

# Anti-TB Drug Side-Effects on the Treatment of Drug-Resistant Tuberculosis (DR-TB) in dr. Zainoel Abidin Hospital Banda Aceh

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### **Abstract**

**Background:** Drug-resistant tuberculosis (DR-TB) is treated with second-line anti-tuberculosis (anti-TB) drugs which are comparatively less effective and more toxic. The increased toxicity of the drugs may lead to the occurrence of side effects throughout the treatment. The study aims to assess DR-TB patients' side effects and clinical profile at the dr. Zainoel Abidin Hospital, Banda Aceh.

**Methods:** Observational descriptive study of DR-TB patients who underwent treatment from 2020 to 2022 at dr. Zainoel Abidin Hospital, Banda Aceh. The data was taken from medical records of patients which are then analysed using univariate analysis.

**Results:** Out of 49 patients, most of them were male with 23 people (65,3%), belonging to the age group of 46-55 with 11 people (22,4%), worked as entrepreneurs with 11 people (22,4%), and most came from Banda Aceh and Aceh Besar with 14 people each (28,6%). Twenty-seven patients (65,1%) were suspected of secondary infection, most of which were cases of relapse from 10 people (20,4%). 39 of the patients (79,6%) had rifampicin-resistant tuberculosis. 36 patients (73,4%) were given individualized treatment with Lfx - Bdq - Lzd - Cfz - Cs being the most common drug combination given to 16 people (32.7%). All patients experienced side effects from the treatment, with the most common being nausea from 28 people (57,1%) followed by peripheral neuropathy from 19 people (38,8%).

**Conclusion:** Side effects are commonly found in the treatment of DR-TB and may become more prevalent as the treatment continues. Educating the patient and treating side effects is important to maintain patient compliance.

Keywords: anti-tuberculosis drug, drug-resistant tuberculosis, side effects

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# INTRODUCTION

Tuberculosis is an airborne disease caused by Mycobacterium tuberculosis which is spread through droplets in the air.<sup>1</sup> TB is treated using first-line antituberculosis (anti-TB) drugs (drugs that consist of isoniazid, rifampicin, ethambutol, and pyrazinamide for 6 months.<sup>2</sup> However, inadequate treatment can be the cause of drug resistance developing in the bacteria.<sup>2,3</sup> Tuberculosis that resists one or more anti-TB drugs is called drug-resistant tuberculosis (DR-TB).<sup>2</sup>

Globally, in 2022, 6.2 million people were diagnosed with pulmonary TB, with 63% being bacteriologically confirmed. From 73% of pulmonary TB cases were bacteriologically confirmed, 149,511 patients had Multi Drug Resistant (MDR)/ Rifampicin

Resistant (RR)-TB, and 27,075 had pre-extensive Drug Resistant (XDR-TB) or XDR-TB.<sup>4,5</sup>

The estimated annual number of people who developed MDR/RR-TB globally was relatively stable between 2020 and 2023. The estimated number in 2023 was 400,000. In the Southeast Asia Region, after an increase in 2021 and 2022, the estimated number of people who developed MDR/RR-TB stabilized in 2023. The estimated number of incidence cases of MDR/RR-TB in Indonesia in 2023 was 30,000.4

Drug Resistant-Tuberculosis (DR-TB) treatment in Indonesia is carried out by giving long-term and short-term drug regimens.<sup>2</sup> Short-term regimen is done by giving a standardized anti-TB drug for DR-TB patients that are eligible for the criteria. Patients that are not eligible for short-term

regimens are instead given long-term/individualized regimens which are carried out by administering anti-TB drugs accordingly.<sup>2</sup> Short-term treatment regimens may last for as long as 9 to 11 months while long-term regimens may last for as long as 18 to 24 months.<sup>2</sup>

The treatment of DR-TB is a significant challenge due to its prolonged duration, the complexity of its regimens, and the toxicity of its agents, which are likely to cause adverse drug reactions (ADRs).6 Adverse effects that may occur from the treatment of DR-TB are teratogenesis, cardiac symptoms, gastrointestinal symptoms, arthralgia, arthritis, skin discoloration, peripheral neuropathy, depression, hypothyroidism, sleep disorder, liver function disorder, tendinopathy, hematological disorder, lactate acidosis, seizures, vision impairment, hearing impairment, vestibular disorder.<sup>2,7</sup>

In 2019, the World Health Organization (WHO) recommended the discontinuation of injectable drugs and a switch to oral drug treatment with the addition of bedaquiline.<sup>8</sup> Anti-TB drug injection, which includes amikacin and streptomycin, are known to cause hearing and balance impairment in patients undergoing treatment.<sup>2</sup>

Patient compliance in receiving the treatment is an important factor in determining the outcome of the treatment. The occurrence of adverse effects, a lack of patient awareness, and the lengthy duration of treatment may result in the cessation of therapy.

