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Analysis of predictive factors for adverse effects of antituberculosis treatments

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ABSTRACT

Objective? Anti-tuberculosis chemotherapy is likely to cause a number of serious side effects that require treatment to be stopped and the dose reduced. The aim of this study was to identify the risk factors that may increase the likelihood of developing adverse reactions to anti-tuberculosis drugs. **Materials and methods.** We conducted a descriptive cross-sectional study using a questionnaire, including 80 patients with active tuberculosis undergoing first-line anti-tuberculosis treatment at the Tuberculosis and Respiratory Diseases Control Service in Sidi Bel Abbes (Algeria). **Results.** The sex ratio F/M of our patients was 1.85 in favour of women, with a mean age of 36 years. Pulmonary involvement was present in 32.5% of cases and extrapulmonary involvement in 67.5%. These patients benefited from four-drug RHZE anti-tuberculosis therapy in 93.80% of cases. Adverse effects occurred in 76.25% of patients, of which 15.16% were serious adverse effects. Digestive disorders were the most common adverse event (33.1%), followed by arthralgia (18.4%), peripheral neuropathy (15.60%), skin disorders (15.60%), hematological disorders (7.5%) and liver disorders (5.7%). Univariate analysis showed that certain classes of self-medication had a significant effect on the occurrence of adverse reactions to anti-tuberculosis drugs (p=0.05). In addition, female sex was associated with joint pain (p=0.029) and nausea and vomiting (p=0.01). Co-infection was associated with hematological (p=0.021) and liver disorders (p=0.05), while digestive and skin disorders were associated with drug allergy and use of phytotherapy (p<0.05). **Conclusion.** Adverse effects of tuberculosis treatment are not uncommon and require rigorous clinical and biological monitoring to reduce treatment-related mortality and morbidity.

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1. INTRODUCTION

Tuberculosis was first identified in the 19th century and has since been recognized as one of the most lethal diseases in human history. [1] It continues to cause significant morbidity and mortality, particularly in developing countries. [2]

The African Region has made progress in the fight against tuberculosis, with a 19% reduction in cases between 2015 and 2020. [3] Between 1962 and 2010, Algeria, which once had a high prevalence of tuberculosis, transitioned to a country with a moderate prevalence by the early 1980s. In 2020, more than 20,000 cases of tuberculosis were reported in the country. Although this number is lower than in previous years, tuberculosis remains a major concern for the health system in Algeria. [4]

The management of tuberculosis treatment follows established protocols using a combination of several anti-tuberculosis drugs recommended by the World Health Organization (WHO). [5,6]

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These drugs are categorized into "first-line" and "second-line" based on criteria such as efficacy, resistance, toxicity, tolerability, quantity, and price, as outlined by WHO guidelines. [7]

First-line treatment lasts six months. It involves the daily administration of isoniazid (INH) and rifampicin (RIF) for six months. For the first two months (initial phase), treatment also includes pyrazinamide (PZA) and ethambutol (EMB). INH and RIF are continued alone for the next four months (continuation phase). [8]

The incidence, severity, and nature of adverse events associated with anti-tuberculosis treatment have always been a concern. Side effects increase patient discomfort and result in significant additional costs due to repeated outpatient visits, laboratory tests, and even hospitalization in severe cases. They are also considered a major cause of non-adherence to tuberculosis treatment, which can lead to prolonged treatment, drug resistance, and treatment failure. [6] This can also increase the morbidity and mortality associated with the disease.

Given the current interest in this topic in tuberculosis-endemic countries, such as Algeria, we thought it appropriate to conduct a study to identify the risk factors that may increase the likelihood of developing adverse drug reactions. This would help to ensure the safety and efficacy of treatment and provide a practical approach to this clinical situation.

2. METHODS

Setting and type of study

This was a cross-sectional descriptive study conducted from 14 November 2023 to 14 January 2024, a period of two months. Our study took place in the Sidi Bel Abbes (Algeria) Tuberculosis and Respiratory Diseases Control Service, which is responsible for organizing the screening, monitoring and treatment of tuberculosis cases in the area.

