

Stress ulcer prophylaxis guidelines: Are they being implemented in Lebanese health care centers?

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Abstract

AIM: To evaluate the current practice of stress ulcer prophylaxis (SUP) in Lebanese Health care centers.

METHODS: A multi-center prospective chart review study was conducted over 8 mo. A questionnaire was distributed to pharmacy students who collected data on demographics, SUP medications, dose, route, duration and associated risk factors. The appropriateness of SUP use was determined as per American Society of Health-System Pharmacists guidelines. Institutional review board approval was obtained from each hospital center.

RESULTS: A total of 1004 patients were included. 67% of the patients who received prophylaxis did not have an indication for SUP. The majority (71.6%) of the patients who were administered parenteral drugs can tolerate oral medications. Overall, the regimen of acid-suppressant drugs was suboptimal in 87.6% of the sample. This misuse was mainly observed in non-teaching hospitals.

CONCLUSION: This study highlighted the need, in Lebanese hospitals, to establish clinical practice guidelines for the use of SUP; mainly in non-critical care settings.

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Key words: Stress ulcer prophylaxis; Lebanese hospitals; Proton-pump inhibitors; Histamine 2 receptor antagonists; American Society of Health-System Pharmacists guidelines

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INTRODUCTION

Stress ulcers are single or multiple gastroduodenal mucosal defects that cause a broad range of clinical manifestations from superficial mucosal erosions or mild-severe ulceration to life-threatening bleeding^[1,2]. When patients are hospitalized, the risk of stress ulcers increases. This is particularly true for patients admitted to intensive care settings following the physiologic stress of serious illness such as surgery or trauma^[2]. Within 24 h of admission to the intensive care unit (ICU), endoscopic evidence of stress-related mucosal disease (SRMD) was documented in 75% to 100% of critically ill patients^[3]. Although mucosal erosions may be of little clinical significance because of rapid healing, they cannot be ignored. Stress ulcers present a risk of clinically important bleeding,

which is associated with hemodynamic instability, such as hypotension, tachycardia or respiratory failure, or results in anemia or the need for transfusion^[3].

Clinically significant bleeding occurs in approximately 1% to 4% of critically ill patients with a mortality rate that approaches 50%^[3,4].

The pathophysiology of SRMD is unclear but probably is related to a reduction in mucosal blood flow or a breakdown in other normal mucosal defense mechanisms in conjunction with the injurious effects of acid and pepsin on the gastroduodenal mucosa^[5]. Since acid does appear to be involved in the pathogenesis of these lesions, acid-suppressive regimens have the potential to prevent SRMD^[5-7].

Treatment of stress ulceration usually begins with prevention. Several consensus guidelines for stress ulcer prophylaxis (SUP) have been published^[8-10]. The most recent guidelines available on SUP were published by The American Society of Health-System Pharmacists (ASHP) in 1999^[9]. These guidelines provide evidence-based recommendations for the practice of SUP in non-critically ill medical and surgical patients, critically ill patients and ICU pediatric populations^[9] (Table 1). Although little evidence supports its use^[11,12], acid-suppressive therapy (AST) is largely prescribed in hospitalized patients.

Several studies evaluated the practice pattern of SUP in American and European healthcare centers^[12-16]. Gullotta *et al.*^[12], in a multicenter cohort study at an Italian hospital, showed that 51.4% of hospitalized patients received inappropriate prescription of AST. Similarly, Scagliarini *et al.*^[15] found that AST was overused in hospital settings with the main reason for inadequate prescriptions being ulcer-prophylaxis in low-risk patients. Moreover, Pham *et al.*^[16], in a retrospective chart review study at the University of Michigan Hospital, demonstrated that only 10 % of the patients receiving acid suppressants were found to have an acceptable indication. This highlighted the need for the implementation of practice guidelines and selection criteria to avoid excessive and unmotivated use of AST. However, there are insufficient data in the literature to describe the appropriateness of SUP use in healthcare centers in the Middle East region.

Therefore, the extent to which SUP guidelines are implemented in Lebanese healthcare centers needs to be further assessed and discussed. The following study is an effort to evaluate the appropriateness of SUP practice in a number of Lebanese hospitals from different regions of the country. Our objective was to assess SUP practice in terms of proper indication, drug choice, dose, route of administration and duration of prophylaxis.

MATERIALS AND METHODS

Design, setting and sample selection

This medication use evaluation (MUE) study, conducted between July 2009 and February 2010, used a multicenter prospective design, where centers from all parts of Lebanon were selected for data collection. Sixteen hos-

pitals participated in this study. The institutional review board of each hospital granted approval for the study. To facilitate data analysis, the hospitals were divided into six teaching hospitals and ten non-teaching hospitals. The data collection extended over a period of 8 mo. Pharmacy students at the Lebanese American University School of pharmacy, on rotation at the selected hospitals, were in charge of data collection. Each student was instructed to select and follow up twenty newly admitted patients from the following services; internal medicine (IM), ICU, critical care unit (CCU), surgery, obstetrics and gynecology, and pediatrics.

Patients were excluded from data collection if they had one of the following: (1) a history of active gastrointestinal (GI) ulceration or bleeding of a duration of more than 1 year; (2) an active GI bleeding or an active peptic, gastric or duodenal ulcer at the time of admission or during their hospital stay; (3) are using non steroidal anti-inflammatory drugs (NSAID) treatment at home or in the hospital; or (4) were taking any acid suppressive therapy as home medication. All other patients, receiving acid suppression therapy for SUP, were considered eligible for this study.

A pharm D candidate reviewed the collected data on weekly basis as part of her pharmD project. The pharm D student's responsibility was to supervise patient selection and data abstraction. One thousand six hundred and ninety charts were reviewed; 1004 patients covering different units such as IM, ICU, CCU, surgery, and others were included in the study. Subsequently, patients were then classified as candidates or non-candidates for SUP based on ASHP criteria (Table 1).

