



STRESS ULCER PROPHYLAXIS AS A RISK FACTOR FOR TRACHEAL COLONIZATION AND HOSPITAL-ACQUIRED PNEUMONIA IN INTENSIVE CARE PATIENTS: IMPACT ON LATENCY TIME FOR PNEUMONIA

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SUMMARY – Stress ulcer prophylaxis is associated with bacterial colonization of respiratory tract. The aims of our study were to determine risk factors for trachea colonization (TC), colonization of pharynx (CP) or stomach (CD) and hospital-acquired pneumonia (HAP), and divide the factors into those with high risk and low risk. The study population (ventilated intensive care unit (ICU) patients eligible to receive stress ulcer prophylaxis) was randomized to receive one of three different treatment protocols: ranitidine, sucralfate, and no stress ulcer prophylaxis (control group). Clinical data relative to pre-specified risk factors for TC or HAP were recorded, as follows: APACHE II score (second risk factor), duration of intubation or tracheotomy (third risk factor), duration of mechanical ventilation (fourth risk factor) and duration of hospitalization in the ICU (fifth risk factor). Gastric pH was recorded and microbiological data regarding stomach, pharynx and trachea were collected on the 1st, 2nd, 3rd and 5th day. Fifty-eight out of 81 patients developed HAP (including ventilator-associated pneumonia), which occurred later in patients with gastric content pH <4 or those that were tracheotomized. Stress ulcer prophylaxis was not associated with HAP; however, it was proved as a risk factor for TC. TC was detected in tracheotomized patients and was caused by gram-negative pathogens. CP was associated with TC, since the majority of patients had CP before TC. A combination of risk factors (APACHE II >18, age >65, mechanical ventilation and sedation) caused a higher incidence of HAP and lower incidence of TC. HAP was more frequent in patients staying in the ICU for >10 days and those with cardiovascular disease as the underlying disorder. Sedation and previous antibiotic therapy correlated with longer latent period (LAT), while higher values of gastric content pH were related to shorter LAT. The longest LAT was found in patients colonized with *Acinetobacter* spp. Risk factors that accelerated the occurrence of HAP were found to have caused previous colonization. A combination of risk factors increased the likelihood of TC and HAP, and shortened LAT between TC and HAP.

Key words: *Peptic ulcer; Bacteria – growth and development; Healthcare-associated pneumonia; Intensive care units; Risk factors; Tracheostomy*

Introduction

Stress ulcer prophylaxis has traditionally been used as the prevention of upper gastrointestinal bleeding in critically ill patients. A randomized trial comparing patients receiving prophylaxis against stress ulcers and those with no prophylaxis indicated that the use of

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prophylaxis prevented clinically important gastrointestinal bleeding. On the other hand, the study suggested the higher gastric pH to be associated with bacterial growth in intestinal tract, tracheobronchial colonization, and nosocomial pneumonia¹. In the past, it was shown that the agents that raise gastric pH may promote proliferation of bacteria in the stomach, particularly gram-negative bacilli that may originate in the duodenum. Passive esophageal reflux and micro-aspiration of the gastric content along the endotracheal tube may lead to colonization of the trachea and then to pneumonia².

Nosocomial or hospital-acquired pneumonia (HAP) is defined as an infection of lower respiratory tract, which was not present in the emergency room but emerged 48 hours after hospital admission³. HAP is one of the most common nosocomial infections in the intensive care unit (ICU). It occurs in 5 to 10 per 1000 admitted patients, and is up to 20 times more frequent in patients with mechanical ventilation (MV), mainly known as ventilator-associated pneumonia (VAP)⁴. HAP that occurs in patients on MV is divided into early HAP (48 hours to 4 days of MV), which is usually primary endogenous, or late HAP occurring after 4 days of MV and is typically secondary endogenous or exogenous^{4,5}. HAP prolongs hospital stay by 4-9 days; mortality is 33%-50%, and even higher in patients infected with *Staphylococcus aureus*, *Pseudomonas* spp., *Acinetobacter* spp., *Klebsiella pneumoniae*, and *Enterobacter* spp. (45%-71%)^{3,6,7}. Microorganisms that colonize the pharynx and trachea can come from digestive tract (endogenous route) or outer environment (exogenous route). Previous colonization of upper digestive system is the main cause of HAP^{8,9}. Digestive system colonization may occur due to migration of bacteria from the environment or reproduction of bacteria from intestinal flora^{10,11}. Patients that are intubated, tracheotomized or MV have a greater possibility of ascending pharyngeal colonization and subsequent colonization of trachea (TC) is thus easier. Microorganisms that colonize the stomach will gradually colonize the pharynx and frequently come in the respiratory tract with aspirations and cause pneumonia^{12,13}.

Thus, TC is the main source of HAP. It is present before the onset of pneumonia in 80% of patients¹⁴⁻¹⁶. Literature offers a vast knowledge about risk factors for HAP, but less about TC in ICU patients. The independent risk factors include intubation, tracheotomy,

MV, impaired consciousness, Acute Physiology and Chronic Health Evaluation II (APACHE II) score >16, and feeding through nasogastric tube¹⁷⁻²⁰. The question is whether these factors and what combination of factors influence the occurrence of TC. There are scarcely any literature data on the relationship of risk factors and temporal occurrence of TC and HAP, and on the impact of risk factors and time between TC and HAP (latency time, LAT). Knowing these facts, we could differentiate patients at a high or low risk of the occurrence of TC and HAP. The data obtained could suggest whether the risk of TC means an equal risk of HAP.

