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# Rational use of acute gastric mucosal injury prophylaxis in intensive care unit without compromising patient safety: a cohort study

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## Abstract

Background Acute gastric mucosal injury poses a significant risk of gastrointestinal bleeding in intensive care unit patients. Prophylaxis is frequently applied but its indiscriminate use may cause adverse effects. **Objective:** To evaluate the effectiveness and safety of a rational prophylaxis protocol for acute gastric mucosal lesions in critically ill patients based on clinical risk criteria. **Methods:** Retrospective observational study with a comparative analysis between two periods: cohort 1 (January to December 2021), before the protocol implementation, and cohort 2 (January to December 2022), after adopting the protocol based on the criteria proposed by Ye et al. (2020). The outcomes analyzed were the use of proton pump inhibitors (PPIs), upper gastrointestinal bleeding (UGIB), ventilator-associated pneumonia (VAP), and *Clostridioides difficile* infection. **Results:** A total of 1,614 patients were included, 641 in the pre-exposure group and 973 in the post-exposure group. There was no difference in age, sex, disease severity, previous comorbidities, or use of intensive therapies between groups. The results indicated a significant reduction in proton pump inhibitors use, from 51% in the pre-exposure group to 40% in the post-exposure group ($P < 0.001$). Furthermore, no significant differences were observed between groups for diagnostic outcomes of gastrointestinal bleeding, respiratory complications, healthcare-associated infections, duration of mechanical ventilation, length of hospital stay, or mortality. **Conclusion:** The protocol for the rational use of proton pump inhibitors was effective in reducing the use of these drugs without compromising the safety and clinical outcomes of intensive care unit patients. These results must be confirmed by randomized control trials.

**Keywords:** Critical care; Patient safety; Stress ulcer; clinical pharmacy.

# Uso racional da profilaxia de lesão aguda da mucosa gástrica na unidade de terapia intensiva sem comprometer a segurança do paciente: um estudo de coorte

## Resumo

Introdução: A lesão aguda da mucosa gástrica representa um risco significativo de sangramento gastrointestinal em pacientes internados na unidade de terapia intensiva (UTI). A profilaxia é frequentemente utilizada, mas seu uso indiscriminado pode causar efeitos adversos. **Objetivo:** Avaliar a efetividade e a segurança de um protocolo racional para a profilaxia de lesão aguda da mucosa gástrica (LAMG) em pacientes internados em unidade de terapia intensiva (UTI), com base em critérios clínicos de risco. **Método:** Estudo observacional retrospectivo com duas coortes de pacientes internados em unidade de terapia intensiva (UTI): coorte 1 (janeiro a dezembro de 2021), antes da implementação do protocolo, e coorte 2 (janeiro a dezembro de 2022), após sua adoção. O protocolo recomendava a prescrição de IBPs apenas para pacientes com fatores de risco absolutos, como ventilação mecânica sem nutrição enteral, coagulopatia ou doença hepática, conforme os critérios clínicos propostos por Ye et al. (2020). A exposição avaliada foi a implementação do protocolo, o desfecho primário foi a taxa de uso de IBPs, e os desfechos secundários foram hemorragia digestiva alta (HDA), pneumonia associada à ventilação mecânica e infecção por *Clostridioides difficile*. O tempo de seguimento correspondeu à permanência dos pacientes na UTI. **Resultados:** Um total de 1.614 pacientes foi incluído, sendo 641 no grupo pré-exposição e 973 no grupo pós-exposição. Não houve diferença entre os grupos em relação à idade, sexo, gravidade da doença, comorbidades prévias ou uso de terapias intensivas. Os resultados indicaram uma redução significativa no uso de IBPs, de 51% no grupo pré-exposição para 40% no grupo pós-exposição ($P < 0,001$). Além disso, não foram observadas diferenças significativas entre os grupos nos desfechos clínicos avaliados, incluindo diagnóstico de sangramento gastrointestinal, complicações respiratórias, infecções associadas aos cuidados de

saúde, duração da ventilação mecânica, tempo de internação hospitalar ou mortalidade. **Conclusão:** Conclusão: O protocolo para o uso racional de IBPs foi eficaz na redução do uso desses medicamentos sem comprometer a segurança e os desfechos clínicos dos pacientes na UTI. Estes resultados devem ser confirmados por estudos randomizados controlados.

