Study of Prescribing Patterns for Prophylaxis and Treatment of Complications of Liver Cirrhosis in Hospitalised Patients at A Tertiary Care Teaching Hospital

Chandresh B Dumatar*, Rakesh Ashok Malpure**

* Associate Professor, ** Resident Doctor, Departmentof Pharmacology, B J Medical College, Ahmedabad.

Abstract: Introduction: Managing patients with cirrhosis can be a challenge and requires an organized and systematic approach. Adherence to available guidelines for management of cirrhosis complications and optimal treatment in actual practice is low. Aims and Objectives: To study the prescribing pattern of the drugs used for treatment of complications of liver cirrhosis on admission and on discharge and to study adverse drug reactions of drugs.Methods: Continuous, longitudinal, prospective, observational, single centre study conducted at in-patient ward of Medicine department, Civil Hospital Ahmedabad. Result: Alcohol was most common aetiology. Ascites with hepatic encephalopathy were most common combination of complications. Thirteen different drug groups were prescribed like antimicrobials, antiemetics, ulcer protective, laxatives, anti-haemorrhagics, LOLA, diuretics, blood components, minerals, vasoactive agents, beta blockers and chologogues. Most common drug group causing ADRs was diuretic and most common drug was Furosemide. Conclusion: Some deficient areas in quality of care of complications of cirrhosis patients were observed.[Malpure R NJIRM 2017; 8(3):98-104]

Key Words: Cirrhosis, Prescription Pattern.

Author for correspondence*:* Rakesh Ashok Malpure, Matrumangal, Shivaji Nagar, Near KMC Bank, At post, Tal: Kalwan Dist: Nashik Pin:423501 E-Mail: malpurerakesh@yahoo.co.inM: 9404801212

Introduction: Liver cirrhosisisa diffuse process characterized by liver fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.[1] Liver cirrhosis is a clinical syndrome reflecting the final common pathway for most chronic liver diseases such as alcoholic hepatitis, viral hepatitis and non-alcoholic fatty liver disease. Other causes are drugs, toxins, vascular, autoimmune, metabolic disorders and cryptogenic. Liver cirrhosis is an important cause of morbidity and mortality worldwide. Much of the morbidity and mortality of liver cirrhosis is attributable to decompensation of liver function. In 2010, India alone accounted for almost one-fifth of global liver cirrhosis deaths.[2.] Decompensation of cirrhosis is considered when a patient first develops one of the major complications of cirrhosis. Major complications of cirrhosis are ascites, hepatic encephalopathy, variceal haemorrhage, bacterial infections (SBP), hepatorenal syndrome (HRS), hepatocellular carcinoma and hepatic failure. The quality of life and survival of patients with cirrhosis can be improved by the prevention and treatment of these complications.Treatment of Liver cirrhosis is expensive and is largely inaccessible in most parts of the world.Managing patients with cirrhosis can be a challenge and requires an organized and systematic approach. There is no specific drug therapy for cirrhosis. Liver transplantation is only definitive treatment. Available drug therapy for complications of cirrhosis only minimally improve the long-term survival. Despite advances in the evidence base for treating cirrhotic complications, the adherence to guidelines and optimal treatment in actual practice is low[3].Very few studies have been done to evaluate the utilization of drugs in the treatment of complications of cirrhosis especially in India. The present study was intended to expand current knowledge of prescribing patterns in patients with complications of liver cirrhosis.

Aims and Objectives: To study the prescribing pattern of the drugs used for treatment of complications of liver cirrhosis on admissionand on discharge andto monitor adverse drug reactions of drugs prescribed in these patients.

Methods: This was a continuous, longitudinal, prospective, observational, single centre study conducted at in-patient ward of Medicine department, Civil Hospital, Ahmedabad (a tertiary care Government teaching hospital). The study was carried out for a total duration of 20months from October 2014 to July 2016. Patients above 18 years of age, willing to participate in the study and give informed consent were included in the study.Patients managed in outpatient department or having non-cirrhotic portal hypertension or non-cirrhotic ascites were excluded from study. Prior permission was obtained from Head of Department of Medicine and Institutional Ethics Committee (IEC) to conduct the study. The patient fulfilling the inclusion criterion and willing to give informed consent were enrolled.

