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Original Article

Intravenous proton pump inhibitor uses for stress ulcer prophylaxis in the critically ill: a single-center study in Pakistan

Saba Noureen[1,2], Waseem Ullah[1,3], Mahnoor Asad[1,4], Zita L Szabó[5], Márió Gajdács[6], Lua P Lin[7], Long C Ming[8], Suresh Shanmugham[9], Mian J Ahmed[10], Shazia Jamshed[9,11]

[1] *Shifa College of Pharmaceutical Sciences, Shifa Tameer-e-Millat University, 44000 Islamabad, Pakistan*
[2] *Boots Community Pharmacy, M1 Manchester, United Kingdom*
[3] *Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Lahore University of Biological and Applied Sciences, 53400 Lahore, Pakistan*
[4] *Rawal General and Dental Hospital (RG&DH), 44000 Islamabad, Pakistan*
[5] *Doctoral School of Experimental and Preventive Medicine, University of Szeged, 6720 Szeged, Hungary*
[6] *Department of Public Health, Albert Szent-Györgyi Medical School, University of Szeged, 6720 Szeged, Hungary*
[7] *Department of Pharmacy Practice, Faculty of Pharmacy, Universiti Sultan Zainal Abidin (UniSZA), 21300 Terengganu, Malaysia*
[8] *School of Medical and Life Sciences, Sunway University, Sunway City, Kuala Lumpur, Malaysia*
[9] *Department of Pharmacy Practice, School of Pharmacy, IMU (International Medical University), 57000 Kuala Lumpur, Malaysia*
[10] *Mufti Mehmood Memorial Hospital Kuchlak, 86700 Balochistan, Pakistan*
[11] *Department of Pharmacy Practice, Jinnah University for Women, Karachi 74600, Pakistan*

Abstract

Introduction: Irrational use of intravenous (IV) proton pump inhibitors (PPIs) for stress ulcer prophylaxis (SUP) in critically ill patients increases the risk of adverse drug reactions (ADRs), and may lead to longer stays in the intensive care unit (ICU).

Methodology: A single-center, retrospective, observational study was conducted to assess the practices with prescribing IV SUP in critically ill adult patients treated at ICUs between January 2020–December 2022. Data was collected from electronic medical records, using a pre-designed checklist. Appropriateness of SUP administration was determined using the American Society of Health-System Pharmacists (ASHP) recommendations.

Results: Medical records of 1076 patients were analyzed; majority of patients (80.9%; n = 873) received IV SUP during their ICU stay, with the most commonly prescribed drug being omeprazole (99.2%). 75.5% of patients had no major or minor risk factors based on ASHP guidelines. The rationale of SUP was deemed appropriate in 51.7% of cases. Among patients treated at specific ICU wards, male patients were less likely (OR: 0.587 [95% CI: 0.345–0.998]; $p = 0.048$), while ventilated patients were more likely (OR: 2.525 [95% CI: 1.219–5.233]; $p = 0.013$) to receive SUP. Furthermore, ≥10 days of hospital stay corresponded to notable increase (OR: 4.076 [95% CI: 0.870–19.098]; $p = 0.086$) in the probability of receiving SUP.

Conclusions: The results may provide a basis for developing protocols related to acid-suppressive therapy in critically ill adults, calling for heightened awareness and tailored interventions to optimize pharmacological care in ICU settings.

Key words: stress ulcer prophylaxis; intensive care unit; ICU; proton pump inhibitor; intravenous; observational study.

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Introduction

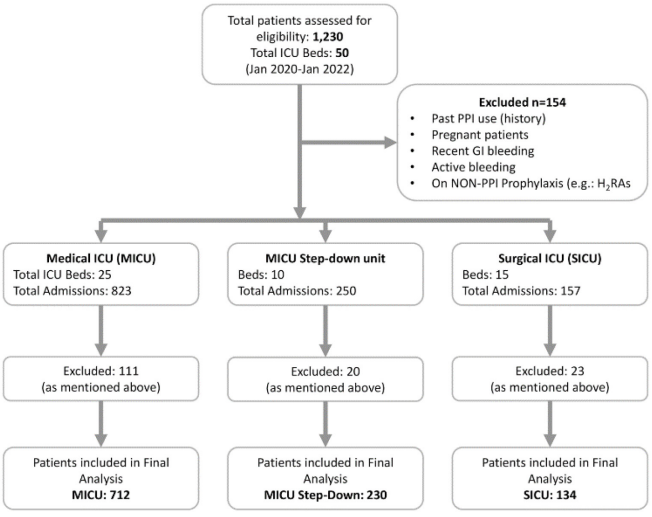
Stress ulcers (SUs; or gastric erosion) refer to adverse events presenting in the upper gastrointestinal (UG) tract, commonly occurring after a patient's hospitalization [1,2]. The first report of SUs dates back to 1969, where post-mortem examinations revealed isolated lesions in the gastric fundus mucosa in critically ill patients treated in intensive care units (ICUs) [3]. The exact mechanisms have not been understood; however, it has been suggested that the concurrence of sympathetic activation (leading to the release of cathecolamines) and release of pro-inflammatory cytokines due to stress may have a causative role, resulting in reduced perfusion and oxygenation, and disturbances in the integrity of the gastric mucosa, leading to greater vulnerability towards gastric acids [4]. Individuals may present with SUs that are asymptomatic, they may have occult bleeding, overt bleeding, or severe, life-threatening bleeding [5]. The risk for UG bleeding may increase if the patient concurrently receives drugs inhibiting prostaglandin (PG) synthesis and cyclooxygenase (COX) activity, including corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors and acetyl-salicylic acid [6,7]. The prevention of the occurrence of UG bleeding in hospitalized patients is

