EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 8
12-23
Year: 2018

PREDICTORS OF INAPPROPRIATE USE OF PROTON PUMP INHIBITORS IN CHILDREN AT MAKASSED GENERAL HOSPITAL IN LEBANON

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Article Received on 22/05/2018 **Article Revised on 11/06/2018** **Article Accepted on 02/07/2018**

ABSTRACT

Introduction: There are growing concerns that the use of proton pump inhibitors (PPIs) may be inappropriate in instances that do not conform to evidence-based indications. This study aimed to investigate the frequency, indications, appropriateness and predictors of PPIs use in hospitalized pediatric patients. **Methods:** All inpatients aged between 0 and 17 years and given any form of proton pump inhibitors during their hospitalization in the pediatric floor or the intensive care units in Makassed General Hospital between January 1, 2009 and December 31, 2014 were documented. Indications for maintaining these patients on PPIs were obtained from the medical records, which were then recorded and cross-referenced against a list of accepted indications adapted from the US Food and Drug Administration (FDA)-approved list. **Results:** Of the 621 inpatients using PPIs, only 10 (1.6 %) fulfilled the FDA-approved indications, while the majority (n =464, 74.7 %) did not, 147 (23.5 %) had borderline indications based on guidelines other than that of FDA. Logistic regression showed that the highly statistically significant variables were the following: poor weight gain, Clo test, PH metry, and hospitalization. Poor weight gain and those who did PH metry during hospitalization were among the predictors of appropriate PPI use. With respect to poor weight gain, the odds ratio = 0.239, 95 % CI: 0.143 -0.399, and P value< 0.0001. As for PH metry, odds ratio: 0.046, 95 % CI: [0.016-0.135], P value < 0.0001. While inappropriate use of PPIs was 10 times higher in patients who were admitted to pediatrics floor, and 2 times higher in patients who did Clo test (odds ratio were shown to be 10.721 and 2.126 respectively, and P values < 0.0001 and 0.007 respectively). **Conclusion:** Although the use of PPIs is prevalent in hospitals, less than half of the hospitalized patients using PPIs in our study had evidence-based indications that supported such use.

KEYWORDS: Proton Pump Inhibitors; Pediatric patients; indications.

INTRODUCTION

One class of medications that has enjoyed steady popularity is proton pump inhibitors (PPIs), which appear near the top of many lists of the most commonly prescribed medications, with annual sales worldwide that have surpassed US $25 billion.[1]

It is well known that they are the most potent medications currently available to reduce gastric acid secretion. The prescription of PPIs without clear indications has been frequently observed in many countries in hospitals and primary care. Reported rates of non-indicated prescriptions on general medical wards range from 40 to 81%, while inadequate acid-suppressive medication is often continued after discharge for long time.[2-5]

The FDA-approved indications for use of PPIs in pediatric patients are limited. They include the short term treatment of symptomatic GERD, and healing of erosive esophagitis. Only rabeprazole is FDA approved for the long term treatment of GERD between ages of 1 and 11 years.[6, 7]

No PPI is approved for use below the age of 1 year, nevertheless many prescriptions are written in this age group. A study was done in the USA to determine the PPI usage rates among newborns and Infants between 2003 and2008 in both the inpatient and outpatient settings. Results showed that PPIs were prescribed for approximately 5000 newborns (0.13%) and 15,000 infants (2.65%) each year in the hospital setting and 1.6% of newborns and infants, as a group in outpatient setting.[8]

Another study was done in Europe to evaluate the implementation of the 2009 North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition-European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines; concerning

gastroesophageal reflux. Results showed that the overall rate of pediatricians overprescribing PPIs was 82%.[9]

Long term treatment with PPI is associated with many side effects. The most common adverse reactions seen in pediatric patients are headache, diarrhea, constipation, and nausea. The use of PPIs has been associated with drug interactions, Clostridium difficile-associated diarrhea and hypomagnesemia.[10, 11]

Chronic acid suppression can minimize the effectiveness of any medication requiring an acidic environment for absorption. Examples are ampicillin esters, digoxin, atazanavir, ketoconazole, and iron salts.[10, 11]

There is also a risk of adverse drug interactions between PPIs and other medications that are metabolized via the cytochrome P450 system.[12]

Although non-evidence-based indications are common place, not much data is available on the inappropriate use of PPIs in the pediatric age group.

Given the paucity of such data, this study was conducted with the aim of identifying the prevalence, indications, appropriateness and predictors of PPI use in pediatric age group at Makassed General Hospital in Lebanon.

MATERIALS AND METHODS

To determine the appropriateness of indications for PPIs prescribed during hospital stay, we carried out a retrospective review of the medical records of pediatric patients aged between 0 and 17 years who were admitted to Makassed General Hospital between January 1, 2009 and December 31, 2014, and who received a specific kind of PPI during their hospital stay.

Patient data regarding age, gender, past medical history, medications taken at home, family history, presenting symptoms, duration of symptoms, physical examination findings, investigations performed, whether hospitalized in pediatric floor or intensive care unit (neonatal intensive care unit "NICU" or pediatric intensive care unit "PICU"), management instituted, and dosage of the specific PPI used, were extracted.

