

# The Appropriate Use of Proton Pump Inhibitors in Adult Patients Admitted in the Intensive Care Unit of a Tertiary Hospital

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## Abstract

**Introduction:** Proton pump inhibitors (PPI) have been used as stress ulcer prophylaxis (SUP) in intensive care unit (ICU) patients due to their high risk for stress-related upper gastrointestinal (GI) bleeding. With its dramatic increase in prescription, studies have noted its misuse and associated complications. This study aimed to determine the appropriateness of the use of PPIs in adult patients in the ICU of Medical Center Manila (ManilaMed).

**Methods:** This eight-month study conducted a retrospective chart review, and analyzed through descriptive statistics using Stata 13. Out of 292 patients, 188 satisfied the inclusion and exclusion criteria. The indication of use of PPI was based on the American Society of Health-System Pharmacists (ASHP) Therapeutic Guidelines on SUP.

**Results:** The patients were mostly male, median age of 62 years, stay in the ICU of five days, overall hospital stay of 13 days, and 75% were admitted from the emergency room. About 58% of PPIs were prescribed in the intravenous route for an average of 10 days, 38% of which is prescribed by cardiology consultants. Of the 73% of patients prescribed

PPIs, most were septic and intubated for >48 hours, as well as being older and with longer overall hospital stay. Only 53.7% were prescribed appropriately; adverse outcomes included pneumonia, GI bleeding, anemia, renal failure, combined complications and overall mortality.

**Discussion:** The 46% inappropriate use of PPIs may indicate its routine use was common. The adverse outcomes, despite appropriate use, cannot be concluded as having causative effect owing to the nature of the study and given the possibility that these patients may have been sicker on admission hence prescribed the PPI.

**Conclusion:** Results indicated that PPI prescription in the ICU were mostly guidelines compliant. This paper recommends the development of ManilaMed's own strategies to minimize its inappropriate use, in turn allowing proper allocation of funds and maximizing medical treatment.

**Keywords:** appropriate use, proton pump inhibitors, adult patients, ICU

## Introduction

Over the last decade, the use of proton pump inhibitors (PPI) has been recommended in critically ill patients. Use of PPIs has dramatically increased in the last 30 years since its introduction. Besides being the most common gastrointestinal (GI) medication, it is one of the prescribed medications. The annual expenditure for one brand PPI (esomeprazole - nexium) in particular, is estimated to total to \$6.1 billion worldwide. According to unpublished reports of the most frequently the sales of the pharmacy of ManilaMed, PPIs ranked first in out-patient prescriptions, while it is ranked second or third for in-patient prescriptions. The use of the intravenous (IV) PPIs in the intensive care unit (ICU) setting

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for prophylaxis of stress related mucosal injury has been the subject of cost-effective analysis<sup>1</sup> in a tertiary hospital in Saudi Arabia, revealing the inappropriate use of acid suppressing agents during the study period was \$15,760, with a one-year estimated cost being \$63,000. To date there are no studies in the Philippines of PPI prescribing practice.

Proton pump inhibitors (PPIs) were first introduced into the international market in 1989 as potent gastric suppressing agent and since then their use has been popular in clinical practice.<sup>2</sup> This class of drugs is substituted benzimidazoles that irreversibly blocks the H<sup>+</sup>/K<sup>+</sup> ATPase enzyme of the gastric parietal cells in a dose-dependent manner. They have been established to be more potent than histamine H<sub>2</sub> receptor antagonists, as PPIs inhibit the final pathway involved in acid secretion. With prolonged use of the histamine H<sub>2</sub> receptor antagonists, tolerance develops, hence PPIs have become the drug of choice when potent inhibition of acid secretion is required.<sup>3</sup> PPI's are available in both oral and intravenous form. Currently in the Philippines there are six PPIs available, namely pantoprazole, lansoprazole, esomeprazole,

omeprazole, rebepirazole and dexlansoprazole. The first four of which are available in the IV form.

