A study on prescription pattern of drugs used in the treatment of peptic ulcer disease in a tertiary care hospital

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Abstract

Purpose : To study the prescribing pattern of medications used in the management of peptic ulcer disease and to identify and manage the drug related problems.

Methods : A prospective interventional study was conducted over a period of nine months in the department of gastroenterology among both in-patients and out-patients, JSS Hospital, Mysuru. Patients diagnosed endoscopically with PUD were enrolled in the study after obtaining inform consent form.

Results : A total of 180 PUD patients were included in the study with 108 (60%) out-patients and 72 (40%) in-patients. About 111 (61.66%) participants were started on fixed drug - dose combination therapy for *H. pylori* eradication followed by PPI maintainance treatment for 42.12±5.94 days. In-patients with complicated PUD (UGIB) were administered with PPI 80mg bolus followed by PPI infusion 8mg/hr for a period of 19.5±6.69 hours.

Conclusion: Clarithromycin based *H. pylori* kit is the prevalent therapy used in *H. pylori* eradication. The majority of drug related problem encountered was drug-drug interactions followed by sub-therapeutic dose and failure to receive maintainance dose of PPI.

Keywords : Peptic ulcer disease, Prescribing pattern, Drug Related Problem.

Peptic ulcer disease (PUD) is a common problem around the world and remains an important cause of increased morbidity and health care costs [1]. A peptic ulcer is defined as disruption of the mucosal integrity of the stomach and/or duodenum that extends beyond the muscularis mucosa leading to a local defect or excavation due to active inflammation and measures between 3mm to centimetres. The most common sites of ulcers are stomach (gastric ulcer) and proximal duodenum (duodenal ulcer) [2].

Warren and Marshall's discovery of the association between *Helicobacter Pylori* and development of peptic ulcer disease changed into a big breakthrough within the pathogenesis and remedy of peptic ulcer disease [3]. There have been many etiologies proposed for the causation of ulcers. The integrity of the upper gastrointestinal tract is often dependent on the balance between hostile factors such as gastric acid, *H. pylori*, non steroidal anti inflammatory drugs, pepsin, and protective factors such as prostaglandins, mucus, bicarbonate limits blood flow to mucosa. *H. pylori* is the most common cause of peptic ulcer disease and its infection correlates well with socio-economic status and is higher with poor environmental hygiene, crowdedness, low income and low literacy level (Enroth and Engstrand, 2001) as is typical of most developing countries [4].

Peptic ulcer disease predominantly affects older population i.e., common in the age group of 55 - 65 years. Ulcer disease was once predominant in the older population is now leading in adults as well [5]. Duodenal ulcers are more common in men than gastric ulcers while the context is opposite in women. Also, patients will suffer from the complicated PUD like hemorrhage and perforation and the other being gastric outlet obstruction, and gastric cancer [4, 6].

Globally, the annual incidence of PUD was estimated to be about 4 million. The annual incidence of PUD ranges from 0.10% to 0.19% for physician-diagnosed PUD and from 0.03% to 0.17% for PUD diagnosed during hospitalization. The physician-based PUD and hospitalized based PUD over 1-year prevalence was 0.12 to1.5% and 0.10 to 0.19% respectively [7, 8]. Mortality from peptic ulcer bleeding shows 7% to 8% for four decades [9]. These complications not only increases mortality but also increases the health care cost.

In Indian scenario, the frequency of both duodenal and gastric ulcer has declined from 12% to 2.9% and 4.5% to 2.7 % respectively for the time being 1988 to 2008. Although PUD affects both males and females alike in the West, the scenario in India dictates men are 18 times more prone to PUD than women. Studies from different parts of India shows the prevalence of 70%, 77.2%, 78% and 59.2%of *Helicobacter* infection [10]. Though peptic ulcer is frequently occurring in India, studies on its prevalence are sparse. On an average, prevalence is noted to be around 8 per 100,00 [11]. The latest WHO reports in 2017 published that the total deaths in India have reached up to 57,658 or 0.66% and India ranks 53 in the world with the age-adjusted death rate is 5.79 per 100,000 [12].