The objectives of this study were to evaluate patients on stress ulcer prophylaxis at the highest risk of both bleeding and pneumonia and to determine which factors influence TC in these ICU patients. We tried to find a causal link between the number of risk factors and the occurrence of colonization and HAP, and to determine LAT between colonization and HAP. Thus, we tried to classify the risk factors into those associated with a high risk and those less likely to cause TC or HAP.

Material and Methods

Inclusion and exclusion criteria

The study was designed as a randomized trial and lasted for 10 years, but data were analyzed retrospectively. Ethics Committee of the Republic of Slovenia approved the study design and was run under register 02/03/98. The study included ICU patients that were hospitalized, intubated, tracheotomized, or were on MV, and received protection against stress ulcers. The criteria for patient inclusion were expected duration of hospitalization in the ICU for at least 24 hours and age >15 years. Only patients with nasogastric tube that were intubated or tracheotomized participated in the study. Exclusion criteria for patients were the presence of HAP at admission to the ICU, immunocompromised patients or leukopenia (less than $2 \times 10^9/L$), aspiration at admission, previous intake of antacids, H₂ blockers or sucralfate (in the previous 24 hours) and visible bleeding from the stomach or duodenum (Fig. 1). Termination of the experiment was set at the occurrence of HAP, removal of tube or cannula, 72 hours after discharge from the ICU, hospital death, or 21 days of hospitalization.

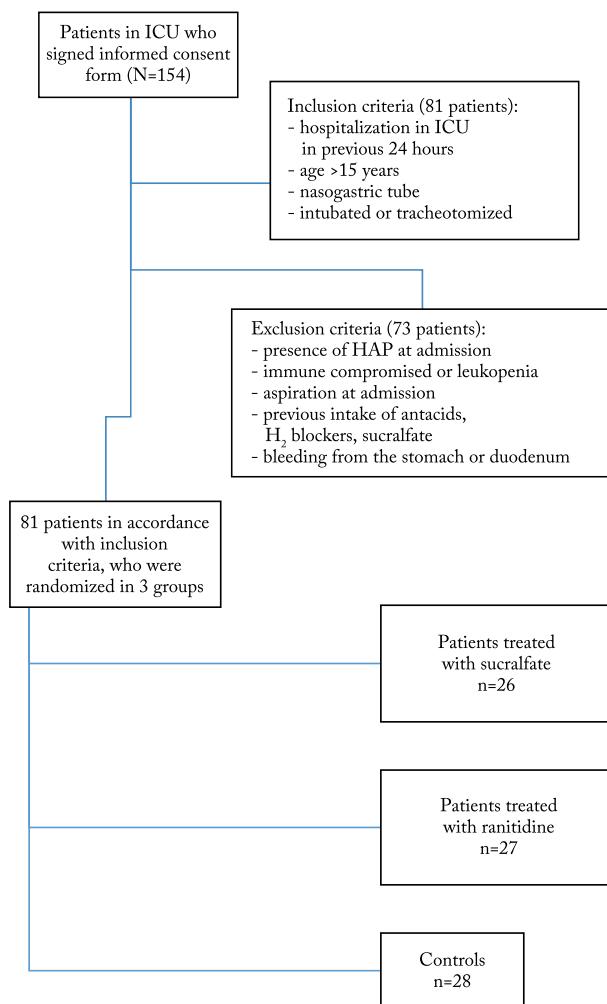


Fig. 1. Work flow of experimental design and group distribution.

Participants and data collection

A total of 1054 patients were admitted to the medical ICU. Of all eligible patients during the study period, 154 were randomly assigned to a final group and were eventually intubated or tracheotomized for more than 24 hours. In accordance with inclusion criteria, 81 patients could be analyzed. The patients were randomly divided into specified groups using the method of randomized numbers. All patients had equal opportunity to be selected into the control group as the impact of systematic factors on the choice was avoided. Of these patients, group 1 included patients treated with sucralfate (6 g/24 h; 26 patients) (first risk factor for TC/HAP) and group 2 patients were administered ranitidine, a histamine H₂-receptor blocker (300

mg/24 h; 27 patients). Ranitidine was administered in the form of tablets, 150 mg/12 h, which ensured at least 50% reduction in gastric acid secretion. When macroscopic bleeding was visible, patients received ranitidine parenterally. Sucralfate was prescribed only in the form of granules, 4 to 6 times a day. Meanwhile, 28 patients were selected as controls. The severity of patient condition was evaluated by APACHE II score (second risk factor). We recorded the duration of intubation and tracheotomy (third risk factor), duration of MV (fourth risk factor) and duration of ICU hospitalization (fifth risk factor).

Clinical monitoring of patients

The patients were fully checked at admission, and if necessary the medical history and clinical picture from the admission department was completed. During testing, we routinely measured vital functions every 3 hours (heart rate, respiration, temperature, blood pressure, intake and excretion of fluids, oxygen saturation) and controlled laboratory values (complete blood count, C-reactive protein, electrolytes, hepatogram, arterial blood gas measurement). The pH value of stomach content was measured in the morning on an empty stomach, using a Universal Indicator pH-meter (Merck, Germany) with a range of 1 to 10. The presence of blood in the stomach aspirate was determined each morning using the Hemdetect reagent (DIPRO, Austria). Bleeding was established as the presence of fresh blood or blood mass in the stomach aspirate (or melena), or with positive hematest.