Diagnosis of cirrhosis was established by clinical, biochemical, endoscopic, and ultrasonographic criteria or byhistopathology, whenever available. A detailed history, physical examination, laboratory tests including complete blood cell count, liver profile, renal function test, electrolytes, urine examination and ascitic fluid examination (if present) was done in all patients. Assessment for aetiology and complications of liver disease like ascites, SBP, encephalopathy, gastrointestinal bleeding, and HRS was done. The severity of liver disease was assessed using the Child-Turcott-Pugh (CTP) score.When an adverse drug reaction (ADR) was suspected the followingcharacteristics were analysed: symptoms or signs,drug(s) probably implicated, mechanism, probability, severity, treatment, duration and outcome.

Results:

Baseline characteristics: In this single center study, 225 patients with cirrhosis of liver were analysed;187(83%) were male, and 38 (17%) were female. Mean age of patients was 56.8 ± 13 years. The most common aetiology of cirrhosis was alcohol, seen in 138 (61%) patients. Other aetiologies were hepatitis B (n=40, 18 %), hepatitis C (n=18, 8%), Cryptogenic cirrhosis (n=18, 8%), combined alcoholic+ hepatitis B (n=5, 2.2%) non-alcoholic steatohepatitis (NASH) (n=3, 1.3%), autoimmune (n=3,1.3%).Majority of the patients belonged to Child Pugh B (50.2%) and Child Pugh C class (40%) with Median Child-Pugh score of 10 (range 6 - 15) and mean Child-Pugh score of 9 (±2).

Complication characteristics: As shown in Figure 1, out of 225 patients, most patients had multiple complications at the time of admission; 138 (61.4%) had ascites,89(39.6%) had hepatic encephalopathy, 46 (20.4%) had variceal bleeding, 31(13.7%) had subacute bacterial peritonitis and 18(8%) patients had hepatorenal syndrome.3(1.3%) patients had hepatocellular carcinoma post-cirrhosis in present study. Ascites coexisting with hepatic encephalopathy in 32(14.2%) patients constituted the commonest combination of complications. Majority of patients with ascites had severe ascites (tense) [n=88, 63.8%] followed by moderate ascites [n=34, 24.6%]and mild ascites [n=16, 11.6%]. Out of 89 patients of hepatic encephalopathy, 18(18%) patients had grade 1 HE, 44(50%) patients had grade 2 HE and27(30%) patients were from grade 3 and 4 together.

Figure 1: Distribution of complications of cirrhosis

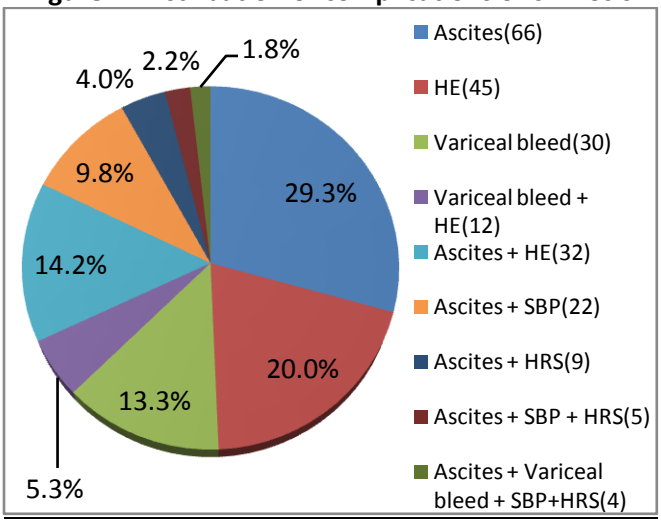


Figure 2: Prescriptions pattern of drugs according to generic and brand names used in complications of cirrhosis.