There is no data on the side effects that occur in patients with DR-TB in Aceh. Therefore, this study aimed to assess the side effects and clinical profile of patients receiving DR-TB treatment at dr. Zainoel Abidin Hospital in Banda Aceh, one of the DR-TB service places and the center of DR-TB services in Aceh.

#### **METHODS**

This was a cross-sectional observational descriptive study that used secondary data from the medical records of all patients undergoing DR-TB treatment at the Integrated Tuberculosis Service

Facility of dr. Zainoel Abidin Hospital Banda Aceh in January 2020 - December 2022. Samples of this study were patients who are undergoing or have finished treatment for DR-TB and have fulfilled the inclusion criteria. The inclusion criteria of this study are patients who have undergone DR-TB treatment for >1 month and patients with medical records and lab results for DR-TB. The exclusion criteria of this study are patients <17 years old, extra-pulmonary patients without pulmonary infection, and DR-TB patients who have HIV/AIDS.

This study was conducted by recording the research variables in the medical record, including age, occupation, duration of treatment, case criteria, resistance type, lesion area from thoracic photographs, and laboratory examination results. Additionally, the side effects of anti-tuberculosis drugs were documented, including digestive disorders, liver function disorders, kidney function disorders, heart function disorders, musculoskeletal disorders, dermatological disorders, neurological disorders, psychiatric disorders, thyroid hormone disorders, hearing disorders, and hematological disorders.

The occurrence of adverse effects associated with the treatment regimen was monitored through the periodic review of patients' treatment records, which were documented in the medical record every month. Despite a period of data collection on patients diagnosed with DR-TB, there was no record of any pregnant DR-TB patients at the outset of their treatment or during their treatment.

Moreover, the data were analyzed to statistical analysis using the Statistical Program for Social Sciences (SPSS) for Windows, version 24. The descriptive data in numeric form was presented as mean and standard deviation, whereas the nominal or categoric data was given as percentages. We used the STROBE checklist to ensure the writing of this research was appropriate.

The data used is secondary data from medical records so there is no direct informed consent to the patient. Storage of medical record data is adjusted to the provisions and rules for data storage at dr. Zainoel Abidin Hospital Banda Aceh. This study

received ethical approval from dr. Zainoel Abidin Hospital Banda Aceh Health Ethics Committee on 28<sup>th</sup> of November, 2022 No 092/ETIK-RSUDZA/2022.

#### **RESULTS**

The population of this study consisted of 79 patients who are undergoing or have finished treatment for DR-TB from 2020 – 2022.