**Palavras-chave:** Cuidados críticos; Segurança do paciente; Úlcera de estresse; farmácia clínica.

## Introduction

Acute gastric mucosal injury (AGMI) comprises a wide range of conditions beyond stress ulcers that can cause gastrointestinal bleeding. This disorder includes erosive gastritis, mucosal erosions, gastric and duodenal hemorrhage, Mallory-Weiss syndrome, and other causes of upper gastrointestinal bleeding (UGIB)[1].

The etiology of AGMI is multifactorial. The main mechanisms involved in the pathophysiology of AGqMI are decreased blood supply to the gastric mucosa, increased vascular permeability and luminal irritation. Risk factors such as physical stress, trauma, serious illnesses, and the use of medications such as nonsteroidal anti-inflammatory drugs, corticosteroids and anticoagulants, as well as coagulation disorders and infections, can alter the delicate balance between protective and harmful factors of the gastric mucosa. These changes cause damage to the mucosal barrier, triggering inflammation, localized ischemia and, in more severe cases, the formation of ulcers and bleeding[2].

Prophylaxis of AGMI aims to prevent these injuries and complications and comprises pharmacological and non-pharmacological methods. Examples of non-pharmacological measures are adequate mechanical ventilation, patient positioning, and optimization of gastrointestinal function through enteral nutrition[3-4]. Recent evidence supports enteral nutrition as a viable alternative to pharmacological prophylaxis in select populations, reducing reliance on acid-suppressive therapies[5].

Pharmacological prophylactic measures for AGMI include the use of proton pump inhibitors (PPIs), such as omeprazole and pantoprazole, and of H2 receptor antagonists, such as famotidine, to reduce the risk of gastric injury and bleeding[6]. The choice of medication and the duration of treatment should be individualized and should consider factors such as the severity of the underlying disease, risk of bleeding, and drug interactions[7-8].

PPIs are widely used for AGMI prophylaxis because of their greater potency and efficacy in reducing acid secretion. These drugs exert more complete and prolonged suppression of acidity, promoting better protection of the gastric mucosa [9]. On the other hand, the excessive use of PPIs is associated with significant adverse effects, including infections, electrolyte imbalances, and organ dysfunction. Herzig et al.[10] demonstrated that indiscriminate PPI use increases the risk of ventilator-associated pneumonia by up to 30%, while recent studies highlight additional risks such as hypomagnesemia[11]and acute kidney injury[12]. Furthermore, long-term PPI exposure has been linked to chronic kidney disease [13-14], underscoring the need for cautious prescribing.

Barletta et al. [5]identified PPIs as the most commonly chosen class of drugs and concluded that AGMI prophylaxis is often administered to patients who are not at high risk of clinically important bleeding. Furthermore, a systematic review conducted by Tawam et al.[15]found a possible association between the use of PPIs and infection with *Clostridium difficile*. There is also evidence that the prolonged and unnecessary use of PPIs may contribute to the development of chronic kidney disease [14-16].

Some authors have raised concerns about the possible risks associated with the prolonged use of PPIs, suggesting "deprescribing" protocols or the rationale prescription of these drugs[17-19]. On 6th January 2020, the BMJ Rapid Recommendations published guidelines on AGMI prophylaxis in intensive care unit (ICU) patients, as reported by Ye et al [20].

In 2022, a rational prescription protocol of PPIs in ICUs (Appendix I) based on the 2020 guidelines (see supplementary material) was implemented in a private tertiary hospital in southern Brazil. Coordinated by the hospital's clinical pharmacist, the main objective of this initiative was to optimize the use of AGMI prophylaxis in line with the most recent recommendations. The experience with this implementation at Unimed Hospital Center sparked interest in investigating the results obtained and motivated this study. To evaluate the effectiveness and safety of a rational prescription protocol for proton pump inhibitors (PPIs) in intensive care units.