The indications for PPI use were reviewed based on definite documentation, suggestive symptoms, discharge summaries of patients, problem lists, investigations and documented management. These indications were then cross-referenced with those approved by the United States Food and Drug Administration (FDA), as shown in (Table 1).

Inpatients on PPIs were categorized into three groups, according to: (a) those who fulfilled the FDA indications; (b) those with borderline indications; and (c)those who had no clear indications. 'Borderline indications' was defined as indications that were not strictly FDA-approved but deemed acceptable based on guidelines other than the FDA, such as those from the UK National Institute for Health and Clinical Excellence (NICE), and European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), in addition to other evidence based studies (Table 1).

Patients were also classified into 3 groups according to age group; group A included those aged less than 1 year, group B included those aged between 1 and 5 years, and group C included those aged more than 5 years.

The FDA approved indications and the borderline indications were categorized in one group; named group of appropriate indications. This group along with the group of no clear indications was compared regarding the different variables mentioned above (including gender, family history, past medical history, presenting symptoms, investigations, etc...). This was done in order to identify the predictors of PPIs inappropriate use.

As this was a retrospective survey, no blinding was necessary. Approval was obtained from the respective institutional review board.

Statistical Analysis

Data were analyzed by SPSS version 19. Chi square test was used to assess differences between the groups. Logistic regression was done to determine the predictors of PPI use among children. Data were reported as frequency (%). P-value<0.05 was considered significant.

RESULTS

Among the 12,310 pediatric patients aged between 0 and 17 years, and admitted to Makassed General Hospital between January 1, 2009 and December 31, 2014, 621 (5 %) pediatric inpatients were prescribed PPIs.

There was a 2.5 fold increase in the usage of PPI from 10 % in the year 2009 to 26.6 % in the year 2014 (Figure 1). Of these 621 patients, 10 (1.6 %) fulfilled the FDA-approved indications, 147 (23.5 %) had borderline indications and 464 (74.7 %) had no clear indications for PPI use(Figure 2).

FDA approved indications included short term treatment of symptomatic GERD (80%), and healing of erosive esophagitis (20%) (Table 2).

Among all pediatric patients on PPIs with no clear indications, a group of indications classified as others was the main non-indication associated with inappropriate PPI use(34.5 %) (Table 2).

This others group includes: abdominal pain (26.4 %), abdominal pain associated with vomiting (15.6 %), upper GI bleeding (10.6 %), Nil per os (NPO)(10.6 %), vomiting (8.1 %), foreign body ingestion (8.1 %), asthma

(5.6 %), GERD diagnosed by upper GI (5%), rectal bleeding (4.4%), along with antiepileptic drugs (3.1 %), PUD without H pylori associated infection (1.3 %), Crohn's disease (0.6 %), hemoptysis(0.6 %)(Table 2).

Other subsequent reasons behind inappropriate PPI use were found to be as follows : (a) prevention of aspirin/non-steroidal anti-inflammatory drugs (NSAIDs)/steroid gastropathy(29.5 %); (b) empirical trial of PPIs in infants and young children with symptoms suggestive of GERD with no diagnostic evaluation(19.4 %); (c) gastritis diagnosed endoscopically with no associated H-pylori infection(8%); (d) ulcer prophylaxis for patients with malignancy (5.4 %); (e) H-pylori infection diagnosed by detected antibodies (IgG) against H-pylori in serum, or using urea breath test (2.6 %); (f) improving the absorption of pancrelipase/ pancreatin in patients with cystic fibrosis (0.6 %)(Table 2).

Borderline indications seen in our study included, in descending order of frequency : prophylaxis of GI haemorrhage in critically ill children (on mechanical ventilation, coagulopathy, shock,

neurosurgery, respiratory failure, sepsis) (61.9 %), infants (aged less than 1 year) diagnosed with GERD or esophagitis (13.6 %), H-pylori infection detected by biopsy based method in the absence of PUD (12.2 %), asthmatic patients in those with heart burn, with nocturnal asthma, and with steroid dependent or difficult to control asthma (5.4 %), infants or young children with overt regurgitation associated with flattered growth, feeding difficulties, or severe distress (3.4 %), empirical trial of PPIs for symptomatic treatment of heart burn and chest pain in older children and adolescents (2.1%), H-pylori positive PUD (1.4 %)(Table 2).

Patients in our sample group were classified into 3 groups according to age: group A) less than 1 year of age, group B) between the age of 1 and 5 years, and group C) more than 5 years of age.

Those in group A constituted 205 out of 621 patients (33 %), those in group B constituted 167 patients (27 %), and those in group C constituted 249 patients (40 %).

We compared the indications of PPIs use among the 3 age groups.

In those less than 1 year of age, 69.8 % had no clear indication for PPI use and 30.2 % had border line indications, and 0 % had FDA indications. With respect to patients between 1 and 5 years of age, 4.2 % had FDA approved indications for PPI use, 75.4 % had no clear indications, and 20.4 % had border line indications. As for patients more than 5 years of age, 1.2 % fulfilled the FDA approved indications, 78.3 % had no clear indications, and 20.5 % fulfilled the borderline indications with statistically significant P value (P value = 0.002)(Table 3).

