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Risk for Hospital-Acquired Pneumonia from Proton Pump Inhibitor or Sucralfate in Intensive Care Units

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ABSTRACT

The increased risk of pneumonia from proton pump inhibitors (PPI) has been addressed in recent studies. This study aimed to investigate the risk of hospital-acquired pneumonia (HAP) in critically ill patients receiving PPI or sucralfate. This retrospective observational cohort study analyzed patients who were prescribed with PPIs or sucralfate for stress ulcer prophylaxis in intensive care units (ICU). A propensity score and other risk factors were used to calculate the adjusted odds ratio (OR) for the two groups. The final cohort comprised 388 patients with 302 patients on PPI and 86 patients on sucralfate therapies. HAP developed in 63 patients (20.86%) on PPI, and 8 patients (9.30%) on sucralfate (adjusted OR 3.37, 95% CI 1.35-8.45, *p*-value 0.009). The enrolled patients on PPI therapy with an APACHE II score > 13 (adjusted OR 3.70, 95% CI 1.04-13.10, *p*-value 0.043), or those on PPI therapy with an ICU stay of more than 8 days (adjusted OR 9.04, 95% CI 1.94-42.06, *p*-value 0.005) had the highest risk of developing HAP. Patients in medical ICU treated with PPIs had a higher risk of developing HAP than those treated with sucralfate. For the ICU patients requiring stress ulcer prophylaxis, sucralfate can be considered as a priority treatment. The risk and benefit of PPI treatment should be evaluated for patients who may have a longer ICU stay or have a high APACHE II score.

Key words: hospital-acquired pneumonia, pneumonia, proton pump inhibitor, sucralfate, stress ulcer prophylaxis, acid-suppressive pharmacologic agents

INTRODUCTION

Concerns for the risk for pneumonia limited the use of proton pump inhibitor (PPI) for stress ulcer prevention[(1)]. Acid-suppressive pharmacologic agents, such as histamine-2 receptor antagonists (H2RAs) and PPIs, raise the gastric pH and thus, promote the proliferation of gram-negative bacilli in stomach. Retrograde colonization of the aerodigestive tract and the micro-aspiration of gastric fluid into the upper respiratory tract and lung have been shown to facilitate the occurrence of pneumonia[(2,3)]. Studies have demonstrated that antacids and H2RAs, used for preventing stress ulcers, may increase the risk of hospital-acquired pneumonia (HAP) in critically ill patients[(4-6)]. The use of PPIs linked to an increased risk of community-acquired pneumonia (CAP) in ambulatory settings was also noted in many studies[(7-11)].

Despite the controversial association between PPI and pneumonia, an increased use of PPI in intensive care units (ICU) has been observed in recent years[(12)]. The American Thoracic Society (ATS) has not endorsed the use of PPI in preventing stress ulcers in ICU patients[(13)]. However, PPI was suggested as a treatment to prevent stress ulcers by the newer international guidelines for management of severe sepsis and septic shock in 2008 as the surviving sepsis campaign[(14)]. According to a report on a retrospective cohort study performed by Beaulieu *et al*., no significant difference in the risk of HAP was observed between ICU patients treated with PPI and those who were not (Adjusted Hazard Ratio

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0.63, 95% CI 0.39-1.01)[15]. However, conflicting results were found in a cohort study in 2009, which reported an increased risk of HAP with pantoprazole use when compared with ranitidine for stress ulcer prophylaxis for patients more than 18 years old in surgical ICUs (adjusted OR 2.7, 95% CI 1.1-6.7, *p*-value 0.034)[16]. Since the risk of bleeding in critical care patients with respiratory failure or coagulopathy is high, it is necessary to ensure appropriate treatment and prophylaxis for stress ulcers[17].

Sucralfate, a cytoprotective agent, has been listed as an acceptable prophylaxis for stress ulcer by practice guidelines, with a slightly higher rate of clinically significant gastric bleeding compared with H_2 antagonists[13,18]. It has been showed with less impact on stomach acidity and associated with lower incidence of late onset pneumonia compared to antacids and H2RAs[5]. Randomized trials also suggested a trend toward reduced ventilator-associated pneumonia (VAP) with sucralfate[19]. This study aimed to investigate the association between HAP and the use of stress ulcer prophylaxis for patients in medical ICUs. To find the adequate stress ulcer prophylaxis for patients with high risk of pneumonia, sucralfate was selected as the comparator vis-à-vis PPI in this study. The risk factors related to HAP were also analyzed to identify the high risk groups for supporting the prevention of stress ulcer.

