Review Article

The Diagnosis and Treatment of Tuberculosis

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Summary

Background: Around 10 million people worldwide contract tuberculosis every year. According to the World Health Organization (WHO), approximately one-quarter of the world's population is latently infected with *Mycobacterium tuberculosis*. In Germany, the incidence of tuberculosis was in decline over several decades but rose in 2015 to 7.3 new cases per 100 000 persons. In 2018, a total of 5429 new cases were documented, corresponding to 6.5 new cases per 100 000 persons.

Methods: This article is based on literature retrieved by a selective search in PubMed and on the authors' clinical experience.

Results: Tuberculosis involves the lungs in almost 75% of patients but can generally involve any organ. In Germany, the majority of patients come from high-incidence countries. If a patient's differential diagnosis includes tuberculosis, the main tests for the detection of the pathogen in sputum and tissue samples are culture (the gold standard), microscopy, and nucleic acid amplification tests. Imaging studies are also used for diagnosis and follow-up. The standard treatment consists of a combination of isoniazid, rifampicin, ethambutol, and pyrazinamide, followed by a combination of isoniazid and rifampicin only. Liver damage is one of the more common adverse effects of this treatment, arising in 2.4% of patients. Multidrug-resistant tuberculosis, which is rare in Germany (around 100 cases per year), should be treated in specialized centers.

Conclusion: Rapid diagnosis and targeted treatment are essential to prevent an unfavorable course of the disease as well as its transmission to other individuals. In patients presenting with unclear symptoms, tuberculosis should always be considered as a differential diagnosis. The diagnosis of latent tuberculosis and decision-making regarding its treatment are difficult because of the lack of specific biomarkers and of relevant data from clinical trials.

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Tuberculosis (TB) is one of the ten leading causes of death worldwide (1). In Germany and other highly developed countries, however, TB occurs relatively seldom and can almost always be treated successfully. The rarity of TB means that not all physicians regularly encounter the disease, and the pronounced variability of the symptoms often leads to delayed diagnosis. TB is a "medical chameleon," in that its manifestations differ widely and almost any organ may be affected. The trend towards increasing global migration is raising the profile of TB in our country, to the point where every physician should have basic familiarity with the prevailing recommendations for the diagnosis and treatment of this illness. This review article describes the clinical presentations and current management of TB, based on a selective survey of publications in PubMed backed up by the authors' own research and clinical experience.

Epidemiology

The World Health Organization (WHO) estimates that 1.8 billion people—around one fourth of the global population—are infected with *Mycobacterium tuberculosis* (2). In 2017, roughly 10 million people contracted TB and 1.6 million died of the disease (1).

In Germany, the incidence of TB decreased from the introduction of electronic documentation in 2001 up to 2014, when it occurred in 5.6 cases per 100 000 inhabitants. The number of newly diagnosed cases rose sharply to 7.3 per 100 000 in 2015 (3). A slight decrease was noted in 2017 (6.6 cases per 100 000), and the figures for 2018 are practically unaltered (5429 cases of TB registered, i.e., 6.5 per 100 000 inhabitants) (4). The trend in numbers of cases documented was determined largely by changes in migration and active case finding through screening as stipulated in §36 of the Protection Against Infection Act (*Infektionsschutzgesetz*; IfSG). A large proportion of the tuberculosis patients in Germany were born in other countries: 42% in 2001 (5), rising steadily to 73% in the latest statistics (6). Particularly in the years 2015 (21.5%) and 2016 (16.5%), most of the TB cases were detected by screening according to §36 IfSG. The corresponding figure in 2017 was lower, at 9% (3, 6, 7).

In 2017, almost three quarters of the cases of TB registered in Germany affected the lungs, and four fifths of these patients had infectious pulmonary TB (6). Lymph node Tb accounts for about half of all extrapulmonary cases; the rest is accounted for by

BOX

"Red flags" for tuberculosis (TB)

- **TB symptoms**
  - Persistent (productive) cough
  - Hemoptysis
  - Night sweats
  - Weight loss
  - Fever
  - Abnormal fatigue
  - Lymph node swelling
  - Thoracic or abdominal pain

various other organ manifestations (6). Multidrug-resistant tuberculosis (MDR-TB) continues to account for only a small proportion (3%) of cases in Germany (6). The subgroup of patients born in the countries of the former Soviet Union showed the highest proportion of MDR-TB cases in 2017 (19.3%). For comparison, in the same year the corresponding figure for the subgroup of patients born in Germany was around 1% (6).

The prognosis for persons with TB in Germany is good overall, with a mortality rate of 1.9% (6).

Microbiology and pathogenesis

Mycobacterium tuberculosis, the most common TB-causing pathogen, is a nonmotile, aerobic, rod-shaped bacterium.

Transmission occurs almost exclusively through droplet infection. Whether infection ensues depends essentially on:

- The frequency of contact with a person who has infectious pulmonary TB
- The duration of contact
- The closeness of contact
- The amount and virulence of pathogen transferred
- The susceptibility of the person exposed (8).

After inhalation, extracellular and intracellular bacterial growth takes place preferentially in the well-ventilated upper levels of the lungs, especially in the alveolar macrophages. At 3 to 4 weeks post infection, healthy or non-immunocomprised individuals develop T-cell immunity, leading to decreased intracellular growth of the bacteria. The bacteria can nevertheless survive intracellularly—initially without causing clinical symptoms. In the course of immune defense mechanisms tuberculous granulomas arise, typically with central caseation (9). Especially in children or immunosuppressed individuals, clinically manifest TB may develop shortly after infection. Such cases are referred to as progressive primary TB.