The lifetime prevalence was estimated to be 8.8% whereas the point prevalence being 3.4% for an active peptic ulcer, the ratio for duodenal to gastric ulcer was 12:1 [10]. Patients with complicated ulcers (bleeding, perforated) had higher mortality than those with uncomplicated ulcers and it was found to be 30-day mortality ranging from 31% to 43% of patients [13].

Further, the mortality rates from peptic ulcer disease are low, the higher prevalence and the resulting pain, suffering, and associated management cost are very costly and can have an adverse impact on the patients [4, 14, 15]. While these are not generally life threatening conditions, they can significantly impair patients' quality of life [16].

The preferred management involves the use of acid-suppressing drugs and eradication of *Helicobacter Pylori* infection. According to guidelines, American College of Gastroenterology and the Maastricht Consensus Conference recommend clarithromycin triple therapy for 7 - 14 days and bismuth quadruple therapy 10 - 14 days as first-line regimens. A recent study says most commonly prescribed regimen for *Helicobacter pylori* being esomeprazole containing triple therapy followed by pantoprazole based triple therapy with 59.7% and 41.3% with the maintenance therapy of PPI for a period of 6.89±2.25 weeks with the most common ADR's belonging to the gastrointestinal system [1, 14]. A recent study from India shows that rabeprazole, amoxicillin, and metronidazole are found to be more cost effective comparing to pantoprazole, amoxicillin, and metronidazole based triple therapy.

Peptic ulcer correlates with lower socio-economic class and with increased consumption of restaurant food, meat, non- filtered water, meat, fish and beverages. Consumption of alcohol and tobacco was not significant in causing ulcers [11].

However, the studies concerning the treatment strategies employed for PUD eradication in India are limited and thus warrants for the current study, wherein understanding the prescription pattern of drugs used in PUD can improve the overall health outcomes. Further, with the promotion of rational use of PPI's and H2 blockers and determining any drug related problems in the patient care will improve the overall patient treatment satisfaction and health outcomes. substantial socioeconomic burden and negatively impacts on quality of life [4, 5]

Results

Demographic details of the patients with peptic ulcer disease

A total of 180 participants who met the inclusion criteria were enrolled in the study. Among them, 108 (60%) were from ambulatory setting and were 72 (40%) hospitalized. It was found that 140 (77.77%) were male and 40 (20.22%) belonged to female population. It was observed that the mean age of the patients was 51.47±15.14 years and were within the age group of 30 – 70 [143 (79.44%)]. The body mass index of 96 (55.17%) study population was normal followed by 45 (25.86%) belonged to pre-obese category. Further about 49 (27.22%) were smokers and 51 (28.33%) were alcoholics whereas, 36 (20%) of the study population were both smokers and alcoholics. Details on demographics and social history are represented in the below Table 1.

Table 1: Demographics and Social details

Demographic characteristics		No. of study population (%) (N = 180)
Age [51.47 ± 15.14]	10 - 29	15 (8.33)
	30 - 49	61 (33.89)
	50 - 69	82 (45.51)
	70 - 89	21 (11.67)
	> 90	1 (0.55)
Gender	Male	140 (77.78)
	Female	40 (22.22)
Patient intake	Ambulatory patients	108(60)
	Hospitalized patients	72(40)
Smoking	Smokers	49 (27.22)
	Reformed smokers	30 (16.66)
	Non-smokers	101 (56.11)
Alcoholism	Alcoholics	51 (28.33)
	Reformed alcoholics	32 (17.77)
	Non-alcoholics	97 (53.88)
	Smoking + Alcoholism	36 (20)
	Non smokers nor alcoholics	79 (43.88)
Comorbit conditions	Alcoholic /Chronic liver disease	60 (33%)
	Diabetes mellitus	35 (19%)
	Hypertension	35 (19%)
	Diabetes mellitus + Hypertension	20 (11%)
	Ischemic heart disease	13 (7%)
	Others	19 (11%)
Socio- economic class	Upper (I)	1 (0.55)
	Upper Middle (II)	37 (20.55)
	Lower Middle (III)	55 (30.55)
	Upper Lower (IV)	80 (44.44)
	Lower (V)	7 (3.88)
Past medication history	NSAID	18 (10)
	Anti platelet agents	15(8.33)
Blood Group	A+	21 (22.3)
	A-	1 (1.06)
	B+	17 (18.08)
	O+	49 (52.12)
	O-	4 (4.25)
	AB+	2 (2.12)
	Unknown	86 (47.77)

