Alper Sener · Hakan Erdem *Editors*

Extrapulmonary Tuberculosis

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Contents

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Chapter 1
Epidemiology of Extrapulmonary Tuberculosis

Ekaterina Kulchavenya, Kurt G. Naber, and Truls Erik Bjerklund Johansen

1.1 Introduction

Tuberculosis (TB) remains one of the world's deadliest communicable diseases and is regarded a major global health problem. In 2012, an estimated 8.6 million people developed TB, and 1.3 million died from the disease (including 320,000 deaths among HIV-positive people). In 2013, an estimated 9.0 million people developed TB, and 1.5 million died from the disease, 360,000 of whom were human immunodeficiency virus (HIV)-positive. In 2014, TB again killed 1.5 million people (1.1 million HIV-negative and 0.4 million HIV-positive). Worldwide, 9.6 million people were estimated to have fallen ill with TB in 2014: 5.4 million men, 3.2 million women, and 1.0 million children. Globally, 12% of the 9.6 million new TB cases in 2014 were HIV-positive. Thus, there is a negative trend with increased incidence from 8.6 million people to 9.6 million people and mortality – from 1.3 million to 1.5 million during 3 years (from 2012 until 2014) [1–4]. Given that most deaths from TB are preventable, the death toll from the disease is unacceptably high.

TB is a multisystem disease with a myriad of presentations and manifestations; it can affect almost any organ or tissue, excluding only hair and nails. While the WHO has recognized TB as a global problem, this applies to TB as a whole and especially to pulmonary TB (PTB). TB in general has not only medical but also

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great social importance as extrapulmonary TB (EPTB) is one of the most common reasons for both male and female infertility, especially in endemic regions, and in some studies, sexual transmission of TB has also been described [5–7].

1.2 Epidemiology of Extrapulmonary Tuberculosis

Over the last decades, extrapulmonary locations of the disease have become more frequent. This is thought to be due to the increased prevalence of acquired immune deficiency syndrome and the increased number of organ transplants [8, 9]. Although extrapulmonary tuberculosis (EPTB) is less frequent than PTB and is a secondary target for national TB control programs, its significance has increased worldwide during the HIV epidemic [10]. The proportion of EPTB varies according to geographical region, comorbidity, presenting symptoms, epidemic situation, time period, etc. The most commonly affected sites of EPTB in Korea were pleura, followed by lymph nodes. Gastrointestinal organs, bones and joints, the central nervous system, and urogenital TB (UGTB) were the least common sites [11].

In Bangladesh EPTB constitutes about 15–20% of all cases of TB patients, and it is more common in low socioeconomic groups (60%). The incidence of EPTB was as high as 55% in the age group 16–45 years (mean age 35.67 ± 14.6 years) where female patients accounted for 60% of cases [12]. The rate of EPTB in Brazil increased from 6.8 per 100,000 people in 1981 to 7.0 per 100,000 people in 1991. In the period between 2001 and 2009, a 23.7% reduction was seen in the number of PTB cases, but only a 5.9% reduction in the number of cases of EPTB was found [10].

EPTB constitutes 15–20% of tuberculosis cases in India. The outcome of directly observed treatment short-course treatment of EPTB has been evaluated in 2219 patients. There were more males in the age group 15–45 years. Overall treatment completion rate was 84% in EPTB patients. Treatment completion rate was 66% in HIV-positive patients compared to 86% in HIV-negative EPTB patients. Individually, observed treatment completion rates were as follows: lymph node TB 90.9%, UGTB 92.6%, bone and joint TB 86%, pleural effusion TB 84.7%, abdominal TB 76%, and central nervous system (CNS) TB (tuberculoma and meningitis) 63.7%. The site of EPTB was not recorded in 173 (7.8%) patients [13].

In most cases, EPTB occurs in immunosuppressed patients as part of a severe illness due to hematogenous spread. In some regions authors have found that extrathoracic involvement most often means abdominal organs and the urogenital tract and less commonly the central nervous system (CNS) and the musculoskeletal system. Most frequently, computed tomography (CT) is used for detecting extrathoracic TB manifestations, except for CNS and musculoskeletal manifestations, where contrast-enhanced magnetic resonance imaging (MRI) is the gold standard. Due to unspecific symptoms, the diagnosis is often delayed [14].

Among 253,299 cases, reported from 1993 to 2006 in the United States, 73.6% were PTB, and 18.7% were EPTB, including lymphatic (40.4%), pleural (19.8%),

bone and/or joint (11.3%), genitourinary (6.5%), meningeal (5.4%), peritoneal (4.9%), and unclassified EPTB (11.8%) cases. Compared with PTB, EPTB was associated with female sex and foreign birth, almost equally associated with HIV status, and negatively associated with multidrug resistance and several tuberculosis risk factors, especially homelessness and excess alcohol use [15].

