

East African Medical Journal Vol. 96 No. 6 June 2019

PREDICTORS OF INAPPROPRIATE PRESCRIBING OF ACID SUPPRESSIVE MEDICATIONS AMONG MEDICAL INPATIENTS IN A REFERRAL HOSPITAL IN KENYA

Carolyne Naliaka Odeo, BPharm, MPharm, Assistant Chief Pharmacist, Ministry of Health, Bungoma County Referral Hospital, P.O. Box 14-50200 Bungoma, David Gitonga Nyamu, BPharm, MPharm, PhD, Senior Lecturer of Clinical Pharmacy, Department of Pharmaceutics and Pharmacy Practice, University of Nairobi, P.O. Box 19676-00202 Nairobi, Eric Muriithi Guantai, BPharm, PhD, Senior Lecturer of Pharmacology & Therapeutics, Department of Pharmacology and Pharmacognosy, University of Nairobi, P.O. Box 19676-00202 Nairobi, Rugendo Alfred Birichi, BPharm, MPharm, Deputy Chief Pharmacist, Department of Pharmacy Kenyatta National Hospital, P.O. Box 20723-00202 Nairobi.

Corresponding author: Carolyne Naliaka Odeo, BPharm, MPharm, Assistant Chief Pharmacist, Ministry of Health, Bungoma County Referral Hospital, P.O. Box 14-50200 Bungoma, Email: naliakacarol07@gmail.com.

PREDICTORS OF INAPPROPRIATE PRESCRIBING OF ACID SUPPRESSIVE MEDICATIONS AMONG MEDICAL INPATIENTS IN A REFERRAL HOSPITAL IN KENYA

C. N. Odeo, D.G. Nyamu, E. M. Guantai and R.A. Birichi

ABSTRACT

Objective: To characterize the patterns and determinants of acid suppressive medications use among adult medical inpatients of Kenyatta National Hospital.

Design: Cross-sectional study.

Setting: Medical wards in the hospital.

Participants: Inpatients aged ≥ 18 years.

Interventions: Demographic, clinical characteristics and details of acid suppressant use were examined both by records review and patient interview

Main outcome measures: Demographic characteristics: age, gender; Acid suppressant use: prevalence, types, indication; Factors associated with inappropriate prescribing of acid suppressants.

Results: 272 patients were included in the study. The mean age was 45.4 ± 16.6 years. 55.9% of the participants were on acid suppressive medications, majority (57.0%) being females. Proton pump inhibitors were the most frequently used acid suppressants (95.2%). Acid suppressive medications were inappropriately prescribed in 178 (65.4%) patients. Internationally recognized indications of acid suppressive therapies accounted for 27 (28.7%) while stress ulcer prophylaxis was indicated in 55 (58.5%) of the patient in whom it was justified. Logistic regression revealed that use of cardiovascular drugs ($P = 0.020$), corticosteroids ($P = 0.001$) and anti-cancers ($P = 0.012$) as well as a diagnosis of pneumonia ($P = 0.016$) were significantly associated with inappropriate prescription of acid suppressive therapies.

Conclusion: Acid suppressive medication use is high and generally unjustified among the medical inpatients of the Kenyatta National Hospital. Measures

aimed at controlling their use by intensifying the evaluation of patients' in need for appropriate prescribing should be encouraged. Future studies should assess prescribers and hospital contextual factors associated with appropriate use of acid suppressive medications.

INTRODUCTION

Acid suppression therapy (AST) has of recent past been revealed as one of the most highly utilized therapies in hospitalized patients for either treatment or prevention of gastric acid related conditions (1,2). The approved indications for AST include: treatment of upper gastrointestinal (GI) bleeding, gastro-esophageal reflux disease (GERD), peptic ulcer disease (PUD), erosive esophagitis, *Helicobacter pylori* eradication, dyspepsia, treatment of hyper-secretory conditions like Zollinger-Ellison Syndrome and stress ulcer prophylaxis (SUP) (3–5).