In patients less than 1 year of age, no FDA approved indications were found (P value < 0.0001; highly statistically significant). Concerning the no clear indications; 49 % were due to symptoms suggestive of GERD with no appropriate investigations, 23.8 % were due to prevention of Aspirin/NSAIDs/steroids associated gastropathy, 21 % were due to the group classified as others. The remaining indications were; H-pylori infection diagnosed by IgG or IgA in serum, whole blood, or urine (2.7 %), gastritis diagnosed endoscopically with no associated H-pylori infection (2.1 %), improving the absorption of pancrelipase/pancreatin in patients with cystic fibrosis (1.4 %).The P value was highly statistically significant (< 0.0001) (Table 4).

In the same age group, border line indications constituted the following; prophylaxis of GI haemorrhage in critically ill patients being the most common (53.2 %), followed by infants diagnosed with GERD/erosive esophagitis (32.2 %), H-pylori detected by biopsy (6.5 %) and recurrent vomiting or regurgitation associated with flattered growth, feeding difficulty, or severe distress (6.5 %), and asthmatic patients with heart burn, nocturnal asthma, or difficult to control one (1.6 %) with high statistical significance (P value < 0.0001) (Table 4).

In patients aged between 1 and 5 years, out of the 4.2 % who had FDA approved indications, 85.7 % received PPI for short term treatment of symptomatic GERD, and 14.3 % for healing of erosive esophagitis with high statistical significance (P value < 0.0001) (Table 5).

Out of the 75.4 % with no clear indications, 37.3 % were due to the group classified as others (P value < 0.0001) (Table 5).

The most common border line indication in this age group was prophylaxis of GI haemorrhage in critically ill patients (76.5 %) (P value is highly statistically significant, P < 0.0001) (Table 5).

The most common FDA indication in patients more than 5 years of age is short term treatment of symptomatic GERD (66.7 %), followed by healing of erosive esophagitis (33.3 %) with high statistical significance (P value <0.0001) (Table 6).

The most common no clear indication in this age group is the group classified as others (42.6 %).(P value is highly statistically significant, P < 0.0001)(Table 6).

Moreover the most common border line indication in this age group is prophylaxis of GI haemorrhage in critically ill patients (62.7 %) (P value <0.0001) (Table 6).

Due to the small percentage of FDA approved indications, we subdivided the indications of PPI use into

2 groups; the appropriate indications (FDA indications plus borderline ones), and the no clear indications. We compared the 2 groups according to the following variables; gender, family history, past medical history, medications taken at home, presenting symptoms, investigations (including PH metry, Upper GI (UGI), endoscopy, biopsy 'histopathology and culture', Clo test, urea test, and H-pyloryIgG) ,hospitalization (intensive care versus pediatric floor), along with medications used with PPI. This was done to figure out the predictors of PPI inappropriate use in children admitted to our hospital (Tables 7, 8).

When comparing age group, gender, family history, past medical history, use of at home medications among the 2 groups of indications, we found no statistical significance. With P-values equal to 0.11, 0.02, 0.56, 0.461, and 0.963 respectively (Table 7).

When comparing presenting symptoms of patients with respect to the 2 groups of indications, we found statistical significance among patients presenting with abdominal pain (P value = 0.01), upper GI bleeding (P value = 0.014), difficulty in breathing (P value =0.009), chest pain (P value = 0.005), and heart burn (P value = 0.003) (Table 7).

Furthermore a high statistical significance was found among patients with failure to thrive and poor weight gain (P value < 0.0001) (Table 7).

Most patients presenting with abdominal pain belonged to the group of no clear indications (82.7 %), as well as upper GI bleeding (57.1 %), failure to thrive (58.7 %), and poor weight gain (54.2 %) (Table 7).

On the other hand all the patients presenting with heart burn (100%) and most of the patients presenting with chest pain (80 %) belonged to the appropriate indications group(Table 7).

When comparing patients' in hospital management among the two groups of indications, we noticed that there was no clear indication for PPI use in 83.6 % of patients admitted to pediatric floor (P value < 0.0001; highly significant), where as 57.9 % of patients admitted to intensive care unit lied in the group of appropriate indications (P value < 0.0001) (Table 8).

Regarding hospital medications; it was found that 100% of patients who were on aspirin and 96.3 % of patients who were on NSAIDs during hospitalization had no clear indications for PPI use, with statistically significant P value (P-value = 0.002 and 0.008 respectively) (Table 8).

With respect to the comparison of the investigations, done during hospitalization, among the two groups of indications; we found that only 22 patients out of 621 underwent PH metry (3.5 %).

Out of the 22 patients who did PH metry, 17 patients had GERD and took PPI under the category of appropriate indications, with statistically highly significant P value (P value < 0.0001) (Table 8).

Moreover, there was no statistical significance among patients undergoing H-pylori serum IgG, and urea breath test (P values = 0.695 and 0.648 respectively) (Table 8).

On the other hand patients undergoing upper GI (UGI) and H-pylori detected by gastric biopsy had high statistical significance (P value < 0.0001). Among the 44 patients who underwent UGI; 29 patients (65.9 %) had inappropriate use of PPI, with no diagnosis of GERD (P value < 0.0001; highly significant) (Table 8).

A total of 103 patients out of 621 underwent endoscopy (16.5 %), and erosive esophagitis was among the predictors of appropriate use of PPI with statistically significant P value (P value = 0.046) (Table 8).

