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STUDY ON DRUG RELATED PROBLEMS IN TUBERCULOSIS PATIENTS WITH COMORBIDITIES IN A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

The presence of comorbidities in tuberculosis patients like hepatic disorders, renal failure, diabetes mellitus and hypertension etc. require more attention to improve the effectiveness of drug therapy and reducing drug related complications like hepatic toxicity, hyperuricemia, renal failure etc. To understand the drug related problems in tuberculosis patient with comorbidities, a prospective observation based study on drug related problems in tuberculosis patient with comorbidities was conducted in 1000 bedded tertiary care teaching hospital over a period of six months from November 2015 to April 2016. The data was collected from 100 in-patients using specially designed data collection form. Out of 100 patients, 45 cases with hepatic impairment, 30 cases with diabetes, 17 cases with lower respiratory tract infection, 5 cases with hypertension and 3 cases with chronic obstructive pulmonary disease were found. In this study, total 585 drugs related problems have been identified in 100 patients by using 8 categories of Pharmaceutical Care Network Europe drug related problems classification. Drug interactions (50.26%) was the most common drug related problems found, which was clinically significant in tuberculosis patients with comorbidities. Drug choice problem (40.68%) was the second most common drug related problems found, which consists of inappropriate use of drugs (74.37%) like antibiotics and acid suppressant drugs. Hepatic impairment was common for most of the tuberculosis patients with anti-tubercular drugs but in future we have to give more attention on management of tuberculosis in diabetes, hypertension and other comorbidities and associated drugs related problems.

KEYWORDS: Tuberculosis, Comorbidities, Drug Related Problems, Drug Interactions, Drug Choice Problems.

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease. It is one of the leading causes of mortality and morbidity around the world, infecting approximately 8 million people; with an annual death rate of close to 1 million. India shares almost a third of this global TB burden. With nearly 2 million incident cases and half a million deaths annually, TB is certainly an enormous public health problem in our country.[1]

The causative organism of TB i.e. Mycobacterium tuberculosis is resistant to single drug treatment. The effective treatment requires multiple drug regimens, due to the requirement of multiple drugs, the aspects of disease and its management has a huge impact on the overall well-being of the patient and the burden of these factors can equal and even exceed the physical impact of illness. The presence of comorbidities in TB patients like hepatic disorders, renal failure, diabetes mellitus (DM), hypertension, Lower respiratory tract infection (LRTI) and Chronic obstructive pulmonary disorder (COPD) etc. require more attention to improve the effectiveness of drug therapy and reducing drug related complications like hepatic toxicity, hyperuricemia, renal failure etc.

In order to improve the rational use of drugs, the pharmacist have an important role in identifying and solving the problems which has correlation with the use of drugs and potential or actual Drug Related Problems (DRPs).[2] DRPs are defined as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.[3] DRPs are one kind of problem that appear in the using of the drugs or medicine therapy which was potentially or actual can influence the outcome of the patient therapy, increasing the caring cost and also can block the attained of the therapy purposed. The appearance of DRPs usually caused by the increasing of the kinds and the number of the drugs that was consumed by the patient (polypharmacy) to overcome many kinds of disease that was suffered.[2]

To understand the drug related problems in tuberculosis patients with comorbidities, a prospective observation

based study on drug related problems in tuberculosis patient with comorbidities was conducted in 1000 bedded tertiary care teaching hospital.

MATERIALS AND METHODS

A prospective study was carried out from November 2015 to April 2016 during which the data was collected from a total of 100 case sheets of the inpatient of all departments (except OBG) of Navodaya Medical College Hospital and Research Centre, Raichur. The study was approved by Institutional Ethics Committee of Navodaya Medical College Hospital & Research Centre.

Inclusion criteria

1) TB patients with comorbidities.
2) Patients of all age groups.

Exclusion criteria

1) Patients with only TB.
2) Pregnant and lactating women.

Data analysis: All the case sheets were checked for DRPs by using Micromedex, Drugs.com database and various textbooks along with interview from patients and evaluated as per PCNE classification.

Statistical methods

The present study was analysed by using descriptive statistics. Data were collected in predesigned Microsoft Excel and Word 2010. For descriptive statistics, results were expressed in terms of percentages and presented using tables and diagrams according to the types of tool used.

