Majalah Farmaseutik
ISSN-e: 2614-0064 | ISSN-p: 1410-590x
Volume 20(3), 316-323

Comparison Among Proton Pump Inhibitor Inducing Pneumonia in Hospital: Narrative Review

Juwita Permata Sari[1*], Agung Endro Nugroho[2], Widyati[3]
[1] Master of Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada
[2] Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada
[3] Faculty of Pharmacy, Universitas Pertahanan
Corresponding author: Juwita Permata Sari; Email: uwitapermatasari@mail.ugm.ac.id
Submitted: 02-09-2023 *Revised: 21-09-2023* *Accepted: 25-09-2023*

ABSTRACT

Critically ill patients requiring intensive care unit are highly vulnerable to the emergence of stress-related gastrointestinal bleeding, a condition associated with unfavorable clinical outcomes. Despite advancements in preventive measures, antimicrobial therapies, and supportive medical care, ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) continue to effect morbidity and mortality rates significantly. Proton pump inhibitors (PPIs) are used prophylactically to manage stress ulcers in critically ill patients. However, recent scholarly literature has drawn attention to a potential link between using acid-suppressing medications and an increased susceptibility to pneumonia. The primary objective of this study was to assess the prevalence of pneumonia associated with different types of proton pump inhibitors. We conducted an extensive literature search using keywords such as "(omeprazole or pantoprazole or lansoprazole or esomeprazole or rabeprazole), ICU, Pneumonia" on two prominent electronic databases: Scopus and PubMed. We identified fourteen articles meeting our inclusion criteria, which were categorized into four groups: omeprazole, esomeprazole, lansoprazole, and pantoprazole. The results of this narrative review revealed varying risk levels associated with using different proton pump inhibitors for pneumonia. Esomeprazole had the highest risk level, at 48.84%, followed by lansoprazole at 27.85%, omeprazole at 22.5%, and pantoprazole at 19.94%.
Keywords: Pneumonia; Omeprazole; Pantoprazole; Lansoprazole; Esomeprazole

INTRODUCTION

Critically ill patients requiring intensive care unit (ICU) care are highly vulnerable to the emergence of stress-related gastrointestinal bleeding, a condition intricately tied to unfavorable clinical outcomes. They typically stem from inflammatory, erosive, and acute pathologies, precipitating acute upper gastrointestinal hemorrhage. It is imperative to underscore that stress ulcers in the ICU exhibit a considerably elevated risk of mortality. Patients afflicted by gastrointestinal bleeding demonstrate a markedly higher fatality rate than their non-bleeding counterparts. A comprehensive study elucidated that patient who had recently encountered gastrointestinal bleeding contributed to a staggering 47% of the overall mortality cases, whereas those devoid of such bleeding constituted 30%. Rigorous statistical analysis underscored a substantial distinction between the two cohorts by a p-value of less than 0.001 (Kumar et al., 2017)

Ventilator-associated pneumonia (VAP) and Hospital-acquired pneumonia (HAP) have a significant effect on morbidity and mortality rates, despite advancements in preventive measures, antimicrobial treatments, and supportive medical interventions. Hospital-acquired pneumonia (HAP) is characterized as a form of pneumonia that does not manifest during the period of hospital admission but rather emerges 48 hours or later after the patient has been admitted. In contrast, VAP emerges beyond 48 hours after installing an endotracheal tube (Kalil et al., 2016) Prophylactically, proton pump inhibitors (PPIs) find application in managing stress ulcers among critically ill patients in the intensive care unit who present with gastrointestinal bleeding and require mechanical ventilation (Varon, 2021) However, the inquiry unveiled an elevated susceptibility to pneumonia associated with PPI utilization compared to alternative therapeutic selections (Alhazzani et al., 2018)

