Diagnosis and Treatment of Tuberculous Pleural Effusion in 2006

Arun Gopi, Sethu M. Madhavan, Surendra K. Sharma and Steven A. Sahn

*Chest* 2007;131:880-889
DOI 10.1378/chest.06-2063

The online version of this article, along with updated information and services can be found online on the World Wide Web at: [http://chestjournals.org/cgi/content/abstract/131/3/880](http://chestjournals.org/cgi/content/abstract/131/3/880)
Tuberculous (TB) pleural effusion occurs in approximately 5% of patients with *Mycobacterium tuberculosis* infection. The HIV pandemic has been associated with a doubling of the incidence of extrapulmonary TB, which has resulted in increased recognition of TB pleural effusions even in developed nations. Recent studies have provided insights into the immunopathogenesis of pleural TB, including memory T-cell homing and chemokine activation. The definitive diagnosis of TB pleural effusions depends on the demonstration of acid-fast bacilli in the sputum, pleural fluid, or pleural biopsy specimens. The diagnosis can be established in a majority of patients from the clinical features, pleural fluid examination, including cytology, biochemistry, and bacteriology, and pleural biopsy. Measurement of adenosine deaminase and interferon-γ in the pleural fluid and polymerase chain reaction for *M. tuberculosis* has gained wide acceptance in the diagnosis of TB pleural effusions. Although promising, these tests require further evaluation before their routine use can be recommended. The treatment of TB pleural effusions in patients with HIV/AIDS is essentially similar to that in HIV-negative patients. At present, evidence regarding the use of corticosteroids in the treatment of TB pleural effusion is not clear-cut.

Key words: adenosine deaminase; diagnosis; corticosteroids; interferon-γ; pathogenesis; polymerase chain reaction; treatment; tuberculous pleural effusions

Abbreviations: ADA = adenosine deaminase; AFB = acid-fast bacilli; CXCR3 = receptor 3 for CXC chemokines; EPTB = extrapulmonary tuberculosis; IFN = interferon; IL = interleukin; PCR = polymerase chain reaction; TB = tuberculosis; Th1 = T-helper type 1

TB cases in developing countries. TB pleural effusion, considered as a form of extrapulmonary TB (EPTB), constitutes a frequent clinical problem and is particularly important in the present era of HIV infection, when EPTB is more commonly encountered in clinical practice. A pleural effusion occurs in approximately 5% of patients with TB.

**Epidemiology**

A total of nine million new cases and approximately two million deaths from TB were reported in 2004. Although the African region has the highest estimated incidence (356 per 100,000 population per year), the majority of patients with TB live in the most populous countries of the Asian subcontinent, which accounts for nearly half of the new cases that arise yearly. The frequency of pleural involvement...
in TB has been variably reported (4% in United States to 23% in Spain).6,7

TB pleural effusion is the second most common form of EPTB, only less frequent than lymph node TB. TB pleural effusion is being increasingly recognized, even in developed nations,2 as the incidence of EPTB has more than doubled following the HIV pandemic. The incidence of TB pleural effusions in HIV/AIDS has been variably reported from 15 to 90%,8,9 with an effusion being more common in patients with higher CD4+ counts.10,11

Pathogenesis

TB pleural effusions can manifest as primary or reactivated disease. Rupture of a subpleural caseous focus in the lung into the pleural space is considered the initial event in the pathogenesis of primary TB pleural effusions.12 The entry of mycobacterial antigens into the pleural space is followed by an interaction with predominantly CD4+ T-lymphocytes resulting in a delayed hypersensitivity reaction.13 The accumulation of fluid in pleural cavity results predominantly from increased capillary permeability and secondarily from impairment of lymphatic clearance of proteins and fluid from the pleural space because of occlusion of pleural stomata.14,15 In contrast, reactivation disease is frequently associated with parenchymal lesions.