The prevalence of AST use among hospitalized medical patients has been evaluated across the world to be in the range of 53% - 85% (2,6,7). Proton pump inhibitors (PPIs) are the most commonly prescribed acid suppressant (AS) drugs, accounting for 89% of prescriptions in some parts of the world (2,7). However, studies have also shown a rather high percentage of prescriptions for acid suppressant (AS) drugs prescriptions to be lacking valid indications, up to 84% of patients on AST in the United States of America (USA) (6), with studies elsewhere reporting proportions of 33.8% to 65.3% (2,7,8).

In recent years, the reason for AST in medical wards has changed with prescriptions being written more frequently for stress ulcer prophylaxis (SUP) than other uses with a study in Malaysia reporting up to 75.5% use of AST for SUP (9). However, in reference to international guidelines (5), inappropriate use of AST for SUP has been demonstrated in up to 88.5% of patients in the USA (10). Similarly, in the Middle east,

58% - 67% of patients on SUP had received it with no justification (9,11)

Several predictors of AST prescription either appropriate or inappropriate have been identified. Prior use of AST, hospital length of stay and liver disease are among some of the determinants of inappropriate AST in the Western world (12). Female gender has been shown to be a risk factor for receiving unjustified AS drugs (6). Use of antihypertensive drugs, antidiabetics, anticoagulants, corticosteroids, NSAIDs, and presence of other conditions, such as hypertension, diabetes, cardiovascular disease, respiratory and neurological disorders have been significantly associated with AST use (12,13).

With the knowledge that up to 84% of AST use is without justified indication (6), significant costs to health care systems and incidences of adverse events following use of AST is of major concern especially in resource constrained settings. There is however scarcity of data concerning AST utilization in Kenya and Africa at large. Therefore, this study aimed at characterizing the patterns and predictors of inappropriate AST use among hospitalized medical patients in a national referral hospital in Kenya.

MATERIALS AND METHODS

This was a cross sectional study conducted in May through June 2017. It involved reviewing of medical records of and interviewing adult patients on acid suppressant therapy in the medical wards of Kenyatta National Hospital (KNH), the largest referral hospital in Kenya.

Patients aged 18 years and above admitted to the medical wards during the study period were eligible if they had received at least a dose of an AS drug in any dosage form. However, those who had been transferred into the wards from the intensive care unit and those for whom AST had been prescribed prior to admission were excluded.

Using an estimated prevalence of AST use of 69%, the Fischer's formula was used to calculate the minimum target sample size. A minimum sample of 259 was obtained and systematic random sampling technique was utilized to identify study participants for inclusion.

A designed and pretested questionnaire was used to collect data from patient medical records, treatment sheets and laboratory reports. Patient's demographics such as age, gender, marital status and education level were obtained. The type of acid suppressant drug being utilized including the dosage and route of administration were documented. Prescribers' notes and laboratory records were reviewed to ascertain the indication of AS use in a given patient. Co-morbidities and other medications used by the patient were also recorded. Acid suppressant therapy was termed rational if at least one of the approved indications was identified in patient's record. SUP was considered appropriate if a patient had one absolute indication or at least two relative indications (5).

The data collected were cleaned and coded before input into IBM Statistical Package of Social Scientists (SPSS) version 21.0 for analysis was used for data analysis.

Descriptive statistics was performed and summarized as means with standard deviation and as medians with interquartile range for normally distributed and skewed distributed continuous variables respectively. Categorical variables were

presented as frequencies and percent proportions.

Multivariate logistic regressions analysis was used to examine for associations between predictor and outcome variables for acid suppressant use.

Acid suppressant therapy was termed rational if at least one of approved indications (treatment of *Helicobacter pylori* infection, GERD, esophagitis, peptic ulcers, upper gastrointestinal bleeding (UGIB); maintenance of healed reflux esophagitis, duodenal ulcers and extended treatment of pathological hyper secretory conditions like Zollinger–Ellison syndrome. Also gastritis, relief of dyspepsia and prevention of NSAID-induced ulcers in high-risk individuals (PPI only) (14) was identified in patient's record. SUP was considered appropriate if a patient had one absolute indication (mechanical ventilation > 48 hours, coagulopathy (platelet count < 50,000/mm³, INR > 1.5) state) or at least two relative indications (sepsis, occult bleeding, use of high dose corticosteroid (250 mg of hydrocortisone equivalent), hepatic failure, renal failure, enteric feeding and use of anticoagulants) for SUP (5). The level of significance was set at 5% (p-value ≤ 0.05).