Most of the participants [124 (68.88%)], were from the department of gastroenterology followed by general medicine [39 (21.66%)], surgery [8 (4.44)] and ENT [9 (5%)]. Liver disease (chronic or alcoholic) were the most common concurrent illness and were seen in 60 (21.58%) while 35 (12.58%) with type 2 diabetes mellitus 35 (12.58%) with hypertension. The reported history of NSAID usage was seen in [18 (10%)] study participants and on antiplatelet agents (aspirin alone or in combination with clopidogrel were 15 (8.33%).

Of the study participants, majority of them belonged to the socio - economic class of upper lower class 80 (44.44%), followed by lower middle class 55 (30.55). Presenting complaints is shown in the Figure 1. Pain abdomen was presented in 108 (48%) followed by vomiting in 36 (16%) of study population. As the single study participant might have more than 1compliant, the total percentage is more than 100.

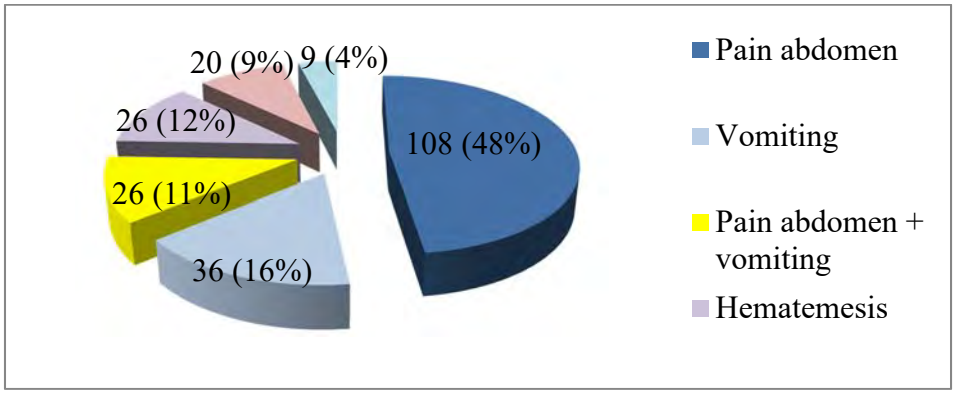


Figure 1: Categorization of presenting complaints

Prescribing pattern for patients with peptic ulcer disease

In this study, we found that the duodenal ulcer was diagnosed amongst 89 (49.44%) participants followed by gastric ulcer in 68 (37.77%) and rest were diagnosed with gastroduodenal ulcer 23 (12.77%). Overall, only 94 (52.22%) were subjected to rapid urease test and out of them, 67 (71.27%) were tested positive as presented in Table 2.

Table 2: Rapid urease test findings

Clinical diagnosis	No. of study population % (N = 94)
RUT positive	67 (71.27)
Gastric ulcer	21 (31.34)
Duodenal ulcer	36 (53.73)
Gastroduodenal ulcer	10 (14.92)

The total number of drugs prescribed in ambulatory settings were 307 for 108 study population giving a mean of 2.84 per encounter. The total number of drugs prescribed during hospitalization were 368 with mean of 5.11 per encounter. On discharge the total number of drugs prescribed were 329 with mean of 4.56 per encounter.