The delayed hypersensitivity reaction responsible for the pathogenesis of TB pleural effusions is mediated by T-helper type 1 (Th1) cells that activate macrophages to switch on mechanisms responsible for the killing of mycobacteria. A strong Th1-like immunity (interferon [IFN]-γ dominant) is essential for the containment of M tuberculosis, while these protective effects are antagonized by T-helper type 2 cytokines, primarily interleukin (IL)-4. The predominant of Th1 immunity in TB pleural effusions is demonstrated by the significantly higher levels of IFN-γ in pleural fluid compared to peripheral blood of the same patient.16 Flow cytometry and in vitro polyclonal stimulation studies have also demonstrated high levels of Th1 cells, which are predominantly of memory phenotype (CD45RA−). The memory T cells in TB pleural effusions typically display a surface phenotype CD62L−CD11a+ consistent with a Th1-like cytokine profile. Therefore, selective homing of IFN-γ–biased memory T cells in TB pleural effusion is evident. The mononuclear cells infiltrating the pleura are predominantly CD4+/CD45RO+ T cells expressing C-C chemokine receptor 5 and receptor 3 for CXC chemokines (CXCR3). A strong expression of their ligands was observed in the pleural tissue of patients with TB pleural effusions. Interleukin expression in pleural fluid shows low albumin and high globulin, hemoglobin, and higher C-reactive protein.88 The presence of leukocytes and lymphocytes in the pleural fluid is evident, with the most common being mononuclear cells, which represent more than 90% of the total cell count. The pleural fluid of patients with TB pleural effusion is typically hemorrhagic.

Clinical Features

In contrast to pulmonary TB, most TB pleural effusions manifest as an acute illness, with approximately one third of patients being symptomatic for <1 week and two thirds for <1 month.18 The most common presenting symptoms are pleuritic chest pain (75%) and nonproductive cough (70%).19 TB pleural effusion was considered a disease of the young, with a mean age of 28 years, compared to 54 years for parenchymal tuberculosis.20 However, Epstein and colleagues21 demonstrated a rise in the median age (56 years) at presentation of TB pleural effusions with 19% of patients having reactivation disease. Therefore, pleural tuberculosis should be considered in any adult or elderly patient with a unilateral pleural effusion.

TB pleural effusions, typically unilateral and small to moderate in size, usually occupy less than two thirds of a hemithorax.22 HIV-positive patients with TB pleural effusions tend to be older, are more likely to be pleural fluid smear and culture positive for M tuberculosis, have a higher propensity for positive pleural biopsy,23 and show a higher incidence of disseminated disease.24 Fever, dyspnea, night sweats, fatigue, diarrhea, marked tachypnea, hepatosplenomegaly, and lymphadenopathy are more common in HIV-infected patients. These patients tend to have a negative tuberculin skin test results, lower hemoglobin, and higher β2-microglobulin; their pleural fluid shows low albumin and high globulin levels.24

Chronic TB empyema, an entity distinct and much less common than tuberculous pleural effusion, represents chronic, active infection of the pleural space. TB empyema can occur in several settings: (1) progression of a primary tuberculous pleural effusion...
that is usually large to massive in size; (2) direct extension of infection into the pleural space from thoracic lymph nodes or a subdiaphragmatic focus; (3) hematogenous spread; (4) following pneumonectomy; and (5) following therapeutic pneumothorax that leads to lung entrapment, after Lucite ball plombage, or oleothorax. Chronic TB empyema can present as an abnormality on a routine chest radiograph or after the development of a bronchopleural fistula or empyema necessitatis.25

**DIAGNOSIS**

The definitive diagnosis of TB pleural effusions depends on the demonstration of *M tuberculosis* in sputum, pleural fluid, or pleural biopsy specimens. Supportive evidence includes demonstration of classical TB granulomas in the pleura and elevated adenosine deaminase (ADA) and IFN-γ levels in pleural fluid.14

**Sputum Examination**

Traditional dogma has stated that patients with pleural TB without concomitant pulmonary disease are sputum negative and, therefore, noncontagious. However, one study26 reported a remarkably high yield of mycobacterial culture (52%) in a single specimen of induced sputum with sputum smear positivity in 12% of cases. Even in patients with normal lung parenchyma on chest radiography, the yield of sputum culture in induced samples approached 55%.26 Therefore, sputum induction should be pursued in resource-limited countries where invasive diagnostic procedures, such as pleural biopsy, are less accessible.