## Methods

### Study design

This was a retrospective comparative study of two observational cohorts, following the STROBE cohort reporting guidelines[21]. The study was conducted in the adult ICU of Hospital Unimed Joinville, a high-complexity private hospital and referral center for tertiary care in Joinville, Santa Catarina, Brazil. The hospital has a total of 190 beds. The ICU is a general adult unit with 19 beds, admitting medical and surgical patients based on clinical severity. The multidisciplinary ICU team includes intensive care physicians, nurses, physical therapists, and clinical pharmacists. A clinical pharmacist is present daily (44 hours per week), participating in multidisciplinary rounds and reviewing all prescriptions. Data collection was completed in December 2023. The sample consisted of all adult patients admitted to the adult ICU of Unimed Hospital Center.

Patients were divided into two cohorts based on admission period:

- **Pre-exposure cohort**: January to December 2021 (before protocol implementation).
- **Post-exposure cohort**: January to December 2022 (after protocol implementation).

The exposure in this study was the implementation of a rational PPI prescribing protocol, based on the guideline by Ye et al. (2020), which recommended prophylaxis only in the presence of at least one absolute or two relative risk factors for stress ulcer development. The protocol adopted followed the Ye et al. guideline (Supplementary table 1), which stratified gastrointestinal bleeding risks into three categories: absolute risks (mechanical ventilation without enteral nutrition, coagulopathy, and chronic liver disease), moderate risks (mechanical ventilation with enteral nutrition,

sepsis, acute kidney injury, and shock), and relative risks (use of anticoagulants, corticosteroids, cancer, and male sex). Prophylaxis was recommended only for patients with at least one absolute risk or two moderate risks. Relative risks alone did not justify prophylaxis unless associated with other higher-risk conditions.

No formal sample size calculation was performed, as all eligible patients admitted during the pre- and post-implementation periods of the proton pump inhibitor (PPI) rational use protocol were included, characterizing a census sampling by convenience.

### Eligibility criteria

Eligible participants were adult patients (>18 years old) admitted to the ICU for more than 24 hours during the study periods and received prophylaxis for acute gastric mucosal injury in accordance with the protocol established during the period from January 2022 to December 2022.

Patients were excluded if they had a confirmed diagnosis of COVID-19, did not receive prophylaxis for acute gastric mucosal injury in accordance with the protocol established during the period from January 2022 to December 2022, had incomplete or missing data for retrospective analysis, or if they were transferred to another unit before completion of the observation period.

### Assessment of prescription and deprescription of PPIs in the ICU

To evaluate prescribing practices, we analyzed variables related to the indication of stress ulcer prophylaxis, including the presence of absolute and relative risk factors, and recorded the duration of PPI use.

### Assessment of patient's severity

Patient severity was assessed using the Simplified Acute Physiology Score (SAPS) III. Clinical variables such as chronic liver disease, coagulopathy, history of UGIB, use of vasoactive drugs, and renal replacement therapy were recorded, as these are associated with both the risk of gastrointestinal bleeding and PPI prescription practices.

### Outcomes

The primary outcome was the occurrence of upper gastrointestinal bleeding during ICU stay. Secondary outcomes included PPI prescription and deprescription rates, incidence of ventilator-associated pneumonia (VAP), *Clostridium difficile* infection and in-hospital mortality.

### Data sources / measurement

All data were obtained retrospectively from the hospital's electronic medical record system (Tasy, Philips Healthcare). UGIB was identified through clinical documentation of hematemesis, melena, positive fecal occult blood, or endoscopic confirmation. VAP was diagnosed based on institutional protocols including clinical and radiological criteria. In-hospital mortality was defined as any death occurring during hospitalization. PPI prescription and deprescription were extracted from timestamps in the EMR. SAPS III scores were automatically calculated by the system upon ICU admission.

### Statistical analysis

Statistical analysis was performed using the MdCalc (https://www.mdcalc.com/). Distribution of the data was evaluated using the Kolmogorov-Smirnov test. Normal continuous variables were expressed as mean and standard deviation and were compared by the Student's t-test. Non-normally distributed variables were expressed as median and IQR and were compared by the Mann-Whitney U test. Categorical variables were presented with numerator, denominator and percentages and analyzed using the chi-square test. Kaplan-Meier curves were constructed to analyze the outcome of gastrointestinal bleeding and compared between groups by the log-rank test. A p-value <0.05 was considered significant.