Criteria for diagnosis

Colonization of trachea and HAP were diagnosed according to the Center for Disease Control (CDC) criteria, as follows: presence of microorganisms in the tracheobronchial aspirates in at least one sample and presence of clinical and laboratory signs for HAP, or presence of the same microorganism in 2 consecutive isolates without clinical signs for HAP²¹. Since pneumonia after mechanical ventilation (ventilator associated pneumonia, VAP) is acquired in hospital units, we defined VAP patients as part of the HAP group.

Criteria for HAP were as follows: criterion I was physical examination for chest percussion or hypophony and one of the following: purulent sputum (presence of >25 leukocytes and <10 epithelial cells in the

Table 1. Demographic data

	S group (n=26)	R group (n=27)	Control group (n=28)	Total (N=81)	p-value
Gender (F/M)	18/8	21/6	24/4	63/18 (77.8%/22.2%)	0.5
Age (years), median	67.1	68.8	74.2	70.2	0.2
Intubated	19	19	22	60 (74.1%)	0.3
Tracheotomized	7	8	6	21 (25.9%)	0.3
MV	15	16	21	52 (64.2%)	0.4
APACHE II	19.0	19.7	19.3	19.5 (12-24)	0.1
Underlying disease:					
encephalitis	7	8	2	15 (18.5%)	0.1
other*	19	19	26	66 (81.5%)	
Consciousness:					
no disturbance	0	2	0	2 (2.5%)	0.3
somnolence	11	11	13	35 (43.2%)	
coma	13	16	15	44 (54.3%)	
Relaxation	14	12	12	38 (46.9 %)	0.9
Sedation	27	21	22	70 (86.4 %)	0.2
Previous antibiotic treatment	7	7	3	17 (21 %)	0.2
pH value of gastric juice**	3.8 (3-5.2)	4.8 (4.2-6.3)	4.2 (3-6.5)	4.3 (3-6.5)	**

F/M = female/male; MV = mechanical ventilation; APACHE = Acute Physiology and Chronic Health Evaluation; *febrile state, polyradiculoneuritis; **statistically significant difference ($p=0.002$) was found between sucralfate (S) and ranitidine (R) groups; comparison of patients who did not receive protection to those receiving S or R showed no statistical difference ($p=0.3$); comparison of control group and S group showed a statistically significant difference ($p=0.03$) in pH values.

visual field), positive hemoculture, isolation of microorganisms from aspirate or bronchoalveolar lavage (BAL), biopsy. Criterion II were positive patchy infiltrations on chest x-ray and one of the following: purulent sputum, positive hemoculture, isolation of microorganisms from aspirate or BAL, biopsy and histology. All patients also had to have elevated leukocyte values ($>10 \times 10^9/L$) and elevated body temperature ($>38^\circ\text{C}$) considered as diagnosing criteria.

Bacteriological monitoring to confirm pneumonia

Samples for microbiological examination were obtained in the morning on days 1, 2, 3 and 5, and then every 48 hours. Gastric juice was collected by nasogastric tube. Blind profound aspiration of trachea and non-bronchoscopic BAL were the basic methods for gathering material for microbiological determination of TC or HAP. When the samples were unrepresentative, we repeated sampling using bronchoscope. Samples were sent for cultivation on blood, chocolate, McConkey agar and thioglycolate broth. Latency time in days between TC and pneumonia was established with

confirmation of the same bacterial culture from trachea and lungs. Colonization was determined at three different sites, i.e. stomach, pharynx and trachea. When the same microorganism was isolated from the lung sample and colonizing site, the infectious route was determined.

Statistical analysis

Statistical analysis was performed by SPSS 21 software (IBM, New York, USA). Univariate analysis compared continuous variables by Student's t-test for data that were normally distributed, or by Wilcoxon rank sum test for abnormal distribution of variables. The χ^2 -test was used for evaluation of categorical variables. Statistical differences were considered to be significant at $p<0.05$. Logistic regression revealed the impact of a combination of variables (risk factors) on the occurrence of colonization, HAP and LAT. Moreover, Hosmer-Lemeshov test assessed the influence of independent variables (risk factors) on the dependent variable (colonization). The effect of risk factors on latency was shown by the Cox model analysis.

Table 2. Causative pathogens for colonization of the stomach (CS), pharynx (CP) and trachea (TC)

