hepato-toxicity. In patients with no pre-existing liver disease and normal liver function, standard four drug therapy may be started safely. Anti-tuberculous therapy should be discontinued if the patient's transaminase level increases three times above normal with symptoms or five times above normal without symptoms [26]. The optimal approach to resumption of anti-tuberculous therapy is uncertain. Three new drugs (e.g., an aminoglycoside and two oral agents, such as ethambutol and a fluoroquinolone) could be started until the transaminase concentration returns to less than twice the upper limit of normal (or to near baseline levels) [27]. For patients with severe unstable liver disease who require a regimen with no hepatotoxic agents, streptomycin, ethambutol, a fluoroquinolone and another second line oral drug may be used for a duration of 18 to 24 months. Alteration in dosing of antitubercular therapy, particularly of ethambutol and pyrazinamide, is necessary in patients with renal insufficiency. Lengthening the dosing interval is preferable to reducing the dose in order to optimize peak serum concentrations. Administration of all anti-TB drugs immediately after hemodialysis facilitates directly observed therapy (three times weekly) and minimizes premature removal of the drugs. In critical care, it is important to administer pyridoxine with isoniazid in order to avoid isoniazid-induced neuropathy. Isoniazid can also cause cytopenias, which may be synergistic with other toxicities or co-morbidities in the critically ill. Rifampin is a potential cytochrome P450 inducer. It is essential to review the entire drug chart in patients receiving rifampin to anticipate potential serious drug-drug interactions. Ethambutol may cause irreversible optic neuritis.

Drug-resistant TB

Certain demographic and historical features may raise suspicion of drug-resistant TB, including previous treatment for TB. The availability of rapid molecular drug sensitivity testing has made this diagnosis faster and easier. Modifications of conventional treatment are essential. Moxifloxacin may be a suitable alternative for patients who are intolerant of isoniazid or are infected with isoniazid-resistant *M. tuberculosis* [28]. Because rifampin is the cornerstone of all six-month regimens, resistance to this drug requires prolongation of treatment [26]. Treatment of MDR-TB (resistance to isoniazid and rifampin) should be guided by drug susceptibility testing whenever possible (Table 1). In many parts of the world, however, drug susceptibility testing is not available (at least initially), and empiric therapy must be used. The initial empiric therapy of TB in areas with a known high prevalence of MDR-TB or in patients who contract TB after contact with a patient with known MDR-TB, should include the standard recommendations plus whatever additional drugs are necessary to assure that at least four drugs effective against the most prevalent drug-resistant strains are included in the regimen [26].

XDR-TB is defined as resistance to both isoniazid and rifampin with additional resistance to at least one fluoroquinolone and one injectable agent (amikacin, kanamycin, or capreomycin). There are no randomized controlled trials on which to base strong recommendations for the pharmacotherapy of XDR-TB. In this scenario, the existing four-drug regimen should be strengthened, while waiting for results of drug susceptibility testing. An injectable agent (e.g., capreomycin),

Table 1. Suggested treatment regimens for the management of patients with drug-resistant pulmonary tuberculosis

Drug resistance	Suggested regimen	Duration (months)	Comments
INH	RIF, PZA, EMB (an FQN may strengthen regimen)	6	6-month regimens have yielded 95 % success rates despite resistance to INH [29]. Result was best if PZA was also used throughout the 6 months [30].
RIF	INH, PZA, EMB (a FQN may strengthen the regimen)	9–12	An injectable agent may be added in the initial 2 months of therapy.
INH and RIF (± SM)	FQN, PZA, EMB, IA, ± alternative agent	18–24	Resection surgery may be considered
INH, RIF (± SM), and EMB or PZA	FQN , IA, and two alternative agents	24	Resection surgery should be considered.

EMB: ethambutol; FQN: fluoroquinolone (most experience with ofloxacin, levofloxacin, or ciprofloxacin); INH: isoniazid; PZA: pyrazinamide; RIF: rifampin; SM: streptomycin; IA: injectable agent (streptomycin, amikacin, kanamycin or capreomycin). Alternative agents: ethionamide, cycloserine, p-aminosalicylic acid, clarithromycin, amoxicillin/clavulanate, linezolid.

if the patient is not already on an injectable medication, one or two oral second-line medications (e.g., ethionamide and cycloserine or terizidone) and a third-line agent (e.g., amoxicillin-clavulanate, clarithromycin, linezolid or clofazamine) should be added. This may require that seven or more drugs be given until drug susceptibility results are obtained. Therapy should then be tailored according to drug susceptibility testing when available. The duration of therapy often extends for an average of 18 months after sputum conversion [31, 32].

Newer Anti-tubercular Therapy

Research has now accelerated for search of new therapies for TB. Moxifloxacin and gatifloxacin are currently being investigated in phase 3 trials to shorten the duration of treatment in drug-susceptible tuberculosis. The diarylquinoline, TMC207, offers a new mechanism of anti-TB action by inhibiting mycobacterial synthase. Preliminary phase 2 trial results for this agent in the setting of MDR-TB appear promising [33]. Nitroimidazoles (PA824 and OPD67683) have demonstrated good anti-mycobacterial activity in a mouse model and *in vitro* for drug sensitive and resistant strains of TB [34, 35].

Adjunctive Therapy

Corticosteroids

Current recommendations on steroids in the treatment of TB are based on limited evidence. The presence of associated adrenal insufficiency is an absolute indication for steroid therapy. Corticosteroid therapy may be beneficial in TB sepsis with TB meningitis, large pleural or pericardial effusion, acute respiratory distress syndrome (ARDS), immune complex nephritis and histiocytic phagocytosis.

Drotrecogin alfa

Only one report of the use of drotrecogin alfa (activated) in TB sepsis is available in the literature [36]. Further use in TB sepsis should be based on generally approved guidelines for the use of this product.

Immunotherapy

Uncontrolled trials and anecdotal reports suggest that adjunctive immunotherapy with IFN- γ may be useful in the management of MDR-TB [37].

Surgery

Surgical debulking of areas of pulmonary cavitation and localized disease has been advocated as an adjunct to medical therapy. In a carefully selected population of HIV-negative patients, resective surgery (lobectomy, wedge resection, or pneumonectomy) can help achieve relatively rapid sputum culture conversion and provide durable cure in patients with MDR- and XDR-TB [26, 38, 39]. Further research is needed regarding the selection of surgical candidates, timing of surgery, optimal medication regimens, and duration of therapy following surgery.

Micronutrient supplementation

The few trials available have demonstrated conflicting results regarding any potential benefits of this approach [40–42]. Further studies are needed before any recommendations can be made.

Conclusion

With the increasing populations of patients with HIV or diabetes and the widespread use of immunosuppressive medication, we may see increasing proportions of patients presenting with TB sepsis in the years to come. With the various diagnostic and therapeutic dilemmas surrounding TB, this may represent another menace in infectious disease management in the critical care setting. Many methods for fast diagnosis and newer drugs have emerged. But these methods have not gained widespread acceptance in health programs of countries with high disease prevalence. One of the biggest hurdles is the cost. With the greatest prevalence of TB in developing countries and among poorer populations, the focus should be on the development of cost-effective strategies and practical strategies of management. Ultimately, the major purpose of research is to develop solutions that can benefit the populations who need them most. The last decade has seen aggressive research in this field to address these larger issues also and it seems that we are just on the right track.

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