Most patients, however, develop a latent TB infection (LTBI) accompanied by scarring or calcification of the tuberculous granuloma, which is not always visible on diagnostic imaging. In around 5% to 10% of patients, decreasing cellular immunity leads to reactivation of the LTBI, resulting in postprimary TB (10). Reactivation most commonly occurs within 2 years of primary infection. HIV patients are at very high risk of reactivation (10), particularly if their CD4+ T-cell count is low (e1). The risk of TB reactivation is therefore around 20 times higher in the case of untreated HIV infection than for HIV-negative persons (11). However, the risk of reactivation is also increased by other immunosuppressive conditions, e.g., diabetes mellitus (e2), terminal kidney failure (e3), or treatment with inhibitors of tumor necrosis factor-alpha (TNF-α) (12).

Clinical presentation of tuberculosis

Latent tuberculosis infection (LTBI)

LTBI is infection with vital, non-replicating TB pathogens. The infected person has a positive result on immunological testing (e.g., interferon gamma release assays; see "Diagnosis" below), but shows no symptoms of disease. Furthermore, diagnostic tests (at least chest radiography) reveal no sign of active TB. These patients are not infectious. In the presence of weakened T-cell immunity, however, LTBI can turn into active disease at any time (13). The risk of developing clinically manifest TB is about 5% during the first 18 months after infection with *M. tuberculosis* and circa 5% over the remaining life span (14).

Forms of disease

Pulmonary tuberculosis

The typical symptoms of pulmonary TB include fever, night sweats, abnormal fatigue, productive cough, and hemoptysis. In non-immunocomprised adults the disease advances only slowly, in contrast to children and immunocompromised persons, who may experience fulminant TB with abrupt onset. Persistence of cough for more than 3 weeks should always prompt consideration of TB *(Box)*.

Extrapulmonary and disseminated tuberculosis

In 2017, 1375 (26%) of all TB cases in Germany were exclusively extrapulmonary (6). Recent data from some industrialized countries show increasing incidence of extrapulmonary manifestations: in some regions of Spain, 37% of cases of TB detected in 2013 fell into this category (15).

The clinical symptoms can take many forms and are determined by the specific organ(s) involved.

Disseminated TB (affecting two or more organ systems), previously observed almost exclusively in children or in persons with immune suppression, is now increasingly being found in adults with no apparent immune defect (16, e4). Most of these patients are immigrants from countries with moderate to high TB incidence. Various factors such as the language barrier and frequent relocation hamper access of asylum seekers and others to the healthcare system, which may delay diagnosis and thus facilitate progress of the disease (16, 18) (e4).

Diagnosis

The detection of LTBI has to be distinguished from the diagnosis of active TB. Indirect procedures such as the interferon-gamma release assays (IGRA) are the modern standard for diagnosis of LTBI in adults. These assays detect the secretion of interferon-gamma (IFN-γ) by T lymphocytes, which are stimulated by means of relatively TB-specific antigens. Prior bacille Calmette–Guérin (BCG) vaccination usually does not lead to false-positive results. IGRA are used principally to investigate the persons who have been in contact with an index patient who has contagious pulmonary TB. Another indication is testing for LTBI in advance of administration of drugs to achieve immunosuppression (see "Preventive treatment" below). IGRA are not suitable for diagnosis of clinically manifest TB, because they do not distinguish between latent TB and active disease.

The principal techniques for diagnosis of active TB are direct microscopic demonstration of the pathogen, culture, and nucleic acid amplification tests (NAAT; generally polymerase chain reaction [PCR]–based procedures). The sample for testing should be obtained before the commencement of treatment, and investigation for *M. tuberculosis* should be specified on the request form, as it does not always form part of the routine program. Open pulmonary tuberculosis can be excluded if microscopy fails to detect acid-fast rods in samples of sputum collected on three separate days. Demonstration of *M. tuberculosis* in culture also demonstrates infectivity but TB diagnosis by culture takes several weeks to become positive. Microscopy of samples of sputum, bronchial secretion, or bronchoalveolar lavage (BAL) fluid is economical, quick, and represents a marker for the patient's infectiousness. However, its sensitivity is very variable (20% to 80%) and differs among investigators (19). The specificity of microscopy is also limited, because it cannot distinguish *M. tuberculosis* from nontuberculous mycobacteria (NTM). At least several days' culture are required for a positive result when fluorescence-based detection systems are used, while the growth of visible colonies on solid culture media can take up to 8 weeks. Culture nevertheless remains the gold standard of TB diagnosis (20, 21) and is of central importance for resistance testing. NAAT-based methods are characterized by their swiftness, relatively good sensitivity, and very high specificity (22). Moreover, many PCR-based methods permit conclusions regarding resistance to the commonly used substances to be drawn directly from sputum or other PCR-positive materials, thus enabling early detection of monoresistant or multiresistant TB. However, comprehensive testing of resistance to all available substances, e.g., via whole-genome sequencing of the strain concerned, requires culture. If extrapulmonary TB is suspected, aspirates, biopsy samples, or body fluids (urine, sperm, stool, cerebrospinal fluid) must also be investigated using the methods described above. It is essential to include TB among the differential diagnoses and send material not just for histopathology but also for microbiological examination.