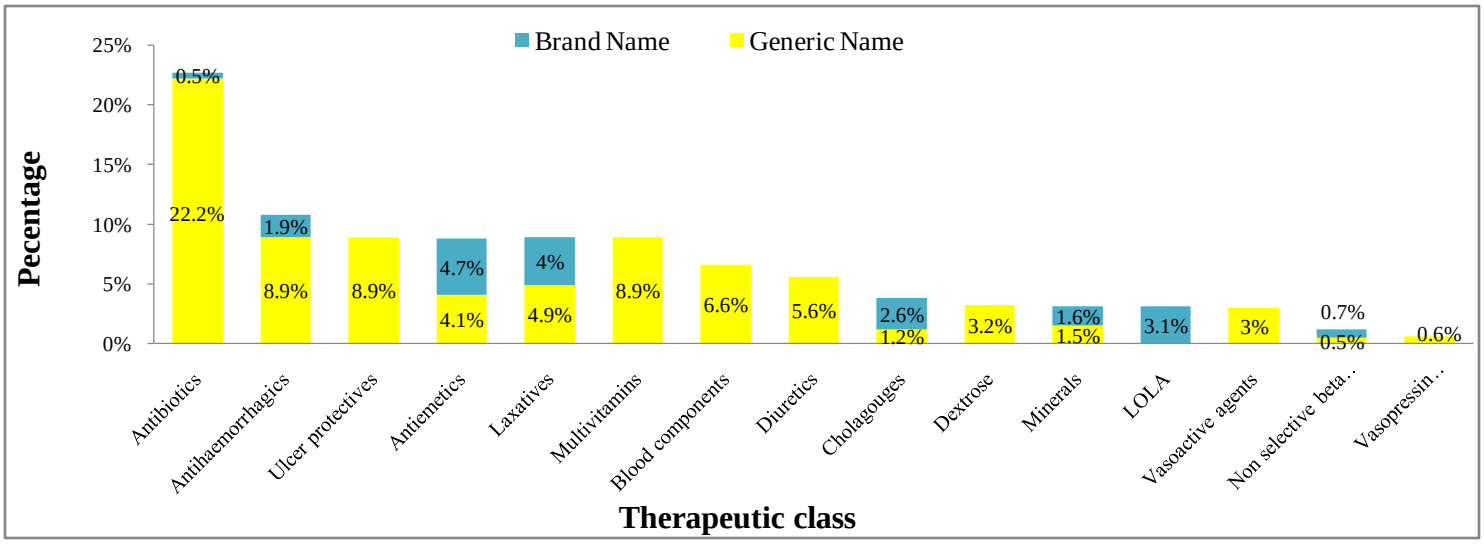


Table 1: Analysis of drug utilization study as per WHO Core indicators

WHO Core indicators	Observations	
	Admission	Discharge
Average number of drugs per prescription (mean ±SD)	9.9 ± 1.8	4.8 ±1.1
Drugs prescribed by generic name	80.8%	71%
Prescriptions with an antimicrobial(s)	22.3%	11.2%
Prescriptions by FDC	8.8%	3.8%
Prescriptions with an injection(s) prescribed	80.2%	0%
Drugs prescribed from 19th WHO EML (2015)	81.4%	88.5%
Drugs prescribed from National EML (2015)	85.4%	88.5%
Drugs prescribed from Gujarat State EDL (2016)	90.1%	88.5%

Mean number of drugs prescribed on admission was9.9 ± 1.8 (range from 6 to 14) while upon discharge 4.8 ±1.1(Table 1).

Cefotaxime with metronidazole in combination, Proton pump inhibitors (PPIs), antiemetic, laxatives, vitamins K injection and multivitamins were prescribed in all the hospitalised patients. A clear indication for PPIs use was reported in only 22 patients, mainly to treat erosive gastropathy. Vitamin K was given in all hospitalized patients (n=225) irrespective of their coagulation profile.Tranexamic acid and Hemocoagulase injection was given in patients with active bleeding (n=24, 10.7%). One fourth of hospitalised patients with cirrhosis received transfusion during their admissions with a mean of 4.4 transfusions per transfused patient. Around 55% transfusions were for bleeding conditions and 45% were transfusions for non-bleeding conditions. Common non-bleeding condition was correction of abnormal coagulogram. Upon evaluation of the secondary variceal prophylaxis (46), 21(63%) patients received beta blocker propranolol as secondary prophylaxis.In present study, 61 patients received human albumin for indications like hypoproteinemia with edema (15), refractory ascites (22) and hepatorenal syndrome (18). Mean albumin dose was20.7 gm ± 3.9 gm/day. Administration of albumin was not in accordance withAASSLD recommended guidelines.[8]

