Characterization of the use of acid-suppressive therapy for stress ulcer prophylaxis in pediatric intensive care unit (ICU) patients: a retrospective, single-center study

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KEYWORDS

acid suppressive, stress ulcer prophylaxis, proton pump inhibitor, histamine 2 receptor antagonist, gastrointestinal bleeding, critically ill children, PICU

ABSTRACT

Introduction: Acid-suppressive drugs are routinely prescribed prophylactically in children admitted to the pediatric intensive care units (PICUs) to reduce the incidence of gastrointestinal bleeding; however, there is constrasting evidence and no universally accepted guidelines on the administration of stress ulcer prophylaxis (SUP) in this specific patient group. The present study aimed to assess the characteristics and appropriateness of SUP in the PICU of Shifa International Hospital (SIH), Islamabad, Pakistan.

Methodology: A retrospective, descriptive cross-sectional study was carried out, involving the medical records of critically ill children admitted between the time period of January 2020 to December 2022. Data collection was performed using a pre-designed checklist, with main areas including demographic characteristics, relevant diagnoses, treatments and prophylactic medications, medications used and duration of SUP, and adverse events.

Results: Out of the *n*=727 children admitted, *n*=588 (80.9%) patients met the inclusion criteria of the study. Mean age of the patients in the study was 6.58 years (range: 4 months – 17 years), with a majority of males (*n*=357; 60.7%). Mean length of PICU stay was 9.28 days (range: 1-20 days); 44.1% of PICU patients had a length of stay of ≥5 days. Most pediatric patients were admitted to the PICU due to respiratory (*n*=120; 20.4%) and neurological (*n*=112; 19.0%). illnesses. 61.4% (*n*=361) of children admitted received an acid suppressant throughout their PICU stay, with *n*=256

(70.9%) received the drug only for the duration of their hospital stay. 55.9% of patients receiving non-steroidal anti-inflammatory drugs, 57.0% on systemic steroids, 63.5% on sedatives, 68.8% on anti-epileptics, 70.0% on antibiotics, 83.3% on antifungals and 100.0% of patients receiving anticoagulants also had SUP prescribed as well. No case of clinically-relevant gastrointestinal bleeding was observed.

Conclusions: The frequency and use of different classes of SUP among children, as well as possible facilitators for their prescribing in PICUs were assessed. Acid suppressive drugs in the PICUs are still crucial component in the treatment plan. Our results suggest the need to introduce evidence-based protocols, both locally and internationally, to avoid the unnecessary use of SUP, especially in the context of possible adverse events associated with their use over an extended period of time or the impact of acid suppression on gut health.

1. Introduction

Stress ulcers (SU) – or the occurrence of gastric erosions – is an adverse events most commonly observable in critically ill patients treated at intensive care units (ICUs) [1]. The expression of gastric bleeding due to stress, and the development of SUs was first described by Lucas in 1971 [2], where changes in the gastric mucosa, localized at proximal parts of the stomach in critically ill patients, were described, and suggested that the use of prophylactic medications might benefit the clinical outcomes in these patients [3]. Although the exact pathomechanism of the development of SUs has not been fully understood, it is thought that they are a result of physiological stress resulting in visceral hypoperfusion, and the activation of the sympathetic nervous system, causing an increase in catecholamine release and higher levels of inflammatory cytokines [4]. Due to these inflammatory physiological responses, the integrity of the gastric mucosa becomes damaged, owing to the combined reduction in blood perfusion to the gastrointestinal (GI) tract, compromised oxygenation, and compromised bicarbonate secretion, disturbing the mucosal barrier [4]. Furthermore, reduced gut motility following splanchnic hypoperfusion may extend the duration of exposure of the mucosa – characterized by impaired protective mechanisms – to gastric acids resulting in ulceration [5]. In addition, the inhibition of prostaglandin (PG) synthesis and cyclooxygenase (COX) activity at a cellular level, through the use of multiple medications (e.g., aspirin [6], non-steroidal anti-inflammatory drugs [7], selective COX-2 inhibitors [8], and corticosteroids [9]) in critically ill patients may further promote mucosal vulnerability to gastric acid [3].