Data collection

A special data sheet was created, for medical chart data abstraction, which included the following eight sections: (1) Patient's demographics: general characteristics of the patients such as age, gender, unit, length of hospital stay and allergies. These data are important to assess patients' risks for SUP^[8,9,17,18]; (2) Disease state: including chief complaint, history of present illness, diagnosis and prescribed medications. These data are crucial to check for the eligibility of the patients to the study^[9,19,20]; (3) SUP regimen (agents used, dose, route, frequency, and duration) in addition the discharge medications were listed to allow the assessment of SUP appropriateness^[14,21,22]. According to ASHP guidelines on SUP, histamine 2 antagonists (H2-RAs), antacids, and sucralfate are recommended for the prevention of stress ulcers. The choice of the drug is institution-specific^[9,23-27] and should take into account concerns regarding ease of administration, adverse events and cost^[14,26,28]. When the ASHP guidelines were published, there was insufficient data available on the efficacy and safety of misoprostol and proton pump inhibitors (PPIs) to allow their recommendation. However, multiple studies examined the effects of PPIs in reducing SRMD-related bleeding, but all were either small or observational with PPI as the only treatment arm^[29].

Table 1 American Society of Health-System Pharmacists recommendations for stress ulcer prophylaxis

Population	Treatment recommendations	Grade
Non-critically ill medical and surgical patients	Prophylaxis not recommended	B ¹
Critically ill patients with one of the following:		
Coagulopathy (i.e. platelet count of < 50000 mm ³ , INR of 1.5)	Prophylaxis recommended	C
Mechanical ventilation for > 48 h		C
History of gastrointestinal ulceration or bleeding within 1 year of admission		D
Glasgow Coma score of ≤ 10		B, D ²
Thermal injury to > 35% of body surface area		B, D ³
Partial hepatectomy		C, D ⁴
Multiple trauma (injury severity score of ≥ 16)		D
Hepatic or renal transplantation		D
Spinal cord injury		D
Hepatic failure		D
Two or more of the following risk factors: sepsis, ICU stay of greater than 1 wk, occult bleeding lasting at least 6 d, and high-dose corticosteroids (> 250 mg/d of hydrocortisone or equivalent daily)		D
Pediatric patients with one of the following:		
Respiratory failure	Prophylaxis recommended	C
Coagulopathy		C
Pediatric Risk of Mortality Score of ≥ 10		C
Thermal injuries		D

¹Strength of evidence = B for general medical and surgical patients with fewer than two risk factors for clinically important bleeding; strength of evidence = D for patients with two or more risk factors; ²Strength of evidence = B for histamine H2-receptor antagonist (H2-RAs); strength of evidence = D for antacids and sucralfate; ³Strength of evidence = B for antacids; strength of evidence = D for H2-RAs and sucralfate; ⁴Strength of evidence = C for H2-RAs; strength of evidence = D antacids and sucralfate. INR: International normalized ratio; ICU: Intensive care unit.

Similarly, the small patient populations limit the results of comparative studies (PPIs *vs* placebo or H2-RAs)^[30-32]. Data available indicate that PPIs are safe and efficacious for SUP^[7,32-34]. However, PPIs should be used only as an alternative to H2-RAs or sucralfate pending further comparative studies with large sample size and pharmacoeconomic analysis^[29-34]. As for misoprostol, the profile of side effects, drug interactions, lack of overall efficacy and availability of alternatives preclude its use in current medical practice^[35]. To sum up, options for prophylaxis include antacids, H2-RAs, sucralfate and PPIs. In order to evaluate the adequacy of dosing these agents, a review of the literature was needed to extract the recommended doses since most of the medications used for SUP are not FDA approved for this indication (Table 2)^[9,35,36]. Thus, a prescribed dose was considered correct if it coincides with the extrapolated doses. The route of administration (oral or parenteral) was also recorded. Regarding the duration of prophylaxis, the ASHP guidelines recommend discontinuing the prophylaxis once the risk factors are resolved^[9,19]. Therefore, the duration of the prophylaxis and the discharge medications were documented to assess guideline compliance; (4) Past medical history/ Past medical treatment: This section of the data sheet identified the patients to be excluded. It mainly recognized patients with a history of GI ulceration or bleeding, patients on AST for the treatment of GI disease (gastroesophageal reflux disease, eosophagitis *etc.*) or patients on chronic NASID therapy. Those patients were not included in our study since it is not known if a history of GI ulcerations and bleeding increases the risk of acute stress-induced bleeding^[8,9]. Similarly, NSAIDs were not thoroughly studied as risk factors for stress ulcers although their long-

Table 2 Dosage regimens for agents used for stress ulcer prophylaxis

Medication	Adult raNGe
Cimetidine	300 mg <i>qid</i> po, NG, or iv or 50 mg/h by continuous iv infusion
Famotidine	20 mg <i>bid</i> po, NG, or iv or 1.7 mg/h by continuous iv infusion
Ranitidine	150 mg <i>bid</i> po or NG, 50 mg every 6-8 h iv, or 6.25 mg/h by continuous iv infusion
Nizatidine	150 mg <i>bid</i> po or NG
Antacids	30-60 mL po or NG every 1-2 h
Sucralfate	1 g <i>qid</i> po or NG
Omeprazole	40 mg LD then 20-40 mg daily po, NG or iv
Lansoprazole	30 mg daily po, NG or iv
Esomeprazole	20-40 mg daily po, NG or iv
Rabeprazole	20 mg daily po or NG
Pantoprazole	40 mg daily po or NG or iv

LD: Loading dose; NG: Nasogastric tube.

