IOSR Journal of Applied Geology and Geophysics (IOSR-JAGG)
e-ISSN: 2321–0990, p-ISSN: 2321–0982.Volume 10, Issue 1 Ser. III (Jan. – Feb. 2022), PP 01-08
www.iosrjournals.org

PCNE and Cipolle Classification for Drug-Related Problems in Tuberculosis: A Review

Annisa Fauziah Em[1], Widya Kardela[1], Rezlie Bellatasie[1]
[1] *Department of Pharmacology and Clinical Pharmacy, School of Pharmaceutical Sciences (STIFARM) Padang, West Sumatra, Indonesia, 25147*

Abstract:
Background*: The high number of Tuberculosis (TB) cases globally, without proper treatment, can lead to high mortality rates. Treatment of tuberculosis requires a combination of several drugs that increases the possibility of Drug-Related Problems (DRPs).*
Objective: *To identify the frequency and types of DRPs that occur in TB patients and become useful literature to prevent the occurrence of DRPs in patients.*
Research Methods*: A literature search was conducted systematically from January 2010 to December 2020 using PubMed, Google Scholar, and ResearchGate databases. The keywords used were "Drug-Related Problem AND tuberculosis".*
Results*: There are a total of five articles, two articles were found using the PCNE classification and three articles using the Cipolle classification. The most common drug-related problems are drug interactions, followed by high doses of drugs.*
Conclusion: *The incidence of drug-related problems has an impact on the morbidity and mortality of treatment outcomes. Pharmacists play an important role in identifying, overcoming, and preventing drug-related problems, both potential and actual. Therefore, it is necessary to optimize the work of health workers, especially pharmacists, to improve the quality of life of TB patients.*
Key Word*: Drug-Related Problem; Tuberculosis; Drug Interaction.*

Date of Submission: 13-02-2022 Date of Acceptance: 28-02-2022

I. Introduction

Tuberculosis (TB) is an infectious disease caused by the *Mycobacterium tuberculosis* bacillus. *M. tuberculosis* is a gram-positive bacterium, rod-shaped, its cell wall structure is composed of a glycolipid lipid complex which has a waxy substance, making it difficult for chemicals to penetrate [1]. These bacteria were identified as resistant to acid staining during microscopic examination of sputum, so they were known as acid-fast bacilli (BTA). *M. tuberculosis* can survive in humid and dark conditions so that it is susceptible to direct sunlight. These bacteria are also dormant in body tissues for a very long time. About 80% of TB bacteria attack the lungs. Pulmonary TB develops rapidly in the body because it can multiply in phagocytic cells [2].

In 2019, around 10 million people developed TB, and 1.4 million of them died. Based on World Health Organization (WHO) data in 2019, the largest TB cases were estimated in Southeast Asia (44%), Africa (25%), and the Western Pacific (18%). In 2020, as many as 198 countries reported that more than 99% of the world's population is estimated to have TB cases [3]. The Department of Gender and Women's Health of WHO stated that the incidence and prevalence of tuberculosis are more common in males than in female adults [4]. A higher incidence of TB was found in men in all age categories, except in childhood, where women were predominately infected with TB. This can happen because the male hormone, testosterone, can increase the effect of immunosuppressants so that the body's ability to fight bacteria is reduced. While the hormone estrogen works the other way around, which triggers a high immunostimulant immune power [5,6].

TB treatment aims to cure patients, prevent death, prevent a recurrence, break the chain of transmission and prevent the occurrence of bacterial resistance to antituberculosis drugs. TB treatment is divided into two stages: the intensive stages for 2 months and the advanced stage for 4 months [7]. The recommended treatment for TB patients is 6 months of therapy using first-line ATD consists of isoniazid, rifampin, ethambutol, and pyrazinamide. The recommended treatment options for TB prevention are: a weekly dose of rifapentine and isoniazid for 3 months (3HP), daily dose of rifampin plus isoniazid for 3 months (3HR), daily dose of rifampicin plus isoniazid for 1 month (1HP), daily dose of rifampin for 4 months (4R), and a daily dose of isoniazid for 6 months (6H) or longer [3].