MATERIALS AND METHODS

I. *Study Design and Subjects*

In this retrospective cohort study, patients were included as those admitted into the ICU of Keelung Chang Gung Memorial Hospital, a regional teaching hospital, during the period of January 1, 2000 to December 31, 2009. The study protocol was approved by the institutional review board (IRB) of the hospital. All data were collected from the electronic medical records in the Healthcare Information System of the hospital. Patients more than 18 years old, with an ICU stay of more than 48 h and who received either PPI (omeprazole, pantoprazole, esomeprazole, lansoprazole) or sucralfate were enrolled in the study. Patients who received a combined therapy or switched therapy of PPIs, sucralfate, or H2RAs were excluded. Other exclusion criteria were those who (1) had a diagnosis of pneumonia during three months before admission, (2) had documented aspiration before their ICU admission, (3) had a history of dysphagia, or (4) had a history of immunosuppression (defined as steroid treatment use more than 6 months, receipt of chemotherapy within the previous year, or treatment with any anti-rejection medications within the previous year). For patients who had multiple hospital admissions during the study period, only the first admission was eligible for inclusion.

II. *Outcome of Interest*

HAP is defined as pneumonia that occurs 48 h or later after ICU admission[20]. The National Nosocomial Infection Surveillance system algorithm was applied as the criteria of pneumonia[13]. The diagnosis of pneumonia can be confirmed if the patient has at least two of the following clinical features: (1) a new onset of fever, (2) leukocytosis or leucopenia, (3) a new onset of purulent sputum, a change in the character of the sputum, increased respiratory secretions, or increased suctioning requirements, (4) a new onset of worsening cough, dyspnea, tachypnea, or (5) a decline in oxygenation (by PaO2/fraction of inspired oxygen [FIO2] < 40%), increased oxygen requirements, or an increased ventilation demand. In addition, confirmation of progressive infiltration, consolidation or cavitation must be evaluated in two or more serial chest radiographic exams. Pneumonia that occurred after the use of PPIs or sucralfate was documented as a single case. The previous uses of PPIs and sucralfate before ICU admission in the same admission within the hospital were also documented.

III. *Statistical Analysis*

The statistical analysis used the X^2 test for categorical variables and an independent t-test for continuous variables. The differences between the groups were considered significant if *p*-values were less than 0.05. All of the variables with a *p*-value less than 0.1 in the univariate tests were selected for a forward stepwise logistic regression.

Crude and adjusted odds ratios were evaluated using multivariable logistic regression.

The covariates included into the initial analysis were age, sex, length of intensive care unit stay, mechanical ventilator use, comorbidities (gastroesophageal reflux disease [GERD], diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease [COPD], cerebrovascular disease and asthma), acute physiology and chronic health evaluation II (APACHE II) scores, status of tobacco use and medications. The *International Classification of Diseases, Ninth Revision, Clinical Modification* code (ICD-9 CM code) was used to identify the comorbidities in the electronic medical records. These were GERD (530.81), diabetes mellitus (250), asthma (493), heart failure (428), cerebrovascular disease (433, 434), and COPD (496). The medications included as covariates in the analysis were benzodiazepines, barbiturates, antipsychotics, opiates, neuromuscular blocking agents, nonsteroid anti-inflammatory drugs, systemic steroids (cortisone acetate, hydrocortisone, prednisolone, methylprednisolone, dexamethasone), and anticoagulant agents (enoxaparin, heparin, warfarin). Propensity score (PS) analysis was conducted to account for nonrandom treatment allocation by using all covariates to estimate a score for each patient[21]. The final multivariable regression model included a total of 11 covariates, including the PS, age, sex, ICU stays, APACHE II score, length of mechanical ventilator use, comorbidities of GERD, diabetes mellitus, congestive heart failure, COPD and the use of corticosteroids.

The optimal cutoff points of ICU stay and APACHE II score were determined by the receiver operating characteristic

(ROC) curves and Youden's index.

