Pericardial Tuberculosis

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Extrapulmonary tuberculosis

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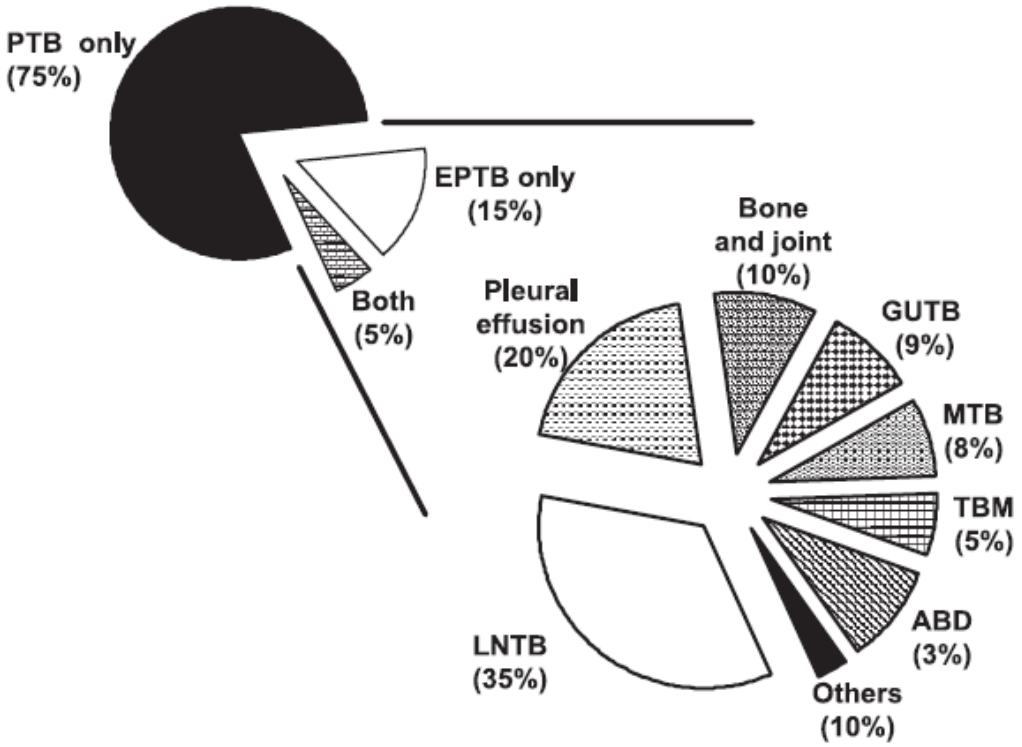


Fig.1a. Distribution of tuberculosis cases by anatomical site in HIV-negative patients. Data derived from references 3,5,6,10,11. PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; GUTB, genitourinary tuberculosis; MTB, miliary tuberculosis; TBM, tuberculosis meningitis; ABD, abdominal tuberculosis; LNTB, lymph node tuberculosis.