TB treatment is a long-term therapy with a combination of several drugs consumed by the patient (polypharmacy). This condition can cause patient non-compliance problems and drug costs, so that it can increase the possibility of Drug-Related Problems (DRPs). DRPs are a type of problem that arises in the use of drugs or drug therapy that can potentially affect patient's therapeutic outcomes, increase treatment costs, and can also hinder the achievement of therapeutic goals [8,9]. Drug-related problems (DRPs) are conditions or events related to drug therapy, which potentially or actually affect the patient's clinical outcome. Actual DRPs are problems that have occurred to patients and pharmacists should try to solve these problems. Meanwhile, Potential DRPs are a problem that might occur, and patients are at risk of experiencing DRPs if the pharmacist does not take preventive measures [10].

There are 14 types of DRPs classifications found in the international journal literature, each of which has differences in terms of understanding and categories of problems related to the drugs used [8,11]. This classification system is useful for assisting healthcare professionals in the process of documenting drug-related problems [12]. To increase rational use of drugs, pharmacists are expected to play an active role in eliminating problems during the use of antituberculosis drugs. This role can be initiated by identifying drug-related problems that occur in each patient, both potential and actual, then resolve them appropriately and quickly and seeking to prevent drug-related problems with pharmaceutical services. Of the various existing DRPs classification systems, in this article the classification system used is PCNE V5.01 and Cipolle. PCNE has a basic classification of problems, causes, interventions. The PCNE problem has 6 primary domains and 21 subdomains. The 6 primary domains are adverse reaction, drug choice problem, dosing problem, drug use problem, interaction and others. The Cipolle DRPs classification consists of, need for additional therapy, unnecessary therapy, wrong drug, dosage it too low, adverse drug reaction, dose too high and adherence problem [12,13].

In increasing rational use of drugs, pharmacists are expected to play an active role in eliminating problems during the use of antituberculosis drugs. This role can be initiated by identifying drug-related problems that occur in each patient, both potential and actual, then resolve them appropriately and quickly and seeking to prevent drug-related problems with pharmaceutical services [13].

II. Methods

The literature search was carried out systematically using PubMed, Google Scholar, and ResearchGate. Based on the title of this review, the keywords used in PubMed and ResearchGate were "drug-related problems AND tuberculosis" for articles published from January 2010 to December 2020. The following keywords were used to find relevant articles on Google Scholar "Drug-related problems AND Tuberculosis". The use of 'AND' was to improve the accuracy of the literature search so that the results obtained include both keywords used.

The inclusion criteria for articles included in this review are free full-text articles that focus on DRPs in tuberculosis patients using the Pharmaceutical Care Network Europe (PCNE) V5.01 and Cipolle classification systems. The exclusion criteria were case studies or reviews and articles that did not use English/Indonesian.

III. Result

Based on the results of article screening from Figure 1, the obtained 5 articles are used as shown in Tables 1 and 2