The effects of dose on the risk of pneumonia were also evaluated by the defined daily dose (DDD) established by the World Health Organization. DDD is defined as the assumed average daily maintenance dose given for the main indication of a drug[22]. The patients were therefore categorized into three groups according to the DDD defined: ≤ 1, 1.1-1.9, and ≥ 2. All statistical analyses in this study were performed using the Statistical Package for the Social Science 12.0 Software (SPSS, Inc., Chicago, IL, USA), except the sample size calculation by the Statistical Package for the Power analysis and Sample Size 11.0 Software (PASS 11. NCSS, LLC. Kaysville, Utah, USA).

RESULTS

At first, 1,158 patients admitted into the ICU were identified for possible inclusion in this study. Of these, 770 were deemed ineligible. The final cohort comprised 388 patients, of whom 302 patients received PPIs and 86 patients sucralfate (Figure 1). Table 1 shows the demographic and clinical characteristics of the participants. The percentages of patients on PPI and sucralfate before ICU admission within the hospital were not significantly different between the two groups. The patients on PPI therapy were significantly older than those who were treated with sucralfate (mean age 71.83 ± 13.02 vs. 68.17 ± 15.46, $p = 0.047$). They also had a significantly higher incidence of cerebrovascular disease (22.18% vs. 5.81%, $p = 0.001$) and a significantly higher APACHE II score (16.92 ± 6.96 vs. 15.27 ± 6.11, $p = 0.047$) than the corresponding group on sucralfate therapy. In contrast, patients on PPI therapy showed a significantly shorter length of mechanical ventilation than the sucralfate group (4.92 ± 8.15 days vs. 8.60 ± 11.57 days, $p = 0.007$). They also had shorter ICU stays (9.61 ± 7.47 days vs. 12.63 ± 10.36 days, $p = 0.013$). Table 1 summarizes the significant differences observed in baseline characteristics between the two groups.

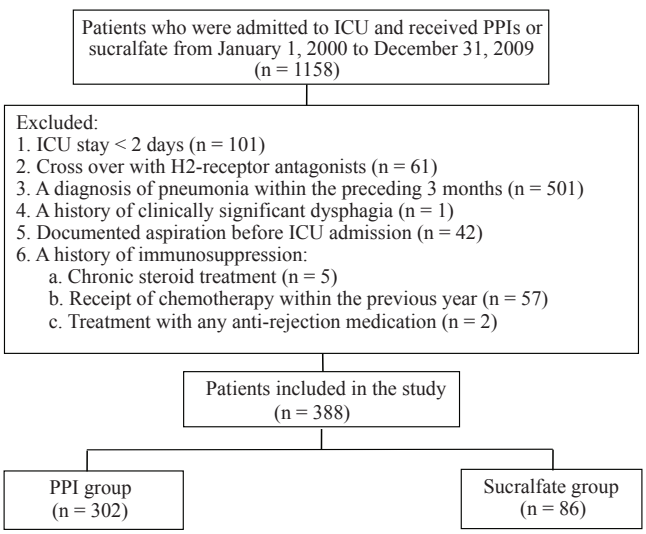

Figure 1. Study flow chart.

HAP developed in 63 out of 302 patients (20.86%) in the PPI group and 8 out of 86 patients (9.30%) in the sucralfate group (unadjusted OR 2.57, 95% CI 1.18-5.60). The area of ROC was 0.769, indicating acceptable predictability of the logistic regressions for estimating PS. After adjusting to PS and other variables, the odds ratio of HAP was 3.37 (95% CI, 1.35-8.45) (Table 2).

Two factors were also associated with the occurrence of HAP in the multivariable-adjusted logistic regression model. These were the length of intensive care unit stay (OR 1.09, 95% CI 1.02-1.16) and APACHE II scores (OR 1.07, 95% CI 1.02-1.13). The optimal cutoff points, determined by analyzing the area under ROC curve and using Youden's index, were ≤ 8 days for ICU stays, and ≤ 13 for an APACHE II score.

