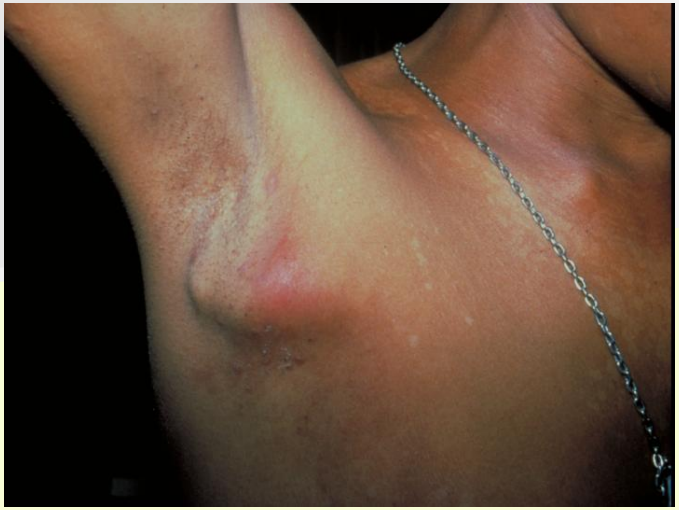
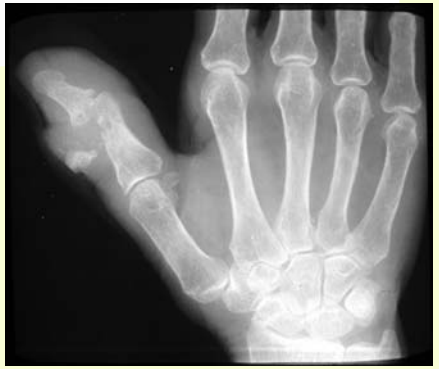
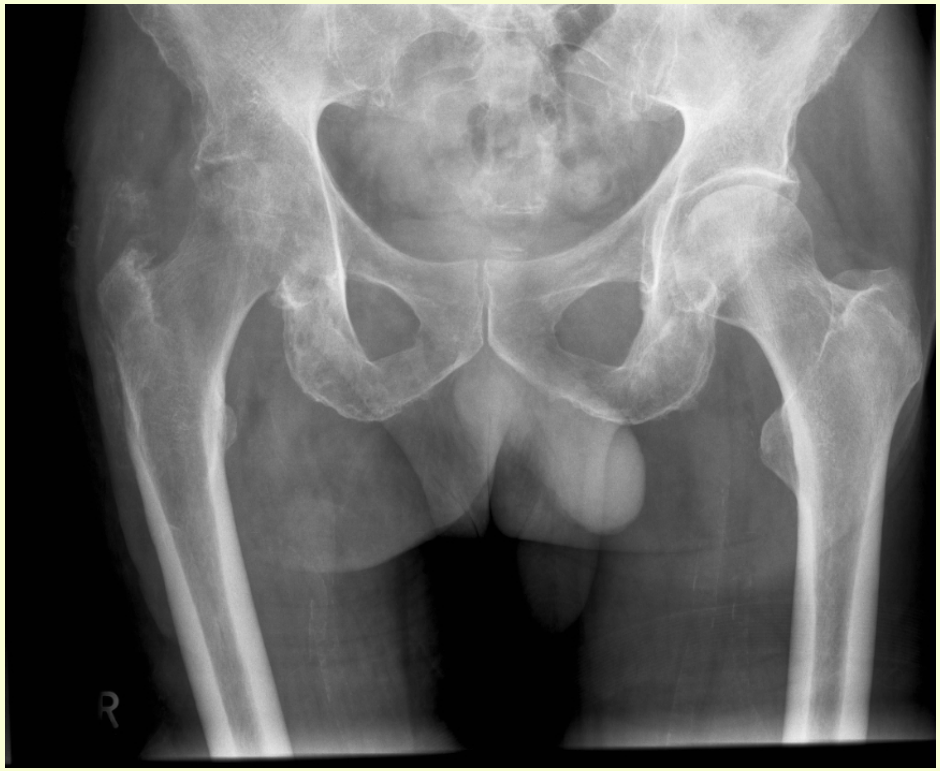
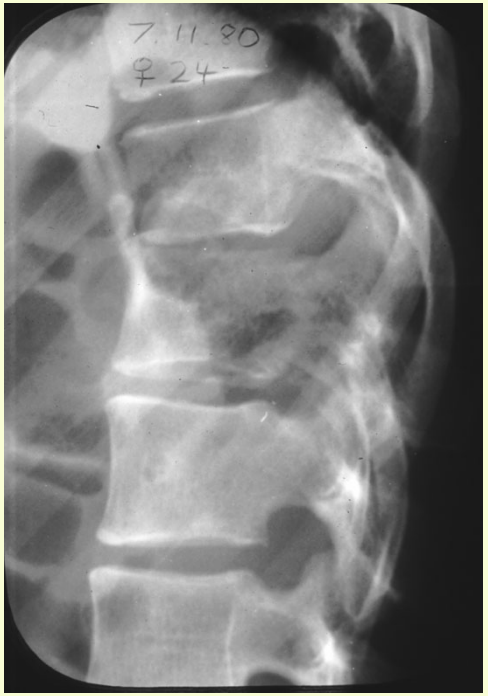
Extrapulmonary TB