A multivariate logistic regression was performed to investigate the association between implementation of the PPI protocol and the incidence of UGIB, controlling for confounding factors. Variables with p <0.1 in the univariate analysis or clinically relevant variables such as age >65 years, male sex, SAPS III > 50, hemodialysis, mechanical ventilation, use of vasopressors, and a history of liver disease, coagulopathy or UGIB were included.

### Bias

We included all eligible patients during the study period to avoid selection bias, included only patients with complete data and with standardized definitions to all outcomes to avoid information bias, and performed a multivariate analysis including clinically relevant covariates to address confounding bias.

### Ethical Approval and Informed Consent Statement:

The study was conducted in accordance with the ethical guidelines and legislation (Resolução 466/12) and approved by the institutional ethics committee [Ethical Clearance Certificate: 75411923.3.0000.5362]. Informed consent was waived due to the retrospective observational nature of the study.

## Results

A total of 1,614 patients were included, 641 in the pre-exposure group and 973 in the post-exposure group. Figure 1 shows the patient selection process and reasons for exclusion.

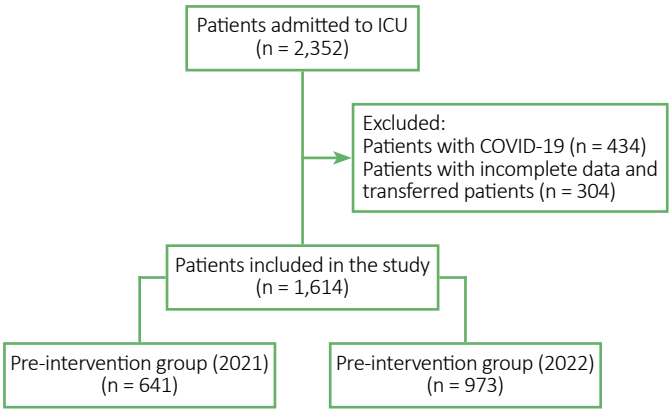


**Figure 1.** Flow diagram of patient inclusion in the study.

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Table 1 shows the characteristics of the patients. There were no significant differences between groups for age, sex, SAPS III, chronic liver disease, use of vasoactive drugs, hemodialysis, MV or a history of UGIB or coagulopathies.

**Table 1.** Characteristics of the patients in the pre- and post-exposure groups.

| Variable | Pre-exposure group (n = 641) | Post-exposure group (n = 973) | p-value |
|---|---|---|---|
| Age (years), median (IQR) | 65 (51.7-75.0) | 66 (51.7-75.0) | 0.97 |
| Male sex, n (%) | 370 (57) | 538 (55) | 0.33 |
| SAPS III, median (IQR) | 42 (34-50) | 41 (34-50) | 0.83 |
| Chronic liver disease, n (%) | 0 | 1 (0.1) | 0.41 |
| History of coagulopathies, n (%) | 0 | 0 | - |
| History of UGIB, n (%) | 0 | 0 | - |
| Use of vasoactive drugs, n (%) | 163 (24) | 253 (26) | 0.79 |
| Hemodialysis, n (%) | 42 (6.5) | 59 (6) | 0.69 |

**IQR:** interquartile range; SAPS III: Simplified Acute Physiology Score III; UGIB: upper gastrointestinal bleeding; PPI: proton pump inhibitor. Statistically significant difference ($p < 0.001$).

Table 2 shows the main clinical outcomes observed. The frequency of UGIB was similar between the pre-exposure group and the post-exposure group. However, differences were observed in the use of PPIs and the duration of use, indicating a change in prescription after the AGMI protocol implementation, with lower prescription and use for a shorter period when indicated in post-exposure group. There was no difference in the outcomes of ventilator-associated pneumonia (VAP), *Clostridium difficile* infection, ICU length of stay, and in-hospital mortality between the pre-exposure and the post-exposure groups.