RESULTS

Table 1: Demographics of Patients

Characteristics	Number of patients (%)
Gender	
Male	63 (63)
Female	37 (37)
Age distribution	
Pediatrics	2 (2)
Adults	74 (74)
Elderly	24 (24)
Weight Distribution	
>60 kgs	20 (20)
<60 kgs	80 (80)
Family History of TB	
Yes	10 (10)
No	90 (90)
DOTS Category	
Category I	71 (71)
Category II	27 (27)
MDR	2 (2)
Social Habits	
Smoker	28 (28)
Alcoholic	22 (22)
Smoker & Alcoholic	24 (24)
No Social Habits	26 (26)

Table 2: Comorbidities

Sl. No.	Comorbidities	Number of Cases	Percentage (%)
1	Hepatic impairment	45	45
2	DM	30	30
3	LRTI	17	17
4	Hypertension	5	5
5	COPD	3	3

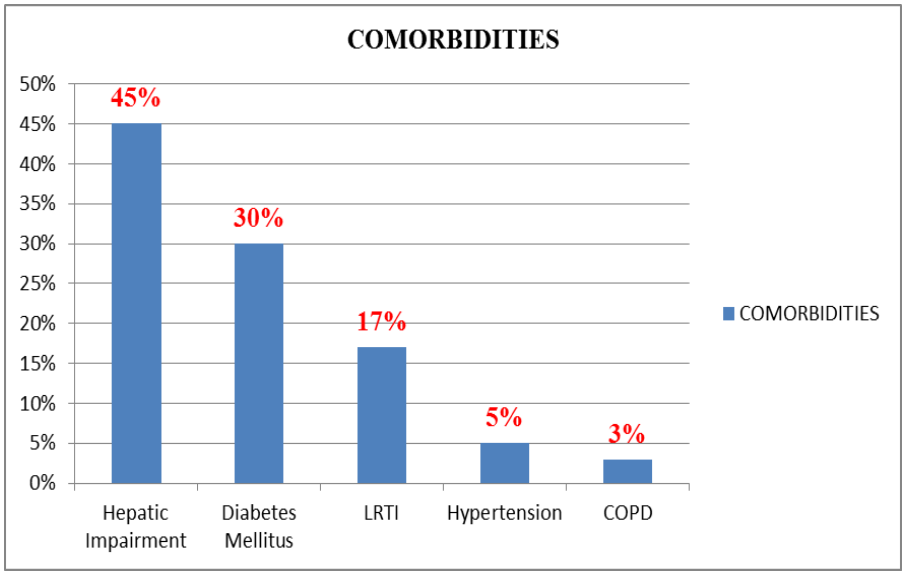

Fig. 1: Co-morbidities.

DRUG RELATED PROBLEMS (PCNE)

Table. 3: Detailed PCNE Classification.

Code	Problems	No. of problems	Percentage (%)
P1	**ADVERSE REACTION**	**5**	**0.85**
P1.1	Side effects suffered (non-allergic)	5	0.85
P2	**DRUG CHOICE PROBLEMS**	**238**	**40.68**
P2.1	Inappropriate drug	177	74.37 of DCP
P2.2	Inappropriate drug form	52	21.85 of DCP
P2.3	Inappropriate duplication of therapeutic group or active ingredient	4	1.68 of DCP
P2.4	Contraindication for drug	1	0.42 of DCP
P2.5	No clear indication for drug use	4	1.68 of DCP
P3	**DOSING PROBLEMS?**	**3**	**0.51**
P3.2	Drug dose too high or dosage regimen too frequent	3	0.51
P4	**DRUG USE PROBLEMS?**	**6**	**0.68**
P4.2	Wrong drug taken/administered	6	0.68
P5	**DRUG INTERACTION**	**294**	**50.26**
P5.1	Potential Interaction	294	50.26
P6	**OTHERS**	**39**	**6.67**
P6.2	Insufficient awareness of health and diseases	39	6.67

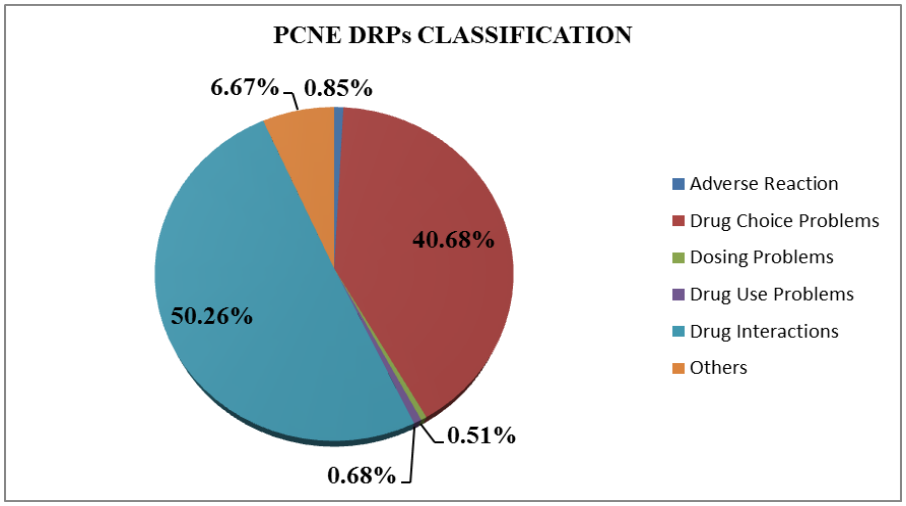

Fig.2: PCNE DRPs Classification.

