Contents lists available at IOCS

Science Midwifery

journal homepage: www.midwifery.iocspublisher.org

Analysis of factors influencing the incidence of adverse drug reaction (ADR) in the use of first-line anti-tuberculosis drugs in pulmonary tuberculosis patients at Randegansari Husada Gresik Hospital

Fardhiyanti[1], Em Sutrisna[2]

[1,2]Magister Farmasi, Sekolah Pascasarjana, Universitas Muhammadiyah Surakarta, Indonesia

ARTICLEINFO

Article history:

Received Aug 1, 2024
Revised Aug 15, 2024
Accepted Aug 30,2024

Keywords:

Adverse Drug Reactions
Anti-Tuberculosis Drugs
Tuberculosis

ABSTRACT

The success of TB treatment is one of the levels of patient compliance in undergoing treatment, TB patients who are not compliant in undergoing treatment are due to long-term drug use, possible side effects, and lack of awareness of their disease. Dangerous and unexpected responses from a drug that occur at a common dose are called Adverse Drug Reactions (ADR). This study aims to determine the factors that influence the incidence of ADR in the use of pulmonary anti-tuberculosis drugs at Randegansari Husada Hospital. This study uses an observational study type with a cross-sectional design through retrospective data through medical records of category I pulmonary TB patients using the first-line OAT regimen at Randegansari Husada Hospital. Descriptive data analysis to determine the incidence of ADR and Chi Square tests were carried out. Correlation between factors using logistic analysis regression method. The results showed that the highest level of ADR severity was reddish urine, more than 50% of patients experienced ADR of more than 3. The risk factors found in this study were age, gender, occupation, OAT drugs used, history of comorbidities, and receiving additional drugs. Therapy for handling the side effects of tuberculosis has been carried out according to the symptoms experienced.

Corresponding Author:

Fardhiyanti,
Magister Farmasi,
Universitas Muhammadiyah Surakarta,
Addres, Surakarta, 57169, Indonesia,
Email: v100200033@student.ums.ac.id

INTRODUCTION

TB is caused by a bacterium (Mycobacterium tuberculosis) and most commonly attacks the lungs. TB spreads through the air when people with pulmonary TB cough, sneeze or spit out. A person only needs to inhale a few germs to get infected (Nortajulu, Susianti, & Hermawan, 2022), (Afifah Febriarini, 2023). Every year, 10 million people fall ill from tuberculosis (TB). Most TB germs are often found to infect the pulmonary parenchyma and cause pulmonary TB, but these bacteria also

have the ability to infect other organs of the body (extra pulmonary TB) such as the pleura, lymph nodes, bones, and other extra lung organs (Guo, Xin, & Gao, 2023), (Shalsabilla, 2021).

Most people will not continue to develop TB disease and some will clear the infection. Those who are infected but have not (yet) become sick with this disease cannot transmit it (Yuzar, 2020) Tuberculosis is a chronic infectious disease caused by the bacterium Mycobacterium tuberculosis. This bacterium is rod-shaped and acid-resistant, so it is often known as Acid-Resistant Bacilli (BTA) (Febriani, Hidayat, Muthiadin, & Zulkarnain, 2022), (AGUSTIN, 2021)

Tuberculosis is currently among the top 10 causes of death in the world (Singh, Prasad, Balasubramanian, Gupta, & Gupta, 2015) African countries, India, China and Indonesia are the countries with the highest cases of tuberculosis in the world(Annashr, n.d.) . The incidence of tuberculosis in Indonesia according to WHO in 2019 was reported as many as 360,565 cases with a cure rate of 85% while in 2018 the cases recorded were 563,879 cases, consisting of new and recurrent cases with a recovery rate of 85% (Ujiani & Nuraini, 2020).

In 2020, the number of discovery and treatment of all TB cases in East Java ranked eighth in Indonesia with 42,922 cases . The total number of tuberculosis cases is 1463, the highest number of no. 10 among 38 other districts. And of the several districts in Gresik, driyorejo ranks 3rd with the highest number of tuberculosis cases (Mulyati, n.d.)