During discharge, lactulose and rifaximin were prescribed as secondary prophylaxis for hepatic encephalopathy(48/48, 100%). Norfloxacin as secondary prophylaxis for post SBP (9/9, 100%). Propranolol for secondary prophylaxis variceal bleeding patients (24/24, 100%). UDCA was prescribed in 35% of discharge patients. Furosemide and spironolactone in combination were prescribed maintenance therapy post ascites. Ranitidine and multivitamins was prescribed in all the patients.

Table 2: Prescription pattern for complications of cirrhosis during Hospitalisation

Drug Class	Drug Name	Dose Range	Dosage strength and form	Route	% of patients (n=225)
Antibiotics	Cefotaxime	1 gm BD	1gm,INJ	IV	100%(225)
	Metronidazole	1 gm BD	500mg,INJ	IV	100%(225)
	Rifaximin	550 mg	550mg,Tablet	Oral	36%(81)
Antiemetics	Ondansetron	4mg BD	2mg/ml, INJ	IV	100%(225)
Ulcer Protective	Pantoprazole	40-80 mg	40mg/ml, INJ	IV	100%(225)
Laxatives	Lactulose	30-45 ml BD, SOS	10 g/15 mL, Syrup	Oral,enema	100%(225)
Antihaemorrhagics	Vitamin K	20 mg for 3 days	20mg per 10mL	IV	100%(225)
	Tranexamic Acid	1 mg TDS, SOS	1 mg /ml, INJ	IV	10.7%(24)
	Haemocoagulase	1 Amp TDS, SOS	1CU/ml,INJ	IV	10.7%(24)
Multivitamins	Multivitamins	1 Unit OD	INJ	IV	74%(167)
LOLA	L-ornithine-L-aspartate	5 gm TDS, 5-7 days	5 gm/10 ml, INJ	IV	42.7%(96)
Diuretics	Spironolactone	50-400mg OD	50 mg, Tablet	Oral	34.6%(78)
	Furosemide	40-80 mg OD	40 mg, INJ	IV	30.2%(68)

Blood components	Human albumin	1 Vial BD	10gm/50ml, INJ	IV	27%(61)
	FFP	4-10 Pints	250ml/pint	IV	22%(50)
	PRBC	2-8 Pints	450ml/pint	IV	10%(22)
	Platelets	1-2 Pint	50 ml/pint	IV	4%(9)
	Factor VII	1 Unit	1.2mg/Vial	IV	0.5%(1)
Minerals	KCl	1.5-3 mg	1.5 g/10mlINJ	IV	22.7%(51)
	Sodium chloride	1 INJ OD	3%, INJ	IV	13.3%(30)
Vasoactive agents	Octreotide	100 mcg TDS for 5 day	100mcg,INJ	SC,IV	13.3%(31)
	Terlipressin	1 gm TDS	1 gm, INJ	IV	5.3%(12)
	Norepinephrine	0.1-0.5 mcg/kg/min Infusion	1mg,INJ	IV	2.7%(6)
Non selective beta blocker	Propranolol	20-40mg OD	20mg, Tablet	Oral	13.3%(31)
Cholagogue	UDCA	300mg OD	300 mg, Tablet	Oral	12%(27)

PRBC: Packed red blood cells, FFP: Fresh frozen plasma, KCl: Potassium chloride UDCA: Ursodeoxycholic acid

Adherence to quality indicators (QIs): Table 3 displays the number of cases included in our implicit review for each of the 9 Quality Indicators.[3]

