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Research Article

Pharmacy practice for good health Promotion

Study on Prescribing Patterns of Antimicrobial Agents In Liver Disease Patients

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Abstract: The present study aims at analyzing the prescribing patterns of antimicrobial agents in different liver diseases and to identify the drug-drug interactions among the prescribed drugs. A cross sectional observational study was conducted from February to July 2018. A total of 120 cases of patients receiving antimicrobials having different types of liver diseases were included. Statistical analysis shows that 80% of the popuation were male and 64% of the population was above the age of 50 years. . Liver disease like Liver Cirrhosis, Non alcoholic steato hepatitis, Viral hepatits, Jaundice, Hepatocellular carcinoma was found to be present among the study population, 50% of the population was overweight and 32% were alcoholic. Majority of them had ascites, abdominal distention and pedal edema as chief complaints and complications were hepatic encephalopathy and esophageal varices. The prescribed antimicrobial agents were antibiotics (95%) viz., Piptaz, rifaximin and taxim. antivirals (4%) such as entecavir and antifungals (1%) likeflucanazole. The drugs were prescribed according to the guidelines of the hospital. Mostly broad spectrum antibiotics were used in the management of liver disorders like Linezolid, Meropenem, Ertapenem, and Tobramycin. In severe cases combination of antimicrobials were given for effective therapy. Patient's transplantation was based on the MELD score, as the MELD score increases, the mortality rate also increases. MELD score =40 indicates mortality rate is >70%.

Keywords: Antimicrobials, Drug interactions, hepatic encephalopathy, Liver disorders, MELD-model

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1. INTRODUCTION

Any condition that damages the liver and prevents its normal functioning is defined as a liver disease. The types of liver diseases include: Hepatitis, inflammation of the liver, Alcoholic liver disease which is a hepatic manifestation of alcohol overconsumption including fatty liver disease, alcoholic hepatitis and cirrhosis.[1] Hereditary diseases like hemochromatosis, Wilson's disease, Gilbert's syndrome, can cause mild jaundice and hepatocarcinoma. An epidemiological study says that around 10 lakh patients of liver cirrhosis are newly diagnosed every year in India. According to the latest WHO data published, in India of the total deaths, 2.44% are caused by Liver diseases[2]. At present the need for liver transplantation in India is estimated to be around 20/million population. The current rate of liver transplantation in India is around 1.2/million population[3]. Hepatocellular carcinoma (HCC), is the second most common cause of death due to malignancy in the world. [4] Liver infections were classified as viral**,** bacterial, fungal and protozoal infections. Complications in liver disease include ascites, hepatic encephalopathy, esophageal varices and UGI bleed. Broad-spectrum beta-lactam antibiotics have proved efficient for the treatment of severe infections, limitation of third-generation cephalosporins is their ineffectiveness against enterococci.