(P1) ADVERSE DRUG REACTIONS
(P1.1) Side Effects suffered (Non-Allergic): 5
Table. 4: ADR

Sl. No.	Drug	ADR	No. of cases
1	Isoniazid (H), Rifampicin (R), Pyrazinamide (Z)	Elevation of LFT	4
2	Chloramphenicol	Anemia (Decrease in Hb)	1

Table. 5: (P2.1) Inappropriate Drug.

Sl. No	Drugs	No. of cases
	Antimicrobial Agents: Antibiotics	
	Beta-lactams	
1.	Piperacillin	18
2.	Ceftriaxone	27
	Fluroquinolones	
3.	Moxifloxacin	15
	Aminoglycosides	
4.	Gentamicin	2
5.	Amikacin	1
	Others	
6.	Linezolid	15
7.	Chloramphenicol	1
	Acid Suppressant Drugs	
	Proton Pump Inhibitor	
8.	Pantoprazole	76
	H2 Receptor Antagonist	
9.	Ranitidine	22

Table. 6: (P2.2) Inappropriate Drug Form.

Sl. No	Drug dosage form	Appropriate dosage form	No. of cases
1.	Pantoprazole Injection (Inj.)	Oral Tablet (Tab.)	40
2.	Ranitidine Inj.	Oral Tab.	8
3.	Paracetamol Inj.	Oral Tab.	4

Table. 7: (P2.3) Inappropriate Duplication of Therapeutic group / Active drug.

Sl. No	Drug	Therapeutic group	No. of cases
1.	Gentamicin Inj.	Streptomycin Inj. : Aminoglycosides	1
2.	Paracetamol Inj.	Paracetamol Tab.	1
3.	Diclofenac Inj.	Diclofenac Tab.	1
4.	Doxofylline Tab.	Acebrophylline (Tab. Pulmoclear) : Methylxanthines	1

Table. 8: (P2.4) Contraindication of Drug:

Sl. No	Drug	Reason	No. of cases
1.	Chloramphenicol	Bone marrow suppressant (Anemia)	1

Table. 9: (P2.5) No Clear Indication of Drug Use.

Sl. No	Drugs	No. of cases
	Antimalarials	
1.	Lumefantrine + Artemether	4

(P3) DOSING PROBLEM

Table. 10: (P3.2) Drug Dose is too high / Dosage Regimen too.

Sl. No.	Drug	Reason	No. of cases
1.	Isoniazid/ Rifampicin/ Pyrazinamide	Dose should be adjusted for patient with Alcoholic induced hepatic impairment based on liver function test.	3

(P4) DRUG USE PROBLEMS

Table. 11: (P4.2) Wrong Drug Administered.

Sl. No	Drug	Reason	No. of cases
1.	Montelukast	It is only indicated in chronic asthma / Exercise induced asthma and Seasonal Allergic Rhinitis.	6

(P5) DRUG INTERACTIONS

Table. 12: Types of Drug Interactions.

Type of interaction	No. of interactions
(5.1) Potential	
Major	4
Moderate	285

Table. 13: Major Drug Interactions (ATT with concomitant drugs) (5.1).

Sl. No.	Interacting drugs	Effect	No. of cases
1.	R↔Artemether	Decrease concentration of Artemether	4

Table. 14: Other Major Drug Interactions (Other than ATT) (5.1).

Sl. No	Interacting drugs	Effect	No. of cases
1.	Moxifloxacin↔Lumefantrine	Prolong QT interval, increase risk of ventricular arrhythmia.	6

Table 15: Moderate drug interactions (ATT with concomitant drugs) (5.1)

Sl. No	Interacting drugs	Effect	No. of cases
1.	R↔ Pantoprazole	Decrease plasma conc. of Pantoprazole	76
2.	Streptomycin↔Pantoprazole	Increase risk of hypomagnesemia	27
3.	Streptomycin↔Ceftriaxone	Increase risk of Nephrotoxicity.	27
4.	R↔Ondansetron	Decrease effect of Ondansetron	8
5.	HRZ & Ethambutol (E) ↔ Linezolid	Increase risk of Peripheral neuropathy.	15
6.	HRZE↔ Chloramphenicol	Increase risk of Peripheral neuropathy.	1
7.	Streptomycin↔Piperacillin	Inactivation of Streptomycin.	18
9.	Streptomycin↔Amikacin	Increase risk of Ototoxicity and Nephrotoxicity.	1
11.	Streptomycin↔Gentamicin	Increase risk of Nephrotoxicity.	1
12.	R↔Chloramphenicol	Decrease Chloramphenicol serum level.	1

Clinically Significant Drug interactions (Potential/ Moderate) of ATT with concomitant drugs or Comorbid Disease Conditions.

Table. 16: Hepatic Impairment (5.1).