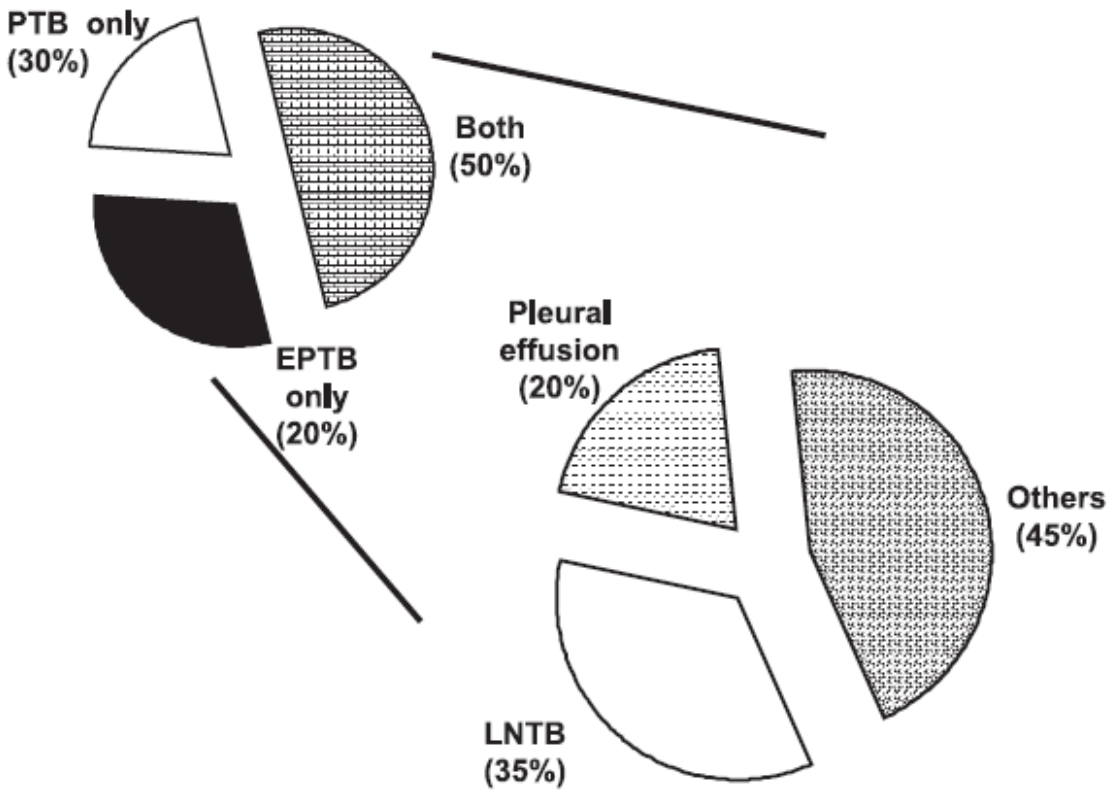


Fig.1b. Distribution of tuberculosis cases by anatomical site in HIV-positive patients data derived from references 14-22. PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; LNTB, lymph node tuberculosis.

- Pericardial involvement in tuberculosis may result in acute pericarditis, chronic pericardial effusion, cardiac tamponade or pericardial constriction.
- In India, TB accounts for nearly two thirds of the cases of constrictive pericarditis.
- TB has been reported to be the cause of acute pericarditis in 4% of patients in developed world and 60 to 80 % of patients in the developing world.

- TB Pericarditis has been estimated to occur in 1 to 8 % patients with pulmonary tuberculosis.
- In industrialised countries TB Pericarditis is not so common except in patients with HIV infection and AIDS.

- Pericardial involvement most commonly results from direct extension of infection from adjacent mediastinal lymph nodes,

Or

- through lympho-haematogenous route from a focus elsewhere.

TB Pericarditis Stages

- Following stages:
  (i) Dry stage;
  (ii) Effusive stage;
  (iii) Absorptive stage; and
  (iv) Constrictive stage

The disease may progress sequentially from first to fourth stage or may present as any of the stages.

Sometimes, pericardial TB can persent as fever with no clinical localization.

Presence of cardiomegaly on the chest radiograph may be the only diagnostic clue and echocardiography may reveal pericardial effusion.

Clinical Feautures

- TB Pericarditis occurs most commonly in the third to fifth decade of life.
- The disease has an insidious onset and presents with fever, malaise and weakness.
- The patients may manifest pericardial rub, vague chest pain or cardiomegaly on a chest radiograph .
- **Acute onset has been reported in 20 per cent of patients and some patients can present with cardiac tamponade**.
- **Dyspnoea, cough, and weight loss are common symptoms. Chest pain, orthopnoea and ankle oedema occur in nearly 40 to 70 per cent of patients.**

- Pericardial effusion: Patients with TB pericarditis usually present with chronic pericardial effusion.

- Patients may also present acutely with cardiac tamponade and may manifest severe distress, retrosternal compression, tachycardia and raised jugular venous pressure (JVP) with blunt γ descent, distant heart sounds, pericardial rub and pulsus paradoxus may be evident.

Effusive Constrictive Pericarditis

- constriction can be due to thickening of either the visceral or the parietal pericardium.
- Cardiomegaly, pedal oedema and raised JVP with a blunt γ descent may be present.
- After removal of fluid, JVP is still raised with a prominent γ descent. This stage could occur within few weeks of TB pericarditis.
- With effective AKT, some cases may resolve. Commonly, chronic constriction ensues.