One of the successes in TB treatment is the level of patient compliance in undergoing treatment, TB patients who do not comply in carrying out treatment, one of which is due to long-term drug use, possible side effects, and lack of awareness for patients about the disease (Dasopang, *et., al.,* 2019) (Meyrisca, Susanti, & Nurmainah, 2022). Education is very important to inform patients so that patients understand that the symptoms that arise during treatment are due to the use of OAT so that patients are more compliant and do not stop treatment if there is an occurrence of these side effects (Dasopang, *et., al.,* 2019), (Dwiningrum, Wulandari, & Yunitasari, 2021).

A dangerous and unexpected response from a drug that occurs at a common dose is referred to as an Adverse Drug Reaction (ADR). According to a study, ADR can affect the quality of life of patients (Yuliza Anggraini, Astuti, Astuti, & Edo Duanda Putra, 2022), (Kriswandini et al., 2023). Adverse Drug Reaction (ADR) is a common occurrence in a person with drug therapy, from a study it was stated that 30% of patients who are undergoing tuberculosis treatment with the standard regimen of isoniazid, rifampicin, pyrazinamide and etambutol experience major ADR with an incidence of 7.3 cases per 100 people. Another study found that 56 out of 100 subjects could experience more than one type of ADR during treatment (Denholm *et.,al.,*, 2014).

Adverse Drug Reaction is defined as an undesirable effect related to drug use that arises as a chart of pharmacological action of a drug whose occurrence may not be foreseen (Suryati et al., 2023). Adverse Drug Reactions can range from the mildest to very severe and can cause death. ADR can exacerbate the underlying disease we are about to treat, add new problems and even death. Poisoning and anaphylactic shock are examples of severe ADRs that can lead to death, while mild examples are itching and drowsiness. There are many types of ADR, from those that can be predicted to arise to those that we do not estimate that have the potential to endanger the safety of patients. (Mariyono & Suryana, 2008). The incidence of ADR is quite frequent, especially in TB patients, it is very important for us to monitor ADR to ensure safety during treatment and improve the patient's quality of life considering the many types of drugs used and the long duration of treatment (Lucia Vita Inandha Dewi, Lukman Hakim, Sismindari, Ngatidjan, 2019). Various negative impacts caused by ADR events include causing congenital abnormalities and causing patients to be hospitalized with a percentage of 24%, even in geriatric patients reaching 88%. Other impacts include threatening the patient's life and causing death. One of the dangerous and unexpected effects of drug use is damage to herpar function or hepatotoxicity (Ningrum & Megasari, A.,, 2010).

Based on Dewi's research (2019), TB patients as many as 11.76% of the total sample experienced major ADR in the form of itching on the skin and visual impairment, while the rest (88.2%) experienced minor ADR. Based on the results of the interview, the most experienced minor ADR is indigestion, followed by muscle cramps and fever. A total of 66.6% of subjects with ADR admitted that the onset of the reaction began between week 1 and week 4 of treatment, but did not affect the level of adherence to the patient's medication (Dewi, 2019)

The increase in the prevalence of Tuberculosis is caused by various problem factors caused by the lack of knowledge of patients about the dangers of TB, patient compliance with the treatment carried out is often ignored due to other factors, one of which is due to the appearance of discomfort due to drug side effects caused by Antituberculosis (OAT) drug treatment therapy (Wiyati, Irawati, & Budiyono, 2014).

Morbidity and mortality of TB disease is still often a serious problem, especially due to the emergence of drug side effects so that some TB patients feel unbearable to the side effects experienced during treatment. Polypharmacy with a long time shows the existence of drug side effects (ESO) ranging from mild to severe such as hepatotoxicity, indigestion, allergic reactions, arthralgia and neurological disorders. The incidence rate of ESO varies greatly in the range of 5.1%-83.5% (Musdalipah, Nurhikmah, Karmilah, & Fakhrurazi, 2018).

