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Alcoholism and other socio-demographic risk factors for adverse TB-drug reactions and unsuccessful tuberculosis treatment – data from ten years' observation at the Regional Centre of Pulmonology, Bydgoszcz, Poland

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Background: Tuberculosis (TB) is one of the most dangerous infectious diseases and has one of the highest mortality rates. For decades a strong association has been evident between certain socio-economic factors and TB adverse events and failure of treatment, yet there is a limited quantity of literature available on this subject, especially in the Polish literature.





Material/Methods: We examined epidemiological data from 2025 TB patients treated at the Regional Centre of Pulmonology in Bydgoszcz, Poland between 2001 and 2010. This article focuses on the association between all forms of unsuccessful TB treatment outcomes or adverse drug reaction (ADR) and socio-demographic characteristics, condition on admission, and other biological, clinical, social, and healthcare access factors.

Results: The rate of TB-ADR during hospitalization was 38.9%. Multivariate logistic regression analysis showed that age ($P < 0.001$) and alcohol abuse ($P = 0.007$) were independently associated with the occurrence of TB-ADR. The rate of unsuccessful TB treatment was 10.5%. After adjusting for confounding variables, age ($P < 0.001$), alcohol abuse ($P = 0.002$), and education ($P = 0.01$) were significantly associated with unsuccessful treatment. Smoking did not have any significant influence on occurrence of either TB-ADR during hospitalization or unsuccessful treatment.

Conclusions: Among our TB patients treated between 2001 and 2010, alcohol abuse significantly worsened the treatment outcome. This information will be crucial in developing strategies targeted at this demographic group.

MeSH Keywords: **Tuberculosis – drug therapy • Alcoholism • Drug-Related Side Effects and Adverse Reactions**

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Background

Tuberculosis is one of the most dangerous infectious diseases and has one of the highest mortality rates of all infectious diseases. In 2011, the global incidence of TB was estimated by the World Health Organization (WHO) to be 125 cases per 100 000 people, which is equivalent to 8.7 million newly diagnosed patients (incident cases). The number of prevalent cases has trended downwards since 1990; the same is true for the incidence of new cases, although there was a slight increase in the latter at the beginning of the 21st century [1,2]. The WHO has divided European countries by the incidence of TB into 3 categories: 1) countries with a low incidence (<20/100 000 population), 2) countries with mean incidence (20–50/100 000), and 3) countries with high incidence (>50/100 000). Poland has a relatively low incidence of TB. The population is 38.5 million people and the annual TB incidence is under 10 000. During the 10 years of our study, a decline in incidence was observed, from 27.6/100 000 in 2001 to 19.7/100 000 in 2010. The data from the last 2 years show the incidence to be less than 20/100 000. The annual TB incidence in the province where our hospital is located, the Kuyavian-Pomeranian province, in the northern part of the country, is slightly smaller than the mean for the whole country at 21.4 per 100 000 in 2001 and 19.7 per 100 000 in 2010 [3].

While the current disease burden of TB is enormous, and TB qualifies among the 10 most fatal and disabling disease categories, its relative impact has been decreasing over time. Monitoring TB treatment outcome is an essential part of TB disease surveillance to ensure that the disease is successfully controlled. Published studies show that unsuccessful outcomes due to incomplete treatment are associated with persistent TB transmission in the community, development of resistant strains, and mortality [4]. The relationship between the occurrence of adverse effects during treatment and unsuccessful treatment plays an important role in the control of TB. Due to the limited number of publications in the Polish literature on this subject, we undertook to analyze the data on TB patients treated at our hospital. This paper presents our analysis of data from the TB patients treated at the Regional Centre of Pulmonology in Bydgoszcz between 2001 and 2010.