Tuberculosis. Site of disease

- Pulmonary case

  A case with TB affecting the lung parenchyma, the tracheo-bronchial tree or the larynx.

- Extrapulmonary case (EPTB)

  TB affecting any site other than pulmonary as defined above.

  Pleural TB and intrathotacic lymphatic TB without involvement of the lung parenchyma are classified as extrapulmonary

ECDC, 2012

http://www.ecdc.europa.eu/en/publications

- The diagnosis of EPTB can be elusive, necessitating a high index of suspicion.
- Physicians should obtain a thorough history focusing on risk behaviors for human immunodeficiency virus (HIV) infection and tuberculosis.

Epidemiology

- 10-70% of patients TB will manifest in organs other than lungs Depending on age, gender, race and immunological competency.

Cowie RL et al, 1997; Yang H et al, 2005

A high incidence of EPTB has become somehow synonymous with the HIV infection

- EPTB accounts about 10–50% of all cases of TB

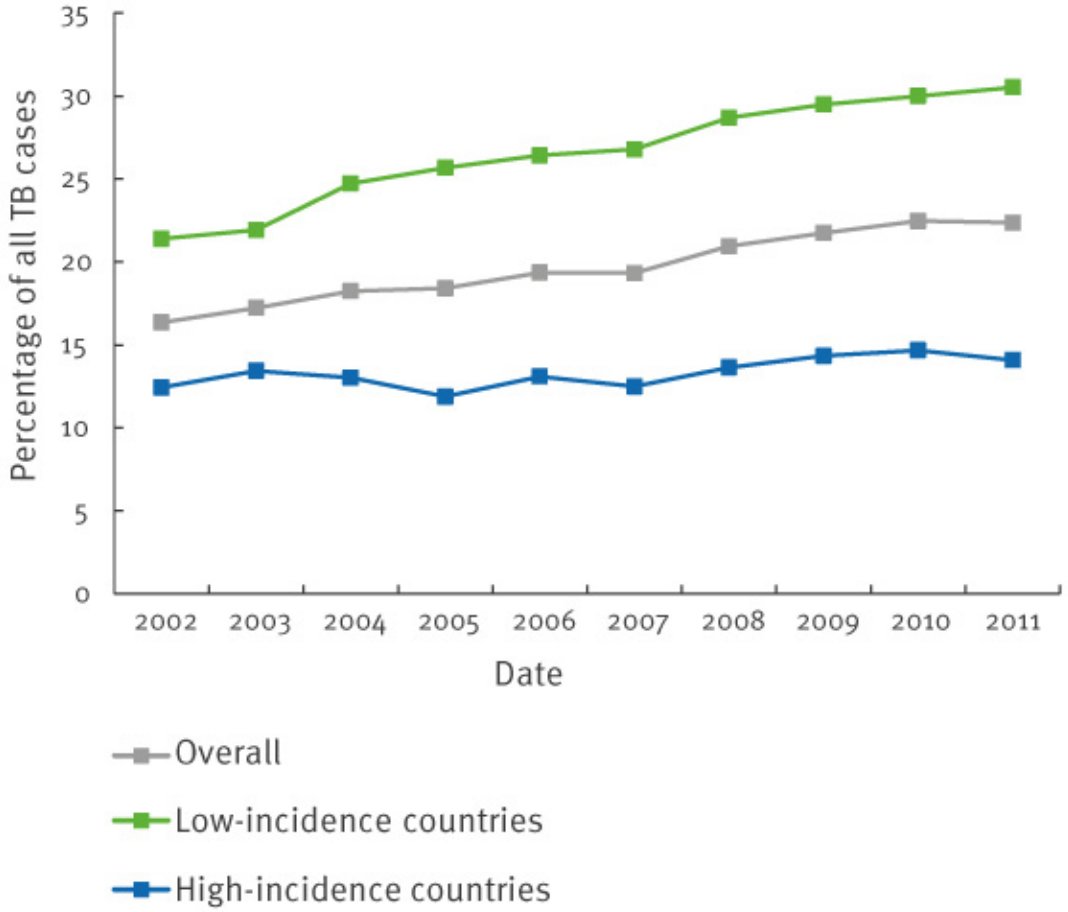
In the era before the HIV pandemic
In studies involving immunocompetent adults

- EPTB accounts for more than 50% (35-70%) of all cases of TB

In HIV-positive patients

FIGURE 2

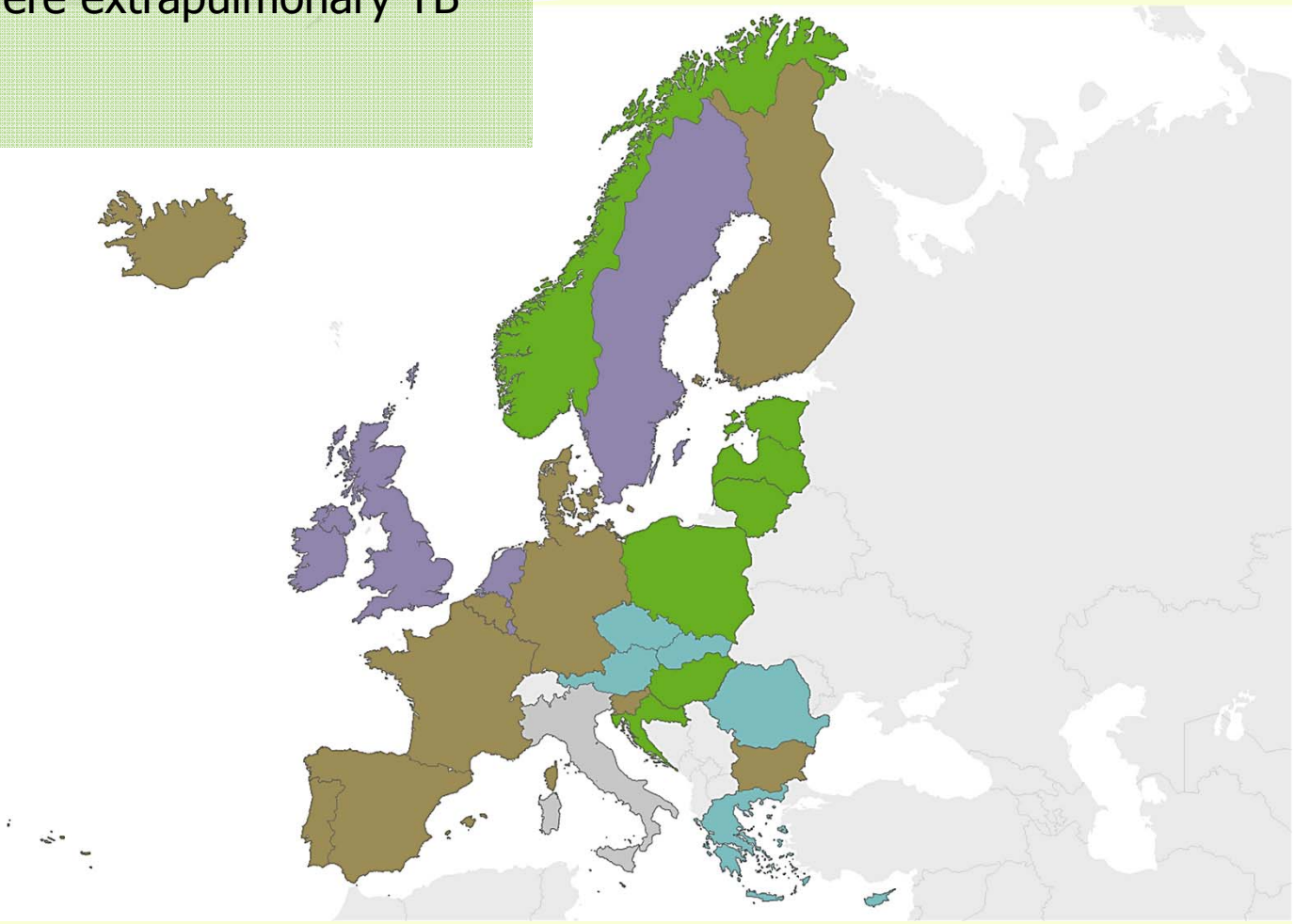
Proportion of extrapulmonary tuberculosis, by year and incidence level, EU/EEA Member States, 2002–11