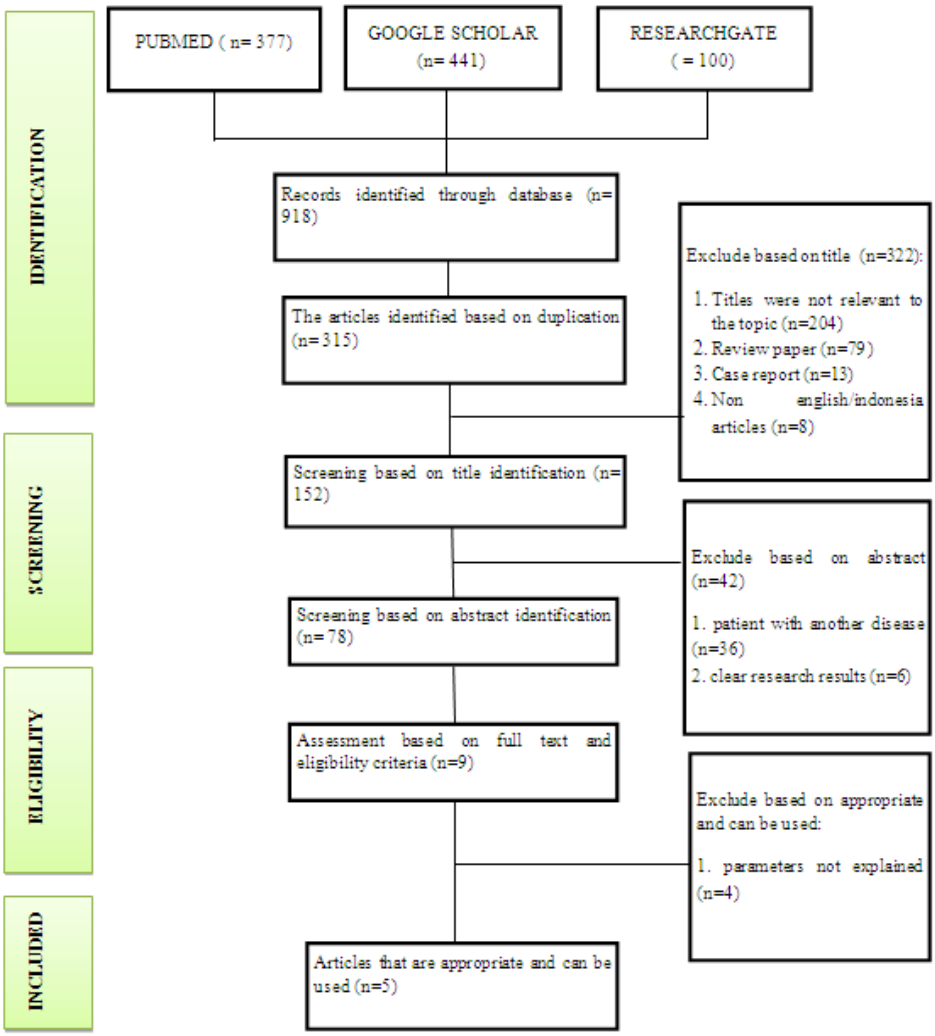

Figure 1. Prisma Flowchart of Literature Search

.

IV. Discussion

This review aims to describe what forms of drug-related problems occur in TB patients using a classification system. The classification system used is PCNE V5.01 and Cipolle. The PCNE classification system has a hierarchical structure and consists of codes for problems, causes, and interventions that are hierarchically structured to make it easier for researchers to categorize drug-related problems. The PCNE problem has 6 primary domains and 21 subdomains. The 6 primary domains are adverse reaction, drug choice problem, dosing problem, drug use problem, interaction, and others [12]. The Cipolle classification divides the problem into 8 problems and is more directed to "drug therapy problems" rather than "drug-related problems". The Cipolle DRPs classification consists of, need for additional therapy, unnecessary therapy, wrong drug, dosage it too low, adverse drug reaction, dose too high and adherence problem [14]. The Cipolle method generally refers to a problem system approach in the drug therapy chain and from the patient's point of view. Therefore, a good understanding and knowledge is needed in order to harmonize these differences, which actually have the same aims and objectives.

Schaefer explained that 8 criteria define an appropriate coding system. Taking into account these criteria, there are 5 main requirements for the classification of DRPs. The DRPs classification must have a clear definition; have publication validation; be used in practice; have a hierarchical structure; have the processes and outcomes of drug use and separate problems from causes [15]. PCNE meets these criteria, and has a hierarchical structure consisting of separate codes for problems, causes, and interventions to be used as international standards [11]. Cipolle does not meet all of Schaefer's requirements. However, This classification is still widely used by the pharmaceutical community in the US for the evaluation of pharmaceutical activity in daily pharmaceutical services [16].

DRPs in tuberculosis using the PCNE V5.01 classification system

There are 2 articles that use PCNE classification to identify DRPs in TB patients in Table No. 1. The prospective technique is used in this articles. The PCNE classification system is organized in a hierarchical structure. For problems, causes, and interventions, PCNE offers codes.

Table 1:DRPs in TB patients based on PCNE classification

Ref.	Methods	DRPs PCNE V5.01			Conclusion
		Problem (P)	Causes (C)	Intervention (I)	
[17]	Prospective (November 2015-April 2016)	P1. 0,85% P1.1. 0,85% P2. 40,68% P2.1. 74,37% P2.2. 21,85% P2.3. 1,68% P2.4. 0,42% P2.5. 1,68% P3. 0,51% P3.2. 0,51% P4. 0,68% P4.2 0,68% P5.50,26% P5.1 50,26% P6. 6,67% P6.2 6,67%	-	-	Drug interactions (50.26%) were the most common drug-related problems, followed by drug selection (40.685) and inappropriate drug use (74.37%) (Number of patients = 100; number of DRPs identified = 585)
[18]	Prospective (November 2018 – April 2019)	P1. 10,89% P2. 16,83% P2.2.6,93% P2.3 4,95% P2.5 4,95% P4. 8,9% P4.2 8,9% P5. 41,58% P6.2 21,75%	-	-	The most common DRP found was drug interactions 41.58%. (Number of patients = 70; number of DRPs identified = 101)

