



# **Tuberculose pleural effusion TPE**



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Tuberculosis (curable) is one of the most frequent causes of **pleural effusions**, especially in developing countries.

TPE is the second most common form of **extrapulmonary tuberculosis**.

The pleural fluid is an **exudate** that usually has predominantly **lymphocytes**.



The proportion of patients with tuberculosis who have **pleural effusions** has varied from population to population.

In the USA, although the total number of patients with **TPE** decreased between 1993 and 2003, the proportion of patients with **TPE** compared to the total number of tuberculosis cases remains relatively stable (**3.6 %**).



## The proportion of TPE in total pleural effusions.

<b>Country</b>	<b>n</b>	<b>TPE (%)</b>
<b>China</b>	<b>833</b>	<b>40</b>
<b>South Africa</b>	<b>51</b>	<b>82.4</b>
<b>India</b>	<b>68</b>	<b>23.5</b>
<b>New Zealand</b>	<b>51</b>	<b>5.9</b>
<b>United Kingdom</b>	<b>56</b>	<b>5.6</b>
<b>Spain</b>	<b>93</b>	<b>3.2</b>
<b>France</b>	<b>149</b>	<b>2.7</b>
<b>Denmark</b>	<b>146</b>	<b>2.1</b>
<b>United States</b>	<b>51</b>	<b>0</b>



# Clinical manifestations



TPE predominates in men more than women **2:1** .

Epidemiological analysis from the USA, the mean age of patients with **TPE** is **49** years: about **50 %** were younger than **45** years and **30 %** were over **65** years .

In contrast, **TPE** affects mainly younger individuals (mean age =**34** years) in **higher tuberculosis burden areas**.



**TPE** usually manifests as an **acute illness**, especially in younger patients who are more immunocompetent.

Symptoms had been present for less than a month (**71 %**) and for less than **1 week (35 %)**.

**TPE** is usually unilateral and can be of any size.



**333 patients**, pleural fluid occurred on the left side in **38.1%**, on the right in **48.4%**, and both sides were affected in **13.5%** .

In unilateral or bilateral effusion, **20.4%** small size, **19.2%** moderate size , and **60.4%** large size of pleural effusions.

Approximately **20 %** of patients with TPE have coexisting parenchymal disease on chest radiograph (CT Scan).

## The most frequent symptoms of TPE are :

- ❑ **Nonproductive cough.**
- ❑ **Pleuritic chest pain** (the pain usually precedes).
- ❑ Most patients are **febrile** but approximately **15 %** will be afebrile.
- ❑ **Dyspnea** can be present in some **TPE** patients with large effusion.
- ❑ Other symptoms include **night sweats, weight loss, malaise.**

# Diagnosis

- Demonstration of *Mycobacterium tuberculosis* in the **sputum**, **pleural fluid**, or **pleural biopsy specimens**.
- Demonstrating granuloma in the parietal pleura.
- **adenosine deaminase** (ADA) in pleural fluid.
- Elevated concentrations of **interferon- $\gamma$**  in pleural fluid.

## Tuberculin skin tests

In **low tuberculosis prevalence areas**, or **no vaccination**:

A **positive** tuberculin skin test result is supportive evidence in the diagnosis of **TPE**.

A **negative** result can be seen in **1/3** of patients.

**Since** a negative test **does not rule out** the diagnosis of **TPE**, tuberculin skin test is being utilized less and less in patients suspected of having **TPE**, especially in high tuberculosis burden countries.

If the patient is **immunosuppressed with HIV infection** or is **severely malnourished**, the skin test is always **negative**.

## Mycobacterial stain and culture

It is necessary to obtain **sputum** in addition to **pleural fluid** for the acid-fast bacilli smear and ***Mycobacteria tuberculosis*** culture in patients with suspected **TPE**, even in the absence of parenchymal involvement.

Prospectively evaluated **84** patients with **TPE** :  
**Smear positive** in **12 %** and **culture-positive** in **52 %** of cases .



In a study of **254** patients with **TPE**, **93** patients (**36.6 %**) had positive of pleural fluid cultures for ***Mycobacteria tuberculosis*** in the Löwenstein-Jensen medium.

Thus, **pleural fluid cultures** should be performed in any patient with an **undiagnosed** pleural effusion.

The combination of **pleural fluid** and **sputum** cultures in the diagnostic workup of **TPE** seems a reasonable initial approach, with a combined diagnostic yield of **79%** .