Recent scholarly literature has highlighted a connection between using acid-suppressing medications and an augmented susceptibility to pneumonia. The precise mechanism through which

these acid suppressors might heighten pneumonia risk remains enigmatic. However, there exists a postulation that the modification in gastric pH engendered by these drugs can disrupt the equilibrium of typical microorganisms in the gastrointestinal and oropharyngeal regions. This perturbation might hinder the expulsion of pathogens or facilitate their colonization, thereby amplifying the potential for pneumonia occurrence. The elevation of gastric pH triggered by acid suppressors undeniably fosters the proliferation and propagation of microorganisms within the oral cavity and oropharynx. The attenuation of gastric acid assumes a significant role in immunity against infections, furnishing a plausible rationale for the linkage between proton pump inhibitors (PPIs) and an escalated pneumonia risk (Lambert et al., 2015)

Meta-analysis show underscoring a robust correlation between the utilization of PPI medication and an augmented susceptibility to community-acquired pneumonia was demonstrated to exhibit variations contingent on the duration of proton pump inhibitor (PPI) usage. The study revealed that individuals presently employing PPI therapy for one month displayed approximately twice the risk of pneumonia compared to those abstaining from PPI usage. Moreover, the study indicated that the risk of community-acquired pneumonia experienced a slight elevation in individuals' PPI for an extended period and at a lower dosage. However, the risk showcased a significant escalation in those who underwent high-dose PPI medication (Nguyen et al., 2020). The primary objective of this study was to assess the incidence of pneumonia associated with different types of proton pump inhibitors (PPIs).

METHODS

Data Sources

We conducted a thorough literature search using the keywords "(omeprazole or pantoprazole or lansoprazole or esomeprazole or rabeprazole), ICU, Pneumonia" across two prominent electronic databases: Scopus and PubMed. The criteria for inclusion in this narrative review encompassed the following aspects: (1) articles sourced from open-access journals featuring original research; (2) literature composed in the English language; (3) studies involving critically ill patients; (4) research with study designs that included randomized controlled trials and cohort studies, experimental or observational study; (5) literature published within 15 years.

Data Extraction

The data extraction procedure encompassed identifying and retrieving pertinent material that met the pre-established criteria for incorporation.

RESULT AND DISCUSSION

In this narrative review, 14 articles were included for analysis. These articles were divided into different categories: 1 article on esomeprazole, 1 article on omeprazole, two articles on lansoprazole, and ten articles on pantoprazole. One of the studies focused on esomeprazole and employed a retrospective cohort study method. This study included 387 patients, with 49 patients in the esomeprazole 20 mg group and 338 patients in the esomeprazole 40 mg. The study found that the incidence of pneumonia was higher in the esomeprazole 40 mg group (48.84%) compared to the esomeprazole 20 mg group (28.95%) with a p-value<0.05. This indicates a significant difference in the incidence of pneumonia between the two esomeprazole dosage groups (Al Sulaiman et al., 2020). This result inline with other research, PPI increase risk of pneumonia (1.2; 1.03-1.41) (MacLaren et al., 2014).

In the following study, omeprazole was compared to cimetidine and placebo, involving a total sample size of 165 participants. These participants were divided into three groups: 58 received omeprazole, 54 received cimetidine, and 53 received a placebo. The study found that pneumonia occurred in 24.1% of omeprazole, 22.2% of cimetidine, and 15.1% of placebo. Importantly, no significant difference was observed among these groups, with a p-value greater than 0.05. This suggests that there was no significantly distinction in the incidence of nosocomial pneumonia between the omeprazole, cimetidine, and placebo groups (Liu et al., 2013). Indeed, variations in study outcomes can occur due to differences in sample sizes, research methods, and other factors. The case of omeprazole and its potential association with pneumonia incidence highlights the importance of