[5] Piperacillin, like other beta-lactam antibiotics are effective. Meropenem monotherapy is effective and safe for the initial therapeutic regimen of bacterial infection. Rifaximin works within the gastrointestinal system and helps preventing hepatic encephalitis in people with liver disease[1]. Antibiotic resistance is a global health crisis and is one of the 'greatest challenges for public health. Overuse of antibiotics is the primary risk factor for antibiotic resistance and can cause adverse drug events. Antibiotic resistance due to overuse of antibiotics has been a persistent public health problem. Several studies have reported that a high percentage (>50%) of outpatient visits result in prescription of antibiotics. It also helped to eliminate financial incentives associated with antibiotic prescriptions for hospitals and physicians. During 2015–2017, a nationwide campaign of rational antibiotic use was implemented at secondary and tertiary hospitals to establish clinical infrastructure for antibiotic management, to reinforce regulation and clinical guidelines for rational antibiotic use, to set specific targets for antibiotic prescriptions and to develop surveillance systems to monitor and audit antibiotic prescriptions[6]. Alcoholism accounts for major cause of liver diseases. Alcoholism results in an estimated 2.5 million deaths annually worldwide, representing 4% of all mortality. It is the leading risk factor for mortality for ages 15-59 in males and the eighth leading risk factor for mortality for all ages in both sexes. Although alcoholism is associated with more than 60 diseases, most mortality from alcoholism results from alcoholic liver disease (ALD).[3] ALD includes alcoholic steatosis, alcoholic hepatitis, and alcoholic cirrhosis, in order of increasing severity ALD accounts for 40% of mortality from cirrhosis. Annual mortality for ALD is 4.4/1,00,000 in the general population. Development of ALD is dose-dependent and drinking ≥30 g/d of alcohol increases the risk of ALD in both sexes. Women have a greater risk of ALD than men, likely secondary to differences in ethanol metabolism. Several drugs are currently being used in ALD, which include pentoxifylline, ursodeoxycholic acid (UDCA), metadoxine, corticosteroids and some alternative medicines like Liv 52 and Silymarin but with varied success. In addition, some drugs are used to treat the complications of ALD like antibiotics for infections; lactulose, rifaximin and L-ornithine L-aspartate (LOLA) for encephalopathy; furosemide and spironolactone for ascites and octreotide, propranolol and ethamsylate for variceal bleeding; disulfiram and naltrexone for decreasing the craving and dependence of alcohol; chlordiazepoxide for treating withdrawal symptoms The study of prescribing patterns seeks to monitor, evaluate and suggest modifications in practitioners prescribing habits so as to make medical care rational and cost-effective.[7] A Medline search of prescribing pattern of drugs in ALD has not shown any positive results. Hence, we planned this study to evaluate the prescribing pattern of drugs used in patients. As nutritional deficiency is very common in these patients, prescription of vitamin and mineral and hepatoprotectives for normal functioning. Antiulcer drugs were the third most commonly prescribed drug in as long-term intake of alcohol damages the gastric mucosa to a large extent. As liver is an important site for fighting against microbes, its damage leads to increased risk of bacteremia in these patients requiring antibiotics for therapeutic or prophylactic purpose. Cephalosporins and metronidazole were the most common antibiotics prescribed which can be explained as these drugs cover the mixed infection with anaerobes of peritonitis that is common in these patients. This is in accordance with the guidelines so that drugs like macrolide antibiotics, including erythromycin, azithromycin, clindamycin along with chloramphenicol and tetracyclines as these drugs should be avoided in patients with ALD[8,11] Complications such as hepatic encephalopathy and variceal bleeding are an important part of ALD patients and treatment of them is of utmost importance to prevent morbidity and mortality[10]. As raised ammonia level is the cause for hepatic encephalopathy, lactulose inhibits intestinal ammonia production by a number of mechanisms .[9]