According to the results of the study (Abbas (2017) that the most common type of side effects of the drug experienced by sufferers was joint pain with a percentage of 81%, and other effects experienced were nausea (79.3%), itching (77.6%), lack of appetite (75.9%), dizziness (67.2%), tingling (50%), and hearing loss (6.9%). Handling of side effects needs to be done because it is likely to have adverse effects such as therapy failure (Abbas, 2017). Handling side effects must be carried out continuously in TB patients. In this case, it is necessary to communicate, information, and educate the public and health workers in minimizing the risk of drug side effects (Musdalipah et al., 2018).

Identification of OAT side effects problems is very necessary with adequate treatment. These side effects have an impact on patient compliance in treatment. Finally, it causes a TB epidemic that is difficult to treat (Rosamarlina et al., 2017). Therefore, it is very important to always monitor the patient's clinical condition during the treatment period so that mild to severe side effects can be immediately known and treated appropriately (Seniantara, Ivana, & Adang, 2018).

Faktor yang mempengaruhi kepatuhan pasien terhadap pengobatan dipengaruhi oleh beberapa faktor utama, antara lain keinginan pasien untuk sembuh, cara berfikir pasien, dan pengetahuan pasien tentang penyakit TB Paru (Gunawan, 2017). Hasil ini sejalan dengan penelitian yang dilakukan oleh Amran (2021) dikatakan bahwa kepatuhan pasien minum obat anti tuberkulosis (OAT) didapatkan pasien yang patuh (86,8%) lebih banyak dibandingkan pasien yang kurang patuh (13,2%).

A lack of alignment regarding ADR reporting between patients and doctors was reported in one of the studies. Patients reported more ADRs than documented by physicians (Kelly et al, 2016). This reflects the difference in perception of ADR between doctors and patients. The complex nature of the regimen in the presence of comorbidities leads to a higher risk of developing ADR, as widely reported in the published literature (Mouton et al., 2016 ; Schaaf et al., 2016 ; Merid, et al, 2019).

Anti-tuberculosis drugs such as linezolid, cyclosine, isoniazid, fluoroquinolones, SLD, etambutol, and etionamide are blamed for causing peripheral neuropathy (Gupta, et al., 2020). These drugs interfere with pyridoxine metabolism through various mechanisms. In this study, only cycloserine was suspected of causing neuropathy. Pyridoxine has been prescribed for the management of peripheral neuropathy along with a tricyclic antidepressant, usually amitriptyline. In severe cases, one or more interfering medications are discontinued or temporarily eliminated (Brust et al., 2013 ; Gupta et al., 2020).

The novelty of this study with previous studies is that this study not only presents data on the incidence of ADR and its percentage but also knows the effectiveness of ADR treatment therapy. This study also presents data on the influence of age, gender, type of TB, TB treatment category, length of treatment, and type of comorbidities on the incidence of ADR. The sample selected was a pulmonary TB patient who received category I treatment at Randegansari Husada Hospital which had never been studied before.

RESEARCH METHOD

This study uses a type of observational research with a cross-sectional design through retrospective data tracing through the medical records of category I pulmonary TB patients who use the first-line OAT regimen at Randegansari Husada Hospital. Patients were identified with ADR that occurred using the Naranjo instrument, the effectiveness of ADR treatment therapy was analyzed, as well as risk factors for ADR. In the form of age, gender, occupation, comorbidities, types of OAT, additional therapies in patients that affect the incidence of ADR. This research was carried out for 2 months, starting from June 2024 – July 2024 at Randegansari Husada Hospital. The research data used patient data from January 2022 – May 2024. The subjects of the study were pulmonary TB patients who used a category I OAT therapy regimen with a sequential random sampling technique that met the inclusion criteria, namely adult pulmonary TB patients over 17 years old, using a first-line OAT therapy regimen and complete data on age, gender, occupation, comorbidities, types of OAT, and additional therapies in patients. The data analysis technique uses the Statistical Package for Social Science 21 (SPSS) software. Correlation analysis of age and number of ADRs events using simple linear regression, multivariate analysis using logistic regression.