Microorganism	CS (%)	CP (%)	TC (%)	Total (%)
<i>Pseudomonas aeruginosa</i>	4 (6.8)	4 (0.8)	6 (11.3)	14
<i>Acinetobacter calcoaceticus</i>	–	16 (16.2)	7 (13.2)	23
<i>Klebsiella pneumoniae</i>	9 (15.3)	3 (8.1)	6 (11.3)	18
<i>Klebsiella</i> spp.	9 (15.3)	2 (5.4)	2 (3.8)	13
<i>Escherichia coli</i>	10 (16.9)	7 (18.9)	3 (5.7)	20
<i>Enterobacter</i> spp.	9 (15.3)	3 (8.1)	7 (13.2)	19
<i>Citrobacter</i> spp.	1 (1.7)	1 (2.7)	–	2
<i>Serratia</i> spp.	–	1 (2.7)	–	1
<i>Haemophilus influenzae</i>	–	–	1 (1.9)	1
Gram-negative	42	37	32	111 (69.8)
<i>Staphylococcus aureus</i>	3 (5.1)	8 (21.6)	11 (20.8)	22
MRSA	–	1 (2.7)	1 (1.9)	2
<i>Streptococcus faecalis</i>	5 (8.5)	–	–	5
<i>Streptococcus faecium</i>	1 (1.7)	–	–	1
<i>Streptococcus pneumoniae</i>	–	–	5 (9.4)	5
<i>Streptococcus</i> spp.	2 (3.4)	–	–	2
Gram-positive	11	9	17	37 (23.3)
<i>Candida albicans</i>	2 (3.4)	–	1 (1.9)	3 (1.9)
<i>Candida</i> spp.	4 (6.8)	1 (2.7)	3 (5.7)	8 (5.0)
Total	59 (37.1)	47 (29.6)	53 (33.3)	159 (100)

Results

Demographic data

At randomization, no statistically significant difference was found among the three groups in terms of patient characteristics and other underlying characteristics (Table 1). In addition, no statistically significant difference was found among the three groups in the number of patients at risk with intubation ($p=0.3$), tracheostomy ($p=0.3$) or mechanical ventilation ($p=0.4$) (Table 1). The median stay at ICU for all 81 patients was 38.4 days. APACHE II <16 was recorded in five (6.2%), APACHE II 16-20 in 53 (65.4%) and APACHE II >20 in 23 (28.4%) patients. In total, bleedings were determined in 18 (22.2%) patients. Most of these were microbleedings, while serious bleeding occurred in one patient from the sucralfate group. More bleedings were noticed in sucralfate group as compared with ranitidine group, but the difference was not statistically significant ($p=0.4$). Moreover, in the control group (no prophylaxis against stress ulcer), no bleedings were noticed compared to the other two

groups, and a higher gastric juice pH was recorded compared to ranitidine group (Table 1).

Colonization of stomach, pharynx and trachea

Colonization of stomach (CS) occurred in 59 (82.8%) patients, mostly on days 2 and 3 after inclusion in the study (38 patients, 64.3%), less on day 4 or 5 (13 patients, 22.1%). The median time to CS was 3.2 (range 1-9) days. The most common bacteria that colonized digestive system are presented in Table 2. Colonization of pharynx (CP) was recorded in 37 (45.7%) patients and occurred later. On days 2 and 3, colonization was detected in 15 (40.5%) patients, and on days 4 and 5 in 14 (37.8%) patients. Early colonization (day 1) was observed in two (5.4%) patients. The median time was 4.2 (range 1-15) days. TC occurred in 53 (65.4%) patients, mostly on days 2 and 3, or on days 4 and 5 (18 (34%) patients both). Between days 6 and 7, colonization occurred in seven (13.2%) patients, early colonization was found in two (3.8%) patients and late colonization (after day 7) in eight (14.1%) patients. The median time was 4.96 (range 1-18) days. Patients

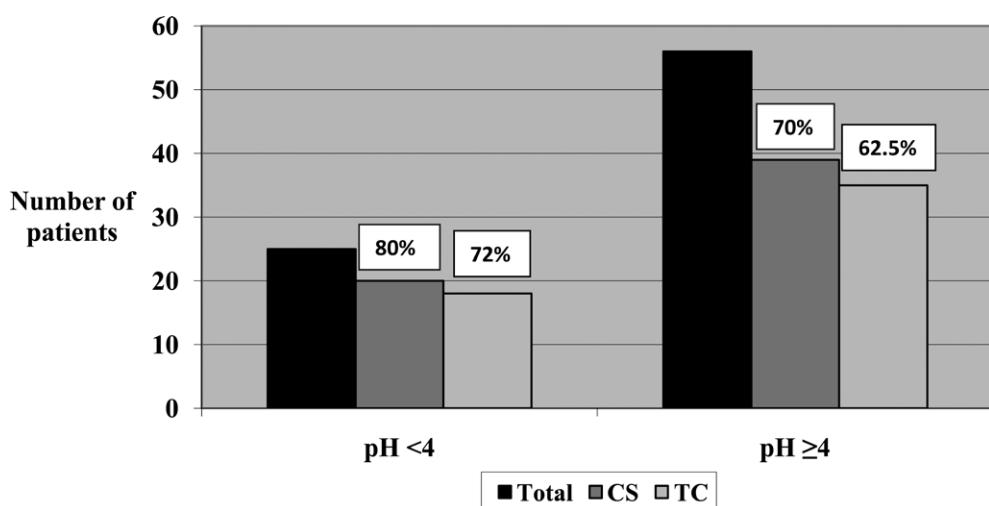


Fig. 2. Colonization of the stomach (CS) and trachea (TC) according to gastric juice pH value.