Study population

Patients diagnosed with pulmonary tuberculosis (PTB) or extrapulmonary tuberculosis (EPTB) who had received first-line anti-tuberculosis treatment, irrespective of age and sex. The sample consisted of 80 participants. The inclusion criteria were as follows:

Participants who had discontinued treatment before the start of the study were excluded. All participants were volunteers and were informed of the study's purpose and objectives before completing the questionnaire. Participants who had stopped treatment before the start of the study were excluded.

The municipality of Sidi Bel Abbes has 248,631 inhabitants and the incidence of PTB and EPTB is estimated at 39.4 cases/100,000 inhabitants, so the population size is estimated at 100 new cases/year. **[9]** The minimum sample size required for the study is 80 persons, with a margin of error of 5% and a confidence interval of 95%.

Data collection

Data were collected using an anonymous questionnaire administered face-to-face by us to patients receiving anti-tuberculosis therapy during free treatment. The questionnaire consisted of three parts: the first part concerned general information and comorbidities. A second section dealt with anti-tuberculosis treatment (molecules, type of treatment regimen, total duration of treatment, time of intake, compliance, reasons for non-adherence and adverse effects observed). A third section dealt with tuberculosis and treatment monitoring (tests used to monitor infection, adverse effects, and complications).

Statistical analysis

Data were analysed using SPSS software (IBM Statistics 22.0). Quantitative variables were expressed as mean ± standard deviation (SD) and qualitative variables as percentages. The chi2 test was used to test for differences between categorical variables. The difference was considered significant if the p-value was less than or equal to 0.05 (95% confidence interval).

Ethical aspects

Free and informed consent: respondents were informed of the intended use of the information collected and their consent was obtained prior to the interview. The information obtained will only be used within the strict framework of this study and we will ensure that no one is harmed by its use.

3. RESULTS

Our overall results concerned 80 cases of tuberculosis, all forms combined, who met our inclusion criteria and who had received anti-tuberculosis treatment. These patients benefited from four-drug RHZE (RIF, INH, PZA and EMB) anti-tuberculosis therapy in 93.80% of cases.

Sociodemographic characteristics

Table 1 shows the distribution of tuberculosis cases by age showed that the most affected age groups were those in the active age ranges of [20-50] years, accounting for 68.75% of cases. The mean age of our patients was 36.6875 ± 15.49569, with extremes ranging from 05 years for the youngest to 80 years for the oldest.

Women were the most affected by tuberculosis in our study, comprising 65% of the cases, with a female-to-male sex ratio of 1.85. Among the tuberculosis patients, 45% were single, 46.3% married, 3.8% widowed, and 5% divorced.

Only 8.8% of the patients included in our study were out of school. More than half (57.4%) had secondary education and more than a quarter (27.5%) had tertiary education.

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Among the patients surveyed, nearly 42% were unemployed, just over 10% were students, and only 5% were retired.

Table 1. Distribution of patients by socio-demographic characteristics.

Parameter		(N =80)	(%)
Age	05-20 ans	11	13.75
	20-50 ans	55	68.75
	>50 ans	14	17.25
Sex	Women	52	65
	Men	28	35
Marital status	Married	37	46.3
	Single	36	45.0
	Widowed	3	3.8
	Divorced	4	5.0
Educational level	Not enrolled	7	8.8
	Primary	5	6.3
	Secondary	46	57.4
	Tertiary	22	27.5
Socio-economic level	0_15000DA	46	57.50
	15001_50000DA	27	33.80
	>50000DA	7	8.80
Toxic habits	Alcohol	04	5.00
	Tobacco	13	17.00
Comorbidities	Yes	26	32.60
	No	54	64.40
Type of tuberculosis	PTB	26	32.50
	EPTB	54	67.50

In our study, low-income people (0_15000DA) accounted for more than half (57.7%) of the population with tuberculosis. In contrast, the rate of tuberculosis was significantly lower (8.8%) in the high-income population (50000DA). Two-thirds (32.6%) of the patients in the study had associated chronic diseases, namely hypertension (38%), diabetes (27%), asthma (12%) and thyroiditis (23%). In our study, a minority were smokers and alcohol consumers, with percentages of 17% and 5% respectively.