Adverse drug reaction

The most common adverse drug reaction in TB patients is gastritis followed by anemia, flu-like syndrome, itching and rash with a high percentage of 10.89% [18–20]. The use of anti-TB such as H, R, Z increased liver function test (LFT) values and anemia with the lowest percentage of 0.85% [17]. First-line anti-TB drugs have the potential to cause hepatotoxicity. First-line anti-TB drugs such as H, R, and Z cause hepatotoxicity such as transaminitis and fulminant renal failure. The incidence of hepatotoxicity induced by ATD was found to be between 2% to 28% based on the diagnostic criteria for hepatotoxicity. Patients are given hepatoprotectors such as curcumin to prevent hepatotoxicity, but not all patients get this hepatotoxic prevention. Hepatitis due to ATD is more common in the use of H and R. Where H produces hydrazine which is a hepatotoxic metabolite. This hydrazine is more produced when combined with R.. Risk factors for hepatotoxicity include high alcohol consumption, elderly, chronic liver disease, chronic viral hepatitis B (HBV) and hepatitis C virus (HCV) infection, human immunodeficiency virus (HIV) infection, advanced TB, Asian ethnicity, concomitant administration of enzymes inducers, inappropriate use of drugs and poor nutritional status [21,22].

Drug choice problem

Drug choice problems were identified in the two articles with different sub-domain categories. First, the sub-domain category of **inappropriate drug** with a high percentage of 74.37% [17]. In this article, different antibiotics were prescribed, some of which prescribed the ceftriaxone antibiotic. At its discretion, ceftriaxone is used for epiglottitis, brain abscess, bacterial meningitis, pyelonephritis in children, empiric treatment of septicemia in children, bacterial peritonitis in ascites, skin and soft tissue infections for outpatient or with an IV course of antibiotics at home, acute septic monoarthritis if allergic to penicillin, as well as spontaneous bacterial peritonitis [23]. Therefore, the use of other antibiotics such as ceftriaxone is not necessary because it is not effective and the use of ceftriaxone is not indicated in patients. Inappropriate use of ceftriaxone can cause resistance to microbial agents that can lead to treatment failure [24]. Drug-related problems with **inappropriate drug form** sub-category in both articles with a presentation of 21.85% and 6.93%, respectively. Reportedly, pantoprazole injection and ranitidine were prescribed as an oral substitute without clear indications. The use of paracetamol injection was also found in prescription, where the patient only had a mild fever [17,18]. Problems related to **inappropriate duplication of therapeutic group or active ingredient** drugs have been reported using aminoglycosides such as gentamicin with streptomycin injection given concurrently because both drugs

belong to the same class of antibiotics. Drug related problem **Contraindications for drugs** reported a decrease in Hb after being prescribed chloramphenicol, which is contraindicated for anemia. Administration of chloramphenicol can cause bone marrow depression [17,25]. Lastly, **no clear indication of drug use** reported the administration of pantoprazole which indicated for GERD while the patient did not have these symptoms [18].

Dosing Problem

It is reported that 0.51% problems related to high doses in patients with alcoholic conditions whose LFT values are not normal [17]. The dose of TB drugs such as isoniazid, rifampicin, and pyrazinamide should be adjusted. Alcoholism is a major risk factor exacerbating hepatotoxicity when anti-TB is induced. For all types of liver disease caused by alcohol, the main treatment is to stop consumption of alcohol completely [21].

Drug Use Problems

It was found that 0.68% patients were prescribed the wrong drug [17]. The drug given is Montelukast which is a leukotriene modifier targeted for the inflammatory pathway in asthma. Montelukast is used as an option for controller therapy, especially in children [26]. and only indicated in patients due to chronic asthma and allergic rhinitis due to seasons.

Interactions

As much as 41,58% and 50.26% of drug interactions occurs [17,18]. Drug interactions have an impact on TB patients with comorbidities such as liver disorders, diabetes mellitus (DM), hypertension, and chronic obstructive pulmonary disease (COPD). Concomitant use of isoniazid with paracetamol may increase the risk of hepatotoxicity. In TB patients with diabetes, the use of anti-TB drugs such as R and H can interfere with blood sugar control. The use of rifampin reduces the blood sugar lowering effect of gliclazide and glibenclamide. Rifampicin also decreases the Area Under Curve (AUC) and the effects of repaglinide and nateglinide. It is necessary to monitor the use of rifampin concurrently with drugs that lower blood sugar levels.

In most cases, a dose increase is likely to be necessary. It was also reported that an increase in blood pressure in a hypertensive patient was associated with the interaction of enalapril and rifampicin. Rifampicin can reduce levels of active plasma metabolites of imidapril and spirapril [27].