2. MATERIALS AND METHODS

The cross sectional observational study was conducted from February to July 2018 for a period of 6 months in the department of Hepatology, Gleneagles Global Hospital, Chennai, Tamilnadu, India. This study was approved by the Institutional Ethics Committee of Gleneagles Global Hospital, Chennai, India. A written informed consent was obtained from all the study participants as a part of our study procedure. A total of 120 patients were included in the study. All the relevant patient information required for the study was collected from the case sheets and from computerized database system. Patients above the age of 18 who were admitted in the hepatology department for liver transplantation were included in the study. MELD (Model for End stage Liver Disease) scoring was used for assessing the severity of chronic liver disease, measures mortality risk and helps to prioritize allocation of organs for transplant.

MELD score = 10× (0.957×ln (creatinine)) = (0.378×ln (bilirubin)) + (1.12×ln (INR)) + 6.43**.**

As the MELD score increases, the mortality rate also increases. MELD score ≥40 indicates mortality rate is >70%.[10] MICROMEDEX online software was used to find the drug-drug interaction[12].

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3. STATISTICAL ANALYSIS

Statistical analysis was primarily descriptive with all the data expressed as percentage based on age, sex, BMI, social habits and prescribing pattern. Percentage frequency was done with 95% confidence interval.

4. RESULTS

A total of 120 prescriptions of in-patients with different types of liver diseases were analyzed, out of which 80% were male and 20% were female. The majority of patients belonged to the age group of 51-70 years (56%) followed by 41-50 years (15%) (Table 1), more than 90% were on non-vegetarian diet. 50% of the patients were under the class of overweight according to the WHO BMI classification. (Figure 1) The percentage of patients having the habit of alcohol intake was 32.4% (Figure 2). Majority of patients presented with chief complaints of ascites, abdominal pain and edema. 53% had Hypertension, 42% had diabetes mellitus and 6% had thyroid disorders as coexisting conditions of the patient population (Figure 3). Most common complaints amongst this population was abdominal pain, ascites and edema (13%) followed by abdominal pain, fever, jaundice and cognitive impairment (10%)(Figure 4). Chief complaints were of ascites and abdominal pain in most of the liver disease patients, 21% had hepatic encephalopathy and 16% had esophageal varices, more than 40% had no complications (Table 2). Model for end-stage liver disease (MELD) score has been used to assess prognosis of liver disease, only a smaller percentage were at high risk of mortality 71.3%, most of them had a score of 6% mortality rate according to the MELD score. (Table 3) In the present study, 43% of the population had liver cirrhosis, followed by NASH (Non Alcoholic steatohepatitis) 25% and hepatocellular carcinoma 13% (Figure 5). Blood culture was performed to 62 patients and the culture report indicated high prevalence of gram negative organisms like E.coli 40%.*Candida albicans* 27%, *Klebsiella* 18% and *Staphylococcus* 15% (Figure 6). Urine culture indicated high prevalence of *Candida* 57% followed by *E.coli*43% (Figure 7). PMN (polymorphonuclear neutrophils) was measured amongst the study population. Patients who had PMN >250 cells/mm^3 were treated with cefotaxime in about 67% of cases and with amoxicillin+clauvulonic acid up to 29% remaining were on cefriaxone. (Table 4) Among 120 prescriptions, antimicrobials prescribed were 95%, 2.5 % were antivirals and 1% was antifungals (Table 5). Mostly prescribed antibiotics were piptaz 50% followed by rifaximin 20%, taxim 10%, ugmentin 6%, eropenem 5%, metrogyl 4%, tigecycline 3% and monoceff 2% (Table 6). Combinations drugs of piptaz and rifaximin was prescribed, alsothispiptaz was also prescribed as monotherapy in most cases of liver disorders (Table 7). Mostly prescribed antiviral was entecavir and flucanozole 200 mg (od) for fungal infections. Supportive therapy was given for all liver disease patients which includes hepatoprotectants, vitamins, calcium, anti ulcers, diuretics and laxatives. (Table 8) During prescription analysis,33 drug-drug interactions was identified using micromedex software, 18% of pharmacodynamic drug interaction and 9% pharmacokinetic drug interaction and 73% with no drug drug interaction. (Figure 8) Major interactions were found to be 9%, moderate 61% minor 30% (Table 9).