**Table 2.** Outcomes of patients in the pre- and post-exposure groups.

| Variable | Pre-exposure group (n = 641) | Post-exposure group (n = 973) | p-value |
|---|---|---|---|
| Primary outcome | | | |
| Diagnosis of UGIB, n (%) | 7 (1) | 9 (1) | 0.74 |
| Secondary outcomes | | | |
| Use of PPIs, n (%) | 333 (51) | 396(40) | < 0.001 |
| Days of PPI use, median (IQR) | 2 ( 1-3) | 1 (1-2) | < 0.001 |
| Diagnosis of VAP, n (%) | 5 (0.8) | 6 (0.6) | 0.69 |
| Diagnosis of Clostridium, n (%) | 0 | 3 (0.3) | 0.15 |
| Days of hospital stay, median (IQR) | 4.5 (2.2-10.7) | 5.0 (2.3-10.9) | 0.28 |
| Death, n (%) | 64 (10) | 100 (10) | 0.84 |

**IQR:** interquartile range; UGIB: upper gastrointestinal bleeding; PPI: protom pump inhibitor; VAP: ventilation-associated pneumonia; MV: mechanical ventilation.

Table 3 shows the analysis of the association between risk factors for UGIB and the use of the prophylaxis protocol with PPIs. None of the variables tested demonstrated a statistically significant association with the occurrence of UGIB in the multivariate analysis. The low number of events (16 cases) may have compromised the stability and power of the analysis.

**Table 3.** Univariate and multivariate analysis of factors associated with upper gastrointestinal bleeding.

| Variable | Univariate OR (95% CI) | p-value (n = 973) | Multivariate OR (95% CI) | p-value |
|---|---|---|---|---|
| Post-exposure group | 1.45 (0.50-4.20) | 0.48 | 1.45 (0.50-4.20) | 0.49 |
| Age > 65 years | 1.01 (0.37-2.70) | 0.98 | 0.99 (0.36-2.68) | 0.99 |
| Male sex | 1.29 (0.46-3.59) | 0.61 | 1.31 0.47-3.64) | 0.81 |
| SAPS III > 50 | 1.15 (0.32-4.08) | 0.82 | 1.16 0.32-4.20) | 0.60 |
| Hemodialysis | 0.99 (0.13-7.63) | 0.99 | 1.17 (0.13-10.26) | 0.88 |
| Mechanical ventilation | 0.70 (0.20-2.49) | 0.59 | 0.56 (0.10-3.04) | 0.71 |
| Use of vasoactive drugs | 0.95 (0.30-2.99) | 0.94 | 1.31 (0.2905.86) | 0.50 |

**IQR:** interquartile range; UGIB: upper gastrointestinal bleeding; PPI: protom pump inhibitor; VAP: ventilation-associated pneumonia; MV: mechanical ventilation.

The Kaplan-Meier curves shown in Figure 2, compared the occurrence of UGIB between the pre-exposure (2021) and post-exposure (2022) groups. Analysis using the log-rank test showed no statistically significant difference between the groups in the occurrence of UGIB over time.

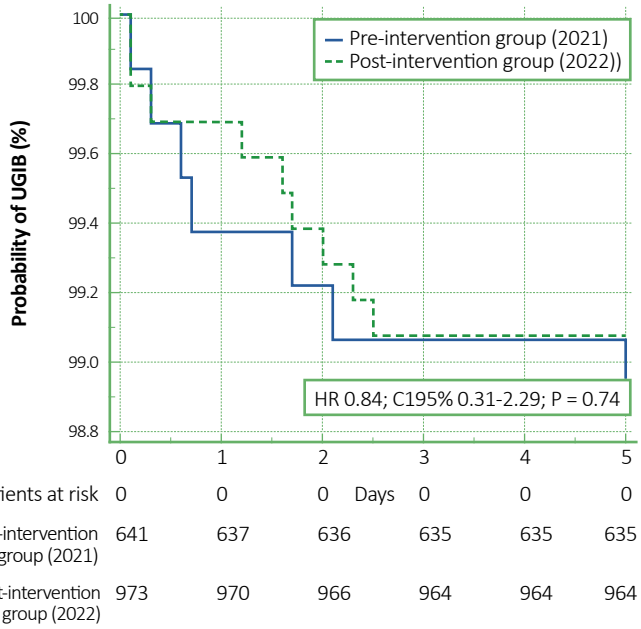


**Figure 2:** Kaplan-Meier curves comparing the occurrence of upper gastrointestinal bleeding (UGIB) between the pre-exposure (2021) and post-exposure (2022) groups.