It was noticed that 95.2 % of patients having diagnosed H-pylori infection by microscopic examination of gastric biopsy were categorized in the appropriate indications group, with highly significant P value (P value < 0.0001) (Table 8).

Whereas the 72 % of patients diagnosed to have gastritis by gastric biopsy were in the no clear indications group, but with no statistical significance (P value = 0.635).

Despite having negative Clo test, patients were prescribed PPI inappropriately. In fact10 patients out of the 15 patients who did the Clo test and had negative results for H-pylori were given PPI inappropriately (66.7 %) (P value = 0.042) (Table 8).

Logistic regression was done to specify more the variables that significantly affected the use of PPI in children.

Results showed that patients presenting with poor weight gain and those who did PH metry as an investigation during hospitalization were among the predictors of appropriate PPI use.

With respect to poor weight gain; odds ratio = 0.239, 95 % CI = [0.143 -0.399], and P-value < 0.0001 (Table 9) .

As for PH metry; odds ratio = 0.046, 95 % CI = [0.016-0.135], P-value < 0.0001 (Table 9).

While inappropriate use of PPIs was 10 times higher in patients who were admitted to pediatrics floor, and 2 times higher in patients who did Clo test (odds ratio were shown to be equal to 10.721 and 2.126 respectively, and P values < 0.0001 and 0.007 respectively) (Table 9).

The commonly prescribed PPIs used were omeprazole, esomeprazole, rabeprazole, and lanzoprazole, with

esomeprazolebeing the most commonly used drug (50%), followed by omeprazole (33%). The average dose of PPI used was 1 mg/kg/day. The route of administration was found to be mainly PO (64.6 %) (401 out of 621 patients), followed by the IV route (32.6 %) (203 out of 621 patients), and both routes in 2.7 % (17 patients).The average duration of treatment was 5 days, with minimum duration of 1 day and maximum of 90 days.

Table 1: FDA and Borderline Indications of PPI use

FDA approved indications for PPI use
1. Short term treatment of symptomatic GERD (4-8 weeks) in children aged 1-17 years.[7, 10]
2. Rabeprazole for long term treatment of GERD between the ages of 1 to 11 years.[7, 10]
3. Healing of erosive esophagitis in children aged 1-17 years.[7, 10]

Border line indications for PPI use
1. H-pylori positive pepticulcerdisease (PUD).[15]
2. H-pylori infection detected by biopsy based method in the absence of PUD.[15]
3. Children who are infected by H-pylori and whose first degree relative has gastric cancer.[15]
4. Empirical trial of PPIs for symptomatic treatment of heart burn and chest pain in older children and adolescents.[13]
5. Asthmatic patients in the following circumstances :
a) Those with heart burn
b) Those with nocturnal asthma
c) Steroid dependent or difficult to control asthma.[13]
6. Prophylaxis of GI haemorrhage in critically ill children (on mechanical ventilation, coagulopathy, shock, neurosurgery, respiratory failure, sepsis).[16]
7. Treatment of eosinophilic esophagitis in infants aged 1 to 11 months (esomeprazole).[17]
8. Pediatric patients with endoscopically diagnosed reflux esophagitis or non erosive reflux disease.[13]
9. Congenital chloride diarrhea.[18]
10. Infants/young children with overt regurgitation associated with flattered growth, feeding difficulties, or severe distress.[19]
11. Infants (< 1 year of age) diagnosed with symptomatic GERD (by PH metry or endoscopy) or erosive esophagitis [13].

Table 2: Specific indications for PPI use among Children.

Indications	**Frequency**
FDA approved indications	**10 (1.6%)**
Short term treatment of symptomatic GERD (1-17 years)	8 (80.0%)
Short term treatment of erosive esophagitis (1-17 years)	2 (20.0%)
Border line indications	**147 (23.5%)**
Prophylaxis of GI haemorrhage in critically ill children	91 (61.9%)
Infants diagnosed with symptomatic GERD or erosive esophagitis	20 (13.6%)
H-pylori detected by gastric biopsy	18 (12.2%)
Nocturnal asthma/steroid dependent asthma/associated with heart burn	8 (5.4%)
Vomiting associated with flattered growth, severe distress or feeding difficulty	5 (3.4%)
Symptoms of heart burn, chest pain in older children	3 (2.1%)
H-pylori positive PUD	2 (1.4 %)
No clear indication	**464 (74.7%)**
Prevention of aspirin/steroid/NSAIDs gastropathy	137 (29.5%)
Symptoms suggestive of GERD with no appropriate investigations	90 (19.4%)
Gastritis diagnosed endoscopically with no associated H-pylori infection	37 (8.0%)
Prophylaxis of gastric ulcer in malignancy	25 (5.4%)
H-pylori diagnosed by serum IgG	12 (2.6%)
Improving the absorption of pancreatic enzymes in cystic fibrosis	3 (0.6%)
Others	160 (34.5%)
Abdominal pain	42 (26.4%)
Abdominal pain and vomiting	25 (15.6%)
Upper GI bleeding (UGI)	17 (10.6%)
NPO	17 (10.6%)

Vomiting	13 (8.1%)
Ingestion of foreign body	13 (8.1%)
Asthma	9 (5.6%)
GERD diagnosed with UGI	8 (5.0%)
Rectal bleeding	7 (4.4%)
With antiepileptic drugs	5 (3.1%)
PUD without H-pylori	2 (1.3%)
Crohn's disease	1 (0.6%)
Hemoptysis	1 (0.6%)

Table 3: Comparison of patient's age group with respect to PPI indication

	FDA approved	No indication	Border line	P-value
Age group				
<1 year	0 (0%)	143 (69.8%)	62 (30.2%)	
1-5 years	7 (4.2%)	126 (75.4%)	34 (20.4%)	
>5 years	3 (1.2%)	195 (78.3%)	51 (20.5%)	0.002

Table 4: Specific indications of PPIuse for patients < 1 year old.