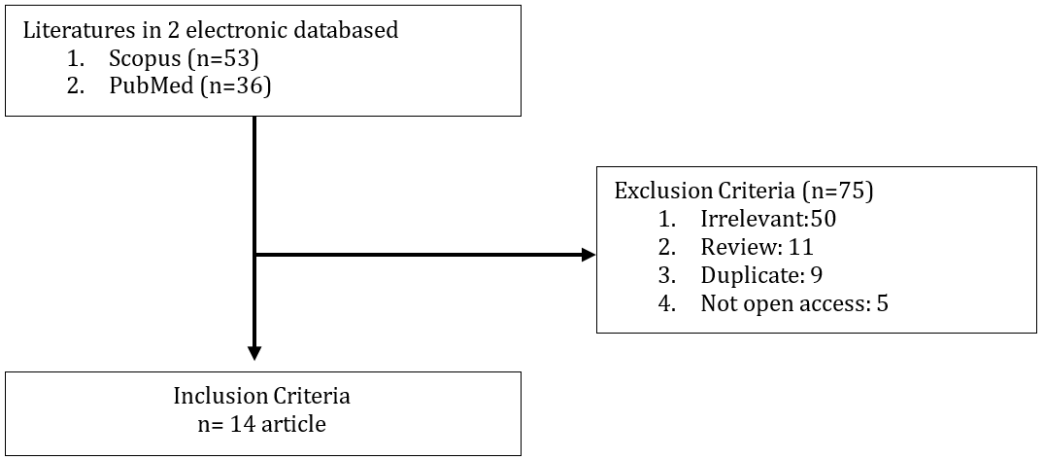

Figure 1. Data Extraction

conducting further research with larger sample sizes and employing randomized controlled trial (RCT) methods. RCTs are considered a gold standard in medical research for assessing causal relationships between interventions (such as omeprazole use) and outcomes (like pneumonia incidence). These RCTs can help provide more robust and conclusive evidence regarding the potential impact of omeprazole on pneumonia risk, allowing for a clearer understanding of any causal relationship. Researchers can consider factors such as dosages, treatment duration, and patient characteristics in such studies to obtain more precise insights. Ultimately, the aim is to establish a more definitive understanding of the relationship between omeprazole and pneumonia, which can inform clinical practice and patient care (Chen et al., 2021). Previous research also supports the results of this study, namely a study comparing PPIs and H2RAs and sucralfate with results in PPIs with a higher incidence of pneumonia (1.7%) compared to sucralfate (1.2%) (Li et al., 2022).

Two articles examined lansoprazole compared to placebo using the same randomized controlled trial method, and the number of samples is similar. A study conducted from June 1, 2009, to February 29, 2012, with a total sample of 120, showed that the incidence of pneumonia in lansoprazole was lower than placebo (6.7% vs. 10%) with a p-value>0.05 so there was no statistically significant difference while a study conducted from July 2009 to December 2011 with a total sample of 119 showed that Lansoprazole was more at risk of causing pneumonia than placebo (49% vs. 18%) with a p-value <0.05 so there was a statistically significant difference. In terms of percentage, there are differences in the results of these studies. One article showed lansoprazole was higher in increasing the incidence of pneumonia, while the other article said the opposite, but the results of the p-value did not show different things; lansoprazole with a lower percentage did not show statistically different things compared to the placebo group so that lansoprazole or placebo are comparable in terms of increasing the risk of pneumonia (Lin et al., 2016; Takatori et al., 2013). According to previous research, there was no difference in the pneumonia rates between the two groups PPI and H2RA (49.6% vs 41.6%) (Huang et al., 2021). The mean percentage on incidence of pneumonia caused by lansoprazole was 27.85% (mean of 6.7% and 49%).

Ten articles discuss pantoprazole in causing pneumonia. Four out of 10 articles showed that pantoprazole has a risk of pneumonia incidence with significantly different results (p-value <0.05). Two out of 3 compared pantoprazole with ranitidine, one article compared pantoprazole and sucralfate, and the other article compared oral and IV pantoprazole. The incidence of pneumonia with pantoprazole was higher than ranitidine and sucralfate (30% vs. 10%; 9.3% vs. 1.5%; 36.4% vs. 14.1%), and oral pantoprazole was higher than iv pantoprazole (30% vs. 12%) (Bashar et al., 2013; Khorvash et al., 2014; Miano et al., 2009; Salarian et al., 2021). In 6 out of 10 articles that discussed pantoprazole, 4 out of 6 compared pantoprazole with placebo, while two articles compared pantoprazole with Histamine-2 Receptor Antagonist (H2RA). The six articles showed no significantly difference in the pantoprazole and H2RA or placebo groups in causing pneumonia incidence