Based on these scores, the patients were further categorized into two groups of lower and higher risk. Patients in the sucralfate group with ICU stays ≤ 8 days served as the reference group. Patients in the PPI group with ICU stays > 8

Table 1. Characteristics of the Study Population

Variable	PPI N = 302	Sucralfate N = 86	*p* Value
Age, mean (range), y	71.83 ± 13.02 (18-95)	68.17 ± 15.46 (20-89)	0.047*
Male, No. (%)	170 (56.29)	39 (45.35)	0.073
Comorbidities, No. (%)			
GERD	12 (3.97)	1 (1.16)	0.348
Diabetes mellitus	138 (45.70)	40 (46.51)	0.893
Congestive heart failure	115 (38.1)	28 (32.6)	0.349
COPD	40 (13.2)	7 (8.1)	0.200
Cerebrovascular disease	67 (22.18)	5 (5.81)	0.001*
Asthma	12 (4.0)	3 (3.5)	0.837
History of tobacco use	106 (35.1)	29 (37.2)	0.813
Mechanical ventilation, d	4.92 ± 8.15	8.60 ± 11.57	0.007*
ICU stay, mean (range), d	9.61 ± 7.47 (3-45)	12.63 ± 10.36 (3-54)	0.013*
APACHE II score	16.92 ± 6.96	15.27 ± 6.11	0.047*
Previous PPI, No. (%)	15 (4.97)	1 (1.63)	0.118
Previous sucralfate, No. (%)	5 (1.66)	3 (3.49)	0.291
DDD, mean ± SD	1.71 ± 1.13	1.63 ± 0.51	0.302
In-ICU medications, No. (%)			
Sedative	72 (23.84)	29 (33.72)	0.065
NSAID	78 (25.83)	27 (31.40)	0.504
Anticoagulant	80 (26.49)	16 (18.60)	0.135
Systemic steroid	78 (25.83)	27 (31.40)	0.305

Abbreviations: GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; DDD, defined daily dose; NSAID, nonsteroidal anti-inflammatory drug.
A Chi-square test was used to compare categorical variables and an independent t test for continuous variables. *$p < 0.05$

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Table 2. Rates of Hospital-Acquired Pneumonia

Outcome	n (%)		Odds ratio	
	PPI (n = 302)	Sucralfate (n = 86)	Unadjusted (95% CI)	Adjusted* (95% CI)
Hospital-acquired pneumonia	63 (20.86)	8 (9.30)	2.57** (1.18-5.60)	3.37** (1.35-8.45)

Abbreviations: CI, confidence interval.
*Regression adjustment was used. All variables include propensity score, sex, age, ICU stay, ventilator days, APACHE II score, chronic obstructive pulmonary disease, diabetes mellitus, congestive heart failure, gastroesophageal reflux disease and systemic steroid use.
** $p < 0.05$

Table 3. The Association between ICU stays, Sucralfate, PPI and Hospital-Acquired Pneumonia

Outcome	ICU stays aOR (95% CI)	
	≤ 8 days	> 8 days
Sucralfate (n = 86)	1.0 (n = 42)	2.50 (0.43-14.51) (n = 44)
PPI (n = 302)	1.56 (0.33-7.35) (n = 184)	9.04* (1.94-42.06) (n = 118)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.
Adjusted variables include: sex, age, ventilator days, APACHE II score, chronic obstructive pulmonary disease, diabetes mellitus, congestive heart failure, gastroesophageal reflux disease, asthma and systemic steroid use.
* $p < 0.05$

Table 4. The Association between APACHE II score, Sucralfate, PPI and Hospital-Acquired Pneumonia

Outcome	APACHE II score aOR (95% CI)	
	≤ 13	> 13
Sucralfate (n = 86)	1.0 (n = 38)	0.73 (0.14-3.77) (n = 48)
PPI (n = 302)	1.19 (0.29-4.86) (n = 101)	3.70* (1.04-13.10) (n = 201)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.
Adjusted variables include: sex, age, ventilator days, APACHE II score, chronic obstructive pulmonary disease, diabetes mellitus, congestive heart failure, gastroesophageal reflux disease, asthma and systemic steroid use.
* $p < 0.05$

days had the highest risk for HAP (adjusted OR 9.04, 95% CI 1.94-42.06) (Table 3). A similar finding was observed in the PPI group with APACHE II scores > 13 (adjusted OR 3.70, 95% CI 1.04-13.10) (Table 4).

The sample size was then confirmed under the following conditions: the R-square of group with other covariates was equal to 0.13, the HAP of P_0 (sucralfate) was equal to 0.093, and HAP of P_1 (PPI) was equal to 0.257. The percentage of PPI in group was equal to 77.8%. The calculated total sample size, with a defined ratio of study group as 1 : 3, to reach 80% of power was 294, and the sample size of present study was 388 (Appendix 1).