EU/EEA: European Union/European Economic Area; TB: tuberculosis.

Notified extrapulmonary TB cases, EU/EEA, 2014

21.8% of TB cases were extrapulmonary TB (range 3.2–46.0%)



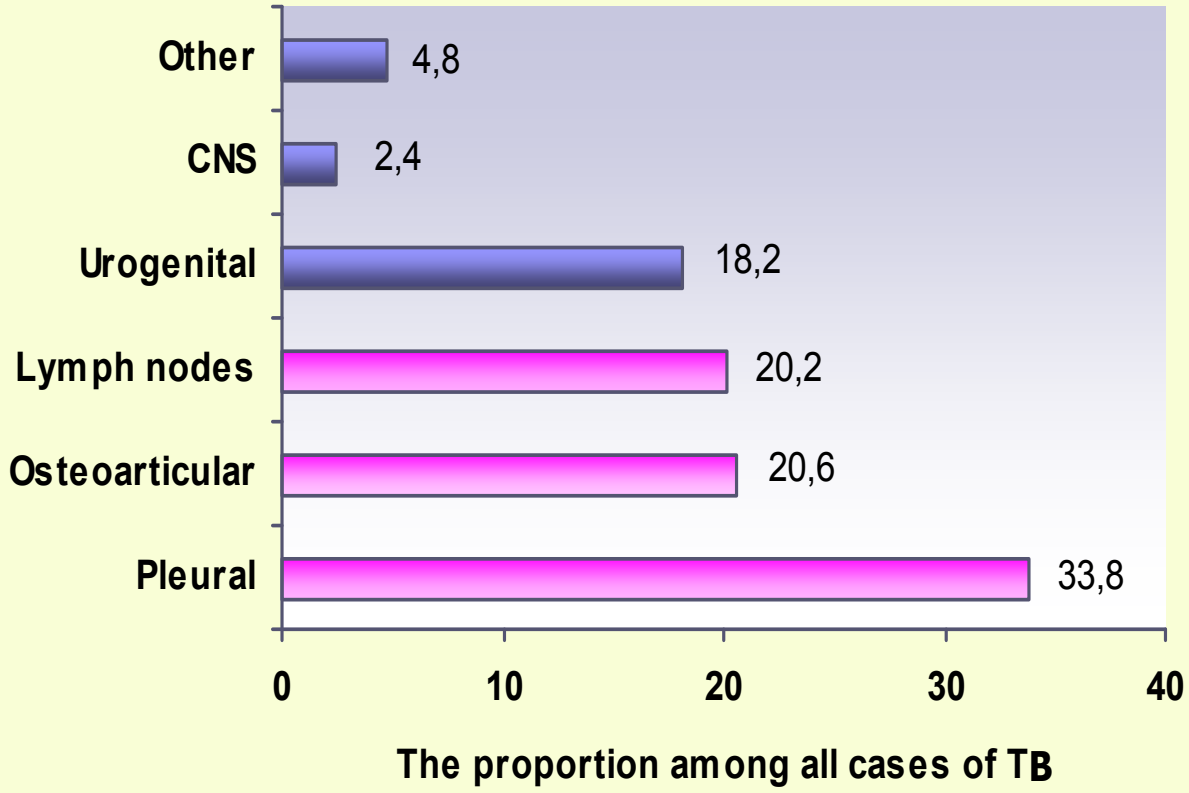
Source: European Centre for Disease Prevention and Control. TB surveillance and monitoring in Europe, 2016.