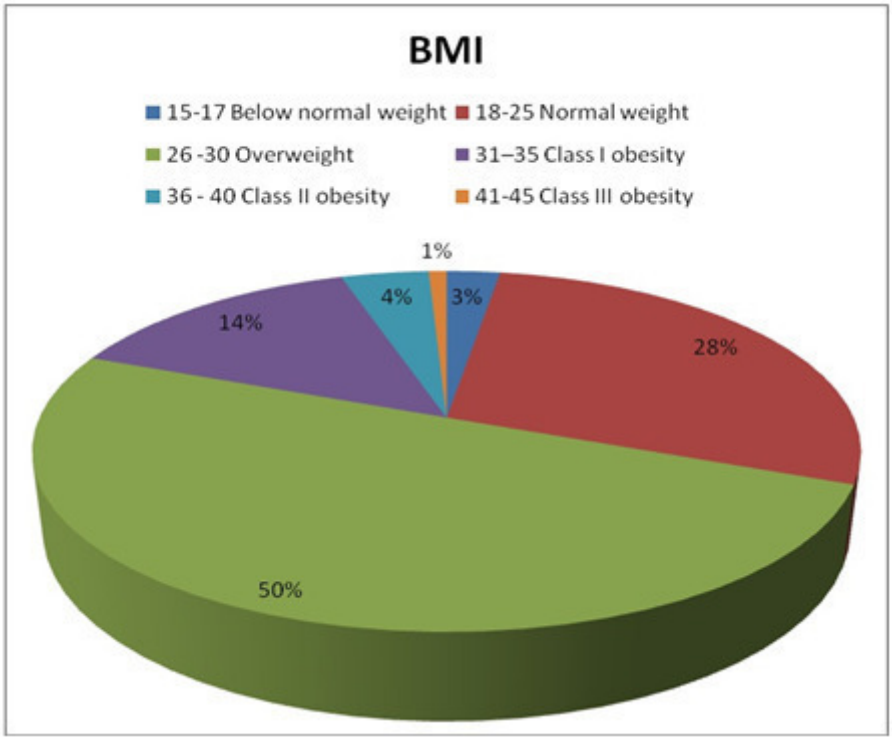

Fig 1. BMI Distribution (n= 120) According to US, FDA

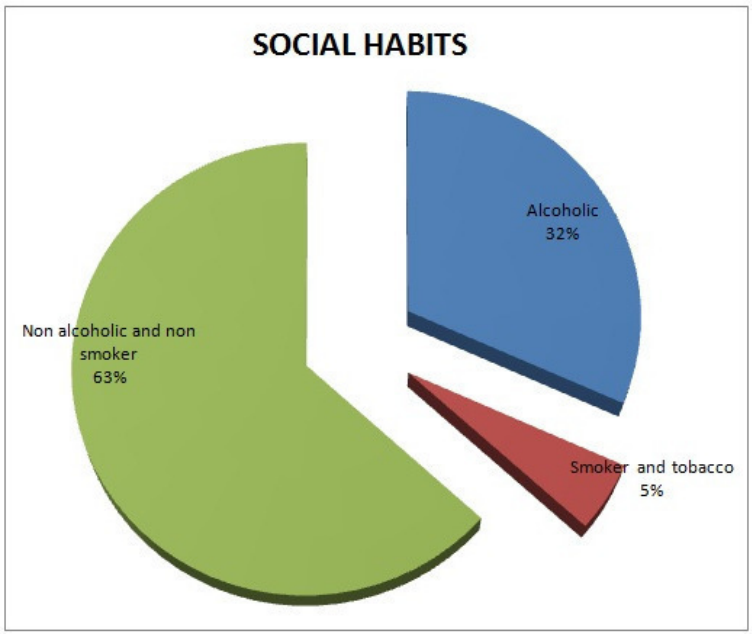

Fig 2. Social habit (n=120)

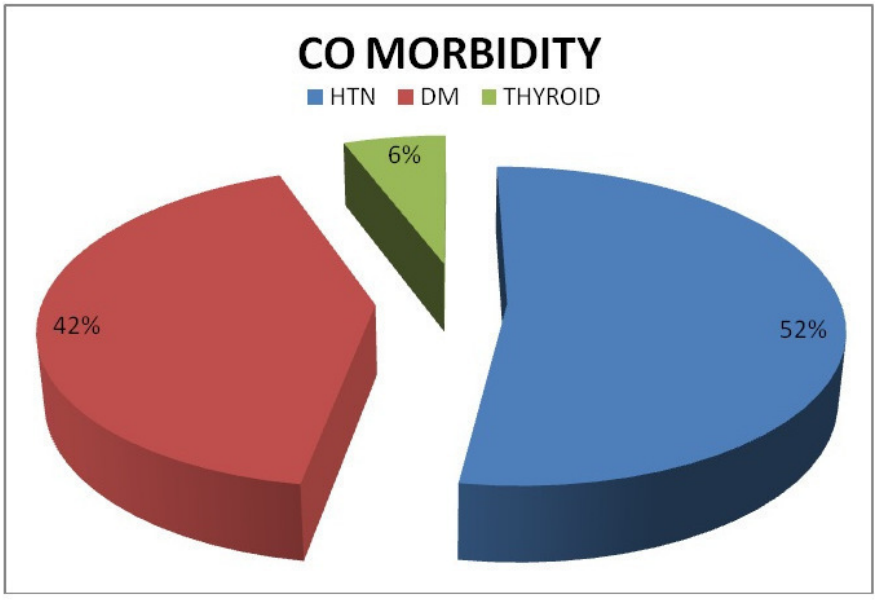

Fig 3. Comorbidity (n= 120)