All forms of tuberculosis were present in our study, with the highest rate observed for extrapulmonary tuberculosis, which was 67.5%.

Adverse reactions

Table 2 shows that the vast majority of our patients (76.25%) experienced unpleasant side effects after treatment with anti-tuberculosis drugs, while 23.75% did not. Digestive disorders were the most common adverse event in our study (33.1%), followed by joint disorders, peripheral neuropathy and skin manifestations (18.40%, 15.6% and 15.6%, respectively). Hematological and hepatic disorders occurred in 7.5% and 5.7% of cases, respectively.

Table 2. Types of adverse effects observed with anti-tuberculosis treatment.

Adverse effects	Number of Cases	Percentage (%)
Adverse effects / patients (n:80)	61	76.25%
Adverse effects/types		
Digestive effects		
Nausea/vomiting	43	33.1%
Abdominal pain	20	
Diarrhea	3	
Loss of appetite	4	
Joint effects	39	18.4%
Skin effects		
Skin Rash	27	15.6%
Acne	6	
peripheral neuropathy	33	15.6%

Factors associated with the occurrence of adverse reactions to anti -tuberculosis drugs

Table 3 shows that the occurrence of adverse reactions to anti-tuberculosis treatment was associated with the duration of treatment (more frequent at the beginning of treatment) and with certain classes of self-medication.

Table 3. Incidence of adverse reactions according to sociodemographic, clinical and therapeutic characteristics.

Parameter		Adverse effects		p value
		Presence	Absence	
Sex	Men	19(23.8%)	9 (11.3%)	0.196
	Women	42(52.5%)	10(12.5%)	
Co-infection	Yes	5 (6.4%)	0 (0%)	0.197
	No	56(70.0%)	19 (23.8%)	
Allergy/Drug intolerance	Yes	5 (6.3%)	0 (0%)	0.197
	No	56 (70 %)	19 (23.8 %)	
Self-medication	Yes	51 (63,8%)	9(11.3%)	0.06
	No	10(12.5%)	10(12.5%)	
Toxic habits	Yes	13 (16.3%)	5 (6.3%)	0.648
	No	48 (60.0%)	14 (17.5%)	
Phytotherapy	Yes	43 (52.5%)	9 (11.3%)	0.065
	No	18 (23.8%)	10 (12.5%)	
Medication	Analgesic	28 (35.0%)	6 (7.5%)	
	Antibiotic	8 (10.0%)	2 (2.5%)	**0.05**
	NSAIDS*	8 (10.0%)	0 (0%)	
	Others	4 (5.1%)	2 (2.6%)	
Duration of treatment	≤6months	44	9	**0.044**
	>6months	17	10	

*NSAIDS: Non-Steroidal Anti-Inflammatory Drugs

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Table 4 shows an association between the manifestation of cutaneous and gastrointestinal adverse events and patients with drug allergy or intolerance. Nausea and vomiting were also associated with gender.

Table 4. Type of adverse reactions to anti-tuberculosis drugs according to drug allergy and intolerance.