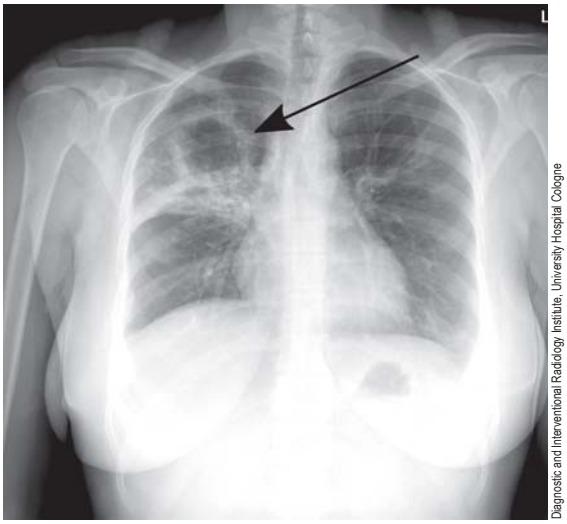

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Figure 1: Pulmonary tuberculosis with a large cavity (arrow) in the upper field of the right lung (chest radiograph, p.a. view)

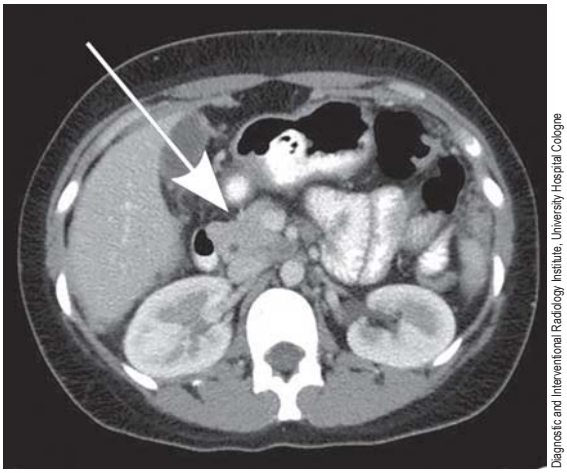

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Figure 2: Extrapulmonary manifestation of TB with abscess formation around the abdominal aorta (arrow) (abdominal computed tomography, axial section)

Imaging

Biplanar chest radiography remains the standard method for diagnosis of TB and for monitoring the effect of treatment *(Figure 1)*. Computed tomography (CT) achieves good results in the assessment of both lymphadenopathy (23) and endobronchial extension (24) and is superior to chest radiography for evaluation of disease activity (25, 26). Low-dose CT is recommended.

In primary TB, which is found principally in children and adolescents, one finds mostly inflammatory infiltrates—similar to lobar pneumonia—accompanied by lymphadenopathy. Around one fourth of patients with primary TB have pleural effusion,

TABLE 1

Drug treatment of tuberculosis

Drug	Duration of treatment (months)	Dosage (mg/kg BW/d)	Minimum/ maximum dose (mg) *
Isoniazid (INH)	6	5	200/300
Rifampicin (RMP)	6	10	450/600
Pyrazinamide (PZA)	2	25	1500/2500
Ethambutol (EMB)	2	15	800/1600

* The WHO guidelines only recommend maximum doses for INH and RMP.
The minimum doses for INH and RMP and the mimimum and maximum doses for PZA and EMB come not from the WHO, but from the pertinent consensus-based German guidelines (20).
BW, body weight; d, day

whereas cavity formation tends to be rare. Immunosuppressed persons, the elderly, and the very young are at elevated risk of miliary TB. In this case, multiple pulmonary nodules are seen particularly clearly on CT *(eFigure 1)*. In postprimary TB there is often cavity formation with necrosis and tissue destruction, preferentially in the upper lobes.

Various imaging modalities are available for diagnosis and monitoring of extrapulmonary manifestations, such as CT, magnetic resonance imaging (MRI), and sonography *(Figure 2, eFigure 2, eFigure 3)*. An algorithm for the diagnostic imaging of TB is shown in *eBox 1*.

Drug treatment

Standard treatment

The standard treatment for pulmonary TB comprises 2 months of quadruple therapy with isoniazid (INH), rifampicin (RMP), ethambutol (EMB), and pyrazinamide (PZA) followed directly by a further 4 months' dual administration of RMP and INH (20, 21, 27, 28) *(Table 1)*. Extrapulmonary and disseminated forms of TBsometimes require more extended treatment: lymph-node TB, 6 months (20, 29); articular or osseous TB, 9 months; TB of the central nervous system, 12 months (20, 21, 28). Particularly in disseminated TB, the duration of treatment should be individually adjusted according to the disease course. Doses higher than those listed in *Table 1* are generally not necessary. TB during pregnancy represents an indication for treatment *(eBox 2)*. In 2018, the Robert Koch Institute reported that information on the outcome of treatment was available for 84.5% of TB patients (5025 of 5949 cases) (6). The success rate was 81%. The data related to the year 2016; owing to the extended nature of treatment for TB, results for 2017 were not yet available. At 83%, the success rate for treatment of drug-susceptible TB was below the WHO target of 90%, but much higher than the success rate for drug-resistant TB (72%).

Resistance to standard drugs

Resistance to at least one substance (INH, EMB, RMP, PZA, streptomycin) was recorded for 12% to 14% of patients with TB in Germany between 2013 and 2017; in 3% of cases, multiple resistance (MDR-TB) was documented (6). By definition, MDR-TB is present whenever resistance at least to INH and RMP is found (20). In patients with monoresistance to RMP or INH, a fluoroquinolone (moxifloxacin, levofloxacin) can be used instead. The duration of treatment is then increased to a total of 6 to 9 months (INH resistance) or 18 to 20 months (RMP resistance), depending on the individual course (20). Patients with MDR-TB should be treated at centers possessing the necessary expertise.