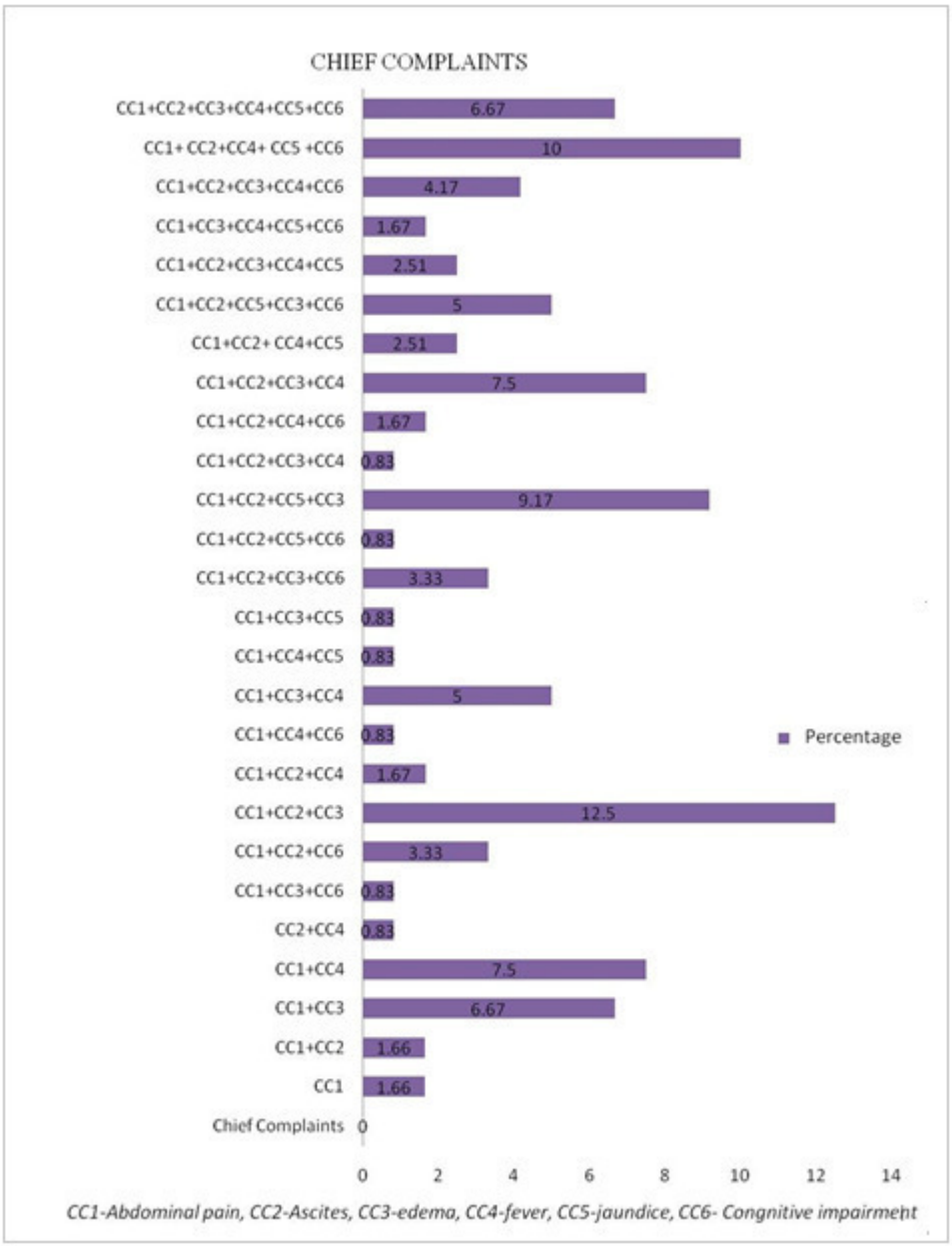

Fig 4. Chief Complaints (n= 120)

