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REVIEW

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Extrapulmonary Tuberculosis in Federation of Bosnia and Herzegovina

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ABSTRACT

Introduction: Health Introduction: The two types of tuberculosis (TB) are: pulmonary TB (PTB) and extrapulmonary TB (EPTB). Objective: to represent the frequency of ETPB of all localization, ratio between EPTB and PTB and demographic characteristics of EPTB in FBiH in the period of four years: from 2014 to 2017. Material and methods: This is the retrospective analysis of all the reported cases of TB in FBiH with the special insight in EPTB from 2014 to 2017. A standard set of data for TB patients is used which is included in the standardized form—"Minimum information for reporting tuberculosis" which has been used according to the recommendation of the WHO and IUATLD all over the Europe and elsewhere in the world. Results: we registered 2588 patients with TB and among them there were 316 patients or 12.21% with EPTB. In the 2014 there were 795 cases of TB and of that 103 (13.0%) were EPTB; in 2015 of 728 cases of TB 91 (12.5%) were EPTB; in 2016 of 573 cases of TB 69 (12%) were ETPB; 2017 of 492 cases of TB 53 (11%) were ETPB. ETPB is more frequent in males but with no statistical significance. The most cases of EPTB were in the group of patients aged from 21 to 30 years because of frequency of tuberculous pleurisy. The tuberculous pleuritis is the most frequent form of ETPB ($p < 0.01$). Conclusion: The frequency of TB and ETPB in FBiH decreases over the years. This indicates good control and therapeutic regimen of TB in FBiH. The ratio of PTB and EPTB remains approximately the same—about 12% of all TB cases are EPTB. Thus we are getting close to the situation in developed countries.

Keywords: pulmonary TB (PTB), extrapulmonary TB (EPTB), FBiH

1. INTRODUCTION

The two types of clinical manifestation of tuberculosis (TB) are: pulmonary TB (PTB) and extrapulmonary TB (EPTB). PTB is much more frequent. EPTB refers to TB involving organs

other than the lungs (e.g. pleura, lymphonodes, abdomen, genitourinary tract, skin, joints and bones, spine, meninges, etc.). A patient with both pulmonary and EPTB is classified as a case of PTB. For example, military TB is classified as PTB because there are lesions in the lungs. On the other hand, tuberculous intrathoracic lymphadenitis (mediastinal and/or hilar) or tuberculous pleuritis, without radiographic abnormalities in the lungs, constitutes a case of EPTB (1).

Diagnosing EPTB is challenging because samples obtained from relatively inaccessible sites may be paucibacillary, thus decreasing the sensitivity of diagnostic tests. Every effort should be made to obtain appropriate specimens for both mycobacteriologic and histopathological examinations. The measurement of biochemical markers in TB-affected serous fluids (adenosine deaminase or gamma interferon) and molecular biology techniques such as polymerase chain reaction may be useful for diagnosis of EPTB. Surgery is required mainly to obtain valid diagnostic specimens and to manage complications. Because smear microscopy or culture is not often available to monitor patients with EPTB, clinical monitoring is the usual way to assess the response to treatment (2).

A definitive diagnosis of TB can be made only by culturing *Mycobacterium tuberculosis* from a specimen obtained from the patient or by histopathological examination. Since the conventional smear microscopy has a low sensitivity with a range of 0%-40%, negative results cannot exclude TB. The reported yields of mycobacterial culture vary from 30% to 80%, but it usually takes 2-8 weeks to receive the results, which is too slow to help treatment decisions (3).

About 10%-50% of EPTB patients have concomitant PTB. Therefore, all suspected cases of EPTB should be assessed for PTB to determine whether the case is infectious and to assist with diagnosis. Some EPTB patients have positive sputum culture results despite normal chest radiography. The sensitivity of sputum culture varied in previous

studies by site of EPTB: 28%-50% for abdominal TB, 10%-11% for TB pericarditis, 24%-29% for TB meningitis, and 5%-14% for TB lymphadenitis. Bronchoscopic evaluation or sputum induction with nebulized hypertonic saline can increase diagnostic sensitivity (4, 5). In one prospective study of patients with suspected pleural TB, the yield of sputum culture in induced samples approached 52% (5). In one study microscopic examination for *Mycobacterium tuberculosis* was positive in 4.44% and negative in 95.56%, but in 88.89% positive and 11.11% negative by cultural examination in patients with tuberculous pleurisy. Results were positive only in patients with tuberculous pleurisy associated with PTB (6).