Adverse effects of treatment

Severe adverse effects leading to a change in treatment occur in 4% to 9% of patients who receive the classic quadruple combination of INH, EMB, RMP, and PZA (30–32). Most adverse effects, however, are milder, such as gastrointestinal effects (nausea, vomiting) or exanthema (32), and should initially be treated symptomatically (20). Severe hepatic toxicity (elevation of transaminases to more than 3 to 5 times normal) occurs in 2.4% of cases and may necessitate temporary discontinuation of treatment (20, 21, 30, 32). Once the transaminase levels have returned to normal, the four antibiotics can be reintroduced one by one, enabling identification of the drug responsible for the toxicity in the given patient. This substance can then be replaced as advised in the guidelines (20, 33). Ophthalmological examination at 4-week intervals is recommended for early detection of the rare cases of optic neuroma (<1%) that occur in patients taking EMB (20, 32). Neurological complications such as peripheral neuropathy and psychosis are equally rare (<1%) (32, 34). Neuropathy occurs particularly in high-risk patients (e.g., existing pyridoxine deficiency, manifest polyneuropathy, pregnancy) receiving INH and can be avoided by administering 50 mg/d pyridoxine together with the INH (29). PZA regularly causes a usually clinically irrelevant elevation in serum uric acid. In the context of standard treatment, dose adjustment in the presence of kidney failure is required only for EMB and PZA.

Preventive treatment

The goal of preventive treatment is elimination of "resting" tuberculosis bacteria in persons with LTBI, reducing the likelihood of later reactivation. One indication for exclusion of LTBI is newly diagnosed HIV infection *(eBox 3)* (20). A comprehensive list of the indications for testing (by means of IGRA) and information on the subsequent preventive measures can be found in the pertinent guidelines (11, 20). Following a positive IGRA result, clinically manifest TB must be excluded before initiation of chemoprophylaxis. This is achieved by specific history taking, physical examination, and review of at least a chest radiograph (20). The guidelines supply precise directions for preventive treatment and describe the advantages and disadvantages of the different regimens (20).

TABLE 2

The estimated risk for the reactivation of tuberculosis during treatment with different biologics and recommendations for screening to detect latent tuberculosis (modified from [36–38])

Drug	Mechanism of action	Risk of reactivation	Recommendation
Anakinra Canakinumab Gevokizumab	IL-1 inhibition via receptor antagonism (anakinra), Ab to IL-1-β (canakinumab, gevokizumab)	Unknown (theoretical risk of development of active TB)	IGRA to screen for LTBI before commencement of treatment*
Mepolizumab Reslizumab	Ab to IL-5 (reduction of eosinophil granulocytes)	No apparent increase in infection risk	No screening (IGRA)
Tocilizumab Siltuximab	Ab to IL-6 receptor (tocilizumab), Ab to IL-6 (siltuximab)	General infection risk comparable with observations of anti-TNF-α treatment (probably somewhat lower for TB)	IGRA to screen for LTBI before commencement of treatment*
Ustekinumab	Ab to IL-12 and IL-23 (inhibits T-cell differentiation)	Unknown (theoretical risk of development of active TB)	IGRA to screen for LTBI before commencement of treatment*
Secukinumab Ixekizumab Brodalumab	Ab to IL-17A (secukinumab, ixekizumab), Ab to IL-17 receptor (brodalumab)	Rather low (theoretical risk of development of active TB)	IGRA to screen for LTBI before commencement of treatment*
Omalizumab	Ab to IgE	No	No screening (IGRA)
Eculizumab	Ab to complement factor C5 (inhibits formation of membrane attack complex of complement system)	No	No screening (IGRA)
Blinatumomab	Ab to CD3 (T cell) and CD19 (B cell)	No	No screening (IGRA)
Rituximab Ocrelizumab Ofatumumab Obinutuzumab	Ab to CD20 (B cell)	No	No screening (IGRA)
Alemtuzumab	Ab to CD52 (destroys CD52-positive B cells and T cells)	General infection risk comparable with observations of anti-TNF-α treatment (probably somewhat lower for TB)	IGRA to screen for LTBI before commencement of treatment*
Abatacept	Fusion protein with binding to CD80/86 (inhibits T-cell response)	Unknown (theoretical risk of development of active TB)	IGRA to screen for LTBI before commencement of treatment*

* If the IGRA test result is positive, preventive anti-TB treatment should be carried out before the immunosuppressive treatment.
Ab, Antibody; CD, cluster of differentiation of surface antigens; Ig, immunoglobulin; IGRA, interferon-gamma release assay; IL, interleukin; LTBI, latent tuberculosis infection; TB, tuberculosis

Chemoprophylaxis in patients receiving immunosuppressive drugs

Numerous immunosuppressive drugs (biologics) for the treatment of autoimmune diseases and cancer have ben developed in recent years. For many of these substances the degree of risk for reactivation of latent TB is not yet known. It has been confirmed that treatment with TNF-α antagonists is associated with elevated risk. Thus, LTBI has to be excluded before these agents are given. Testing for LTBI and administration of chemoprophylaxis should also be considered prior to planned immunosuppression in organ or bone marrow transplantation. Estimates of the risk for reactivation of TB involved in treatment with other immunomodulatory drugs can be found in *Table 2* (35–38). These recommendations are based on expert opinion formed by experimental findings from animal studies and by clinical observation.

