Mycobacterium tuberculosis: Ca. 30 % of humankind are infected with this pathogen, 10 % sicken from manifested tuberculosis. The special feature of these bacteria is that they are very acid-fast, they grow very slowly, and can survive in macrophages. This way, they are a great challenge in terms of therapy and prevention for physicians and scientists. The following article distinctly presents you all the relevant facts for exams concerning tuberculosis which are needed for the second state examination and clinical practice.

Epidemiology of Tuberculosis

Worldwide distribution of tuberculosis
Tuberculosis is spread worldwide and is one of the most frequent infectious disease besides AIDS and malaria. According to the Robert-Koch-Institut (RKI), one third of the world population is infected with tuberculosis, during their life, 5-10 % develop tuberculosis that has to be treated. Worldwide, tuberculosis is the bacterial infectious disease that most frequently leads to death and could be treated. Like this, it is the leading cause of death in patients with HIV.

Most infected people live in Africa, South East Asia, and in the Western Pacific region.

Almost 9 million people sicken from tuberculosis every year. 1.4 million people die every year (WHO).

Risk of disease at tuberculosis

**Risk patients** are people from countries with high tuberculosis-prevalence, institutionalized patients, drug-addicted people with intravenous abuse, and immune deficient patients, e.g. with diabetes mellitus and Hodgkin’s disease.

**High-risk patients** exhibit a suspicious x-ray finding, close contact with patients with active tuberculosis, and HIV-infected or otherwise immune suppressed people. High-risk countries are Sub-saharan Africa, Indian sub-continent and former USSR.

Etiology and Pathogenesis of Tuberculosis

Pathogen and reservoir at tuberculosis

Tuberculosis pathogens are acid-fast aerobic gram-positive bacteria from the family of *Mycobacteriaceae*. In the following table, the pathogens of the Mycobacterium tuberculosis complex are listed with the respective reservoirs.
### M. tuberculosis (most frequent pathogen)

**Image:** "Mycobacterium bovis" von Y tambe. Lizenz: CC BY-SA 3.0

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Host</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. tuberculosis</td>
<td>Human</td>
</tr>
</tbody>
</table>

### M. bovis (ssp. bovis and caprae)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Host</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. bovis</td>
<td>Human and cattle (infections via non-pasteurized milk)</td>
</tr>
</tbody>
</table>

Pathogenically, the pathogens are especially effective via triggering severe cell-mediated immune response.

### Paths of infection at tuberculosis

The infection with tuberculosis is almost exclusively **airborne** (droplet infection) via aerosols < 5 µm of diameter via infected patients with active/infectious tuberculosis.

**Note:** Active tuberculosis means that the disease has pulmonary connection and can be transmitted to the environment airborne. Extrapulmonary tuberculosis normally does not pose an infectious risk in the context of social contacts. Contagion does not necessarily occur as easily as e.g. at measles or chicken pox. If a person is infected with tuberculosis depends on many factors.

- Frequency, duration, and closeness of the contact with a patient with infectious tuberculosis
- Amount and virulence of the inhaled pathogen
- Susceptibility of the exposed person

### Symptoms and Clinic of Tuberculosis

### Incubation time at tuberculosis

6 – 8 weeks pass between exposure and a measurable immune response. The risk of disease is greatest in the first two years after the infection. Infants and immune-suppressed people have the greatest risk to become diseased.
Clinic of tuberculosis

Tuberculosis is not characterized by a specific clinic. **Primary tuberculosis**, which mostly presents asymptomatically or as a flu, is mostly not recognized. In the event of onset of the disease, most infected people later sicken from **post-primary tuberculosis**.

Primary tuberculosis

This latent tuberculosis infection is a first infection with positive indirect pathogen detection (e.g. Mendel-Mantoux). However, there is no pathological radiological finding. The symptoms are mostly unspecific like B-symptoms, fatigue, or it has a completely asymptomatic course. Pulmonary, productive cough with hemoptysis develops.