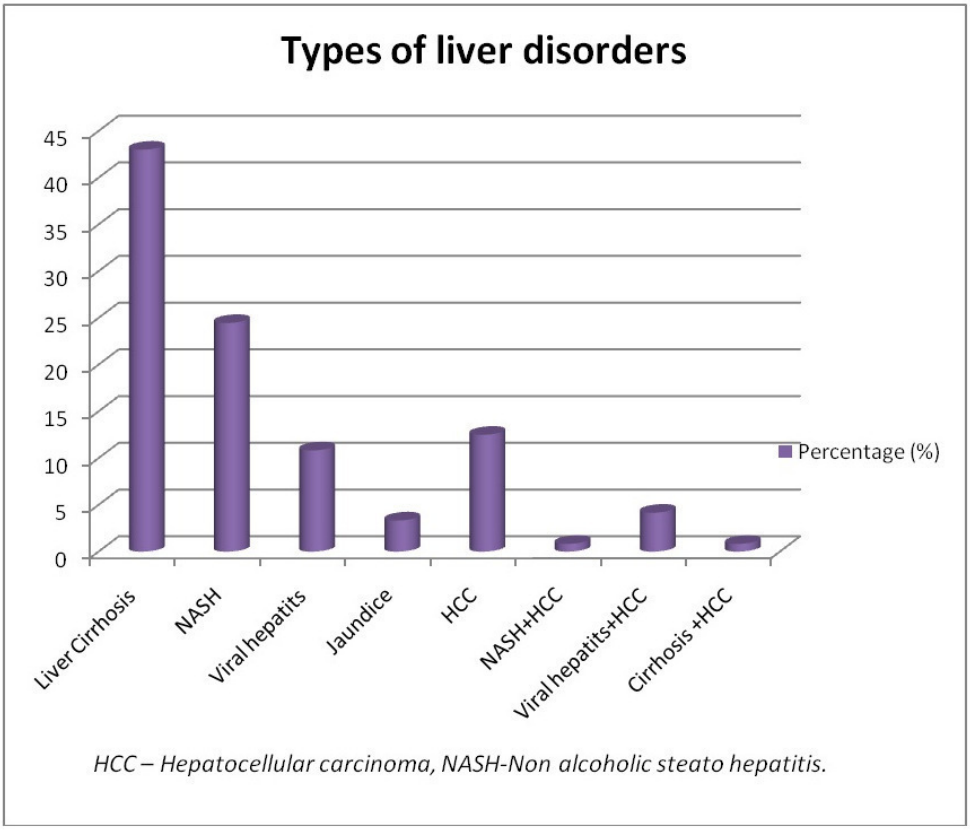

Fig 5. Epidemiology of liver diseses (n=120)

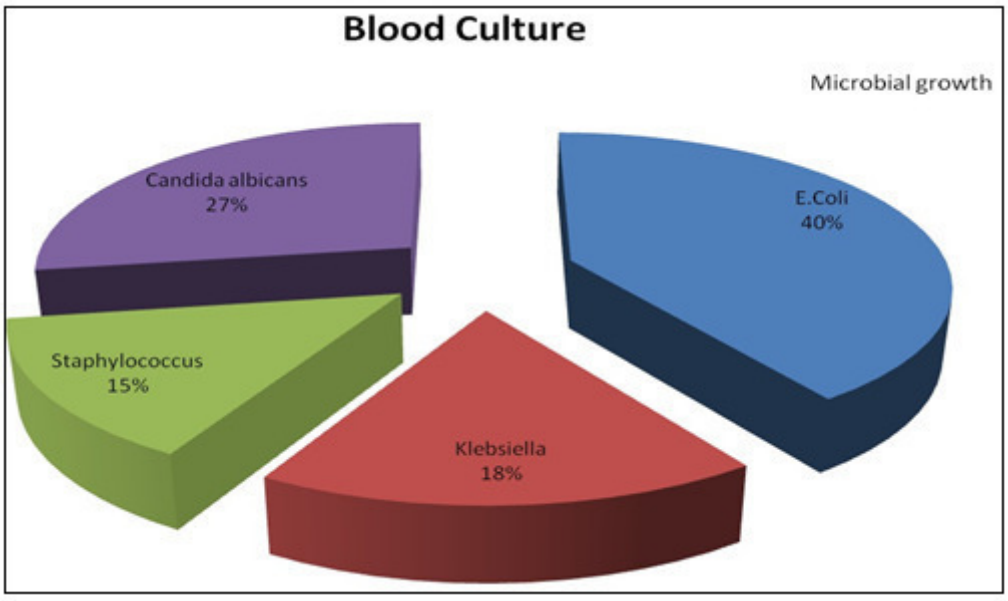

Fig 6. Blood culture (n=62)