Table I. Article Extraction

uthor	Study Design	Setting	Intervention	Sample	Study Period	Outcome	Result
man et 020)	Retrospective cohort study	adult patient in ICU at King Abdulaziz Medical, Riyadh	Esomeprazole 20 mg vs Esomeprazole 40 mg	387	January-December 2018	Incidence of Pneumonia	The occurrence of pneumonia was notably higher in esomeprazole 40 mg compared to those using esomeprazole 20 mg (48.84% vs 28.95%), with p value <0.05
har et 013)	Randomized Controlled Trial	trauma patients in the ICU in northwest Iran	Pantoprazole 40 mg vs Ranitidine 50 mg	120	July 2011-July 2012	Incidence of VAP	The occurrence of VAP was significantly higher in the pantoprazole group compared to the ranitidine group, with rates of 30% vs. 10% (p<0.05)
g et al., 3)	Multicenter Randomized Controlled Trial	33 ICUs in 6 countries	Pantoprazole 40 mg vs placebo	3291	January 2016-October 2017	Incidence of new-onset pneumonia	The occurrence of pneumonia was slightly higher in the placebo group than the pantoprazole group, with rates of 16.9% vs. 16.8% and p value >0.05
rvash , 2014)	Randomized clinical trial	ICU patients with MV in Isfahan	Pantoprazole vs sucralfat	137	Early 2010-Mid 2011	Incidence of nosocomial pneumonia	The occurrence of pneumonia was significantly higher in the pantoprazole group compared to the sucralfate, with rates of 36.4% vs. 14.1% (p<0.05)
et al., 6)	Randomized Controlled Trial	Medical and surgical ICU in Taiwan	Lansoprazole 30 mg OD vs placebo	120	June 2009-February 2012	Incidence of VAP	The occurrence of pneumonia was slightly higher in the placebo group compared to the lansoprazole group, with rates of 10% vs. 6.7% (p>0.05)
et al., 3)	Randomized Controlled Trial	Surgical ICU in Xijing Hospital, China	Omeprazole 40 mg vs Cimetidine 300 mg vs placebo	165	April 2006-December 2008	Incidence of nosocomial pneumonia	The occurrence of pneumonia was slightly elevated in the omeprazole compared to the cimetidine and placebo groups, with rates of 24.1% vs. 22.2% vs 15.1% (p>0.05)
no et 009)	Retrospective cohort study	Cardiothoracic Surgery in Wake Forest Medical center	Pantoprazole vs Ranitidine	834	January 2004-March 2007	Incidence of nosocomial pneumonia	The occurrence of pneumonia was significantly higher in the pantoprazole compared to the ranitidine, with rates of 9.3% vs. 1.5% (p<0.05)