referred to as stress ulcer prophylaxis (SUP), the benefits of which were already suggested in the early 1970s [3,8]. Critically ill patients—both in adult and pediatric contexts—in intensive care units (ICUs) are at high risk of developing UG bleeding, for which they may receive prophylactic therapy [5,9,10]. According to previous studies utilizing endoscopic examinations, subepithelial bleeding and stress-related mucosal erosions impact ~74%–100% of critically ill patients within 24 hours of admission [2]; in comparison, the prevalence of clinically significant GI bleeding may range between 2–10% [11,12]. UG bleeding is a prevalent issue in ICUs, which may considerably influence the length of ICU stay, associated treatment costs, and mortality of affected patients [13]. The currently established clinical practice guidelines strongly support the use of SUP for the prevention of SUs in critically ill patients [14].

The American Society of Health-System Pharmacists (ASHP) and the Surviving Sepsis Campaign (SSC) guidelines identify high-risk patients (i.e. ones with major risk factors)—for whom SUP is recommended)—as those presenting with coagulopathy, neurological insults, or mechanical ventilation for more than 48 hours [15,16]. Furthermore, these guidelines also account for additional (minor) risk factors, such as sepsis, acute renal and hepatic failure, high-dose usage of corticosteroids (> 250 mg/day), and upper GI hemorrhage. The guidelines recommend that SUP be prescribed for a single major or two or more of these minor risk factors [15,16]. Histamine-2 receptor antagonists (H2RAs), sucralfate, and proton pump inhibitors (PPIs) are the most commonly used drugs for the purposes of acid-suppressive therapy [17,18]. H2RAs are shorter-acting drugs, with their effects mediated through the inhibition histamine-stimulated acid secretion, while PPIs are often longer-acting drugs, impairing the activity of the proton (H+) pumps in the parietal cells [19]; as an adjunctive treatment, sucralfate may also be added as a mucoprotective agent, which forms a protective layer against gastric secretions. A meta-analysis by Alshamsi *et al*. has concluded that PPIs are more effective as compared to H2RAs in the context of SUP [20]. An international survey conducted in 11 countries, including 97 adult intensive care units, reported that among all acid-suppressive drugs, PPIs were most commonly used for SUP [21]. However, in parallel to providing clinical benefits to patients, the (over)use of PPIs is associated with the occurrence of adverse drug reactions (ADRs), including cardiovascular events, decreased absorption of various ions and vitamins, heightened risk of respiratory infections (ventilator associated pneumonia, VAP), disturbances in the gut microbiota, and the development of *Clostridioides difficile* (*C. difficile*) infections [22,23]. PPIs are overprescribed for UG bleeding and SUP in hospital settings [24]. Various studies have questioned the safety (in terms of their risk-benefit ratio) of PPIs in SUP in the context of the ICU population, due to related infectious complications; however, these observations were not sufficient to lead to an amendment of clinical practice guidelines [25].

Irrational use of intravenous PPIs for SUP in critically ill patients increases the risk of ADRs, the development of complications and associated morbidity, and may lead to longer ICU stays and increased healthcare costs [26]. The frequency of UG bleeding caused by stress in the ICU may be reduced with current medical care. Previous research has demonstrated that regular SUP use in hospitalizations at ICUs may be unnecessary and is sometimes inappropriate [27,28]. Additional studies are needed to improve the definition of SUP indications in the ICU, by identifying patients who are at risk, and would benefit the most. The continuation of SUP in patients when transferred to general wards or discharged from a hospital is commonplace, if medication reconciliation or deprescribing does not take place [29]. Furthermore, patients treated in non-ICU wards are routinely provided SUP, despite mounting concerns about its potentially serious adverse effects [30]. The above phenomena may lead to over-utilization of acid suppressive therapy, which causes medication

Figure 1. Flowchart of the study population (N = 1076).



ICU: intensive care unit; PPI: proton pump inhibitor; GI: gastrointestinal; H2RA: histamine-2 receptor antagonist; MICU: medical intensive care unit; SICU: surgical intensive care unit.

overburden on patients, in addition to increasing iatrogenic risks and healthcare costs [31]. There is currently a paucity of information regarding the principles and practices associated with SUP at healthcare institutions. According to the study of Rauch *et al*., a significant portion (68%) of acute care hospitals in the northeastern region of Germany has no standard operating procedures (SOPs) developed for SUP; additionally, where an SOP existed for SUP, 47.6% of healthcare-professionals authorized to prescribe SUP were unaware of the existence of these SOPs, and among the ones who were aware of the SOP, merely 42.9% were familiar with its contents [30]. Furthermore, their study highlighted that the rate of re-evaluation of SUP-prescriptions following the transfer of the patients from the ICU to other wards, or before discharge, was also poor [30].