Ethical approval was obtained from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UON-ERC) reference number KNH-ERC/A/137. Subsequently permission granted by KHN administration reference number KNH/AD-MED/42B/VOL.1/.

A written informed consent was obtained from patients as a prerequisite to enrollment into the study. Confidentiality, integrity, respect and dignity of the patients whose data was collected was ensured through use of the patient's record numbers instead of their names.

RESULTS

A total of 572 patients were enrolled and records reviewed for AST use of which 320 (55.9%) patients were on AST. However, of these, only 272 patient files were eligible complete and used for data analysis in the study. Females (155, 57%) were more predominantly found to be on AST compared to males. The mean age of patients on AST was 45.4 ± 16.6 years, with the majority of them in the age group of 18 – 40 years (43.8%). Over half of the participants were on more than three drugs regimen. An average of 6 (SD: ± 2.5) drugs were found to have been prescribed per patient along with an acid suppressant. An

average of 1.4 (SD: ± 1.1) comorbidities per patient was found with majority (37.1%) having at least one comorbidity accompanying the admitting diagnosis.

Malignancy (14.3%), anemia (8.5%), upper gastrointestinal bleeding (7.4%) and acute kidney injury (5.5%) were the most common reasons for which these patients were admitted.

Infections (HIV, TB, pneumonia) (23.6%) and cardiovascular disorders (cardiac and hypertension) (20.3%) were the most common comorbidities in patients undergoing AST followed by renal and hematological disorders. The characteristics of 272 patients on AST are shown in Table 1.

Table 1
Demographic and clinical characteristics of patients on AST

Variable	n (%) (N=272)
Gender	
Male	117 (43)
Female	155 (57)
Age category	
18 – 40 years	119 (43.8)
41 – 60 years	99 (36.4)
Above 61 years	54 (19.9)
Mean = 45.4 ± 16.6 years	
Median = 44 (IQR: 32-58) years	
Number of comorbidities	
0	56(20.6)
1	101(37.1)
2	69(25.4)
3	34(12.5)
4	12(4.4)
Mean \pm SD (1.4 ± 1.1)	
Number of medications	
1-3	45(16.6)
4-6	113(41.7)
7-9	92(33.9)
10 or more drugs	21(7.7)
Mean \pm SD (6 ± 2.5)	
Admitting diagnosis	
Malignancy (tissue and blood)	39(14.3)
Anemia	23(8.5)
Upper gastrointestinal bleeding	20(7.4)
Acute kidney injury	15(5.5)
Gastroenteritis/diarrhea	14(5.1)

Meningoencephalitis	13(4.8)
Heart failure	12(4.4)
CVA/Stroke	12(4.4)
End stage renal disease/CKD	11(4)
Dermatological	9(2.6)
Pneumonia	8(2.9)
Pleural effusion	7(2.6)
TB	7(2.6)
Jaundice	7(2.6)
Others	87(28.4)
Comorbidities	
Infections	86(23.6)
Cardiovascular disorders	74(20.3)
Renal disorders	47(12.9)
Haematological disorders	40(11)
Gastroenterological conditions	25(6.9)
Diabetes	21(5.8)
Malignancy	17(4.7)
Respiratory disorders	16(4.4)
Liver disorders	8(2.2)
Others	30(8.2)

Key: SD-Standard Deviation; IQR-Interquartile Range

The medications prescribed concomitantly with AST varied. Antibacterial agents (antibiotics and anti-TBs) (15.1%), analgesics (13.1%), thrombolytic agents (heparin, warfarin and aspirin) (12.3%) and cardiovascular agents (antihypertensive

drugs, diuretics and inotropic agents) (96, 10.8%) were most commonly prescribed concurrently with AST. The concomitant medications prescribed to the patient are shown in Figure 1.