RESULTS AND DISCUSSIONS

The study was conducted at Randegansari Husada Hospital on 149 patients with a diagnosis of tuberculosis who met the inclusion criteria. The results of the study are presented in the form of percentages and described descriptively. The independent variable and the bound variable were statistically analyzed using the SPSS 22.0 statistical program. The instrument was tested by Chi-Square and Logistic Regression tests. The characteristics of the research respondents are as follows

Table 1. Subject characteristics

Characteristic	Frequency	Percentage (%)
Umur		
17- 20 years old	8	5,4
20-30	20	13,4
31-40	30	13,4
> 40 years	101	67,8
Gender		
Man	88	59,1
Woman	61	40,9
Work		
Farmers/breeders	6	4
PNS	1	0,7
Students/students	7	4,7
Self employed	7	4,7
Laborer	8	5,4
IRT	21	14,1
Private officer	5	3.4
Not Working	2	1,3
Unknown	91	61,1
TNI/Polri	1	0,7

Table 1 above shows the characteristics of patients based on age where it can be seen that patients are dominated by more than 40 years old by 110 patients (67.8%), respondents (53%). Characteristics of patients by gender, it was found that there were more male patients when compared to female patients amounting to 88 patients (59.1%). Meanwhile, the characteristics of patients based on the most occupation were unknown, namely 91 people (61.1%).

Characteristics of Comorbidity Categories

Table 2. Characteristics of comorbidity categories

Disease History	Frequency	Percentage (%)
Diabetes	22	14.8
Hypertension	6	4.0
Gout	18	12.1
Heart	1	.7
None	83	55.7
diabetes+hypertension	5	3.4
Diabetes+Gout	6	4.0
diabetes+heart	2	1.3
hypertension + heart	5	3.4
hypertension+gout	1	.7

The disease history showed that most of the respondents did not have a history of a specific disease (55.7%), with a total of 83 people. Meanwhile, patients with a history of disease were 44.3. In individuals with normal immune systems, 90% will not develop TB disease and only 10% of cases will develop active TB disease. This decrease in the respiratory immune system can be in the form of mucociliary damage due to cigarette smoke toxins and decreasing the antigen response so as to increase the susceptibility to pulmonary TB (Kemenkes RI, 2019).

The Use of Anti-Tuberculosis Drugs at Randegansari Husada Hospital

The management of tuberculosis therapy at Randegansari Husada Hospital uses the guidelines of the Regulation of the Minister of Health of the Republic of Indonesia Number 67 of 2016 concerning tuberculosis control. In this study, the antituberculosis drug (OAT) combination used is category 1: 2 (HRZE)/4 (HR). OAT category 1 alloys are available in fixed-dose combination drug packages (OAT-KDT) and combipak packages. OAT – KDT consists of a combination of 2 and 4 types of drugs in one tablet. Meanwhile, the kombipak package is a loose drug package consisting of Isoniazid (H), Rifampisin (R), Pirazinamid (Z), and Etambutol (E). (Kemenkes, 2016).

Table 3. Drug package consisting of Isoniazid (H), Rifampisin (R), Pirazinamid (Z), and Etambutol (E)