Patients admitted to the ICU comprise a special population in whom the highly stressful events leading to their admission cause different physiologic changes resulting in GI bleeding. The basic mechanism is focused on hypoperfusion of the mucosa in the upper GI tract. Along with ischemic tissue damage, hypoperfusion itself reduces the protective mechanisms (including mucus, phospholipids, bicarbonate, trefoil factor family peptides and heat shock proteins) that exist in a health stomach. These changes may result in gastric erosions and may progress to ulceration and bleeding.<sup>4</sup>

The landmark study by Cook et al.,<sup>5</sup> of 2252 patients, noted that the risk factors associated with clinically important GI bleeding in the ICU were respiratory failure, coagulopathy, sepsis, hepatic failure, renal failure, enteral feeding and glucocorticoid administration. However, on multiple regression analysis only two risk factors were significant predictors of stress induced bleeding: respiratory failure and coagulopathy. The frequency of bleeding was 3.7% if one or both of these risk factors were present, and only 0.1% if neither factor was present.

The estimates of overt GI bleeding range from 1.5-8.5% among ICU patients, but may be as high as 15% in those not given stress ulcer prophylaxis (SUP), hence the development of randomized control trials and guideline recommendations (ASHP Therapeutic Guidelines on SUP<sup>6</sup> and Update on SUP in critically ill patients<sup>7</sup>) for SUP in the critically ill patients who are at high risk of GI bleeding namely:

- Mechanical ventilation for >48 hours
- Coagulopathy
- History of GI ulceration or bleeding within the past year
- Traumatic brain injury, traumatic spinal injury, or burn injury
- Two or more of the following minor criteria: sepsis, an ICU stay of more than one week, occult GI bleeding for more than or equal to six days, or glucocorticoid therapy (>250 mg hydrocortisone or the equivalent)

The Danish Society of Anesthesiology and Intensive Care Medicine developed a guideline for SUP in 2014 for the ICU based on systematically searched literature on PubMed and Cochrane Library. They concluded that routine SUP for adult critically ill patients in the ICU is not recommended outside of randomized control trials. No strong evidence supports recommendations for subpopulations in the ICU such as septic shock, burn, trauma, cardiothoracic or enterally fed patients. However, in situations where SUP is indicated in individual patients, PPIs are suggested over histamine 2 receptor antagonists.<sup>8</sup>

In general, PPIs are well tolerated with a reported adverse event rate of one to three percent. The untoward

events include headaches, nausea, abdominal pain, constipation, flatulence, diarrhea, rash, and dizziness. Long term and short term trials have reported a similar tolerability profile.<sup>9-12</sup> Freedberg et al. reviewed the class effect of PPIs, which included kidney disease, dementia, bone fracture, myocardial infarction, small intestinal bacterial overgrowth, spontaneous bacterial peritonitis, clostridium difficile infection, pneumonia, micronutrient deficiencies, and GI malignancies to name a few. At present, the quality of the evidence underlying these associations are low.<sup>13</sup>

Another study summarized the biological explanations proposed for the adverse outcomes linked to PPI. The decrease in gastric acidity leading to reduced Vitamin B12 absorption has been proposed to cause dementia, anemia and bone fractures. This mechanism could alter the intestinal flora predisposing patients to clostridium difficile infection. It may also lead to growth of aerobic bacteria in the stomach which may proceed to microaspiration and colonization in the lungs. PPIs may compete with the hepatic enzyme cytochrome P450 2C19 isoenzyme inhibiting activation of clopidogrel or increase asymmetric dimethylarginine leading to reduced endothelial nitrous oxide resulting in thrombosis and hence acute coronary syndrome. The mechanism for acute and chronic kidney disease revolved around the idiosyncratic effect of the drug culminating to recurrent acute interstitial nephritis.<sup>14</sup>

The FDA has listed a number of indications for PPIs which is a wide range of GI conditions making clinicians more inclined to prescribe them. Since their introduction in the 1990's, the use of PPIs has increased by 456%,<sup>15</sup> making them one of the most prescribed medications in the world. Owing to their favorable safety profile, this has led to their overuse or over prescription. Published reports noted total cost expenditure worldwide, estimated at over US\$11 billion annually, with British data estimating £2billion spent unnecessarily worldwide.<sup>16</sup>