Sl. No	Interacting drugs	Effect	No. of cases	Management
1.	H↔Paracetamol	Increase risk of Hepatotoxicity	45	Monitor LFT Dose Adjustment

Table. 17: Diabetes Mellitus (5.1).

Sl. No.	Interacting drugs	Effect	No. of cases	Management
1. 2.	H/ R↔Insulin/ Oral Antidiabetics	Interfere with glucose control	29	Monitor glucose level; HbA1C Dose Adjustment

Table. 18: Hypertension (5.1).

Sl. No.	Interacting Drugs	Effect	No. of cases	Management
1. 2.	Amlodipine & Losartan ↔ R	Decrease the effects of Antihypertensive drugs	4 1	Monitor BP Dose Adjustment

Table. 19: COPD/LRTI / (Common drugs for TB respiratory symptoms) (5.1).

Sl. No.	Interacting Drugs	Effect	No. of cases	Management
1.	H ↔ Theophylline	Increase the serum level of Theophylline	12	Monitor serum level / effects Dose Adjustment
2.	H ↔ Budesonide	Increase the level of Budesonide	12	Monitor Effects Dose Adjustment
3.	R ↔ Theophylline	Decrease the level of theophylline	12	Monitor serum level / effects Dose Adjustment

(P6) OTHERS

(P6.2) Insufficient awareness of health and disease: 39 Cases.

DISCUSSION

A substantial proportion of hospitalized patients experience medication-related harm that is preventable. Drug errors have been estimated to account for over a quarter of causes of adverse drug events. Strategies to prevent such problems are being developed. One such strategy is the structured review of patient medication by pharmacists to identify patients with medication errors that may lead to harm. The advantage is that the complete clinical status of each patient is taken into account when identifying problems.[4]

The gender distribution of study population showed that among 100 patients, 63 (63%) were male and 37 (37%) were female as shown in table 1. This data showed that males are at more risk to get infection than female because of hormonal differences owned by male and female. Hormone testosterone, which is owned by male, may increase the effects of immune-depression so the body ability to fight the bacteria has decreased. Meanwhile, the hormone estrogen works vice versa so that it can trigger an immune or immune stimulatory high power. Other researchers also reported that the risk of infection in postmenopausal female were almost equal to male. This corresponds to a decrease in the amount of the hormone estrogens and it was found that many dehydroepiandrosteron. 5-reductase enzyme can be converted from dehydroepiandrosteron hormone into dehydrotestosteron which lowers the body's immune system.[5]

In this study, 74(74%) patients were adult, elderly 24 (24%) and children, 2 (2%) as shown in table 1. This result may be due to more adult people are exposed to risk factors/infections compared to elderly and children.

In this study, 80 (80%) of patients weigh less than 60kg and 20 (20%) patient weigh more than 60kg as shown in table 1.

Out of 100 patients, majority of the patients, 90 (90%) are not having any family history of TB as shown in table 1.

Out of 100 patients, majority of the patients, 71 (71%) comes under Category 1 TB and 27 (27%) of category 2 TB and 2 patients with MDR TB as shown in table 1.

Out of 100 patients, 28 (28%) of patients were smoker, 22 (22%) alcoholics and 24 (24%) patients were both smoker and alcoholics. Only 26 (26%) patients were not having any social habits as shown in table 1. Studies have shown that smoking is associated with increased risk of tuberculosis mortality, tuberculosis treatment failure and relapse after treatment completion. Among patients with pulmonary tuberculosis in India, smokers were found to have a threefold greater risk of recurrent tuberculosis than non-smokers. Biological mechanisms that related to smoking are that, it impairs host defence and increase the risk of Mycobacterium tuberculosis infection probably contribute to the relatively poor results of tuberculosis treatment among smokers. For example, smoking may have an irreversible inhibitory effect on nitric oxide synthase – the enzyme needed by alveolar macrophages to form nitric oxide to inhibit the multiplication of Mycobacterium tuberculosis. Cigarette smoking can increase the availability of iron in the lower respiratory tract and iron may bind with nitric oxide to generate toxic radicals that can interfere with alveolar macrophages. Smoking also probably reduces the ability of alveolar macrophages to mount an effective pulmonary immune defence by altering the cell's expression of pro-inflammatory cytokines. Smoking is an independent risk factor for poor tuberculosis treatment

outcomes. Smoking cessation programs need to be targeted at tuberculosis patients both by clinicians specializing in tuberculosis and by national tuberculosis control initiatives. The effectiveness of such programs in reducing smoking among tuberculosis patients and improving tuberculosis treatment outcomes also needs to be assessed.[6]

Isoniazid has been shown to be metabolized more quickly in chronic heavy alcohol users, which can lead to decreased drug effectiveness. In addition, the alcohol-isoniazid combination has been associated with an increased risk of isoniazid-associated hepatotoxicity as well as risk of disulfiram-like reactions. Therefore, patients should always be cautioned to avoid alcohol consumption during and for several days after and antibiotic regimens are known to interact with alcohol. Patients should be informed about unsuspected sources of alcohol and be advised to talk to their physicians regarding any alcohol use.[7]

Out of 100 patients, 45 cases were diagnosed with hepatic impairment, 30 cases with DM, 17 cases with LRTI, 5 cases with hypertension, 3 cases with COPD as shown in table 2 and fig. 1.