Table 3: Prescribing pattern for patients with PUD

	Ambulatory patients, No. of study population % (N = 108)	Hospitalized patients, No. of study population % (N = 72)	Total, No. of study population % (N = 180)
Fixed dose combinations	73 (67.59)	38 (52.77)	111 (61.66)
Monotherapy	35 (32.40)	31 (43.05)	66 (36.66)
None	0	3 (1.66)	3 (1.66)

Table 4: Distribution based on type of therapy received

Types of H. Pylori Kit prescribed to the study population		No. of study population % (N*= 111)
Clarithromycin based triple therapy n= 104 (57.77%)	Esomeprazole based HP kit	90 (86.53)
	Pantoprazole based HP kit	14 (13.46)
Tinidazole based triple therapy	7 (3.88%)	
	Esomeprazole	24 (29.62)
	Pantoprazole	23 (28.39)

Monotherapy n= 81 (45%)	Sucralfate	21 (25.92)
	Antacids	5 (6.17)
	Esomeprazole + Domperidone	3 (3.70)
	Rabeprazole	2 (2.47)
	Pantoprazole + domperidone	2 (2.47)
	Rabeprazole + Domperidone	1 (1.23)

*As the single study participant might have received more than 1 type of medication, the total percentage is more than 100.

Hospitalized participants who were admitted with secondary complications of PUD i.e, hemorrhage/bleeding were 21 (29.16%). Pantoprazole bolus 80 mg was prescribed to 19 (90.47%) of the study population followed by pantoprazole infusion 80mg to 21 (100%) for a period of 19.5±6.69 hours. Other details are as in Figure 2. Among 21 hospitalised participants with bleeding PUD, 6 (28.57%) were on antiplatelet agents. Others hospitalized patients who were admitted for other co-morbidities were 51 (70.83%). PPI IV was administered to 26 (50.98%) and PPI oral to 31 (60.78%) on hospitalization. Upon discharge 38 (52.77%) they were started on different H. pylori kit. The duration of hospitalization stay was 5.13±2.22 days for complicated ulcers participants. Reoccurence was seen in [14 (7.78%)] participants, out of them [10 (71.42%)] received clarithromycin based HP kit whereas 1 (7.14%) with tinidazole based HP kit.

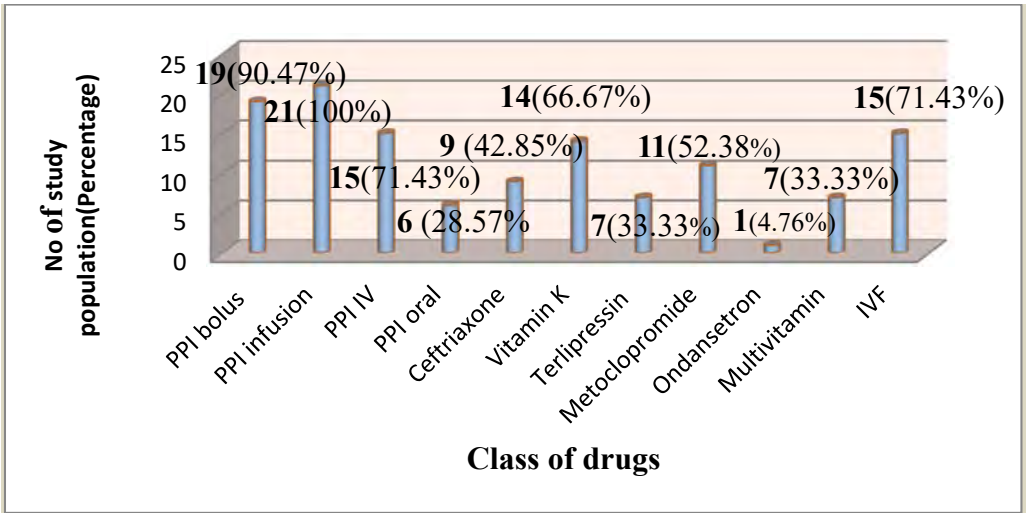


Figure 2: Prescribing pattern for patients with secondary complication (bleeding PUD) during admission