Table II. Continued

Author	Study Design	Setting	Intervention	Sample	Study Period	Outcome	Result
ayyedi et 2019)	Multicenter Randomized Controlled Trial	Stable atherosclerotic vascular disease	Pantoprazole 40 mg vs vs placebo	17598	March 2013-May 2016	Incidence of pneumonia	The occurrence of pneumonia v found to be equal between t pantoprazole and placebo groups, bo recording a rate of 3.6% (p>0.05)
tpour et 2020)	Longitudinal descriptive study	General ICU of Loghman Hakim Hospital, Iran	Pantoprazole vs Ranitidine	143	March 2017-March 2018	Incidence of VAP	The occurrence of pneumonia v higher in the ranitidine vs pantopraz (44.7% vs 37.2%) (p>0.05)
arian et 2021)	Randomized Controlled trial	PICU of Mofid Children Hospital, Tehran, Iran	Oral pantoprazole vs IV pantoprazole	80	-	Incidence of nosocomial pneumonia	The occurrence of pneumonia v higher in the oral pantoprazole gro (30%) compared to the IV pantopraz group (12%). (p>0.05)
vanderan ., 2016)	Randomized Controlled Trial	University medical-surgical ICU	Pantoprazole vs placebo	214	January 2014-January 2015	Incidence of pneumonia	The occurrence of pneumonia v higher in the pantoprazole vs place (11.3% vs 7.4%) (p>0.05).
nberg et 2008)	Multicenter Randomized Controlled Trial	14 ICU centers across the United States	Pantoprazole vs cimetidine	202	June 2000-September 2001	Incidence of pneumonia	The incidence of pneumonia v slightly higher in the pantoprazole cimetidine (10% vs 9%) (p>0.05)
xatori et 2013)	Randomized Controlled Trial	patients with dysphasia who required gastrostomy feeding	Lansoprazole vs mosapride vs placebo	119	July 2009-December 2011	Incidence of pneumonia	The occurrence of pneumonia v indeed significantly elevated in t lansoprazole (49%) compared to bo the mosapride (40%) and place (18%) groups, as indicated by a p-va < 0.05.
et al., 1)	Randomized Controlled Trial	patients with a diagnosis of ACS	Pantoprazole 40 mg vs placebo	665	May 2008-April 2010	Incidence of pneumonia	The occurrence of pneumonia v slightly higher in the Pantopraz group (7.2%) compared to the place group (6.6%) (p>0.05)

(p>0.05). Although there was no significantly difference, the percentage of pantoprazole-causing pneumonia incidence was higher than in the placebo or H2RA groups. (16.9% vs 16.8%; 3.6% vs 3.6%; 44.7% vs 37.3; 11.3% vs 7.4%; 10% vs 9%; 7.2% vs 6.6%) (Krag et al., 2018; Moayyedi et al., 2019; Nikpour et al., 2020; Selvanderan et al., 2016; Somberg et al., 2008; Wu et al., 2011). This result in line with other research, there is no significant difference between PPI vs H2RA (p>0.05) (Mekhail et al., 2023; Selvanderan et al., 2016; Song et al., 2021). The mean percentage incidence of pneumonia caused by pantoprazole was 19.94% (mean percentage from 10 pantoprazole journals).

These findings align with the outcomes of the study published in 2018; a substantial connection between the utilization of proton pump inhibitors (PPIs) and infection was determined, that the odds ratio for PPI exposure compared to uninfected controls was 3.37 (1.84-6.18). Similarly, the odds ratio for ESBL infection compared to non-ESBL disease was calculated as 1.15 (95% CI 0.68-1.95). Moreover, a notable relationship was observed in the type of medication employed for stress ulcer prevention and the incidence of ventilator-associated pneumonia(Cunningham et al., 2018). Among the complete cohort who were administered SUP, a subset of 48 individuals (11.3%) encountered adverse effects. Notably, 15 patients (31.25%) were diagnosed with nosocomial pneumonia within this affected subgroup (Alagha & Mohammed Al Mabhouh, 2022; Wang et al., 2022). The data presented in this narrative review are consistent with numerous studies that have indicated a significant prevalence of pneumonia among patients undergoing treatment with proton pump inhibitors. The results of this narrative review showed that the highest risk level of proton pump inhibitor use for pneumonia was influenced by Esomeprazole 40 mg 48.84%, Lansoprazole 27.85%, omeprazole 22.5% and pantoprazole 19.94%.

CONCLUSION

Pantoprazole has many articles supporting the association of pantoprazole with the risk of pneumonia, while the other therapies have few supporting articles on causing pneumonia. Of the total number of articles, pantoprazole caused the most pneumonia, but of the total percentage that caused the highest pneumonia was Esomeprazole. All articles in this narrative review in percentage terms showed an association between PPI and the incidence of pneumonia. In contrast, the p-value still showed differences in opinion (significantly different and insignificant). Therefore, more research on esomeprazole, omeprazole, and lansoprazole needs to be done with a large sample size to prove the relationship between these three drugs and pneumonia.