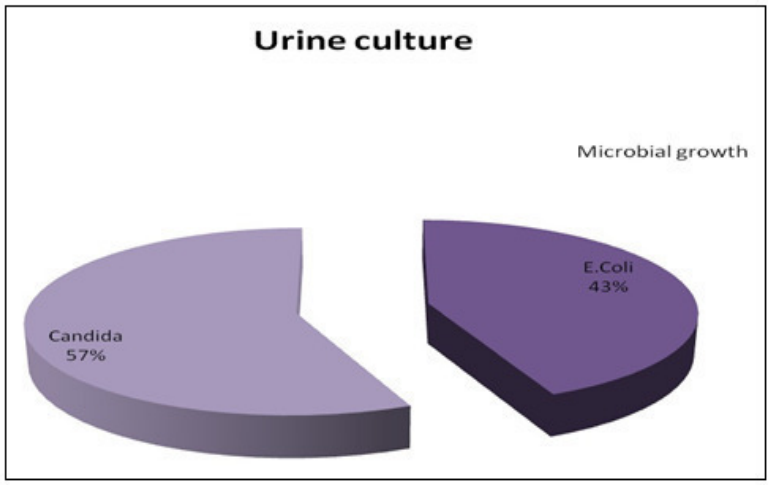

Fig 7. Urine culture (n=30)

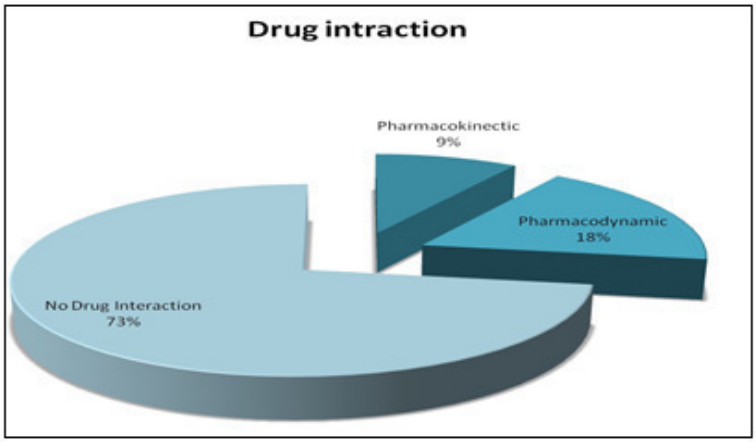

Fig 8. Drug interactions (n=120)

Table 1. Age distribution (n=120)

Age (Years)	Frequency (n)	Percentage (%)	C.I 95 %
≤40	24	20	13.3-28.3
41-50	18	15	9.1-22.7
51-60	34	28	20.5-37.3
61-70	34	28	20.5-37.3
≥71	10	8.3	4.1-14.8

Table 2. Complications (n=120)

Complications	Number of Patients (n)	Percentage (%)
E Vx	19	15.34
E Vx+PVT	2	1.66
HE	25	21
HE+Evx	4	3.34
HE+Evx+UGI Bleed	3	2.5
He+PVT	2	1.66
HE+Sepsis	2	1.66
HE+UGI Bleed	4	3.34
PVT	2	1.66
Sepsis	2	1.66
Sepsis+EVx	1	0.84
UGI Bleed	4	3.34
No complications	50	42

*** EVx – Esophageal varices , HE – Hepatic Encephalopathy , PVT – Portal vein thrombosis , UGI – Upper gastro intestinal*

Table 3. MELD Score (n = 120)

Meld Score	Mortality Rate %	Number of Patients (n)	Percentage %
1-9	1.9%	17	14.16
10-19	6%	51	42.5
20-29	19.6%	32	26.6
30-39	52.6%	16	13.3
40-49	71.3%	4	3.3

Table 4. Antibiotics used: PMN > 250 Cells/mm^3 (n=42)

Drugs	Number :of Patients (n)	Percentage (%)
Cefotaxime	28	66.66
ceftriaxone	2	4.76
Amox+clauv	12	28.57

Table 5. Drugs Prescribed (n=120)