A study in the US reviewing the patterns and predictors in the PPI prescription in non-academic and academic institutions revealed that 50% of prescriptions from the academic institutions were guidelines compliant compared to the 29% from the non-academic hospitals. In the academic hospitals, the most common indication for the compliant prescription is dyspepsia (33%) while that for non-academic hospitals is SUP (35%). GI prophylaxis is also the most common indication for PPI in non-compliant prescriptions on both institutions. It was concluded that quality and safety improvement interventions are needed to reduce the excess cost and potential harm from PPI.<sup>15</sup>

Alsultan et al. revealed that from a total of 225 patient receiving IV PPI, in the non-ICU setting, 71.4% received IV PPI inappropriately as SUP; while 28.3% who received it

appropriately for PUD and UGIB. In the ICU setting on the other hand, a higher percentage of patients (80.2%) received PPI appropriately. Among the appropriate IV PPI recipients, 20.8% had endoscopically proven UGIB, 11.5% had PUD, and 19.8% were on mechanical ventilator requiring SUP.<sup>1</sup>

The results of this study can serve as a benchmark in identifying the prescription pattern of PPI in the ICU setting as no local data has yet been published. The widespread use of PPI with associated inappropriate use justifies the need for local guidelines to guide medical practitioners in their use. Other medical institutions can also apply the results of the study to identify areas of improvement of their standard of care.

### Methods

This was a retrospective study conducted at a tertiary hospital in Manila, Philippines. This 250-bed tertiary teaching medical center has an average census of 400 patients annually in the ICU. Medical care is supervised by attending physicians and delivered by the medical and nursing staff. Data was extracted from the chart records using a structured instrument. A concise listing of the demographic characteristics and clinical diagnoses of the patients was done along with the appropriate usage of PPIs as predefined based on materials from available literature and guidelines. The patient must satisfy one major criterion or two or more minor criterion:

Major criteria

1. Mechanical ventilation for >48 hours
2. Coagulopathy
3. History of GI ulceration or bleeding within the past year
4. Traumatic brain injury, traumatic spinal injury, or burn injury

Minor criteria

1. Sepsis
2. ICU stay of more than one week

3. Occult GI bleeding for more than or equal to 6 days
4. Glucocorticoid therapy (>250 mg hydrocortisone or the equivalent)

Inclusion criteria

1. All patients admitted at the ICU between January to August 2017
2. Aged 18 and above

Exclusion criteria

1. Patients admitted for post-operative monitoring
2. Patients admitted for <24 hours
3. Patients admitted who have undergone esophago-gastroectomy
4. Patients admitted who have contraindication to the use of PPIs
5. Patients admitted who have GI malignancy

All patients who were admitted at the ICU within the said timeline, were included unless they satisfied one or more of the exclusion criteria. Selecting all the patients within the prescribed period of observation was done to ensure the representativeness of the sample and reduce the possibility of selection bias – since there is no current data available on the use PPIs among these patients in the country. (Figure 1)

Once the investigator has extracted the data, all the information was manually entered into an electronic spreadsheet file with subsequent data processing and analysis using the statistical software, Stata 13.

Descriptive statistics such as mean and standard deviation for continuous variables; or frequency and percentage were used for the categorical data to provide an overview of the study population. A Chi-square test of association or independent t-test, whichever is applicable, were done to determine if there is a significant difference in the baseline clinico-demographic variables between the study groups.