Types of OAT	Frequency	Percentage (%)
2KDT	3	2
4KDT+2KDT	64	43
4KDT	82	55

The table above shows the highest data on the type of OAT use as 55% of patients get 4KDT. The use of OAT 4 KDT therapy is a caplet consisting of 4 types of Isoniazid/Rifampicin/Pirazynamid/ethambutol (H/R/Z/E) drugs with a sequential content of 75mg/150mg/400mg/275mg which is used in the intensive stage taken every day for 56 days. The use of OAT 2KDT therapy is a caplet consisting of 2 types of drugs consisting of Isoniazid and Rifampicin (HR) with a sequential content of 150/150 used in the advanced stage taken 3 times a week for 16 weeks/4 months (Kemenkes RI, 2014). WHO, provides recommendations for fixed-dose combination drugs (KDT) in order to reduce the risk that can occur in the form of drug-resistant TB caused by monotherapy. With this KDT, patients cannot choose the drug to take, the

number of drugs taken is less, which affects the increase in patient compliance and minimizes prescription errors by doctors due to the calculation of the dosage given on the basis of body weight (Kemenkes RI., 2013).

Patients who received OAT three times a week had higher rates of drug resistance compared to those who received daily treatment. Therefore, WHO recommends treatment with a therapy regimen 2(HRZE)/4(HR)3 in patients with new cases of pulmonary TB that must be accompanied by direct supervision by a drug swallowing supervisor (PMO) (KemenkesRI, 2013).

Dditional Medications

Table 4. Dditional medications

Drug therapy other than OAT	Frequency	Percentage (%)
<=3 medicine	45	30.2
>3 medicine	104	69.8

In the data on additional drugs used other than OAT, most respondents received more than 3 additional therapies. The large number of patients who receive additional therapy can be caused by the high number of patients with comorbidities. Most patients receive additional vitamin therapy and herbal medicines, namely fibumin which is useful for maintaining the body's immunity and increasing albumin levels in the body.

Identifying ADR (Adverse Drug Reaction)

Adverse Drug Reactions (ADR) according to the WHO are dangerous reactions that arise in the body that occur after the use of a drug in normal doses (Edwards and Aronson, 2000). ADR is the number four and sixth cause of death. The impact of ADR is a reduction in quality of life, an increase in the number of hospitalizations, an increase in economic burden, and an increase in the number of deaths (Saini et al., 2015). ADR is a very common reaction in patients undergoing OAT therapy. ADR should be managed with supportive care to maintain a better quality of life during OAT treatment (Jamali et al., 2018).

Table 5. ADR should be managed with supportive care to maintain a better quality of life during OAT treatment

Side effects	Frequency	Percentage (%)
None	19	12.8
There is	130	87.2

The majority of respondents experienced side effects (87.2%), with 130 people reporting side effects, while only 19 people (12.8%) did not experience side effects. These data suggest that drug side effects are a common problem among respondents, which may require further attention in medical management and patient monitoring.

An evaluative analysis of the ADR of the use of antituberculosis drugs based on the guidelines used. The reference used for evaluation in this study is the Naranjo Algorithm (BPOM RI, 2012).

Table 6. The reference used for evaluation in this study is the naranjo algorithm

Score	Category	Frequency	Presentase(%)
9+	Very likely	72	48,3
5-8	Maybe	58	38,9
1-4	Enough	4	2,7
0	Nervous	15	10

The results of the evaluation are grouped into several categories which are then calculated as a percentage in each category. The percentage of DRPs categories can be seen in table 2.

Table 7. Adverse drug reaction RS Randegansari Husada

Category: ADR	Number of Cases	Percent (%)
Redness Rash	19	12.8
Itch	79	53.0
Can't hear	5	3.4
Blurred vision/blurred vision	11	7.4
Kidney failure	1	.7
Shock/seizures	0	0
Lots / little amount of urine	2	1.3
Urine Color:		
Turbid	1	.7
Yellow	2	1.3
Red	148	99.3
Pain:		
joints	146	98.0
Muscle	55	36.9
Bone	25	16.8
Tingling	54	36.2
Swollen legs	21	14.1
Numbness/burning sensation in the hands/feet	9	6.0
Vertigo/balance disorder	13	8.7
Dizzy	15	10.1
Sleepy	18	12.1
Digestion		
No appetite	148	99.3
Weight loss	97	65.1
Mual/muntah	87	58.4
Stomach ache	60	40.3
Flu :		
Fever/chills	27	18.1
Headache	33	22.1
have a cold	3	2.0
Cough	144	96.6
Crowded	13	8.7
Anemia :	78	52.3
Pimple	1	.7
Stress/gelisah	5	3.4
Excessive sweating	11	7.4
Slogans	5	3.4
BAB:		
Normal	59	39.6
Constipation / difficult	1	7
Diarrhea	3	2.0