term use was associated with GI bleeding problems^[37-39]; (5) Current GI bleeding: Patients with active GI bleeding were also excluded from the study since those patients will be receiving AST as a pharmacologic intervention for the management of upper GI bleeding. Moreover, prophylaxis has no role and is not indicated in this population^[40-42]; (6) Lab tests including complete blood count, liver function tests and stool exam were documented to monitor for bleeding^[43-45]; (7) Stress ulcers risk factors: A stress ulcer risk stratification, adopted from the ASHP guidelines, divided patients into three categories: non-critically ill medical patients, ICU populations and pediatrics. The recommendation for prophylaxis was based on the risk factors for clinically important bleeding. According

to the ASHP guidelines, SUP is not recommended for non-critically ill patients with fewer than two risk factors for clinically significant bleeding^[8,9,19]. As for the ICU population, prophylaxis is recommended in (a) patients with coagulopathy; (b) patients requiring mechanical ventilation for more than 48 h; (c) patients with a history of GI ulceration or bleeding within 1 year before admission; and (d) patients with at least two of the following risk factors: sepsis, ICU stay of more than 1 wk, occult bleeding lasting 6 d or more, and use of high-dose corticosteroids (> 250 mg/d of hydrocortisone or the equivalent)^[9]. Moreover, special ICU populations such as patients with a Glasgow Coma Score of ≤ 10 or thermal injuries to > 35% of their body surface area, and so forth, may benefit from prophylaxis (Table 1). For pediatrics, patients with any risk factor for clinically important bleeding (respiratory failure, coagulopathy, and a Pediatric Risk of Mortality Score of ≥ 10) or patients with thermal injuries are candidate for SUP^[9]. Therefore, we subdivided our study populations into three groups (non-ICU, ICU and pediatric populations) to evaluate the SUP appropriateness per ASHP guidelines; and (8) The route of administration of AST, being oral or parenteral, was recorded in this section since parenteral therapy should only be used when the oral therapy is not tolerated^[46,47]. To identify the patients who can tolerate oral medications, the routes of administration of other prescribed medications were also reported.

Data analysis

Abstracted data were coded and entered into the SPSS version 18 for analysis. Summary statistics, including frequency percent means and standard deviations were calculated to summarize the data. Differences in proportions were tested using the Pearson chi-square when assumptions were met; if not, the Fisher's exact test was used. Differences in the hospital duration stay were tested using the Mann-Whitney non-parametric test. Practice of SUP was classified as either appropriate or inappropriate taking into consideration the indication for SUP, agents used, route, dose, frequency and the duration of the prophylaxis. In addition, SUP practice was compared across different patient populations (non-ICU, ICU and pediatrics) and hospital type (teaching *vs* non-teaching). All analyzes were carried out at the 0.05 significance level.

RESULTS

A total of 1690 surveys were completed; of which 1004 were eligible for enrollment in the study. The mean age was 54.6 ± 21.2 and the gender distribution was 52.5% males and 47.5% females. The surveys were collected from sixteen different Lebanese hospitals across the country. The mean number of surveys filled per hospital site was 63 (range: 13-172). The 1004 patients were divided among different hospital units: 236 (23.5%) were from critical care units (ICU and CCU), 728 (72.5%) were from other units, whereas the remaining 40 (4.0%)

Table 3 General characteristics of the sample ($n = 1004$)

Patients characteristics	n (%)
Gender	
Males	527 (52.5)
Females	477 (47.5)
Age (yr, mean \pm SD)	54.6 \pm 21.2
Unit	
ICU	142 (14.1)
IM	468 (46.6)
Surgery	190 (18.9)
CCU	94 (9.4)
Pediatrics	40 (4.0)
OBGYN	28 (2.8)
Others	42 (4.2)
Hospital stay: Median and IQR (d)	4.0 (5.0) ¹
Acid-suppressant drugs	
PPIs	618 (61.6)
Omeprazole	477 (47.5)
Lansoprazole	50 (5.0)
Esomeprazole	5 (0.5)
Rabeprazole	86 (8.6)
H2-RAs	386 (38.4)
Ranitidine	384 (38.2)
Nizatidine	2 (0.20)
Duplicate therapy	0 (0)

¹The median was reported since this variable was positively skewed. ICU: Intensive care unit; IM: Internal medicine; CCU: Critical care unit; OBGYN: Obstetrics and gynecology; IQR: InterQuartile range; PPIs: Proton-pump inhibitors; H2-RAs: Histamine 2 receptor antagonist.

were from the pediatric unit (Table 3). Since the length of hospitalization is critical to determine the duration of the prophylaxis, hospital stay was also assessed, and the median hospital stay was found to be 4 d. Of the 1004 patients, 618 (61.6%) received PPIs of which omeprazole was the most commonly used (477 out of 618), and 386 (38.4%) received H2-RAs of which ranitidine was the most commonly prescribed (384 out of 386). Moreover, PPIs were administered orally in 48.4% of the patients, whereas oral H2-RAs were given in only 5.2% of the patients ($P < 0.001$).

The SUP was classified as either appropriate or inappropriate according to the ASHP guidelines (Table 1). Of 1004 patients receiving AST, 67% ($n = 673$) did not have an indication for SUP according to our ASHP-based guidelines. 771 (76.8%) patients were administered the drug parenterally, of which 551 (71.6%) patients were able to tolerate the oral route. Although 89% of the patients received the appropriate dose, overall, only 12.4% of the sample population was candidate for SUP and was administered the acid-suppressive regimen (dose, frequency and route) appropriately (Table 4).