Table 1. Characteristics of Patients

Gender         Male         32         65,3           Female         17         34.7           Age         17-25         8         16.3           26-35         7         14.3         36-45         9         18.4           46-55         11         22.4         56-65         10         20.4         >65         4         8.2           Occupation         Laborer         3         6.1         Teacher         3         6.1         Teacher         3         6.1         Housewife         9         18.4         Pivate Employee         4         8.2         Student         4         8.2         Celaning Service         1         2.0         Farmer         4         8.2         Cleaning Service         1         2.0         Civil Worker         5         10.2         Unemployed         4         8.2         Entrepreneur         11         22.4 <t< th=""><th>Table 1. Characteristics of Patients  Variable</th><th>n</th><th>%</th></t<>	Table 1. Characteristics of Patients  Variable	n	%
Female       17       34.7         Age       17–25       8       16.3         26–35       7       14.3         36–45       9       18.4         46–55       11       22.4         56–65       10       20.4         >65       4       8.2         Occupation       3       6.1         Laborer       3       6.1         Teacher       3       6.1         Housewife       9       18.4         Private Employee       4       8.2         Student       4       8.2         BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin         Aceh Barat       3       6.1         Aceh Basar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Bandar Baru       1       2.0         Pidie       1 <td></td> <td>···</td> <td>70</td>		···	70
Age         17-25       8       16.3         26-35       7       14.3         36-45       9       18.4         46-55       11       22.4         56-65       10       20.4         >65       4       8.2         Occupation           Laborer       3       6.1         Teacher       3       6.1         Housewife       9       18.4         Private Employee       4       8.2         Student       4       8.2         BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       1       22.4         Origin       3       6.1         Aceh Basar       14       28.6         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2	Male	32	65,3
17-25       8       16.3         26-35       7       14.3         36-45       9       18.4         46-55       11       22.4         56-65       10       20.4         >65       4       8.2         Occupation           Laborer       3       6.1         Teacher       3       6.1         Housewife       9       18.4         Private Employee       4       8.2         Student       4       8.2         Student       4       8.2         BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin       2       4         Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Ba	Female	17	34.7
26-35       7       14.3         36-45       9       18.4         46-55       11       22.4         56-65       10       20.4         >65       4       8.2         Occupation       Laborer       3       6.1         Teacher       3       6.1         Housewife       9       18.4         Private Employee       4       8.2         Student       4       8.2         BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin       Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Siglie <td>Age</td> <td></td> <td></td>	Age		
36-45       9       18.4         46-55       11       22.4         56-65       10       20.4         >65       4       8.2         Occupation       3       6.1         Laborer       3       6.1         Teacher       3       6.1         Housewife       9       18.4         Private Employee       9       18.4         Private Employee       4       8.2         Student       4       8.2         BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin       2       4         Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0	17–25	8	16.3
46–55 11 22.4 56–65 10 20.4 >65 4 8.2 Occupation  Laborer 3 6.1 Teacher 3 6.1 Housewife 9 18.4 Private Employee 4 8.2 Student 4 8.2 BUMN Employee 1 2.0 Farmer 4 8.2 Cleaning Service 1 2.0 Civil Worker 5 10.2 Unemployed 4 8.2 Entrepreneur 11 22.4 Origin Aceh Barat 3 6.1 Aceh Besar 14 28.6 Aceh Jaya 7 14.3 Aceh Utara 1 2.0 Banda Aceh 14 28.6 Bandar Baru 1 2.0 Lhokseumawe 1 2.0 Pidie 1 2.0 Pidie Jaya 3 6.1 Sabang 2 4.1 Siglie 1 2.0 Simeulu 1 2.0 Comorbidity Diabetes 19 38.8 Anemia 4 8.2 Pleura Effusion 1 2.0 Lymphadenopathy 1 2.0	26–35	7	14.3
56-65       10       20.4         >65       4       8.2         Occupation       3       6.1         Laborer       3       6.1         Teacher       3       6.1         Housewife       9       18.4         Private Employee       4       8.2         Student       4       8.2         BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin       2       4         Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Siglie       1       2.0         Simeulu       1       2.0         Com	36–45	9	18.4
>65       4       8.2         Occupation       3       6.1         Laborer       3       6.1         Teacher       3       6.1         Housewife       9       18.4         Private Employee       4       8.2         Student       4       8.2         BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin       2       4         Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Siglie       1       2.0         Simeulu       1       2.0         Simeulu       1       2.0         Com	46–55	11	22.4
Occupation       1         Laborer       3       6.1         Teacher       3       6.1         Housewife       9       18.4         Private Employee       4       8.2         Student       4       8.2         BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin       3       6.1         Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Comorbidity       1       2.0         Diabetes </td <td>56–65</td> <td>10</td> <td>20.4</td>	56–65	10	20.4
Laborer       3       6.1         Teacher       3       6.1         Housewife       9       18.4         Private Employee       4       8.2         Student       4       8.2         BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin       2       4         Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Banda Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Comorbidity       1       2.0         Diabetes       19       38.8	>65	4	8.2
Teacher       3       6.1         Housewife       9       18.4         Private Employee       4       8.2         Student       4       8.2         BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin       3       6.1         Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity       1       2.0         Diabetes       19       38.8	Occupation		
Housewife       9       18.4         Private Employee       4       8.2         Student       4       8.2         BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin       3       6.1         Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Comorbidity       1       2.0         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0	Laborer	3	6.1
Private Employee       4       8.2         Student       4       8.2         BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin	Teacher	3	6.1
Student       4       8.2         BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin       2       4         Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Comorbidity       1       2.0         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Housewife	9	18.4
BUMN Employee       1       2.0         Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin       3       6.1         Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity       1       2.0         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Private Employee	4	8.2
Farmer       4       8.2         Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin       22.4         Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity       0       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Student	4	8.2
Cleaning Service       1       2.0         Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin	BUMN Employee	1	2.0
Civil Worker       5       10.2         Unemployed       4       8.2         Entrepreneur       11       22.4         Origin	Farmer	4	8.2
Unemployed       4       8.2         Entrepreneur       11       22.4         Origin	Cleaning Service	1	2.0
Entrepreneur       11       22.4         Origin       3       6.1         Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Civil Worker	5	10.2
Origin       3       6.1         Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity       1       2.0         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Unemployed	4	8.2
Aceh Barat       3       6.1         Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity       0       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Entrepreneur	11	22.4
Aceh Besar       14       28.6         Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity       0       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Origin		
Aceh Jaya       7       14.3         Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Aceh Barat	3	6.1
Aceh Utara       1       2.0         Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity       0       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Aceh Besar	14	28.6
Banda Aceh       14       28.6         Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Aceh Jaya	7	14.3
Bandar Baru       1       2.0         Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Aceh Utara	1	2.0
Lhokseumawe       1       2.0         Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Banda Aceh	14	28.6
Pidie       1       2.0         Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Bandar Baru	1	2.0
Pidie Jaya       3       6.1         Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Lhokseumawe	1	2.0
Sabang       2       4.1         Siglie       1       2.0         Simeulu       1       2.0         Comorbidity       Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Pidie	1	2.0
Siglie       1       2.0         Simeulu       1       2.0         Comorbidity       38.8         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Pidie Jaya	3	6.1
Simeulu       1       2.0         Comorbidity       19       38.8         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Sabang	2	4.1
Comorbidity       19       38.8         Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Siglie	1	2.0
Diabetes       19       38.8         Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Simeulu	1	2.0
Anemia       4       8.2         Pleura Effusion       1       2.0         Lymphadenopathy       1       2.0         Lung Metastasis       1       2.0	Comorbidity		
Pleura Effusion 1 2.0 Lymphadenopathy 1 2.0 Lung Metastasis 1 2.0	Diabetes	19	38.8
Lymphadenopathy 1 2.0 Lung Metastasis 1 2.0	Anemia	4	8.2
Lung Metastasis 1 2.0	Pleura Effusion	1	2.0
	Lymphadenopathy	1	2.0
	Lung Metastasis	1	2.0
CVD 1 2.0	CVD	1	2.0
COPD 1 2.0	COPD	1	2.0
Kidney Stones 1 2.0	Kidney Stones	1	2.0