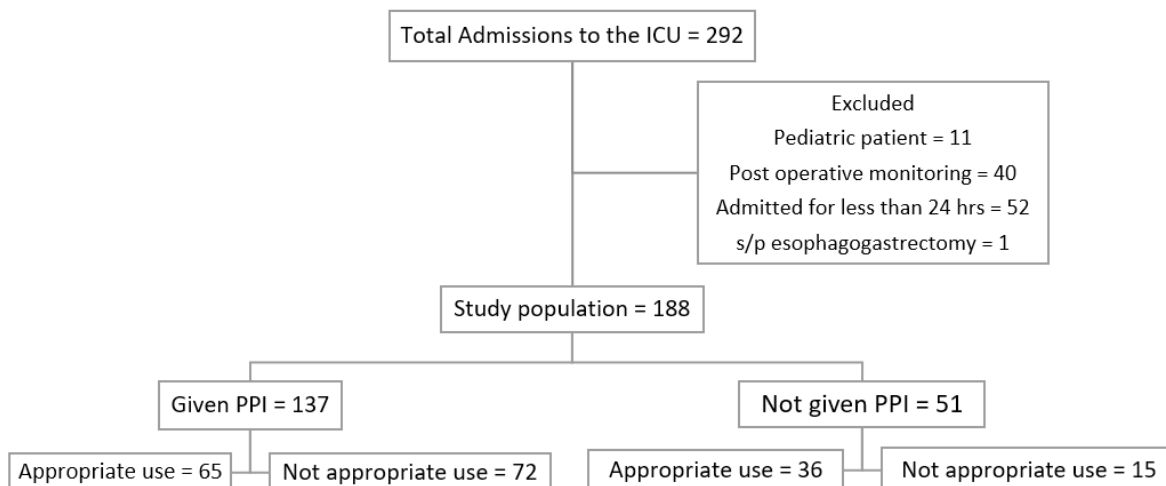


Figure 1. Flowchart of the study population

Proportion per categories of the qualitative variable such as presence of other comorbidities, indicative use of PPI, presence of select outcomes, etc. were also described. Point and interval estimates of the proportion (or relative risk) of the outcomes among the study groups were also computed. The level of significance for all sets of analysis was set at  $p$ -value  $<0.05$  using two-tailed comparisons. The significance levels were adjusted for multiple comparisons performed, if applicable.

The patients were identified using control numbers that were only accessible to the researcher. The identities of the physicians involved were likewise kept confidential. Also, the study conformed to the Data Privacy Act of 2012 (Republic Act No. 10173) and the principles in the Declaration of Helsinki, and in accordance to this, the paper was subjected to approval by the ManilaMed Ethics Review Committee. The collected data was eventually shredded and cross shredded after the completion of the data analysis.

## Results

From the overall census of the ICU of 292 from January to August 2017, 188 admissions met the inclusion/exclusion criteria.

The baseline characteristics of the study group are listed in Table I. The patients averaged in age of 62 years, with more males (55.3%). They had an average ICU stay of five

days and an average hospital stay of 13 days. Seventy five percent of the patients were admitted from the emergency room with significantly higher proportion prescribed with PPIs. Conversely, there is a significantly higher proportion of patients not given PPI who were admitted from a regular room. Almost 41% of the patients admitted on PPIs were septic followed by 25% being intubated for more than 48 hours.

The prevalence of PPIs use was 72.9% establishing that almost  $\frac{3}{4}$  of the patients were either prescribed or indicated with PPIs within the confinement period. The patients who were given PPIs were older and stayed in the hospital longer, based on the independent  $t$ -test performed. Majority (58%) of the PPIs were given as IV form for an average of 10 days.

More than one third of the PPI prescriptions were that from the cardiology consultants, then by the internal medicine (IM) residents followed by the neurology consultants. (Figure 2)

Table III revealed that patients who were prescribed PPIs appropriately had longer ICU and overall hospital stay. There was also a significant number of these patients who were intubated, with coagulopathy, history of GI bleeding, sepsis, more than seven days stay in the ICU and on glucocorticoid therapy.

For the patients who were not given PPIs, there was significantly more patients appropriately withheld from PPI who were on glucocorticoid therapy with a  $p$ -value of 0.02.