The practice pattern of SUP was further analyzed by comparing each component of the AST (drug class, dose, frequency, route and duration) in patients who were candidate for prophylaxis *vs* those who were not. There was no statistically significant difference in the prescription of PPIs between the two groups: 62.8% of patients who had an indication for SUP and 60.9% of patients who did not, were on PPI ($P = 0.557$) (Table 5). Moreover, the

Table 4 Assessment of stress ulcer prophylaxis practice

SUP variable	n (%)
Indication	
Non-Candidates for SUP ¹	673 (67)
Candidates for SUP ²	331 (33)
1 major risk factor ³	53 (25.2)
2 minor risk factors ⁴	204 (20.3)
7 d stay in ICU and 1 minor risk factor	38 (3.8)
Dose	
Appropriate	891 (88.9)
Inappropriate	111 (11.1)
Route	
Oral	232 (23.2)
Parenteral	770 (76.8)
Inappropriate ⁵	551 (71.6)
Duration (d)	
Median (IQR)	4.0 (5) ⁶
Regimen (dose + route + duration)	
Appropriate	124 (12.4)
Inappropriate	880 (87.6)

¹Non-candidates are patients receiving stress ulcer prophylaxis (SUP) without an appropriate indication; ²Candidates are patients receiving SUP with an appropriate indication according to American Society of Health-System Pharmacists guidelines; ³Major risk factors are: coagulopathy, mechanical ventilation > 48 h or history of gastrointestinal ulceration or bleeding within 1 year of admission; ⁴Minor risk factors are all other risk factors listed in Table 1; ⁵Inappropriate route is defined as the use of parenteral drugs when oral drugs can be tolerated; ⁶The median was reported since this variable was positively skewed. ICU: Intensive care unit; IQR: Interquartile range.

majority of patients in both groups received omeprazole as PPI and ranitidine as H2-RAs. Inappropriate dosing was defined as receiving doses that did not coincide with the tabulated doses (Table 2). Appropriate dosing was observed in 84.9% of the candidates for SUP and in 90% of the patients who did not have a justified indication for SUP ($P = 0.004$). Duration of prophylaxis was 5 d in the “candidates” group compared to 3 d in the “non-candidates” group ($P < 0.001$). For further evaluation of the duration of the prophylaxis, the discharge medications were also assessed. A discharge plan was missing in 499 out of 1004 surveys. Of the 505 available surveys, 119 (23.6%) patients were discharged on SUP and 386 (76.4%) patients were not. The majority of patients for which SUP was indicated were discharged on AST (28.8% in the “candidates” group *vs* 20.9% in the “non-candidates” group, $P = 0.047$) (Table 5).

The appropriateness of SUP was further assessed within teaching and non-teaching hospitals. The sample was divided into two groups resulting in 405 (40.3%) patients from teaching hospitals and 599 (59.7%) patients from non-teaching hospitals. 37.8% and 28.7% of the patients who receive AST in teaching and non-teaching hospitals respectively had an indication for SUP ($P = 0.008$). Furthermore, there was a statistically significant difference in the adequacy of dosing acid-suppressants between teaching hospitals (86.4% appropriate dosing) and non-teaching hospitals (90.6% appropriate dosing, $P = 0.038$). However, overall dosing practice (dose and

Table 5 Assessment of stress ulcer prophylaxis practice per indication n (%)

SUP variable	Candidates	Non-candidates	P-value
Acid-suppressant drugs			
PPIs	208 (62.8)	410 (60.9)	0.557
H2-RAs	123 (37.2)	263 (39.1)	
Dose			
Appropriate	281 (84.9)	610 (90.0)	0.004
Inappropriate	50 (15.1)	61 (9.1)	
Route			
Appropriate	150 (45.3)	301 (44.7)	0.859
Inappropriate	181 (54.7)	372 (55.3)	
Dose and route			
Appropriate	124 (37.5)	265 (39.4)	0.558
Inappropriate	207 (62.5)	408 (60.6)	
Duration (d)			
Median (IQR)	5.0 (7.0)	3.0 (4.0)	< 0.001 ¹
Discharge on SUP			
Yes	49 (28.8)	70 (20.9)	0.047
No	121 (71.2)	265 (79.1)	

¹P-value derived using the Mann-Whitney *U* test; P-value remained significant even after controlling for hospital stay. SUP: Stress ulcer prophylaxis; PPIs: Proton pump inhibitors; H2-RAs: Histamine 2 receptors antagonists; IQR: Interquartile range.

route) was more adequate in teaching hospitals than in non-teaching hospitals (44% *vs* 35.2% respectively, $P = 0.005$). This significant difference in appropriate dosing was only detected when the drug was administered parenterally (93.1% *vs* 84.9% in teaching and non-teaching hospitals respectively, $P < 0.001$). PPIs were more frequently used in teaching hospitals compared to non-teaching hospitals (65.7% *vs* 58.8%, $P = 0.027$). Patients from teaching hospitals tended to receive SUP for a longer duration (5 d *vs* 3 d in non-teaching hospitals, $P < 0.001$).

The difference between hospital types according to candidate status was also assessed. Furthermore, SUP practice was analyzed by looking at its appropriateness by both indication and hospital type (Table 6).

DISCUSSION

This study assessed real-world dosing practices in 1004 hospitalized patients, in sixteen Lebanese hospitals, using a multi-center survey method. Hospitals from all regions of the country were selected to maximize the generalizability of the results. Our results showed that only 33% of Lebanese inpatients were prescribed AST in accordance with the ASHP guidelines for SUP. Therefore, 67% of hospitalized patients received unjustified prophylaxis. The fact that the majority of the patients who were on SUP therapy were non-critically ill medical and surgical patients raises major concern.

According to the ASHP guidelines, SUP is not recommended for general medical and surgical patients in non-ICU settings with fewer than two risk factors for clinically important bleeding, or for patients with two or more risk factors (Table 1). Few studies^[12,47-49] to date have effectively examined the role of SUP in non-ICU patients.