This study aimed to determine the factors associated with unsuccessful outcomes and adverse TB-drug reactions (TB-ADR) in TB patients in Kuyavian-Pomeranian region, specifically, socio-demographic characteristics and biological, clinical, social, lifestyle, and healthcare access factors. Particular attention was given to alcohol abuse among the TB patients, as alcohol abuse is a major social problem in Poland. The number of people abusing alcohol in Poland is estimated at about 2.8–3.5 million, including 0.6–0.9 million addicts. Poland has the highest rate of consumption of spirits in the world, and

our consumption is rising. When the first records were kept, starting in 1937, the average rate of consumption was not more than 0.7 liters per capita per year; by the 1950s it had reached 3–4 liters; then after a period of relative stability, the 1980s brought another jump to more than 10 liters of pure alcohol per capita per year. Similar values were reported to the Kuyavian-Pomeranian region [5]. In the earlier Polish studies it can be seen that late diagnosis of tuberculosis and poor cooperation from the patient during treatment usually appear in conjunction with alcoholism [6]. This information will be crucial in developing strategies targeted at this demographic group to prevent the rise of similar problems in the future.

Material and Methods

This was a retrospective study of 2025 patients with tuberculosis hospitalized and treated between January 2001 and December 2010 at the Regional Centre of Pulmonology in Bydgoszcz.

The drug regimen for new cases includes pyrazinamide, isoniazid, rifampicin, and ethambutol or streptomycin for the first 2 months and isoniazid and rifampicin for the last 4 months. Re-treatment uses the same drugs as for new cases, plus ethambutol for the full 6 months. The data from confirmed cases of TB are routinely recorded and entered into a central database of hospitals. All patients were administered medication in a directly observed treatment (DOT) program.

Tuberculosis can only be diagnosed if *Mycobacterium tuberculosis* bacteria are found in a clinical specimen taken from the patient. While other types of tests may strongly suggest tuberculosis as the diagnosis, they cannot confirm it. A complete medical evaluation for tuberculosis (TB) must include a medical history, a physical examination, a chest X-ray, and a microbiological examination (of sputum or some other appropriate sample). It may also include other scans and X-rays, and a surgical biopsy. Tuberculosis is diagnosed if a patient (1) has a positive culture for *M. tuberculosis*, (2) is culture-negative with clinico-radiological features and a response to treatment consistent with TB; or (3) has histological findings and response to treatment consistent with TB.

TB treatment outcome categories were defined according to WHO and the International Union Against Tuberculosis and Lung Disease guidelines with some modifications [7,8]. WHO defines successfully treated patients as all those who both have completed treatment and are cured. In keeping with these criteria, treatment outcomes were categorized as either: a) successful outcome, in which pulmonary TB (PTB) patients completed treatment and were cured (i.e., negative smear microscopy at the end of treatment and in at least 1 follow-up

and resolution of symptoms) or b) unsuccessful outcome, in which treatment ended in failure (i.e., remaining smear-positive after 5 months of treatment), default (i.e., interruption of treatment for two or more consecutive months after registration), or death. Patients who transferred out to other districts were excluded from the treatment outcome evaluation because information on their treatment outcome was unavailable. The main purpose of this paper was to identify the socio-demographic risk factors such as age, alcoholism, smoking, and education that could have an impact on adverse drug reaction and unsuccessful TB treatment outcomes of patients [7].

An adverse drug reaction was defined as an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product, or from alteration of the dosage regimen or withdrawal of the product, which can be expected to recur upon future administration, alteration or withdrawal, and which warrants prevention or specific treatment [9]. The causality of each ADR was evaluated according to the WHO Uppsala Monitoring Centre System [10].

TB-ADR were classified as: 1) toxicity-like serious or potentially life-threatening reactions that may require treatment and/or hospitalization, dose changes, or stopping the drug; 2) adverse effects such as hepatitis, kidney failure, serious allergic reactions, vision changes, neurological problems, thrombocytopenia, neutropenia, or anaemia; or 3) unpleasant reactions that are not damaging to health and do not usually require changes in therapy, such as gas, bloating, discoloration of body fluids, sleeping problems, photosensitivity, or irritability [11].