Conclusion

Tuberculosis is a rare disease in Germany nowadays, but for that very reason it should not be forgotten. A timely specific diagnostic work-up followed by prompt treatment can effectively prevent further spread of the disease and avoid a severe course of illness in the individual patient (39). In industrialized countries, TB occurs most frequently in immigrants and in persons with impaired immune defenses. The growing use of immunosuppressive drugs to treat various illnesses broadens the spectrum of persons at risk. IFN-γ release assays (IGRA) are increasingly being applied to detect latent TB infection (LTBI) in these groups of patients so that they can receive preventive treatment.

Conflict of interest statement
Dr. Rademacher has received lecture fees from Omniamed.
The remaining authors declare that no conflict of interest exists.

Key messages

- The immigration of people from regions of high tuberculosis incidence requires elevated awareness of this disease in Germany.
- Pulmonary tuberculosis is the most commonly occurring but by no means the only form of the disease. Extrapulmonary and disseminated manifestations are increasingly being observed, and in 2017 extrapulmonary tuberculosis accounted for 26% of the cases in Germany.
- An effective vaccine would have a huge effect on the global burden of tuberculosis. Studies are under way, but no vaccine is yet available for routine application.
- Alongside microscopy and culture, the recently developed nucleic acid amplification tests (NAAT) represent an important means of diagnosis and are also useful for the swift detection of multiresistant strains of tuberculosis.
- The proportion of cases of tuberculosis caused by resistant strains is increasing worldwide. In Germany, resistance to at least one of the substances used in first-line treatment was documented in 12% to 14% of the cases registered during the period 2013 to 2017. This trend has considerable effects on the response to treatment, the prognosis, and the treatment costs.

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References

1. WHO: Global Tuberculosis Report. 2018. www.who.int/tb/publications/global_report/en/ (last accessed on 1 August 2019).
2. Houben RM, Dodd PJ: The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med 2016; 13: e1002152.
3. Brodhun B, Altmann D, Hauer B, et al.: Bericht zur Epidemiologie der Tuberkulose in Deutschland für 2015. Robert Koch-Institut 2016. www.rki.de/DE/Content/InfAZ/T/Tuberkulose/Download/TB2015.pdf (last accessed on 1 August 2019).
4. Perumal N, Hauer B: Ein historisches Signal für den Kampf gegen Tuberkulose – Deutschland muss das Momentum nutzen. Epid Bull 2019; 11/12: 95–6
5. Haas W: Bericht zur Epidemiologie der Tuberkulose in Deutschland für 2001. 2003. www.rki.de/DE/Content/InfAZ/T/Tuberkulose/Download/TB2001.pdf?__blob=publicationFile (last accessed on 1 August 2019).
6. Brodhun B, Altmann D, Hauer B: Bericht zur Epidemiologie der Tuberkulose in Deutschland für 2017. Epidemiologisches Bulletin 2018; 1–99. www.rki.de/DE/Content/InfAZ/T/Tuberkulose/Download/TB2017.pdf (last accessed on 1 August 2019)
7. Brodhun B, Altmann D, Hauer B, et al.: Bericht zur Epidemiologie der Tuberkulose in Deutschland für 2016. Epidemiologisches Bulletin 2017; 1–102. www.rki.de/DE/Content/InfAZ/T/Tuberkulose/Download/TB2016.pdf (last accessed on 1 August 2019).
8. Churchyard G, Kim P, Shah NS, et al.: What we know about tuberculosis transmission: an overview. J Infect Dis 2017; 216: 629–35.
9. Stewart GR, Robertson BD, Young DB: Tuberculosis: a problem with persistence. Nat Rev Microbiol 2003; 1: 97–105.
10. WHO: Guidelines on the management of latent tuberculosis infection. 2015. https://apps.who.int/iris/bitstream/handle/10665/136471/9789241548908_eng.pdf;jsessionid=1513688E04508E6CC7FAE60613511D41?sequence=1 (last accessed on 1 September 2019)
11. WHO: Latent TB Infection: Updated and consolidated guidelines for programmatic management. 2018. https://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf (last accessed on 1 September 2019)
12. Murdaca G, Spano F, Contatore M, et al.: Infection risk associated with anti-TNF-alpha agents: a review. Expert Opin Drug Saf 2015; 14: 571–82.
13. Furin J, Cox H, Pai M: Tuberculosis. Lancet 2019; 393: 1642–56.
14. Zumla A, Raviglione M, Hafner R, von Reyn CF: Tuberculosis. N Engl J Med 2013; 368: 745–55.
15. Gonzalez-Garcia A, Fortun J, Elorza Navas E, et al.: The changing epidemiology of tuberculosis in a Spanish tertiary hospital (1995–2013). Medicine (Baltimore) 2017; 96: e7219.
16. Suarez I, Maria Funger S, Jung N, et al.: Severe disseminated tuberculosis in HIV-negative refugees. Lancet Infect Dis 2019; pii: 1473–3099 (19) 30162–8. [Epub ahead of print].
17. Bradby H, Humphris R, Newall D, Phillimore J: Public health aspects of migrant health: a review of the evidence on health status for refugees and asylum seekers in the european region. Copenhagen: WHO Regional Office for Europe; 2015. WHO Health Evidence Network Synthesis Reports. www.euro.who.int/__data/assets/pdf_file/0004/289246/WHO-HEN-Report-A5–2-Refugees_FINAL.pdf (last accessed on 1 August 2019).
18. ECDC: Migrant Health: Background note to the 'ECDC Report on Migration and Infectious Diseases in the EU'. 2009. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/0907_TER_Migrant_health_Background_note.pdf (last accessed on 1 September 2019)
19. Pfyffer G: Mycobacterium: General characteristics, laboratory detection, and staining procedures. In: Murray PR, Baron EJ, Landry, ML, Jorgensen JH, Pfaller MA, eds.: Manual of clinical microbiology, 9th edition, Washington DC: American Society for Microbiology Press 2007; 543–72.
20. Schaberg T, Bauer T, Brinkmann F, et al.: [Tuberculosis guideline for adults – guideline for diagnosis and treatment of tuberculosis including LTBI testing and treatment of the German Central Committee (DZK) and the German Respiratory Society (DGP)]. Pneumologie 2017; 71: 325–97.
21. WHO: Treatment of tuberculosis: guidelines—4th edition. World Health Organization Press 2010. https://apps.who.int/iris/bitstream/handle/10665/44165/9789241547833_eng.pdf (last accessed on 1 September 2019).
22. WHO: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. https://www.who.int/tb/publications/xpert-mtb-rif-assay-diagnosis-policy-update/en (last accessed on 1 August 2019).
23. Im JG, Itoh H, Shim YS, et al.: Pulmonary tuberculosis: CT findings--early active disease and sequential change with antituberculous therapy. Radiology 1993; 186: 653–60.
24. Lee KS, Im JG: CT in adults with tuberculosis of the chest: characteristic findings and role in management. Am J Roentgenol 1995; 164: 1361–7.
25. Yeh JJ, Chen SC, Teng WB, et al.: Identifying the most infectious lesions in pulmonary tuberculosis by high-resolution multi-detector computed tomography. Eur Radiol 2010; 20: 2135–45.
26. Geng E, Kreiswirth B, Burzynski J, Schluger NW: Clinical and radiographic correlates of primary and reactivation tuberculosis: a molecular epidemiology study. JAMA 2005; 293: 2740–5.
27. World Health Organization: WHO guidelines approved by the Guidelines Review Committee. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and Rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children: Policy Update. Geneva: World Health Organization. 2013. www.ncbi.nlm.nih.gov/books/NBK258608/pdf/Bookshelf_NBK258608.pdf (last accessed on 1 September 2019).
28. Nahid P, Dorman SE, Alipanah N, et al.: Official American Thoracic Society/Centers for disease control and prevention/infectious diseases. Society of America Clinical Practice Guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis 2016; 63: e147–e95.
29. WHO: WHO treatment guidelines for drug-resistant tuberculosis (2016 update). www.hoint/tb/areas-of-work/drug-resistant-tb/treatment/resources/en/ 2016. (last accessed on 1 August 2019).
30. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D: Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med 2003; 167: 1472–7.
31. Ormerod LP, Horsfield N: Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. Tuber Lung Dis 1996; 77: 37–42.