The overuse of PPIs in the context of SUP has been well documented in the literature, especially in Western countries; however, scarce evidence is available in the context of developing regions. To the best of our knowledge, information about the current institutional practices of PPI use for SUP in critically ill patients in Pakistan is very limited and needs further investigations on a national level [32]. Therefore, the aim of this observational study with real-world data was to assess the current practices of the use of IV PPIs in critically ill adult patients for SUP, in addition to assessing the alignment with ASHP guidelines, and the potential facilitators of prescribing SUP, to provide evidence for the judicious use of these medicines in the Pakistani context.

Methodology

Study design, setting, duration

The present single-center, retrospective, observational study was carried out to assess the current SUP prescription practices and the influencing factors of IV SUP prescriptions in critically ill adult patients treated at the ICUs of Shifa International Hospital (SIH) Ltd., located in Islamabad, Pakistan. SIH is a 550-bed, tertiary-care hospital, accredited by the Joint Commission International (JCI); SIH possesses 50 ICU beds and has multiple facilities for organ transplantation (e.g., kidney, liver, bone marrow, and cornea). The study included data on patients treated at the ICUs over a 3-year period, between January 2020 to December 2022.

Study population, inclusion and exclusion criteria, data collection procedures

The target study population was critically ill adult (aged ≥ 18 years) patients who received IV PPIs during their hospital stay at the critical treatment wards of SIH. Data for the study was collected through non-probability sampling, accessing patients' files, as well as from electronic medical records (EMRs) through the Medication Ordering and Administration Records (MOAR) system. Critically ill adult patients admitted at the medical intensive care unit (MICU), surgical intensive care unit (SD), and the general intensive care unit (SICU) of SIH were taken as the sample population. The sample size required for the study was determined using the Raosoft Sample Size Calculator [33], based on the formula described below:

$$n = N\frac{x}{(N-1)E2+x}$$

where "x" is the expected prevalence and "E" is the margin of error. The population was set to N = 20,000 (default setting of the software, as the total size of the target population was unknown) [10]; the required confidence level was 95%; the acceptable margin of error was 5%; and the sample size determination was carried out considering a 50% prevalence of receiving SUP in ICU patients in Pakistan, due to the lack of reliable data in the area of investigation [32]. Overall, a minimum sample size of n = 377 patients was determined for the completion of this study.

Adult (aged ≥ 18 years) patients in critical care, who received IV PPIs during their ICU stay were eligible for data collection. On the other hand, patients with incomplete information in their medical records, a past medication history of PPI use, those who were pregnant, patients with a recent history of gastrointestinal (GI) bleeding, those with active bleeding, and patients receiving stress ulcer prophylaxis with agents other than PPIs (e.g., H_2RAs) were excluded from the study. EMRs were obtained from the medical coding department of the hospital. The medical record (MR) numbers were entered in the hospital's Medical Information System (MIS) to collect patient's data based on a pre-designed checklist, including demographic characteristics (age, gender), past medication history, current medications received in the hospital, PPI agent used for SUP, appropriateness of SUP, length of hospital stay, and discharge medications. Specifically, data on the presence of major and minor risk factors, including mechanical ventilation, coagulopathy, sepsis, acute renal failure, acute hepatic failure, and use of hydrocortisone > 250 mg/day, were also collected. The data was de-identified prior to being used by the researchers per the

institutional data privacy policy and de-identification standards; therefore, information could not be traced back to the patients/individuals treated at the healthcare facility [10]. Data collection was performed retrospectively for the 3-year period (January 2020 to December 2022) between July-August 2023.

Outcome measures

The primary outcome variable assessed was the use of IV PPIs for SUP in critically ill patients, admitted to the MICU, SICU, and SD wards of SIH. The secondary outcome measures were: i) the influencing factors associated with the initiation of SUP, and ii) the appropriateness of the initiation of SUP. According to ASHP guidelines, the use of SUP is appropriate when 1 major or more than 1 minor risk factors are present in the patient [15,16,34,35]. The patients were divided into 4 groups based on the data to enable risk stratification: group 1 included patients with one or more major risk factors; group 2 included patients with one or more minor risk factors; group 3 included patients with no major or minor risk factors; group 4 included patients with both major and minor risk factors.

Statistical analysis

The data collected during the study was managed in a Microsoft Excel (Microsoft Corp. Redmond, WA, USA) spreadsheet, which was transferred to Statistical Package for Social Sciences (SPSS) v.22.0 (IBM Corp., Endicott, NY, USA) for analysis, after data management and coding. All categorical variables were described as frequencies and percentages (n, %) during descriptive statistical analyses, while continuous variables were expressed as means (with standard deviations [SD]). Normality testing was performed using Q-Q diagrams and Kolmogorov–Smirnov tests (these tests resulted in $p > 0.05$, indicating normal distribution of data, and the use of parametric tests). During univariate analysis, associations between categorical variables were assessed using χ^2-tests and Fisher's exact tests. Univariate binary logistic regression analysis was used to assess the association between independent variables (demographic and clinical characteristics) and the binary outcome (receipt of IV SUP medication). The results were expressed as odds ratios (ORs) and 95% confidence intervals (95% CI). p values < 0.05 were considered as strong evidence against the null hypothesis of no effect, p values between 0.05–0.1 were considered as moderate evidence against the null hypothesis of no effect, and $p > 0.1$ indicated weak/no evidence against the null hypothesis of no effect.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki (1975, last revised in 2024) and national and institutional ethical standards. Ethical approval for the study was obtained from the Institutional Review Board (IRB) and the ethics committee of SIH, Islamabad (ethical approval ID: 0144-23; approval date: 21 June 2023). The present retrospective study was based on EMRs, which is exempt from informed consent (with the exception of patients, who made any prior declaration of his/her non-consent for participation in any type of study or research). The data reviewed was a secondary analysis of existing data, which did not involve intervention or interaction with human subjects. Furthermore, data received and used by the researchers were de-identified, per institutional data privacy policy and de-identification standards; therefore, information could not be traced back to patients/individuals treated at the healthcare facility [10].