Table 3: Quality of care in patients with cirrhosis

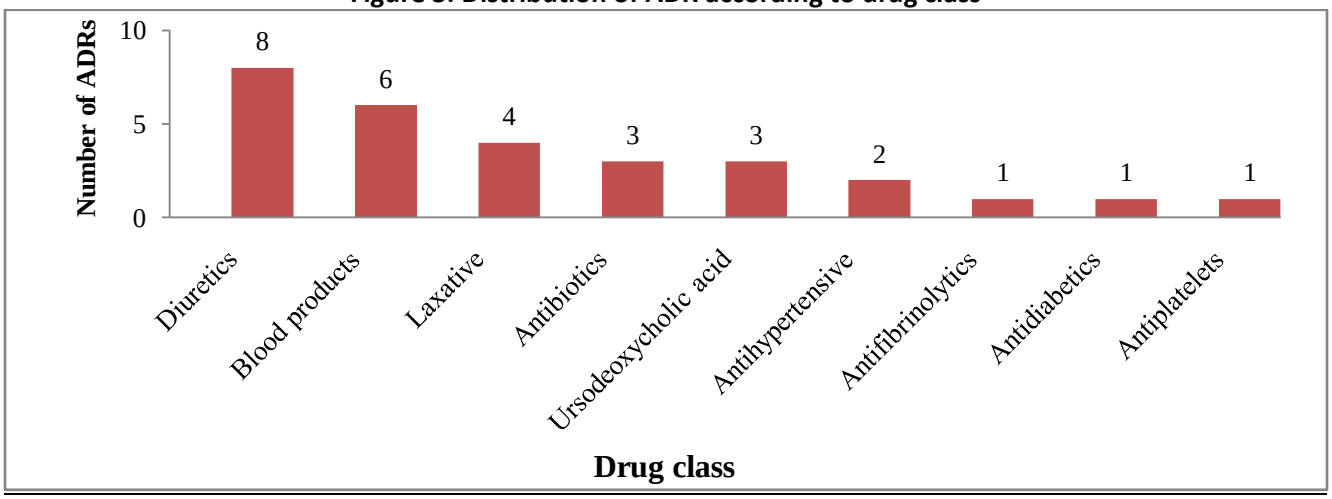
Domain of cirrhosis care	The quality indicators (QIs)	No of patients eligible for each indicator	No of patients received the recommended care N (%)
Ascites	Patient received empiric antibiotics within 6 hours of ascitic tapping	22	22 (100%)
Ascites	Patient received salt restriction and diuretics (combination of spironolactone and furosemide) with ascites	58	58(100%)
Variceal bleeding	Patient received octreotide within 12 hours of presentation with variceal bleeding	35	35(100%)
Variceal bleeding	Patient received EVL obliteration, beta-blockers, or a combination or EVL and beta-blockers as secondary prophylaxis	46	46 (100%)
Hepatic encephalopathy	Patient received lactulose and or rifaximin for hepatic encephalopathy	89	89(100%)
Spontaneous bacterial peritonitis	Patient receiving intravenous albumin within 6 hours on day 1 and on day 3 following diagnosis of spontaneous bacterial peritonitis	31	0(0%)
Spontaneous bacterial peritonitis	Patients who received prophylactic antibiotics against nosocomial acquired SBP	150	150 (100%)
Hepatorenal Syndrome	Patients who received vasoconstrictors and albumin	18	18(100%)
Vaccination	Vaccination for HAV, HBV, Influenza, Pneumococcal	150	0(0%)

Clinical outcome: The mean duration of hospitalization was 6.3 ± 0.1 days (range: 2 days to 14 days). However, 33% patients were re-admitted within a month after discharge. Hepatic encephalopathy (60%) and recurrence of ascites were common complication during readmission. During follow up,

150/225 admitted patients responded to treatment given while 75 (33.3%) patients succumbed and died during hospitalization. Majority (77.3%) of the patients belonged to Child Pugh C class. Cause of death was reported as decompensated liver disease in 51 patients (68%) and variceal bleeding in 24 patients(32%).

Adverse drug reactions: Total 29 ADR were observed in 225 patients. ADR were mildin 15(55%) andmoderate in 8(23%). Only 6(22%) reactions were consideredas severe: hepatic encephalopathy [3],acute kidney failure [2] and hypoglycaemia [1]. In 76% ADR, it was necessary to change drug therapy i.e., discontinue drug, reduce dosage or administer another drug to correct ADR. 68% of ADR were dose-related effects and 32% were dose independent.Most of the drugs were possibly related with ADR according to WHO-UMC causality assessment and Naranjo's causality score.[15,16]According to Hartwig and Siegelscore, 60% ADRs were preventable.[17]Most common group was diuretics and most common drug causing ADRswasFurosemide (Figure 3).