Chronic Constrictive Pericarditis

- The inflow of blood is impeded due to thickened unyielding pericardium, especially in the late diastole

- Consequently, these patients have systemic as well as pulmonary venous congestion and manifest exertional dyspnoea, orthopnoea, ankle oedema and ascites.

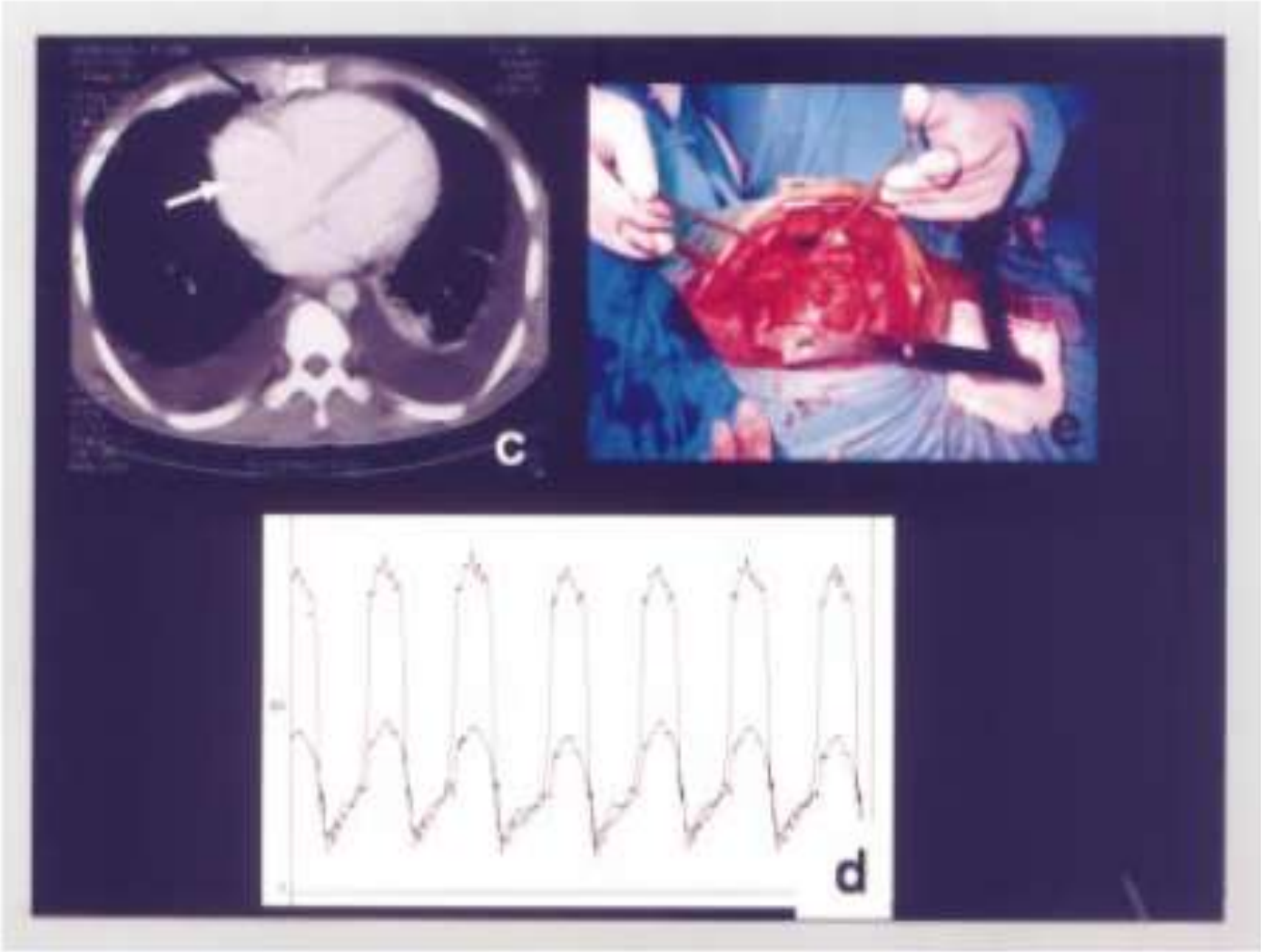


Fig.3c, 3d and 3e. Contrast enhanced CT scan of the chest of a patient with constrictive pericarditis showing thickened pericardium (black arrow) and dilated right atrium (white arrow) **(c)**. Right and left ventricular pressure tracings (paper speed 100 mm/sec and 100 mm Hg gain) of the same patient showing markedly elevated and equal diastolic pressures with mild elevation of right ventricular systolic pressure (45 mm Hg) **(d)**. Operative photograph showing thickened pericardium **(e)**.