## Discussion

The results of our study demonstrated that adoption of a rational prescribing protocol in ICUs reduced the excessive utilization of these drugs without compromising patient safety. There was a decrease in PPI use and treatment duration in the post-exposure group, with no significant differences in clinical outcomes such as upper gastrointestinal bleeding, ventilator-associated pneumonia, *Clostridium difficile* infection, hospital length of stay, and in-hospital mortality.

Studies have shown that interventions aimed at reducing unnecessary PPI use can decrease exposure to these drugs without increasing the incidence of UGIB. For example, a meta-analysis of randomized controlled trials conducted in 2016 confirmed that PPIs are effective in reducing the risk of clinically significant gastrointestinal bleeding in critically ill patients. However, the study also indicated that in some situations, such as patients at lower risk of bleeding, reducing PPI use may be safe and even beneficial, minimizing risks associated with their prolonged use such as infections[22].

The use of PPIs was significantly reduced in the post-exposure group, with no increase in the incidence of UGIB. This result is in line with evidence showing that, although PPI prophylaxis is effective in preventing gastrointestinal bleeding in high-risk groups, it may be overused, especially in lower risk patients[20]. The exclusion of COVID-19 patients aligns with current gaps in AGMI prophylaxis evidence for this population. Recent reappraisals stress that COVID-19-specific risks, such as hypercoagulability and prolonged ventilation, may necessitate tailored protocols[23], a topic requiring future investigation. Several studies have shown a high prevalence of inappropriate prescriptions of PPIs in both ICUs and other hospital settings that many of these cases have no appropriate clinical justifications, highlighting the need for more rigorous revision and regulation of the use of these medications[24-27]. In critical care settings where PPIs are commonly adopted as stress ulcer prophylaxis, the indiscriminate use of these drugs may result in unnecessary adverse effects and additional costs for the healthcare system.

The protocol applied in the present study followed the BMJ Rapid Recommendations for AGMI prophylaxis in ICU patients, published on 6th January 2020 by Ye et al. [28]. That study evaluated the benefits and harms of PPIs in 12,660 critically ill patients included in 72 clinical trials. The results showed that PPIs reduce the risk of clinically important bleeding compared to no prophylaxis. However, the magnitude of this benefit depends on the baseline risk of bleeding without prophylaxis. In higher-risk patients (>8%), PPI prophylaxis resulted in a clinically important reduction of 3-5% in bleeding risk.

In contrast, in critically ill patients at low risk (<2%), the clinically important reduction was less than 1%. The guidelines categorized patients into four groups according to the risk of clinically important gastrointestinal bleeding, reducing the indications for prophylaxis when compared to previous guidelines. In the very high-risk group (risk >8%), prophylaxis was recommended only for critically ill patients with coagulopathy or chronic liver disease or those on mechanical ventilation but not for those receiving enteral nutrition. These new recommendations require the adaptation of institutional protocols in order to reduce the indiscriminate use of PPIs in ICUs. Despite the routine practice of AGMI prophylaxis, the clinical relevance of these injuries may be limited, as indicated by Krag et al.[29,30]

The 2015 study was a multicenter prospective cohort study that included 1,034 patients from 97 ICUs in 11 countries[29]. Clinically important gastrointestinal bleeding was observed in 2.6% of the patients. There was no association between clinically important gastrointestinal bleeding and increased adjusted 90-day mortality [29]. In 2018, the same research group conducted a multicenter, double-blind, randomized clinical trial comparing pantoprazole with placebo. The study included a total of 3,298 patients (1,645 in the pantoprazole group and 1,653 in the placebo group). The authors concluded that, among adult ICU patients at risk of gastrointestinal bleeding, 90-day mortality and the number of clinically important events were similar for both the pantoprazole group and the placebo group [30].