Multiple studies have aimed to explore the possible risk factors that prompt prescribers to initiate use of acid suppressing drugs in critically ill patients [10-13]. Some of the risk factors identified were mechanical ventilation, the presence of an intracranial pathology, thrombocytopenia, prior history of gastric ulceration, renal insufficiency and sepsis, out of which, mechanical ventilation was regarded as a key factor in initiating SUP in critically ill children [14]. Prior history of gastric ulceration, neurological insults and coagulopathy were also relevant risk factors that influenced prescribing behavior for initiating stress ulcer prophylaxis (SUP) in critically ill patients [15]. Among the suggested risk factors listed, at least two must be present for an indication of SUP in critically ill children [16].

For the purpose of acid suppression, histamine-2 receptor antagonists (H2RAs) or proton-pump inhibitors (PPIs) are used as prophylactic medications most commonly, to manage the occurrence of SUs or episodes of gastrointestinal bleeding in ICU patients [17]. H2RAs reversibly and competitively inhibit the activity of histamine-stimulated acid secretion, while PPIs interfere with the function of the acid proton pump in the parietal cells of the stomach,

thereby inhibiting the release of gastric acid [18]. Compared to H2RAs, PPIs are longer acting, thus facilitating once daily dosing [19]; PPIs are therefore considered relevant agents in acid suppression and they are some of the most commonly prescribed anti-secretory drugs [9]. Furthermore, in these clinical situations, sucralfate may also be administered, which exerts mucoprotective activity by forming a thin protective layer on mucosal cells, protecting them from gastric secretions [4]. Thus, these agents, either directly or indirectly inhibit acid secretion and/or its contact with the mucosal lining, and ultimately raise pH levels of the stomach, thereby preventing mucosal injury and the development of SU. Nevertheless, it must be noted that the use of acid-suppressive medication may also present considerable adverse events [20]. Aggressive acid suppression may disrupt the normal gut microbiota and favor colonization of exogenous pathogens, not only in the gut, but also in the respiratory tract, thereby increasing the risk of ventilator associated pneumonia (VAP) [21]. Moreover, patients receiving acid-suppressive therapy are at heightened risk of developing *Clostridioides difficile* (*C. difficile*) associated diarrhoea and associated pathologies [22]. This concern may be explained by the fact that – under physiological conditions – the low gastric pH has a bactericidal effect, and the absence of acidic environment enhances the susceptibility to other infections [23].

The prevalence of the use of SUP medications varies greatly among institutions and healthcare-settings globally [24]. The incidence of upper gastrointestinal bleeding also shows considerable variation based on different clinical settings [25]. Krag *et al.* [26] has shown that the incidence of clinically significant bleeding varies from 0.6% to 7%, and that even if stress lesions form, only a limited fraction of them progress to bleeding if any. Overall, the condition affects around 6% to 10% of children in critical condition, with clinically significant upper gastrointestinal bleeding occurring in less than 1% of cases [15]. Aljawadi *et al.* explored the routine use of SUP, the researchers found only 5.6% of the cases of GI bleeds to be clinically significant [27]. Numerous studies have explored the use of PPIs, H2RAs and sucralfate as medications in the indication of SUP, to reduce the incidence of gastrointestinal bleeding. For example, a study conducted by Cook *et al.*, at Massachusetts Medical Society, described the comparison of ranitidine and sucralfate used as SUP medications in a placebo-controlled randomized trial on mechanically ventilated adults. The results highlighted that those receiving intravenous (iv.) ranitidine as SUP had lower incidence of gastrointestinal bleeding as compared to those receiving sucralfate (1.7 vs. 3.8%). On the other hand, no significant differences were observed in the occurrence of VAP after the receipt of either drugs, however, a relative risk assessment indicated a lower rate of pneumonia in patients treated with sucralfate [28]. To describe the prevalence, the primary outcome of developing GI bleeding and the use of acid-suppressing drugs, a cohort study by Barletta *et al.* included critically ill adult patients from a total of 11 countries. Their results have shown that the prevalence of clinically significant bleeding is rare (2.6% in their study cohort), while the use of acid-suppressive medications was frequent. Various comorbidities, coagulopathy and organ failure were shown as independent risk factors associated with GI bleeding [29]. A similar study by Aljawadi *et al.* was performed, to evaluate prescription patterns for SUP demonstrated that almost 80% of the patient cohort was receiving SUP medication without any relevant indication, while 79% of the patients were receiving it with an indication present [27]. Furthermore, the result of the study by Lakshmanan M *et al.* has highlighted the use of alternative medications (prostaglandin analogs, antacids, H_2 inhibitors, anticholinergic and ulcer protectants) to treat peptic ulcers has decreased with the advent of proton pump inhibitors [30]. A multi-centric, observational cohort study by Duffett *et al.* in Canada examined SUP practice patterns of seven pediatric intensive care units (PICUs) of Canada. Their observations highlighted that 70% of all critically ill children received SUP during their PICU stay; the most frequently prescribed acid suppressing medication class was histamine-2 receptor antagonists (66%) followed by PPIs (47%).