Figure 3: Distribution of ADR according to drug class



Discussion: Rational prescribing is essential part of patient care. WHO has developed an essential drug list for promotion of rational therapy[4].In present study most drugs were supplied from hospital pharmacy. As our hospital formulary is based on WHO essential medicine list, it has direct impact on number of rational prescriptions. Majority of medicines for management of complications of cirrhosis were available in civil hospital as they were included in Gujarat state EDL.[5]During the past decades, the use of broad-spectrum antimicrobials in Gastroenterologyhas increasedparticularly among patients with cirrhosis and spontaneous bacterial peritonitis (SBP).[6]In present study, vaccination practice for cirrhosis patient was lacking for all vaccine-preventable infections investigated. Similar pattern was observed in another study where vaccination rates remained suboptimal in patients with cirrhosis.[7]This study emphasizes the need for antibiotic stewardship and treatment standardization in the care of cirrhotic patients because most of the antibiotics were prescribed empirically (71%). Present study demonstrates that in high-risk SBP patients, albumin was underutilized and its administration did not follow recommended guidelines.[8] Given the known benefits of albumin in high-risk SBP patients, these deficits must be addressed.PPIs should be prescribed only to recognized indications of liver cirrhosis patientsbecause of association ofmore infections in PPI users compared to non-users[9]. Ondansetron was prescribed in all the patients even in the absence ofnauseaor vomiting. The reason could be to prevent vomiting due to gastric irritation by drugs. However, further analysis is needed to see whether the frequent use of these drugs is rational.In present study all the patients admitted with decompensation of cirrhosis received Vitamin K with regimen of 6 mg stat on day 1 and day 3, irrespective of their coagulation profile.Vitamin K administration had no effect on the INR.[10]Still it is common practice in India. Ursodeoxycholic acid (UDCA) is administered to majority (12%) of admitted patients with cirrhosis.This reason can be attributed to possible underlying cytoprotective, anti-apoptotic, and anti-oxidative effects of UDCA on hepatocytes.According to AASLD practice guidelines, UDCA is recommendedonly in

patients with primary biliary cirrhosis and its role in other aetiology is questionable. In a multicentric study by Lawate P et al (2016) in Indian population it was found that UDCA improves clinical and biochemical parameters in patient with cholestatic chronic liver disease due to secondary aetiologies of intrahepatic cholestasis due to ALD, viral hepatitis and NAFLD[11]. Similar improvement in clinical and biochemical parameter was reported by Qureshi H et al (2006) in Pakistan. Wide variation of transfusion practice was observed in present study. Effective measures to control and reduce empirical correction of abnormal coagulation tests through transfusing fresh frozen plasma should be strengthened urgently. This study clearly shows that there is a tendency to prescribe proton pump inhibitors, antiemetic, vitamins K injection, hepatoprotective agents and multivitamins.Lack of compliance to the drug treatment and large dietary sodium intake were leading cause for reoccurrence of hepatic encephalopathy and ascites. Educational intervention of patient and his/her caretakers will surely help in this matter.Better quality of care is inversely proportional to patient's worsening liver disease severity and hospital readmissions.The clinical outcome of the patients is favourable since improvement was seen in around 70% of patients. Given the known benefits of albumin in high-risk SBP patients, these deficits must be addressed.Empirical correction of abnormal coagulation tests with fresh frozen plasma is not recommended.[12]Effective measures to control and reduce empirical correction of abnormal coagulation tests through transfusing plasma should be strengthened urgently. Present study demonstrates high levels of adherence (100%) to most quality indicators for patients of cirrhosis complications. Resident doctors are typically the first line of doctors in our institution. We recommend educational intervention with adherence to recommended guidelines to further improve Quality of care. It must be emphasized that several ADRs could have been prevented with patient/care taker education about disease, adequate dose adjustments or appropriate laboratory investigations or replacement therapy with potassium chloride. Although we believe that our study yields important results, it has several limitations. It is a study at a single institution of a relatively uncommon patient group. A large, multi-centre study would be valuable to evaluate mortality, quality of life and cost.