**Table I. Clinical characteristics of the study population (N =188)**

Characteristics	Overall (N=188)	with PPI (n=137)	without PPI (n=51)	$p$ -value
<b>Socio-demographic data</b>				
Age in years (SD)	62 ±17.6	63±17.5	57 ±16.7	0.04*
<b>Sex of the patient</b>				
Female	84 (44.7%)	65 (47.4%)	19 (37.3%)	0.21
Male	104 (55.3%)	72 (52.6%)	32 (62.7%)	
<b>Institutional characteristics</b>				
Duration in the ICU in days	5 ±10.8	6±11.3	5 ± 7.4	0.17
Duration in the hospital in days	13±15.1	14±15.8	12 ± 12.9	0.01*
Admitted direct to ICU	10 (5.3%)	7 (5.1%)	3 (5.9%)	0.42
Admitted from emergency room	142 (75.5%)	109 (79.6%)	33 (64.7%)	0.02*
Admitted to from regular room	36 (19.2%)	21 (15.3%)	15 (29.4%)	0.01*
<b>Clinical characteristics</b>				
Intubated for >48 hours	48 (25.5%)	38 (27.7%)	10 (19.6%)	0.23
with coagulopathy	23 (12.2%)	18 (13.1%)	5 (9.8%)	0.11
History of GI ulceration	2 (1.1%)	1 (0.7%)	1 (2.0%)	0.55
History of GI bleeding	4 (2.1%)	4 (2.9%)	0 (0%)	0.52
Traumatic brain injury	4 (2.1%)	4 (2.9%)	0 (0%)	0.52
with sepsis	77 (41.0%)	54 (39.4%)	23 (45.1%)	0.30
>7 days at the ICU	25 (13.3%)	21(15.3%)	4 (7.8%)	0.13
With occult GI bleeding	2 (1.1%)	0 (0%)	2 (3.9%)	0.55
On glucocorticoid therapy	33 (17.6%)	20 (14.6%)	13 (25.5%)	0.56
<b>Pattern of prescription</b>				
Intravenous route	80 (58.4%)	-	-	-
Oral route	57 (41.6%)	-	-	-
Duration of PPI use (days)	10 ± 11.1	-	-	-

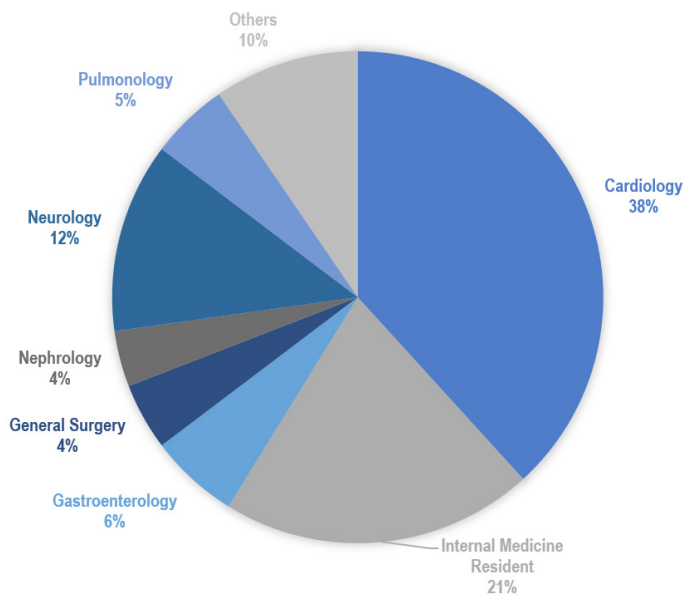


Figure 2. Service Prescribing the PPI

According to Table II, there was a significant number of patients appropriately prescribed with PPI who had pneumonia, GI bleeding, anemia, renal failure, combined complications and overall mortality.

### Discussion

The study revealed that the patients in the ICU averaged an age of 62 years, mostly (55%) male, had an average ICU confinement of five days and overall hospital confinement of 13 days. There was significantly more patients prescribed PPI who were admitted from the ER. Most (58%) of the PPIs were given as IV route for an average of 10 days. Thirty eight percent of the patients were prescribed with PPI by the cardiology consultants. This may not necessarily correlate to a certain set of knowledge in terms of the use of the PPI by a certain service, but rather the patient load. A significant number (72.9%) of ICU patients were prescribed PPIs with varied indications most of which were due to sepsis and intubation.

