Original article

Characterization of patients with symptoms suggestive of adverse reactions to antituberculosis drugs

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Abstract
Introduction. The appearance of adverse reactions to antituberculosis drugs may condition the patient to require dose adjustments and modifications in the administration schedules. This represents a risk for adherence to treatment, which could lead to its suspension and, consequently, delay both cure and completion of treatment. In addition, these reactions may require hospital care, increasing the health expenditure for patient care. **Objective.** Characterize patients with symptoms suggestive of adverse reactions to antituberculosis drugs. **Methodology.** This was a descriptive cross-sectional study in a population of 89 patients. It was oriented to identify characteristics such as age, sex, occupation, comorbidities and symptoms suggestive of adverse reactions to antituberculosis drugs in patients who received such drugs. Quantitative techniques were used, obtaining results from the review of clinical files. **Results.** The most frequent age range during the study corresponded to people between 18 and 41 years, and 59.6 % were male. The most frequent symptoms in patients with adverse reactions to antituberculosis drugs were anorexia and epigastralgia, which accounted for 26.9 % of the reported reactions. The population from rural areas was the most affected. **Conclusion.** The symptoms reported in patients with adverse reactions to antituberculosis drugs were mainly gastrointestinal. The most frequent comorbidity was diabetes *mellitus*.

Keywords
Tuberculosis, Antitubercular Agents, Drug-Related Side Effects and Adverse Reactions.

Resumen
Introducción. La aparición de reacciones adversas a medicamentos antituberculosis puede condicionar al paciente a requerir ajustes de dosis y modificaciones en los horarios de administración, esto representa un riesgo para la adherencia al tratamiento, lo que podría conducir a su suspensión y, en consecuencia, retrasar tanto la curación como la finalización del mismo. Además, estas reacciones pueden requerir atención hospitalaria, incrementando el gasto en salud para la atención de los pacientes. **Objetivo.** Caracterizar a los pacientes con síntomas sugestivos de reacciones adversas a fármacos antituberculosis. **Metodología.** Se desarrolló un estudio descriptivo transversal en una población de 89 pacientes. Se orientó a identificar las características como edad, sexo, ocupación, comorbilidades y síntomas sugestivos de reacciones adversas a fármacos antituberculosis en los pacientes que recibieron dichos medicamentos. Se utilizaron técnicas cuantitativas, obteniendo resultados a partir de la revisión de expedientes. **Resultados.** El rango de edad más frecuente durante el estudio correspondió a personas entre los 18 y los 41 años. El 59,6 % de la población estudiada fue de sexo masculino y los síntomas más frecuentes en personas con reacciones adversas a medicamentos fueron la anorexia y la epigastralgia, representando un 26,9 % de las reacciones reportadas. La población proveniente del área rural fue la más afectada. **Conclusión.** Los síntomas mas frecuentes en personas con reacciones adversas a fármacos antituberculosis fueron principalmente gastrointestinales. Dentro de los pacientes con tuberculosis, la diabetes *mellitus* fue la comorbilidad más frecuente.

Palabras clave
Tuberculosis, Antituberculosos, Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos.

Introduction

According to the World Health Organization (WHO), tuberculosis is an infectious disease that mainly affects the lungs, generating respiratory and systemic symptoms.[i]

In 2022, an estimated 10. 6 million people worldwide were ill with tuberculosis and 1. 3 million died from it.[i] The Pan American Health Organization (PAHO) warns that "every day, about 4400 people lose their lives to tuberculosis and about 30 000 people fall ill with this preventable and curable disease ".[ii]

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Caracterización de pacientes con síntomas sugestivos a reacciones adversas a fármacos antituberculosis

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In El Salvador, there are prevention and control measures for this disease, focused on the individual, the family and the community. Medical management is also established through guidelines and norms; however, the treatment can cause adverse reactions that are associated with patient factors or conditions.[iii]

The occurrence of adverse reactions to antituberculosis drugs can lead to the need to adjust doses or schedules, suspend medication and require in-hospital treatment.[iv] In a study carried out in South Korea, which evaluated the incidence of adverse reactions to first-line antituberculosis drugs, 17 843 cases of adverse reactions were recorded, the most frequent being nausea, alterations in liver enzymes, rash, pruritus, vomiting, urticaria and anorexia, among others.[v]