Table 6 Assessment of stress ulcer prophylaxis practice per hospital type *n* (%)

SUP variable	Teaching	Non-teaching	P-value
Indication			
Candidates	153 (37.8)	178 (29.7)	0.008
Non-candidates	252 (62.2)	421 (70.3)	
Dose			
Appropriate	350 (86.4)	541 (90.6)	0.038
Inappropriate	55 (13.6)	56 (9.4)	
Route			
Appropriate	206 (50.9)	245 (40.9)	0.002
Inappropriate	199 (49.1)	354 (59.1)	
Dose and route			
Appropriate	178 (44.0)	211 (35.2)	0.005
Inappropriate	227 (56.0)	388 (64.8)	
Acid-suppressant drugs			
PPIs	266 (65.7)	352 (58.8)	0.027
H2-RAs	139 (34.3)	247 (41.2)	
Duration (d)			
Median (IQR) ¹	5 (10)	3 (3.75)	< 0.001 ¹
Discharge on SUP			
Yes	53 (26.2)	66 (21.8)	0.248
No	149 (73.8)	237 (78.2)	

¹P-value lost significance when controlling for hospital stay. SUP: Stress ulcer prophylaxis; PPIs: Proton pump inhibitors; H2-RAs: Histamine 2 receptors antagonists; IQR: Interquartile range.

Qadeer *et al.*^{49]}, in a retrospective case-control study at an American tertiary care center (*n* = 17 707 patients), demonstrated that hospital-acquired bleeding is uncommon in non-critically ill patients, thus, routine prophylaxis is unnecessary in most hospitalized patients. Moreover, a second retrospective study done by Heidelbaugh *et al.*^{47]} showed that SUP in the non-ICU setting results in significant cost expenditures without beneficial impact on the quality of care. These results, taken together with the results of our study, highlight the need to establish well-defined risk factors for stress ulcers and implement appropriate prevention strategies in the non-ICU setting.

Concerning the choice of the acid-suppressive agent, PPIs and H2-RAs were the only drug classes prescribed in our study, with a higher frequency use of PPIs. The ASHP recommends antacids, H2-RAs and sucralfate as options for prophylaxis. In a meta-analysis by Cook *et al.*^{25]}, various prophylactic therapies, including antacids, sucralfate, and H2-RAs, were found to reduce the incidence of clinically important bleeding compared with no prophylaxis. However, antacids are no longer considered a viable therapeutic option because of the labor-intensive dosing frequency and potential side effects^{135]}. Another option is sucralfate: a meta-analysis^{27]} assessing the efficacy of sucralfate compared with H2RAs (nine studies) and antacids (eight studies) for the prophylaxis of stress ulcers indicated that sucralfate was at least as effective as the other agents. Nevertheless, sucralfate is not available on the Lebanese pharmaceutical market.

Although H2-RAs are the most widely used drugs for SUP worldwide^{17]}, its use was overwhelmed by the prescription of PPIs in Lebanese hospitals. This can be

explained by the following: (1) Tolerance to H2-RAs acid inhibition develops as early as 72 h after administration; (2) PPIs are the most potent antisecretory agents available; (3) PPIs are at least as effective as H2-RAs in SUP; (4) PPIs can be administered through a nasogastric tube or jejunum or parenterally when oral medication is not tolerated; and (5) PPIs are well-tolerated with a low incidence of adverse effects^{33,50,51]}.

Overall, 11.1% of the Lebanese inpatients received incorrect doses and SUP was indicated in the majority of them. This is predictable because recommendations are lacking for prophylactic dosing of most acid-suppressive agents. Only cimetidine, sucralfate and the powder suspension of omeprazole are FDA approved for SUP indication^{10,52,53]}.

Furthermore, the route of administration was inadequate in the majority of the patients: 70% of the patients who were receiving parenteral drugs can tolerate oral medications. Our study suggests that the inadequacy in administering the drugs is due to the misconception that parenteral medications are more effective than oral ones. However, studies^{54-56]} failed to show any efficacy or safety advantages of one formulation over the other. Thus, to minimize the potential adverse effects and additional costs of parenteral administration^{9,54-56]} the parenteral route should be reserved for patients who cannot tolerate oral medications.

The median hospital stay and the median duration of SUP coincide. Further comparison showed that patients who have an acceptable indication for SUP were maintained on the prophylaxis for longer than the “non-candidate” group. These results are expected since prophylaxis should be discontinued upon discharge from the hospital or until the resolution of risk factors^{9]}. Nevertheless, a large number of patients (*n* = 120), mainly in the “candidates” group, was discharged on AST. This practice is unjustified, and there is no evidence-based data that support the continuation of AST at discharge^{157,58]}. Furthermore, long-term use of acid-suppression medications was associated with an increase in unnecessary expenses^{47,57]}, and most importantly with an increased risk of pneumonia^{159]}, hip fracture^{160]} and *Clostridium difficile* colitis^{161,62]}.

In order to explore whether teaching hospitals are more compliant with SUP guidelines, patients were stratified into two groups, resulting in statistically significant differences: a higher proportion of inpatients in teaching healthcare centers received adequate prophylaxis compared to patients in non-teaching hospitals. Therefore, SUP was significantly better practised in teaching hospitals. Such results are not surprising because teaching hospitals are more likely to follow guidelines and recommendations^{163,64]}.

This study reinforces the results of previous studies undertaken in the Middle East. Recently, Khudair *et al.*^{165]}, in a MUE study conducted at Hamad General Hospital in Qatar (389 patients) assessing the prescribing pattern of acid-suppressive medications in medical inpatients, found that the usage of SUP was unjustified in 66% of patients.

Moreover, a second observational study by Mayet^[66] ($n = 661$) was carried out at King Khalid University Hospital, a tertiary teaching hospital in Saudi Arabia. Its objective was to evaluate the improper use of pantoprazole and ranitidine. The results showed that improper use of these medications was observed in 43% of the patients, emphasizing the need to implement practice guidelines in order to reduce the misuse of AST^[66].