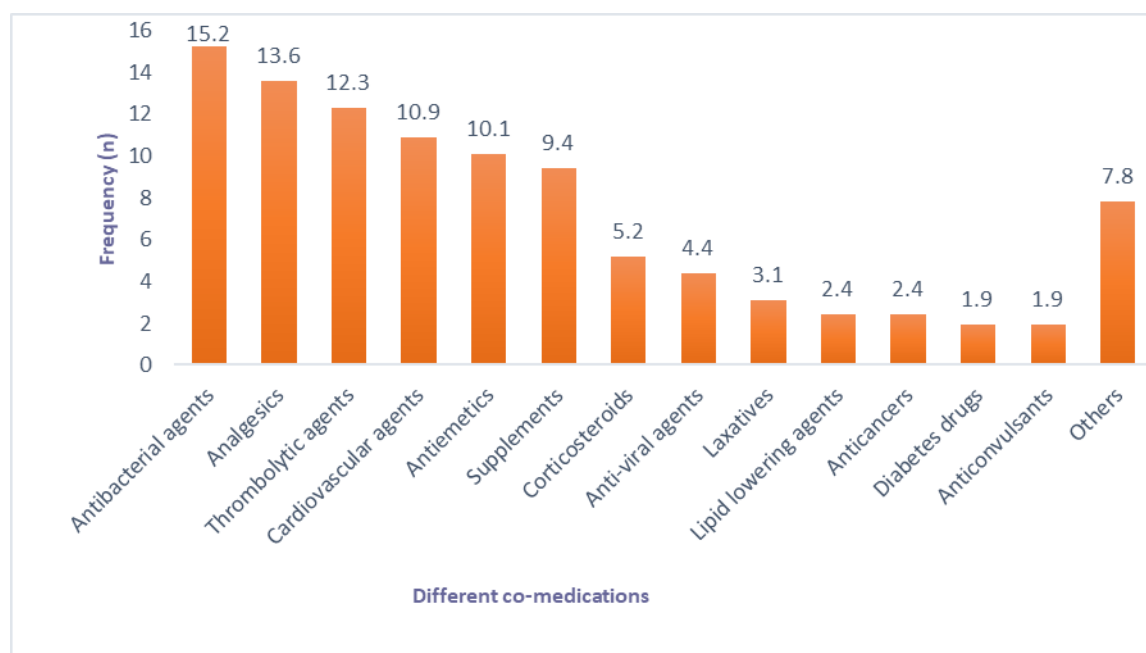


Figure 1: Medications concomitantly used with AST

Proton pump inhibitors were majorly (259, 95.2%) prescribed for acid suppressant therapy of which omeprazole (74.3%) was the most common followed esomeprazole (21.0%). Ranitidine was used in only 4.4% of the patients as premedication. Oral route was predominantly (192, 70.6%) used for acid suppressant drugs followed by the parenteral (80, 29.4%) route.

Use of AST was justified in 94 (34.6%) patients of which 55 (58.5%) had stress ulcer prophylaxis with approved indications of

AST based on international recommendations.

Among the patients of whom AST use was justified, 22 (23.4%) had at least one absolute indication and 33 (35.1%) had two or more relative indications for SUP. Upper gastrointestinal bleeding (UGIB) indication accounted for the majority 22 (23.4%) of the non-SUP justified indications followed by peptic ulcer disease. Ranitidine was justified for use as premedication in cancer therapy in 12 (12.77%) patients. (Table 2)

Table 2
Indications for appropriate AST

Indication	Frequency n (%)
Approved indications (n = 27)	
Upper gastrointestinal bleeding (UGIB)	22(23.4)
Peptic ulcer disease (PUD)/Duodenal ulcers	4(4.26)
Prophylaxis of acid aspiration	1(1.06)
Stress ulcer prophylaxis indication (n=55)	
Absolute indication (at least one)	22(23.4)
Two or more relative indicators	33(35.11)
Other AST Use (n = 12)	
Premedication	12(12.77)

Overall, appropriate/rational AST use was in 94 (34.6%) patients of whom AST was prescribed. Use in the majority of the patients 178 (65.4%) was inappropriate/unjustifiable.

AST use predictor variables identified to be clinically significant on bivariate analysis were included in multivariable logistic regression model, to determine the key predictors of appropriateness AST. They included number of co-morbidities, route of administration, definitive diagnosis of UGIB, jaundice, anemia, pneumonia, pleural

effusion, CVA, presence of cardiovascular disorder as a co-morbidity and use of cardiovascular agents, analgesics, corticosteroids, antivirals and anti-cancers.

These variables were all fit into the model and a step by step backward elimination method applied where highly non-significant variable was eliminated in each given step.