- Cardiac output is mildly reduced at rest.
- Tachycardia, raised JVP with a **prominent y descent** occur.
- The JVP may rise further on inspiration (Kussmaul's sign). **Pulsus paradoxus is seen in less than one-third of cases and signifies presence of some fluid or a relatively elastic pericardium**.
- Cardiac size is normal.
- A systolic retraction of apex can be evident.
- A pericardial knock may be present but murmurs are not common.

- **The ascites is disproportionate to the oedema (ascites praecox).**
- Severe elevation of venous pressure may result in congestive splenomegaly and protein losing enteropathy resulting in hypoalbuminaemia.
- After many years of hepatic venous congestion **cardiac cirrhosis** may develop in some patients.
- The disease worsens gradually and in chronic cases, significant myocardial atrophy occurs due to extension of inflammation and possibly disuse of the muscle. Such patients have suboptimal improvement and higher mortality with pericardiectomy.

Table I. Tuberculin positivity in various forms of extrapulmonary tuberculosis

Site	Tuberculin positive (%)
Lymph node tuberculosis[33,34,36,180,181]	74-98
Pleural effusion[75,180,182-184]	73-93
Abdominal tuberculosis[185-189]	58-100
Pericardial[115,190]	75-100
Cutaneous tuberculosis[133]	67
DTB/MTB[156,166,169,180,191]	21-62

Numbers in superscript indicate reference numbers
DTB, diseminated tuberculosis
MTB, miliary tuberculosis

Table III. Characteristic body fluid findings in patients with various forms of extrapulmonary tuberculosis

Variable	Pleural fluid	Pericardial fluid	Cerebrospinal fluid
Appearance	Straw coloured	Straw coloured or serosanguinous	Clear early; Turbid with chronicity
*p*H	7.3-7.4 Rarely <7.3 Never >7.4	Not well described	Not well described
Cell count Total count Differential count Cytology	1000-5000 50-90% lymphocytes, eosinophils <5% Few mesothelial cells	Not well described Leukocyte count is usually increased. PMN preponderant early. Later, up to mononuclear cells predominate	100-500 Rarely >1000 PMN preponderant early. Later, up to 95% Mononuclear
Protein	Usually high (>2.5g/dl)	Usually high	Usually high (100-500 mg/dl) Can be very high with blockage or extreme chronicity
Glucose	Usually less than serum concentration	Low	Usually 40-50 mg/dl (about 50% of blood glucose)

PMN, polymorphonuclear leukocytes
Data derived from references 71-75,84-86,88,104,113,115,117,180
Details regarding ascitic fluid are described in reference 77

Table IV. Yield of various tissues and body fluid specimens by the conventional smear and culture methods in patients with extrapulmonary tuberculosis

Variable	Pleural fluid	Pericardial fluid	Cerebrospinal fluid
Smear microscopy	< 10%	< 1%	5-37%
Mycobacterial culture	12-70%	25-60%	40-80%
Data derived from references	71-75,84-86,88,104,113,115,117,180		

X Ray Chest

- Cardiomegaly
- Pericardial Calcification
- Associated pulmomary lesions and pleural effusion or empyema

CT Scan or MRI

- Use to identify extent of Pericardial involvement, size of pericardial thickening & fluid collection

- Lymph node enlargement
- Pleural loculation or empyema or septation
- Pulmonary Lesions

- Associated bony involvement
- for surgical approach planning

Echocardiography

- Is useful for detecting the presence of pericardial fluid and features such as collapse of right atrial or right ventricular free wall in diastole which are diagnostic of cardiac tamponade.
- In fact, these features may some times precede the other clinical evidence of pericardial tuberculosis.
- Is not an accurate test to detect pericardial thickening.
- Indirect echocardiographic signs such as flat posterior left ventricular wall motion in the diastole, premature opening of the pulmonary valve, may suggest chronic constrictive pericarditis.