The proportion of EPTB cases in Europe, 2013 %

	EPTB only	PTB + EPTB
Estonia	**7,6**	**12**
Austria	**19**	**9**
Albania	**38**	**0**
Sweden	**38**	**11**
Denmark	**12**	**7**
Hungary	**4,3**	**1,4**
France	**27**	**14**
Usbekistan	**38**	
Czech Rep	**14**	**3**
UK	**47**	**10**
Latvia	**9**	**6**
Iceland	**18**	**32**
Netherlands	**45**	**12**

ECDC, 2015

Pleural, osteoarticular and lymph node TB were the three leading sites of EPTB 1991–2000, Estonia

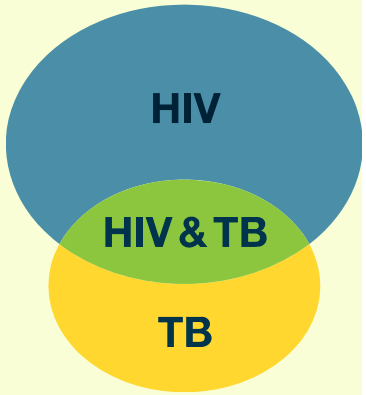


HIV

- The incidence of EPTB is considered to be quite constant in societies where immunocompromising infections are of low prevalence.