Furthermore, out of the cases of GI bleeding, 0.8% was deemed clinically significant, while the incidence of *C. difficile* infection was rare, i.e. 1% [17].

Despite limited data regarding the safety and efficacy of acid-suppressive medications and the high uncertainty in terms of their benefit-to-risk ratio, their prophylactic use is common [17]. There are no widely accepted clinical guidelines on the use of dtress-related mucosal disease prophylaxis in children. Although literature surveys indicate the prevalent use of H2RAs in adult ICUs, uniform prescribing patterns among critically ill adult patients have not been observed [15]. As much as the use of SUP is common practice in the adult population, its usefulness in the critically ill pediatric population remains unresolved and requires further evidence [31]. The use of acid-suppressive therapy has become a standard preventive measure in the management of critically ill patients [32]. As mentioned earlier, one may find consistent evidence in the literature in the context of the use of SUP for the adult population, but available data is conflicting at best when debating the use of SUP in for pediatric patients. Guidelines on the use of SUP were initially published by the American Society of Health System Pharmacists (ASPH) in 1999 [33]. These guidelines provide evidence-based recommendations on the use of SUP, based on relevant criteria for the non-critically ill, critically ill adult, and critically ill pediatric population, respectively [34], nevertheless, mixed evidence exists regarding its use and these guidelines were not widely accepted, making the practice of prescribing SUP to be influenced more out of institutional practices. Furthermore, insufficient literature data is available on the use of SUP medications in the cohort of Pakistani pediatric ICU population. Therefore, the present study aimed to evaluate the current institutional practices regarding prophylactic acid suppressive therapy in the population of critically ill children, in addition to assessing the potential facilitators of prescribing SUP for these patients.

2. Aims and Objectives

- The aim of our study is to assess the current practice of SUP prescription in pediatric patients in the PICUs
- To determine the frequency of PPI (e.g., omeprazole, esomeprazole), H2RAs and sucralfate use for acid suppression
- To determine the facilitators for prescribing SUP for PICU patients

3. Material and methods

3.1. Study design

A retrospective, descriptive cross-sectional study was designed to evaluate current SUP prescription patterns, and the facilitators of prescribing acid suppressive therapy in relation to SUP in the PICU of Shifa International Hospital (SIH), situated in Islamabad, Pakistan.

3.2. Study setting, duration

This study was conducted at SIH, a 550-bed tertiary care hospital, accredited by Joint Commission International (JCI).The study was carried out between January-December 2023.

3.3. Study population

This study population involved all critically ill children admitted to the two PICU units of SIH between the time period of January 2020 to December 2022. The age range of the children included in the study was between 4 months to 17 years.

3.4. Data collection procedure

The medical record numbers of all pediatric patients admitted to PICU units of SIH during the study period were obtained from the Medical Coding Department of SIH. Data for the research was accessed through patients' files as well as from the (EMR) electronic medical record through the Medication Ordering and Administration Records (MOAR). All the data was collected on the predefined parameters that included demographic characteristics of the patients, relevant diagnoses, treatments and prophylactic medications, medications used for

SUP, duration of SUP, and adverse effects associated with SUP use. The data collection process was performed from July to August 2023.