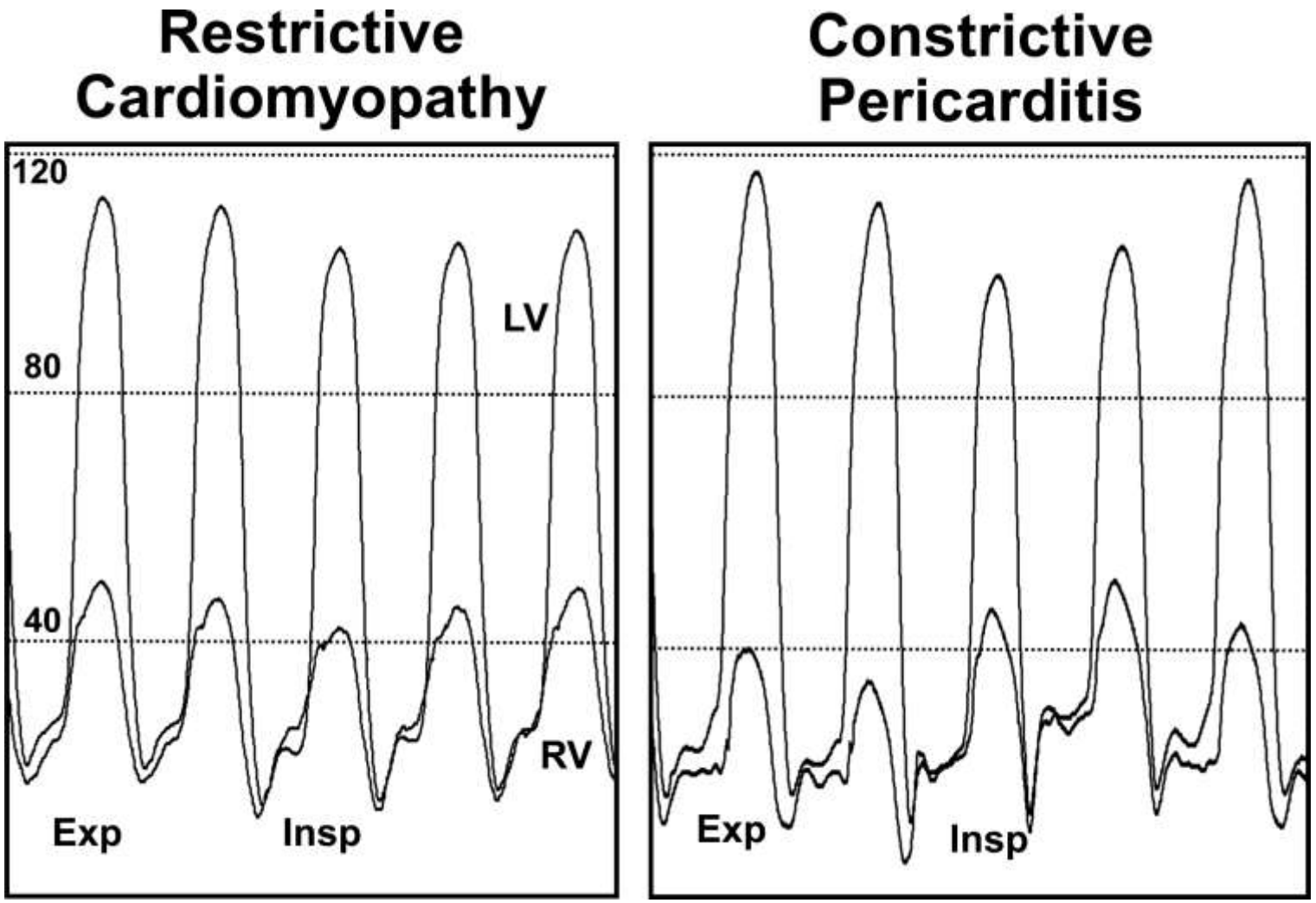
Cardiac Cath

- In cardiac tamponade, cardiac catherisation revelas a prominent γ descent in the right atrial tracing.

- In chronic constrictive pericarditis, a prominent γ descent in the atrial pressure tracing and a dip-plateau ventricular pressure tracing are characteristic of chronic constrictive pericarditis.

- Cardiac tamponade as well as chronic constrictive pericarditis produce a similar elevated right and left atrial, right and left ventricular end-diastolic pressures (Fig.3d).