Specific indications for patients < 1 year	Frequency (%)	P-value
FDA approved	**0 (0%)**	<0.0001
No indication	**143(69.8%)**	
Symptoms suggestive of GERD with no appropriate investigations	70 (49.0%)	
Prevension of Aspirin/steroid gastropathy	34 (23.8%)	
Others	30 (21.0%)	
H-pylori infection detected by serum IgG	4 (2.7 %)	
Gastritis diagnosed endoscopically without H-pylori infection	3 (2.1%)	
Improving the absorption of pancreatic enzymes in cystic fibrosis	2 (1.4%)	
Border line	**62(30.2%)**	
Prophylaxis of GI haemorrhage in critically ill children	33 (53.2%)	
Infants diagnosed with symptomatic GERD or erosive esophagitis	20 (32.2%)	
H-pylori detected by biopsy	4 (6.5%)	
Vomiting associated with flattered growth, severe distress or feeding difficulty	4 (6.5%)	
Nocturnal asthma/steroid dependent asthma	1 (1.6%)	

Table 5: Specific indications of PPI use for patients between 1-5 years.

Specific indications for patients 1-5 years	Frequency (%)	P-value
FDA approved	**7(4.2%)**	<0.0001
Short term treatment of symptomatic GERD in children aged 1-17 years	6 (85.7%)	
Healing of erosive esophagitis	1 (14.3%)	
No indication	**126(75.4%)**	
Others	47 (37.3%)	
Prevention of aspirin/steroid/NSAIDs gastropathy	42 (33.3%)	
Symptoms suggestive of GERD with no appropriate diagnosis	14 (11.1%)	
Prophylaxis of ulcer in malignant patients	13 (10.3%)	
Gastritis diagnosed endoscopically with no H-pylori infection	8 (6.3%)	
H-pylori infection detected by serum IgG	2 (1.7%)	
Border line	**34(20.4%)**	
Prophylaxis of GI haemorrhage in critically ill children	26 (76.5%)	
Nocturnal asthma/steroid dependent asthma	5 (14.7%)	
H-pylori detected by gastric biopsy	2 (5.9%)	
Vomiting associated with flattered growth, severe distress or feeding difficulty	1 (2.9%)	

Table 6: Specific indications of PPI use for patients> 5 years old.

Specific indications for patients >5 years	Frequency (%)	P-value
FDA approved	**3(1.2%)**	
Short term treatment of symptomatic GERD	2 (66.7%)	
Healing of erosive esophagitis	1 (33.3%)	
No indication	**195(78.3%)**	
Prevention of aspirin/steroid/NSAIDs gastropathy	61 (31.3%)	

Others Gastritis diagnosed endoscopically with no associated H-pylori infection Prophylaxis of gastric ulcer with malignancy Symptoms suggestive of GERD with no appropriate diagnosis	83 (42.6 %) 21 (10.8%) 17 (8.7%) 6 (3.1%)	<0.0001
H-pylori diagnosed by serum IgG	6 (3.1%)	
Improving the pancreatic enzymes absorption in cystic fibrosis	1 (0.5%)	
Border line	**51(20.5%)**	
Prophylaxis of GI haemorrhage in critically ill patients H-pylori detected by gastric biopsy	32 (62.7%) 12 (23.5%)	
Symptoms of heart burn or chest pain in older children	3 (5.9%)	
Nocturnal asthma/steroid dependent asthma	2 (3.9%)	
PUD associated with H-pylori infection	2 (3.9%)	

Table 7: Comparison of patients' characteristics among the two groups of PPI indication