Others

2 articles discussed others with a presentation of 21.75% and 6.67% [17,18] subdomains of **insufficient awareness of health and diseases**. It was reported that the lack of awareness of the disease was caused by good knowledge about the causes and treatment of TB in TB patients, but there were also misunderstandings. Misconceptions about disease transmission lead to discrimination, such as separating food and drink utensils that are used. A TB diagnosis is associated with increased anxiety, fear of losing income, and stigma that threatens self-esteem and quality of life. Mass media can be put to good use to eliminate misunderstandings in society. As described in this study, psychosocial reactions to TB should be addressed through counseling and communication during treatment at DOTS centers. It can contribute to the success rate of TB control programs [17,28,29].

DRPs In tuberculosis using the Cipolle classification system

Based on the above table, there were 3 articles that used the Cipolle classification in table no 2. 2 articles used the retrospective method and 1 article used the prospective method.

Tabel 2: DRPs in TB patients based on Cipolle classification

Ref.	Methods	Parameter	Result	Conclusion
[30]	Prospective (January – December 2009)	Cipolle 1990	1. Wrong drug 52,94 % 2. Over dose 1,76% 3. Low dosage 29,41% 4. Drug interactions 98,24%	The most common DRPs were drug interactions with 167 cases, then 90 cases of wrong drug, less dose 50 cases, and more than 3 cases. (Number of patients = 70; number of DRPs identified=310)
[31]	Prospective (March 2014)	Cipolle 1998	1. Drugs without indications 19,05 % 2. Medication without related indications 11,90% 3. High doses of drugs 2,38 % 4. Low dose drugs 14, 29% 5. Wrong drug selection 7,14% 6. Adverse drug reactions (ADR) were 9,52% 7. Drug interactions 16,67% 8. Failure to receive drugs 19,05%	The most frequently encountered DRPs were drug administration without indication and treatment failure with the same percentage of 19.05%. (Number of patients = 8; number of DRPs identified= 38)

[32]	A study cross-sectional Retrospective (July 2018 – December 2018)	Cipolle 1998	1. Unnecessary drug therapy 2,85 % 2. Need additional drug therapy 6,85% 3. Drugs are not effective 1.54% 4. Overdose 5,46% 5. Low dose 7,00% 6. Drug interactions 66,18%	The most common drug-related problems were drug interactions (66.18%) (Number of patients= 133; DRPs identified= 383).

Need for additional therapeutic drugs

2 articles were discussing the **need for additional therapeutic drugs** with a percentage 11, 90% and 6,89% [31,32]. Therapeutic drugs are needed to prevent and treat certain medical conditions. Prescriptions are given for additional therapeutic drugs only to relieve TB symptoms but do not treat TB bacterial infection; for example, patients have only prescribed guaifenesin and vitamin B or are only given salbutamol without being prescribed anti-TB drugs. TB therapy without antibiotics can lead to more severe infection, recurrence, and retention if the patient undergoes only a few TB therapy procedures [32].

Unnecessary drug therapy

The next drug-related problem is **unnecessary drug therapy,** administration of drugs that are not needed if there are no clinical indications with percentage 19,05% and 2,85% [31,32]. Administration of drugs that are not needed can lead to resistance, especially for antibiotics, and also can cause unwanted effects. Unnecessary use of medication occurs because doctors focus on symptoms rather than the diagnosis. Some patients also want the symptoms to disappear and encourage doctors to prescribe drugs to treat symptoms [32]. For example, the use of ceftriaxone which indicated for gram-positive and gram-negative bacterial infections [31].

TB therapy causes side effects of nausea, vomiting, and epigastric pain, elevated liver enzymes, arthralgia, acne, and skin pruritus [33]. Therefore, in addition to anti-TB drugs, additional drugs are also given to overcome the side effects of therapy. To cope with the side effects of pruritus, itching and rashes, loratadine, cetirizine, and chlorpheniramine maleate are prescribed. For nausea and vomiting, domperidone, ranitidine, omeprazole, and antacids are prescribed [32].

Ineffective medicine/wrong drugs

There are 3 articles on drug-related problems regarding **ineffective medicine/wrong drugs** with percentages of 52.94%, 7.14% and 1.88% [30–32]. The first article discusses ineffective medicine and the second article discusses wrong drugs where both articles discuss contraindications to drugs [30,32]. The same drug problem was found, namely the use of dexamethasone was contraindicated with TB. Dexamethasone is an anti-inflammatory agent that works by inhibiting cytokines and reducing cellular immunity. If immunity decreases, TB patients are more susceptible to infection with TB bacteria. Giving dexamethasone also relieves symptoms so that the patient feels healed, but the infection remains so that the patient does not undergo anti-TB drug therapy [32].