The table above shows that almost all patients experience symptoms of red urine and anorexia, which is 148 patients or 99.3%. No appetite can cause weight loss, which can be seen in the results of a study of 97 patients or 65% of patients who lost weight. In addition, almost most patients feel joint pain, namely 146 patients or 98%. The highest occurrence of side effects also appeared in nausea and vomiting (87 patients or 58.4%) and itching (79 patients or 53%). The severity can be seen from patients who have more than 3 side effects having the highest percentage of 36.2% in 54 patients out of 149 patients. And 40 or 26.8% of the 149 patients experienced only 1 side effect.

One type of OAT, namely rifampicin, can cause the appearance of red in urine and sweat. It is actually the color pigment of the drug, not because of the bleeding. Commonly consumed TB drugs such as Isoniasid, Rifampicin, Pirazinamide and Etambutol. The side effects that patients often feel are tingling and tingling in the hands and feet, nausea, urine, pink. loss of appetite and mild abdominal pain, sometimes diarrhea, rashes on the skin, joint pain, fever, visual impairment and sometimes hearing loss.

Another ADR symptom that many patients felt was loss of appetite experienced by 148 patients or 99.3%. The appearance of side effects of no appetite is caused by the drug Rifampicin.

ADR Risk Factors

Adverse Drug Reactions (ADR) is one of the causes of patients having to prolong their stay and drug interactions, including one of the causes of ADR. ADR related to drug interactions is a clinical problem that requires proper prevention. The risk factors found in this study were age, gender, occupation, OAT medication used, history of comorbidities, and getting additional medications.

Table 8. The risk factors found in this study were age, gender, occupation, OAT medication used, history of comorbidities, and getting additional medications

Parameter	Bivariat			Multivariat			
	ADR Incidence				CI 95%		
	No ADR	There is ADR	Value-P	Odds Ratio (OR)	Lowest	highest	Value-P
Miscellaneous factors							
Age							
17- 20 year	0	8	0,009	0,342	0,072	0,00	-
20-30	7	13					
31-40	3	17					
> 40 year	9	92					
Jenis kelamin							
Man	16	72	0,017	-	-	-	-
woman	3	58					
Work							
Farmers/breeders	1	5	Chi square	5999	0,00	0,00	0,86
PNS	1	0	=0,008				
Students/students	3	4	Kolmogorov-				
Self employed	0	7	smirnov				
Laborer	3	5	=0,214				
IRT	0	21					
private employees	0	5					
Not Working	0	2					
Unknown	11	80					
TNI/Polri	0	1					
Riwayat Penyakit							
Diabetes	1	21	Chi square =	-	-	-	-
Hypertension	1	5	0,821				
Gout	2	16	Kolmogorov-				
Heart	0	1	smirnov =				
None	14	69	0,97				
diabetes+hypertension	0	5					
Diabetes+Gout	0	6					
diabetes+heart	0	2					
hypertension + heart	1	4					
hypertension+gout	1	9					
Types of OAT							
2KDT	0	3	Chi square =	-	-	-	-
4KDT+2KDT	5	59	0,020				
4KDT	14	68	Kolmogorov-				
			smirnov =				
			0,435				
Additional therapies							
≤ 3Drugs	15	30	0,001	0,094	0,26	0,346	0,01
> 3Drugs	4	100					

The analysis of the factors that have been carried out is summarized in table no., which shows that the results of the chi square test have several factors that affect the occurrence of ADR,

including age (p: 0.09), gender (p: 0.017), occupation (p: 0.008), type of OAT (p: 0.020) and additional therapy (p: 0.01). In addition to OAT, it can affect the occurrence of side effects of tuberculosis drugs

CONCLUSION

Based on the results of this study, it is known that the highest severity of ADR is reddish urine, more than 50% of patients experience ADR more than 3; The risk factors found in this study were age, gender, occupation, OAT drugs used, history of comorbidities, and getting additional drugs and therapy to treat epilepsy side effects of tuberculosis have been carried out according to the symptoms experienced.