# Adenosine deaminase

**ADA** is a predominant T-lymphocyte enzyme that catalyzes the conversion of adenosine to inosine and deoxyadenosine deoxyinosine.

**ADA** in pleural fluid for the early diagnosis of **TPE**.  
**Easy** and **inexpensive** method for diagnosing **TPE**.

Meta-analysis of **63** studies for high levels of **ADA** in pleural fluid in the diagnosis of TPE → **Sensitivity: (92 %)** .... **Specificity: (90 %)**.



**ADA** levels in pleural fluid are also elevated in **HIV patients** even with very low CD4<sup>+</sup> T cells.





Almost all patients with **TPE** have a pleural fluid **ADA > 40 U/L**, which is the accepted value for the diagnosis of **TPE**.

The higher the level, the greater the chance of patients having **TPE**.

the lower the level the lesser the chance of the patient having **TPE**.

## Instances with high pleural fluid ADA:

- parapneumonic effusions.
- Empyemas.
- Brucellosis.
- Q fever.
- Lymphomas.
- Rheumatoid arthritis.



**2/3 of empyemas and 1/3 of parapneumonic effusions: ADA > 40U/L.**

The differential diagnosis of **TPE** from these conditions is not difficult:

Both **clinical picture** and **polymorphonuclear leukocytes** predominant pleural fluid of patients with parapneumonic effusions and empyemas are total different from those of patients with TPE.

**ADA** has two molecular forms, ADA1 and ADA2:

- **ADA1** is found in lymphocytes and monocytes.
- **ADA2** is found only in monocytes.

**ADA2** is responsible for the increased total **ADA** in **TPE**, whereas high **ADA** in nontuberculous effusions is due to an increase in the **ADA1**.

**ADA2** isoenzyme is as sensitive and more specific than total **ADA** for diagnosing **TPE**.



pleural fluid **ADA** is routinely employed in the diagnostic workup of pleural effusions in **high tuberculosis burden countries**.



# Interferon-gamma

**Interferon- $\gamma$**  is a cytokine released by activated CD4<sup>+</sup> T cells that increases the mycobactericidal activity of macrophages.

**Meta-analysis of 22 studies** of **782** patients with **TPE** and **1,319** patients with **nontuberculous effusions**:

The **sensitivity** of the **interferon- $\gamma$**  was **89%**.

The **specificity** was **97%**.



The long historical success of **ADA** and the fact that it is **simpler** and **less expensive** than the **interferon-γ** makes it the preferred test.

There are now two commercially available **interferon-γ**: (**QuantiFERON-TB Gold** and **T-SPOT.TB**) for clinical use.

These tests are good at identifying patients who have been infected with ***Mycobacterium tuberculosis***, but they are much less useful in identifying patients with **TPE**.

## Nucleic acid amplification tests

Amplification of ***Mycobacterium tuberculosis*-specific nucleic acid** from specimens such as sputum and pleural fluid.

**Systematic review** and **meta-analysis** of **40** studies assessing the use of pleural fluid **nucleic acid amplification tests** for diagnosing **TPE** : .

**high specificity (97%).**

**poor and variable sensitivity (62%).**



**The low sensitivities of nucleic acid amplification techniques may be due to:**

- ❖ The presence of inhibitory substances in pleural fluid.
- ❖ The small amount of ***Mycobacterium tuberculosis*** in pleural fluid.
- ❖ Technical defect of nucleic acid extraction.



**So:**

The inconsistent results of different studies and the high cost of **nucleic acid amplification** tests limit their use to investigational settings.

## Other biochemical tests

**B-cell response, complement activation, leptin, lysozyme, and the other cytokines.**

The evidence does not support the use of this biomarkers for the diagnosis of **TPE** because of their low **sensitivity** or/and **specificity**.

**Interleukin 27** in **TPE** is higher than those in **pleural effusions with the other etiologies** → **Pleural Interleukin 27** levels can be used for diagnosing **TPE**, with **sensitivity: 92.7%** and **specificity: 98.8%** .