REFERENCES

Al Sulaiman, K., Al Aamer, K., Al Harthi, A., Jaser, S., Al Anazi, A., Al Subaie, S., & Vishwakarma, R. (2020). Comparison between esomeprazole 20 mg Vs 40 mg as stress ulcer prophylaxis (SUP) in critically ill patients: A retrospective cohort study. *Pharmacology Research & Perspectives*, *8*(4). https://doi.org/10.1002/prp2.624

Alagha, H., & Mohammed Al Mabhouh, N. (2022). EVALUATION OF CURRENT PRACTICE OF STRESS ULCER PROPHYLAXIS IN PATIENTS ADMITTED TO INTENSIVE CARE UNITS IN THE GAZA STRIP- PALESTINE. *Bulletin of Pharmaceutical Sciences. Assiut*, *45*(2), 845–857. https://doi.org/10.21608/bfsa.2022.271660

Alhazzani, W., Alshamsi, F., Belley-Cote, E., Heels-Ansdell, D., Brignardello-Petersen, R., Alquraini, M., Perner, A., Møller, M. H., Krag, M., Almenawer, S., Rochwerg, B., Dionne, J., Jaeschke, R., Alshahrani, M., Deane, A., Perri, D., Thebane, L., Al-Omari, A., Finfer, S., … Guyatt, G. (2018). Efficacy and safety of stress ulcer prophylaxis in critically ill patients: A network meta-analysis of randomized trials. *Intensive Care Medicine*, *44*(1), 1–11. https://doi.org/10.1007/s00134-017-5005-8

Bashar, F. R., Manuchehrian, N., Mahmoudabadi, M., Hajiesmaeili, M. R., & Torabian, S. (2013). Effects of Ranitidine and Pantoprazole on Ventilator-Associated Pneumonia: A Randomized Double-Blind Clinical Trial. *Tanaffos*, *12*(2), 16–21. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4153243/

Chen, C., Liu, H., Duan, R., Wang, F., & Duan, L. (2021). The efficacy and safety of acid suppressants for gastrointestinal bleeding prophylaxis in cardiac care unit patients. *Journal of Gastroenterology and Hepatology*, *36*(8), 2131–2140. https://doi.org/10.1111/jgh.15432

Cunningham, R., Jones, L., Enki, D. G., & Tischhauser, R. (2018). Proton pump inhibitor use as a risk factor for Enterobacteriaceal infection: A case-control study. *The Journal of Hospital Infection*, *100*(1), 60–64. https://doi.org/10.1016/j.jhin.2018.05.023

Huang, M., Han, M., Han, W., & Kuang, L. (2021). Proton pump inhibitors versus histamine-2 receptor blockers for stress ulcer prophylaxis in patients with sepsis: A retrospective cohort study. *Journal of International Medical Research*, *49*(6), 03000605211025130. https://doi.org/10.1177/03000605211025130

Kalil, A. C., Metersky, M. L., Klompas, M., Muscedere, J., Sweeney, D. A., Palmer, L. B., Napolitano, L. M., O'Grady, N. P., Bartlett, J. G., Carratalà, J., El Solh, A. A., Ewig, S., Fey, P. D., File, T. M., Restrepo, M. I., Roberts, J. A., Waterer, G. W., Cruse, P., Knight, S. L., & Brozek, J. L. (2016). Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clinical Infectious Diseases*, *63*(5), e61–e111. https://doi.org/10.1093/cid/ciw353

Khorvash, F., Abbasi, S., Meidani, M., Dehdashti, F., & Ataei, B. (2014). The comparison between proton pump inhibitors and sucralfate in incidence of ventilator associated pneumonia in critically ill patients. *Advanced Biomedical Research*, *3*, 52. https://doi.org/10.4103/2277-9175.125789