Although our study was limited to Lebanese healthcare centers, its results can serve as a base for national and international future clinical studies. Indeed, SUP is a wide practice in medicine worldwide. The current practice of SUP may vary among countries as well as various hospitals in the same country; yet comparing this variability between different clinical settings may help in the establishment of clear, well-defined clinical practice guidelines for the prevention of stress ulcers, specifically in the non-critical care settings.

This study has a number of limitations. Missing data was a major limitation, especially information about the continuation of SUP after discharge, which was lacking in half the sample. Secondly, the correlation between appropriate SUP practice and clinical outcomes, in terms of safety and efficacy of AST, were not assessed in our study. Thirdly, although pharm D students were auditing and precepting the process of data collection, the chance for inter-rater variation and inconsistency still exists since data abstraction was carried out by 60 different pharmacy students.

There are also several strengths in this study that should also be addressed. Firstly, the inclusion of sixteen hospitals from different geographical areas increases the external validity of the study, making it better representative of the population. Secondly, the number of patients recruited was large which increases the power of the study. Thirdly, this study, evaluating the practice pattern of SUP in Lebanese healthcare centers is the first of its kind in Lebanon. Moreover, the study evaluated the appropriateness of prophylaxis in three different populations and was not limited to critically ill patients. Finally, a biostatistician was consulted, which increases the accuracy of our results.

In conclusion, this study assessed the appropriateness of SUP practice in correlation with the only available guideline, the ASHP guidelines. Lebanon suffers from widespread suboptimal practice of SUP in hospital practice. The results of this study highlight the need for the implementation of correction measures and practice guidelines in critical care as well as non-critical care settings. More awareness and education should be considered in Lebanese hospitals, especially in non-teaching sites where the practice of evidence-based medicine may be minimal. In the absence of firm recommendations, the non-critically ill population requires additional attention. This can be achieved by: (1) clearly defining the risk factors for clinically significant bleeding in this population; and (2) periodically monitoring the practice pattern of SUP to further minimize its overuse in non-critically

ill patients.

COMMENTS

Background

The incidence of stress ulcers increases when patients are hospitalized. Progression of stress ulcers to clinically important bleeding is associated with a mortality rate of approximately 50%.

Research frontiers

Since acid may be involved in the pathogenesis of stress-related ulcerations, acid suppressive regimens have been shown to prevent these lesions; and consensus guidelines for stress ulcer prophylaxis (SUP) have been published by The American Society of Health-System Pharmacists. However, the way SUP guidelines are implemented in Lebanese healthcare centers has not been unequivocally addressed. In this study, the authors evaluate the practice of SUP in Lebanese healthcare centers to improve the effectiveness of acid suppressive therapy on preventing stress ulcers, and simultaneously reducing adverse reactions.

Innovations and breakthroughs

Several studies demonstrated that acid suppressive therapy is inappropriately prescribed in American and European hospitals. This is the first study that assesses the SUP practice in Lebanese health care centers.

Applications

The study results highlight the need for the implementation of SUP practice guidelines in Lebanese hospitals, particularly in the non-critical areas where firm recommendations are still lacking.

Peer review

The authors examined the use of SUP in a multicenter study of sixteen Lebanese hospitals. It revealed that in the majority of the patients, acid suppressive therapy was administered without any scientific evidence. The results are interesting and may be applied to many other countries (than Lebanon) world-wide.

REFERENCES

- 1 **Mutlu GM**, Mutlu EA, Factor P. GI complications in patients receiving mechanical ventilation. *Chest* 2001; **119**: 1222-1241
- 2 **Andersberg B**, Sjö Dahl R. Prophylaxis and management of stress ulcers. *Scand J Gastroenterol Suppl* 1985; **110**: 101-104
- 3 **Fennerty MB**. Pathophysiology of the upper gastrointestinal tract in the critically ill patient: rationale for the therapeutic benefits of acid suppression. *Crit Care Med* 2002; **30**: S351-S355
- 4 **Ben-Menachem T**, McCarthy BD, Fogel R, Schiffman RM, Patel RV, Zarowitz BJ, Nerenz DR, Bresalier RS. Prophylaxis for stress-related gastrointestinal hemorrhage: a cost effectiveness analysis. *Crit Care Med* 1996; **24**: 338-345
- 5 **Cho CH**, Koo MW, Garg GP, Ogle CW. Stress-induced gastric ulceration: its aetiology and clinical implications. *Scand J Gastroenterol* 1992; **27**: 257-262
- 6 **Cook DJ**, Fuller HD, Guyatt GH, Marshall JC, Leasa D, Hall R, Winton TL, Rutledge F, Todd TJ, Roy P. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. *N Engl J Med* 1994; **330**: 377-381
- 7 **Martindale RG**. Contemporary strategies for the prevention of stress-related mucosal bleeding. *Am J Health Syst Pharm* 2005; **62**: S11-S17
- 8 **Tryba M**, Cook D. Current guidelines on stress ulcer prophylaxis. *Drugs* 1997; **54**: 581-596
- 9 ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998. *Am J Health Syst Pharm* 1999; **56**: 347-379
- 10 **Wilcox CM**, Spenny JG. Stress ulcer prophylaxis in medical patients: who, what, and how much? *Am J Gastroenterol* 1988; **83**: 1199-1211
- 11 **Grau JM**, Casademont J, Fernández-Solá J, Cardellach F, Urbano-Márquez A. Prophylaxis of gastrointestinal tract bleeding in patients admitted to a general hospital ward.