Repeating tests improve diagnostics. In patients with urinary tract TB, three to six first-void morning urine specimens improve the likelihood of a positive acid-fast bacilli (AFB) culture result, with approximately 80%-90% (only 30%-40% of single specimens are positive) (3). Repeated lumbar punctures and cerebrospinal fluid (CSF) examination increase diagnostic yield. AFB smears and culture positivity approached 87% and 83%, respectively, in four serial CSF samples (7). Stool cultures for tubercle bacilli are not recommended for diagnosis of gastrointestinal TB because positive results are more likely in patients with PTB who are swallowing infected sputum (8).

The types of EPTB are:

- TB pleuritis is the most common form of EPTB and the main cause of pleural effusion in many countries. The incidence of tuberculous pleurisy is higher in states with high tuberculosis prevalence. Rupture of a subpleural caseous focus from the lung into the pleural space is the initial event in the pathogenesis of tuberculous pleurisy (9).
- Genitourinary TB. Infection of the kidneys may manifest as pyelonephritis with sterile pyuria. Infection commonly spreads to the bladder and, in men, to the prostate, seminal vesicles, or epididymis. Infection may spread to the perinephric space and down the psoas muscle causing an abscess on the anterior thigh. Salpingo-oophoritis occurs after menarche and leads to sterility or ectopic pregnancy.
- TB meningitis. In the developed countries it is most common among the elderly and immunocompromised, in areas where TB is common- among children and usually occurs between birth and 5 yr with high mortality. Stroke results from thrombosis of a cerebral vessel. Focal neurological symptoms suggest a tuberculoma.
- TB pericarditis develops from focuses in mediastinal lymph nodes or from pleural TB. Pericardial tamponade may occur.
- TB lymphadenitis (scrofula) typically involves the lymphonodes in the posterior cervical and supraclavicular sites. Infection occurs due to spread from intrathoracic lymphatics. Mediastinal lymphonodes are enlarged.
- Cutaneous Tuberculosis (Scrofuloderma). Cervical tuberculous lymphadenitis is characterized by progressive swelling of the affected nodes. Nodes become inflamed; the overlying skin may break down, resulting in a draining fistula.
- TB of bones and joints and spine. Weight-bearing joints are most commonly involved, but bones of the wrist,

hand, and elbow may be affected. Symptoms include progressive or constant pain in involved bones and chronic or subacute arthritis (usually monoarticular). Pott disease is spinal infection, which begins in a vertebral body and spreads to adjacent vertebrae causing the narrowing of the disk space between them. Untreated, the vertebrae may collapse, possibly impinging on the spinal cord. Spinal cord compression produces neurological deficits, including paraplegia; paravertebral swelling may result from an abscess.

- TB peritonitis –peritoneal digestive TB Peritoneal infection results from seeding from abdominal lymphonodes or from salpingo-oophoritis. Peritonitis is particularly common among alcoholics with hepatic cirrhosis. Because the entire gastrointestinal mucosa resists TB invasion, infection requires prolonged exposure and enormous inoculum. Intestinal invasion causes an inflammatory bowel syndrome. It may mimic appendicitis. Ulceration and fistulas are possible.
- TB of the liver is common in patients with advanced pulmonary TB and miliary TB. It heals without sequelae when the principal infection is treated. It occasionally spreads to the gallbladder, leading to obstructive jaundice.
- Other sites. Rarely, TB develops on abraded skin in patients with cavitory PTB. TB may infect the wall of a blood vessel and even rupture the aorta. Adrenal involvement, leading to Addison disease is rare. Tubercle bacilli may spread to tendon sheaths (tuberculous tenosynovitis) by direct extension from lesions in bone or hematogenously from any infected organ.

2. THE OBJECTIVE

The objective of this study is to represent the frequency of ETPB of all localization, ratio between EPTB and PTB and demographic characteristics of EPTB in FBiH in the period of four years: from 2014 to 2017..

3. MATERIAL AND METHODS

This is the retrospective analysis of all the reported cases of TB of all localization within the area of FBiH with the special insight in EPTB, from the beginning of 2014 to the end of 2017. A standard set of data for TB patients is used which is included in the standardized form –“Minimum information for reporting tuberculosis” which has been used according to the recommendation of the WHO (World Health Organization) and IUATLD (International Union Against Tuberculosis and Lung Disease) all over the Europe and elsewhere in the world. We registered EPTB of different localization: pleura, intrathoracic lymphonodes, extrathoracic lymphonodes, spine, bone and joint, meninges, CNS (central nervous system), genitourinary tract, peritoneal-digestive tract, disseminated form –more than one organ involved except lungs, other localization-cutaneous TB, scrofuloderma, pericarditis, polyserositis, tenosynovitis, and other rare localization

4. DIAGNOSIS

Diagnosis In the 2014 there was totally 795 reported cases of TB of all localization and of that 103 (13.0%) were EPTB; in 2015 of 728 cases of TB 91 (12.5%) were EPTB; in 2016 of