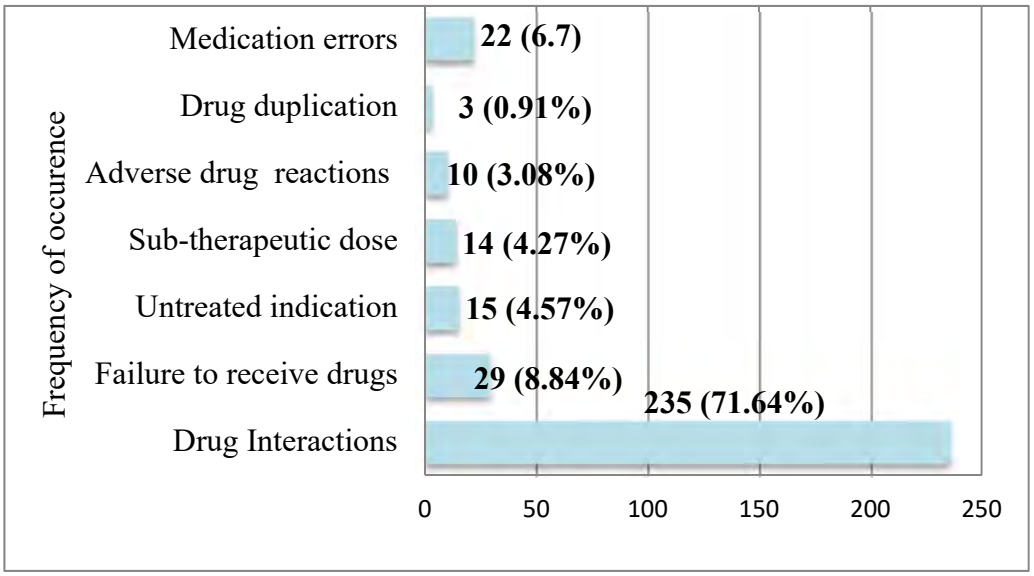
Table 5: Prescribing pattern in hospitalized patients with co-morbidities

Medications	No. of study population (%) (N = 51)
PPI IV	26(50.98)
PPI Oral	31(60.78)
PPI IV to Oral	9(17.65)

Drug Related Problems

Among the overall drug related problems seen, drug interactions were observed in majority of the study participants [235 (71.64%)] followed by failure to receive drugs [29 (8.84%)]. The other drug related problems are represented in Table 6.

Table 6: Drug Related Problems



Drug interactions

Out of total study population, 138 (76.66%) participants encountered at least one drug-drug interaction and drug interactions accounted for 71.64% of overall drug related problems. Among 235 DDI's, minor interactions were 149 (63.40%), the interactions to be monitor closely were 74 (31.49%) and serious interactions were 12 (5.10%).

Failure to receive drugs

No PPI maintenance therapy after *H. pylori* eradication therapy being prescribed was seen in 29 (8.84%) participants among 111 who had received *H. pylori* eradication regimen, as PPI maintainance therapy is necessary in preventing reoccurrence.

Untreated indication

Untreated indication was another drug related which was encountered in 15(4.57%) of patients. Among untreated indication, 7 (46.67%) were not treated for *H. pylori* bacteria even on confirmation of *H. pylori* by RUT. Anemia was not treated in 5 (33.33%) of study population (Hb: > 8g/dl) amd 3 (20%) of participants did not receive treatment for PUD.

Sub-therapeutic dose

The study population who received *H. pylori* eradication regimen, 14 (4.27%) were prescribed with only amoxicillin 750 mg (i.e, the kit contains amoxicillin 750 mg + clarithromycin 500 mg + PPI 40 mg) whereas standard amoxicillin dose to be prescribed is amoxicillin 1000mg. Hence along with the *H. pylori* eradication kit, another amoxicillin 250 mg should be prescribed which was one of the problems encountered.

Adverse drug reactions

Overall 10 (3.08%) experienced ADR as a drug related problem. Among 108 (60%) ambulatory patients, 10 (9.25%) experienced adverse drug reaction. Among them, 4 (40%) patients reported having vomiting, 4 (40%) patients reported to have diarrhea and 2 (20) with nausea.