**Tuberculin Skin Test**

A positive tuberculin skin test result is supportive evidence in the diagnosis of TB pleural effusions in areas of low prevalence (or no vaccination); however, a negative tuberculin skin test result may occur in approximately one third of patients.22 A negative test result could result from the following: (1) anergy secondary to immunosuppression or malnourishment; (2) recent infection; (3) circulating mononuclear cells suppressing the specifically sensitized circulating T-lymphocytes in the peripheral blood27,28; or (4) sequestration of purified protein derivative-reactive T-lymphocyte in pleural space.28 However, results of a tuberculin skin test repeated 6 to 8 weeks later will almost always be positive.

**Imaging**

Chest radiography usually reveals a small-to-moderate unilateral pleural effusion. Various studies4,22 report the prevalence of associated parenchymal lesions to range from 20 to 50%; although one study26 reported associated parenchymal lesions in 67% of cases. Ultrasonography helps by demonstrating fibrin bands of varying lengths, mobile delicate septations, encysted pleural effusion, pleural thickening, and occasionally pleural nodules.30 Contrast-enhanced CT improves the diagnostic accuracy by documenting associated parenchymal lesions and lymphadenopathy. Lung parenchymal lesions were observed in 86% of patients with TB effusion using chest CT with 37% showing features of radiologically active pulmonary TB.29 CT can also detect complications associated with TB pleural effusions, such as pleural thickening, calcification, loculated effusions, empyema, empyema necessitatis, and bronchopleural fistula.31

**Thoracocentesis**

**Pleural Fluid Examination**

A TB pleural effusion is typically clear and straw colored; however, it can be turbid or serosanguinous but is virtually never grossly bloody. The effusion is virtually always an exudate.14 Pleural fluid pH is usually between 7.30 and 7.40 (rarely ever > 7.40), although it can be < 7.30 in approximately 20% of cases.25 Pleural fluid glucose concentration is > 60 mg/dL in 80 to 85% of cases.22 Pleural fluid glucose is < 30 mg/dL in approximately 15% of cases.21 Although in the initial stage of illness (up to first 2 weeks), the differential cell count may reveal predominantly neutrophils,18 serial thoracenteses show a shift toward lymphocyte predominance.9 The older literature suggested that > 5% mesothelial cells in pleural fluid were rarely compatible with TB pleural effusions. This finding is most likely the result of chronic pleural inflammation that prevents exfoliation of mesothelial cells into pleural cavity.33 However, there have been case reports of TB pleural effusions with numerous mesothelial cells4 analogs to reports in HIV-infected individuals.35 Similarly, pleural fluid eosinophilia considerably reduces the probability of TB unless the patient has a concomitant pneumothorax or a previous traumatic thoracentesis that has resulted in pleural space hemorrhage.36

**Pleural Fluid Smear and Culture**

Direct examination of pleural fluid by Zeihl-Neelsen staining requires bacillary densities of 10,000/mL37 and, therefore, detects acid-fast bacilli (AFB) in < 10% of cases.2,19,21,22,38,39 However, in patients with HIV coinfection, the yield of pleural
fluid microscopy is $>20\%$. Culture requires a minimum of 10 to 100 viable bacilli and, therefore, is more sensitive with a yield ranging from 12 to 70%. With the majority of series showing diagnostic yields of $<30\%$, sensitivity of mycobacterial culture can be improved by bedside inoculation of pleural fluid and by using liquid culture media or BACTEC system. Moreover, the use of radiometric mycobacterial culture systems (BACTEC-460; Becton Dickinson; Rockville, MD) yields results more rapidly than the conventional method (18 days vs 33 days).