Table II. Clinical characteristics of the study population based on indication of PPI (n=188)

Characteristics	Overall (N=188)	with PPI (n=137)	With indication (n=65)	Without indication (n=72)	p-value	without PPI (n=51)	Without Indication (n=36)	With indication (n=15)	p-value
Age (years)	62 ± 17.6	63 ± 17.5	65.1 ± 18.3	62.3 ± 17.1	0.18	57 ± 16.7	58 ± 17.0	56 ± 16.4	0.37
Sex of the patient									
Female	84 (44.7%)	65 (47.4%)	35 (53.8%)	30 (41.7%)	2.03	19 (37.3%)	15 (41.7%)	4 (26.7%)	1.02
Male	104 (55.3%)	72 (52.6%)	30 (46.2%)	42 (58.3%)		32 (62.7%)	21 (58.3%)	11 (73.3%)	
ICU duration in days	5 ± 10.8	6 ± 11.3	9.6 ± 15.7	3.9 ± 3.2	0.002*	5 ± 7.4	6 ± 8.8	4 ± 1.4	0.19
Hospital duration in days	13 ± 15.1	14 ± 15.8	19.8 ± 19.5	10.0 ± 6.9	0.00005*	12 ± 12.9	11 ± 14.3	13 ± 9.4	0.33
Intubated for >48 hours	48 (25.5%)	38 (27.7%)	38 (58.5%)	0 (0%)	0.00001*	10 (19.6%)	7 (19.4%)	3 (20%)	0.48
Coagulopathy	23 (12.2%)	18 (13.1%)	17 (26.2%)	1 (1.4%)	0.00001*	5 (9.8%)	5 (13.9%)	0 (0%)	0.07
History of GI ulceration	2 (1.1%)	1 (0.7%)	1 (1.5%)	0 (0%)	0.15	1 (2.0%)	0 (0%)	1 (6.7%)	0.06
History of GI bleeding	4 (2.1%)	4 (2.9%)	4 (6.2%)	0 (0%)	0.02*	0 (0%)	-	-	-
Traumatic brain injury	4 (2.1%)	4 (2.9%)	3 (4.6%)	1 (1.4%)	0.13	0 (0%)	-	-	-
with sepsis	77 (41.0%)	54 (39.4%)	37 (56.9%)	17 (23.6%)	0.00002*	23 (45.1%)	16 (44.4%)	7 (46.7%)	0.44
>7 days at the ICU	25 (13.3%)	21 (15.3%)	18 (27.7%)	3 (4.2%)	0.00005*	4 (7.8%)	4 (11.1%)	0 (0%)	0.09
with occult GI bleeding	2 (1.1%)	0 (0%)	-	-	-	2 (3.9%)	2 (5.6%)	0 (0%)	0.18
Glucocorticoid therapy	33 (17.6%)	20 (14.6%)	17 (26.2%)	3 (4.2%)	0.0001*	13 (25.5%)	12 (33.3%)	1 (6.7%)	0.02*

Table III. Adverse outcomes and presence of PPI in the study population (n=188)