Table 7: Adverse drug reactions

Suspected drugs	ADR	No. of patients with same ADR, %, (N = 10)	Causality according to Naranjo's scale
Amoxicillin/Clarithromycin/ Esomeprazole	Nausea	2 (20)	Possible
Amoxicillin/Clarithromycin/ Esomeprazole	Vomiting	4 (40)	Possible
Amoxicillin/Clarithromycin/ Esomeprazole	Diarrhea	4 (40)	Possible

Drug duplication

Drug duplication was seen in 3 (0.91%) study subjects. They were prescribed with additional PPI who were already on triple therapy for PUD which contains PPI which indicates drug duplication.

Medication errors

a. Improper Duration of Regimen

Out of total 180 patients, 8 (4.44) patients received the improper duration of *H. pylori* eradication regimen, i.e, they received therapy for a more number of days than standard 7 - 14 days. 3 patients received 15 days of therapy, 2 with 17 days, 3 participants each with 16, 21 and 24 days of therapy respectively. A single day therapy was administered to one participant.

b. Brand substitution

Among the study population, 13 (3.96%) were encountered with the problem of brand substitution i.e. they were prescribed with tinidazole based HP kit instead of clarithromycin based HP kit. This was seen because of absence of prescribing the name specific HP kit. The brand 'HP kit' is a tinidazole-based kit. When the prescriber mentioned 'HP kit' in the prescription, the patients are likely to be dispensed with the same though the prescriber meant clarithromycin-based therapy. 13 patients with this drug related problems were observed, 5 of them were intervened and required changes were made.

Discussion

Based on literature searches, scarce data in the country on the management pattern of PUD including both ambulatory and hospitalized patients. Peptic ulcer disease is a common disease worldwide with varying prevalence in different geographical locations.

Previous studies from USA, Japan, Norway and India identified male population as an independent risk factor for PUD and similar predominance of males (71.78%) was seen in the present study [17-20]. The sex ratio (male:female) of 3.5:1 was seen consistent with studies by Dong *et al* (3.95:1) and Rosenstock et al (2.2:1) [20, 21]. The mean age of the study population was 51.47 which is similar to a recent study conducted in South India with mean age of 51.86. Consistent to the findings by Dong et al in China (age group 20-50 years) and Ramakrishan et al in US (age group 25-64 years), the present study showed majority of study population in the age group 30-69 years [2].

The study populations of upper lower and lower middle class classified according to Kuppuswamy socio - economic classification 2018, were more likely to suffer from *H. pylori* infection which correlates with the study carried out by Rahul S M et al [11]. However, as per other study, the risk of infection is associated with overall sanitary conditions and exposure to other infected humans, also risk of infection among higher socioeconomic class depends on household hygiene [22].

In this study, it was found that only 27.22% were smokers. However, researchers have found close association between smoking and PUD as the nicotine in cigarette smoking produces more acid secretion and thus high chances of getting an ulcer and with higher relapse rate of peptic ulcer diseases [21, 23, 24]. Among 94 patients whose blood group was identified, 56.38% had blood group O, which can be additional risk factor for PUD as people with blood group O partly have higher density of colonized *H. pylori* compared with other blood groups supported by studies of Keller et al, Mattos et al, Martins et al, Abdulridha MK and Kanbay M et al [25-29].

In developing nations, the prevalence of *H. pylori* infection in adults peaks at more than 80% and in the Indian population it ranges from 31 to 84% and more in rural areas. Likewise, predominant risk factor for development of PUD was *H. pylori* infection with similar findings of *H. pylori* infection in 61.67% of study population was seen, thereafter the eradication being utmost important.

The mean number of drugs per encounter were 2.84 which could be comparable with studies from Nepal (2.91) and India (2.7). However the mean number of drugs in hospitalized patients were higher and mean was more than 4 as they had multimorbidities. Since the WHO has put forward the standard number of drugs to be 2 per prescription, polypharmacy is a noteworthy parameter which could lead to drug related problems [30].