If no radiological or pathological changes are detectable, one speaks of a **latent tubercular infection (LTBI)** in case of a positive tuberculin-reaction.

**CAVE:** At all lung symptoms, one has to consider tuberculosis in terms of differential diagnoses.

5-6 weeks after the infection, a primary focus forms. In histology, the primary focus is characterized by a **granuloma with epitheloid cells** and Langhans giant cells with central caseation. Via the lymphogenic path of infection, the primary focus spreads to regional lymph nodes.

The primary focus and reaction lymph nodes = **primary complex**.

Weeks or even months can pass until this primary complex (up to 90 % in the lungs)
heals completely. Often, scarred and calcified structures remain, which can stay detectable in x-rays. B symptoms rarely occur.

### Important complications at primary tuberculosis

<table>
<thead>
<tr>
<th></th>
<th>Miliary tuberculosis</th>
<th>Pleuritis exudativa tuberculosa</th>
<th>Landouzy sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genesis</strong></td>
<td>Via hematogenic, lymphogenic spread of tubercular bacilla out of the primary complex</td>
<td>Out of foci close to the pleura</td>
<td></td>
</tr>
<tr>
<td><strong>People affected</strong></td>
<td>Children, immune-deficient adults</td>
<td>Teenagers and adults &gt; 40 years</td>
<td>Immune-deficient people</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>High fever, severe malaise</td>
<td>B symptoms, thoracic pain, pleural effusion</td>
<td>Septic course of primary tuberculosis, high fever, spleen swelling, headache</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Chest x-ray: miliary spot shadowing; lumbar puncture: tubercular meningitis; ocular fundus: tubercles in choroidea</td>
<td>Pleural puncture: exudation with low sugar concentration and increased adenosine-desaminases (ADA-test), chest x-ray</td>
<td></td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>Early, intensive parenteral chemo therapy</td>
<td>Tuberculosis standard-therapy (see below)</td>
<td>Mostly lethal course</td>
</tr>
</tbody>
</table>

### Post-primary tuberculosis

The **post-primary tuberculosis** (chronic tuberculosis) means every form of tuberculosis, which follows primary infection. In most cases, the onset is based on re-infection, not a new infection.

**Features and symptoms of post-primary tuberculosis**

- Apical pulmonary foci
- Simon foci: fuzzy, small, infra- or supraclavicular spots
- Assmann’s early infiltrations
- A completely asymptomatic course is also possible!

**Absent therapy:**

Great probability for detection of tubercular bacteria in sputum >> active,
infectious tuberculosis

- Destruction and cavernization of growing lung parts >> hemoptysis, hemopnea

Extrapulmonary tuberculosis

Tuberculosis can affect every organ system and trigger an unlimited variety of symptoms and complications. The following table gives an overview of the most important extrapulmonary manifestations.

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal gland</td>
<td>Mostly bilateral, adrenal gland insufficiency (Addison’s disease)</td>
</tr>
<tr>
<td>CNS</td>
<td>Tubercular meningitis with typical brain nerve damage</td>
</tr>
<tr>
<td>Bones, joints and cartilage</td>
<td>Spondylitis tuberculosa, depression abscesses, laryngeal tuberculosis</td>
</tr>
<tr>
<td>Kidney</td>
<td>5 years after the infection at the earliest, hematuria with sterile pyuria</td>
</tr>
<tr>
<td>Pericardium</td>
<td>Pericardial effusion, pericarditis, constrictive pericarditis</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Vomiting, diarrhea, abdominal pain, weight loss</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Complications of primary tuberculosis, cervical lymph nodes are mostly affected, generalized lymphadenopathy</td>
</tr>
<tr>
<td>Skin</td>
<td>Lupus vulgaris (typically, in the cheek region of women), tuberculides</td>
</tr>
</tbody>
</table>

Diagnostics of Tuberculosis

Anamnesis at tuberculosis

It is important to ask for exposition, previous infections, trips, and increased risk of disease (HIV, alcohol abuse).