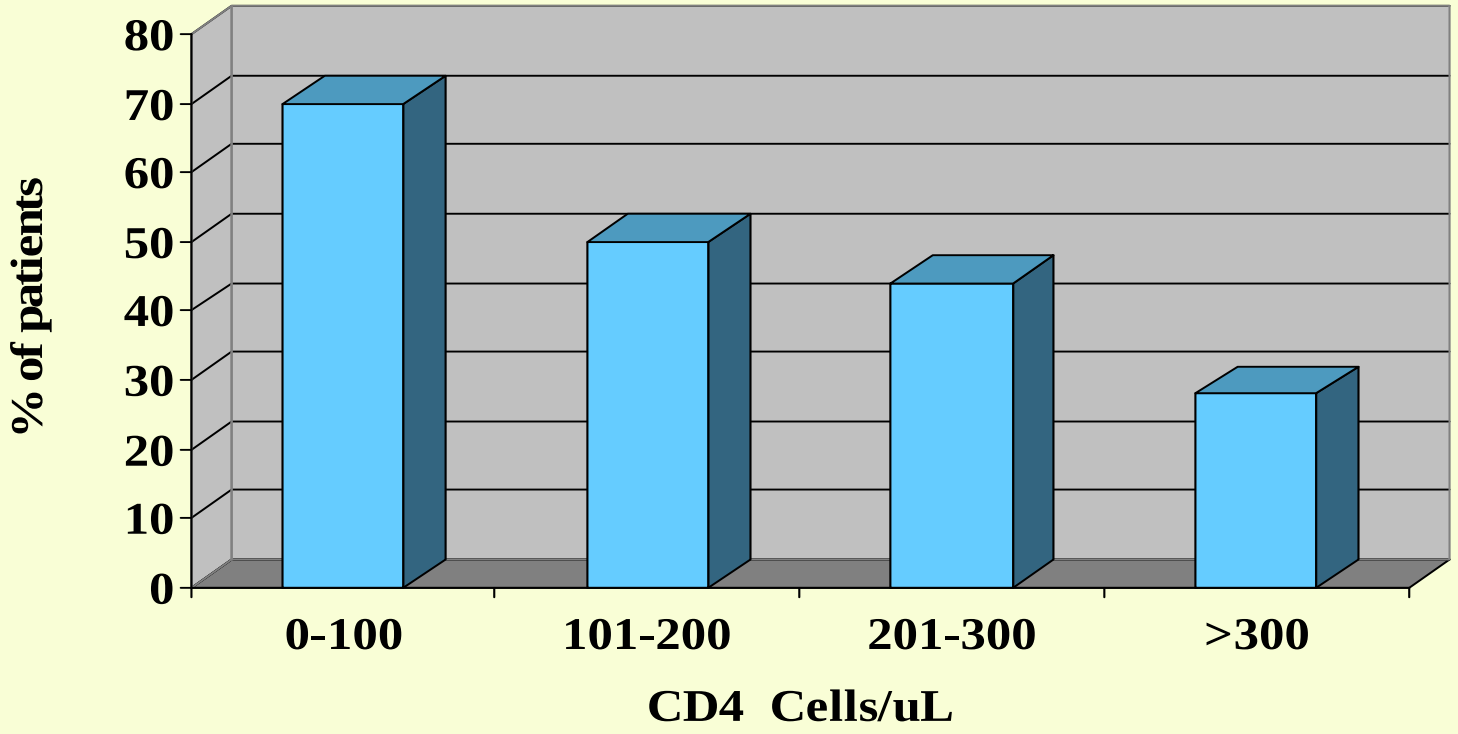
- Most forms of EPTB among infants, children, and adolescents represent recent infection, EPTB with a short latent period: pleural TB, tuberculous lymphadenitis

- Among older persons, except these with AIDS, most cases of EPTB represernt late reactivation, remote in time from primary infection (long latent period): osteoarticular TB, urogenital TB



EPTB in immunocomromised persons

Frequency of EPTB among persons with various levels of CD4 Lymphocyte Counts



The risk of EPTB and mycobacteremia increases with advancing immunosuppression

BE Jones et al, 1993

EPTB in immunocomromised persons

- **1. HIV/AIDS**

- **2. Immunocompromised individuals (other than HIV/AIDS)**

  - **Solid organ and stem cell transplants**
  - **Tumor-necrosis factor (TNF-α) blocking medication**
  - **Renal failure**
  - **Corticosteroid medication**
  - **Neoplasia / malignancy**
  - **Diabetes**
  - **Silicosis**
  - **Gastro-intestinal surgery**
  - **Aging**

Tumour-necrosis factor (TNF-α) blocking medication

Tumour necrosis factor:

- key role in mediating immune responses in acute and chronic inflammatory diseases
- - key cytokine in the host immune response against *Mycobacterium tuberculosis* (granuloma integrity

- TNF-α blocking medication increasingly used for treatment of:
- - rheumatoid arthritis
- - inflammatory bowel disease (morbus Crohn)
- - psoriasis
- - morbus Bechterev)