High-fidelity manometer-tipped catheters in the left ventricle (LV) and right ventricle (RV) during the respiratory cycle.



Rick A. Nishimura, and Blase A. Carabello Circulation. 2012;125:2138-2150

- High-fidelity manometer-tipped catheters in the left ventricle (LV) and right ventricle (RV) during the respiratory cycle.

- **Left**, In this patient with restrictive cardiomyopathy, there is a drop in left ventricular pressure and a drop in right ventricular pressure during inspiration (Insp).

- This indicates that the elevation of ventricular filling pressures is due to a myocardial restrictive disease

.

- **Right**, In this patient with constrictive pericarditis, there is ventricular discordance, with an increase in right ventricular pressure and a decrease in left ventricular pressure during inspiration.
- This is due to the enhancement of ventricular interaction and dissociation of intrathoracic and intracardiac pressures. Exp indicates expiration.

Adenosine Deaminase (ADA)

- ADA is an enzyme of purine metabolism which catalyses adenosine into inosine and is found in most human tissues particularly in the lymphoid tissues.
- ADA estimation has been found to be useful in the diagnosis of tuberculosis pleural effusion and ascites.
- High ADA levels have also been reported in effusions due to rheumatoid arthritis, lymphoma, chronic lymphatic leukaemia, empyema, parapneumonic effusions, and mesothelioma.
- The sensitivity andspecificity of ADA estimation in the diagnosis of EPTB is shown in Table VI.

ADA 1 & ADA 2

- ADA exists as two isoenzymes, ADA1 and ADA2,
- each with unique biochemical properties.
- The ADA1isoenzyme is found in all cells with the highest activity in lymphocytes and monocytes,
- Where as ADA2 isoenzyme appears to be found only in monocytes.
- **In tuberculosis pleural effusion,**

  ADA2 isoenzyme is considered to be primarily responsible for total ADA activity, while in parapneumonic effusions, the ADA1 isoenzyme Is the major isoenzyme of ADA.

- Thus,measurement of individual isoenzyme of ADA can enhance the diagnostic utility of ADA estimation in pleural effusions.

Interferon-γ

- Is a cytokine produced by activated T-lymphocytes.
- It plays a fundamental role in the immune response to tuberculosis.
- High levels of IFN-γ have been reported in tuberculosis pleural effusions, possibly related to in situ stimulation of CD4+ T lymphocytes by tuberculosis antigens.
- A few studies have shown a better sensitivity and specificity of pleural IFN-γ levels as compared to ADA levels.
- The sensitivity and specificity of IFN-γ in the diagnosis of pleural tuberculosis are shown in Table VI

Molecular Methods

- Many of the molecular methods are research tools and are not widely available.
- olymerase chain reaction (PCR) has often been applied to the CSF and pleural fluid to detect various sequences representing the DNA of M. tuberculosis (Table V).
- Though the diagnostic utility of PCR in blood, other body fluids such as ascitic fluid, urine, pericardial fluid, pus from cold abscesses, and tissue biopsy specimens has been studied,
- Available evidence is far from convincing.
- These test results must be interpreted in the appropriate clinical situation with caution.
- PCR alone must not be the sole evidence on which antituberculosis treatment is initiated or withheld.

Table VI. Sensitivity and specificity of some commonly used non-conventional diagnostic tests in the diagnosis of extrapulmonary tuberculosis

Test	Pleural fluid			Pericardial fluid			Cerebrospinal fluid		
	Cut-off ≥	Sensitivity	Specificity	Cut-off ≥	Sensitivity	Specificity	Cut-off ≥	Sensitivity	Specificity
ADA (IU/l)									
Villegas *et al*[224]	45.5	0.88	0.86	-	-	-	-	-	-
Reechaipichitkul *et al*[225]	48	0.8	0.81	-	-	-	-	-	-
Sharma *et al*[226]	35	0.83	0.67	-	-	-	-	-	-
	100	0.40	1.00						
Perez-Rodriguez *et al*[227]	40	0.89	0.92	-	-	-	-	-	-
Ocana *et al*[228]	45	1.00	0.97	-	-	-	-	-	-
Burgess *et al*[229]	50	0.91	0.81	-	-	-	-	-	-
Dogan[230]	-	-	-	50	1.00	0.83	-	-	-
Burgess *et al*[231]	-	-	-	30	0.94	0.68	-	-	-
Aggeli *et al*[232]	-	-	-	72	1.00	0.94	-	-	-
Gambhir *et al*[233]	-	-	-	-	-	-	8	0.44	0.75
Mishra *et al*[234]	-	-	-	-	-	-	5	0.89	0.92
IFN-γ									
Villegas *et al*[224]	6*	0.86	0.97	-	-	-	-	-	-
Wongtim *et al*[235]	240†	0.95	0.96	-	-	-	-	-	-
Sharma *et al*[180]	134†	0.89	0.97						
Burgess *et al*[231]	-	-	-	200†	1.00	1.00	-	-	-