In the eastern region of Ghana, a cohort study conducted in a population treated with first-line antituberculosis drugs, adverse reactions were observed in the gastrointestinal tract, including nausea, vomiting, abdominal pain and diarrhea[vi]. In another study carried out in Bolivia, out of a total of 52 patients included, gastric alterations were the most frequent adverse reactions to antituberculosis drugs, followed by dermal reactions in second place and hepatic reactions in third place.[vii]

In the prevention of drug-related adverse effects, the importance of pharmacovigilance stands out, with the aim of detecting, evaluating and preventing adverse reactions to drugs used for the treatment of tuberculosis. This contributes to improving adherence to treatment and reducing the risk of microbial resistance, allowing decisions to be made on the use of second-line drugs.[viii]

A study conducted at Dr. José Matías Delgado University in El Salvador revealed that the most prevalent adverse drug reaction (ADR) was drug-induced hepatitis.[ix] In 2019, the department of Santa Ana documented 117 cases of tuberculosis. This number decreased to 93 cases in 2021 and 84 cases in 2022.[x] However, there are no reports of ADR for those years.

In many countries, adverse reaction reports are infrequent, which could indicate a lack of knowledge among healthcare workers about the importance of pharmacovigilance. Therefore, the actual frequency of such effects is often unknown.[xi] For the success of tuberculosis treatment, treatment adherence is vital. One of the factors related to non-adherence is treatment abandonment due to adverse effects of anti-tuberculosis drugs.[xii] The research aimed to characterize patients with symptoms suggestive of ADR and their comorbidities.

Methodology

A descriptive cross-sectional study was developed from a population of 171 patients who received treatment for sensitive tuberculosis during the years 2019 and 2021, from family health units of the city of Santa Ana, who registered more than three cases of treatment-sensitive tuberculosis in both years. Eight community health units were included according to the above criteria. Five health units were excluded because they did not present cases of tuberculosis in the years included in the study.

The sample calculation was performed using the formula for finite populations, with 95 % reliability and a 5 % margin of error, resulting in a sample of 118 patients, who were randomly selected by drawing lots from the list of patients in each health unit. The inclusion criteria to select the patients were the following: new cases and those who have been prescribed the four first-line drugs (isoniazid, rifampicin, pyrazinamid, and ethambutol), who presented bacteriologically confirmed or clinically diagnosed pulmonary tuberculosis, bacteriologically confirmed extra pulmonary cases and who had completed treatment for sensitive tuberculosis. The exclusion criteria were patients deprived of liberty, with loss of follow-up, classified as treatment failures, pending bacteriological study, with tuberculosis resistant to treatment, under 18 years of age, and pregnant women.

Eighty-nine patient files that met the inclusion criteria were included in the final analysis because two of the selected health facilities mentioned that they did not currently have a patient data registry book for 2019. The data collection process was meticulously executed in two phases. In the initial phase, a systematic approach was undertaken to the health units within the city of Santa Ana. This approach entailed the preliminary review of files to identify and select participants who met the predetermined inclusion criteria. The second phase entailed the actual data collection process.

This study included the following variables: epidemiological characteristics (age, sex, origin, occupation), symptoms associated with adverse drug reactions (epigastralgia, nausea, vomiting, among others) and comorbidities in patients (diabetes mellitus, hypertension).

The data were processed using the Microsoft Excel program, and subsequently filtered to generate frequency tables. The

research was carried out in accordance with the ethical principles of beneficence, non-maleficence, respect for human dignity, and justice, as well as the confidentiality and privacy of the data obtained from the data collection process. This study was approved by the ethics committee of the Western Health Region (act No. 01/2023).

Results

From the selected health facilities in the department of Santa Ana, a total of 89 patients with sensitive tuberculosis management were recorded.

The patients with symptoms suggestive of adverse reactions to treatment with antituberculosis drugs are characterized by being mostly male, with 58. 6 %, and the most frequent age range is from 18 to 41 years, representing 48. 2 % (Table 1).