32. Gulbay BE, Gurkan OU, Yildiz OA, et al.: Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. Respir Med 2006; 100: 1834–42.
33. Sharma SK, Singla R, Sarda P, et al.: Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clin Infect Dis 2010; 50: 833–9.
34. Kass JS, Shandera WX: Nervous system effects of antituberculosis therapy. CNS drugs 2010; 24: 655–67.
35. Cantini F, Nannini C, Niccoli L, et al.: Guidance for the management of patients with latent tuberculosis infection requiring biologic therapy in rheumatology and dermatology clinical practice. Autoimmun Rev 2015; 14: 503–9.
36. Mikulska M, Lanini S, Gudiol C, et al.: ESCMID Study Group for Infections in Compromised Hosts (ESGICH). Consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (Agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). Clin Microbiol Infect 2018; 24 (Suppl 2): 71–82.
37. Winthrop KL, Mariette X, Silva JT, et al.: ESCMID Study Group for Infections in Compromised Hosts (ESGICH). Consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). Clin Microbiol Infect 2018; 24 (Suppl 2): 21–40.
38. Epstein DJ, Dunn J, Deresinski S: Infectious complications of multiple sclerosis therapies: implications for screening, prophylaxis, and management. Open Forum Infect Dis 2018; 5: 174.
39. van Cutsem G, Isaakidis P, Farley J, Nardell E, Volchenkov G, Cox H: Infection control for drug-resistant tuberculosis: early diagnosis and treatment is the key. Clin Infect Dis 2016; 62 (Suppl 3): 238–43.

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Supplementary material
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eBoxes, eFigures:
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CLINICAL SNAPSHOT

Acute Abdomen in Chronic Anorexia Nervosa with Episodes of Bulimia

A 48-year-old woman reported acute abdominal pain for the previous 3 hours. Clinical examination of the underweight patient (BMI 17.4) found a tight abdomen with diffuse guarding and no bowel sounds. Abdominal computed tomography showed a massively dilated, tightly filled stomach extending into the pelvis. The duodenal bulb and the descending part of the duodenum were dilated, but all other small intestinal loops were narrow. An endoscope was inserted and large quantities of brown fluid and partly digested food were aspirated. Inspection as far as the descending duodenum revealed no obstruction. After endoscopy the patient's abdomen was no longer dilated and she was free of pain. She reported that before the pain started she had eaten food amounting to around 6000 kcal and drunk 3 liters of cola, all in the space of 1 hour. In contrast to her bulimic episodes over the foregoing 24 years, she had been unable to induce vomiting. High small intestinal ileus caused by obstruction of the horizontal segment of the duodenum due to acute gastric dilatation is a rare, potentially fatal (gastric necrosis, gastric rupture) complication of extreme overeating.

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The authors declare that no conflict of interest exists.