Out of the 79 people in the population, 49 were chosen as a sample as they had fulfilled the inclusion and exclusion criteria. The remaining 30 were not chosen as 28 did not continue treatment at the Integrated Tuberculosis Service Facility of dr. Zainoel Abidin Hospital Banda Aceh for more than 1 month and 2 of the patients were under 17 years old.

Table 1 shows the characteristics of the patients in this study. Based on the table above, most patients were male (65,3%), with the highest age range based on the age category of the Indonesian Ministry of Health in the age range of 46-55 years old (22,4%), working as entrepreneurs (22,4%), and originated from Banda Aceh (28,6%) and Aceh Besar (28,6%). Diabetes was the most common comorbidity (38,8%) followed by anemia (8,2%).

Table 2 shows the suspected criteria under which patients are given treatment for DR-TB. Most patients were suspected of secondary infection (65,1%) with the most common cause being relapse (20,4%).

Table. 2 History of Previous TB Therapy

Variable	n	%
No history of TB therapy	22	34.9
Secondary	27	65.1
Failed category 1 TB therapy	2	4.1
Failed category 2 TB therapy	5	10.2
Relapse	10	20.4
Loss to Follow Up	3	6.1
Stopped Medication	7	14.3

Table 3 shows the type of resistance found in the patients of this study. Monoresistance (79,6%) was found in a majority of the patients.