ADA
ADA is an enzyme in the purine salvage pathway that catalyzes the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine with the release of ammonia. Although ubiquitous in distribution, it plays an important role in differentiation of lymphoid cells and is most abundant in lymphocytes (predominantly active T-lymphocytes) whose concentration is inversely related to the degree of differentiation. Piras and colleagues for the first time in 1978 reported high levels of ADA in patients with TB pleural effusions. Subsequently, several studies (Table 1) have explored the usefulness of estimation of ADA activity in the diagnosis of TB pleural effusions. It was determined that a pleural fluid ADA level $>70$ IU/L is highly suggestive of TB, while a level $<40$ IU/L virtually excludes the diagnosis. A metaanalysis of 40 studies published from 1966 to 1999 concluded that the test performance of ADA (sensitivity range 47.1 to 100%, and specificity range 0% to 100%) in diagnosing TB pleural effusions is reasonably good (adequate to avoid pleural biopsy in young patients from areas with high prevalence of TB). The discrepancies in the results among the reported studies can be attributed to the use of different methods of ADA analysis, with the most frequent being the calorimetric assay by Guisti and Galanti. The specificity is increased when the lymphocyte/neutrophil ratio in pleural fluid ($>0.75$) is considered in conjunction with an ADA concentration $>50$ IU/L. When the prevalence of disease is low (ie, $<1\%$), as in developed countries, the positive predictive value may be as low as 15%, although the negative predictive value increases. In contrast, in areas of high prevalence, ADA measurement is an inexpensive, minimally invasive, rapid, and readily accessible test that has gained popularity because the sensitivity and specificity reach 95% and 90%, respectively. However, elevated ADA in lymphocyte-rich pleural effusions has been reported in other diseases, such as rheumatoid arthritis, bronchoalveolar carcinoma, mesothelioma, mycoplasma and chlamydia pneumonia, psittacosis, paragonimiasis, infectious mononucleosis, brucellosis, mediterranean fever, histoplasmosis, coccidioidomycosis, and in most patients with empyema. The levels of ADA in HIV/AIDS and postrenal transplant patients are comparable to immunocompetent individuals. Two isoenzymes, ADA1 and ADA2, based on their selective affinity for deoxyadenosine as a substrate, are known. ADA1 is found in all cells, with the highest activity observed in lymphocytes and monocytes; whereas ADA2 isoenzyme is predominantly found in monocytes/macrophages. A study has found ADA2 isoenzyme to be primarily responsible for the increased ADA activity in TB pleural effusions with a median contribution of 88%. Therefore, pleural effusion with high ADA level and ADA1/total ADA ratio of $<0.45$ makes the diagnosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Threshold, IU/L</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piras et al$^{43}$</td>
<td>1978</td>
<td>54</td>
<td>30</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Ocana et al$^{44}$</td>
<td>1983</td>
<td>182</td>
<td>45</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>Segura et al$^{45}$</td>
<td>1989</td>
<td>600</td>
<td>71</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>Valdes et al$^{46}$</td>
<td>1992</td>
<td>405</td>
<td>47</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>De Olivera et al$^{47}$</td>
<td>1994</td>
<td>276</td>
<td>40</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>Burger et al$^{48}$</td>
<td>1995</td>
<td>462</td>
<td>50</td>
<td>90</td>
<td>89</td>
</tr>
<tr>
<td>Valdes et al$^{49}$</td>
<td>1996</td>
<td>350</td>
<td>47</td>
<td>100</td>
<td>91</td>
</tr>
<tr>
<td>Villena et al$^{30}$</td>
<td>1996</td>
<td>228</td>
<td>33</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>Perez-Rodriguez et al$^{31}$</td>
<td>1999</td>
<td>103</td>
<td>40</td>
<td>89</td>
<td>92</td>
</tr>
<tr>
<td>Villegas et al$^{52}$</td>
<td>2000</td>
<td>140</td>
<td>45.5</td>
<td>88</td>
<td>86</td>
</tr>
<tr>
<td>Sharma et al$^{53}$</td>
<td>2001</td>
<td>75</td>
<td>35</td>
<td>83</td>
<td>67</td>
</tr>
<tr>
<td>Sharma et al$^{53}$</td>
<td>2001</td>
<td>75</td>
<td>100</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>Reechapichitkul et al$^{54}$</td>
<td>2001</td>
<td>132</td>
<td>48</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>Lima et al$^{55}$</td>
<td>2003</td>
<td>45</td>
<td>40</td>
<td>68</td>
<td>72</td>
</tr>
<tr>
<td>Diacon et al$^{56}$</td>
<td>2003</td>
<td>51</td>
<td>50</td>
<td>95</td>
<td>89</td>
</tr>
<tr>
<td>Tahhan et al$^{57}$</td>
<td>2003</td>
<td>62</td>
<td>40</td>
<td>91</td>
<td>89</td>
</tr>
</tbody>
</table>
of TB highly likely, suggesting that isoenzyme estimation could increase the diagnostic utility of ADA in pleural effusion.