As a TB-ADR, liver dysfunction was defined as an increase in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin to a level greater than twice the upper limit of normal (ULN) in 1 test or higher than the ULN in 2 continuous tests conducted 2 weeks apart, not considering the symptoms. Hepatotoxicity was defined as an increase in ALT or AST to a level greater than 3 times the ULN or an increase in total bilirubin to a level greater than twice the ULN [38]. Hyperuricemia was defined as an increase in uric acid level to greater than 8 mg/dl. Anemia was defined as hemoglobin (Hgb) concentration <11 g/dl in males or <10 g/dl in females in patients without a history of anemia or a drop in Hgb concentration of more than 1 g/dl after anti-TB treatment. Neutropenia was defined as a drop in absolute neutrophil count to 1500 cells/mm³ or less, and thrombocytopenia was defined as a drop in platelet count to less than 150 000 cells/mm³. Except for liver dysfunction, hematologic system disorders and renal impairment, which were determined based on laboratory data, all other ADRs (including allergic reactions, arthralgia and nervous system disorders) were determined based on symptoms. Nervous system disorders included auditory nerve damage, optic nerve damage, peripheral nervous system damage, and central nervous system damage.

For this study, ADR led to a discontinuation or final termination of 1 of the drugs included in the standard therapy. Clinical monitoring was performed by daily visits and laboratory monitoring by weekly investigations. All adverse effects were observed during the hospital stay of the patients.

Hepatotoxicity was accepted as a cause for temporary discontinuation of therapy if previously normal values of liver enzymes increased to more than 3 times the upper normal limit during therapy. As a reason for definitive discontinuation of therapy, hepatotoxicity was assumed if re-exposure to the drug induced a new and rapid increase of liver enzymes to more than 3 times the upper normal limit. In the case of exanthema, only generalized cutaneous lesions resulted in a discontinuation of the suspected drug and re-exposure to the suspected drug was tried in most cases before final cessation of treatment. Arthralgia was accepted as a cause for stopping administration of a drug only when the patient was severely handicapped. All other types of adverse effects leading to drug termination had been classified as severe by experienced chest physicians. When severe adverse effects occurred, the drug responsible was identified in 1 of 2 ways: either by terminating the suspected drug alone; or by discontinuing all 3 drugs, followed by a step-by-step reintroduction of at least 2 of the 3 substances.

Excessive alcohol use is not defined quantitatively; instead, the U.S. Centers for Disease Control and Prevention provide general guidelines for public health staff to use when assessing alcohol consumption. The suggested criteria for identifying excessive alcohol use in the previous 12 months among tuberculosis patients include evidence of participation in an alcohol treatment program, documented medical conditions associated with excessive alcohol use (e.g., cirrhosis, pancreatitis) and a diagnosis of alcoholism in medical records [12]. For the purposes of this analysis, TB patients were considered to abuse alcohol if they had a confirmed history of treatment for alcoholism or alcohol-related therapy or a confirmed diagnosis of alcohol dependence syndrome, or if they repeatedly showed signs of alcohol consumption during the course of their hospital stay. All patients meeting 1 or more of these criteria were classified into the alcohol-abusing group.

The Statistica software program, version 10.0, was used for the statistical analysis. Comparisons between categorical variables were performed using the chi-square test of independence. To check the difference between 2 sample means, the t-test was used. We performed multivariate logistics regression to estimate adjusted odds ratios with 95% confidence intervals (OR; 95% CI) for the association between occurrence of TB-ADR, unsuccessful TB treatment, and alcoholism, taking into account potential confounding factors. The occurrence of TB-ADR and unsuccessful TB treatment were considered as

binary dependent variables. All variables significant for the univariate analysis were incorporated into the multivariate model. P values lower than 0.05 were considered significant.

The study protocol was accepted by the Ethics Committee of Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, in March 2013 (KB 168/2013).

Results

We studied a total of 2025 patients with TB: 1889 patients (93.3%) with the pulmonary form, 1813 (89.5%) with successful outcomes (271 with documented cures and 1542 with documented completion of treatment), and 212 (10.5%) had unsuccessful outcomes (13 stopped treatment, 41 failed treatment, and 158 died), of whom 1360 were male, 413 were older than 65 years, and 534 were alcoholics. The sample sizes for various analyses within the study ranged from 1834 to 2025 because of missing or incomplete data for some patients. Patient age, given here and below as age at the time of admission to the hospital, ranged from 16 to 98 years; the mean age was 51.5 years (SD 16.7 years).