Table 3. Resistance Type of Patients

Variable	n	%
Monoresistance R	39	79.6
Multidrug Resistance	3	6.1
Pre-XDR	6	12.2
Extensively Drug Resistant	1	2.0

Based on the type of treatment the patients received, 7 received short-term regimen (14,3%), 7 received injection short-term regimen (14,3%), and 35 received long-term treatment (71,4%). The commonly used drug combination is Lfx - Bdq - Lzd - Cfz – Cs (28,6%) (Table 4).

Table 4. Anti tuberculosis Drug regiment

Variable	n	%
Short Term Regiment		
Bdq -Lfx - Cfz - H - Z - E	7	14.3
Injection Short Term Regiment		
Mfx - Cfz - E - Z -Eto - H - Km	7	14.3
Long Term Regiment		
Lfx - Bdq - Lzd - Cfz - Cs	16	28.6
Lfx - Bdq - Lzd - Cfz - Cs - E	2	32.7
Lfx - Bdq - Lzd - Cfz - Cs - E - Z - Eto - H	2	14.3
Bdq - Lzd - Cfz - Cs - Eto	1	14.3
Bdq - Cfz - Cs - E - Eto	1	4.1
Bdq - Lzd - Cfz - Cs - E - Dlm - Z - Eto	1	4.1
Lfx - Bdq - Cfz - Cs - Dlm	1	2.0
Lfx - Bdq - Cfz - Cs - Dlm - Eto	1	2.0
Lfx - Bdq - Cfz - Cs - E	1	2.0
Lfx - Bdq - Cfz - Cs - E - Dlm	1	2.0
Lfx - Bdq - Cs - E - Z	1	2.0
Lfx - Bdq - Lzd - Cfz - Cs - Dlm	1	2.0
Lfx - Bdq - Lzd - Cfz - Cs - E - Dlm	1	2.0
Lfx - Bdq - Lzd - Cfz - Cs - E - Z	1	2.0
Lfx - Bdq - Lzd - Cfz - Dlm - PAS	1	2.0
Lfx - Lzd - Cfz - Cs - Dlm	1	2.0
Lfx - Mfx - Bdq - Cfz - Z - Eto - H	1	2.0
Mfx - Bdq - Cfz - Dlm - Eto	1	2.0

Table 5 shows the side effects that are experienced by the patients or are detected from laboratory testing performed monthly during treatment. The most common side effect is nausea (57,1%), followed by peripheral neuropathy (38,8%). From the medical records of the 49 patients with DR-TB who were studied, all of them reported at least one side effect of the treatment.

Table 5. Side Effects

Variable	n	%
Gastrointestinal		
Nausea	28	57.1
Vomiting	16	32.7
Dyspepsia	13	26.5
Anorexia	17	34.7
Diarrhea	1	2.0
Kidney Function		
Urea Abnormality	1	2.0
Creatinine Abnormality	1	2.0
Liver Function		
SGOT Abnormality	2	4.1
SGPT Abnormality	1	2.0
Total Bilirubin Abnormality	1	2.0
Cardiovascular		
QT elongation	13	26.5
Palpitations	6	12.2
Musculoskeletal		
Athralgia	10	20.4
Arthritis	9	18.4

Table 5. Side Effects (cont.)

Variable	n	%
Dermatological		
Skin Discoloration	13	26.5
Allergy	9	18.4
Neurological		
Peripheral Neuropathy	19	38.8
Seizures	6	12.2
Body Ache	4	8.2
Optical Neuropathy	3	6.1
Headache	2	4.1
Psychiatric		
Sleep Disorder	7	14.3
Depression	2	4.1
Behavior Change	1	2.0
Anxiety	1	2.0
Audiovestibular		
Vertigo	7	14.3
Hearing Impairment	2	4.1
Hematological		
Hypochloremia	3	6.1
Hyponatremia	2	4.1
Anemia	1	2.0
Respiratory		
Lethargy	17	34.7
Dyspnea	2	4.1
Other		
Tiredness	2	4.1
Gout	1	2.0

## **DISCUSSION**

The rise of drug-resistant tuberculosis (TB) has become a significant global concern due to its infectious nature and potentially fatal outcomes. Managing patients effectively is further complicated by the intricate regimen of drug therapies and their associated adverse drug reactions (ADRs). This study found that all patients experienced at least one side effect of DR-TB drugs. This study is similar to other studies that show the same thing as the research by Ganiyu et al<sup>8</sup> which reported 99% of patients experienced at least 1 adverse drug reaction to DR-TB drugs and a Chinese study that reported adverse drug reactions in DR-TB patients (90.7%).<sup>9</sup>