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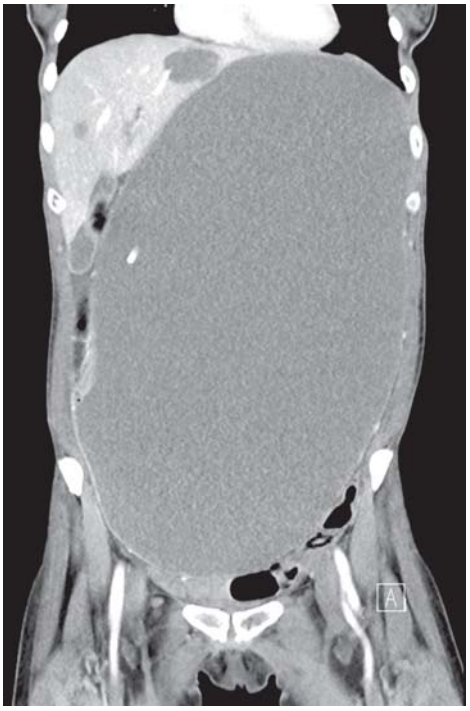

Dilated stomach extending into the pelvis

Supplementary material to:

The Diagnosis and Treatment of Tuberculosis

by Isabelle Suárez, Sarah Maria Fünger, Stefan Kröger, Jessica Rademacher, Gerd Fätkenheuer, and Jan Rybniker

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eReferences

e1. Ellis PK, Martin WJ, Dodd PJ: CD4 count and tuberculosis risk in HIV-positive adults not on ART: a systematic review and meta-analysis. Peer J 2017; 5: e4165.

e2. Yorke E, Atiase Y, Akpalu J, Sarfo-Kantanka O, Boima V, Dey ID: The bidirectional relationship between tuberculosis and diabetes. Tuberc Res Treat 2017; 2017: 1702578.

e3. Rogerson TE, Chen S, Kok J, et al.: Tests for latent tuberculosis in people with ESRD: a systematic review. Am J Kidney Dis 2013; 61: 33–43.

e4. Odone A, Tillmann T, Sandgren A, et al.: Tuberculosis among migrant populations in the European Union and the European Economic Area. Eur J Public Health 2015; 25: 506–12.

e5. Getahun H, Gunneberg C, Granich R, Nunn P: HIV infection-associated tuberculosis: the epidemiology and the response. Clin Infect Dis 2010; 50 (Suppl 3): 201–7.

e6. UNAIDS: Joint United Nations Programme on HIV/AIDS. www.unaids.org/en (last accessed on 29 August 2019).

e7. Karo B, Haas W, Kollan C, et al.: Tuberculosis among people living with HIV/AIDS in the German ClinSurv HIV Cohort: long-term incidence and risk factors. BMC Infect Dis 2014; 14: 148.

e8. Aabye MG, Ravn P, PrayGod G, et al.: The impact of HIV infection and CD4 cell count on the performance of an interferon gamma release assay in patients with pulmonary tuberculosis. PLoS One 2009; 4: e4220.

e9. Telisinghe L, Amofa-Sekyi M, Maluzi K, et al.: The sensitivity of the QuantiFERON((R))-TB Gold Plus assay in Zambian adults with active tuberculosis. Int J Tuberc Lung Dis 2017; 21: 690–6.

e10. University of Licerpool: Druginteractions. www.hiv-druginteractions.org. (last accessed on 29 August 2019).

e11. Seelbach-Göbel: 240. Stellungnahme des DZK in Zusammenarbeit mit FZB, DGI, DGPI, GPP, DGGG, DRG und DGMP zum Tuberkulosescreening bei Schwangeren im Kontext von § 36 (4) Infektionsschutzgesetz (IfSG). 2017.

e12. Feiterna-Sperling C, Brinkmann F, Adamczick C, et al.: [Consensus-based guidelines for diagnosis, prevention and treatment of tuberculosis in children and adolescents – A guideline on behalf of the German Society for Pediatric Infectious Diseases (DGPI)]. Pneumologie 2017; 71: 629–80.

eBOX 1

Algorithm for diagnostic imaging in tuberculosis

- **Radiography**
  - Primary imaging procedure for:
    - Suspected tuberculosis
    - Screening
    - Diagnosis
    - Treatment monitoring
- **Computed tomography**
  - Secondary procedure for more detail regarding:
    - Lymphadenopathy
    - Exclusion of differential diagnoses
    - Complications
    - Assessment of tuberculosis disease activity
- **Magnetic resonance imaging**
  - Specific investigation of extrapulmonary tuberculosis

eBOX 3

Tuberculosis and HIV infection

The risk of tuberculosis (TB) is 20 times higher in HIV-positive persons than in those who are negative for HIV (1, e5–e6). The incidence of tuberculosis in the HIV-infected population in Germany is not precisely known, but is low overall. Nevertheless, because the risk of reactivation is high the German guidelines recommend that every new diagnosis of HIV should be followed by IGRA to exclude LTBI. In the event of a positive IGRA result, clinically manifest TB must be definitively ruled out, since failure to recognize active TB might have serious consequences for the patient. In the nationwide German KlinSurv cohorts, a total of 233 cases of active TB were registered in 11 693 HIV patients between 2001 and 2011 (e7). When interpreting the IGRA test results, it must be remembered that the sensitivity of immunological diagnostic techniques is reduced at low levels of CD4+ T cells (e8–e9). In addition, an HIV test should always be carried out—with the patient's written consent—after a new diagnosis of TB (20).