Workers in various occupations predominated, with 34. 5 %, followed by housewives with 20. 7 %. According to origin, 51. 7 % of the patients who presented symptoms suggestive of adverse reactions were from rural areas (Table 1).

Thirty-two point six percent of patients reported symptoms suggestive of ADR. The most common symptoms were gastrointestinal discomfort (26. 9 %), including anorexia, nausea, vomiting, epigastralgia, and combinations of two or more symptoms.(Table 2).

Figure 1 shows the most frequent comorbidities found in patients with tuberculosis. More than 50 % of the patients had a history of one or more comorbidities, three out of ten had diabetes *mellitus*, and two out of ten patients had arterial hypertension (Table 3).

Discussion

Tuberculosis is still a threat in El Salvador, with a rate of 32. 3 cases per 100 000 inhabitants (2042 cases of tuberculosis) in 2020,[x] resulting from the active search for cases in high-risk groups, in addition to the use of new diagnostic methods. This results in a greater number of patients who require treatment with anti-tuberculosis drugs for their cure and which directly expose them to adverse reactions to these drugs. The risk may increase when there are risk factors that place patients undergoing treatment at a disadvantage, such as pre-existing diseases, hereditary factors, age, among others. Pre-existing diseases can alter the pharmacokinetics of drugs, as well as the body's response to drugs, increasing the risk of adverse effects.[xiii]

The findings of the study reveal that a significant majority of participants were male. This trend aligns with observations made in the National Multisectoral Strategic Plan for Tuberculosis Control in El Salvador, covering the years 2017 to 2021. According to the Ministry of Health, men are diagnosed with tuberculosis at higher rates than

Table 1. Characterization of patients with symptoms suggestive of adverse reactions to antituberculosis drugs..

Population	Total of patients (N= 89)	Presence of symptoms suggestive of RAFA	Ausencia de síntomas sugestivos a RAFA
Sex			
Male	53 (59.6 %)	17 (58.6 %)	36 (60.0 %)
Female	36 (40.4 %)	12 (41.4 %)	24 (40.0 %)
Age			
From 18 to 29	23 (25.8 %)	9 (31.0 %)	14 (23.3 %)
From to 30 to 41	22 (24.7 %)	5 (17.2 %)	17 (28.3 %)
From 42 to 53	14 (15.7 %)	7 (24.1 %)	(12.27-31.71)
From 54 to 65	13 (14.6 %)	3 (10.3 %)	7 (11.7 %)
From 66 to 77	14 (15.7 %)	4 (13.8 %)	10 (16.7 %)
From to 77 years	3 (3.4 %)	1 (3.4 %)	2 (3,3 %)
Occupation			
Employer	11 (12.4 %)	2 (6.9 %)	9 (15.0 %)
Homemaker	22 (24.7 %)	6 (20.7 %)	16 (26.7 %)
Various trade	32 (36.0 %)	10 (34.5 %)	22 (36.7 %)
Unemployed	12 (13.5 %)	7 (24.1 %)	5 (8.3 %)
Retired	2 (2.2 %)	0 (0.0 %)	2 (3.3 %)
Student	10 (11.2 %)	4 (13.8 %)	6 (10.0 %)
Origin			
Urban	52 (58.4 %)	14 (48.3 %)	38 (63.3 %)
Rural	37 (41.6 %)	15 (51.7 %)	22 (36.7 %)

Table 2. Symptoms associated with RAFA in patients undergoing treatment for sensitive tuberculosis.

Symptoms	Frequency	Percentage
None	60	67.4 %
Anorexia	6	6.7 %
Epigastralgia	5	5.6 %
Epigastralgia and Nausea or vomiting	5	5.6 %
Epigastralgia and Anorexia	3	3.4 %
Nausea or vomiting	3	3.4 %
Nausea or vomiting and Anorexia	2	2.2 %
Joint pains	1	1.1 %
Skin alterations (erythroderma)	1	1.1 %
Jaundice	1	1.1 %
Nausea or vomiting and joint pains	1	1.1 %
Burning sensation	1	1.1 %
Total	89	100,0 %