However, smaller frequencies were found in studies conducted in South Africa (38.9%), India (47%) and Ethiopia (51%). These differences in frequency across studies may be due to differences in attitudes towards therapy, such as lack of adherence to treatment, default rates, differences in opinion between patients and physicians concerning ADR reporting, ability to detect, patterns of drug use,

differences in support programs, initial assessment, and management of ADRs.<sup>10</sup>

A lack of alignment regarding reporting of ADRs between patients and physicians was reported in one of the studies. Patients reported more ADRs than clinicians documented. This reflects the different perceptions of ADRs between doctors and patients. Another study reported a lack of provision of necessary information about the regimen. Inadequate knowledge about drugs and druginduced ADRs leads to misreporting of ADRs by patients. The complex nature of the regimen in the presence of comorbidities leads to a higher risk of ADRs, as widely reported in the published literature.

This study found that all patients experienced at least one side effect. The most common side effect that patients experience is nausea (57,1%), peripheral neuropathy (38,8%), anorexia (34,7%), lethargy (34,7%), and vomiting (32,7%). A study found that 37,1% of patients out of 256 would experience one or more side effects.<sup>8,9,11,12</sup>

Another study reported that 69,2% of patients experienced side effects. The drugs used in MDR-TB treatment are a major factor contributing to adverse reactions, increasing the risk by approximately 11 times compared to first-line therapies. A previous study on MDR-TB patients in Peru found that 95% of those treated experienced some type of adverse reaction to second-line TB drugs, with 54% of these being toxic reactions. Other research has also shown a high prevalence of adverse drug reactions (over 50%) among MDR-TB patients.<sup>8,9,11,12</sup>

The most common comorbidity in this study is diabetes with 19 patients (38,8%) followed by anemia with 4 patients (8,2%). This result is different when compared to the study done by Mukati where the most common comorbidity is anemia (73,84%), followed by bronchiectasis (23,84%), and diabetes (9,23%).<sup>13</sup>

Similar results were found by Rosdiana et al, who found that 26.5% of 113 patients with DR-TB were accompanied by co-morbid DM. Many previous studies have found a 2.1 to 8.8 times increased risk of MDR-TB among TB patients co-morbid with diabetes. In addition, observational studies from

Israel, Georgia, and Mexico showed that TB patients with DM had a higher risk of developing MDR-TB.<sup>14,15</sup>

The mechanism behind this may be due to lower plasma concentrations of anti-TB drugs, especially rifampicin, caused by changes in absorption, distribution, metabolism, and excretion in TB patients with diabetes. Diabetics tend to have reduced intestinal motility, which slows gastric emptying, alters pH levels, and delays drug absorption. Research has shown that serum rifampicin levels in TB patients with diabetes were 53% lower compared to those without diabetes. This low plasma concentration of anti-TB drugs is thought to contribute to poor treatment outcomes, with the risk of treatment failure being almost nine times higher in patients with low drug exposure compared to those with higher exposure. 16

Additionally, this condition is linked to acquired drug resistance. Another possible explanation involves mutations in the katG gene, which helps *Mycobacterium tuberculosis* withstand oxidative stress and encodes catalase-peroxidase, enabling the activation of isoniazid. In diabetic patients, there may be an increase in reactive oxygen species production, allowing strains with these mutations to survive more readily.<sup>16</sup>

This study shows 22 patients (34,9%) were suspected of primary infection while 27 patients (65,1%) were suspected of secondary infection. Out of the 27 patients that are suspected of secondary infection, 10 (20,4%) of them are caused by relapse, 7 patients (14,3%) caused by stopping the medication, and 5 patients (10,2%) were caused by failed category 2 treatment. This is supported by a study done by Tao, where most cases are caused by secondary infection (17,1%).<sup>17</sup>

A high number of secondary infections are indicator of inadequate treatment, poor treatment compliance, poor treatment monitoring, and an ineffective TB control program where as the primary infection is caused by the spread of drug-resistant strain to a healthy person.<sup>17</sup>