Reporting standards

This paper adheres to the 'strengthening the reporting of observational studies in epidemiology' (STROBE) guidelines for cross-sectional studies to ensure methodological rigor, transparency, and reproducibility [36]. The use of this structured reporting framework supports the clarity and consistency of this observational study [36].

Results

Demographic characteristics of the study population

A total of N = 1230 adult patients' data were assessed for eligibility in the study during the 3-year study period (January 2020 to December 2022). After consideration of the inclusion and exclusion criteria, the total analyzed cohort included N = 1076 patients undergoing treatment in one of the SIH's ICUs. The detailed breakdown of the study population is presented in Figure 1. Out of the total pool of eligible patients, 66.1% (n = 712) were admitted to the MICU ward, 21.5% (n = 230) were in the SD, while 12.4% (n = 134) were in the SICU; the largest number of patients (n = 111) were excluded from the MICU population. The summary of demographic characteristics of the study population is presented in Table 1. 58.5% (n = 629) of patients were male, the majority of them (37.8%; n = 405) were between 59–78 years of age. 71.5% (n = 770) had spent less than 5 days in the hospital. The age range of patients was 18–98 years.

Distribution and clinical characteristics of the population in the ICUs

The clinical characteristics and distribution of the population in the ICUs (MICU n = 712, SICU n = 134, and SD n = 230) of SIH are described in Table 2. No relevant differences among the ICUs were noted in gender distribution (p = 0.487). Overall, majority of patients (80.9%; n = 873) received IV SUP, whereas MICU patients received SUP more commonly, compared to patients treated in the SICU and SD wards (p < 0.001); most patients (99.2%; n = 866) were prescribed omeprazole (p = 0.982). Among the major risk factors, mechanical ventilation was needed in 8.5% (n = 91, more commonly among MICU patients, p < 0.001); while coagulopathy was observed in 3.4% (n = 36; more commonly among MICU patients, p < 0.001) of cases. Among the minor risk factors, 4.8% (n = 52) received > 250 mg/day hydrocortisone, 5.5% (n = 59) had sepsis, 2.6% (n = 28) had acute kidney injury (AKI), and 0.5% (n = 5) had acute hepatic failure (AHF); 3.1% (n = 34) of patients who were septic and received steroids; 0.3% (n = 3) septic patients also presented with AKI, and 0.3% (n = 3) of patients had concurrent AKI and AHF, respectively (Table 2). 22.1% (n = 238) received acid-suppressive SUP drugs as discharge medications (more commonly among MICU patients, p < 0.001). The most common drugs prescribed during discharge were omeprazole (89.0%; n = 212), followed by dexlansoprazole (5.5%; n = 13), esomeprazole (2.9%; n = 7), and pantoprazole (2.6%; n = 6), respectively.

Table 1. Demographic characteristics of the study population (N = 1076).

Characteristics	*n* (%)
Wards	
MICU	712 (66.1%)
SICU	134 (12.4%)
SD	230 (21.5)
Gender	
Male	629 (58.5%)
Female	447 (41.5%)
Age (years)	
18–38	233 (21.6%)
39–58	332 (30.8%)
59–78	405 (37.8%)
79–98	106 (9.8%)
Length of hospital stay	
< 5 days	770 (71.5%)
≥ 5 days	306 (28.5%)

MICU: medical intensive care unit; SD: surgical intensive care unit; SICU: general intensive care unit.

Relationship between clinical characteristics and SUP

The results of the univariate binary logistic regression analyses, assessing the association between independent variables (demographic and clinical characteristics) and the main outcome (receipt of IV SUP medication) are shown in Tables 3–5, for patients admitted to the MICU, SD, and SICU wards of SIH,

Table 2. Summary of clinical characteristics of the patient population (N = 1076).

Variables	MICU (*n* = 712) *n* (%)	SD (*n* = 230) *n* (%)	SICU (*n* = 134) *n* (%)
Gender			
Male	420 (59.0%)	137 (59.6%)	72 (53.7%)
Female	292 (41.0%)	93 (40.4%)	62 (46.3%)
Receipt of SUP			
No	37 (5.1%)	122 (53.1%)	44 (32.8%)
Yes	675 (94.8%)	108 (46.9%)	90 (67.2%)
Agent for IV SUP			
Omeprazole	671 (99.4%)	106 (98.2%)	89 (99.0%)
Esomeprazole	4 (0.6%)	2 (1.8%)	1 (1.0%)
Major risk factors			
Mechanical ventilation			
No	625 (87.8%)	230 (100.0%)	130 (97.0%)
Yes	87 (12.2%)	0 (0.0%)	4 (3.0%)
Coagulopathy			
No	688 (96.6%)	228 (99.1%)	124 (92.5%)
Yes	24 (3.4%)	2 (0.9%)	10 (7.5%)
Minor risk factors			
Hydrocortisone > 250 mg/day	44 (6.2%)	5 (2.2%)	3 (2.2%)
Sepsis	32 (4.5%)	24 (10.4%)	3 (2.2%)
Sepsis + Hydrocortisone	39 (5.5%)	1 (0.4%)	0 (0.0%)
AKI	19 (2.7%)	5 (2.2%)	4 (3.0%)
AHF	4 (0.6%)	1 (0.4%)	0 (0.0%)
Sepsis + AKI	1 (0.1%)	2 (0.9%)	0 (0.0%)
AHF + AKI	3 (0.4%)	0 (0.0%)	0 (0.0%)
Receipt of SUP as discharge medication			
No	554 (77.8%)	205 (89.0%)	79 (59.0%)
Yes	158 (22.2%)	25 (11.0%)	55 (41.0%)