	FDA approved /Border line	No indication	P-value
Age group			
<1 year	62 (30.2%)	143 (69.8%)	
1-5 years	41 (24.6%)	126 (75.4%)	
>5 years	54 (21.7%)	195 (78.3%)	0.110
Gender			
Male	91 (29.4%)	219 (70.6%)	
Female	66 (21.2%)	245 (78.8%)	0.020
Family history			
Gastritis	0 (0%)	1 (100.0%)	0.560
Peptic ulcer	1 (33.3%)	2 (66.7%)	0.748
Past medical history			
None	90 (26.5%)	250 (73.5%)	
Disease needing PPI treatment	11 (30.6%)	25 (69.4%)	
Disease not needing PPI treatment	56 (22.9%)	189 (77.1%)	0.461
Home medication			
None	129 (25.5%)	377 (74.5%)	
PPI	8 (25.0%)	24 (75.0%)	0.963
Presenting symptoms			
Vomiting	61 (29.0%)	149 (71.0%)	0.123
Regurgitation	8 (17.4%)	38 (82.6%)	0.201
Abdominal pain	26 (17.3%)	124 (82.7%)	0.010
Upper GI bleeding	15 (42.9%)	20 (57.1%)	0.014
Dysphagia	0 (0%)	2 (100.0%)	0.410
Melena	2 (50.0%)	2 (50.0%)	0.254
Irritability	10 (21.7%)	36 (78.3%)	0.566
Diarrhea	25 (29.4%)	60 (70.6%)	0.346
Failure thrive	52 (41.3%)	74 (58.7%)	<0.0001
Poor weight gain	49 (45.8%)	58 (54.2%)	<0.0001
Electrolyte disturbance	12 (48.0%)	13 (52.0%)	0.008
Cough	47 (25.3%)	139 (74.7%)	0.996
Difficulty in breathing	57 (32.6%)	118 (67.4%)	0.009
Chest pain	4 (80.0%)	1 (20.0%)	0.005
Heart burn	3 (100.0%)	0 (0%)	0.003
Recurrent chest infection	5 (17.9%)	23 (82.1%)	0.355

Table 8: Comparison of patients' inhospital management among two groups of indication

	FDA approved /Border line	No indication	P-value
Hospitalization			
Intensive care	77 (57.9%)	56 (42.1%)	
Pediatric floor	80 (16.4%)	408 (83.6%)	<0.0001
Hospital medications used with PPI			
Aspirin	0 (0%)	27 (100.0%)	0.002
NSAID	1 (3.7%)	26 (96.3%)	0.008
Steroids	30 (21.0%)	113 (79.0%)	0.177
Antiplatelet	0 (0%)	1 (100.0%)	0.560
H-pylori IGg			
Negative	4 (25.0%)	12 (75.0%)	
Positive	4 (36.4%)	7 (63.6%)	
Not done	149 (25.1%)	445 (74.9%)	0.695
Urea test			
Negative	2 (33.3%)	4 (66.7%)	
Not done	155 (25.2%)	460 (74.8%)	0.648
PH metry	17 (77.3%)	5 (22.7%)	<0.0001
Gastroesophagal reflux	16 (100.0%)	0 (0%)	<0.0001
Upper GI	15 (34.1%)	29 (65.9%)	0.163
Gastroesophagal reflux	15 (100.0%)	0 (0%)	<0.0001
Endoscopy	31 (30.1%)	72 (69.9%)	0.218
Gastritis	21 (31.3%)	46 (68.7%)	0.707
Gastric ulcer	0 (0%)	1 (100.0%)	0.510
Duodenal ulcer	0 (0%)	1 (100.0%)	0.510
Reflux esophagitis	6 (42.9%)	8 (57.1%)	0.263
Erosive esophagitis	3 (75.0%)	1 (25.0%)	0.046
Clo test			
Negative	5 (33.3%)	10 (66.7%)	
Positive	7 (53.8%)	6 (46.2%)	
Not applicable	145 (24.5%)	448 (75.5%)	0.042
Biopsy done	25 (31.6%)	54 (68.4%)	0.164
H-pylori	20 (95.2%)	1 (4.8%)	<0.0001
Gastritis	7 (28.0%)	18 (72.0%)	0.635
H-pylori culture			
Negative	1 (100.0%)	0 (0%)	
Positive	0 (0%)	1 (100.0%)	
Not applicable	156 (25.2%)	463 (74.8%)	0.192

Table 9: Results of logistic regressions for predictors of PPI use in children

Selected parameters	Odds ratio	95 % CI	P-value
Poor weight gain	0.239	0.143-0.399	<0.0001
Hospitalization	10.721	6.709-17.132	<0.0001
PH metry	0.046	0.016-0.135	<0.0001
Clo test	2.126	1.231-3.669	0.007

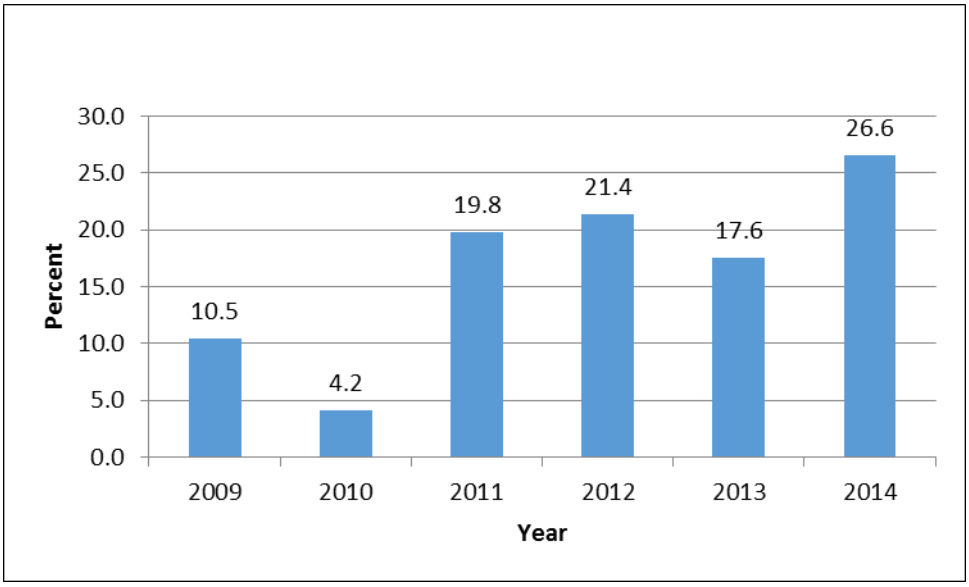

Figure 1: Trend of PPI use among hospitalized children between 2009 and 2014.