These findings are comparable to the results of the REVISE study published in the New England Journal of Medicine, which investigated stress ulcer prophylaxis during invasive mechanical ventilation[22]. In this international double-blind randomized study, 4821 patients were assigned to receive intravenous pantoprazole or placebo. The results showed that pantoprazole reduced the risk of clinically important gastrointestinal bleeding compared to placebo (1.0% vs. 3.5%; hazard ratio, 0.30; 95% CI, 0.19 to 0.47; $p < 0.001$). However, there was no effect in 90-day mortality between groups (29.1% in the pantoprazole group vs. 30.9% in the placebo group[22]; hazard ratio, 0.94; 95% CI, 0.85 to 1.04; p=0.25).

Similarly, the current study found no significant differences in mortality, reinforcing the need for the judicious and rational use of PPIs in critically ill patients. Furthermore, neither the current study nor the REVISE study identified significant differences in important secondary outcomes such as respiratory complications and healthcare-associated infections, suggesting that reducing PPI use may be safe and effective when guided by well-defined protocols[22].

An observational study conducted by Franchitti et al. evaluated the adequacy of prescribing stress ulcer prophylaxis in the ICU[18]. The results indicated the need for revision and appropriate deprescription of PPIs in this setting in order to ensure a more rational and individualized prescription for each patient. A recent study conducted by Jones et al. investigated the impact of discontinuation of stress ulcer prophylaxis in critically ill patients on mechanical ventilation[19]. Patients following the guideline had a significantly lower percentage of patient-days of inappropriate stress ulcer prophylaxis (25% vs. 50%, p <0.01), as well as higher rates of prophylaxis discontinuation before extubating (71% vs. 12%, p <0.01) and during ICU stay (93% vs. 50%, p <0.01). Furthermore, the incidence of stress ulcer prophylaxis at hospital discharge was significantly lower among patients following the guideline (4% vs. 35%, p <0.01).

In the Brazilian context, observational data suggest a frequent and often unjustified use of proton pump inhibitors (PPIs) in hospitalized patients, particularly in intensive care units. Matoso et al. (2020), for example, analyzed 462 hospitalized patients in a university hospital and found that 39.3% received PPI therapy, with 73.5% of them in ICU[31]. Notably, 50.8% of the prescriptions lacked evidence-based indication. Similarly, Bischoff et al. (2021) reported a high prevalence of inappropriate intravenous omeprazole prescriptions in a high-complexity hospital, highlighting unnecessary costs and overuse[32]. In contrast, Cardoso et al. (2022) described the implementation of a local protocol for stress ulcer prophylaxis that included criteria for PPI withdrawal once risk factors were controlled, illustrating a practical strategy for deprescription in the hospital setting[33].

Multivariate logistic regression analysis also did not identify an association between the use of the PPI protocol and the occurrence of UGIB after adjustment for potential confounders. This finding suggests that the reduction in PPI use did not increase the risk of adverse events related to the gastrointestinal tract. Analysis of the occurrence of UGIB using Kaplan-Meier curves revealed differences between the pre-exposure (2021) and post-exposure groups (2022).

### Strengths and weaknesses

As strengths of these studies, we can mention: the implementation of a clinical protocol for the rational use of PPIs in ICU is effective in reducing the excessive use of these drugs and the protocol is safe. This study has weaknesses. The observational before-and-after cohort design makes it difficult to identify causal relationships and to control for confounding variables. Retrospective data collection from electronic medical records may lead to errors or incomplete information. The fact that the sample was from a single private hospital limits generalization of the findings and the data collection period may not capture important temporal variations. The absence of a prior sample size calculation may have limited the statistical power to detect small differences between the evaluated periods. These limitations must be considered when interpreting the results.

### Further research

Due to the retrospective nature of the study, multicenter randomized controlled trials are needed to confirm the effectiveness and safety of the clinical protocol for the rational use of PPIs in ICUs.

## Conclusion

The present results show that adoption of a rational prescribing protocol in ICUs reduced the excessive utilization of these drugs without compromising patient safety. These findings highlight the importance of the rational use of PPIs, focusing on prophylaxis for high-risk patients and avoiding indiscriminate use in low-risk cases. Future studies are needed to confirm these findings.

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### Conflicts of interest

The authors declare that they have no conflict of interest.

### Authors' Contributions

LCR: Study conception and design; LCR, ABP, and FCM:

Data analysis and interpretation; LCR, ABP, and FCM:

Manuscript drafting and critical revision of the intellectual content.

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