MICU: medical intensive care unit; SD: surgical intensive care unit; SICU: general intensive care unit; SUP: stress ulcer prophylaxis; AKI: acute kidney injury; AHF: acute hepatic failure.

Table 3. Associations between underlying characteristics of patients treated at the medical intensive care unit ward and receipt of stress ulcer prophylaxis.

Variables	*n*	Receipt of SUP during ICU stay		Odds ratio (OR)	*p* value	95% CI
		No (*n* = 37)	Yes (*n* = 675)			
Gender						
Female (Ref.)	292	14	278	1	0.687	---
Male	420	23	397	0.869		0.440–1.719
Age (years)						
18–38 (Ref.)	154	2	152	1	0.591	---
39–58	225	13	212	0.536		0.187–1.536
59–78	262	16	246	0.506		0.182–1.409
79–98	68	3	65	0.713		0.165–3.071
Mechanical ventilation						
No (Ref.)	625	36	589	1	0.094	---
Yes	87	1	86	5.256		0.711–38.83
Coagulopathy						
No (Ref.)	688	37	651	1	n.r.	---
Yes	24	0	24	n.r.		---
Minor risk factor present						
No (Ref.)	570	34	536	1	0.077	---
Yes	142	3	139	2.93		0.890–9.710
Length of hospital stay						
1–15 days (Ref.)	676	35	641	1	0.921	---
16–30 day	36	2	34	0.928		0.241–4.021
Receipt of SUP as discharge medication						
No (Ref.)	554	37	517	1	n.r.	---
Yes	158	0	158	n.r.		---

MICU: medical intensive care unit; SUP: stress ulcer prophylaxis; Ref: reference category; n.r.: not relevant; CI: confidence interval; OR: odds ratio.

respectively. Among the MICU patients, a moderately strong evidence was shown for the association between the presence of minor risk factors (OR: 2.930 [95% CI: 0.890–9.710]; $p = 0.077$) and need for the mechanical ventilation (OR: 5.256 [95%CI: 0.711–38.83]; $p = 0.094$), and the receipt of SUP medication; while no relevant association was shown in the context of other variables (Table 3). Among the SD patients, male patients were 41.3% less likely (OR: 0.587 [95% CI: 0.345–0.998]; $p = 0.048$) to receive SUP compared to female patients, while the need for mechanical ventilation increased the rate of receiving SUP by 2.5-fold (OR: 2.525 [95% CI: 1.219–5.233]; $p = 0.013$); other variables did not show relevant associations with the receipt of SUP medications (Table 4). In the case of patients treated at the SICU ward, length of hospital

Table 4. Associations between underlying characteristics of patients treated at the surgical intensive care unit ward and receipt of stress ulcer prophylaxis.

Variables	*n*	Receipt of SUP during ICU stay		Odds ratio (OR)	*p* value	95% CI
		No (*n* = 122)	Yes (*n* = 108)			
Gender						
Female (Ref.)	93	42	51	1	**0.048***	---
Male	137	80	57	0.587		0.345–0.998
Age (years)						
18–38 (Ref.)	36	24	12	1	0.277	---
39–58	65	35	30	1.714		0.735–4.0
59–78	101	48	53	2.208		0.997–4.892
79–98	28	15	13	1.733		0.628–4.787
Mechanical ventilation						
No (Ref.)	230	122	108	1	n.r.	---
Yes	0	0	0	n.r.		---
Coagulopathy						
No (Ref.)	228	122	106	1	n.r.	---
Yes	2	0	2	n.r.		---
Minor risk factor present						
No (Ref.)	192	109	83	1	**0.013***	---
Yes	38	13	25	2.525		1.219–5.233
Length of hospital stay						
1–15 days (Ref.)	221	118	103	1	0.60	---
16–30 days	9	4	5	1.432		0.375–5.475
Receipt of SUP as discharge medication						
No (Ref.)	205	122	83	1	n.r.	---
Yes	25	0	25	n.r.		---

SD: surgical intensive care unit; SUP: stress ulcer prophylaxis; Ref: reference category; n.r.: not relevant; CI: confidence interval; OR: odds ratio; *p* values <0.05 are denoted in **bold** font.

Table 5. Associations between underlying characteristics of patients treated at the general intensive care unit ward and receipt of stress ulcer prophylaxis.