Five variables were found to be statistically significantly associated with appropriateness of AST.

Table 3
Factors associated with appropriateness of AST use

Variable	Crude OR (95% CI)	P value	Adjusted OR (95% C.I)	P value
Number of comorbidities				
≥ 2	2.29 (1.10-5.30)	0.047	1.30 (0.56-3.00)	0.536
Route of administration				
IV route	0.27(0.15-0.46)	< 0.001	2.29 (1.06 – 4.94)	0.035
Admitting diagnosis				
UGIB	1.27(1.14–1.41)	< 0.001	- - -	0.998
Anemia	0.26(0.08–0.90)	0.023	1.45 (0.37 – 5.66)	0.593
Pneumonia	5.97(1.18–30.17)	0.015	0.11 (0.02 – 0.67)	0.016
Co-medications				
Cardiovascular drugs	1.86(1.11–3.11)	0.019	0.31(0.16 – 0.67)	0.020
Analgesics	0.53(0.31– 0.89)	0.015	1.25 (0.58 – 2.67)	0.568
Corticosteroids use	4.75(2.42– 9.30)	< 0.001	0.20 (0.08– 0.51)	0.001
Antivirals	0.44 (0.19–1.00)	0.046	0.57 (0.19 – 1.67)	0.305
Anti-Cancers	9.60 (0.03–0.32)	< 0.001	0.14(0.03 – 0.66)	0.012

KEY: IV =Intravenous, UGIB = Upper gastrointestinal bleeding, CVA = Cerebrovascular accident

Intravenous route of AST administration was 2.3 times as likely to be associated with appropriate use (Adjusted OR 2.3, 95% CI: 1.06 – 4.94, P = 0.035) as compared to that with the oral route. Contrary, appropriate AST use among those with admitting diagnosis of pneumonia was 0.11 times less likely (Adjusted OR 0.11, 95% CI: 0.02 – 0.67, P = 0.016) compared to those with other diagnosis.

Presence of cardiovascular agents, anti-cancers and corticosteroids on patients' prescriptions were significantly associated with inappropriate AST use. Patients receiving cardiovascular agents among their medications were 0.69 times as likely (Adjusted OR 0.31, 95% CI: 0.16 – 0.67, P = 0.02) to have appropriate AST use compared to those with no cardiovascular agents.

Similarly, the adjusted odds ratios for having appropriate AST use among patients with corticosteroids and anti-cancers on their prescriptions was 80% (Adjusted OR 0.20, 95% CI: 0.08– 0.51, P = 0.001) and 86% (Adjusted OR 0.14, 95% CI: 0.03 – 0.66, P = 0.012) less likely, respectively compared to those with none of the individual drugs on their prescriptions.

DISCUSSION

Very limited information on acid suppressive drugs use is available in Kenya. This study has characterized the use and appropriateness of acid suppressant therapies among the patients admitted to the medical wards of the largest referral hospital in East and Central Africa. A prevalence of

55.9% of AST use in the medical wards was revealed, with PPIs predominantly (95.2%) used. AST was found justified in 94 (34.6%) patients which included stress ulcer prophylaxis, 55 (58.5%) and non-SUP approved indications 39(41.5%). Unjustified use was found in 65.4% of the patients on AST.

Indeed, these finding indicates overuse of AS drug just as demonstrated by studies across the globe. These findings are in concordance with a study in Qatar which found a prevalence of 53% with unjustified use in 64% of the patients (7). Nardino *et al.* in the USA had similar findings of 54% of patients on AST of which 65% was unjustified (15) with Memom *et al.* in Pakistan also reporting unjustified use in 65.3% of patients on AST (8). However, Sheikh-Taha *et al.* in Lebanon reported a much higher extent of AST use of 85%, with unjustified use in 33.4% of these patients, but found PPIs use in 95.4% of these patients on AST (2), a finding similar to ours.