Drugs	Number. of Patients (n)	Percentage (%)
Antibiotics	114	95
Anti Virals	5	4.16
Anti Fungals	1	0.83

Table 6. Antibiotics Prescribed (n=120)

Antibiotics	Dose	Frequency	Number of Patients (n)
Inj.Piptaz	4.5 gm	TDS	80
T.Rifaximin	450 mg	BD	40
T.Rifaximin	550 mg	BD	34
T.Augmentin	1.2 gm	BD	12
T.Taxim	1 gm	BD	28
Inj.Monocef	1 gm	BD	2
Inj.Metrogyl	500 mg	BD	3
Inj.Meropenem	1gm	BD	11
T.Tigecycline	100 mg	BD	3

Table 7. Monotherapy (n=24)

Drugs	Number of Patients (n)	Percentage (%)
Piptaz	14	58.333
Rifaximin 450mg	2	8.333
Rifaximin 550mg	1	4.166
Taxim	6	25
Meropenem	1	4.166

Table 8. Supportive therapy

S.No	Category	Name
1	Liver protectants	T.udiliv-300mg
2	Vitamins	T.neurobion forte
3	Calcium	T.shelcal-500mg
4	Diuretics	T.furosemide- 40 mg lasilactone -10mg
5	Anti-ulcers	T.pantoprazole-40 mg, neksium -40mg
6	Lactulose	sypduphalac -15ml

Table 9. Severity of Drug Interaction (n=33)

Severity	Number of Patients(n)	Percentage %
Major	3	9.1
Moderate	20	60.6
Minor	10	30.30

5. DISCUSSION

The liver is notable for its capacity to regenerate unless cirrhosis has developed.[1] The spectrum of liver disease extends from mild, self-limiting conditions to serious illnesses which may carry significant morbidity and mortality. Epidemiological studies reveal that around 10 lakhs patients of liver cirrhosis were newly diagnosed every year in India. [16] The present study shows that liver disease is found in 80% of male population. The male population had significantly higher risk of developing liver diseases than the female population Vijayan *et al*[8] reported the same. Patients over 50 yrs of age are at high risk of developing liver disease due to immunological and functional disturbances, there is a link between obesity and risk of liver disease Loomis K *et al.*[13] 32.4% patients with liver disease were alcoholic, 32.3% were nonalcoholic having NASH and Viral hepatitis. Partha S. Mukherjee *et al.* [16] Kolasani *et al.*[7]revealed in their study that alcoholism is associated with liver disease. Co morbidities like DM, HTN has association with liver diseases. Barritt A *et al.,*[14] Model for End stage liver disease (MELD) was initially created to predict the survival of patients undergoing TIPS (trans jugular intrahepatic porto systemic shunt). It is scoring system for assessing the severity of chronic liver disease, measures mortality risk and helps to prioritize allocation of organs for transplant. (Munir Pirmohamed *et al.,)*[15] In this study, among the antimicrobials prescribed, 95% were antibiotics, 3% were antivirals and 1% were antifungals. Mostly prescribed antibiotics were cephalosporin 59% followed by penicillin 17% andMeropenem 2%. In the current study 50% was Piptaz followed by rifaximin 20%, taxim 10%, Meropenem 5%, Metrogyl 4%, Tigecycline 3% and Monoceff 2%. Mostly prescribed anti-viral agent was entecavir for hepatitis B patients. Flucanozole 200 mg was given for fungal infections (cooper *et al*.,). [17]

6. CONCLUSION

The drugs were prescribed according to the guidelines of the hospital. Mostly broad spectrum antibiotics were used and restricted antibiotics were not prescribed. In severe cases combination of antimicrobials are given for effective therapy. As most of the patients undergo liver transplantation, based on the MELD score patients are allotted for the transplant.

7. ACKNOWLEDGEMENT

Study was carried out by the Department of Pharmacy Practice at Gleneagles global hospital.

8. AUTHORS CONTRIBUTION STATEMENT

Dr. K.N.Chandan Kumar, is the Principle investigator and the study coordinator at the hospital. Professor. K.Bharathi Priya, had guided and reviewed the Adarsh Raj, Christy Sara Saji, Rebekah John Contributed equally to the manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none

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