Variables	*n*	Receipt of SUP during ICU stay		Odds ratio (OR)	*p* value	95% CI
		No (*n* = 44)	Yes (*n* = 90)			
Gender						
Female (Ref.)	62	20	42	1	0.895	---
Male	72	24	48	0.952		0.462–1.964
Age (years)						
18–38 (Ref.)	37	14	23	1		---
39–58	42	12	30	1.522	0.848	0.593–3.908
59–78	45	15	30	1.217		0.491–.020
79–98	10	3	7	1.42		0.315–6.409
Mechanical ventilation						
No (Ref.)	130	43	87	1	0.736	---
Yes	4	1	3	1.483		0.150–14.678
Coagulopathy						
No (Ref.)	124	43	81	1	0.144	---
Yes	10	1	9	4.778		0.586–38.970
Minor risk factors						
No (Ref.)	124	44	80	1	n.r.	---
Yes	10	0	10	n.r.		---
Length of hospital stay						
1–4 days (Ref.)	96	37	59	1		---
5–9 days	23	5	18	2.258	0.086	0.772–6.599
≥10 days	15	2	13	4.076		0.870–19.098
Receipt of SUP as discharge medication						
No (Ref.)	79	38	41	1	**< 0.001**	---
Yes	55	6	49	7..569		2.911–19.684

SICU: general intensive care unit ward; SUP: stress ulcer prophylaxis; Ref: reference category; n.r.: not relevant; CI: confidence interval; OR: odds ratio; *p* values < 0.05 are denoted in **bold** font.

stay was a notable determinant of receiving SUP: a stay of 5–9 days corresponded to a 2.26-fold increase (OR: 2.258 [95% CI: 0.772–6.599]), while a stay ≥ 10 days corresponded to a ~4-fold increase (OR: 4.076 [95% CI: 0.870–19.098]) in receiving SUP ($p = 0.086$), compared to shorter stays (Table 5).

Risk factors stratification, appropriateness of SUP administration

Table 6 summarizes the classification of ICU patients and the use of SUP on the basis of risk stratification categories. Patients in "group 3" were the most common in all the three ICU wards and overall (75.5%; n = 810; MICU: n = 503 (70.6%); SD: n = 193 (83.9%); SICU: n = 114 (85.1%); no relevant differences were observed in the distribution of risk stratified patients among the ICUs ($p = 0.236$) (Table 6). Similarly, patients in group 3 were the ones most commonly receiving SUP (MICU: n = 470 (69.6%); SD: n = 83 (76.9%); SICU: n = 72 (80.0%), with significant differences noted among the ICU wards in the distribution of stratified patient groups ($p < 0.001$). The rationale of SUP use based on ASHP guidelines, was also determined in ICU patients; overall, the rationale of SUP was deemed appropriate in 51.7% (n = 451) of patients. In the MICU ward, 34.0% (n = 242) of SUP use were deemed appropriate, while in the SD and SICU wards, SUP use was appropriate in 62.4% (n = 147) and 46.3% (n = 62) of cases, respectively ($p < 0.001$).

Discussion

SUP is an established practice in current clinical guidelines to prevent ulceration and bleeding in the UG tract in critically ill patients who present with well-defined major and/or minor risk factors [37]; the most commonly used drugs in the indication of SUP are IV PPIs, which have demonstrated reliable efficacy as acid-suppressive therapy [20]. However, due to lack of institutional and/or national practice guidelines, or

Table 6. Risk-stratified analysis of SUP usage among intensive care unit patients in Shifa International Hospital.

Risk groups	Risk stratification in patients in various ICU wards			Frequency of IV SUP use based on risk stratification		
	MICU (*n* = 712)	SD (*n* = 230)	SICU (*n* = 134)	MICU (*n* = 675)	SD (*n* = 108)	SICU (*n* = 90)
1	52 (7.3%)	1 (0.4%)	7 (5.2%)	52 (7.7%)	1 (0.9%)	5 (5.6%)
2	78 (10.9%)	32 (13.9%)	9 (6.7%)	74 (10.9%)	21 (19.4%)	9 (10.0%)
3	503 (70.6%)	193 (83.9%)	114 (85.1%)	470 (69.6%)	83 (76.9%)	72 (80.0%)
4	79 (11.2%)	4 (1.8%)	4 (3.0%)	79 (11.8%)	4 (2.8%)	4 (4.4%)

MICU: medical intensive care unit; SD: surgical intensive care unit; SICU: general intensive care unit; SUP: stress ulcer prophylaxis; ICU: intensive care unit; SIH: Shifa International Hospital.

SOPs in many countries, over-utilization of IV PPIs as SUP has been highlighted in many countries, where reliable pharmaco-epidemiological data is available. Based on previous estimates, 22–88% of patients discharged from or admitted outside of the ICU may continue to receive SUP without the presence of risk factors relevant to stress ulcer development [38]. It must be emphasized that the benefits of SUP administration in patients without the defined risk factors (delineated by ASHP recommendations) present is not well supported by recent evidence. Furthermore, accumulating data on the possible ADRs associated with the use of IV PPIs, especially among hospitalized, ventilated patients, who are at high risk of developing healthcare-associated infections, should urge clinicians to administer them judiciously, to avoid their misuse, and to carefully weigh the risk-benefit associated with their use. Crafting and implementation of clinical practice guidelines should also take into account the potential economic burden resulting from IV PPI overuse, estimated at over £2 billion worldwide (including the burden on patients and the healthcare systems) [39]. Such guidelines could also emphasize the importance of the IV-to-oral shift in therapy to avoid the potential complications associated with their intravenous use (including infections, longer ICU stays, and increased healthcare costs). To improve the rational use of SUP medicines, and to craft and implement locally-adapted SOPs, reliable information on current drug utilization practices is crucial; however, limited data was available on the indications and rationale of acid-suppressant drug use in Pakistan in critically ill patients.