Among a total of 427,548 TB cases, 57,217 (13.4%) were EPTB in Brazil, and 13,989 (3.3%) were concurrent pulmonary and extrapulmonary TB. Patients with EPTB were mainly white (16.7%), and most patients (29.1%) had 5–8 years of education. Among comorbidities, HIV infection was prominent. Ethanol abuse, diabetes mellitus, and mental illness were associated with PTB, but not with EPTB [10].

The spectrum of EPTB in Brazil is shown in Fig. 1.1.

In Brazil, although EPTB primarily affects adults, one-fourth of all cases of EPTB occurred in children less than 14 years of age [10].

For comparison we show the spectrum of EPTB in Siberia in Fig. 1.2 over the years 1999–2011 [16]. The percentage of UGTB went down, and the bone and joint TB went up, in 2011 both representing about one-third of EPTB.

Tuberculosis is a very common disease in Bangladesh. A retrospective histopathological study was performed to assess the distribution of extrapulmonary tuberculosis (EPTB) in various organs by examination of 216 biopsy specimens. The majority of cases were females (126). Lymph nodes were the most common site of EPTB (62.9%) followed by the skin and subcutaneous tissue (17.59%), intestine (11.11%), breast (2.77%), female genital tract (2.31%), male genital tract (1.38%), and bone and joint (1.85%). Out of 136 cases of tubercular lymphadenitis, 96 (70.58%) were cervical, 18 (13.23%) were axillary, 12 (3.82%) were mesenteric, and 10 (7.35%) were inguinal. Cervical lymph nodes are very common sites for EPTB [17].

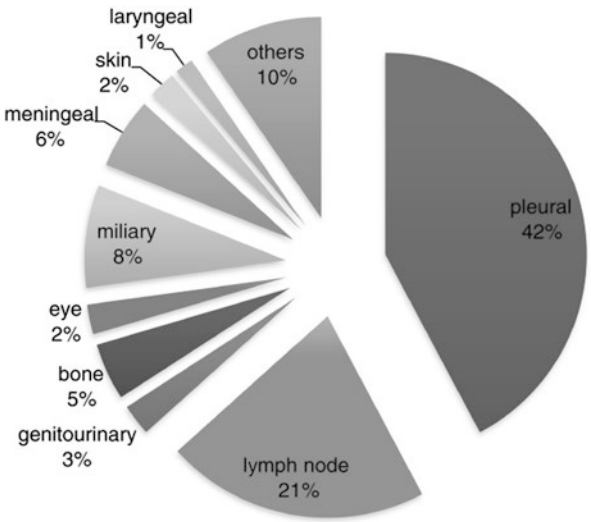

Fig. 1.1 Spectrum of EPTB in Brazil [10]

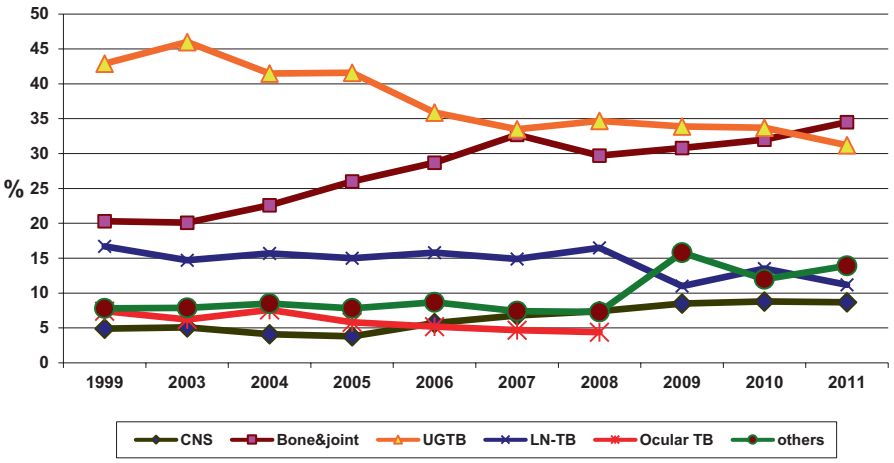

Fig. 1.2 Spectrum of EPTB in Siberia [16]. Annotation: CNS, TB of the central nervous system; bone and joint, TB of the bone and joints; UGTB, urogenital TB; LN-TB, lymphonodal TB

Table 1.1 Percentage of EPTB among all forms of TB in various countries

Country	% of EPTB	Reference
Bangladesh	20	[15]
India	15–20	[16]
Brazil	13.4	[7]
Poland	5.7	[24]

Purely EPTB was diagnosed in 415 patients in Poland in 2013 (5.7% of all registered cases). Most patients had pleural TB (142 cases) followed by peripheral lymph node TB (104 cases), UGTB (58 cases), and bone and joint TB (44 cases) [18].