The prevalence of diabetes mellitus is increasing worldwide, especially in Asia, TB is highly endemic.[8] Therefore the focus of research has now shifted to the previously untargeted risk factors involved in the spread of TB. One such factor is DM. It is well known that DM impairs the immunity of patients and therefore is an independent risk factor for infections such as TB. People with diabetes are more susceptible to infections and suffer from relatively severe illness due to their immuno-compromised status, with reactivation of older foci of TB rather than through fresh contact, and often exhibit lower lobe involvement more commonly than in non-diabetics. Various studies have shown that 5-30% of patients with TB have DM as well. Diabetes is associated with a decrease in cellular immunity. There are fewer T lymphocytes and a decreased neutrophil count in diabetics. A reduced T-helper1 (Th1) cytokine response level, TNF alpha production, and IL-1 beta and IL-6 production is also seen amongst people with concomitant diabetes and TB as compared to non-diabetic individuals.[9]

Total 585 DRPS have been identified in 100 patients by using 8 categories of PCNE DRPs classification as shown in Table 3 and figure 2. In a study, from the 8 category of DRPs that has been evaluated, 38 cases were found to have DRPs, those are:

1. The patients who received the drugs without indication are 19.05%
2. The patients who did not receive the drugs without related indication are 11.90%
3. The patients who received the high dose of drugs are 2.38%
4. The patients who received the low dose of drugs are 14.29%
5. The patients who received the choosing of inappropriate drugs are 7.14%
6. The patients who felt the Adverse Drug Reaction (ADR) are 9.52%
7. The patient who felt the drugs interaction is 16.67%.
8. The patients who felt the failure in getting the drugs are 19.05%.[2]

The present study shows more number of DRPS occurred in TB patients with comorbidities as compared to TB alone, as the chronic comorbid conditions require regular medication that will contribute more potential drug-drug interactions as shown in table 16, 17, 18 and 19.

In this study, 5 patients were reported with ADR and it was categorized as side effects suffered (non-allergic). 4 patients reported with elevated LFT due to H,R,Z, and 1 anaemic patient reported with reduction of haemoglobin level due to chloramphenicol as shown in table 9. Among 5 patients, 1 ADR was found to be Probable ADR according to Naranjo's scale. The first-line anti-TB drugs are potentially hepatotoxic. From first line anti-TB drugs, H, R, and Z cause hepatotoxicity such as transaminasitis and fulminant hepatic failure. The incidence rate of anti-TB induced hepatotoxicity is found to be 2% to 28% based on hepatotoxicity diagnosis criteria. The risk factors for anti-TB induced hepatotoxicity includes high alcohol intake, older age, pre-existing chronic liver disease, chronic viral infection due to hepatitis B (HBV) and hepatitis C viruses (HCV), human immunodeficiency virus (HIV) infection, advanced TB, Asian ethnicity, concomitant administration of enzyme-inducers, inappropriate use of drugs and poor nutritional status.[10]

Drug induced Hb level reduction was found in 1 female patient with anaemia associated with TB, later the offending drug Chloramphenicol was discontinued because it possesses bone marrow depression as side effects.[11]

In this study, drug choice problem is the second most common drug related problem. A total of 238 (40.68%) DCPs were identified as shown in table 3 and fig 2. In this, inappropriate drug and drugs without clear indications contributing 177 (74.37% of DCP) out of 238 DCP as shown in table 5, 52 (21.85% of DCP) DCP due to inappropriate drug form as shown in table 6, 4 (1.68% of DCP) DCP due to inappropriate duplication of therapeutic group or active ingredient as shown in table 7, 1 (0.42% of DCP) DCP due to contraindication of drug used as shown in table 8. 4 (1.68% of DCP) DCP due to no clear indication for drug use as shown in table 9.

In this study, Inappropriate drug contributing DCP (74.37% of DCP) are the drugs which are shown in table

5 were all are prescribed inappropriately. 81 patient were prescribed with 7 different antibiotics, among these 27 prescriptions of ceftriaxone were prescribed inappropriately.