Adverse effects of the drugs were seen in 780 patients (38.9%); these included hepatotoxicity (25.8%), hematological disturbance (19.0%), gastrointestinal disturbance (14.0%), psychiatric disorders (11.7%), neurological disorders (8.7%), arthralgia (5.9%), ototoxicity (5.8%), dermatological effects (4.0%), and others (5.3%).

Table 1 shows a comparison of alcoholics and non-alcoholics with regard to their socio-demographic characteristics. We observed significant differences in gender, age, residence, smoking status, education, employment, and marital status. Men, younger patients, homeless people, and smokers were significantly more likely to be alcoholics. Alcoholics appeared to be less educated and were more likely to be unemployed than non-addicted patients. The proportion of married people was significantly higher among non-addicted patients.

The total proportion of patients experiencing TB-ADR was 38.9%. Table 2 presents the results of a logistic regression analysis for 9 predictor variables. Univariate analysis showed that gender, age, homelessness, alcohol abuse, and education were associated with the occurrence of TB-ADR. There were no significant differences concerning place of residence (rural vs. urban), smoking habits, employment, or marital status. In the multivariable analysis, age and alcohol abuse remained associated with the occurrence of TB-ADR, whereas gender, homelessness, and education became irrelevant after adjustment. Alcoholics had 1.32 times the risk of TB-ADR as non-addicted patients. Smoking remained insignificant after adjusting for

age and alcohol abuse ($P=0.79$). Age was a binary variable in the model; we also checked the results of using age as a continuous variable and found that it changed the odds ratio for alcohol abuse only slightly, from 1.39 to 1.35.

Our analysis of the factors associated with unsuccessful TB treatment is presented in Table 3. The overall rate of unsuccessful TB treatment was 10.5%. This rate was significantly higher among older patients, alcoholics, and less educated people. No significant differences were found for gender, homelessness, place of residence (rural vs. urban), smoking, marital status, or employment. The results of a multivariate logistic regression revealed that age, alcohol abuse, and education were independently associated with unsuccessful TB treatment. We observed that patients over 65 years of age had 3.76 times the odds of unsuccessful TB treatment as younger patients after adjustment for the other factors. Addiction to alcohol also increased the odds of unsuccessful TB treatment by 84%. We confirmed that smoking status was insignificant after adjustment for age and alcohol abuse ($P=0.14$). Using a multifactorial model and taking age as a continuous variable changes the odds ratio for alcohol abuse from 1.84 to 1.83.

We could not determine the association between TB-ADR, unsuccessful tuberculosis treatment, and HIV infection because there were only 7 HIV-positive patients in our study population. For this reason, the effect of alcohol abuse was not adjusted for HIV status.

Discussion

Effective tuberculosis treatment is the most important part of any antimycobacterial tuberculosis control program. The burden of pulmonary tuberculosis among TB cases with unsuccessful treatment outcome is high, underscoring the usefulness of existing TB treatment strategies. It has been evident for decades that there is a strong association between socioeconomic factors, TB-ADR, and unsuccessful treatment [13,14]. The goal of examining this relationship is to minimize unsuccessful outcomes in TB treatment. It is a hazard to public health to leave a patient without therapy, to pause or stop treatment before it is finished, and to finish treatment but fail to cure the patient's TB. Pausing or stopping treatment before it is finished is dangerous because it can lead to disease recurrence and the development of drug resistance, which in the individual can increase the costs of retreatment after recurrence, but in the community can worsen the epidemiological situation for everyone [15,16]. A moderate level of general knowledge about tuberculosis suggests the need to modify current programs of infectious disease education in the curriculum of medical schools [17].

Table 1. Socio-demographic characteristics of the study population at the Regional Centre of Pulmonology, with particular focus on the role of alcohol abuse.