In the current study duodenal ulcer preceded (49.44%) gastric ulcer (37.77%) and gastroduodenal ulcer in 12.77% of study population which varies with the study conducted by Jayaram et al. where gastric ulcer preceded (51.2%) duodenal ulcer (45.8%) and gastroduodenal ulcer in only 3% [1].

As more than half of the study population were infected with *H. pylori*, fixed drug dose combination of *H. pylori* kit was started. Triple therapy combining a proton pump inhibitor with two antibiotics (amoxicillin, clarithromycin and/or metronidazole) has been the most recommended first-line treatment and PPI monotherapy for non *H pylori* infected patients.

From the findings of the study, it was noted that among all patients who received therapy for *H. pylori* eradication regimen, maximum were prescribed with combination of PPI + amoxicillin + clarithromycin for duration of 14 days. Only few were prescribed for 7 – 10 days. Antibiotic resistance, mainly to clarithromycin, seems to be increasing in many geographical areas, and is considered a leading cause for treatment failure. The frequency of clarithromycin resistance is higher in North America and Asia with varying resistance in different parts of India. Though the common confirmatory test for *H. pylori* was rapid urease test (CLO test) in the current setting, it was observed that the test was not performed in all the study population.

The standard WHO and ACG guidelines recommend 7 - 14 days therapy but the duration of therapy differs among different countries. Researchers like Veldhuyzen et al, Duggan AE et al, found 7 day regimen to be effective [31,32,33] whereas in US it is 10 – 14 days. In the present work, majority of the patients were prescribed with esomeprazole containing clarithromycin therapy for a period of 14 days which shows better efficacy than other PPI as shown by the meta-analysis [34]. According to RCT findings there is no difference between clarithromycin and metronidazole based triple regimens for *H pylori* eradication and effectiveness of metronidazole in clarithromycin resistance with cost effectiveness [35]. The clarithromycin based triple therapy was prescribed in 7.77% of study population with reoccurrence.

For hospitalized patients with complicated PUD/ bleeding PUD, the first line therapy was endoscopic therapy and hemodynamic assessment. This was followed by medical therapy with PPI 80mg bolus and PPI continuous infusion 8mg/hr for a period of 19 hours which is inconsistent to the guidelines (72 hours infusion). Some studies have concluded that PPI infusion was not effective for the prevention of reoccurrence of bleeding and IV PPI was sufficient. In the present study, it was seen that prophylactic antibiotic (ceftriaxone) was prescribed to these patients which is inconsistent with the guidelines or studies. However, the use of such prophylactic antibiotic has to be evaluated as there is no supporting evidence for usage of prophylactic antibiotic therapy in bleeding PUD.

The present study quite a number of drug related problems. The common DRP was found to be potential drug-drug interactions as patients with multimorbidities were included. Other identified problems were sub-therapeutic dose, untreated indication and failure to receive maintainance therapy.

The study reveals that the treatment strategy is to start therapy for *H. pylori* eradication. Clarithromycin based *H. pylori* kit is the prevalent therapy used in *H. pylori* eradication. PPI being the most common therapy was prescribed either in combination or alone and use of esomeprazole was the common and well in accordance to ACG guidelines. However, the usage of second line therapy for patients with reoccurence needs to be evaluated. Among hospitalized patients due to complicated ulcers (bleeding ulcers) the prophylactic use of antibiotic has been found. The study enlightens the need for prophylactic PPI therapy to be used in patients on aspirin.

The majority of drug related problem encountered was drug-drug interactions. In other departments, subtherapeutic dose was found to be one of common drug related problem. Inappropriate duration of the regimen followed by failure to prescribe maintainance dose were observed to be other DRPs

Conclusion

The study reveals that the treatment strategy is to start therapy for *H. pylori* eradication. Clarithromycin based *H. pylori* kit is the prevalent therapy used in *H. pylori* eradication. PPI being the most common therapy was prescribed either in combination or alone and use of esomeprazole was the common and well in accordance to ACG guidelines. However, the usage of second line therapy for patients with reoccurence needs to be evaluated. Among hospitalized patients due to complicated ulcers (bleeding ulcers) the prophylactic use of antibiotic has been seen.

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