The percentage of EPTB among all forms of TB is shown in the Table 1.1.

Tables comparing spectra of EPTB can be misleading, as classification of EPTB varies from country to country. In some regions, for example, in Brazil, miliary TB is considered EPTB, although in fact it is not only EPTB but a totally generalized TB. In some countries pleural TB and laryngeal TB are considered EPTB and in others PTB. Some countries count only isolated EPTB as such; others count also EPTB in combination with PTB. Some countries count abdominal TB, skin TB, etc., separately; some classify these forms together as "others." Although the true epidemiological figures of EPTB may be incomplete due to diagnostic problems and different statistical reports, the medical and social importance of EPTB remains undoubted.

1.3 Urogenital Tuberculosis (UGTB)

UGTB is defined as an infectious inflammation of the urogenital system and its organs in any combination, caused by *Mycobacterium tuberculosis* (Mtb) or *M. bovis*. By definition it includes both urological and gynecological TB (female genital TB) [16, 19, 20].

UGTB is one of the most frequent forms of EPTB. UGTB is the fourth most common manifestation of extrapulmonary TB, but it is often underdiagnosed by clinicians because of few and non-specific symptoms and insidious disease courses [21]. Authors from North America considered UGTB even as the third most common form of EPTB after pleural TB and lymphatic TB [22].

Starting with a pulmonary focus, 2–20% of patients develop UGTB through hematogenous spread to the kidneys, prostate, and epididymis; through the descending collecting system to the ureters, bladder, and urethra; and through the ejaculatory ducts to the genital organs. In Brazil UGTB occurs at all ages, but it is predominant in males in their fourth and fifth decades. In other countries the sex-age proportions may be different [23]. UGTB is a serious, insidious disease, generally developing symptoms only at a late stage, which leads to diagnostic delay with the consequence of urogenital organ destruction. There are reports of patients with renal failure as their initial clinical presentation. Figueiredo et al. noted that although the condition has been long recognized by nephrologists, urologists, and infectious disease specialists, UGTB is still largely unknown by other physicians [23].

In the pre-antibacterial era the prevalence of UGTB was higher: every fifth urological inpatient had UGTB, and more than a third of all pyonephrosis cases was due to TB. In that period, UGTB patients were mostly young people, equally male and female [23]. Now UGTB is the most common form of EPTB in countries with epidemic TB, but in countries with low incidence rates, UGTB is rarer [22, 25]. In developed countries, urogenital manifestations are responsible for over 40% of extrapulmonary cases [26]. In Europe UGTB is diagnosed more often in migrants than in the native population [27]. Renal involvement in TB infection is underdiagnosed in most health-care centers, and it can be a part of a disseminated infection as well as a localized urogenital disease [8]. This disease should be suspected in patients with unexplained urinary tract infections, especially in immunocompromised patients and/or in patients coming from endemic areas [8].

Today the proportion of UGTB among all extrapulmonary forms of TB varies depending on region, epidemic situation, comorbidity, awareness of doctors and population, time period, etc. Some authors consider UGTB to be the third most common form of EPTB accounting for 15–20% and even 40% of EPTB cases [22, 25, 26], while other authors report about 4–17% only [8, 25, 26].

In Italy UGTB represents about 27% of all extrapulmonary localizations of TB and may be due either to a disseminated infection or to a primary urogenital localization [9]. Although UGTB is one of the most common forms of EPTB in countries with epidemic TB, the proportion of UGTB is lower in countries with low incidence rates of TB [16, 19, 20]. UGTB was lowest among all extrapulmonary sites in Korea

[11]. Of 135 patients with extrapulmonary TB diagnosed in Korea between 2006 and 2013, only 6 (4.4%) had UGTB [28]. Among 415 Polish patients diagnosed with extrapulmonary TB, 58 (14.0%) had UGTB [18]. In Turkey UGTB was diagnosed in 5.4% of all extrapulmonary sites [29]. Surprisingly, in Bangladesh the proportion of UGTB was also low [12]. Proportion of UGTB among EPTB is shown in Table 1.2.

UGTB is often underestimated by clinicians because of few and non-specific symptoms and insidious disease courses. Reported statistics may therefore be falsely low [19].