Ceftriaxone is currently listed in the antibiotic policy for the following: Epiglottitis, Brain abscess, Bacterial meningitis, Pyelonephritis in children, empiric therapy of septicaemia in children, in ascites for treatment of sub-acute bacterial peritonitis, skin and soft tissue infections managed via out-patients or the home IV antibiotic programme, Acute septic monoarthritis if penicillin allergic, spontaneous bacterial peritonitis.[12]

If a patient received a combination of antibiotics with other antibiotics which were not effective against TB bacteria like ceftriaxone in addition to anti-TB antibiotics for TB while the culture and sensitivity test results show that only bacteria are mycobacteria. In this case, the use of other antibiotics was not needed because there was no indication in patients.[2] Result of one study showed that inappropriate use of ceftriaxone is high which paves a way for the emergence of bacterial strains that are resistant to the available antimicrobial agents, which in turn leads to increase in cost of therapy and treatment failure.[13]

Other antibiotics contributing DCP are 18 prescriptions of Piperacillin, 15 prescriptions of moxifloxacin, 15 prescriptions of Linezolid and 3 prescriptions of aminoglycosides; Gentamicin (2) and amikacin (1) as shown in table 5. Piperacillin-Tazobactum currently listed in the antibiotic policy for the following: Pneumonia or septicaemia in neutropenic patients (+ Gentamicin), as a single agent (or in combination with Gentamicin) for treatment of sepsis which has not responded to first line treatment or if it is not appropriate for gentamicin to be added to first-line therapy.[12]

The following criteria has been proposed to protect the linezolid from overuse, which comes under reserve antimicrobials; severe sepsis as defined by more than one organ failure of new onset and/or elevated serum lactate, clinical failure of other classes of antibiotics over 48 hours in terms of worsening inflammatory markers, unresolving fever and new/worsening hemodynamic instability, underlying severe immuno-suppression, neutropenia, immuno-suppressive therapy, diabetic ketoacidosis and the organism is susceptible to only linezolid, as per culture report.[12]

To Prevent and Control the Emergence and Spread of antimicrobial resistant micro-organisms in Hospitals "Alert antibiotics" list was made available in National Treatment Guidelines for Antimicrobial Use in Infectious Diseases which includes ceftriaxone, moxifloxacin, piperacillin-tazobactam, linezolid (oral/IV) etc., were prescribed in appropriately for TB patients. Collectively, these are among the drugs most frequently prescribed irrationally which is largely responsible for the current escalation of antibiotic costs. They also account for a significant proportion of serious antibiotic toxicity including Clostridium difficile diarrhoea and CNS toxicity/seizures as well as the emergence of major antimicrobial resistance. Safer, cheaper and equally effective alternatives are often available which allow such agents to be kept in reserve for occasions when there are clear cut microbiological indications. It is critical, therefore, that these alert antibiotics be prescribed only on the recommendation of senior medical staff or after discussion with the on-call Clinical Microbiologist or ID physician.[12]

Another important inappropriate prescription included second line anti-tubercular drugs like Amikacin (Group 2 Injectable) and Moxifloxacin (Group 3) which are indicated in drug resistant TB.[14]

Empirical antibiotics are used as initial therapy before culture and sensitivity test results come out, but in reality there was no culture and sensitivity test done so that the antibiotics used remained as empirical therapy. When it is to be used for the therapeutic purpose, it is necessary to culture and conduct sensitivity test to certain the bacteria that caused infections. Appropriate use of antibiotics implies the right type of antibiotic chosen, appropriate dosing regimen, and most importantly, the clinical improvement that occurs after antibiotic use. The use of inappropriate doses of antibiotics can also increase the risk of bacterial resistance to antibiotics used; this is because WBC is a sign of infection.[13]

To optimize rational use of antibiotics, a strategic need of monitoring is required to evaluate the use of antibiotics. Monitoring parameter of the antibiotics treatment can be achieved by assessing the associated DRPs during antibiotic administration. Theoretically, DRPs are defined as unexpected adverse event experienced by patients. It is also defined as the problems caused by drug therapy and are actually or potentially interferes with the outcome of management.[13]

In this study, the second most therapeutic class of drugs contributing DCP are Acid suppressant agents like Pantoprazole (76) and Ranitidine (22) were prescribed inappropriately and without any clear indication as shown in table 5 as the patients does not have any gastric ulcer/ gastrooesophageal reflux disease (GERD) conditions. If patient is experiencing anorexia, nausea, abdominal pain due to antitubercular drugs, give drugs with small meals or just before bedtime, and advice patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side-effect to be major and refer to clinician urgently.[14]

FDA (Food and Drug Administration) approved Indications for Proton Pump Inhibitors in adults states proton pump inhibitors (PPIs) are used for the prevention

and treatment of gastric acid related conditions which includes; healing and maintenance of erosive esophagitis (EE), treatment of GERD, risk reduction for gastric ulcer associated with nonsteroidal antiinflammatory drugs (NSAIDs), helicobacter pylori eradication to reduce the risk of duodenal ulcers (DUs) recurrence in combination with antibiotics, pathological hypersecretory conditions including Zollinger-Ellison syndrome.[15] Inappropriate prophylactic acid suppression therapy is a major concern and may even be underestimated due to the lack of appropriate guidelines. More data is required to guide the selection between PPIs and H2 receptor antagonist (H2RA), with emphasis on the more cost-effective use of H2RA in patients with lower gastrointestinal risk or in whom PPI has no clear advantage.[16]

Inappropriate drug form (52) of prescriptions included Pantoprazole injection (40) and Ranitidine injection (12) were prescribed instead of oral tablets, with no clear indication of drugs. Paracetamol injection was found to be inappropriate in 4 prescriptions instead of oral tab where the patients were having low grade fever, as shown in table 6.