INF-γ

INF-γ, produced by T-lymphocytes, is capable of activating macrophages, increasing their bactericidal capacity against *M tuberculosis* and is involved in granuloma formation. Several studies (Table 2) have found elevated concentrations of INF-γ in TB pleural effusions, which is related to increased production at the disease site by effector T cells. The sensitivity of an elevated level varies from 78 to 100% and specificity from 95 to 100%. Comparison between different studies is not possible, as the method of estimation and units used differed. Other diseases that can cause elevated INF-γ levels in pleural fluid include hematologic malignancies and empyema. Immunosuppressed patients (HIV or after renal transplant) had INF-γ levels similar to immunocompetent individuals retaining its efficacy as a diagnostic test.

A metaanalysis that reviewed articles from 1978 to 2000 concluded that both ADA and IFN-γ appeared to be reasonably accurate in detecting TB pleural effusions with a maximum joint sensitivity and specificity of 93% for ADA and 96% for IFN-γ. Although a few studies have shown IFN-γ levels to be more sensitive and specific than ADA, it is less preferred in resource-limited settings as it is more expensive and less readily available compared to ADA. Two new blood tests (T-SPOT.TB [Oxford Immunotec; Oxford, UK] and QuantIFERON-TB Gold [Cellestis Limited; Carnegie, Australia]) based on detection of IFN-γ in blood have been found to be more accurate than the tuberculin skin test in the diagnosis of latent TB infection. Future research should focus on the potential efficacy of quantification of specifically activated lymphocytes in pleural fluid and blood using IFN-γ release assay in the diagnosis of pleural TB.

**Polymerase Chain Reaction**

Polymerase chain reaction (PCR) is based on amplification of mycobacterial DNA fragments. As TB pleural effusion is paucibacillary disease, the sensitivity could be improved by PCR, as it can detect as few as 10 mycobacteria. Advantages of PCR include rapid diagnosis, improved specificity and sensitivity, and no requirement of intact immunity. Numerous studies (Table 3) evaluating the efficacy of PCR for diagnosis of pleural tuberculosis have shown a sensitivity ranging from 20 to 90% and specificity from 78 to 100%. The sensitivity of the nucleic acid amplification technique depends on the number of mycobacteria, their homogenous distribution in the sample, the presence of amplification inhibitors, the type of primer used, and the genomic sequence amplified.

PCR findings are positive in 100% of culture-positive TB pleural fluids and in only 30 to 60% of culture-negative pleural fluids. Systems amplifying DNA sequences present in multiple copies in the mycobacterial genome may be more sensitive than those that amplify targets present in a single copy. Causes of false-positive results include DNA contamination or presence of nonviable organisms. PCR of pleural biopsy tissue has 90% sensitivity and 100% specificity, the overall accuracy being similar to biopsy culture. The disadvantages of PCR include high cost, risk of contamination, and the technology involved in the procedure does not permit routine diagnostic use at present.