	All %	Alcoholics %	Non-alcoholics %	P value
Gender (n=2005)				<0.001
Males	67.0	90.6	58.4	
Females	33.0	9.4	41.6	
Age, years (n=2005)	51.5 (SD 16.7)	50.0 (SD 11.1)	52.0 (SD 18.3)	0.02
≤65	79.8	92.5	75.1	<0.001
>65	20.2	7.5	24.9	
Homelessness (n=2005)				<0.001
Homeless	5.8	17.6	1.5	
Settled	94.2	82.4	98.5	
Residence (n=1889)				<0.001
Urban	65.0	71.8	62.9	
Rural	35.0	28.2	37.1	
Smoking status (n=1998)				<0.001
Smoker	69.6	93.4	61.0	
Non-smoker	30.4	6.6	39.0	
Education (n=1850)				<0.001
Primary/vocational	81.1	94.3	76.3	
Secondary/above secondary	18.9	5.7	23.7	
Employment (n=2003)				<0.001
Workers/pensioners/students	69.0	42.0	78.8	
Unemployed	31.0	58.0	21.2	
Marital status (n=1986)				<0.001
Single/divorced/widowed	53.9	73.2	46.9	
Married	46.1	26.8	53.1	

Isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin are the principal agents that are successfully used to treat tuberculosis, due to their therapeutic effectiveness and good acceptance among patients. However, a variety of adverse effects have been reported in connection with each. Our data suggest that the treatment of TB is associated with a relatively high frequency of adverse events (39%). A similar percentage of patients with HIV co-infection and a smaller percentage of patients without HIV experienced TB-ADR, as reported by Breen et al. [18]. In a Chinese study of 4304 TB patients, only 649 (15.08%) showed at least 1 ADR [19].

Hepatic toxicity is one of the most common TB-ADRs and is a frequent cause of interruptions in treatment. In our study, most TB-ADRs were hepatic toxicity, which appeared in 25.8% of hospitalized co-infected patients who were undergoing tuberculosis treatment. This proportion is similar to that reported in other studies, in which incidence rates have ranged from 6% to 27.3% and slightly higher in Japan (36%) and India (8% to 36%), as cited by Singla et al. [20,21]. In other studies, the highest incidence is typically found in Asian countries, which may be indicative of an ethnic susceptibility, peculiarities inherent in drug metabolism or the presence of various risk factors such as hepatitis B virus or malnutrition [21]. It should be

Table 2. Association between occurrence of TB adverse drug reaction and alcoholism and other risk factors.

	Rate of TB adverse drug events	Unadjusted OR (95% CI)	P value	Multivariate adjusted OR (95% CI)	P value
Gender (n=2025)					
Male	40.7	1.26 (1.04–1.53)	0.02	1.09 (0.88–1.35)	0.43
Female	35.2	Referent		Referent	
Age, years (n=2025)					
≤65	36.2	Referent		Referent	
>65	49.2	1.70 (1.37–2.12)	<0.001	1.74 (1.36–2.23)	<0.001
Homelessness (n=2025)					
Homeless	51.7	1.74 (1.20–2.54)	0.004	1.32 (0.86–2.03)	0.21
Settled	38.1	Referent		Referent	
Residence (n=1909)					
Urban	38.5	1.05 (0.86–1.27)	0.66		
Rural	37.4	Referent			
Smoking status (n=2016)					
Smoker	38.4	Referent			
Non-smoker	40.0	1.07 (0.88–1.30)	0.50		
Alcohol abuse (n=2005)					
Addicted	45.3	1.45 (1.18–1.77)	<0.001	1.39 (1.10–1.77)	0.007
Unaddicted	36.4	Referent		Referent	
Employment (n=2023)					
Worker/pensioner/student	39.1	1.04 (0.86–1.27)	0.67		
Unemployed	38.1	Referent			
Education (n=1867)					
Primary/vocational	40.0	1.51 (1.18–1.94)	<0.001	1.27 (0.97–1.64)	0.08
Secondary/above secondary	30.6	Referent		Referent	
Marital status (n=2005)					
Single/divorced/widowed	39.6	1.08 (0.90–1.29)	0.42		
Married	37.8	Referent			

noted that most of these studies were of outpatients, while the present study concerns hospitalized patients, as this difference may have contributed to the higher incidence rate in the present study. The incidence of TB-ADRs is also related to alcohol abuse. The present study found high rates of hazardous or harmful drinking (26.3%) among TB patients in northern Poland; this is consistent with other studies conducted in low-income and middle-income countries [22–24].