# Pleural biopsy

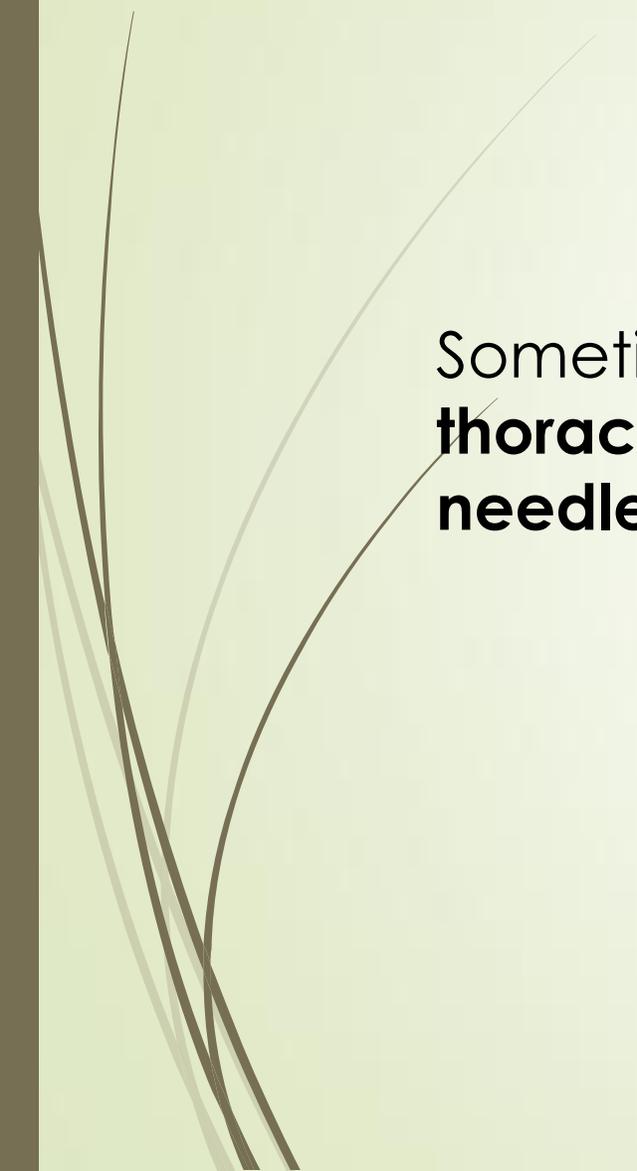
- ❑ Caseating granulomas.
- ❑ Blind needle biopsy of the pleura.

**Study** of **248** patients with **TPE** with Blind needle biopsy:

- **Granulomas** in **80%** of patients,
- **Acid-fast bacilli** stain was positive in **25.8%**.
- ***Mycobacteria tuberculosis*** culture was positive in **56%** .



Sometimes we need more invasive procedures like **medical thoracoscopy** when one or more **thoracenteses** or/and **blind needle biopsy** fail to reach definite diagnosis.





## Meta-analysis

- ❑ No **mortality** with medical thoracoscopy.
- ❑ An the rates of **major complications: 1.5%** and **minor complications: 10.5%**.
- ❑ **Very safe procedure** in the diagnosis of exudative pleural effusions.



In the largest series of **333** patients with **TPE**:  
**Medical thoracoscopy** with pleural biopsies yielded tuberculosis pathology in **330 (99.1%)** patients by demonstration of one or more of following histological abnormalities in pleural biopsy specimen:

- **Acid-fast bacillus.**
- **Caseating granulomas.**
- **Epithelioid cell granuloma** with **no** evidence of other granuloma diseases.



# Treatment



In many cases, **TPE** is a **self-limited disease**  Spontaneous resolution in **4** to **16** weeks.

About **half** of **untreated patients** would develop some form of the **active disease**.



## The goals of the treatment of TPE

- ❑ **Prevent** the occurrence of active tuberculosis.
- ❑ **Relieve** the symptoms of TPE.
- ❑ **Avoid** the presence of a fibrothorax.

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- With appropriate treatment, the symptoms and radiological abnormalities of patients with **TPE** gradually abate.
  - Patient becomes **afebrile** within **2** weeks, but temperature elevations may persist for **2** months.
  - The mean time for the **complete resorption of pleural fluid** is approximately **6** weeks, but it can be as long as **12** weeks.
  - There is no reason to keep the patient at **bed rest** and the patient needs to be **isolated** only if the sputum is positive for ***Mycobacteria tuberculosis***.



## Anti-tuberculosis chemotherapy

- **(2HRZ/4HR) for 6 months .**
- **(HR) for 9 months** may be effective when the organisms are fully susceptible to the drug.
- Directly observed therapy (**DOTS**).
- **16% to 49%** of all patients do not complete the regimen.