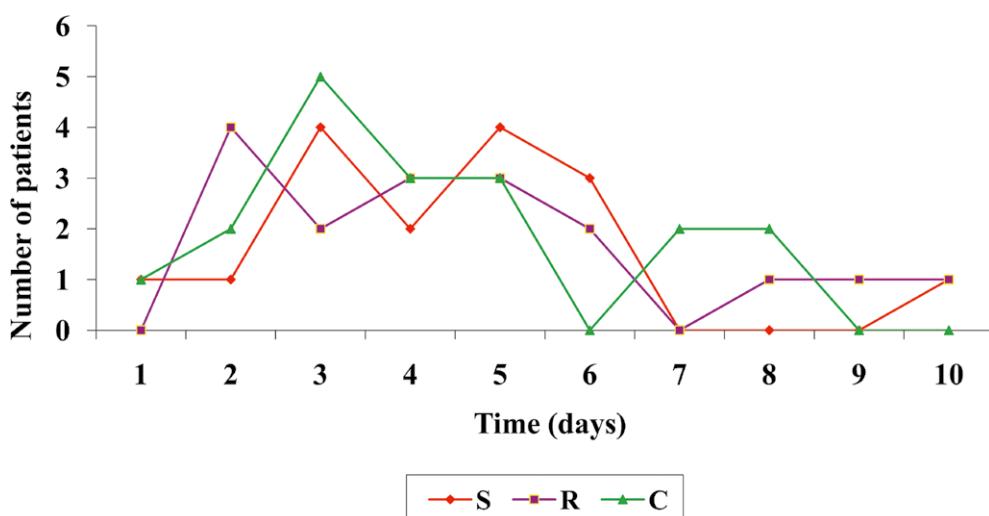


Fig. 3. Pattern of tracheal colonization in patients receiving sucralfate (S), ranitidine (R) and control group (C).

with higher gastric juice pH ($\text{pH} \geq 4$; $n=56$) were more frequently colonized than patients with lower gastric juice pH ($\text{pH} < 4$; $n=25$) (Fig. 2), but CS or TC did not differ between the groups. The colonization and time of colonization onset were not associated with different stress ulcer prophylaxis ($p=0.6$ and $p=0.07$, respectively) (Fig. 3).

Development of hospital-acquired pneumonia

Fifty-eight (71.6%) patients developed HAP, which mostly occurred on days 6 and 7 (≈ 6.4). Seventeen (29.8%) patients developed pneumonia on days 4

and 5, slightly less between days 6 and 7 (15 patients, 26.3%). In ten (17.6%) patients, HAP emerged on days 8-9. Seven (12.3%) patients developed HAP between day 10 and day 14. Seventeen (29.3%) of 58 HAP patients and four (18.2%) of 22 non-HAP patients died. The occurrence of HAP was not associated with different stress ulcer prophylaxis either ($p=0.8$) (Fig. 4).

Causative pathogens of HAP are presented in Table 3. Previous association of pneumonia with colonization of digestive system, pharynx or trachea was demonstrated in 36 (62.1%) of 58 patients. Mean-

Table 3. Isolated pathogens causing hospital-acquired pneumonia and correlation to previous colonization of trachea, pharynx or stomach

Microorganism	HAP n (mean time in days)/(range)	Previous colonization (%)	LAT mean time in days/(range)
<i>Pseudomonas aeruginosa</i>	13 (7.0)/(3-12)	6 (46)	1.8 (1-3)
<i>Klebsiella pneumoniae</i>	8 (6.4)/(4-10)	6 (75)	4.8 (4-5)
<i>Klebsiella</i> spp.	4 (7.3)/(6-9)	4 (100)	2.8 (1-4)
<i>Enterobacter</i> spp.	5 (6.8)/(4-12)	5 (100)	3.6 (2-8)
<i>Acinetobacter calcoaceticus</i>	4 (10.8)/(8-16)	4 (100)	4.8 (4-5)
<i>Haemophilus influenzae</i>	4 (3.8)/(3-5)	1 (25)	1.0 (1)
<i>Escherichia coli</i>	2 (8.0)/(8)	1 (50)	5.0 (5)
<i>Proteus mirabilis</i>	1 (3)/(3)	0	0
Gram-negative	41 (7.5)/(3-16)	27 (65.9)	2.9 (1-6)
<i>Staphylococcus aureus</i>	10 (5.5)/(3-11)	7 (70)	2.9 (1-5)
MRSA	2 (5.5)/(4-7)	1 (50)	2.0 (2)
<i>Streptococcus pneumoniae</i>	2 (3.0)/(3)	1 (50)	2.0 (2)
Gram-positive	14 (5.9)/(3-11)	9 (64.3)	2.7 (1-5)
Total	55 (7.1)/(3-16)	36 (65.5)	2.8 (1-6)

HAP = hospital-acquired pneumonia; LAT = latency time between colonization and development of pneumonia; MRSA = methicillin resistant *Staphylococcus aureus*