* U/ml

† pg/ml

ADA, adenosine deaminase; IFN-γ, interferon-γ

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Table VII. Associated pulmonary/pleural disease in patients with various froms of extrapulmonary tuberculosis

Site	Abnormal chest radiograph (%)
Lymph node tuberculosis[40-42,52,180]	5-44
Pleural effusion[71,74,180,182]	30-50
Abdominal tuberculosis[186,236,237]	20-28
Pericardial[113]	32

Table VIII. Treatment regimens for patients with extrapulmonary tuberculosis

Treatment category	Intensive phase (daily or three times a week)	Continuation phase
Severe forms of EPTB	2HRZE (2HRZS)	6HE
(category I)	$2H_3R_3Z_3E_3$ ($2H_3R_3Z_3S_3$)	4HR
		$4H_3R_3$
Less severe forms of	2HRZ	6HE
EPTB (category III)	$2H_3R_3Z_3$	4HR
		$4H_3R_3$

EPTB, extrapulmonary tuberculosis; R, rifampicin; H, isoniazid; Z, pyrazinamide; E, ethambutol; S, streptomycin
The number before the letters refers to the number of months of treatment. The subscript refers to the number of doses per week.
Some authorities advocate a seven-month continuation phase with daily isoniazid and rifampicin (7HR) for category I patients with tuberculosis meningitis, military tuberculosis and spinal tuberculosis with neurological signs
Adapted from reference 4

Table IX. Summary of recent randomised controlled trials of additional corticosteroid treatment in patients with extrapulmonary tuberculosis

Study	Patients	Treatment regimen employed	Comments
Pericardial tuberculosis:			
Strang *et al* (1987)[107]	Prednisolone (n=53) Placebo (n=61)	Daily streptomycin, isoniazid, rifampicin, and pyrazinamide for 14 wk followed by isoniazid and rifampicin for total a period 6 months	In the absence of a specific contraindication, ATT should be initially supplemented by steroids
Hakim *et al* (2000)[256]	Prednisolone (n=29) Placebo (n=29)	Rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 months, followed by rifampicin and isoniazid for a further 4 months in standard doses Prednisolone (60 mg/day) tapered by 10 mg/week until completion at the end of the sixth week	Adjunctive prednisolone produced a pronounced reduction in mortality No difference in the rate of radiologic and echocardiographic resolution of pericardial effusion

Anti Retroviral Drugs

- If co-existent HIV infection is there,
- the CD4+and CD8+ T lymphocyte counts must be estimated and highly active antiretroviral treatment (HAART)must be administered when indicated.
- Patients with EPTB especially those who are co-infected with HIV may develop paradoxical reactions while on ATT.
- The paradoxical worsening and the immune reconstitution syndrome when HAART treatment is started must be distinguished from poor response due to treatment failure, drug resistance or due to an alternate diagnosis.

- When rifampicin is co-administered along with antiretroviral drugs, by inducing the hepatic P450 pathway,
- Rifampicin may result in dangerously low levels of the antiretroviral agents.
- In this situation, the available therapeutic options include deferring HAART until standard antituberculosis treatment iscompleted; or, discontinuing HAART and treating with a standard short-course regimen; deferring or discontinuing HAART during the initial two month intensive phase when rifampicin is used; using a non-rifampicin containing regimen for the maintenance phase and using HAART among others

Surgery

- **Surgery is often required to procure specimens for diagnostic testing and to ameliorate complications such as tamponade or Constrictive Pericarditis where it may be life saving.**
- **Details regarding surgical management of EPTB is beyond the scope of this review.**

Thank You