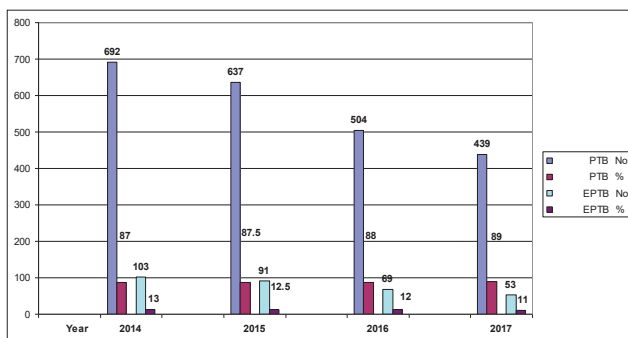


Figure 1. PTB and EPTB registered in four year –period expressed in absolute number and percents. Legend: PTB =pulmonary tuberculosis, ETPB=extrapulmonary tuberculosis, No= absolute number, %= per cent of all TB cases.

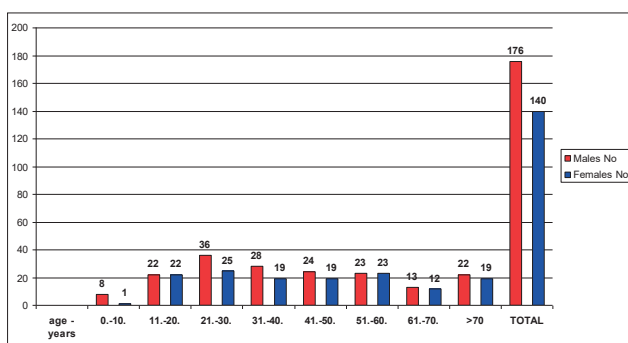


Figure 2. The frequency of EPTB according to age and sex in four-year period. There are 176 males and 140 females with EPTB of different age groups but with no statistical significant differences between age groups and sexes.

573 cases of TB 69 (12%) were ETPB ;in 2017 of 492 cases of TB 53 (11%) were ETPB. There is not statically significant difference in the number of PTB and EPTB between the examined years (Figure 1).

In 2014 there were 34 (4,3% of all TB cases) patients with associated PTB and EPTB; in 2015 - 23 (3, 2%); in 2016 - 10 (1,7%); in 2017 - 20 (4, 1%) patients with associated PTB and EPTB. A patient with both PTB and EPTB is classified as a case of PTB according to the recommendation of WHO (1).

PTB and EPTB in our country occur at all ages -from the first months of life onwards and in both sexes. There is no statistical significance in the number of registered patients with EPTB according to age groups and sex. The most registered number of EPTB was in the group of patients aged from 21 to30 years. It is especially because of frequency of tuberculous pleurisy in this age (Figure 2).

In the investigated period of 4 years (2014-2017), we registered 2588 patients suffering from tuberculosis and among them there were 316 patients or 12.21% with some form of EPTB (Figure 3 and 4).

5. DISCUSSION

Brain The two types of tuberculosis (TB) are: pulmonary TB (PTB) and extrapulmonary TB (EPTB). EPTB refers to TB involving organs other than the lungs. A patient with both PTB and EPTB is classified as a case of PTB (1). TB outside the lung usually results from hematogenous dissemination (1, 2). Sometimes infection directly extends from an adjacent organ (1, 2). Symptoms vary by site but generally include fever, malaise, and weight loss. Diagnosis is most often made

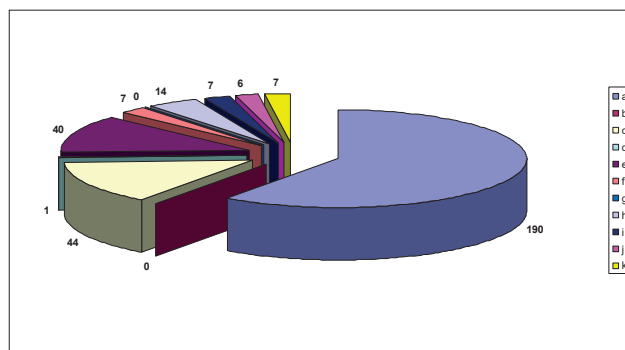


Figure 3. Registered patients with different localization of EPTB in four-year period expressed in absolute number Legend. EPTB localization: a=pleura (190), b= intrathoracic lymphonodes (0), c=extrathoracic lymphonodes (44), d= spine (1), e= bone and joint (40), f=meninges (7), g= CNS (central nervous system) (0), h= genitourinary tract (14), i= peritoneal-digestive tract (7), j=disseminated (6), other localization (7). The tuberculous pleuritis is the most frequent form of ETPB (p<0.01)