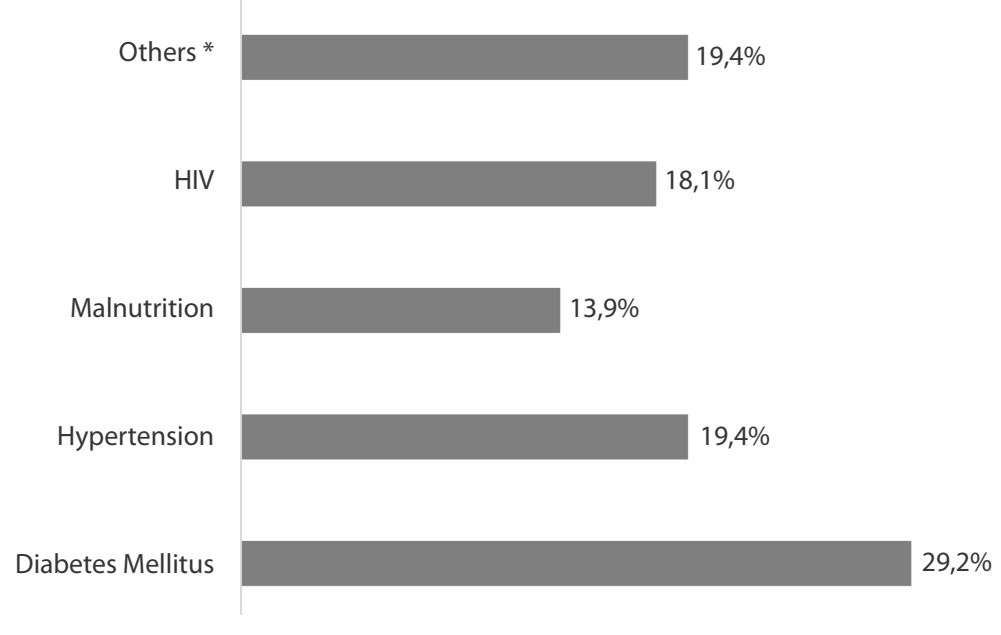

Figure 1. Comorbidities of patients with treatment-sensitive tuberculosis with symptoms suggestive of RAFA in the Health Units of the Municipality of Santa Ana in 2023

*Others: adult malnutrition, renal failure, bronchial asthma, heart disease, chronic obstructive pulmonary disease.

women, and they also experience greater mortality rates due to the disease.[xiv]

A study carried out in Brazil, which characterized patients with adverse drug reactions related to the treatment of drug-sensitive tuberculosis, showed a percentage corresponding to 59. 5 % of the affected male population.[xv].

For this study, the age group most affected by treatment-sensitive tuberculosis was between 18 and 29 years; in a study on the epidemiological situation of tuberculosis in Chile in 2018, the highest rate of tuberculosis cases was reported between 25 and 64 years of age.[xvi] The results of this research present some degree of similarity with a study conducted in Baja California, Mexico, where the most affected age group was 21 to 30 years.[xvii]

The Ministry of Health of El Salvador, through the National Multisectoral Strategic Plan for the Control of Tuberculosis 2022-2026, states that this disease is strongly related to poverty, since although cases occur

Table 3. Patients with sensitive tuberculosis with comorbidities who presented symptoms suggestive of RAFA.

Comorbidity	Presence of symptoms suggestive of RAFA	Absence of symptoms suggestive of RAFA
Diabetes Mellitus	13 (28.3 %)	8 (30.8 %)
Hypertension	6 (13.0 %)	8 (30.8 %)
Malnutrition	8 (17.4 %)	2 (7.7 %)
HIV	8 (17.4 %)	5 (19.2 %)
Others	11 (23.9 %)	3 (11.5 %)

in all social strata, it is the poorest who are most at risk due to overcrowding in housing, work, and transportation, in addition to generally having a weaker immune system due to inadecuate nutrition.[xiv,xviii]

Regarding health-related quality of life and work in patients with tuberculosis, a study in Guadalajara, Mexico, found that more than half of the patients with tuberculosis were unemployed (58. 4 %) while one-fifth were engaged in commerce and one-fifth were employed,[xvii] similar data obtained in this study, where most patients diagnosed with tuberculosis work in various trades, informal commerce or are housewives.

Regarding the comorbidities present in the patients who received treatment for drug-sensitive tuberculosis, most of the participants had diabetes *mellitus* or hypertension, or both conditions simultaneously.