In the Ramatilla article, cases of ATD 4 FDC (Formulasi Fix Dose Combination) and streptomycin were found in the second category of TB patients. The correct treatment in patients diagnosed with TB MDR (INH and Rifampicin resistance) is the use of second generation ATDs such as cycloserine, ethionamide, ciprofloxacin, levofloxacin. Combinations of drugs that are not needed are the use of two or more types of drugs with the same therapeutic class but different classes that aim to increase their activity. One or more drugs in combination as required by the patient.

Dosage too low

The next drug-related problem is **too low dosage** with percentages 29.41%, 14.29%, and 7%, respectively for the 3 articles [30–32]. In Ramatilla article the use of injection ranitidine in which the dose used is 2 x 50 mg was found, the dose that should be used according to the Renal Drug Handbook (2009) is 3 x 50 mg [34]. A case was found in article Kurnianingsih where the use of ethambutol was given at a dose of 2x1, the dose should be according to the standard 15-25 mg/kg/day. The right dose of drug administration is adjusted to the age, weight, and age of the patient and the frequency of administration based on official management. The accuracy of drug dosage in TB therapy is still a problem because low doses can cause retention and cause therapy to fail [30,32].

Dose too high

Problems related to drugs related to the **dose too high** problems were found in 3 articles with a successive percentage of 1.76%, 2.38% and 5.46% [30–32]. A case was found in the article Ramatilla using

ampicillin sulbactam 4 x 1.5 grams, the dose that should be given is 250-1 gram every 4-6 hours. High doses of antibiotics can trigger resistance.

Adverse drug reaction

Adverse drug reaction in the article was found with a percentage of 9.52%. The use of antituberculosis-drugs in 4FDC can cause side effects of vomiting and increase the SGPT (Serum Glutamic Pyruvic Transaminase) score, the use of ethambutol causes dizziness, confusion and blurred vision. The selection of drugs does not only look at the benefits of healing the disease but also must consider the clinical condition. Drugs that are categorized as unsafe in the patient's condition if the drug has the potential to cause harmful side effects or have been proven to cause side effects [31].

Drug interactions

Drug interaction is a condition where the effect of a drug changes in the presence of other drugs, herbal medicines, food, beverages, and other chemicals. Problems related to **drug interactions** were found in 3 articles with percentages of 94.24% and 16.67%, and 66.18% [17,30,32]. A drug interaction is dangerous if it produces a reaction that can increase the toxicity of the drug or decrease the efficacy of the drug. The interaction that occurs between TB drugs, namely INH interacts with Rifampicin should be a concern. The use of isoniazid together with rifampin can increase isoniazid metabolism which results in the formation of hydrazine which is a hepatotoxic carrier [35]. The effect of concurrent use may increase hepatotoxicity in patients. Most TB drugs are hepatotoxic. Therefore, the use of drug combinations that can cause interactions is avoided, and liver function should be monitored by checking the levels of alanine aminotransferase (ALT) and aspartate aminotransferase to prevent hepatotoxicity. To reduce the damage, curcumin is usually prescribed, to protect the liver [22].

Failure to receive drugs

Incidents of drugs that are not received by patients can be caused by a lack of economy, distrust and unwillingness to take drugs**.. Failure to receive drugs** with a percentage of 19.05%. The majority of patients failed to get pain medication and antibiotics. Irregular and untimely use of antibiotics in therapy will cause resistance [31].

Drug resistance caused by the patient's non-adherence to follow treatment instructions can actually cause side effects of TB drugs themselves. TB patients who experience side effects of treatment, the patient is likely to stop treatment unilaterally without notifying health workers. These conditions contribute to the occurrence of ATD resistance. In Dian's 2015 study, it was found that most resistances experienced liver disorders with complaints of nausea, vomiting and laboratory results increased SGOT and SGPT values, increased uric acid with complaints of joint pain and diarrhea. Inadequate treatment and non-adherence in treatment can develop resistance [36].