Therapeutic duplication of drugs/class is found to be less in this study, a total of 4 are identified as shown in table 7. Aminoglycosides like Gentamicin with Streptomycin injection administered together as both drugs fall under same class of antibiotics.[11] Analgesics and NSAID's like Paracetamol and diclofenac is given in the injection form as well as in the tablet form. Oral Methylxanthines like Doxofylline with Acebrophylline is given concomitantly while both drugs fall under same class of bronchodilators.[17]

In this study, 1 anaemic patient was prescribed with chloramphenicol which is contraindicated drug in most of the anaemic conditions and the patient showed lowered haemoglobin level after administration as it is known to cause bone marrow depression[11] as shown in table 8.

In this study, 4 patients were prescribed with antimalarial drugs like Lumefantrine and Artemether as shown in table 9. Over-prescription of Artesunate Combination Therapy (ACT) may result in substantial unnecessary use of this class of drug and the risk of developing resistance. In addition, blind treatment of malaria without parasitological confirmation of the parasite deviates from best practices.[18]

In this study total of 3 (0.51%) Dosing problem was found. Drug dose too high in 3 (0.35%) alcoholic patients with abnormal LFT as shown in table 10. Alcoholism is one of the main risk factor which aggravates the anti-TB induced hepatotoxicity. For all types of liver disease caused by alcohol, the main treatment is to stop consumption of alcohol completely.[10]

In this study, a total of 6 COPD patients were administered with wrong drug Montelukast, Leukotriene modifiers as shown in table 11. Leukotriene modifiers targeted on the one part of the inflammatory pathway in asthma. Used as an option for controller therapy, particularly in children.[19] It is only indicated in patients with chronic asthma / exercise induced asthma and Seasonal Allergic Rhinitis.[20]

In this study, a total of 293 (50.26%) potential drug interactions were found, major 4 and moderate 285 as shown in table 12. Drug-drug interactions having significant impact on TB patients with co-morbid disease conditions like Hepatic impairment, DM, Hypertension and COPD etc. were the chronic illness patients on regular medications.

Hepatotoxicity has been seen with the combination of isoniazid and paracetamol as shown in table 16, usually in patients who have taken more than 4 g of paracetamol daily, but occasionally in those taking normal doses. The ultra-cautious may wish to limit paracetamol intake, but information is very limited and more study is needed to confirm any interaction.[21]

Management of DM in TB should be aggressive. An optimal glycaemic control results in a better patient outcome; therefore vigorous efforts should be made to achieve such control. Insulin therapy should be initiated at the outset, using basal bolus regime or premixed insulin. The American Association of Clinical Endocrinologists recommends the use of modern insulins or insulin analogues, as they are more predictable in action and cause less hypoglycaemia. The use of traditional human insulins is discouraged. In patients with co-existing peripheral neuropathy due to diabetes, it is mandatory to give the patient pyridoxine if isoniazid is to be used. Oral hypoglycaemic agents are contraindicated in severe tuberculosis but may be used with caution once the disease has settled.[9]

The efficacy of insulin and other antidiabetic agents may be diminished by Isoniazid as shown in table 17. Caution is advised when drugs that can interfere with glucose metabolism are prescribed to patients with diabetes. Close clinical monitoring of glycaemic control is recommended following initiation or discontinuation of these drugs, and the dosages of concomitant antidiabetic agents adjusted as necessary.[22]

Rifampicin reduces the levels and blood glucose lowering effects of gliclazide and glibenclamide, and to a lesser extent glimepiride, glipizide as shown in table 17. Rifampicin also reduces the Area Under Curve (AUC) and effects of repaglinide, and possibly nateglinide. Rifampicin reduces the AUCs of rosiglitazone by about 50%, which could be clinically relevant. Monitor the outcome of concurrent use on blood sugar levels and adjust the anti-diabetic treatment accordingly. In many

cases an increase in the dose of the anti-diabetic seems likely to be needed.[21]

An isolated report describes a rise in blood pressure in one hypertensive patient, which was attributed to an interaction between enalapril and rifampicin as shown in table 18. Rifampicin may reduce the plasma levels of the active metabolites of imidapril and spirapril. The general importance of these interactions is unknown (expected to be minor), but bear them in mind in case of unexpected elevations in blood pressure.[21]

Rifampicin reduces the levels of the active metabolite of losartan and the blood pressure lowering effects of losartan as shown in table 18. This interaction is by no means established, but monitors the effects of concurrent use on blood pressure. Consider raising the losartan dose or using an alternative to losartan if problems occur.[21]