Tuberculin skin test and interferon-gamma test

The **tuberculin skin test according to Mendel-Mantoux** is positive if a palpable node of at least 15 mm is visible after 72-96 hours. At risk patients, an induration of > 10 mm is sufficient for the detection of an infection. At high-risk patients, > 5 mm is already sufficient.

The currently more established **interferon-gamma test** is based on the in-vitro
stimulation of memory cells via antigens of Mycobacterium tuberculosis. Hereby, the lymphocytes of the patients are stimulated with a mixture of antigens of M. tuberculosis. If the patient was already affected by a tuberculosis infection or had contact with the pathogen, more interferon-gamma is produced.

**Note:** The results are often positive! This way, only the confrontation of the immune system with the mycobacteria is proven, but no distinction between active and inactive tuberculosis is possible.

**Imaging of tuberculosis**

Chest x-ray can be seen as the guiding diagnostic measure, but no specific statements can be made. The following might be visible:

![x ray of a patient with tuberculosis](image)

**Primary complex:** enlarged hilum lymph node, local shadowing

- **Post-primary tuberculosis:** Simon foci, Assmann’s infiltrations
- **Unspecific:** Shadowing, calcification, caverns, pleural effusion, round foci (tuberculoma), distinction between smooth (new) and hard infiltrations (old), foci can mostly be found in the cranial lung areas.

In **CAT**, hilum lymph nodes and retroclavicular infiltrations can be diagnosed.

**Pathogen detection at tuberculosis**

The bacterial detection can be gained via threefold culture of **morning sputum**, one-time stomach fasting secretion, or via invasive diagnostics like bronchoscopy, pleural puncture, or thorascopy with biopsy.

In HIV patients, **blood cultures** are additionally made since frequent hematogenic spread has to be assumed.

The detection of bacteria succeeds after enrichment in **Ziehl-Neelsen’s stain** or **immune fluorescence stain with auramine**. However, a negative finding is no exclusion criterion for active lung tuberculosis!
Note: A positive culture makes the assignment to the Mycobacterium tuberculosis stem possible and is evidence of active lung tuberculosis. With polymerase chain reaction (PCR), the detection of mycobacteria can be made within 48 hours. Additionally, this measure is characterized by very high sensitivity and specificity. However, a distinction between a previous inflammation and an active infection cannot be made.

Differential Diagnosis of Tuberculosis

The most important differential diagnoses of lung tuberculosis are:

- Chronic bronchitis
- Pneumonia
- Viral diseases
- Lung mycosis
- Bronchial carcinoma

Therapy of Tuberculosis

Anti-tuberculosis drugs at tuberculosis

In 97% of the cases, tuberculosis is curable! Every active tuberculosis is a disease that has to be treated. The patient has to be isolated until there is no more risk for infection. Normally, this state is reached after 4-6 weeks after therapy initiation.

Note: Almost every second state examination asks for anti-tuberculosis therapy and their side effects.

<table>
<thead>
<tr>
<th>Anti-tuberculosis drugs</th>
<th>Effect</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Strongest anti-tuberculosis drug, bactericide effect</td>
<td>Hepatotoxic, neurotoxic (polyneuropathy)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Bactericide (inhibition of DNA-dependent RNA-polymerase)</td>
<td>Hepatotoxic, reddening of body secretion</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Bactericide</td>
<td>Hepatotoxic (transaminases, uric acid)</td>
</tr>
</tbody>
</table>
**Ethambutol**
- Bacteriostatic or bactericide, depending on the dose
- Risk for opticus neuritis with loss of vision, central scotoma (therefore an ophthalmological examination is required before initiation of therapy)

**Streptomycin**
- Bactericide
- Lesion of the vestibular nerve with balance disorders, decrease in audition; kidney insufficiency