Krag, M., Marker, S., Perner, A., Wetterslev, J., Wise, M. P., Schefold, J. C., Keus, F., Guttormsen, A. B., Bendel, S., Borthwick, M., Lange, T., Rasmussen, B. S., Siegemund, M., Bundgaard, H., Elkmann, T., Jensen, J. V., Nielsen, R. D., Liboriussen, L., Bestle, M. H., … Møller, M. H. (2018). Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU. *New England Journal of Medicine*, *379*(23), 2199–2208. https://doi.org/10.1056/NEJMoa1714919

Kumar, S., Ramos, C., Garcia-Carrasquillo, R. J., Green, P. H., & Lebwohl, B. (2017). Incidence and risk factors for gastrointestinal bleeding among patients admitted to medical intensive care units. *Frontline Gastroenterology*, *8*(3), 167–173. https://doi.org/10.1136/flgastro-2016-100722

Lambert, A. A., Lam, J. O., Paik, J. J., Ugarte-Gil, C., Drummond, M. B., & Crowell, T. A. (2015). Risk of Community-Acquired Pneumonia with Outpatient Proton-Pump Inhibitor Therapy: A Systematic Review and Meta-Analysis. *PLOS ONE*, *10*(6), e0128004. https://doi.org/10.1371/journal.pone.0128004

Li, F., Liu, H., Zhang, L., Huang, X., Liu, Y., Li, B., Xu, C., Lyu, J., & Yin, H. (2022). Effects of Gastric Acid Secretion Inhibitors for Ventilator-Associated Pneumonia. *Frontiers in Pharmacology*, *13*. https://www.frontiersin.org/articles/10.3389/fphar.2022.898422

Lin, C.-C., Hsu, Y.-L., Chung, C.-S., & Lee, T.-H. (2016). Stress ulcer prophylaxis in patients being weaned from the ventilator in a respiratory care center: A randomized control trial. *Journal of the Formosan Medical Association = Taiwan Yi Zhi*, *115*(1), 19–24. https://doi.org/10.1016/j.jfma.2014.10.006

Liu, B., Li, B., Zhang, X., Fei, Z., Hu, S., Lin, W., Gao, D., & Zhang, L. (2013). A randomized controlled study comparing omeprazole and cimetidine for the prophylaxis of stress-related upper gastrointestinal bleeding in patients with intracerebral hemorrhage: Clinical article. *Journal of Neurosurgery*, *118*(1), 115–120. https://doi.org/10.3171/2012.9.JNS12170

MacLaren, R., Reynolds, P. M., & Allen, R. R. (2014). Histamine-2 Receptor Antagonists vs Proton Pump Inhibitors on Gastrointestinal Tract Hemorrhage and Infectious Complications in the Intensive Care Unit. *JAMA Internal Medicine*, *174*(4), 564–574. https://doi.org/10.1001/jamainternmed.2013.14673

Mekhail, A., Young, P., Mekhail, A.-M., Tinawi, G., Haran, C., Clayton, N., & Galvin, S. (2023). Stress Ulcer Prophylaxis in Cardiac Surgery: A Retrospective Cohort Study to Analyze the Effects of SUP Cessation. *Journal of Intensive Care Medicine*, 8850666231171327. https://doi.org/10.1177/08850666231171327

Miano, T. A., Reichert, M. G., Houle, T. T., MacGregor, D. A., Kincaid, E. H., & Bowton, D. L. (2009). Nosocomial Pneumonia Risk and Stress Ulcer Prophylaxis. *Chest*, *136*(2), 440–447. https://doi.org/10.1378/chest.08-1634

Moayyedi, P., Eikelboom, J. W., Bosch, J., Connolly, S. J., Dyal, L., Shestakovska, O., Leong, D., Anand, S. S., Störk, S., Branch, K. R. H., Bhatt, D. L., Verhamme, P. B., O'Donnell, M., Maggioni, A. P., Lonn, E. M., Piegas, L. S., Ertl, G., Keltai, M., Bruns, N. C., … Yusuf, S. (2019). Safety of Proton Pump

Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin. *Gastroenterology*, *157*(3), 682-691.e2. https://doi.org/10.1053/j.gastro.2019.05.056