Two short-term studies found that theophylline serum levels were slightly increased by isoniazid as shown in table 19 and a case of theophylline toxicity supports this finding. However, another short-term study found that isoniazid slightly increased theophylline clearance. The outcome of concurrent use is uncertain but it would be prudent to be alert for any evidence of increased theophylline levels and toxicity if isoniazid is given. It may take 3 to 4 weeks for this interaction to develop.[21]

The possibility of increased systemic adverse effects of budesonide should be considered during co administration with CYP450 (Cytochrome) 3A4 inhibitors (Isoniazid) as shown in table 19. If concomitant use cannot be avoided, the dosing times between budesonide and the CYP450 3A4 inhibitor should be separated by as much as possible. Patients should be monitored for signs and symptoms of hypercorticism such as acne, striae, thinning of the skin, easy bruising, moon facies, dorsocervical "buffalo" hump, truncal obesity, increased appetite, acute weight gain, oedema, hypertension, hirsutism, hyperhidrosis, proximal muscle wasting and weakness, glucose intolerance, exacerbation of pre-existing diabetes, depression, and menstrual disorders.[22]

Rifampicin increases the clearance of theophylline by 45%as shown in table 19. In one study rifampicin (with isoniazid) increased theophylline clearance during the initial few days of tuberculosis treatment, but another study suggested that these anti-tubercular's decrease theophylline clearance within 4 weeks. Monitor theophylline levels. An effect has been seen within 36 hours of starting rifampicin. Expect to need to increase the theophylline dose. The picture is less clear when isoniazid is also taken. In this situation it would seem prudent to monitor theophylline levels closely for the first month of treatment.[21]

In clinical practice, several drugs can still be used together, yet close monitoring is fundamental and any toxicity should be identified and immediately followed by corrective actions.

In this study, 39 (6.67%) patients showed insufficient awareness of health and disease as it comes under "others" category of DRPs. Knowledge about cause and treatment of tuberculosis among TB patients was quite good, however, misconceptions also exist. Misconceptions about transmission of disease lead to discrimination like separate utensils for food or drink. Diagnosis of TB is associated with increase anxiety/tension, fear of loss of wage/earning, and stigma threatening self-esteem and quality of life. Mass media can be better utilized to remove misconceptions. Psychosocial reactions towards TB as revealed in this study should be addressed through counselling and communication during treatment in the DOTS centre. This may contribute to success of the national TB control program.[23]

CONCLUSION

100 cases were evaluated by using the 8 categories of Problems under PCNE DRPS classification and the findings of the study were as follows:

P1. Adverse drug reactions (0.85%):
P1.1 Side effects suffered (Non-allergic) 0.85%
P2. Drug choice problems (40.68%):
P2.1 Inappropriate drug 74.37%
P2.2 Inappropriate drug form 21.85%
P2.3 Inappropriate duplication of therapeutic group or active ingredient 1.68%
P2.4 Contraindication for drug 0.42%
P2.5 No clear indication for drug use 1.68%
P3. Dosing Problems (0.51%):
P3.2 Drug dose too high or dosage regimen too frequent 0.51%
P4. Drug Use Problems (0.68%):
P4.2 Wrong drug taken/administered 0.68%
P5. Drug Interactions (50.26%):
P5.1 Potential Interaction 50.26%
P6 Others (6.67%):
P6.2 Insufficient awareness of health and diseases 6.67%

The present study shows DRPs in TB patients with comorbidities are more due to drug interactions of ATT with concomitant drugs which are clinically significant in case of hepatic impairment, DM, COPD, and hypertension. Second most DRPs are DCP or inappropriate use of drugs like antibiotics and acid suppressant drugs. The most common comorbidities found in TB patients were hepatic impairment especially in case of patients with alcoholic use and category 2 TB, which is mainly due to ADR associated with ATT. So, management requires close monitoring and dose adjustment based on LFT. Hepatic impairment is common for most of the tuberculosis patients with anti-tubercular drugs and in future more attention is to be given on management of tuberculosis in diabetes, hypertension, COPD and other comorbidities and associated DRPs. The third most DRPs was found to be

insufficient awareness and health education about disease and medication adherence so patient counselling is a very important role of pharmacist to reduce DRPs in TB patients with comorbidities.

The study shows the need for clinical pharmacist services in healthcare to reduce DRPs by monitoring patient's drug therapy for which Pharm.D (Doctor of Pharmacy) can be suggested as Clinical Pharmacist since they are well versed in the subject areas like Clinical pharmacy, Clinical Pharmacology, Clinical Toxicology and Pharmacotherapeutics. The proper utilization of such professionals in the role of Clinical Pharmacists should be established in the hospital by communicating with medical doctors to accept and initiate clinical pharmacy services to assist the healthcare professionals and to promote pharmaceutical care for monitoring and management of chronic illness which ultimately reduces the DRPs and improves patient care.

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