In this study, most of the cases are monoresistance Rifampicin with 39 patients (79,6%). A study done by Jung in North Korea reported that of

489 TB patients, 76,9% were MDR-TB patients and two patients were cases of XDR-TB.<sup>18</sup>

This study shows that the most common treatment given to DR-TB patients was long-term treatment with 35 patients (71,4%). The most used drug combination was the long-term drug combination, Lfx - Bdq - Lzd - Cfz - Cs with 16 patients (32,7%) which is followed by the short-term drug combination, Bdq - Lfx - Cfz - H - Z - E with 7 people (14,3%) and the injection short term drug combination, Mfx - Cfz - E - Z -Eto - H - Km with 7 patients (14,3%).

This study found that all patients experienced at least one side effect. The most common side effect that patients experience is nausea (57,1%), peripheral neuropathy (38,8%), anorexia (34,7%), lethargy (34,7%), and vomiting (32,7%). A study by Yang found that 37,1% of patients out of 256 would experience one or more side effects.<sup>19</sup>

A study by Törün reported that 69,2% of patients experienced side effects.<sup>20</sup> The incidence of side effects in the current study was found to be consistent with published studies in Nigeria (99%), China (90.7%), Pakistan (72%), including a study in Surabaya that reported 70% of DR-TB patients reported treatment side effects.<sup>8,10,17,21</sup>

The drugs used in MDR-TB treatment are a major factor contributing to adverse reactions, increasing the risk by approximately 11 times compared to first-line therapies. A previous study on MDR-TB patients in Peru found that 95% of those treated experienced some type of adverse reaction to second-line TB drugs, with 54% of these being toxic reactions. Other research has also shown a high prevalence of adverse drug reactions (over 50%) among MDR-TB patients. In contrast, those on first-line therapies typically experience only mild reactions at an expected rate of 5–20%.<sup>11</sup>

In this study, gastrointestinal disorders were the most common ADRs complained of by patients with the most complaints being nausea (57.1%) and vomiting (32.7%) and only 1 patient complained of diarrhea. These results are in line with other studies that reported the occurrence of gastrointestinal disorders with prevalence ranging from 42–75%.

None of the patients who experienced gastrointestinal disorders had to modify DR TB therapy. 19–21

All patients who experienced GI disorders were given additional symptomatic drugs such as antiemetics and proton pump inhibitors. Although GI distress was the most common complaint compared to other side effects, most patients only required symptomatic therapy without the need to discontinue the DR TB drug that caused the GI distress. Gastrointestinal disorders are linked by the usage of Ethambutol, Bedaquiline, Linezolid, Clofazimin and Cycloserine. The combination of linezolid and bedaquiline has been observed to increase gastric acid secretion, which may potentially lead to irritation of the gastric mucosa. Such irritation can result in the onset of nausea and vomiting in patients. 19–21

Meanwhile, clofazimine has lipophilic properties and can accumulate in fatty tissue, including the gastric submucosa. This accumulation can cause irritation, which in turn triggers inflammation. Additionally, other drugs, such as Cycloserine, have the potential to impact the central nervous system, including the vagus nerve, which plays a role in regulating gastrointestinal motility and can contribute to the onset of nausea and vomiting. Another mechanism involves the activation of dopamine D2 receptors in the area postrema of the brain, which may be triggered by metabolites from Linezolid and Cycloserine. This, in turn, can also lead to the manifestation of nausea and vomiting. 19-21

Nervous system disorders were reported in more than 30% in patients. Peripheral neuropathy was the most common neurological disorder experienced by patients (38.8%) in this study. This result is in line with research conducted in Bangladesh (28%) but much greater than the results of research in Pakistan (2.2%). Neurological disorders associated with DR TB therapy have been linked to the use of specific medications, namely Linezolid, Cycloserine, and Isoniazid. Neurological side effects may manifest as peripheral neuropathy, headaches, and even seizures. 19-21

In this study, the most frequently observed neurological disorder was peripheral neuropathy.