Adverse effects	Allergy and Drug intolerance			p value
	Presence		Absence	
Skin rash	Yes	4(5.0%)	23(28.8%)	**0.024**
	No	1(1.3%)	52(65.0%)	
Hepatic disorders	Yes	0(0.0%)	10(12.5%)	0.383
	No	5(6.3%)	65(81.3%)	
Diarrhea	Yes	1(1.3%)	2(2.5%)	**0.048**
	No	4(5.0%)	73(91.3%)	
	Oui	5(6.3%)	38(47.5%)	
	Non	0(0.0%)	37(46.3%)	**0.032**
Nausea /vomiting				
	Women		**Men**	**0.01**
	Yes	35 (43.7%)	8 (10%)	
	No	17 (21.3%)	20 (25%)	

A correlation was established between the presence of adverse effects (skin rash, abdominal pain, hematological, and hepatic disorders) and the use of phytotherapy as well as co-infection status. The analysis shows that skin rash was significantly associated with the use of herbal therapy in patients on anti-tuberculosis drugs **(p = 0.019)**. No significant associations were found between phytotherapy and other adverse effects (p>0.05).

Co-infection was significantly associated with a higher occurrence of hematological disorders **(p = 0.021)** and showed a borderline association with liver disorders **(p = 0.05).** No significant association was found between co-infection and other adverse effects.

Joint pain occurrence in patients on antituberculosis treatment was analyzed by treatment type and sex. Joint pain was significantly more frequent in women than in men **(p = 0.029).** Furthermore, only the combinations containing PZA (RHZE, RHZ) caused arthralgia (100%).

4. DISCUSSION

Sociodemographic characteristics

Tuberculosis can occur at any age. The [20-50] age group is the most affected by tuberculosis, representing 68.75% of the studied population, because they belong to the active and productive population. The mean age was 36.68 ± 15.49 years, with extremes ranging from 5 years for the youngest to 80 years for the oldest. The predominance of young adults could be explained by their intense activity and frequent contact with the outside environment, which exposes them more to sources of tuberculosis infection.

Both sexes were affected, but there was a predominance of females, with 65% of females compared to 35% of males, giving a male/female ratio of 1.85 in favour of females.

This female predominance could be explained by the high incidence of EPT in our study. The predilection of women for the extrapulmonary form may be related to limited access to health care and the prevalence of other risk factors such as smoking. Most strikingly, being female is an independent risk factor for EPTB. **[10]**

According to the Epidemiological Bulletin of the Regional Health Observatory of Oran (Algeria), a male predominance for TP with a sex ratio of 1.5 and a female predominance for EPTB with a sex ratio of 0.6 was found in the western region of Algeria in 2020. **[9]**

In our study, unemployed patients are the most represented with a percentage of 41.30%. This result is in line with what has been reported in the literature. We explain this result by the fact that poverty and low socio-economic status generally lead to promiscuity, which is a risk factor for tuberculosis.

57.50% of the patients surveyed had no source of income or an income of less than 15,000 DA. These results are consistent with a study conducted by Ekono Bit Chong et al. (2018) in Yaoundé, Cameroon, where patients with no source of income constituted the majority. **[11]**

Adverse effects

The major adverse effects of anti-tuberculosis drugs can lead to significant morbidity and compromise tuberculosis treatment regimens. In our study, 76.20% of patients experienced adverse events, of which 15.16% were serious hepatic, hematological and neuropsychiatric reactions. The outcome of adverse events is like 76.5% and 80.3% found by Bégum LN et al in Bangladesh and Ouédraogo et al in Burkina Faso. **[12, 13]**

The occurrence of adverse events was more common in women (52.5%) than in men (23.8%), with a statistically significant association between patient gender and the occurrence of joint pain (p=0.029) and nausea and vomiting (p=0.01). This result is comparable to the 2015 study by Gharsalli et al, who found a female predominance of 70%. **[14]** Studies in the United Kingdom and Canada have also reported that women had a significantly higher incidence of adverse events with anti-tuberculosis drugs. **[15]**

This disparity has been attributed to pharmacokinetic and hormonal differences between the sexes. Women have a slower gastric emptying time, a lower body mass index and differences in total body water compared to men, resulting in greater absorption of anti-tuberculosis drugs. In addition, androgenic activity in men induces hepatic microsomal enzyme activity,

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resulting in more efficient drug metabolism. **[16]** This suggests that special precautions should be taken when prescribing anti-tuberculosis drugs to women.