References

Abbas, A. (2017). Monitoring Efek Samping Obat Anti-Tuberkulosis (OAT) Pada Pengobatan Tahap Intensif Penderita TB Paru Di Kota Makassar. . . *Journal of Agromedicine and Medical Sciences, 3(1),19. Https://Doi.Org/10.19184/Ams.V3i1.4093*.

Afifah Febriarini, S. (2023). ANALISIS TIME SERIES UNTUK MENDAPATKAN TREN PENDERITA TUBERKULOSIS. Institut Teknologi Dirgantara Adisutjipto.

AGUSTIN, R. S. (2021). Analisis Faktor Risiko Kejadian Tuberkulosis di Wilayah Kerja Puskesmas Kelurahan Cipinang Besar Utara Kota Administrasi Jakarta Timur. Universitas Siliwangi.

Annashr, N. N. (n.d.). BAB 1 PENGENDALIAN PENYAKIT TUBERKULOSIS. *PENGENDALIAN*, 1.

Dasopang, E. S., Hasanah, F., & Nisak, C. (2019). Analisis Deskriptif Efek Samping Penggunaan Obat Anti Tuberculosis Pada Pasien TBC Di RSUD Dr. Pirngadi Medan. *Jurnal Penelitian Farmasi & Herbal*.

Denholm JT, McBryde ES, Eisen DP, Penington JS, Chen C, S. A. (2014). Adverse effects of isoniazid preventative therapy for latent tuberculosis infection: aprospective cohort study. *Drug Healthc Patient Saf., Oct 20;6:1*.

Dewi. (2019). Gambaran reaksi obat yang tidak dikehendaki pada pengobatan tuberkulosis di Puskesmas kabupaten "x" Yogyakarta dan hubungannya dengan kepatuhan minum obat. *Majalah Farmasetika, 4(1):132-136*.

Dwiningrum, R., Wulandari, R. Y., & Yunitasari, E. (2021). Hubungan Pengetahuan dan Lama Pengobatan TB Paru dengan Kepatuhan Minum Obat pada Pasien TB Paru Di Klinik Harum Melati. *Jurnal Aisyah: Jurnal Ilmu Kesehatan*, *6*, 209–214.

Febriani, A., Hidayat, K. S., Muthiadin, C., & Zulkarnain, Z. (2022). Gambaran hasil pemeriksaan mikroskopik basil tahan asam pada penderita tuberkulosis paru di BBKPM Makassar. *Filogeni: Jurnal Mahasiswa Biologi*, *2*(1), 21–26.

Guo, T., Xin, H., & Gao, L. (2023). *Interpretation of WHO consolidated guidelines on tuberculosis: Module 1: prevention: tuberculosis preventive treatment*. *Chinese Journal of Antituberculosis* (Vol. 45). https://doi.org/10.19982/j.issn.1000-6621.20230199

Kriswandini, I. L., Indrawati, R., Devijanti, R., Luthfi, M., Arundina, I., Budi, H. S., … Khoswanto, C. (2023). *Buku Ajar BIOLOGI ORAL II Clinical Application*. Airlangga University Press.

Mariyono, H. H., & Suryana, K. (2008). Adverse Drug Reaction Harbanu. *Journal of Chemical Information and Modeling*, *53*(9), 1689–1699.