**Administration of the medicaments at tuberculosis**
- **Overall duration**: at least 6 months
- **Initial phase**: two months of standard therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol
- **Stabilization phase**: four months of treatment with isoniazid and rifampicin, then monitoring of sputum control over a period of two years
- **1 x daily**: Mycobacteria have very slow proliferation kinetics. Thus, the medicaments have to be administered every day all at once to reach synergistic peak levels
- **Control of the side effects**: Liver values, kidney values, audition function, x-ray, ophthalmological controls
- **Maximum doses** must not be exceeded

**Problems of treatment**
1. **Diagnosis**: culture is slow (4 weeks+)
2. **Compliance**: no one likes taking tablets for several months
3. **Toxicity**: especially the liver; raised LFTs common, may need to change treatment
4. **Drug resistance**:
   - Occurs if a patient is given single agent therapy
   - Needs extended treatment (12 months+)
   - The extensively resistant disease is often fatal

![Diagram of 100 Cases]

- **‘Cured’**
  - 82 cases
  -Rx stopped
  -Relapse rare

- **Not Cured**
  - 3.3 cases Rx continues
  - 6.6 died, 50% related to TB

- **Don’t Know**
  - 8 cases
  -Lost to F/U

*“Non-resistant M. tuberculosis is readily curable” Image created by Lecturio*

**Prophylaxis of Tuberculosis**

**Imaging examinations at tuberculosis**

M. tuberculosis is exclusively transmitted among humans. Screening programs in the environment of infected people contain tuberculin tests and x-ray images of the **lungs**.
With an infection risk of under 0.1 % in Germany, the STIKO does not generally recommend the **BCG (Bacille Calmette-Guérin) vaccination**. This vaccination is exclusively indicated at people with very high exposition risk (e.g. employees in shelters for homeless people).

**Note:** Contraindication of the BCG vaccination is present at positive tuberculin reaction, immune suppression, or AIDS.

### Chemoprophylaxis at tuberculosis

Chemoprophylaxis should be considered if...

- ... a newly occurred positive tuberculin reaction is present in risk patients. Treatment is conducted with isoniazid for 9 months. In healthy people, it should initially be waited under x-ray monitoring.
- ... children < 1 year are definitely exposed, monotherapy with isoniazid should be performed for 3 months.
- ... the interferon-gamma-test is positive and bacteriology is negative.

### Review Questions

The correct answers can be found below the references.

1. **A student in the elective period is in the emergency department of a hospital in a large city. During physical examination, the patient, who comes from Eastern Europe, coughs at the physician for several times. On the following day, the student learns that this patient is suspected to have tuberculosis. Which of the following statements is most likely true?**

   A. Incidence of multi-resistant tuberculosis bacteria in Eastern Europe is similar to the one in Germany.
   B. Microscopy of respiratory material stained according to Ziehl-Neelsen has the greatest diagnostic sensitivity of routine methods for detection of tuberculosis bacteria.
   C. According to the Infection Protection Act, the clinical suspicion of tuberculosis already has to be reported namely (obligation to notify the authorities for the treating physician).
   D. According to the Infection Protection Act, the detection of Mycobacterium tuberculosis has to be reported namely (obligation to notify the authorities for the laboratory).
   E. The student should immediately be treated with a fourfold combination of post-exposition prophylaxis.

2. **Anti-tuberculosis drugs are administered in combination. Which is most likely true considering the stabilization phase?**

   A. 4 months isoniazid and rifampicin
   B. 4 months isoniazid and ethambutol
   C. 4 months rifampicin and pyrazinamide
   D. 8 months isoniazid and rifampicin
   E. 8 months isoniazid and pyrazinamide

3. **Which is most likely typical for the x-ray finding of post-primary tuberculosis?**
A. Schaumann bodies
B. Simon foci
C. Asteroid bodies
D. Kerley lines
E. Jet phenomenon

References


Correct answers: 1D, 2A, 3B

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