3.5. Inclusion and exclusion criteria

Patients under 18 years of age, admitted to the PICU, were primarily eligible for data collection in this study. On the other hand, the following exclusion criteria were applied: 1. Patients admitted to PICU with gastrointestinal bleeding on admission; 2. Patients receiving acid suppressive therapy before their admission to the PICU; 3. Patients admitted to the ICU due to any gastrointestinal surgery or procedure; 4. Oncology pediatric patients on acid suppressive therapy with sucralfate, in combination with a PPI; 5. Patients with missing or incomplete information in their medical records.

3.6. Outcome measures of the study

The following outcomes were assessed during the study: prevalence, indications and characteristics of SUP, effectiveness of acid-suppressive therapy, safety, and adverse events, identification of risk factors, gastrointestinal tract bleeding, clinically significant gastrointestinal bleeding, or death. Furthermore drug-drug interactions were analysed using the Lexicomp drug interaction tool (UpToDate™, Wolters Kluwer, Alphen aan den Rijn, Netherlands).

3.7. Statistical analysis

Data collected during the study was entered into a Microsoft Excel (Microsoft Corp. Redmond, WA, USA) spreadsheet, and then transferred to Statistical Package for Social Sciences v.22.0 (SPSS; IBM Corp., Endicott, NY, USA) for analysis. For descriptive analysis, variables were expressed as frequencies (*n*) and percentages (%).

3.8. Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki (and its later amendments), and national and institutional ethical standards. Before initiating data collection, the ethical approval for the study was obtained from the International Review Board (IRB) and ethics committee of SIH, Islamabad (ethical approval ID: 0137-23).

4. Results

4.1. Demographic characteristics of PICU patients

During the study period (from January 2020 to December 2022), a total of *n*=727 children were admitted to the SIH PICU, out of which, medical record were retrieved for *n*=588 (80.9%) patients, who met the inclusion criteria of the study. Table 1 shows the baseline demographic characteristics of our study participants. The mean age of the patients in the study was 6.58 years (range: 4 months – 17 years), with a majority of males (*n*=357; 60.7%). The mean length of PICU stay 9.28 days (range: 1-20 days), while the mean length of hospital stay was 4.61 days (range: 1-23 days). 44.1% of PICU patients had a length of stay of ≥5 days. 59.0% of pediatric patients were mechanically ventilated during their PICU stay.

Table 1. Demographic characteristics of pediatric ICU patients (*n*=588)

Characteristics	***n* (%)**
Age	
0.4 - 1.9 years	48 (8.2)
2 - 6.9 years	295 (50.2)
7 - 11.9 years	131 (22.3)
12 - 17 years	114 (19.3)
Gender	
Male	357 (60.7)
Female	231 (39.3)
Mechanical ventilation	

Ventilated	347 (59.0)
Non-ventilated	241 (41.0)
Length of PICU stay	
<5 days	329 (55.9)
5 – 10 days	238 (40.5)
>10 days	21 (3.6)

PICU: pediatric intensive care unit

Most pediatric patients were admitted to the PICU due to respiratory (*n*=120; 20.4%) and neurological (*n*=112; 19.0%) illnesses; on the other hand, infectious indications (*n*=61; 10.4%), traumatic conditions (*n*=53; 9.0%), gastrointestinal issues (*n*=45; 7.7%), metabolic conditions (*n*=35, 5.9%), cardiac conditions (*n*=28, 4.8%), renal issues (*n*=25, 4.3%), autoimmune conditions (*n*=17, 2.9%), hepatic conditions (*n*=14, 2.4%), dermatological issues (*n*=11, 1.9%), and others (*n*=44, 7.5%) were also prominent reasons for PICU admission.

4.2. Medications received by PICU patients

Majority (93.0%) of PICU patients received systemic antibiotics while 26.0% of the children received NSAIDs, 21.0% received systemic corticosteroids, while 2.3% were on vasopressors or ionotropic support. The summary of medications received by PICU patients is shown in Table 2.