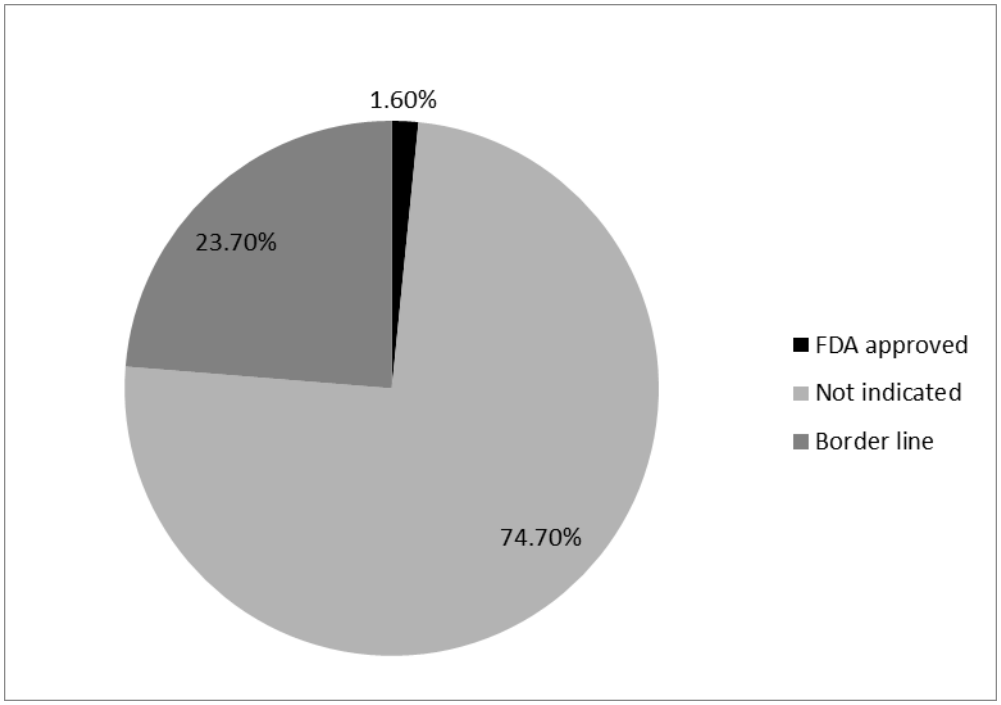

Figure 2: Indications of PPI use among hospitalized children.

DISCUSSION

There is a steady increase in PPI usage between the year of 2009 till the year of 2014, along with the increase of off label prescriptions of PPI, and this is obvious from the results of our study.

Our study shows that only 1.6 % of PPIs prescribed to our inpatients were indicated based on FDA-approved criteria and that the main inappropriate indications was a group classified as others (34.5 %); in which abdominal pain constitutes 26.4 %, followed by abdominal pain and vomiting (15.6 %), along with upper GI bleeding and nil per os (10.6 % each). Even after extending the definition of indications for PPI use to include other guidelines such as NICE and ESPGHAN/NASPGHAN and other evidence based studies, more than half of all PPI prescriptions (74.7 %) at our hospital were found to have no clear indications for their initiation or continued use. This finding was in accordance with previous Western studies done on adults which supported the notion that PPIs are one of the most overprescribed medicines in the medical world. For instance, a Pub Med literature search on 'proton pump inhibitor overuse' showed that the percentages for inappropriate PPI use ranged from 40% to 81%, with a mean of 63%.[2-4]

No study has been done to assess PPI appropriate use in pediatric age group. Though, a study has been done on the implementation of 2009 NASPGHAN-ESPGHAN Guidelines concerning GER/GERD. The latter study

showed that out of 567 European general pediatricians, only 1.8 % of them showed complete adherence to the guidelines, and the overall rate of pediatricians overprescribing PPI was 82 %.[8]

Although the FDA didn't yet approve the use of PPI in children less than 1 year, our study showed that 33% of our sample patients were in this age group (205/621), this is supported by a study done in US by Marta illueca et al, which determined PPI usage rates among newborns and infants in both the inpatient and outpatient settings. The study showed that PPIs were prescribed for approximately 5000 newborns (0.13%) and 15,000 infants (2.65%) each year in the hospital setting and 1.6% of newborns and infants, as a group, in the outpatient setting..[9]

In our study the use of PPIs in infants was most commonly associated with empirical trial of PPIs in infants and young children with symptoms suggestive of GERD with no diagnostic evaluation. In the study mentioned above the most common indication was symptomatic GERD, followed by respiratory distress syndrome.[9]