Nguyen, P. A., Islam, M., Galvin, C. J., Chang, C.-C., An, S. Y., Yang, H.-C., Huang, C.-W., Li, Y.-C. J., & Iqbal, U. (2020). Meta-analysis of proton pump inhibitors induced risk of community-acquired pneumonia. *International Journal for Quality in Health Care: Journal of the International Society for Quality in Health Care*, *32*(5), 292–299. https://doi.org/10.1093/intqhc/mzaa041

Nikpour, S., Mokhber, A., Hajiesmaeili, M., Kazempour, M., Salehi, M., Goharani, R., Zangi, M., & Chouhdari, A. (2020). Prediction of ventilator-associated pneumonia in patients undergoing stress ulcer prophylaxis: A longitudinal descriptive study in Iran. *Journal of Kerman University of Medical Sciences*, *27*(6), 501–509. Scopus. https://doi.org/10.22062/JKMU.2020.91525

Salarian, S., Mirrahimi, B., Hadavand, F., Gharehdaghi, M., & Bagheri, B. (2021). Impact of Intravenous Pantoprazole versus Oral Pantoprazole on Gastric pH in Pediatric Intensive Care Unit: A Randomized Trial. *Journal of Chemical Health Risks*, *11*(Special Issue: Bioactive Compounds: Their Role in the Prevention and Treatment of Diseases). https://doi.org/10.22034/jchr.2021.1915527.1223

Selvanderan, S. P., Summers, M. J., Finnis, M. E., Plummer, M. P., Ali Abdelhamid, Y., Anderson, M. B., Chapman, M. J., Rayner, C. K., & Deane, A. M. (2016). Pantoprazole or Placebo for Stress Ulcer Prophylaxis (POP-UP): Randomized Double-Blind Exploratory Study*. *Critical Care Medicine*, *44*(10), 1842–1850. https://doi.org/10.1097/CCM.0000000000001819

Somberg, L., Morris, J., Fantus, R., Graepel, J., Field, B. G., Lynn, R., & Karlstadt, R. (2008). Intermittent Intravenous Pantoprazole and Continuous Cimetidine Infusion: Effect on Gastric pH Control in Critically Ill Patients at Risk of Developing Stress-Related Mucosal Disease. *Journal of Trauma: Injury, Infection & Critical Care*, *64*(5), 1202–1210. https://doi.org/10.1097/TA.0b013e31815e40b5

Song, M. J., Kim, S., Boo, D., Park, C., Yoo, S., Yoon, H. I., & Cho, Y.-J. (2021). Comparison of proton pump inhibitors and histamine 2 receptor antagonists for stress ulcer prophylaxis in the intensive care unit. *Scientific Reports*, *11*, 18467. https://doi.org/10.1038/s41598-021-98069-7

Takatori, K., Yoshida, R., Horai, A., Satake, S., Ose, T., Kitajima, N., Yoneda, S., Adachi, K., Amano, Y., & Kinoshita, Y. (2013). Therapeutic effects of mosapride citrate and lansoprazole for prevention of aspiration pneumonia in patients receiving gastrostomy feeding. *Journal of Gastroenterology*, *48*(10), 1105–1110. https://doi.org/10.1007/s00535-012-0725-6

Varon, J. (2021). *Handbook of Critical and Intensive Care Medicine*. Springer International Publishing. https://doi.org/10.1007/978-3-030-68270-5

Wang, Y.-H., Svanström, H., Wintzell, V., Ludvigsson, J. F., & Pasternak, B. (2022). Association between proton pump inhibitor use and risk of pneumonia in children: Nationwide self-controlled case series study in Sweden. *BMJ Open*, *12*(4), e060771. https://doi.org/10.1136/bmjopen-2022-060771

Wu, H., Jing, Q., Wang, J., & Guo, X. (2011). Pantoprazole for the prevention of gastrointestinal bleeding in high-risk patients with acute coronary syndromes. *Journal of Critical Care*, *26*(4), 434.e1-434.e6. https://doi.org/10.1016/j.jcrc.2010.12.007