Table 2. Medications received by pediatric ICU patients (*n*=588)

Medications received	***n* (%)**
Systemic corticosteroids	121 (21.0%)
Antibiotics	547 (93.0%)
Anticoagulants	7 (1.2%)
Aspirin or antiplatelet medications	7 (1.2%)
Vasopressors or inotropic drugs	16 (2.3%)
NSAIDs	152 (26.0%)

NSAIDs: non-steroid anti-inflammatory drugs

4.3. Acid-suppressive medication use in PICU patients

Overall, 61.4% (*n*=361) of children admitted to SIH were administered an acid suppressant throughout their PICU stay. With regards to SUP, none of the admitted patients (0%) received sucralfate; among PPIs, the most commonly prescribed medication was omeprazole (95.0%), followed by esomeprazole (3.6%), while famotidine was the only drug among H2RA class, which was prescribed in only *n*=3 (0.8%) of the admitted patients. Only *n*=1 (0.2%) patient received both a PPI (omeprazole) and H2RA (famotidine) agent for acid suppression.

A total of *n*=256 (70.9%) patients – out of those (*n*=361) who were prescribed an acid suppressant medication – received an acid suppressant only for the duration of their hospital stay; only *n*=8 (2.2%) were prescribed a PPI on discharge from the hospital, while for *n*=104 (26.9%) patients' prescription of an acid suppressant drug was continued for the duration of their hospital admission.

Table 3 summarizes the rationale behind SUP prescribing for PICU patients during the study. SUP was most commonly prescribed among children of 2 to 7 years of age, and those who had a length of stay in the PICU ≥5 days. The presence of comorbidities, mechanical ventilation, use of vasopressors, sepsis and septic shock, major surgery and organ failure, prescriptions of NSAIDs and systemic corticosteroids were identified as determinants of SUP prescriptions in the present patient population. A considerably high number of PICU children who had prescriptions for SUP were prescribed NSAIDs and systemic steroids and mechanically ventilated.

Table 3. Characteristics of patients, and the rationale for providing SUP for children treated at the pediatric ICU (*n*=361)

Characteristics	***n* (%)**
Age	
0.4 - 1.9 years	25 (6.9%)
2 - 6.9 years	172 (47.6%)
7 - 11.9 years	90 (24.9%)
12 - 17 years	74 (20.6%)
Comorbidities	
Length of PICU stay	
<5 days	113 (31.3%)
5 – 10 days	227 (62.9%)
>10 days	21 (5.8%)
Medical interventions	
Mechanical ventilation	298 (82.5%)
Use of vasopressors	15 (4.2%)
Sepsis and/or septic shock	24 (6.6%)
Major surgery	10 (2.8%)
Organ failure	8 (2.2%)
Receipt of NSAIDs	90 (24.9%)
Receipt of corticosteroids	87 (24.1%)

PICU: pediatric intensive care unit; NSAIDs: non-steroid anti-inflammatory drugs

4.4. Inappropriate SUP prescriptions

Prescriptions were evaluated for adequacy of the dose of acid suppressants being administered to these children. Out of the SUP prescriptions, *n*=252 (69.8%) prescribed doses were within the range recommended by the institutional dosing protocol, while *n*=97 (26.9%) prescriptions were underdosed and *n*=12 (3.3%) exceeded the recommended dose per kg, according to the institutional dosing protocol.

As PICU patients received multiple medications – in addition to SUP – their prescriptions were also evaluated for potential drug-drug interactions with the acid-suppressant drugs. A total of five such drugs were identified that presented with a potential interaction with omeprazole and esomeprazole; these drugs were diazepam (in 4 out of 5 its prescriptions had concomitant PPI prescriptions as well), warfarin (1 out of 1), phenytoin (15 out of 21), voriconazole (1 out of 2) and fluconazole (4 out of 4), respectively.

The concomitant use of the commonly used medicines with regards to other therapeutic classes, and SUP prescriptions among PICU patients were also evaluated: 55.9% of patients receiving NSAIDs, 57.0% on systemic steroids, 63.5% on sedatives, 68.8% on anti-epileptics, 70.0% on antibiotics, 83.3% on antifungals and 100.0% of patients receiving anticoagulants had an acid suppressant prescribed as well.