The present single-center, retrospective, observational study was conducted to explore the patterns of IV SUP administration practices and their influencing factors in critically ill adult patients treated at ICUs in a Pakistani context. Furthermore, the study aimed to propose strategies for optimizing the use of pharmacological interventions, particularly PPIs, in critically ill patients, ensuring a more rational approach to drug prescribing in ICU settings. In this study, 80.9% patients received IV SUP during their stay in one of the ICUs in the SIH hospital. Furthermore, 22.1% received acid-suppressive SUP drugs as a part of their discharge; most patients were prescribed IV omeprazole. These findings are consistent with previously reported research, which has also highlighted the widespread use of omeprazole in ICU settings for the indication of SUP therapy [31,37,40–41]. Patients who received SUP in the medical ICU most commonly were generally in more severe condition; however, the patients in "group 3" (i.e. patients with no major or minor risk factors) were the most common in the present cohort. This study also explored the rationalization of SUP, taking into account the ASHP guidelines as reference [15,16,35,36]; around half (51.7%) of the SUP prescriptions were considered suitable: the worst guideline adherences were seen for patients in the MICU (34.0%), while the best adherence was shown in the SICU (62.4%). The results show a tendency towards the prescription of SUP if mechanical ventilation was needed and minor risk factors were present in case of MICU patients; for patients at the SICU ward, a longer hospital stay increased the odds of receiving SUP. Finally, male patients in the SICU were considerably less likely to receive SUP drugs.

The results confirm the previous findings of Alsultan *et al*., highlighting the irrational use of IV PPIs (71.7% among non-ICU and 19.8% among ICU patients) in the context of ASHP guidelines in a teaching hospital situated in Riyadh, Saudi Arabia [29]. Furthermore, the findings of Aramesh *et al*. correspond to the phenomenon where there is high prevalence of ICU patients, without the relevant major and minor risk factors ("group 3"), receiving IV SUP medications [42]. Samar *et al.* assessed the appropriateness of PPI prescriptions to patients admitted in a tertiary-care hospital in Karachi, Pakistan in single-center observational study based on the guidelines of the American Gastroenterology Association (AGA) [32]. They highlighted that inappropriate use of PPI is common, with only 33.8% of patients receiving SUP according to AGA recommendations, and 72.8% given PPIs orally. Moreover, in a 2-year cohort study performed in the same settings, Arif *et al*. determined the rationale of SUP use among patients admitted to the pediatric ICU (PICU) [10]: 61.4% of children admitted to the PICU of SIH received SUP medications, of which, omeprazole (95.0%) and esomeprazole (3.6%) were the most commonly prescribed. 69.8% received SUPs in doses in accordance with the institutional dosing protocol, while the rest were either under or overdosed. Their study also highlighted the potential drug-drug interactions (e.g., antimicrobial agents, antiplatelet medications, sedatives, anti-seizure medications) associated with the use of PPIs, due to their microsomal (CYP) enzyme inhibitory properties [10].

In addition to ICU patients, individuals undergoing surgical procedures may also be vulnerable to stress ulcers, due to anxiety and stress associated with procedures (or trauma), and due to starvation [4]. Malik *et al.* conducted a single-center retrospective cohort

study and assessed the rationality of SUP in patients undergoing surgical procedures in Islamabad, Pakistan [43]. They reported that 72.2% of patients were prescribed SUP for an appropriate indication, and in appropriate doses based on ASHP guidelines. Majority (60.2%) of patients received SUP orally; the most frequently prescribed PPIs was omeprazole, both in oral (37.7%) and in parenteral (39.7%) formulations. In contrast, in a similar cohort of patients, the EHR-based study of Wijaya *et al.* found that ~48% of the usage of SUP drugs was not suitable according to ASHP criteria. Furthermore, their study highlighted the considerable economic burden associated with this form of medication overuse [44]. In a Chinese context, Li *et al*. determined the appropriateness of prescribed SUP medications administered to surgical patients between January 2020 to August 2021: 74.4% of the population were prescribed PPIs (with 96.1% receiving PPIs; corresponding to 57.9 defined daily doses (DDDs)/100 patient-days). Most patients (95.3%) received IV SUP, with pantoprazole (46.7%), omeprazole (29.7%), lansoprazole (13.2%), and esomeprazole (10.4%). According to the recently introduced guidelines of the National Health Commission of the People's Republic of China, the receipt of SUP was deemed inappropriate in 42.4% of cases (corresponding to 43.1 DDDs/100 patient-days). Based on regression analyses, patients aged > 65 yrs and with prolonged hospitalization were corresponding with higher odds of prescribing SUP; on the other hand, receipt of corticosteroids or hypertension in the anamnesis were associated with a lower probability of SUP prescriptions [37].