**Pleural Biopsy**

Since its first description in 1955, biopsy of parietal pleura has become the most sensitive diagnostic test for TB pleural effusions. Histologic examination of tissue from the pleural biopsy may demonstrate granulomatous inflammation, caseation necrosis, or AFB. In patients with TB pleural effusions, pleural biopsy reveals granulomas in 50 to 97% of patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Assay Method</th>
<th>Threshold</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribera et al</td>
<td>1988</td>
<td>80</td>
<td>RIA</td>
<td>2 IU/mL</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Shimokata et al</td>
<td>1991</td>
<td>40</td>
<td>RIA</td>
<td>3.48 IU/mL</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>Aoki et al</td>
<td>1994</td>
<td>39</td>
<td>ELISA</td>
<td>Not detectable</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Wongtin et al</td>
<td>1999</td>
<td>66</td>
<td>ELISA</td>
<td>240 pg/mL</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>Villegas et al</td>
<td>2000</td>
<td>140</td>
<td>ELISA</td>
<td>6 IU/mL</td>
<td>78</td>
<td>97</td>
</tr>
<tr>
<td>Villena et al</td>
<td>2003</td>
<td>595</td>
<td>RIA</td>
<td>3.7 IU/mL</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Wong et al</td>
<td>2003</td>
<td>66</td>
<td>ELISA</td>
<td>60 pg/mL</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Sharma and Banga</td>
<td>2004</td>
<td>101</td>
<td>ELISA</td>
<td>138 pg/mL</td>
<td>90</td>
<td>97</td>
</tr>
<tr>
<td>Poyraz et al</td>
<td>2004</td>
<td>45</td>
<td>ELISA</td>
<td>12 pg/mL</td>
<td>87</td>
<td>95</td>
</tr>
<tr>
<td>Gao and Tian</td>
<td>2005</td>
<td>190</td>
<td>ELISA</td>
<td>61.7 pg/mL</td>
<td>84</td>
<td>96</td>
</tr>
</tbody>
</table>

*RIA = radioimmunoassay; ELISA = enzyme-linked immunosorbent assay.*

---

**Table 2—Utility of IFN-γ in the Diagnosis of Tuberculous Pleural Effusion**
and culture yields mycobacteria in 39 to 80%; when both methods of diagnosis are used, the diagnostic yield is 60 to 95%.4,19,21,22,37,38,88,89

Even when granulomas are not visualized, the biopsy specimen should always be examined for AFB (in 10%, only organisms may be seen in the biopsy).19,37 Other causes of granulomatous pleuritis, such as fungal disease, sarcoidosis, rheumatoid arthritis, and nocardial infection, need to be excluded.

Thoracoscopy

Thoracoscopy has been used extensively for the diagnosis of pleural TB and malignancy. Now with the advent of video-assisted thoracoscopic surgery, there has been a renewed interest in use of thoracoscopy. Thoracoscopy may show yellow-white tubercles on the parietal pleura, reddening of pleura, and numerous adhesions. Thoracoscopy also allows targeted biopsy of suspicious lesions, which are most concentrated in the costovertebral angles. In a study56 that compared various diagnostic modalities for TB pleural effusions, thoracoscopy was the most accurate, yet most expensive, tool for establishing the diagnosis with a diagnostic accuracy of 100% on histology and 76% positivity on culture.

Other Diagnostic Tests

Immunodiagnosis: The utilization of immunodiagnostics is hindered by its low sensitivity. Table 4 lists the details regarding various studies90–95 using immunologic markers in the diagnosis of TB pleural effusions. Further studies are required to address the clinical utility of these markers.

Cytokines: Cytokine-producing cells and various cytokines have been demonstrated in pleural fluid from patients with TB pleural effusions. The emerging role of IFN-γ has been discussed (vide supra). Significantly higher levels of IL-6 have been demonstrated in TB effusions compared to parapneumonic and malignant pleural effusions. Furthermore, the serum/pleural fluid IL-6 ratio was significantly higher in TB pleural effusions, making it a novel marker in the differential diagnosis of exudative pleural effusions.96 IL-1α and tumor necrosis factor-α, produced predominantly by mononuclear phagocytes, have been shown to be present in TB pleural effusions, malignant effusions, and parapneumonic effusions with considerable overlap of its cut-off levels among these diseases.96,97 Levels of soluble IL-2 receptors, IL-18, immunosuppressive acidic protein, and IL-12p40 are all significantly elevated in TB pleural effusions with a decreasing order of sensitivity, with soluble IL-2 receptors being a more sensitive marker than ADA (although without statistical significance).98

Miscellaneous Tests: Levels of pleural fluid lysozyme, a bacteriolytic enzyme, have been found to