Use of AST for prevention purposes has progressively surpassed use for treatment of approved indications (9). Overuse of these therapy is highly attributed to SUP indication. There exists guidelines for SUP in critically ill patients but same is lacking for non-critically ill patients. Some clinical conditions in and medications utilized on medical wards predispose patients to gastrointestinal bleeding, hence the need for prescribers to offer AST. However with no specific guidelines for these patients, these therapy end up to patients with low risk of gastrointestinal bleeding (10) despite a cohort study in the USA having demonstrated that there is minimal nosocomial gastrointestinal bleeding of 0.27% among non- critically ill patients to necessitate rampant AST(16). High use of PPIs group of acid suppressants observed could be as a result of PPIs superior efficacy in some gastric acid related conditions over H2RAs (17). Availability on our markets of

affordable generics of PPIs, particularly, omeprazole could also be a contributor.

On multivariate analysis, a diagnosis of pneumonia together with use of cardiovascular agents, corticosteroids and anticancer agents were found predictive of inappropriate AST. However, use of the intravenous (IV) route of AS drug administration was associated with appropriate AST use. Nardino *et al.* in the USA reported pneumonia as the leading reason for admission in patients receiving AST (15) though not predictive to appropriateness of AST use. However, respiratory failure leading to need for mechanical ventilation is a potential predictor for stress ulcers in critically ill patients (5). Perhaps the clinical presentation of dyspnea in pneumonia may require mechanical ventilation and hence reason for clinicians prescribing AST among these patients.

Craig *et al.* in the United Kingdom reported as association between of IV PPI prescriptions and appropriate use, particularly when initiated for non-UGIB indications (18). Our study reported UGIB as the leading non-SUP indication for AST and the IV route of administering AS drugs was utilized majorly for these indication and not for SUP. However, our study did not consider route of administration or dosage of AS drug to define appropriateness of AST but only the indication.

A descriptive observational study conducted in Colombia found an association of antihypertensive drugs use and inappropriateness of AST use (13). Anti-hypertensives are also largely used for cardiovascular disorders. However, the same study had a contradicting finding on corticosteroids, which was found associated with appropriate AST use. Our finding of corticosteroids associated with inappropriate use can however be explained by Nardino *et al.* who reported that SUP prophylaxis issued to patients on low dose

steroids hence inappropriate (15). No study has directly pointed on the use of corticosteroids and anti-cancers with appropriateness of AST, however Tomizawa et al. in a Japan demonstrated that immunosuppressive agents were associated with peptic ulcer bleeding (19). Patients on the medical wards usually present with various comorbidities related to or sometimes not related to the admitting diagnosis. These necessitates use of a ray of medications which may informs the prescribers' decision on AST.

The main concern is the high unjustified used of AST which has been shown to significantly burden the costs of health care to patients with minimal benefit as reported by Heidelbaugh *et al* (1). Though prescribers view AST as harmless, no medication goes without risks. AS drugs have been associated with increased colonization of the upper gastrointestinal tract with potentially pathogenic organisms and imbalance of the normal flora predisposing patients to hospital acquired pneumonia (20) and *Clostridium difficile* related diarrhea (21) following use of AST. Drug-drug interactions involving acid suppressant medications should not be ignored as drug toxicities or treatment failures reported could be a result of AST use. Prescribers' and pharmacist's attention is paramount when using these agents.

This study has some limitation arising from the fact that, AST use is highly variable in that different countries have specific guidelines and different institutions have specific practices. Furthermore, the study population is limited to medical inpatients. The study also utilized medical records with which some parameters could not be verified.

CONCLUSION AND RECOMMENDATIONS

There is high prevalence of AST, specifically PPI use in the medical wards of Kenyatta National Hospital and most of them are unjustified. The hospital needs to develop and implement guidelines regarding AST use in the non-critically ill patients especially in the medical wards settings. Further studies should also be conducted in several facilities of different levels, different study populations including surgical inpatients and outpatients in general. In addition, studies should be done to assess the prescriber factors that are associated with inappropriateness of AST use.