The success of current antituberculous therapy is evidenced by the continuous decrease in the incidence of TB, as well as the relatively high percentage of patients who complete TB therapy and are cured [1,25]. TB treatment should continue past the minimum standard duration of treatment because clinical studies have proven that continuing treatment after this period helps tuberculous patients achieve permanent sputum negativity. The rates of interrupted treatment,

Table 3. Association between unsuccessful Tb treatment and alcoholism and other risk factors.

	Rate of failure	Unadjusted OR (95% CI)	P value	Multivariate adjusted OR (95% CI)	P value
Gender (n=2025)					
Males	11.2	1.27 (0.93–1.74)	0.14		
Females	9.0	Referent			
Age, years (n=2025)					
≤65	7.5	Referent		Referent	
>65	22.0	3.48 (2.59–4.69)	<0.001	3.76 (2.61–5.42)	<0.001
Homelessness (n=2025)					
Homeless	14.7	1.51 (0.88–2.58)	0.13		
Settled	10.2	Referent			
Residence (n=1909)					
Urban	10.5	1.09 (0.80–1.50)	0.58		
Rural	9.7	Referent			
Smoking status (n=2016)					
Smokers	10.4	1.01 (0.73–1.41)	0.93		
Non-smokers	10.3	Referent			
Alcohol abuse (n=2005)					
Addicted	14.2	1.74 (1.29–2.36)	<0.001	1.84 (1.26–2.68)	0.002
Unaddicted	8.7	Referent		Referent	
Employment (n=2023)					
Workers/pensioners/students	10.5	1.03 (0.51–2.06)	0.94		
Unemployed	10.2	Referent			
Education (n=1867)					
Primary/vocational	10.8	2.91 (1.66–5.09)	<0.001	2.11 (1.18–3.77)	0.01
Secondary/above secondary	4.0	Referent		Referent	
Marital status (n=2005)					
Single/divorced/widowed	11.5	1.28 (0.95–1.71)	0.10		
Married	9.2	Referent			

treatment failure, and death cannot exceed 15% together [1,26]. Patient cooperation with treatment is the factor with the strongest influence on therapy results, even when treatment time is shortened to 6 months. Poor cooperation leads to prolonged tuberculation and, when treatment resumes, to the development of drug resistance and an increase in the cost of retreatment [15].

This investigation showed an unusually low rate (10.5%) of unsuccessful tuberculosis treatment. This rate was achieved in part because all patients were hospitalized and therefore were under the strict control of their caregivers. Multivariate logistic regression analysis indicated that age, alcohol abuse, and education were independently associated with treatment failure. Poor treatment outcome is a serious problem facing some national tuberculosis control programs. In a Moroccan

study, for example, 48% of patients experienced treatment failure, a figure similar to those reported by Ottmani and Mas [27–29]. Irregularity of treatment is a factor that can lead to treatment failure, as are non-compliance with treatment, deficient health education of the patient, and poor patient knowledge regarding the disease.

Alcohol abuse has been recognized as a strong risk factor for TB disease in a systemic review by Lönnroth [30]. The rates of alcohol abuse among Polish TB patients are similar to those found in the United States and lower than those found in Russia [15]. Alcoholism has also been found to be a strong predictor for death from TB [31]. In Brazil, alcoholism has consistently been described as a risk factor for death due to TB, together with mental illness and unemployment [32,33]. In Queensland, Australia, no association between alcohol abuse or homelessness and TB death was found [34]; likewise, no association between alcohol use and TB death was found in south India [35]. In our study, however, significantly more deaths occurred in patients who abused alcohol (10.49 vs. 6.39; $p < 0.001$). The treatment records for such patients typically contain many notes of discharge from the hospital, issued repeatedly at the patient's own request, as well as criminal discharges issued because of drunkenness. These patients are the most likely to interrupt their treatment before it is complete, as any situation involving drunkenness necessitates the discontinuation of treatment, and these patients are the most likely to behave in a way that risks spreading TB. Poland has a statutory obligation requiring hospital treatment for tuberculating patients, but there are no regulations accompanying the Act, which makes it difficult to use coercive measures on patients who are a danger to public health [36].