To evaluate the dose and relationship of PPIs with the risk of HAP, the patients in the DDD ≤ 1 were defined as the reference group. The results indicated that patients with higher DDD did not have increased risk for HAP (Data not shown).

Appendix 1.

Logistic Regression Power Analysis

Numeric Results

		Pcnt N					
Power	**N**	**X = 1**	**P0**	**P1**	**Odds Ratio**	**R Squared**	**Alpha**	**Beta**
0.79832	294	77.800	0.093	0.257	3.370	0.130	0.05000	0.20168

Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one.
N is the size of the sample drawn from the population.
P0 is the response probability at the mean of X.
P1 is the response probability when X is increased to one standard deviation above the mean.
Odds Ratio is the odds ratio when P1 is on top. That is, it is [P1/(1-P1)]/[P0/(1-P0)].
R-Squared is the R^2 achieved when X is regressed on the other independent variables in the regression.
Alpha is the probability of rejecting a true null hypothesis.
Beta is the probability of accepting a false null hypothesis.

Summary Statements

A logistic regression of a binary response variable (Y) on a binary independent variable (X) with a sample size of 352 observations (of which 22% are in the group X = 0 and 78% are in the group X = 1) achieves 80% power at a 0.05000 significance level to detect a change in Prob(Y = 1) from the baseline value of 0.093 to 0.240. This change corresponds to an odds ratio of 3.076.

DISCUSSION

The incidence rates of HAP developed in the medical ICU were compared between patients who received PPI and patients who received sucralfate. The PPI group was revealed to have a higher risk of developing HAP than the sucralfate group. In addition, those patients on PPI therapy with ICU stays > 8 days or an APACHE II score > 13 had an even greater risk of developing HAP. To our knowledge, no comparative study has compared the outcomes of PPI and sucralfate therapies for patients in ICUs. No statistically

significant difference in HAP incidence was found in two previous randomized control studies performed in a pediatric ICU and a surgical ICU setting[23,24]. However, the insignificance likely resulted from a type II error with only approximately 40 and 70 patients in each group. The impact of PPI on gastric pH is more significant than that associated with H2RA and sucralfate, which consequently results in an increased risk of HAP caused by gastric colonization with aerobic gram-negative bacilli[25]. Therefore, the incidence rate of HAP was expected to be higher in the PPI group than that in the sucralfate group.

The controversial findings on the association of HAP and PPI in the literatures may result from the ambiguities of acid-suppressive agent induced HAP. Beaulieu *et al*. demonstrated that no significant difference in the risk of HAP existed between patients treated with and without PPI[15]. However, the study defined patients as nonexposed to PPIs if they developed nosocomial pneumonia following the last dosage or a treatment with PPIs for more than 14 days. A selection bias could have been introduced by excluding the late-onset nosocomial pneumonia induced by PPI. In contrast, PPIs related to increased incidence rates of HAP were demonstrated in two recent population-based cohort studies[16,26]. Herzig and colleagues showed that HAP incidence increased by 30% in non-ICU patients receiving PPIs[26]. In another study, conducted by Minao *et al*., PPI was found to be an independent risk factor associated with increased HAP in ICU patients[16], which was consistent with our results.

The optimal cutoff points of ICU stays and APACHE II scores for the development of HAP were also elucidated in this study. Ventilator-associated pneumonia (VAP) is considered the most frequent infection in the ICU. However, as indicated in a previous study, ICU stays were related to the incidence of VAP[27]. To verify the association between HAP and ICU stays, we further demonstrated that patients on PPI therapy had a higher risk of developing HAP if their ICU stays were longer than 8 days (adjusted OR 9.04, 95% CI 1.94-42.06, *p*-value 0.005). Additionally, a high APACHE II score was found to be an independent risk factor for HAP. This was confirmed by previous studies that investigated the risk factors for developing VAP[28,29]. We delineated the optimal cut-off points for APACHE II scores and HAP. The results showed that patients receiving PPI, with an APACHE II score > 13, were at a higher risk of developing HAP (adjusted OR 3.70, 95% CI 1.04-13.10, *p*-value 0.043).