The occurrence of UGTB in the Siberian and Far Eastern Federal Districts of Russia was analyzed for the period 1999–2015. The highest proportion of UGTB among EPTB was found in 2003 (46%), the lowest in 2014 (22.9%). According to outpatient medical records, the proportions of patients with stage 1, stage 2, and cavernous forms of nephrotuberculosis ranged from 21.2% to 37%, 26% to 53.5%, and 21.6% to 37%, respectively. The incidence of prostate tuberculosis ranged from 0 in 2003 and 7.1% in 2008 to 54.2% in 2013, with an average of 33.9% [30].

Currently, it is impossible to estimate the true incidence of UGTB in eastern Russia. Every fourth UGTB patient was under medical evaluation with a wrong diagnosis for 5 or more years. Introduction of new technologies has led to an improvement of bacteriological verification of UGT and increased prostate tuberculosis detection rate to 35.7% of all cases of UGTB [30].

After screening 1036 cases of suspected urinary tuberculosis (UTB) during 2009 to 2014, 193 patients with UTB were enrolled to investigate the epidemiology, clinical features, and drug-resistance profile. The most common presenting symptoms were urinary irritation (61.1%) and lumbago (49.2%). There were high proportions of microscopic hematuria (63.2%) and microscopic proteinuria (45.6%). The positive rate for TB-DNA in urine was 66.3%. The positive rate for culture was 13.1%, and for smear it was 9.8% only. The total rate of drug-resistant Mtb (resistant to at least 1 drug) was 39.7%, of which 20.7% was multidrug-resistant Mtb (resistant to at least rifampicin and isoniazid simultaneously). Molecular diagnostics is crucial for the definite diagnosis of UGTB. Real-time polymerase chain reaction for TB-DNA identification instead of culture and genotype tests for estimation of drug resistance of Mtb is recommended as routine assays for patients with suspected UGTB [31].

To estimate the prevalence and spectrum of kidney TB (KTB) in children and teenagers in an epidemic region, the histories of 131 patients with UGTB in Siberia and 819 patients with UGTB in Kyrgyzstan were reviewed [32]. In Siberia only two

Table 1.2 Proportion of UGTB among EPTB in various countries

Country	% of UGTB among all EPTB	Reference
Italy	27.0	[21]
Korea	4.4	[23]
Poland	14.0	[24]
Turkey	5.4	[25]
Siberia	22.9–46.0	[26]

children and one teenager with UGTB were found (2.3% of the cohort of UGTB); all had KTB stage 1. In Kyrgyzstan 17 children and 21 teenagers were diagnosed with UGTB (4.6% of all UGTB patients). All had a long history and had undergone surgical interventions, six had fistulae, and two teenagers had microcystis (bladder TB stage 4). KTB stage 1 was diagnosed in two children only, KTB stage 2 in four patients, KTB stage 3 in eight, and KTB stage 4 in three children. Thus, 64.5% of patients were diagnosed in a late and complicated stage [32].

UGTB may be due either to a disseminated infection or to a primary urogenital localization [8]. Renal involvement in TB can be part of a disseminated infection or a localized genitourinary disease [9]. Awareness of renal TB is urgently needed by physicians for suspecting this disease in patients with unexplained urinary tract abnormalities, mainly in those with immunosuppression and those coming from TB-endemic areas [9].

The risk of TB is significantly increased in chronic kidney disease [33]. The link between chronic kidney disease and TB has been known for more than 40 years, but the interaction between these two diseases is still poorly understood. Dialysis and renal transplant patients appear to be at a higher risk of TB, in part related to immunosuppression along with socioeconomic, demographic, and comorbid factors [34–36].

1.4 Lymph Node Tuberculosis

The appearance of enlarged lymph nodes in granulomatous diseases, such as TB and sarcoidosis, can be very similar to that of metastatic lymph nodes or lymphomas, and ultrasound is commonly used in the early diagnostic evaluation. Anechoic or hypoechoic areas in a lymph node can represent necrosis or metastatic hemorrhages but also suppuration in inflamed lymph nodes. Patients diagnosed with lymph node abnormalities may be referred for ultrasound-guided targeted fine-needle aspiration biopsy or a lymph node extirpation for histopathological examination and final diagnosis [37].

In Bangladesh lymph nodes are the most common site of involvement (50%) [12]. In India the commonest sites of EPTB were also lymph nodes (34.4%), as well as in Turkey (39.4%) [28]. Lymph node involvement was more common in females (58%) [13].

The diagnostic value of interferon-gamma release assays (IGRA) in TB varies a lot with different sites of infections, with higher sensitivity in chronic forms of TB such as lymph node TB. IGRA exhibits high diagnostic accuracy in TB lymphadenitis. The diagnostic value of IGRA differs by different IGRA methods, ethnicity, and lymphadenitis location. The technology is more applicable in TB prevalent areas [38].