Meyrisca, M., Susanti, R., & Nurmainah, N. (2022). Hubungan Kepatuhan Penggunaan Obat Anti Tuberkulosis Dengan Keberhasilan Pengobatan Pasien Tuberkulosis Di Puskesmas Sungai Betung Bengkayang. *Lumbung Farmasi: Jurnal Ilmu Kefarmasian*, *3*(2), 277–282.

Mulyati, S. (n.d.). METODE PENYEMBUHAN PENDERITA VIRUS COVID-19 DENGAN DZIKIR TQN PONDOK PESANTREN SURYALAYA SIRNARASA (STUDI KASUS LABORATORIUM FALAK RUHANI AL-HIKAM JAKARTA SELATAN). FU.

Musdalipah, Nurhikmah, E., Karmilah, & Fakhrurazi, M. (2018). Efek Samping Obat Anti Tuberkulosis (Oat) Dan Penanganannya Pada Pasien Tuberkulosis (Tb) Di Puskesmas Perumnas Kota Kendari. *Jurnal Imiah Manuntun, 4(1), 67 – 73. Http://Jurnal.Akfarsam.Ac.Id/Index.Php/Jim_ak Farsam/Article/View/144*.

Ningrum., V., D., A., Megasari, A.,. (2010). Hepatotoksisitas pada Pengobatan Tuberkulosis di RSUD Tangerang-Indonesia. *Jurnal Ilmiah Farmasi*, *7N*.

Nortajulu, B., Susianti, S., & Hermawan, D. (2022). Faktor-faktor yang berhubungan dengan kesembuhan Tb

paru. *Jurnal Penelitian Perawat Profesional*, *4*(4), 1207–1216.

Seniantara, I. K., Ivana, T., & Adang, Y. G. (2018). Pengaruh Efek Samping Oat (Obat Anti Tuberculosis) Terhadap Kepatuhan Minum Obat Pada Pasien Tbc Di Puskesmas. . . *Jurnal Keperawatan Suaka Insan (JKSI)*.

Shalsabilla, A. (2021). ASUHAN KEPERAWATAN KLIEN YANG MENGALAMI TB PARU DENGAN MASALAH KETIDAKEFEKTIFAN BERSIHAN JALAN NAFAS DI RSUD PRINGSEWU TAHUN 2021. UMPRI.

Singh, A., Prasad, R., Balasubramanian, V., Gupta, N., & Gupta, P. (2015). Prevalence of adverse drug reaction with first-line drugs among patients treated for pulmonary tuberculosis. *Clinical Epidemiology and Global Health*, *3*, S80–S90. https://doi.org/10.1016/j.cegh.2015.10.005

Suryati, S., Yesika, R., Zuhra, M., Suzana, D., Ifadah, E., Makmuriana, L., … Dari, N. P. D. R. W. (2023). *BUKU AJAR FARMAKOLOGI DALAM KEPERAWATAN*. PT. Sonpedia Publishing Indonesia.

Ujiani, S., & Nuraini, S. (2020). Pengaruh Infeksi Mycobacterium tuberculosis Terhadap Parameter Hematologi Anemia dan Malnutrisi Pasien TB di Puskesmas Bandar Lampung. *Jurnal Analis Kesehatan*, *9*(1), 1–8.

Wiyati, T., Irawati, D., & Budiyono, I. I. (2014). Studi Efek Samping Obat dan Penanganannya Pada Pasien TB Paru di Puskesmas Melong Asih, Cimahi. *Pharmaceutical Science and Technology, III(1), 23 –30*.

Yuliza Anggraini, Y. A., Astuti, Y. M., Astuti, Y. M., & Edo Duanda Putra, E. D. P. (2022). LAPORAN PRAKTEK KERJA PROFESI APOTEKER RUMAH SAKIT UMUM DAERAH (RSUD) dr. MUHAMMAD ZEIN PAINAN. UPERTIS.

Yuzar, D. N. (2020). Penyakit menular dan wabah penyakit covid-19.