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>DNA Sequence Amplified</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murate et al</td>
<td>1990</td>
<td>31</td>
<td>Anti-purified protein derivative antibody</td>
<td>23</td>
<td>95</td>
</tr>
<tr>
<td>Caminero et al</td>
<td>1993</td>
<td>30</td>
<td>IgG anti-A60 antibody</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Banchuin et al</td>
<td>1990</td>
<td>26</td>
<td>Bacille Calmette-Guérin antigen</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>Yew et al</td>
<td>1991</td>
<td>74</td>
<td>Tuberculostearic acid assay</td>
<td>68</td>
<td>52</td>
</tr>
<tr>
<td>Sarnaik et al</td>
<td>1993</td>
<td>413</td>
<td>Anti-tuberculospholipid antibody</td>
<td>87</td>
<td>100</td>
</tr>
<tr>
<td>Caminero et al</td>
<td>1991</td>
<td>30</td>
<td>IgG anti-A60 antibody</td>
<td>55</td>
<td>100</td>
</tr>
</tbody>
</table>
be higher in patients with TB pleural effusions. However, a pleural fluid to serum lysozyme ratio > 1.2 has been found to be a better tool for the diagnosis of TB pleural effusions.100 Likewise, a cut-off value for pleural fluid C-reactive protein ≥ 30 mg/dL was shown to have a sensitivity of 72% with 93% specificity, and the pleural fluid to serum ratio of C-reactive protein with a cut-off value of 0.45 had a sensitivity of 60% and 89% specificity for the diagnosis of TB pleural effusion.100 Pleural fluid neopterin levels with a threshold value of 30 mmol/L had a sensitivity and specificity of 85% and 93%, respectively, for the diagnosis of TB pleural effusions.101

TREATMENT

Antituberculosis Drugs

The natural history of an untreated tuberculous pleural effusion is characterized by spontaneous resolution in 4 to 16 weeks with subsequent development of active pulmonary TB or EPTB in 43 to 65% of cases over the next several years.102,103 These data emphasize the importance of proper diagnosis and treatment of tuberculous pleural effusions. According to the directly observed treatment short-course guidelines, severely ill patients with extensive or bilateral pleural effusions and sputum positivity are given treatment under category I (treated during intensive phase with four drugs: isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months followed by continuation phase of 4 months with isoniazid and rifampin). Those with a solitary TB pleural effusion should be treated with isoniazid, rifampin, and pyrazinamide for 2 months followed by 4 months of two drugs, isoniazid and rifampin.104 Especially in loculated TB pleural effusions, there can be delayed resorption of pleural fluid even after completion of 6 months of treatment.105

Patients with HIV/AIDS and tuberculous pleural effusion are treated similarly to those who are HIV negative. The clinician should be aware of drug interactions between highly active antiretroviral therapy and antituberculosis therapy, adverse drug reactions, and paradoxical reactions, or the immune reconstitution inflammatory syndrome; the latter is manifested by worsening symptoms, an increase in the volume of existing pleural fluid, or the development of pleural effusion during treatment.106

The emergence of multidrug-resistant TB has posed a significant threat to the treatment of all forms of TB. The judicious use of second-line drugs, supervised treatment, focused clinical, radiologic and bacteriologic follow-up, and surgery at the appropriate juncture are key factors in the successful management of these patients. Innovative approaches, such as DOTS-Plus, show promise for the management of patients with multidrug-resistant TB under program conditions and appear to be hopeful for the future.107

Corticosteroids

A hypersensitivity reaction to M tuberculosis results in granulomatous pleuritis. Corticosteroids through their antiinflammatory action may hasten fluid resorption and prevent pleural adhesions during healing. Three randomized trials108–110 have investigated the possible role of adjunctive oral corticosteroids in TB pleural effusion. A dose of 0.75 to 1 mg/kg/d was used for a period ranging from 4 to 12 weeks. Early resolution of clinical symptoms and signs including fever, chest pain, and dyspnea was observed.110 Although there was a trend toward less residual pleural fluid at the end of treatment, there was no difference in the development of residual pleural thickening or adhesions on follow-up. Residual lung function was similar between steroid and control groups at completion of treatment. All three studies108–110 had insufficient power to examine death as an outcome; nevertheless, no deaths occurred in the study groups. The Cochrane review stated that there was insufficient evidence to determine whether steroids are effective in treatment of TB pleural effusions.111 There are concerns regarding the use of steroids in HIV-positive individuals due to the possibility of increased risk of opportunistic infections. On the contrary, suppression of lymphocyte activation and viral replication by steroids may slow the rate of progression of HIV disease. Because there is a lack of survival benefit and increased risk of Kaposi sarcoma, the use of steroids in HIV associated TB pleural effusions is not currently recommended.112