The results of this study provide new evidence to strengthen the current practice of stress ulcer prophylaxis. The American Society of Health-System Pharmacists (ASHP) recommends that for patients in general, such as medical, surgical, respiratory, ICU populations who have respiratory failure or coagulopathies, use H2RA, antacid (level A), or sucralfate to prevent stress ulcers (level B) [30]. ATS states that, if needed, stress bleeding prophylaxis with either H2RA or sucralfate is acceptable (Level I)[13]. Although limited information exists on the association of PPIs with an increased risk of *Clostridium difficile* disease, the ATS still recommends that PPI should not be used solely for stress ulcer prophylaxis in an ICU setting[13]. According to the results of this study, sucralfate could be considered as a favorable option for stress ulcer prophylaxis in ICU patients.

The phenomenon of dose-dependent-HAP was not observed in the participants. No previous study has attempted to evidence the relationship between the dose or duration of PPI use and the risk of HAP. A significant dose-dependent risk was only observed for CAP in current users of PPIs. Persons using more than 1 of DDD had a 2.3-fold increased risk of CAP compared with past use of acid suppressants[7]. A large nested case-control study showed a modest increase in risk for CAP among current PPI recipients with high dosing. But at a daily dose of less than 1.5 times of DDD, current PPI exposure was not associated with an increased risk for CAP[8]. Further studies to confirm the association of longer-term or high dose of current PPI therapy with HAP are warranted.

This was a retrospective chart review research. The main limitations of the present study resided in its observational design and lack of control over treatment assignments. Information was only obtained through review of computerized medical records and some information on adjustable risk factors was not available. This included enteral feeding, nasogastric or oral gastric tube insertion, patient semirecumbent position (30-45°), and oral antiseptic use. Additionally, the study only included patients from one hospital, and the generalizability of the study results was diminished. The information on self-use or prescribed PPI and sucralfate from other hospitals before admission were not available. This might limit the study to detect dose- or duration- dependent-HAP if exists. The sample size of this study was small, and thus estimated OR might need to be confirmed in the future. Our results generates a hypothesis and warrants further prospective randomized clinical trials (RCT) to investigate the optimum criteria for the administration of stress ulcer prophylaxis in ICU patients.

CONCLUSIONS

The present study demonstrated that PPI therapy was associated with a higher risk for HAP in ICU patients than sucralfate therapy. The risk was higher in patients on PPI therapy and with an ICU stay > 8 days or with an APACHE II score > 13. Considering the results obtained by this study and the current clinical practice guidelines, the use of sucralfate should be a priority for stress ulcer prophylaxis in ICU patients. For patients with an APACHE II score > 13 or an expected long ICU stay, the risks and benefits of PPI therapy should be carefully evaluated.