The results suggest that tailored strategies should be implemented to raise medical professionals' awareness to reduce the overuse of SUP during first-time inpatient treatments. Additionally, efforts should focus on encouraging the discontinuation of SUP, when it is no longer necessary, particularly before patients leave the hospital, to prevent stress ulcers in the critical care context. Therapeutic decisions related to drugs, such as SUP and continuation of drug prescriptions under transfer orders, are often authored by residents and junior physicians rather than attending physicians [31], and occasionally with lack the oversight of the attending personnel [45]. This demonstrates the significance of medication reconciliation upon release to prevent the use of improper prescription drugs. However, continuing professional education and awareness campaigns – on their own – are often insufficient to address such problems, without deep-rooted changes in the practices within the healthcare system. This study suggests that a comprehensive strategy involving pharmacists, physicians, nurses, and electronic order sets should be implemented. This strategy would require justification before initiating SUP, to ensure continuity with transfer orders, and should include regular reminders advocating for the cessation of SUP. Furthermore, clinical pharmacists should suggest the most appropriate strategies (preferentially perorally if possible) for medication administration in inpatients.

The limitations of the present study should be addressed, and may serve as a foundation for the planning of future studies. Given the cross-sectional and observational nature of the study, associations identified should not be taken as the only indicators of medical conduct [46]; many other factors may influence physicians' decision to administer SUP, which were outside of the study's scope. This study was carried out in a single-center hospital in Islamabad, Pakistan, affecting the validity and generalizability of the findings to different settings. Specifically, drug costs and availability may have great influence on the choice of SUP in other hospitals. Furthermore, the results may be influenced by selection bias, as the study population originated from a tertiary-care hospital, presumably treating patients in more severe conditions or with more underlying illnesses. The use of univariate binary logistic regression for the analyses should also be mentioned: in future studies, multivariate regression may be applied, to assess the relationship and interlinked effects of studied independent variables. Although the sample size of the entire study was adequate, some subcategories of patients had very low sample sizes due to the fragmentation of data; thus, no inferential analysis could be conducted in these cases. One highlight of this study is that it used real-world data—in the form of EHRs—to evaluate the rationale of SUP prescription practices in the ICU. However, it should be noted that EMRs are often not made and maintained for the purposes of research data collection. Thus, the study findings may be affected by bias, due to the quality and accuracy of recorded data. The data collection did now follow up on the adverse events and outcomes due to SUP administration, as these outcomes may overlap with common adverse events experienced in ICU patients, frequently brought on by the underlying illnesses. As the majority of patients in the study population received IV PPI as SUP, this would have resulted in a minor comparison group; and because confounding by symptoms alone may be responsible for worse outcomes (including frequently brought on by the underlying illness, delirium, *C. difficile* infections) in patients in more severe condition who received SUP.

Moreover, there are additional reasons for UG irritation and bleeding that have not been investigated or validated in earlier research, which this study likewise failed to include [5,47,48].

Conclusions

The present study aimed to explore the patterns and rationale of SUP prescriptions in adult ICU populations in the context of the Pakistani healthcare system. The strength of the study was the utilization of EMRs to provide real-world insights towards SUP utilization practices. The findings highlighted that IV PPIs use, particularly omeprazole, were prevalent in these settings. Furthermore, based on patients' underlying characteristics, a substantial portion of these prescriptions were constituting overuse. This trend is concerning, as prescribing practices were found to be inconsistent with ASHP guidelines, suggesting that knowledge of and adherence to evidence-based protocols needs to be improved. Additionally, a notable number of ICU patients were also discharged on prophylactic medications, raising concerns about the continued use of PPIs beyond the immediate hospital setting. These findings highlight the urgent need to rationalize drug use in critically ill populations, ensuring that medications like PPIs are prescribed appropriately, only when necessary, and in accordance with established guidelines. These results may provide a basis for developing protocols related to acid-suppressive therapy in critically ill adults, calling for heightened awareness and intervention to optimize pharmacological care in ICU settings and reduce unnecessary drug exposure for critically ill patients. Additionally, the findings highlight potential directions for future research, particularly concerning the long-term use of acid-suppressive drugs and their associated ADRs.

Based on these findings, our specific recommendations are as follows: i) hospital specific guidelines should be developed to enhance the appropriateness of SUP (especially their IV use) with the aid and involvement of critical care teams and pharmacists, ii) the awareness of physicians should be improved to both reduce the overuse of SUP and to avoid continuation of SUP after discharge, highlighting the need of inter-professional communication and medication reconciliation, iii) to limit the overuse of PPIs for SUP therapy; and after discharge, it is necessary to develop potential interventions, such as automatic discontinuance orders, justification for therapy commencement, and formulary methods.

Authors' contributions

Conceptualization: SN, WU, MA, MJA; methodology: ZLS, MG, LCM, SS, SJ; software: SN, ZLS, MG; validation: MJA, LPL, SJ; formal analysis: SN, MA, MG; investigation: WU, LPL, SS, MJA; resources: LCM, MJA, SJ; data curation: SN, WU, MA, MJA; writing—original draft preparation: WU, MA, MJA, SS; writing—review and editing: ZLS, MG, LCM, LPL, SJ; visualization: SN, WU, MG; supervision: LCM, LPL, SJ; project administration: MJA, SS; funding acquisition: MG, SJ. All authors have read and agreed to the published version of the manuscript.

Data availability statement

All data generated during the study are presented in this paper.

Corresponding author

Márió Gajdács, PharmD, MPH, MSc, PhD.
Department of Public Health, Albert Szent-Györgyi Medical School,
University of Szeged, 6720 Szeged, Hungary.
Tel: +36-62-342-871
Fax: +36-62-342-871
Email: mariopharma92@gmail.com

Conflict of interest

No conflict of interest is declared.

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