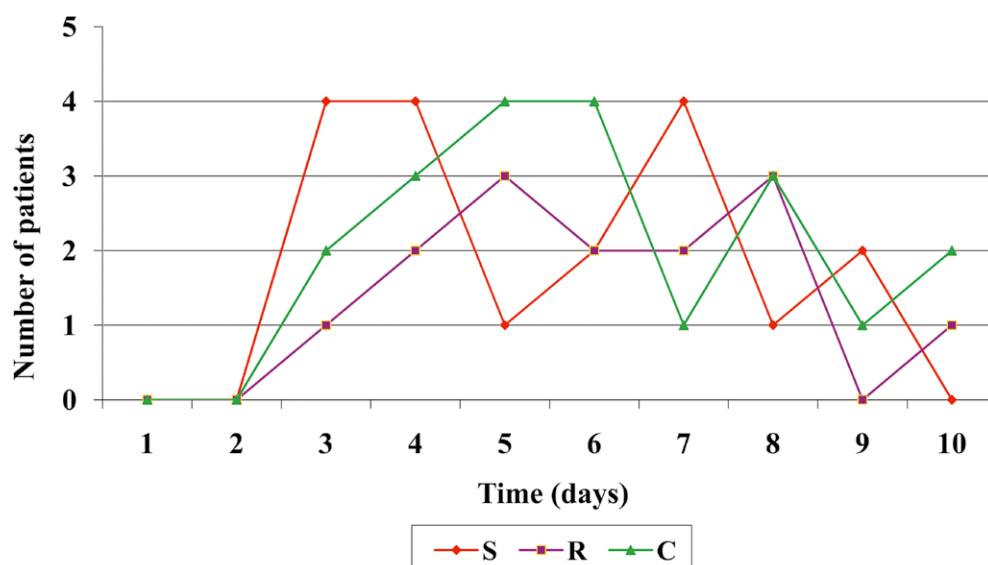


Fig. 4. Pattern of hospital-acquired pneumonia in patients receiving sucralfate (S), ranitidine (R) and control group (C).

while, 22 HAP patients had no connection with previous colonization. Previous TC was recorded in 34 (58.6%) patients; in 15 (41.7%) of them, a direct link between previous TC and HAP was established. Furthermore, an infectious route of the same bacteria from CP to TC and finally to HAP was found in eight

(22.2%) patients. Moreover, in six (16.7%) patients, we proved endogenous route of lower respiratory infection with isolation of bacteria from the stomach first, and then from the pharynx to trachea and to pneumonia. A more accurate route is illustrated in Table 4. The connection between CS and TC was important; 30 out

Table 4. Route of colonization and occurrence of hospital-acquired pneumonia

Colonization	HAP	Causative pathogen	Route	LAT (days)
Stomach	6	<i>Klebsiella pneumoniae</i> (2) <i>Klebsiella</i> spp. <i>Escherichia coli</i> <i>Enterobacter</i> spp. <i>Staphylococcus aureus</i>	CS > CP > TC > HAP	3.0 (1-5)
Stomach	5	<i>Klebsiella pneumoniae</i> (3) <i>Pseudomonas aeruginosa</i> <i>Enterobacter</i> spp.	CS > TC > HAP	2.8 (1-5)
Stomach	2	<i>Klebsiella</i> spp. (2)	CS > HAP	1.5 (1-2)
Pharynx	8	<i>Acinetobacter calcoaceticus</i> (2) <i>Staphylococcus aureus</i> (2) <i>Pseudomonas aeruginosa</i> (2) <i>Enterobacter</i> spp. MRSA	CP > TC > HAP	3.8 (2-6)
Trachea	15	<i>Staphylococcus aureus</i> (4) <i>Pseudomonas aeruginosa</i> (3) <i>Acinetobacter calcoaceticus</i> (2) <i>Enterobacter</i> spp. (2) <i>Klebsiella pneumoniae</i> <i>Klebsiella</i> spp. <i>Haemophilus influenzae</i> <i>Streptococcus pneumoniae</i>	TC > HAP	2.5 (1-5)
No colonization*	22		HAP	

HAP = hospital-acquired pneumonia; CS = colonization of stomach; CP = colonization of pharynx; TC = colonization of trachea; LAT = latency time: *in 22 patients, no colonizing microorganism could be found at any site owing to effective multiple antibiotic therapy administered to patients after symptom onset

of 53 patients with TC had previous CP (95% CI: 1.27-12.4; p=0.01). The median LAT between the occurrence of colonization and pneumonia was 2.9 (1-6) days.

Acinetobacter and *Pseudomonas* were associated with TC, compared to other causative pathogens (p=0.003). In contrast to the aforementioned tests, *Acinetobacter baumannii* had the longest LAT (4.6 days) compared to other pathogens (LAT=2.7 days; p=0.010). The longest time for HAP was also observed with that bacterium (10.8 days; p=0.010). In our experiment, *Acinetobacter baumannii* was closely associated with the development of HAP. The duration of LAT between gram-negative and gram-positive pathogens was not statistically different. The cases of pneumonia were mainly caused by *Pseudomonas aeruginosa* (23.6%) and *Klebsiella pneumoniae* (21.8%).

Besides stress ulcer prophylaxis, other risk factors that could affect TC were analyzed (Table 5). Tested variables showed that tracheotomy compared to intubation represented an independent risk factor that stimulated TC (HR=14.9; p=0.017). Meanwhile, 34 of 52 MV patients and 19 of 29 patients without MV had confirmed TC (p=0.8). Statistically significant differences were recorded in the occurrence of HAP between the two groups. HAP developed in 42 of 52 MV patients and 16 of 29 non-MV patients (80.7% and 55.2%, respectively; p=0.03; 95% CI: 1.11<HR<10.69). When comparing the two groups according to LAT, there was no significant difference. LAT was 2.9 days in the former group and 2.8 days in the latter group (p=0.7). Furthermore, the type of prophylaxis against stress ulcer was not found to be an important risk factor (p=0.07) between the patients on

Table 5. Predictive values of risk factors with calculated hazard ratios (HR) for colonization of trachea (TC)