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REFERENCES

1. Eom, C. S., Jeon, C. Y. and Lim, J. W. *et al*. 2011. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. CMAJ 183: 310-319.
2. Kollef, M. H. 1999. The prevention of ventilator-associated pneumonia. N. Engl. J. Med. 340: 627-634.
3. Hunter, J. D. 2006. Ventilator associated pneumonia. Postgrad. Med. J. 82: 172-178.
4. Driks, M. R., Craven, D. E. and Celli, B. R. *et al*. 1987. Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. the role of gastric colonization. N. Engl. J. Med. 317: 1376-1382.
5. Prod'hom, G., Leuenberger, P. and Koerfer, J. *et al*. 1994. Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer. A randomized controlled trial. Ann. Intern. Med. 120: 653-662.
6. Tryba, M. 1987. Risk of acute stress bleeding and nosocomial pneumonia in ventilated intensive care unit patients: sucralfate versus antacids. Am. J. Med. 83: 117-124.
7. Laheij, R. J., Sturkenboom, M. C. and Hassing, R. J. *et al*. 2004. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA 292: 1955-1960.
8. Sarkar, M., Hennessy, S. and Yang, Y. X. 2008. Proton-pump inhibitor use and the risk for community-acquired pneumonia. Ann. Intern. Med. 149: 391-398.
9. Gulmez, S. E., Holm, A., Frederiksen, H., Jensen, T. G., Pedersen, C. and Hallas, J. 2007. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. Arch. Intern. Med. 167: 950-955.
10. Myles, P. R., Hubbard, R. B., McKeever, T. M., Pogson, Z., Smith, C. J. and Gibson, J. E. 2009. Risk of community-acquired pneumonia and the use of statins, ace inhibitors and gastric acid suppressants: a population-based case-control study. Pharmacoepidemiol. Drug Saf. 18: 269-275.
11. Eurich, D. T., Sadowski, C. A., Simpson, S. H., Marrie, T. J. and Majumdar, S. R. 2010. Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. Am. J. Med. 123: 47-53.
12. Fallell, C. P., Mercogliano, G. and Kuntz, C. L. 2010. Overuse of stress ulcer prophylaxis in the critical care setting and beyond. J. Crit. Care. 25: 214-220.
13. American Thoracic Society. 2005. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am. J. Respir. Crit. Care Med. 171: 388-416.
14. Dellinger, R. P., Levy, M. M. and Carlet, J. M. *et al*. 2008. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intens. Care Med. 34: 17-60.
15. Beaulieu, M., Williamson, D., Sirois, C. and Lachaine, J. 2008. Do proton-pump inhibitors increase the risk for nosocomial pneumonia in a medical intensive care unit? J. Crit. Care. 23: 513-518.
16. Miano, T. A., Reichert, M. G., Houle, T. T., MacGregor, D. A., Kincaid, E. H. and Bowton, D. L. 2009. Nosocomial pneumonia risk and stress ulcer prophylaxis: a comparison of pantoprazole vs ranitidine in cardiothoracic surgery patients. Chest 136: 440-447.
17. Cook, D. J., Fuller, H. D. and Guyatt, G. H. *et al*. 1994. Risk factors for gastrointestinal bleeding in critically ill patients. N. Engl. J. Med. 330: 377-381.
18. Guillamondegui, O. D., Gunter, O. L. and Ronaides, J. A. *et al*. 2008. Practice management guidelines for stress ulcer prophylaxis. Chicago, Eastern Association for the Surgery of Trauma (EAST). http://www.guideline.gov/summary/
19. Cook, D. J., Guyatt, G. and Marshall, J. *et al.*1998. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. N. Engl. J. Med. 338: 791-797.
20. Kieninger, A. N. and Lipsett, P. A. 2009. Hospital-acquired pneumonia: pathophysiology, diagnosis, and treatment. Surg. Clin. North Am. 89: 439-461.
21. Dattalo, P. 2009. Statistical alternatives and supplements to random supplements assignment. In "Strategies to Approximate Random Sampling and Assignment". 1st ed. pp.109-149. Tripodi, T. ed. Oxford University Press. New York, U.S.A.
22. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment, 2010. http://www.whocc.no/filearchive/publications/2010guidelines.pdf
23. Yildizdas, D., Yapicioglu, H. and Yilmaz, H. L. 2002. Occurrence of ventilator-associated pneumonia in mechanically ventilated pediatric intensive care patients during stress ulcer prophylaxis with sucralfate, ranitidine, and omeprazole. J. Crit. Care 17: 240-245.
24. Kantorova, I., Svoboda, P. and Scheer, P. *et al*. 2004. Stress ulcer prophylaxis in critically ill patients: a randomized controlled trial. Hepatogastroenterology 51: 757-761.
25. Eddleston, J. M., Vohra, A. and Scott, P. *et al*. 1991. A comparison of the frequency of stress ulceration and secondary pneumonia in sucralfate- or ranitidine-treated intensive care unit patients. Crit. Care Med. 19: 1491-1496.
26. Herzig, S. J., Howell, M. D., Ngo, L. H. and Marcantonio, E. R. 2009. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. JAMA 301: 2120-2128.
27. Wu, S. C. and Chen, C. C. 2004. Study on factors for ventilator-associated pneumonia in intensive care unit. Taiwan J. Public Health 23: 440-446.
28. Apostolopoulou, E., Bakakos, P., Katostaras, T. and Gregorakos, L. 2003. Incidence and risk factors for

ventilator-associated pneumonia in 4 multidisciplinary intensive care units in Athens, Greece. Respir. Care 48: 681-688.

29. Gacouin, A., Barbarot, N. and Camus, C. *et al*. 2009. Late-onset ventilator-associated pneumonia in nontrauma intensive care unit patients. Anesth. Analg. 109: 1584-1590.

30. ASHP Commission on Therapeutics. 1999. ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. Am. J. Health Syst. Pharm. 56: 347-379.