Tuberculosis and diabetes *mellitus* are associated; people with diabetes *mellitus* are more likely to develop tuberculosis than those without a history of this chronic noncommunicable disease.[xix]

A study on the factors associated with pulmonary tuberculosis in Peru states that, out of 124 patients, 38 (23. 4 %) presented comorbidities such as diabetes and arterial hypertension.[xx] It is important to mention that people with tuberculosis, depending on their immunological response, may present adverse reactions to drugs.

According to a study, patients with type 2 diabetes mellitus are more susceptible to adverse reactions, because diabetes, in addition to compromising their immune system, affects glycemic control and the patients' metabolism is affected by the antituberculosis drugs, making glycemic control even more difficult.[xx] According to the results of this study, diabetes *mellitus* is present in 3 out of 10 patients who underwent treatment for sensitive tuberculosis and hypertension was present in 2 cases out of 10 participating patients.

With respect to the therapy through the drugs that must be prescribed at the time of diagnosis of the patient with sensitive tuberculosis, the treatment can mean a risk for the presence of adverse reactions, which in the most severe cases cause a higher deterioration in the patient's health, These complications have been addressed previously, for example, in a study carried out in Ghana, which describes that in general 47. 9 % of the patients experienced at least one adverse reaction to anti-tuberculosis drugs.[vi]

The proportion of male patients who presented symptoms suggestive of ADR in this investigation is similar to that obtained in a cohort study conducted in Brazil, where 59. 5 % of the male population experienced adverse reactions.[xv]

Although the prevalence of tuberculosis in this study was higher in patients from urban areas, patients from rural areas presented a higher percentage of symptoms suggestive of adverse reactions to antituberculosis drugs. The presence of adverse reactions to antituberculosis drugs may be related to the patient's origin; a study with 29 patients showed that 55. 2 % of the patients undergoing treatment presented adverse effects and that 62 % of the cases were from rural areas.[xxii]

More than a quarter of patients with diabetes and tuberculosis had at least one symptom suggestive of ADR, and approximately one in 10 patients with hypertension and tuberculosis had symptoms related with adverse reactions to antituberculosis drugs.

The development of resistance to antituberculosis antibiotics is a growing problem worldwide. Poor adherence to treatment is a key factor in this development, and it is associated with various factors, including ADRs.[viii] This underscores the critical need to prioritize research on the prevalence of these reactions. Adverse reactions to antituberculosis drugs can lead to changes in the therapeutic regimen, affecting both the patient and the community due to an increased risk of drug suspension or resistance as well as the patient's adverse reactions. Alternative therapeutic regimens may be less effective or require longer treatment times.[iv] The occurrence of side effects and socioeconomic factors are directly related to patient abandonment of treatment.[xxiii]

The lack of information on adverse reactions and their influence on therapeutic adherence highlights the importance of pharmacovigilance in the monitoring and supervision of tuberculosis treatment; therefore, the detection, evaluation, and prevention of the appearance of side effects should be permanent.[viii] The absence of registry books containing patient file numbers in two of the selected facilities limited compliance with the calculated sample, which is a limitation for extrapolating the results to the general population.

Throughout the course of treatment with antituberculosis drugs, adverse effects may occur, which, as far as possible, should not alter or interrupt the treatment regimen. An adequate interrogation can help determine whether the symptoms reported by the patient during therapy are adverse effects related to antituberculosis drugs. [xxiv] For all these reasons, the identification, quantification, and evaluation of the risks associated with the use of drugs promptly can avoid or minimize harm to patients and allow the necessary preventive and curative measures to be adopted.[vii,xxv]

Conclusions

The male gender, between 18 and 41 years of age, was the group most affected by symptoms suggestive of adverse reactions to antituberculosis drugs in the population studied. Patients engaged in trades such as informal commerce, agriculture and construction were mostly from urban areas, although those residing in rural areas presented a higher percentage of symptoms. The predominant symptoms were gastrointestinal (epigastralgias, nausea and vomiting). Diabetes *mellitus* was the most frequent comorbidity, with a greater number of AFRS symptoms compared to patients with other diseases.

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