The data obtained in this series gave no evidence that indirect factors such as occupation, marital status, smoking habits, or race were involved in the outcomes. Increased susceptibility cannot be assessed by this type of study. If alcohol consumption were of prime importance in determining susceptibility to TB, however, the ratio of heavy drinkers to light drinkers would have been significantly greater in the TB patients, and this was not the case. Any increased risk of exposure to TB infection among frequent drinkers is likely to be due to the fact that both regular drinking and tuberculosis are more common among the less educated. More consideration deserves to be given to the management of alcoholics with TB if tuberculosis is to be finally controlled.

Another study reviewed the mortality data for all U.S. residents who died in 1990 with TB as the underlying cause of death or with TB listed anywhere on the death certificate. The results suggested that TB mortality is enhanced by substance abuse (including alcohol abuse), which serves as a contributing cause of death [37]. Alcoholism, which the current study found to be associated with treatment failure and combined

negative outcomes, is a recognized factor increasing the likelihood of both the development of TB and poor treatment outcome [25,38,39]. In a retrospective analysis conducted in Germany, alcohol was a major factor in the failure of TB therapy [40]. Prior Polish studies have argued that the outcome of therapy for bacteriologically confirmed tuberculosis can be affected by the coexistence of tuberculosis and alcoholism [41]. Finally, excessive alcohol use may be significantly associated with increased incidence and severity of TB, as reported in other studies [42].

Older age was also associated with higher rates of treatment failure, dropout, and death in the multivariate models. Other authors have described older age (>65) as an independent predictor of failure, as it is in our results [26].

The present retrospective study was subject to many limitations with regard to the data available in the patients' clinical charts. Patient information was retrieved from medical records or folders available in the TB clinic and the medical records unit of each patient's hospital. Information about tobacco, alcohol, and illicit drug use was not routinely recorded. In particular, information on alcoholism was acquired retrospectively based on hospital data from the time of admission to the hospital. Documentation from the follow-up period was used to confirm the abuse of alcohol. The problem of missing data, which often limits the available sample size in retrospective studies, was minimized in this study by carrying out the study prospectively, while the participants were still active patients in follow-up. This study design avoided the possibility that certain patients' folders had been discarded because the patients had not participated in follow-up for a long time. Data verification was performed by cross-checking the data in the TB clinic with those from the medical records created during hospital admission.

The data show that, in Poland, supervised treatment is performed only in hospitals, especially in the intensive phase of treatment, and that patient cooperation has a strong effect on treatment outcome. In view of the brevity of patient records, it is not clear whether the strict supervision of medication was routinely practiced in the hospitals. Unfortunately, none of the hospital information sheets mention this one way or the other. Further exploration of the risk factors for interruptions in TB treatment may help control programs to identify those patients who are most likely to benefit from targeted interventions such as health education, substance abuse counselling, enhanced tracking, or reinforcement of DOTS supervision [43].

Conclusions

In our group of patients treated between 2001 and 2010, alcohol abuse significantly worsened treatment outcome, and

was correlated with both unsuccessful outcomes and more adverse TB drug events in TB patients. It is necessary to take action aimed at improving treatment supervision strategies, especially for high-risk groups. Better-tolerated therapy should be part of the TB research agenda. Our analysis of alcohol abuse identified some relevant risk factors that should be considered in planning public health interventions.

The clinical and social causes of therapeutic failures in patients with TB in association with alcoholism require further in-depth analysis. These causes may be complex because alcoholism is associated with several other pathological causes of treatment failure, such as interrupted treatment and lower levels of education.

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Competing interests

The authors declare that they have no competing interests.

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