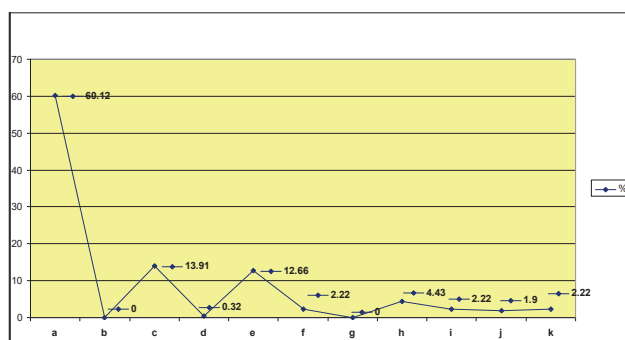


Figure 4. Patients with different localization of EPTB in four-year period expressed in percents of total number of registered EPTB patients. ,Legend. EPTB localization: a=pleura (60.12), b= intrathoracic lymphonodes (0), c=extrathoracic lymphonodes (13.91), d=spine (0.32), e= bone and joint (12.66), f=meninges (2, 22), g=CNS (central nervous system) (0), h= genitourinary tract (4.43), i=peritoneal-digestive tract (2.22), j=disseminated (1.9), other localization (2.22).

by culturing Mycobacterium tuberculosis from a specimen obtained from the patient or by histopathological examination, and increasingly by rapid molecular-based diagnostic tests. Treatment is standard ATL therapy; sometimes including other drugs e.g. corticosteroids, surgery, etc. (2, 3, 10).

EPTB is a bigger diagnostic and therapeutic problem than PTB because it is less common and less familiar to most clinicians. EPTB involves relatively inaccessible sites, and often, because of vulnerability of the areas involved, much greater damage can be caused by fewer bacilli. The combination of small numbers of bacilli and inaccessible sites causes that bacteriologic confirmation of a diagnosis is more difficult, and invasive procedures as surgery are frequently necessary for diagnosis. Surgery may be an important component of the treatment.

EPTB has been reported in almost all global regions, particularly in developed countries (1). The WHO data shows 0.8 million EPTB among the 6.1 million of new TB cases reported in 2013 (13.11%) (1).

In the USA more than 20% of all cases of TB are EPTB. The proportion of EPTB has increased from 1993 to 2006 (10). It is necessary to identify whether certain comorbidities, patient

characteristics, immunologic and genetic susceptibilities, or differences by population and region in endemic tuberculosis strains impact EPTB development. Improved understanding of EPTB risk would enable clinicians to apply a higher suspicion to populations at risk for EPTB (10).

ETPB is increasing in England and Wales. The proportion of cases with ETPB has increased over the study period –from 1999 to 2006. Among all the cases of TB, the proportion with EPTB increased from 48% in 1999 (2717 cases) to 53% in 2006 (4205 cases) ($p < 0.001$). Maybe, it is due to an increasing proportion of non-UK born cases (11). EPTB constitutes about 20% of all cases of TB in Korea (2).

The most common form of EPTB in our country is tuberculous pleurisy (60.12% of all EPTB cases), which is statistically significantly higher than other EPTB localizations. Tuberculous pleurisy accounts for about 4% of all tuberculosis cases in the USA and Brazil, 20% in South Africa, In Korea 2,884 tuberculous pleurisy cases were notified that is 7.3% of new TB cases and 34% of all EPTB cases (2).

We notified a relative great proportion of extrathoracic lymphonodes (13.91% of all registered EPTB) and bone and joint (12.66%) localization, but other localization were relative rare in examined period.

Some authors have identified a higher frequency of EPTB, compared with the frequency of PTB, among patients on particular immunosuppressive therapies (12) or advocated increased suspicion of EPTB in rheumatologic patients (13). Others have investigated possible differences between EPTB and PTB in genetic or immune-mediated predispositions (14, 15). Possibility is that there are geographic differences in circulating Mycobacterium tuberculosis strains (16) or variations in Mycobacterium receptor affinity for certain target organs that influence TB site development. Improved recognition of EPTB risk factors may facilitate earlier diagnosis; prevent progression to the contagious state and sparing patient's significant morbidity and/or mortality (10).

In our study we find that the frequency of PTB and EPTB has a decreasing trend in FBiH, but the ratio of PTB and EPTB remains approximately the same- from 13% in 2014 to 11% in 2017.

5. CONCLUSION

The frequency of TB in FBiH decreases, and so the frequency of ETPB. This indicates good control and therapeutic regimen of TB in our country. The ratio of PTB and EPTB remains approximately the same - about 12% of all TB cases are EPTB, and thus we are getting close to the situation in developed countries..

• **Conflict of interest:** The authors declare that they have no conflict of interest.

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