4. Discussion

Although acid suppressant drugs are widely prescribed prophylactically in critically ill patients of ICUs, little is known about their use in critically ill children treated at PICUs. To our knowledge, this is the first study in Pakistan, evaluating the appropriate use of acid suppressive drugs for SUP in this specific and vulnerable patient population. Out study aimed to assess the existing practices of prescribing acid suppressants in the PICU of a tertiary care hospital, and to determine the frequency of their use based on different pharmacological groups, as well as the facilitators that prompts physicians to prescribe acid-suppressing drugs in these patients. This aspect makes this study unique and further paves the way for the execution of research.

Among the acid-suppressing drugs, PPIs were the most commonly prescribed, with a particular preference towards omeprazole in this setting [35-37]. Data suggests that it is very likely that prescribing omeprazole in critically ill children is an institutional practice. However, no previous study reported a particular reason or factor leading to preferring omeprazole over other acid-suppressing drugs in this setting [38]. A comparison of omeprazole and esomeprazole prescriptions suggests that children who were prescribed esomeprazole were generally older. This study's main finding, that PPIs were the most frequently prescribed acid suppressant is in contrast to many similar studies reporting on the higher prevalence of use of H2RA in the pediatric population. A retrospective cohort analysis by Costarino *et al.*, at 42 children's hospitals throughout the US, exploring the use of acid suppressants in preventing gastrointestinal bleeding in critically ill children reported the use of H2RA in 70.4% of their study population [39]. A multicenter observational study by Duffett M *et al.*, at seven PICUs in Canada reported that ranitidine was the most frequently prescribed drug (73.0%) in their clinical setting [17]. Furthermore, a retrospective study by Nithiwathanapong *et al.*, which aimed to determine the prevalence and risk factors of stress-induced gastrointestinal bleeding, reported the use of ranitidine in 88.0% of children receiving SUP [14]. In contrast to the abovementioned reports, in our study population, famotidine was the only drug prescribed among H2RAs, with a very low prevalence. Our research data indicates that preferences over the choice of drug class is likely due to differences in institutional practices and changes in SUP prescribing practice over time. Esomeprazole was prescribed in older children while patients who were prescribed famotidine as an acid suppressant had an autoimmune disease GBS, teratology of fallot, and stage 5 CKD.

Our results also revealed that more than half of the critically ill children were prescribed an acid suppressant, which treatment continued throughout their hospital stay. This finding is consistent with the findings in previous studies, which mentioned 86.0% of patients received an acid suppressive medication throughout the PICU stay and 54.0% received SUP during the hospital stay, respectively [17]. Costarino *et al.* reported that 78.4% of the children received an acid-suppressive drug in PICU while for 45.0% of them, it was continued to be administered from PICU through the continuation of their hospital stay [39]. Another interesting finding of the current study is that, while around 70.0% of SUP prescriptions were dose-appropriate according to the hospital's PICU SUP dose protocol, the remaining SUP prescriptions were identified as inappropriate because either under- or overdosing.

Some prescriptions showing potential drug-drug interactions with PPIs were also recognized, that were most likely overlooked at the time of prescribing medications. Omeprazole is a weak inhibitor of the microsomal CYP219 enzyme; therefore, it may lead to the increase of serum concentrations of diazepam and warfarin leading to increased sedative and anti-coagulant effects of these drugs, respectively. The area under the curve (AUC) of diazepam increased by 20 to 39% with concurrent omeprazole administration when evaluating the pharmacokinetic parameters of both drugs [40]. Various clinical studies reported an increase in serum concentrations of Vitamin K antagonists with concurrent administration of PPIs. A