	B	HR to predict TC	p-value
Gender (male)	1.3905	4.0170	0.1909
Age	0.0431	1.0441	0.2013
Comorbidity	-0.5657	0.5680	0.9416
Admission diagnosis:			0.4293
encephalitis	10.7813	481110.9820	0.9138
tetanus	13.9228	1113293.4000	0.8889
other	18.6115	121029757.0000	0.8777
Time in ICU	-0.0140	0.9861	0.4794
APACHE II	0.1769	1.1935	0.4491
Intubation /tracheotomy	2.7046	14.9483	0.0178
Prophylaxis against stress ulcers			0.0717
S	0.3512	1.428	0.7134
R	2.2426	9.4162	0.0264
Consciousness	0.9466	2.5770	0.5357
Sedation	-1.1374	0.3207	0.5389
pH value	0.2336	1.2632	0.7114
MV (days)	0.2207	1.2469	0.2496
Previous antibiotics	0.6683	1.9510	0.3918

B = correlation coefficient; ICU = intensive care unit; MV = mechanical ventilation; S = sucralfate; R = ranitidine; APACHE = Acute Physiology and Chronic Health Evaluation

ranitidine and sucralfate, but prophylaxis with ranitidine significantly contributed to TC (HR=9.42, p=0.026).

Assessing the effect of risk factors on LAT, sedation of patients emerged as a stand-alone independent risk factor for shorter LAT (HR=0.11; p=0.053). Patients that were sedated had shorter LAT (Table 6). Moreover, gastric juice pH was associated with longer LAT (HR=2.63; p=0.011). Previous antibiotic therapy was associated with shorter LAT. The use of first generation cephalosporins prior to inclusion in the study was associated with sustained LAT (p=0.022). Other antibiotics did not significantly influence LAT.

Association of risk factors

All patients with APACHE II ≤18 and no underlying disease survived; on the other hand, 16 of 37 pa-

Table 6. Predictive values of risk factors with calculated hazard ratios (HR) for longer latency time (LAT)

	B	HR to predict LAT	p-value
Gender (male)	-0.3774	0.6856	0.4888
Age	0.0172	1.0173	0.4834
Time in ICU	0.0053	1.0053	0.7228
APACHE II	-0.2074	0.8127	0.1884
Intubation/tracheotomy	0.4217	1.5245	0.4217
Prophylaxis against stress ulcer			0.8792
S	-0.1108	0.8951	0.8220
R	-0.3446	0.7085	0.6123
Consciousness	-0.3890	0.6777	0.5891
Sedation	-2.1751	0.1136	0.0533
pH value	0.9685	2.6341	0.0111
MV (days)	0.7368	2.0893	0.3144
Previous antibiotics	-3.2369	0.0393	0.0222

B = correlation coefficient; ICU = intensive care unit; MV = mechanical ventilation; S = sucralfate; R = ranitidine; APACHE = Acute Physiology and Chronic Health Evaluation

tients with APACHE II >18 and with underlying diseases died (95% CI: 1.24<HR<1.73; p=0.009). When combining risk factors, we observed that a combination of APACHE II >18, age >65 and MV, or APACHE II >18, MV and sedation could both statistically significantly predict HAP (p=0.010 and p=0.009, respectively). Death could only be predicted with a combination of APACHE II >18 and MV (p=0.020). APACHE II >18 had no influence on TC, although such patients had longer time to TC (3.25 vs. 4.8 days, p=0.5). APACHE II showed correlation with HAP development. Five (45.5%) of 11 patients with lower score and 53 (75.7%) of 70 patients with higher score developed HAP (p=0.040). Furthermore, LAT was 1 day in the former group and 3 days in the latter group (p=0.009). Combined APACHE II >18 and increased number of days on MV caused HAP (25 of 30 patients, p=0.011), and more patients died (12 out of 30, p=0.02) compared to patients with APACHE II >18 and without MV. If we add sedation as the third risk factor to our combination, the risk of HAP increased from 25 to 31 of 41 patients (p=0.009) (Fig. 5). Furthermore, gram-negative bacteria caused colonization more often in tracheotomized patients than in

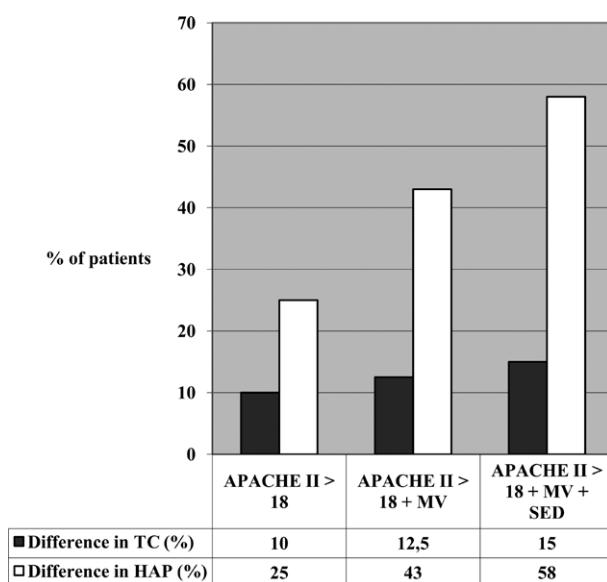


Fig. 5. Effect of combined risk factors on colonization of trachea (TC) and hospital-acquired pneumonia (HAP).

APACHE = Acute Physiology and Chronic Health Evaluation; MV = mechanical ventilation; SED = sedation

intubated patients (95% CI: 0.02<HR<0.85; p=0.029), and in vulnerable and elderly patients (95% CI: 0.00<HR<0.36; p=0.001).