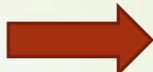
## Recommended doses of first-line anti-tuberculosis drugs for adults

### Recommended dose

#### Daily

#### 3 times per week

Drug	Daily		3 times per week	
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and range (mg/kg body weight)	Daily maximum (mg)
Isoniazid	5 [4–6]	300	10 [8–12]	900
Rifampin	10 [8–12]	600	10 [8–12]	600
Pyrazinamide	25 [20–30]	–	35 [30–40]	–
Ethambutol	15 [15–20]	–	30 [5–35]	–

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- ❑ In the case of resistance to isoniazid  **6-months** of **fluoroquinolone (levofloxacin or moxifloxacin)**.
  - ❑ **6-month (R-Moxifloxacin-PYZ-ETH)** for **2** months, **followed** by **(R-Moxifloxacin)** for **4** months, may be effective .
  - ❑ When **TPE** is caused by **multidrug-resistant *Mycobacteria tuberculosis*** confirmed by either by **culture** or with **DNA**, the initial treatment regimen should be individually tailored according to the **results of drug-susceptibility testing**.
  - ❑ In the absence of this information, **empirical regimens** can be used, but as soon as the results of drug susceptibility testing become available, the treatment regimen should be adjusted.

## Therapeutical thoracentesis

- **Dyspnea** because of a large pleural effusion →  
Therapeutical thoracentesis is recommended.
- The complete clearance of pleural fluid pigtail drainage to an effective anti-tuberculosis regimen **does not** appear significantly to decrease the incidence of **residual pleural thickening** and **other clinical symptom**.

# Fibrinolytics

- ❑ **Fibrinolytic agents** may decrease the degree of residual pleural thickening in patients with loculated **TPE**.
- ❑ **Fibrinolytics**, in addition to **anti-tuberculosis medication**, in patients with symptomatic loculated tuberculosis effusions may reduce the incidence of **residual pleural thickening**.

# Corticosteroids

- The role of corticosteroids in the treatment of **TPE** is controversial.
- Corticosteroids through their **antiinflammatory** action may hasten fluid resorption and prevent pleural thickening.
- **3 Randomized trials** showed early resolution of **clinical symptoms and signs**, but there was no difference in residual lung function and incidence of residual pleural thickening.

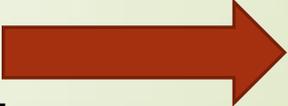
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- In selected patients who continue to have severe systemic symptoms (e.g., **fever, malaise, pleuritic chest pain**) after **2** weeks of anti-tuberculosis treatment and therapeutic thoracentesis, a **short course of corticosteroids may be beneficial.**

A recent **Cochrane** review concluded that there are **insufficient data to support evidence-based recommendations** regarding the use of adjunctive corticosteroids in people with tuberculous pleurisy.

- The use of corticosteroids in **HIV-positive individuals** may increase the risk of opportunistic infections.

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- Randomized study of **197** patients with **HIV** associated **TPE**, the administration of **prednisolone** was associated with an increased risk of **Kaposi sarcoma**.
  - Because there is a **lack of survival benefit** and **increased risk of Kaposi sarcoma**, the use of **steroids** in **HIV** associated **TPE** is not currently recommended.

## Tuberculose empyema

- ❑ Uncommon chronic, active infection of the pleural space, which is characterized by the presence of **thick pus** and the **visceral pleura is usually calcified**.
- ❑ **Acid-fast bacilli smears** and cultures are usually **positive**.
- ❑ **Penetration of anti-tuberculosis** drugs is impaired, and **surgical drainage** is often needed to control the situation.
- ❑ In addition to a standard anti-tuberculosis regimen  **thoracocentesis, extrapleural pneumonectomy or thoracoscopy**.



# CONCLUSION



## The gold standard for the diagnosis of TPE :

- Detection of *Mycobacterium tuberculosis* in pleural fluid, or pleural biopsy specimens, either by microscopy and/or culture.
- Histological demonstration of caseating granulomas in the pleura.
- Adenosine deaminase.
- Interferon- $\gamma$  in pleural fluid.

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- ❑ It can be accepted that in areas with **high tuberculosis prevalence**, the easiest way to establish the diagnosis of TPE in a patient with a **lymphocytic pleural effusion** is to generally demonstrate a **Adenosine Deaminase level above 40 U/L**.
  - ❑ The recommended treatment for TPE is a regimen with **HRP** for **2 months** followed by **4 months** of two drugs, **Isoniazid** and **Rifampin**.



**THANK YOU**