UNRESOLVED ISSUES AND CONCLUSIONS

There have been significant advances in the understanding of pathophysiology of TB pleural effusions. The more frequent use of imaging modalities, such as CT, and bronchoscopic techniques, such as BAL, has lead to detection of underlying pulmonary TB in a larger proportion of patients. However, the implication of these findings in the treatment of patients with TB pleural effusion is unclear. Likewise, the estimation of ADA and IFN-γ in pleural fluid has gained wide acceptance in the diagnosis of TB pleural effusion. However, the use of these investigations may be limited because of availability and quality control, especially in developing nations. Porcel and Vives115 found effective prediction mod-
els to differentiate tuberculous from malignant pleural effusions based on readily available clinical (age, temperature, history of malignancy) and pleural fluid (RBC, protein, ADA, pleural to serum lactate dehydrogenase ratio) data, although further validation is needed. The proper use of corticosteroids in the treatment of TB pleural effusions remains unresolved. It is hoped that further research to clarify these issues will result in better diagnostic and therapeutic approaches to TB pleural effusions.

References
3 Harries AD. Tuberculosis and human immunodeficiency virus infection in developing countries. Lancet 1990; 335:387–390
25 Sahn SA, Isemad MD. Tuberculous empyema. Semin Respir Med 1990; 14:82.87
28 Rossi GA. Pleural effusions: evidence for selective presence of PPD specific T lymphocytes at site of inflammation in the early phase of infection. Am Rev Respir Dis 1987; 136:575–579
Burgess LJ, Mautz FJ, Le Roux I, et al. Combined use of
Guisti G, Galanti B. Methods in enzymatic analysis. New
Lima DM, Colares JK, da Fonseca BA. Combined use of the
Reechaipichitkul W, Kawamatawong T, Teerajetgul Y, et al.
Sharma SK, Suresh V, Mohan A, et al. A prospective study
Villegas MV, Labrada LA, Saravia NG. Evaluation of poly-
deaminase as a diagnostic tool for pleural tuberculosis. Thorax 1995; 50:672–674
Valdes L, San Jose E, Alvarez D, et al. Diagnosis of
tuberculous pleurisy using the biologic parameters aden-
Villegas MV, Labrada LA, Saravia NG. Evaluation of poly-
erase chain reaction, adenosine deaminase, and interferon-
Sharma SK, Suresh V, Mohan A, et al. A prospective study of sensitivity and specificity of adenosine deaminase estima-
Hirschhorn R, Ratech H. Isoenzymes of adenosine deami-
Greco S, Girardi E, Masiangelo R, et al. Adenosine deami-
Sharma SK, Banga A. Pleural fluid interferon-γ and adeno-
**Diagnosis and Treatment of Tuberculous Pleural Effusion in 2006**

Arun Gopi, Sethu M. Madhavan, Surendra K. Sharma and Steven A. Sahn

*Chest* 2007;131;880-889

DOI 10.1378/chest.06-2063

This information is current as of April 26, 2007

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>Updated information and services, including high-resolution figures, can be found at: <a href="http://chestjournals.org/cgi/content/full/131/3/880">http://chestjournals.org/cgi/content/full/131/3/880</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 96 articles, 46 of which you can access for free at: <a href="http://chestjournals.org/cgi/content/full/131/3/880#BIBL">http://chestjournals.org/cgi/content/full/131/3/880#BIBL</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://chestjournals.org/misc/reprints.shtml">http://chestjournals.org/misc/reprints.shtml</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://chestjournals.org/misc/reprints.shtml">http://chestjournals.org/misc/reprints.shtml</a></td>
</tr>
<tr>
<td>Email alerting service</td>
<td>Receive free email alerts when new articles cite this article sign up in the box at the top right corner of the online article.</td>
</tr>
<tr>
<td>Images in PowerPoint format</td>
<td>Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions.</td>
</tr>
</tbody>
</table>