When studying the effect of all the variables on the indications of PPI use, we found that most patients presenting with abdominal pain as well as upper GI bleeding belonged to the group of no clear indications (82.7 %) and (57.1 %) respectively. This is supported by the fact that the initiation of PPIs for the treatment of abdominal pain or UGI bleeding alone; with no associated investigations supporting its use according to the guidelines, is inappropriate. In fact a prospective study conducted from May to August 2010 in a tertiary hospital in Malaysia, where Study patients included were adult inpatients prescribed intravenous pantoprazole, showed that the overall, intravenous PPI was inappropriately prescribed in 52.8% patients for indication, dose or duration. Unexplained abdominal pain (76.4%) was the main driver for prescribing intravenous PPIs empirically, out of which 68.9% were for suspected upper gastrointestinal bleed.[20]

It was also noticed that 83.6 % of patients admitted to pediatric floor received a PPI with no clear indication (P value < 0.0001; highly significant), where as 57.9 % of patients admitted to intensive care unit lied in the group of appropriate indications (P value < 0.0001; highly significant). This is supported by the fact that prophylaxis of GI haemorrhage in critically ill patient using a PPI is indicated according to evidence based studies, since this group of patients is more prone to develop stress ulcer.[16] Also it is inferred from the results that there is a significant overuse of PPIs in the pediatric floor.

Regarding hospital medications; it was found that empirical use of PPI in patients on NSAIDs/Aspirin was one of the main driver for inappropriate use of PPI (P value = 0.008).

Only 22 patients out of 621 underwent PH metry (3.5 %) and only 103 patients underwent endoscopy (16.5 %). This supports the fact that pediatricians empirically treat symptoms suggestive of GERD rather than confirming the diagnosis by appropriate investigations. This is supported by the study done to survey the implementation of 2009 NASPGHAN-ESPGHAN guidelines by European pediatricians, which showed that 46 % of European pediatricians diagnose GERD based on clinical symptoms irrespective of the child age.[9]

Logistic regression showed that the following variables were highly significant; poor weight gain, Clo test, hospitalization and PH metry.

The odds ratio of the variable poor weight gain was 0.239, P value < 0.0001. This indicates that poor weight gain has a protective effect (odds ratio less than 1); that is, patients having poor weight gain were less likely to be in the group of no clear indications. This is supported by the fact that happy spitters; infants having physiologic gastroesophageal reflux without complications, doesn't usually require treatment by antiacids. While those with regurgitation associated with flattered growth requiresuch treatment.[13, 14]

With respect to the Clo test, it had an odds ratio of 2.126, P value = 0.007, this means that it presented a risk factor for misuse of PPI. This is true since the NASPGHAN/ESPGHAN guidelines disapprove the diagnosis of H-pylori infection by Clo test alone. H-pyloriis diagnosed by positive culture of H-pylori in the gastric biopsy or by microscopic examination of the gastric biopsy along with positive Clo test.[15]

The other variable also found to be highly significant was hospitalization, P value < 0.0001, with odds ratio found to be 10.721, CI = [6.709-17.132]; indicating that the latter represented a risk factor for PPI misuse. Use of PPIs was 10 times higher in patients who were admitted to the pediatric floor. Furthermore, prophylaxis of GI haemorrhage is indicated in critically ill patients in intensive care units, since they are more prone to develop peptic ulcer.[16]

The PH metry had an odds ratio of 0.046, 95 % CI = [0.016-0.135], P value < 0.0001. The PH metry has a protective role, since PPI is FDA indicated in patients diagnosed to have GERD. While PH metry or endoscopy is the accepted investigations to diagnose GERD, Upper GI is not accepted.[9]

There were several limitations to our study, including the retrospective nature of the survey. As only a single hospital was surveyed, it may not be possible to generalize our results to the entire pediatric population in Lebanon – the inclusion of other multiregional centers

may have better represented the prevalence of PPI use in Lebanon.

Nevertheless, we are of the opinion that the overall conclusions of a more extensive study are unlikely to significantly differ from our findings, as our results were consistent with previous studies in European population, even though those studies were restricted to the use of PPI for treatment of GER.

We also did not investigate PPI indications in patients with outpatient prescriptions for PPIs. It would be interesting to determine whether hospitalist and non-hospitalist practices differ significantly when it comes to PPI prescription.

Given the magnitude of the problem of inappropriate PPI prescription in medical practice, remedial measures to improve the situation should be considered with alacrity. One possible approach would be to educate medical departments and teams most associated with inappropriate PPI prescriptions in hospitals, as well as junior doctors who most often initiate PPI use in the wards.

Another practical strategy would involve having dedicated pharmacists in the wards or during ward rounds, who could monitor PPI use and undertake medical reconciliation during the admission, step-down care (from high-dependency units to general wards) and discharge processes. This could help to limit the prescription of PPIs to patients with more appropriate indications, as the pharmacists could suggest the discontinuation of PPIs in patients when it is no longer indicated to ward doctors.

A computer-based or online stewardship guide developed for clinicians, which shows the appropriateness of indications for PPI use each time PPIs are ordered online/electronically, could greatly influence and restrict the prescription of these drugs to patients with more appropriate indications.

CONCLUSION

In summary, the present study concludes that more than half of the overall usage may not be clearly indicated. To our knowledge, this is one of the first studies to demonstrate that the overuse of PPIs reported in adult populations is also mirrored in pediatric populations. In view of the universality of inappropriate PPI prescription in medical practice, the drafting and institution of urgent measures to address this troubling problem is necessary.

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