study by Yang *et al.* conducted at China reported the decreased hydroxylation of R-warfarin (the less active enantiomer of warfarin) with the use of omeprazole due to omeprazole-mediated inhibition of warfarin metabolism [41]. Omeprazole may also increase serum concentrations of phenytoin leading to phenytoin toxicity. Prichard *et al.* reported, when evaluating the pharmacokinetics of these drugs, that a dose of up to 40 mg omeprazole increased the AUC of phenytoin to 24%, and decreased its clearance up to 15%, respectively [42]. This interaction is clinically relevant, due to the low therapeutic index and risk of toxicity associated with phenytoin. Omeprazole may also increases the serum concentration of voriconazole; an increased C_{max} and AUC by 15% and 41%, respectively was demonstrated in an 18-subject study, who were simultaenously administered both voriconazole and omeprazole [43]. Omeprazole was identified as the most potent drug that inhibits the metabolism of voriconazole as well as it also abnormally deranged liver function enzymes in an in-vitro study [44]. Conversely, fluconazole is a strong CYP2C19 inhibitor, and it may increase the serum concentration of omeprazole: when administered together, fluconazole increased AUC and C_{max} of omeprazole 8.2 to 13 fold and 3 to 3.3 fold, respectively [45]. Dose adjustment of omeprazole when used for acid suppression alone is not required; however, patients being treated for Zollinger-Ellison Syndrome, who are prescribed higher doses of omeprazole may require dose adjustment. As our patients received multiple medications simultaneously, their prescriptions were also evaluated for potential drug-drug interactions with the acid-suppressant drugs administered. A total of five drugs were identified among the treatment regimens that showed potential interactions with omeprazole and esomeprazole. These drugs included diazepam, warfarin, phenytoin, voriconazole, and fluconazole. Reasons behind such findings could be the absence of clear SUP pediatric dosing guidelines, lack of pediatric dose-related knowledge among healthcare professionals, and weight-based dosing challenges that lead to variability in SUP prescriptions.

In the current study, we found that acid suppressants were used prophylactically in a wide group of diseases but the highest number of SUP prescriptions were seen among children admitted with respiratory and neurological conditions. We also found that the majority of the mechanically ventilated children were prescribed an acid suppressant drug throughout their PICU stay, which is consistent with the findings from previous studies that identified mechanical ventilation as a prominent risk factor for initiating SUP. Previous study mention the presence of mechanical ventilation and coagulopathy as inciting factors for SUP prescribing in their study [4]. Similarly, mechanical ventilation is included as one of the risk factors besides others in a questionnaire-based survey conducted to assess existing opinions about prescribing SUP in critically ill children [15, 46, 47].

This study did not find any incidence of gastrointestinal bleeding in children overall including in those who were not prescribed an acid suppressant prophylactically during admission in hospital. This might indicate a potential association between the use of acid-suppressive drugs and a reduction in gastrointestinal bleeding [48]. Another possible explanation could be that prescribing SUP drug was at the prescribing physician's clinical discretion, and that they focused their prescribing in children with severe illnesses, and that covered up the risk of gastrointestinal bleeding, if any. Furthermore, the development of gastrointestinal bleeding events may take time to occur, and many children may not have stayed in the hospital long enough for them to occur.

One of the key strengths of this study is that it utilized data from electronic health records that may explain ongoing clinical practices in the PICU of the tertiary-care hospital involved in study, which may facilitate in development of institutional SUP practice guidelines targeted for a pediatric population. Furthermore, our study included a diverse patient sample in regards to patient demographics, and underlying medical conditions, which may provide an in-depth analysis of acid-suppressive therapy prescribing patterns in critically ill children. It is

imperative to acknowledge the limitations of this study. The retrospective, single-center nature of the study constraints the extension of results of our study, to more general populations other than this particular patient group. Information retrieved from medical records was not originally maintained for research purposes, therefore, the accuracy and details of the recorded information may introduce bias.

5. Conclusions

This study evaluated the adequacy of the use of acid suppressive therapy in critically ill children treated in the PICU of a tertiary-care hospital in Islamabad, Pakistan. The frequency of the prophylactic use of acid suppressing drugs of different classes among children as well as possible facilitators for their prescribing in the indication of SUP were assessed. The findings of current research revealed that use of acid suppressive drugs in PICU is common, remaining as a crucial component in the treatment plan of critically ill children. Of all the acid suppressing drugs classes, the use of PPIs, i.e. omeprazole was the most common, while the highest number of SUP prescriptions were seen in patients undergoing mechanical ventilation, and receiving prescriptions of NSAIDs and systemic corticosteroids. On the other hand, no case of clinically-relevant gastrointestinal bleeding was observed in our sample. This research study serves as a foundation for protocol-development on acid-suppressive drug therapy in critically ill children; furthermore, our results suggest potential avenues for more in-depth research on acid-suppressive drug use in pediatric population, especially in the context of possible adverse events associated with their use over an extended period of time or the impact of acid suppression on gut health.

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