- Comparative study of sucralfate and cimetidine. *Scand J Gastroenterol* 1993; **28**: 244-248
- 12 **Gullotta R**, Ferraris L, Cortelezzi C, Minoli G, Prada A, Comin U, Rocca F, Ferrara A, Curzio M. Are we correctly using the inhibitors of gastric acid secretion and cytoprotective drugs? Results of a multicentre study. *Ital J Gastroenterol Hepatol* 1997; **29**: 325-329
 - 13 **Nardino RJ**, Vender RJ, Herbert PN. Overuse of acid-suppressive therapy in hospitalized patients. *Am J Gastroenterol* 2000; **95**: 3118-3122
 - 14 **Parente F**, Cucino C, Gallus S, Bargiggia S, Greco S, Pastore L, Bianchi Porro G. Hospital use of acid-suppressive medications and its fall-out on prescribing in general practice: a 1-month survey. *Aliment Pharmacol Ther* 2003; **17**: 1503-1506
 - 15 **Scagliarini R**, Magnani E, Praticò A, Bocchini R, Sambo P, Pazzi P. Inadequate use of acid-suppressive therapy in hospitalized patients and its implications for general practice. *Dig Dis Sci* 2005; **50**: 2307-2311
 - 16 **Pham CQ**, Regal RE, Bostwick TR, Knauf KS. Acid suppressive therapy use on an inpatient internal medicine service. *Ann Pharmacother* 2006; **40**: 1261-1266
 - 17 **Spirit MJ**, Stanley S. Update on stress ulcer prophylaxis in critically ill patients. *Crit Care Nurse* 2006; **26**: 18-20, 22-28; quiz 29
 - 18 **Simons RK**, Hoyt DB, Winchell RJ, Holbrook T, Eastman AB. A risk analysis of stress ulceration after trauma. *J Trauma* 1995; **39**: 289-293; discussion 293-294
 - 19 **Grube RR**, May DB. Stress ulcer prophylaxis in hospitalized patients not in intensive care units. *Am J Health Syst Pharm* 2007; **64**: 1396-1400
 - 20 **Allen ME**, Kopp BJ, Erstad BL. Stress ulcer prophylaxis in the postoperative period. *Am J Health Syst Pharm* 2004; **61**: 588-596
 - 21 **Erstad BL**, Barletta JF, Jacobi J, Killian AD, Kramer KM, Martin SJ. Survey of stress ulcer prophylaxis. *Crit Care* 1999; **3**: 145-149
 - 22 **Lam NP**, Lê PD, Crawford SY, Patel S. National survey of stress ulcer prophylaxis. *Crit Care Med* 1999; **27**: 98-103
 - 23 **Cook D**, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R, Peters S, Rutledge F, Griffith L, McLellan A, Wood G, Kirby A. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med* 1998; **338**: 791-797
 - 24 **Kingsley AN**. Prophylaxis for acute stress ulcers. Antacids or cimetidine. *Am Surg* 1985; **51**: 545-547
 - 25 **Cook DJ**, Reeve BK, Guyatt GH, Heyland DK, Griffith LE, Buckingham L, Tryba M. Stress ulcer prophylaxis in critically ill patients. Resolving discordant meta-analyses. *JAMA* 1996; **275**: 308-314
 - 26 **Messori A**, Trippoli S, Vaiani M, Gorini M, Corrado A. Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials. *BMJ* 2000; **321**: 1103-1106
 - 27 **Tryba M**. Sucralfate versus antacids or H2-antagonists for stress ulcer prophylaxis: a meta-analysis on efficacy and pneumonia rate. *Crit Care Med* 1991; **19**: 942-949
 - 28 **Azevedo JR**, Soares MG, Silva G, Palacio G. Prevention of stress ulcer bleeding in high risk patients. Comparison of three drugs. *Crit Care Med* 1999; **27**: A145
 - 29 **Jung R**, MacLaren R. Proton-pump inhibitors for stress ulcer prophylaxis in critically ill patients. *Ann Pharmacother* 2002; **36**: 1929-1937
 - 30 **Levy MJ**, Seelig CB, Robinson NJ, Ranney JE. Comparison of omeprazole and ranitidine for stress ulcer prophylaxis. *Dig Dis Sci* 1997; **42**: 1255-1259
 - 31 **Laine LA**, Margolis B, Bagin RG, Conrad S, Gabrielly A, Quattrin A, Heta J, Frank W, Rock J, Hepburn B, Laurie L. Double-blind trial of omeprazole immediate release oral suspension (OME-IR SUSP) vs. intravenous cimetidine (IV CIM) for prevention of upper gastrointestinal (UGI) bleeding in critically ill patients. *Gastroenterology* 2004; **126**: A-77
 - 32 **Daley RJ**, Rebeck JA, Welage LS, Rogers FB. Prevention of stress ulceration: current trends in critical care. *Crit Care Med* 2004; **32**: 2008-2013
 - 33 **Spirit MJ**. Stress-related mucosal disease: risk factors and prophylactic therapy. *Clin Ther* 2004; **26**: 197-213
 - 34 **Devlin JW**. Treatment options and formulary considerations in the management of acid suppression in critically ill patients. Introduction. *Am J Health Syst Pharm* 2005; **62**: S2-S3
 - 35 **Shuman RB**, Schuster DP, Zuckerman GR. Prophylactic therapy for stress ulcer bleeding: a reappraisal. *Ann Intern Med* 1987; **106**: 562-567
 - 36 **Zheng RN**. Comparative study of omeprazole, lansoprazole, pantoprazole and esomeprazole for symptom relief in patients with reflux esophagitis. *World J Gastroenterol* 2009; **15**: 990-995
 - 37 **Fasseas P**, Leybiskis B, Rocca G. Omeprazole versus ranitidine in the medical treatment of acute upper gastrointestinal bleeding: assessment by early repeat endoscopy. *Int J Clin Pract* 2001; **55**: 661-664
 - 38 **Lanas A**. Gastrointestinal injury from NSAID therapy. How to reduce the risk of complications. *Postgrad Med* 2005; **117**: 23-28, 31
 - 39 **Soylu A**, Dolapcioglu C, Dolay K, Ciltas A, Yasar N, Kalayci M, Alis H, Sever N. Endoscopic and histopathological evaluation of acute gastric injury in high-dose acetaminophen and nonsteroidal anti-inflammatory drug ingestion with suicidal intent. *World J Gastroenterol* 2008; **14**: 6704-6710
 - 40 **Rivkin K**, Lyakhovetskiy A. Treatment of nonvariceal upper gastrointestinal bleeding. *Am J Health Syst Pharm* 2005; **62**: 1159-1170
 - 41 **Olsen KM**. Use of acid-suppression therapy for treatment of non-variceal upper gastrointestinal bleeding. *Am J Health Syst Pharm* 2005; **62**: S18-S23
 - 42 **Celiński K**, Cichoz-Lach H, Madro A, Słomka M, Kasztelan-Szczerbińska B, Dworzański T. Non-variceal upper gastrointestinal bleeding--guidelines on management. *J Physiol Pharmacol* 2008; **59** Suppl 2: 215-229
 - 43 **Khilnani N**, Hussain N. Gastrointestinal bleeding. *Emerg Med* 2005; **37**: 27-32
 - 44 **Manning-Dimmitt LL**, Dimmitt SG, Wilson GR. Diagnosis of gastrointestinal bleeding in adults. *Am Fam Physician* 2005; **71**: 1339-1346
 - 45 **Green RM**, Flamm S. AGA technical review on the evaluation of liver chemistry tests. *Gastroenterology* 2002; **123**: 1367-1384
 - 46 **Fudge KA**, Moore KA, Schneider DN, Sherrin TP, Wellman GS. Change in prescribing patterns of intravenous histamine2-receptor antagonists results in significant cost savings without adversely affecting patient care. *Ann Pharmacother* 1993; **27**: 232-237
 - 47 **Heidelbaugh JJ**, Inadomi JM. Magnitude and economic impact of inappropriate use of stress ulcer prophylaxis in non-ICU hospitalized patients. *Am J Gastroenterol* 2006; **101**: 2200-2205
 - 48 **Estruch R**, Pedrol E, Castells A, Masanés F, Marrades RM, Urbano-Márquez A. Prophylaxis of gastrointestinal tract bleeding with magaldrate in patients admitted to a general hospital ward. *Scand J Gastroenterol* 1991; **26**: 819-826
 - 49 **Qadeer MA**, Richter JE, Brotman DJ. Hospital-acquired gastrointestinal bleeding outside the critical care unit: risk factors, role of acid suppression, and endoscopy findings. *J Hosp Med* 2006; **1**: 13-20
 - 50 **Beejay U**, Wolfe MM. Acute gastrointestinal bleeding in the intensive care unit. The gastroenterologist's perspective. *Gastroenterol Clin North Am* 2000; **29**: 309-336
 - 51 **Netzer P**, Gaia C, Sandoz M, Huluk T, Gut A, Halter F, Hüslér J, Inauen W. Effect of repeated injection and continuous infusion of omeprazole and ranitidine on intragastric pH over 72 hours. *Am J Gastroenterol* 1999; **94**: 351-357