Nature of adverse reactions

33.1% of the adverse reactions reported were digestive disorders, 18.4% were joint disorders, 15.60% were peripheral neuropathies, 15.60% were skin disorders, 7.5% were hematological disorders.

5.7% were liver disorders, 2.3% were neuropsychiatric effects and 1.8% were ocular disorders. This distribution of adverse events is similar to that found in the study by M. El Hamdouni in Morocco in 2015, where gastrointestinal intolerance (38.9%), skin manifestations (22.7%), liver disorders (19.7%), neuropsychiatric disorders (11.0%) and joint disorders (9.1%) were the most commonly reported adverse events. **[17]**

In another study conducted by H. Gharsalli et al in Tunisia in 2015, the most commonly, described adverse events were skin disorders (70%), gastrointestinal intolerance (30%), joint disorders (25%) and hepatic cytolysis (20%). **[14]**

Joint effects

18.4% of the patients reported joint pain. This result is similar to that of Begum Lutfun Nahar et al. in Bangladesh 2006, who found 35.7%. (14) However, it is higher than that of Schaberg in Germany in 1996, where the rate of arthralgia was 2%. **[18]**

In a multicentre study, arthralgia was reported in 6 of the 617 patients receiving RHZ but none of the 445 patients receiving RH, which is similar to our study where none of the patients receiving RH complained of arthralgia (p=0.083). **[19]** Arthralgia is considered a minor side effect if it is not related to hyperuricemia. It is common with PZA and less common with INH. This is probably due to pyrazinoic acid, the main metabolite of PZA, which inhibits renal tubular secretion of uric acid, thereby increasing its serum concentration and causing joint pain. **[20]**

One study showed that a treatment regimen without RIF was a risk factor for arthralgia. This finding suggests that RIF may indirectly protect against arthralgia. In the study by Nazareth et al, arthralgia was reported in 38% of patients treated with rifampicin and 66% of patients not treated with RIF, a highly significant difference (p<0.001). **[19,21]**

Skin manifestations

Rash or acne may occur during treatment for tuberculosis. It is difficult to identify the causative agent, as all anti-tuberculosis drugs indicated as first-line treatment may cause them. **[22]** The rate of cutaneous adverse events in our sample was 15.60%. This figure is similar to that of Kiran M and Nagabushan H who observed 18 cases or 20.93% of pruritus and rashes. **[23]** In our study, a statistically significant association was found between the occurrence of skin rash and two factors: allergy (p=0.024) and the use of phytotherapy (p=0.019).

Neurological disorders

Neuropsychiatric adverse reactions may occur during anti-tuberculosis treatment. They range from non-serious and transient disorders such as insomnia to serious but less frequent adverse reactions such as depression in pellagra and convulsions. **[24]** In the present study, 2.80% of patients reported convulsions and anxiety. 15.60% of patients in our study complained of peripheral neuropathy.

According to the literature, INH may be responsible for dose-dependent peripheral neuropathies. Clinically, these manifest as paresthesias and numbness of the lower limbs. These symptoms are thought to be associated with a partial pyridoxine (vitamin B6) deficiency. For this reason, vitamin B6 is often systematically combined with anti-tuberculosis treatment. **[25]**

Hepatic disorders

Eleven patients (5.70% of our study population) experienced hepatic disorders, such as hepatic cytolysis, transaminase elevation, and jaundice. This finding aligns with results reported by Moutaouakkil et al. in 2018 in Morocco, where hepatic adverse events were observed in 6.79% (n = 7) of participants**. [24]**

The risk factors associated with an increased incidence of antituberculosis drug-related hepatotoxicity in developing countries are malnutrition, HIV infection and the presence of hepatitis B and C virus infection. **[26]** In addition, certain factors such as advanced age, female sex and pregnancy are related to terrain. In our study, co-infection was the factor statistically associated with increased hepatotoxicity (p=0.05).