Adverse outcomes	Overall events (N=188)	with PPI (n=137)		without PPI (n=51)		RR (95% CI)	p-value
		With indication (n=65)	Without indication (n=72)	With indication (n=15)	Without indication (n=36)		
Pneumonia (hospital and ventilator-acquired)	39 (20.7%)	24 (36.9%)	10 (13.9%)	2 (13.3%)	3 (8.3%)	1.94 (1.05-3.59)	0.04*
Electrolyte imbalance	6 (6.8%)	4 (6.2%)	2 (2.8%)	0	0	1.72 (0.32-9.18)	0.50
Cerebrovascular accident	2 (1.1%)	1 (1.5%)	0	0	1 (2.8%)	4.31 (0.21-88.66)	0.34
Gastrointestinal (GI) bleeding	27 (14.4%)	18 (27.7%)	0	1 (6.7%)	8 (22.2%)	22.40 (3.10-161.67)	0.002*
Significant GI bleeding	18 (9.6%)	12 (18.5%)	0	1 (6.7%)	5 (13.9%)	4.31 (0.51-36.13)	0.17
C. difficile infection	1 (0.5%)	1 (1.5%)	0	0	0	2.58 (0.10-62.73)	0.56
Anemia	67 (35.6%)	39 (60%)	14 (19.4%)	5 (33.3%)	9 (25%)	2.18 (1.39-3.40)	0.001*
Hepatic encephalopathy	1 (0.5%)	1 (1.5%)	0	0	0	2.58 (0.10-62.73)	0.59
Renal failure	17 (9.0%)	12 (18.5%)	2 (2.8%)	0	3 (8.3%)	6.46 (1.51-27.46)	0.01*
Complications (combined)	48 (25.5%)	33 (50.8%)	7 (9.7%)	2 (13.3%)	6 (16.7%)	3.73 (1.91-7.26)	0.0001*
Mortality	56 (29.8%)	36 (55.4%)	8 (11.1%)	4 (26.7%)	8 (22.2%)	3.15 (1.79-5.59)	0.0001*

The use of PPIs in ManilaMed was mostly guidelines compliant (53.7%), but is below that compared to our counterpart in Saudi Arabia<sup>1</sup>, who were 80.2% compliant. This may suggest that the routine or non-indicated use of PPIs was common in the management. Hence, there is a need to review and re-assess the guidelines and practice of using such agents among intensive care patients. Critically ill patients in the ICU are at risk for clinically important bleeding, hence guidelines<sup>6,7</sup> have been formulated to use PPIs prophylactically. The symptoms for severe illness in the elderly subset of patients may take an atypical form such that medical attention is delayed. So, when they are admitted, they may already have organ compromise leading to intubation, use of inotropes etc. The patients who were prescribed PPI appropriately had significantly higher adverse outcomes including the following: GI bleeding, anemia, renal failure, combined complications and overall mortality. The above adverse outcomes, despite appropriate use, cannot be concluded as having direct relationship or causative effect owing to the nature of the study as well on the fact that, these patients may have been sicker on admission hence prescribed the PPI. Although the evidence pertaining to the potential complications for PPIs is weak, as noted by Freedberg et al.,<sup>13</sup> what is undeniable is the economic burden imposed upon the patients and their family when the drug is given without a clear indication. The 87 patients who were prescribed PPIs inappropriately, was done so for an average of 10 days, most of whom were prescribed IV pantoprazole, and would have cost Php 1,305,000.00 during the study period. These funds could have been better allocated to other medications or procedures that the patient would require.

## Conclusion

The use of proton pump inhibitors in the setting critically ill adults in this institution, was mostly appropriate. But on the other end of the spectrum, the percentage of inappropriate use (~46%) should not be overlooked. Therefore, we suggest that Manilamed should develop its own strategies to minimize the inappropriate use of PPIs and develop policies to restrict its use especially in the ICU setting, without compromising patient care. These policies include the use of oral versus IV PPIs, duration of the use and step-down strategies or deprescribing strategies that are now being implemented in our western contemporaries. Accordingly, further research on the pattern of use of PPIs is recommended as per the local setting; using a prospective method involving more medical institutions as well as an extended period to time to attain a better grasp on the issue at hand.

As this is a chart review, the short comings of the study lie in the methodology itself, as such, there is an inability to establish true cause and effect relationships. Accordingly, any complications or benefits incurred by each

subpopulation cannot be concluded as contributory. The quality of information gathered cannot be assured since the investigators relied on individuals not associated with the study for the data collection, therefore there is a risk for incomplete data such as characteristics of the patients that would have otherwise conferred indications for SUP.

**Disclosure:** None to declare

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