Tumour-necrosis factor (TNF-α) blocking medication

- **Relative risk 1.5 - 25 higher compared to patients not receiving TNF-α antagonists:**
- **TNF-α antagonists:** - reactivation of latent TB infection / progression of *de novo* infection - close proximity with start of treatment - rapid progression - disseminated disease
- - TNF-α antagonist used (infliximab (Remicade®) and adalimumab (Humira®) soluble receptor eternacept (Enbrel®)↑

Solid organ and stem cell transplant recipients

- Immunocompromised (impaired cellular immunity) patients have **higher incidence of TB** compared with the general population
- Lung: Relative risk 5.6 times higher compared to other organ transplants
- **Risk already increased due to co-morbidity** / co-medication: (renal failure, liver failure, corticosteroids, methotrexate, azathioprine)
- Balance between cellular immune containment of latent TB infection and bacterial replication is disturbed

Solid organ and stem cell transplant recipients

- **Pathogenesis Immunocompromised patients can differ with respect to:**
- - risk of **progression** to active TB ↑
- - **reactivation** of latent TB infection
- - progression from **primary** infection

- - presentation: -
- -less sputum smear-positivity
- - **more extrapulmonary and disseminated disease**
- risk of Immune Reconstition Inflammatory Syndrome (IRIS

Solid organ and stem cell transplant recipients

Latent TB infection and TB

- - TB occurs early (< 6) months after transplant (enhanced immunosuppression) but in renal and stem cell transplant recipients usually later
- - more extrapulmonary disease

Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplants recipients: impact and implications for management. Clin Infect Dis 1998;27:

Neoplasia / malignancy

- form of malignancy
- extent of spread
- clinical condition
- level of immune suppression

- Higher risk (RR 16) for developing TB
  in haematological malignancies (leukaemia, lymphoma)
  than solid malignancies - high dose corticosteroids! –
  haematopoetic stem cell recipients!

- Higher risk for carcinoma of head and neck (RR 3 – 7)

Screening of immunocompromised individuals

- **Solid organ and stem cell transplant recipients** –
  all candidates should be screened –
  test early (before immunosuppression; treatment completion)

- **TNF-alpha candidates** –
  all candidates should be screened –
  test early (before immunosuppression; treatment completion)

- **But they are more difficult to test for latent TB infection**
  - immune-based testing
  - corticosteroids or other immunosuppressive medication

EPTB. Diagnosis.

1. The diagnosis of EPTB - more difficult to establish than pulmonary TB
   because of the protean nature of the disease and
   lack of a simple screening test such as chest radiography

2. **Important to isolate MBT (smear, culture).**

All secrets, fluids, biopsies. bronchial lavage, pleural effusions, cerebrospinal fluid, urine, gastric aspirates, lymph nodes, bone marrow, blood

3. **Blood**
Special BACTEC 9050 liquid cultire süsteemis

Numerous articles have reported on the **utility of various PCR methods** on miscellaneous material other than sputum
Considerable variability in the results of the studies

Nucleic acid amplification technicues are more sensitive than microscopy

Extrapulmonary TB, diagnosis

The general symptoms of TB disease, pulmonary or extrapulmonary

--- Weight loss
--- Fatigue
--- Malaise
--- Fever
--- Night sweats

The symptoms of extrapulmonary TB disease depend on site of disease.
For example, TB of the spine may cause pain in the back; TB of the kidney may cause blood in the urine. All of these symptoms may be caused by other diseases, but they should prompt the clinician to suspect TB disease.

Previous TB infection or TB disease.