INH, RIF and PZA are responsible for several adverse effects, of which hepatotoxicity is the most common. The occurrence of this effect may be the cause of treatment failure. The exact mechanism of hepatotoxicity is not well defined, but is attributed to toxic metabolites. **[27]**

Among all the anti-tuberculosis drugs, INH is the one that most significantly contributes to the development of hepatotoxicity. In the liver, N-acetyltransferase 2 (NAT2) converts INH to acetyl-INH, which is then hydrolyzed to acetylhydrazine and subsequently oxidized to hepatotoxic metabolites (hydrazine). A slow acetylation phenotype of NAT2 has been demonstrated and represents a significant risk factor for hepatitis. **[28]**

Hematological disorders

In our study, 7.50% of adverse events were hematological disorders, with a statistically significant association with co-infection (p=0.021). This result is higher than that found in the study by Kiran M and Nagabushan who reported 6.97% of hematological disorders. **[23]**

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Among first-line anti-tuberculosis drugs, RIF is most commonly associated with thrombocytopenia. This is probably due to immunological reasons. On the other hand, anemia is common with INH and RIF. INH causes anemia in pyridoxine-deficient individuals, which can be corrected by high doses of pyridoxine. RIF also causes immunologically mediated hemolysis. **[23]**

Visual disturbances

Four patients (1.8%) reported ocular adverse events. The most common adverse effect of EMB is optic neuritis, associated with decreased visual acuity, reduced visual field, central or peripheral scotomas, and altered colour perception (red and green). The degree of ocular toxicity appears to be related to the dose of EMB administered and the duration of treatment; it often occurs after two months of treatment at a daily dose of 25 mg/kg body weight. **[29]**

Gastrointestinal disturbances

Diarrhea, nausea, vomiting, abdominal pain and anorexia are the main manifestations of gastrointestinal intolerance associated with these drugs, which is comparable to the findings of the study conducted by Moutaouakkil et al. 2018 in Morocco. **[24]**

These adverse effects may occur as early as the first week and persist for more than two months, or even throughout the treatment period, and should always prompt a liver assessment to look for signs of associated hepatotoxicity.

According to the WHO, if gastrointestinal intolerance is severe enough to risk treatment interruption, it is recommended to withhold RIF for three or four doses, treat symptoms or, as a last resort, give RIF to the patient.

As a last resort, RIF should be given with small amounts of food so that the drug is not interrupted. Although the concomitant intake of food slightly reduces the absorption of RIF, it is preferable to continue taking the drug. **[30]** Our study found a statistically significant association between drug intolerance and the occurrence of diarrhea (p=0.048) and nausea and vomiting (p=0.032) with anti-tuberculosis drugs.

Drug interactions

In our study, there was a significant association between certain self-medication drugs and the occurrence of adverse reactions to anti-tuberculosis drugs (p=0.05). The clinically significant interactions were mainly with RIF and INH. They may be associated with consequences ranging from therapeutic failure, as with corticosteroids, to toxicity, such as the risk of hepatotoxicity with paracetamol, antibiotics (azithromycin, sulfonamides). Most interactions are pharmacokinetic and involve the activity of cytochrome P450 enzymes. In general, RIF is an enzyme inducer and INH is an enzyme inhibitor. **[31]**

5. CONCLUSION

Despite efforts to control tuberculosis, it remains a significant public health issue. This study found that 76.2% of patients experienced adverse effects during standard tuberculosis treatment, with 22.5% discontinuing therapy, leading to increased morbidity and treatment failure. Severe adverse reactions (15.16%) were more common in patients with risk factors. Co-infection was linked to higher rates of hepatic and hematological issues, while allergies and drug intolerance were associated with digestive and dermatological disorders. Women were more prone to side effects like nausea and joint pain. Phytotherapy and self-medication also contributed to skin disorders and hepatotoxicity. The study emphasizes the importance of integrating pharmacovigilance into treatment programs to improve outcomes and optimize healthcare resources.

Competing interests: The authors declare that they have no competing interest.

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