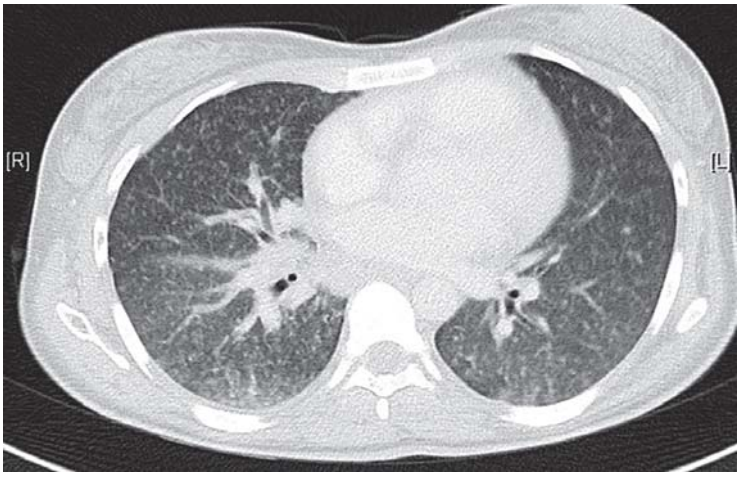
The course of TB is often atypical in patients with HIV coinfection: in some cases oligosymptomatic, in others, severe (14). The treatment of HIV/TB coinfection should take place at a specialized center. The possibility of drug interactions with the antiretroviral treatment (ART) for HIV must always be borne in mind (e10).

Especially in the presence of reduced levels of CD4+ T cells, the initiation of ART may be followed by immune reconstitution inflammatory syndrome (IRIS), characterized by worsening or first occurrence of clinical symptoms (e.g., fever, lymph-node swelling). In severe or moderately severe cases, prednisolone is used (1.5 mg/kg body weight for 2 weeks, then 0.75 mg/kg body weight for a further 2 weeks) (20).

eBOX 2

Tuberculosis and pregnancy

In the event of well-founded suspicion of tuberculosis (TB), chest radiography is justified even in pregnant women (e11). TB during pregnancy is a clear indication for treatment. The conventional first-line drugs (RMP, INH, EMB, PZA) are all considered safe in pregnancy (10). Breastfeeding is possible during treatment, provided the mother does not have infectious pulmonary TB and resistance-oriented prophylaxis can be initiated in the child (e12). Tuberculous mastitis is extremely rare but should be ruled out by clinical examination (e12).



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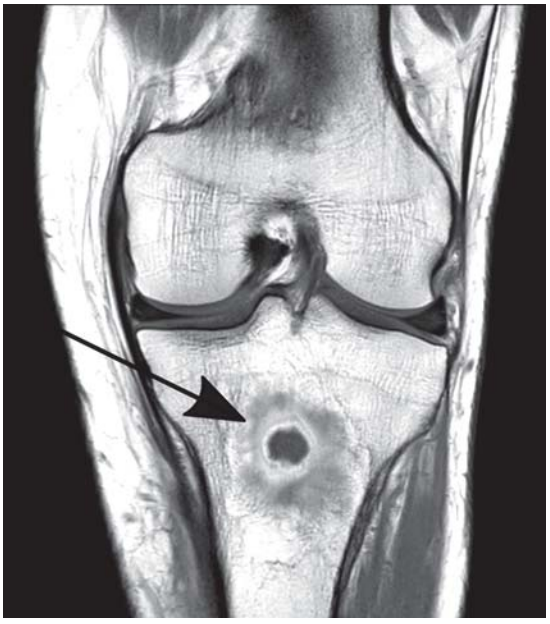
eFigure 1: Typical appearance of miliary tuberculosis in a patient with HIV (thoracic computed tomography, axial section)



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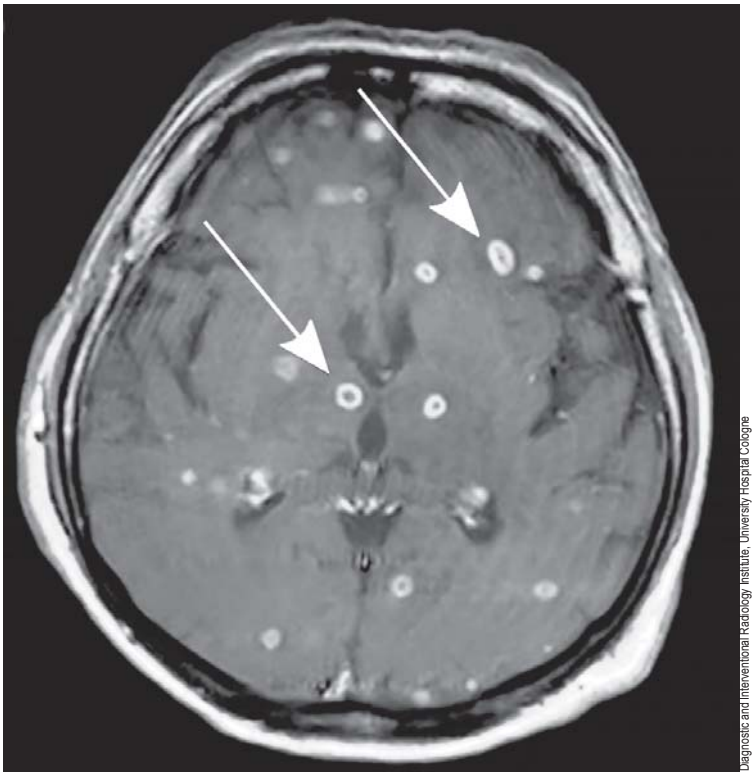
eFigure 2: Osseous tuberculosis with a lesion in the tibial head (arrow) (magnetic resonance imaging, coronal section)



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eFigure 3: Multiple ring-like contrast-enhanced foci in cerebral tuberculosis (arrows) (magnetic resonance imaging, axial section)