V. Conclusion

Based on the results of this review article, it can be concluded that the incidence of DRPs can be measured by several classifications. In this review, the classifications used are PCNE V5.01 and Cipolle. This DRPs classification system helps pharmacists document problems during TB treatment. From the combination of the 2 classification systems. The most frequent and common drug-related problem found is drug interactions, followed by overdose. Drug-related problems in TB patients do not only occur between TB drugs, but also occur with drugs used during TB therapy. TB drug therapy uses a lot of antibiotics, so that if TB therapy is not carried out adequately, such as incorrect diagnosis, treatment does not use the right guidelines, dose, type, and amount of medication and duration of treatment are inadequate, irregular swallowing of ATD and unilaterally stopping treatment, will lead to drug resistance. The incidence of drug-related problems impacts disease mortality and morbidity as well as TB treatment outcomes. Pharmacists play a role in identifying, overcoming, and preventing drug-related problems, both actual and potential. Therefore, it is necessary to optimize the work of health workers, especially pharmacists so that drug therapy can improve the quality of life of tuberculosis patients.

References

[1]. V K, A. K A, J.C A. *Buku Ajar Patofisiologi Robbins. 9th Edn. Edited by I.M. Nasar and S. Cornain*. Singapore: Elsevier Saunders; 2014.
[2]. Prince SA, Wilson LM. *Patofisiologi Konsep Klinis Proses-Proses Penyakit*. 6th ed. Jakarta: Buku Penerbit Kedokteran EGC; 2006.
[3]. WHO. *Global Tuberculosis Report 2020*.; 2020. https://www.who.int/teams/global-tuberculosis-programme/tb-reports.
[4]. Departement of Gender and Women's Health of WHO. *Gender and Tuberculosis*. Geneva: Departement of Gender and Women's Health of WHO; 2002.
[5]. Zabel P, Stu F. Gender Differences in Human Sepsis. 2016;133:1200-1205.
[6]. Adrie C, Azoulay E, Francais A, et al. Influence of Gender on the Outcome of Severe Sepsis. *Chest*. 2007;132(6):1786-1793. doi:10.1378/chest.07-0420