- 52 **Wirth SM**, Macaulay TE, Winstead PS, Smith KM. Stress-related mucosal disease: considerations of current medication prophylaxis. *Orthopedics* 2007; **30**: 1010-1014
- 53 **Sesler JM**. Stress-related mucosal disease in the intensive care unit: an update on prophylaxis. *AACN Adv Crit Care* 2007; **18**: 119-126; quiz 127-128
- 54 **Devlin JW**, Claire KS, Dulchavsky SA, Tyburski JG. Impact of trauma stress ulcer prophylaxis guidelines on drug cost and frequency of major gastrointestinal bleeding. *Pharmacotherapy* 1999; **19**: 452-460
- 55 **Hopefl A**. Rational use of parenteral proton pump inhibitors. *Hosp Pharm* 2001; **36**: 344-350
- 56 **Olsen KM**, Devlin JW. Comparison of the enteral and intravenous lansoprazole pharmacodynamic responses in critically ill patients. *Aliment Pharmacol Ther* 2008; **28**: 326-333
- 57 **Wohlt PD**, Hansen LA, Fish JT. Inappropriate continuation of stress ulcer prophylactic therapy after discharge. *Ann Pharmacother* 2007; **41**: 1611-1616
- 58 **Zink DA**, Pohlman M, Barnes M, Cannon ME. Long-term use of acid suppression started inappropriately during hospitalization. *Aliment Pharmacol Ther* 2005; **21**: 1203-1209
- 59 **Laheij RJ**, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004; **292**: 1955-1960
- 60 **Yang YX**, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006; **296**: 2947-2953
- 61 **Dial S**, Alrasadi K, Manoukian C, Huang A, Menzies D. Risk of Clostridium difficile diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. *CMAJ* 2004; **171**: 33-38
- 62 **Cunningham R**, Dale B, Undy B, Gaunt N. Proton pump inhibitors as a risk factor for Clostridium difficile diarrhoea. *J Hosp Infect* 2003; **54**: 243-245
- 63 **Erstad BL**, Camamo JM, Miller MJ, Webber AM, Fortune J. Impacting cost and appropriateness of stress ulcer prophylaxis at a university medical center. *Crit Care Med* 1997; **25**: 1678-1684
- 64 **Liberman JD**, Whelan CT. Brief report: Reducing inappropriate usage of stress ulcer prophylaxis among internal medicine residents. A practice-based educational intervention. *J Gen Intern Med* 2006; **21**: 498-500
- 65 **Khudair IF**, Sadik ND, Hanssens YI. Prescribing pattern of acid suppressive medications for medical inpatients in a teaching hospital in Qatar. *Saudi Med J* 2009; **30**: 125-129
- 66 **Mayet AY**. Improper use of antisecretory drugs in a tertiary care teaching hospital: an observational study. *Saudi J Gastroenterol* 2007; **13**: 124-128

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