REFERENCES

1. Heidelbaugh JJ, Inadomi JM. Magnitude and Economic Impact of Inappropriate Use of Stress Ulcer Prophylaxis in Non-ICU Hospitalized Patients. *Am J Gastroenterol*. 2006;101(10):2200–5.
2. Sheikh-Taha M, Alaeddine S, Nassif J. Use of acid suppressive therapy in hospitalized non-critically ill patients. *World J Gastrointest Pharmacol Ther*. 2012;3(6):93–6.
3. Provider Synergies. Histamine 2 -Receptor Antagonist Review [Internet]. Ohio; 2010. p. 1–9. Available from: <https://www.oregon.gov/oha/pharmacy/therapeutics/docs/ps-2010-02-h2receptor-antagonist.pdf>
4. Blue Cross and Shield of Illions. Proton Pump Inhibitors Step Therapy Criteria. 2010. p. 1–8.
5. American Society of Health-System Pharmacists. ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998. *Am J Heal Syst Pharm*. 1999;56(4):347–79.
6. Singh A, Bodukam V, Saigal K, Bahl J, Wang Y, Hanlon A, et al. Identifying Risk Factors Associated with Inappropriate Use of Acid Suppressive Therapy at a Community Hospital. *Gastroenterol Res Pract*. 2016;2016:1–8.
7. Khudair IF, Sadik ND, Hanssens YI. Prescribing pattern of acid suppressive

- medications for medical inpatients in a teaching hospital in Qatar. *Saudi Med J*. 2009;30(1):125–9.
8. Memon A, Kumar D, Awaismemon M. Inappropriate use of acid suppression therapy in Internal Medicine wards of a tertiary care teaching Hospital. *IOSR J Dent Med Sci*. 2013;8(6):66–9.
9. Oh AL, Tan AG, Phan HS, Lee BC, Jumaat N, Chew SP, et al. Indication of acid suppression therapy and predictors for the prophylactic use of proton-pump inhibitors vs. histamine-2 receptor antagonists in a Malaysian tertiary hospital. *Pharm Pract (Granada)*. 2015;13(3):633–9.
10. Hong MT, Monye LC, Seifert CF. Acid Suppressive Therapy for Stress Ulcer Prophylaxis in Noncritically Ill Patients. *Ann Pharmacother*. 2015;49(9):1004–8.
11. Zeitoun A, Zeineddine M, Dimassi H. Stress ulcer prophylaxis guidelines: Are they being implemented in Lebanese health care centers? *World J Gastrointest Pharmacol Ther*. 2011;2(4):27–35.
12. Palkovic LB, Coley KC, Sokos DR. Factors associated with inappropriate inpatient prescribing of acid-suppressive therapy. *Int J Pharm Pract* 2009; 2009;17(1):73–5.
13. Jorgeab M-A, Alejandraa F, Daniela C, Felipea C, Andrésa G, Londoño M, et al. Prescribing patterns and economic costs of proton pump inhibitors in Colombia. *Colomb Med*. 2013;44(1):13–8.
14. James M S. The use of proton pump inhibitors in treating and preventing NSAID-induced mucosal damage. *Arthritis Res Ther*. 2013;15(3):S5.
15. Nardino R, Vender R, Herbert P. Overuse of acid-suppressive therapy in hospitalized patients. *Overuse of Acid-Suppressive Therapy in Hospitalized Patients*. *AJG*. 2000;95(11):3118–3122.
16. Herzig SJ, Rothberg MB, Feinbloom DB, Howell MD, Ho KKL, Ngo LH, et al. Risk Factors for Nosocomial Gastrointestinal Bleeding and Use of Acid-Suppressive Medication in Non-Critically Ill Patients. *J Intern Med*. 2012;28(5):683–90.
17. Wang WH, Huang JQ, Zheng GF, Xia HHX, Wong WM, Lam SK, et al. Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: A meta-analysis. *World J Gastroenterol*. 2005;11(26):4067–77.
18. Craig DGN, Thimappa R, Anand V, Sebastian S. Inappropriate utilization of intravenous proton pump inhibitors in hospital practice – a prospective study of the extent of the problem and predictive factors. *Q J Med*. 2010;103(5):327–35.
19. Tomizawa M, Shinozaki F, Hasegawa R, Shirai Y, Motoyoshi Y, Sugiyama T, et al. Immunosuppressive agents are associated with peptic ulcer bleeding. 2017;1927–31.
20. Herzig SJ. Acid-Suppressive Medication Use and the Risk for Hospital-Acquired Pneumonia. *Jama [Internet]*. 2009;301(20):2120. Available from: <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2009.722>
21. Ethan MA, Mitchell CB. Acid Suppression and the Risk of Clostridium difficile Infection. *J Pediatr*. 2014;163(3):627–30.