[7]. Departemen Kesehatan RI. *Pedoman Nasional Penanggulangan Tuberkulosis*. II.; 2007.
[8]. Mil J, Westerlund L, Hersberger K, Schaefer M. Drug-Related Problem Classification Systems. *Ann Pharmacother*. 2004;38:859-867. doi:10.1345/aph.1D182
[9]. Rantucci M. *Komunikasi Apoteker- Pasien*. Edisi kedua. Jakarta: Penerbit Buku Kedokteran EGC; 2009.
[10]. Andayani TM, Rahmawati F, Rokhman MR, et al. *DRUG-RELATED PROBLEMS: Identifikasi, Faktor Resiko, Dan Pencegahannya*. (Wahyu, ed.). Yogyakarta: Gadjah Mada University Press; 2019.
[11]. Pk A, Adepu R. Drug Related Problems : An Over View of Various Classification Systems. *Asian J Pharm Clin Res*. 2014;7(4):7-10.
[12]. Pharmaceutical Care Network Europe: PCNE Classification V5.01. https://www.pcne.org/upload/files/16_PCNE_classification_V5.01.pdf.
[13]. Mulyani UA. Peran serta profesi farmasi dalam permasalahan yang terkait dengan terapi obat tuberkulosis pada anak. *Bul Penelit Sist Kesehat*. 2006;9:100-106.
[14]. Cipolle R, Strand L, Morley P. *Pharmaceutical Care Practice*. New York: McGraw-Hill; 1998.
[15]. Schaefer M. Discussing basic principles for a coding system of drug-related problems : the case of PI-Doc ®. *Pharm World Sci*. 2002;24(7):120-127.
[16]. Hartzema AG, Porta MS, Tilson HH, et al. Drug-Related Problems : Their Structure and Function. *DICP*. 1990;24:1093-1097.
[17]. Shivaraj G, Muralikrishna K, Nijeesh CH, Laloo F, Baburaja B, Doddayya H. Study On Drug Related Problems In Tuberculosis Patients With Comorbidities In A Tertiary Care Teaching Hospital. *Eur J Pharm Med Res*. 2017;4(9):756-767.
[18]. Ranjani G, Evariste S, Mohanta GP, Paari N. Study on drug related problems in tuberculosis patients undergoing treatment. *Int J Basic Clin Pharmacol*. 2020;9(8):1199-1203. doi:http://dx.doi.org/10.18203/2319-2003.ijbcp20203136
[19]. Farazi A, Sofian M, Jabbariasl M, Keshavarz S. Adverse Reactions to Antituberculosis Drugs in Iranian Tuberculosis Patients. *Tuberc Res Treat*. 2014:6. doi:10.1155/2014/412893
[20]. Fei CM, Hadzliana Z, Ali I, Ali H. Evaluation of Adverse Reactions Induced by Anti-Tuberculosis Drugs in Hospital Pulau Pinang. *Malay J Med Sci*. 2018;25(5):103-114.
[21]. Amer K, A MS, Sa A, Nematullah K, Ihtisham S, Maazuddin M. Anti-Tuberculosis Drug - Induced Hepatitis – A Case Report. 2013;6(2):65-67.
[22]. Ninggrum V, Megasari A, Hanifah S. Hepatotoksisitas pada Pengobatan Tuberkulosis di RSUD Tangerang Indonesia. *J Ilm Farm*. 2010;7(1).
[23]. Welfare F. *National Treatment Guidelines for Antimicrobial Use in Infectious Diseases Directorate General of Health Services*. Vol 1.; 2016.
[24]. Abebe FA, Berhe DF, Berhe AH, Hishe HZ, Akaleweld MA. Drug Use Evaluation Of Ceftriaxone: The Case Of Ayder Referral Hospital, Mekelle, Ethiopia. *Int J Pharm Sci Res*. 2012;3(07):2191-2195. doi:10.2147/DHPS.S260364
[25]. Tripathi K. *Essentials of Medical Pharmacology*. 6th Editio. New Delhi: JAYPEE; 2006.
[26]. *Pocket Guide For Asthma Management And Prevention*.; 2015. https://ginasthma.org/wp-content/uploads/2016/01/GINA_Pocket_2015.pdf.
[27]. Baxter K. *Stockley's Drug Interactions Pocket Companion*. London: Pharmaceutical Press; 2010.
[28]. Krishna KG, Ananthakrishnan S, Reddy GT, Veeramani G. Study On Adherence To Anti- Tuberculosis Drugs Under Dots And Non-Dots And The Factors Affecting Adherence. *World J Pharm Pharm Sci*. 2016;5(9):1973-1986. doi:10.20959/wjpps20169-7647
[29]. Tasnim S, Rahman A, Hoque FMA. Patient' s Knowledge and Attitude towards Tuberculosis in an Urban Setting. *Pulm Med*. 2012:5. doi:10.1155/2012/352850
[30]. Kurnianingsih L, Sudirman I, Utaminingrum W. Identifikasi Drug Related Problems (DRPs) Pengobatan Tuberkulosis Pada Pasien Rawat Jalan Di RSUD Kardinah Kota Tegal Tahun 2009. *PHARMACY*. 2010;07(03):50-58.
[31]. Ramatillah DL, Suhartini S, Nongkang N, et al. The Evaluation Of Drug Related Problems (DRPs) Of The Tuberculosis (TB) Patients At The Lung Disease Ward In The Installation Of Stayed Caring Of Centralgeneral Hospital Persahabatan (RSUP Persahabatan). *World J Pharm Res*. 2014;3(4):13-23.
[32]. Puspitasari AW, Yunaz SR, Nadhilah L. Identification Of Drug-Related Problems In Adults With Tuberculosis At The Tebet Subdistrict Health Center From July To December 2018. *Int J Appl Pharm*. 2020;12(1):74-77. doi:http://dx.doi.org/10.22159/ijap.2020.v12s1.FF010
[33]. Arbex MA, Varella M de CL, Siqueira HR de, Mello FAF de. Antituberculosis drugs: Drug interactions, adverse effects, and use in special situations. Part 1: First-line drugs. *J Bras Pneumol*. 2010;36(5):626-640. doi:10.1590/s1806-37132010000500016
[34]. Ashley C, Currie A, eds. *The Renal Drug Handbook*. 3rd ed. New York: Radcliffe Publishing Oxford; 2009.
[35]. Amin Z, Bahar A. *Tuberkulosis Paru, Buku Ajar Penyakit Dalam*. Jakarta: UI; 2006.
[36]. Nugrahaeni DK, Malik US. Analisis Penyebab Resistensi Obat Anti Tuberkulosis. *J Kesehat Masy*. 2015;11(1):8-15. doi:http://dx.doi.org/10.15294/ kemas.v11i1.3341

Annisa Fauziah Em, et. al. "PCNE and Cipolle Classification for Drug-Related Problems in Tuberculosis: A Review."*IOSR Journal of Applied Geology and Geophysics (IOSR-JAGG)*, 10(1), (2022): pp 01-08.