Conclusion: Quality of prophylaxis and treatment of complications of cirrhosis met the accepted standards. However, significant shortfalls remain in two Quality Indicators (QI) of cirrhosis care.Compliance to guideline would definitely help us to take better care of patients. Efforts should be focused on improving physicians' knowledge and attitude regarding guidelines.Until the relative safety of Vitamin K, Tranexamic acid, Hemocoagulase is established, their use should be discouraged among patients with cirrhosis.

References:

1. Lawrence S. Friedman and Emmet B. Keeffe Chapter 9: Cirrhosis and Portal Hypertension: An Overview from Handbook of Liver Disease 3rd edition.
2. MokdadAA,LopezAD,ShahrazS,etal.Livercirrhosismortalityin187countriesbetween 1980 and 2010: a systematic analysis. BMC Med 2014;12:145.
3. Kanwal F, Kramer JR, Buchanan P, et al. The quality of care provided to patients with cirrhosis and ascites in the Department of Veterans Affairs. Gastroenterology 2012; 143:70-77.
4. World Health Organization. WHO model list of essential medicines (adults), 19th ed. Geneva, 2015 (www.who.int/medicines/publications/essentialmedicines/EML2015 8-May-15.pdf).
5. A Government of Gujarat. Essential Drug List of 2016-17(EDL).(https://gmscl.gujarat.gov.in/ images/ pdf/EDL-2016-2017.pdf)
6. Bedini A, Maria N, BuonoM, Bianchini M, ManciniMetal.Antimicrobial stewardship in a Gastroenterology Department: Impact on antimicrobial consumption, antimicrobial resistance and clinical outcome. Digestive and Liver Disease, Volume 48, Issue 10, October 2016, Pages 1142 – 1147.
7. Waghray A, Waghray N, Khallafi H, Menon K. Vaccinating Adult Patients with Cirrhosis: Trends over a Decade in the United States. Gastroenterology Research and Practice.Volume 2016 (2016).
8. Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013Apr.
9. PicardiA,Gentilucci U. Proton pump inhibitor prescription abuse and sepsis in cirrhosis. World J Gastrointest Pharmacol Ther. 2016 Feb 6; 7(1):1–4

10. Meyer, AV, Green M, Pautler H, Korenblat K, Deal E et al. Impact of Vitamin K Administration on INR Changes and Bleeding Events Among Patients With Cirrhosis. Annals of Pharmacotherapy1–5.
11. Lawate P et al. A prospective, multicentre, observational study of patients with chronic cholestatic liver diseases receiving Udilivin India: Splendid study. Int J Basic Clin Pharmacol. 2016 Dec;5(6):2621-2629
12. Amarapurkar PD, AmarapurkarDN.Management of Coagulopathy in Patients with Decompensated Liver Cirrhosis. International Journal of Hepatology.Volume 2011, Article ID 695470, 5 page.
13. Lucena MI, Andrade RJ, Tognoni G, Hidalgo R, de la Cuesta FS, Fraile JM, Cabella R, et al. Multicenter hospital study on prescribing patterns for prophylaxis and treatment of complications of cirrhosis. Eur J Clin Pharmacol 2002;58:435-440.
14. Meenu V, Anisha KA, Arjun SKS, Roshni PR. Clinical Profile and Prescribing Pattern of Cirrhosis in a Tertiary Care Hospital. Ind J of Pharmacy Practice, Vol 7, Issue 3, Jul–Sep, 2014
15. The use of the WHO-UMC system for standardised case causality assessment. Available at http//www.who-umc.org/Graphics/24734.pdf
16. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther.1981;30(2):239-45.
17. Hartwig SC, Siegel J, Schneider PJ (1992) Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 49: 2229–32.

Conflict of interest: None
Funding: None
Cite this Article as: Dumatar CB,Malpure RA. Study of Prescribing Patterns for Prophylaxis and Treatment of Complications of Liver Cirrhosis. Natl J Integr Res Med 2017; 8(3):98-104