Linezolid has the potential to disrupt mitochondrial protein synthesis by inhibiting the 50S subunit of mitochondrial ribosomes. This results in an energy deficiency in peripheral nerve cells, which in turn causes axonal damage and leads to peripheral neuropathy. Conversely, Cycloserine has the potential to influence neurotransmitter (GABA) metabolism, which may lead to peripheral nerve hyperexcitability and neuropathic pain. 19–21

Conversely, Isoniazid has the potential to diminish the levels of pyridoxine (vitamin B6), which is essential for the synthesis of neurotransmitters such as gamma-aminobutyric acid (GABA). A deficiency of GABA increases nerve excitation, which can cause neuropathy and, in severe cases, may result in the onset of seizures. Peripheral neuropathy is characterised by pain, tingling and numbness in the hands and feet; therefore, regular monitoring is essential. Early intervention, such administration of vitamin B6 supplementation or a reduction in medication dosage, can be initiated promptly. 19-21

Cardiovascular side effects reported in this study occurred in 13 patients (26.5%) in the form of QT interval prolongation. The drugs that are thought to cause this are Bedaquiline, Levofloxacin and Moxifloxacin. Bedaquiline can inhibit potassium K+ion channels in the cardiomyocyte membrane thereby prolonging the repolarization phase which is seen on the ECG as a prolongation of the QT interval. Levofloxacin and Moxifloxacin also have a similar mechanism by inhibiting the Human ether-a-go-related gene (HERG) channel, thereby increasing the risk of torsade de pointes which can result in fatal arrhythmias. 19,20

Apart from that, the three drugs above also increase sympathetic nerve activity and cause tachycardia which is caused by the excessive release of norepinephrine which activates the heart's beta-adrenergic receptors, causing palpitations. <sup>19,20</sup> Palpitations were also reported as cardiovascular side effects in 12.6% of patients in this study.

Ototoxicity is generally caused by injection drugs of the Aminoglycoside class. In this study, seven patients were treated with combination drugs

containing Kanamycin, and two patients (4.1%) were observed to have hearing loss. The aminoglycosides are toxic to the cochlea by selectively destroying the basal hair cells of the basilar membrane which are necessary for high frequency hearing. In addition, it can also destroy hair cells in the vestibule. These drugs react with transition metal ions to produce reactive oxygen (free radicals) which damage cells through an oxidative process.

Dermatological side effects, including skin discoloration (26.5%) and allergic reactions (18.4%), were common in the study population. These effects are associated with the use of clofazimine (Cfz), a red-pigmented drug that deposits in tissues, particularly in the skin, giving it a reddish or bronze discoloration. This pigmentation is typically harmless but may cause psychological distress, particularly in patients concerned about cosmetic appearance.<sup>20,21</sup>

Allergic reactions, which were reported in 18.4% of patients, may present as skin rashes or itching. These reactions are often linked to hypersensitivity responses to drugs like ethionamide, cycloserine, and fluoroquinolones. While mild skin reactions can be managed with antihistamines, severe allergic reactions may necessitate a change in the treatment regimen.<sup>20,21</sup>

# **LIMITATION**

A notable limitation of our study was the absence of documentation of ADR severity, which would have facilitated a more comprehensive assessment of its impact on treatment outcomes. Additionally, the absence of treatment records for comorbidities in patients with comorbidities was a significant limitation, as it precluded a thorough evaluation of the impact of these conditions on the overall treatment response. Small number of patients because DR-TB treatment is no longer centralised at dr. Zainoel Abidin Hospital, Banda Aceh, so data may be incomplete. To avoid bias, we do not accept incomplete medical records of DR-TB patients.

## **CONCLUSION**

This study showed that all patients treated for

drug-resistant tuberculosis (DR-TB) at dr. Zainoel Abidin Hospital, Banda Aceh experienced at least one side effect of treatment. The most common side effects were nausea (57.1%), peripheral neuropathy (38.8%), anorexia (34.7%), weakness (34.7%) and vomiting (32.7%). The study also showed that the drug combination Lfx - Bdq - Lzd - Cfz - Cs was the most commonly used long-term treatment regimen (32.7%), while most patients were resistant to rifampicin (79.6%).

The findings of this study emphasize the significance of patient education and management of adverse effects to improve treatment adherence, given the prolonged duration of therapy and elevated levels of drug toxicity. The findings also indicate a need for further research to evaluate DR-TB management more comprehensively, through both primary and secondary data collection. Efforts to increase patient awareness of potential side effects and develop comprehensive management strategies are important steps to improve DR-TB treatment outcomes in Indonesia.

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## **CONFLICT OF INTEREST**

None.

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