The medical history

Simultaneous Pulmonary TB: 18 – 28 %, 33% of EPTB cases
Chest X-ray, CT – alwey in suspicion of EPTB

Nonspecific changes in blood test, biochemistry (Hgl, SR, CRP, Lymphocytopenia)

Recommended tests for diagnosis of EPTB Site Imaging

Site	Imaging	Biopsy	Culture
Lymph node*		• Node	• Node or aspirate
Bone/joint	• Plain X-ray and computed tomography (CT) • Magnetic resonance imaging (MRI) • Ultrasound	• Site of disease	• Biopsy or para-spinal abscess • Site or joint fluid
Gastrointestinal	• Ultrasound • CT abdomen	• Omentum • Bowel	• Biopsy • Ascites
Genitourinary	• Intravenous urography • Ultrasound	• Site of disease	• Early morning urine • Site of disease • Endometrial curettings
Disseminated	• High resolution CT thorax • Ultrasound abdomen	• Lung • Liver • Bone marrow	• Bronchial wash • Liver • Bone marrow • Blood
Central nervous system**	• CT brain • MRI	• Tuberculoma	• Cerebrospinal fluid
Skin		• Site of disease	• Site of disease
Pericardium	• Echocardiogram	• Pericardium	• Pericardial fluid
Cold/liver abscess	• Ultrasound	• Site of disease	• Site of disease

EPTB, microbiological confirmation

Lymphatic TB nodle	the preferred method for diagnosis is biopsy of involved
Pleural TB	thoracocentesis with pleural fluid analysis: smear for MB is rarely positive, some other attributese characteristic of TB pleural biopsy
Genitourinary TB	urine, affected tissues
Bone and Joint TB	synovial fluid, open joint synovial biopsy is the most sensitive method for the diagnosis of tuberculosus arthritis
Central Nervous System	cerebrospinal fluid. Microscopy positive for AFB in 20-37%, culture positive in 40-80%, increase yield with repeat studies
Abdominal TB	laparoscopic evaluation with guided biopsy is the diagnosic procedure of choice. Paracentesis of ascitic fluid - positive smears occur in a minority of cases
Pericardial Tuberculosis	bacteriological study of pericardial tissue or fluid

Pleural Tuberculosis

- Patient from high-risk social, socioeconomic, employment groups
- X-ray: unilateral effusion (500-1000 ml)
- Underlying parenchymal lesions 20 -50% by plain chest radiographs
- Wide array of manifestations of pleural TB

- Symptoms:

chest pain – pleuritic, sharp, associated with respiration

cough – nonproductive

fever – very common

Dyspnea, chills, sweats, weight loss, malaise –occur more commonly with advanced disease

- Duration of symptoms 4,7 – 17,5 days - primary cases
  10,1 – 62 days – reactivateral effusiontion disease
  (Antoniskis, 1990
- Physical examination –minimal abnormalities
  Dullness to percussion, diminished breath sounds
- Tuberculin skin test – falsely negative in a substantial proportion of patients (12%, 31%)

Clinical Clues to Prompt Suspicion of Extrapulmonary Tuberculosis

- Ascites with lymphocyte predominance and negative bacterial cultures
- Chronic lymphadenopathy (especially cervical)
- CSF lymphocytic pleocytosis with elevated protein and low glucose
- Differential diagnosis of Crohn's disease and amebiasis
- Exudative pleural effusion with lymphocyte predominance, negative bacterial cultures, and pleural thickening
- HIV infection
- Joint inflammation (monoarticular) with negative bacterial cultures
- Persistent sterile pyuria
- Tuberculosis-endemic country of origin
- Unexplained pericardial effusion, constrictive pericarditis, or pericardial calcification
- Vertebral osteomyelitis involving the thoracic spine

Golden MP, Vikram HR. American Family Physician 2005;72:1761–1768

Treatment

- The basic principles that underlienthe treatment of pulmonary TB, also apply to EPTB
- Usually 6-9 month regimen (2 + 4-7 months)

- TB meningitis 9-12 months
  Some authors – up to 2 years

Some patients being treated for TB meningits
develop tuberculomas during therapy, perhaps as a form of paradoxal reaction.
This does not necessarily indicate treatment failure

Am J respir Crit Care Med 2003; 167: 603-622