Discussion

No relevant difference was recorded among the three randomization groups. Prophylaxis of stress ulcers did not influence the occurrence of CS or TC, but it was shown that higher gastric juice pH could lead to bacterial spread. However, Prod'hom *et al.*² and Ed-dleston *et al.*²² found that retrograde bacterial colonization from the stomach to the pharynx and trachea occurred more frequently in patients treated with ranitidine than in those treated with sucralfate. The second result section in our study presents results relative to the route of infection leading to HAP in the entire study population. The stomach, pharynx and tracheal colonization are relevant because it can lead to pneumonia. A relationship between TC and HAP was found, which is clinically useful. Secondly, the CS and CP support the hypothesis that these two anatomical regions act as bacterial reservoirs associated with the occurrence of TC or HAP. We assumed that the risk factors for colonization were similar to the risk factors

that influence the occurrence of HAP, but they were not. Chevret *et al.*²³ in their multicentre study found that significant risk factors for HAP were trauma, value of Simplified Acute Physiology Score (SAPS) >9, APACHE II >16, oxygen therapy with >50% oxygen, impaired respiratory reflexes, supported breathing and coma. In our study, we found factors such as APACHE II >18 and presence of MV. There was no difference in HAP between intubated and tracheotomized patients, but an important risk factor was tracheotomy that lasted for >3 days. Meanwhile, intubation time was not a risk factor for TC. This ratio indicated that tracheotomized patients suffered from HAP later than intubated patients. Similar was shown for MV that lasted for >3 days. In the past, MV was also confirmed as an independent risk factor for HAP²⁴. Turković *et al.*²⁵ evaluated the impact of tracheotomy on VAP. Tracheotomy was associated with a reduced duration of MV after VAP onset, but only if patients were tracheotomized at the moment of VAP onset. According to some authors^{26,27}, the risk may be higher in the first 5 days of ventilation, when the incidence of HAP is usually higher. In our study, HAP was more common in the first 7 days after admission to the ICU, which coincided with the results of our previous trial²⁸.

Hospital-acquired pneumonia affected 50% of patients that were tracheotomized for >3 days. With the addition of APACHE II >18 as a risk factor (two risk factors), there were no significant changes in the number of HAP patients. However, when we took into account the third risk factor (MV), the number of patients increased from 50% to 66.7%. Combined with the fourth risk factor (sedation), the percentage of patients that developed HAP increased to 79.6%. Thus, the risk of HAP increased with the increasing number of risk factors, similar to the results published by Chevret *et al.*²³.

A similar study was conducted by Garrouste *et al.*²⁹; they followed risk factors for the development of pneumonia in 86 MV patients. Statistically significant risk factors were parenteral nutrition and progressive underlying disease. Age, duration of hospitalization in the ICU, severity of any disease, immunosuppression or enteral nutrition, previous antibiotic therapy, or drugs against stress ulcer (ranitidine or sucralfate) did not have any effect on the occurrence of HAP. Comparable results were obtained in our study; HAP was not connected with age, time in the ICU, protection

against stress ulcers, disturbance of consciousness, because it was present in most patients. Some authors³⁰ cite an underlying disease as an independent risk factor. We observed a similar pattern (but without statistical significance), i.e. patients that developed HAP frequently had an underlying cardiovascular disease, whereas sex, age, admission diagnosis and relaxation did not affect the incidence of HAP.

Nevertheless, our results differ slightly from the data published by Beck-Sague *et al.*³¹ who found a statistically significant difference in the occurrence of HAP in MV patients receiving H2-receptor antagonists, oral intubated patients and those having previously received cefazolin. In our previous study²⁸, the use of sucralfate or ranitidine had no significant impact on the occurrence of HAP, as we similarly noted in the current research. Considering the fact that elevation of gastric acid pH enables growth of gram-negative bacteria in the stomach, which then can reach the pharynx and lungs by aspiration, the risk of HAP would be greater if we apply a drug against stress ulcers, which raises gastric acid pH^{8,32,33}. However, in our study, despite the difference in the gastric juice pH between sucralfate and ranitidine, the prophylaxis against stress ulcers did not play an important role in the occurrence of HAP. Otherwise the use of drugs against stress ulcers was previously proven as a factor for the occurrence of HAP in patients on MV^{34,35}. Torres *et al.*³⁶ and Bonten *et al.*³⁷ included altered pH of gastric contents and the presence of nasogastric tube as accelerating risk factors for CS. However, these factors did not influence TC. They concluded that gastric juice pH was not significantly different with the administration of sucralfate or ranitidine, and CS was more common at higher pH values. Moreover, our research showed that the use of drugs was an independent risk factor for TC when applying sucralfate or ranitidine ($p=0.03$). The administration of sucralfate or absence of drugs did not affect the occurrence of TC, but taking ranitidine could predict TC, as confirmed by the fact that elevated gastric juice pH shortened LAT between TC and HAP. Although CS was slightly more common in patients with elevated pH (with the administration of ranitidine), the levels of pH in our study did not affect the occurrence of TC.

Furthermore, Bonten *et al.*³⁸ report that long-term MV was an independent risk factor for TC. A correlation was also found with previous CP with the same

microorganism. Microaspiration from colonized pharynx can be the cause of 'early pneumonia' in patients on MV. In our study, no significant difference in the occurrence of TC was determined when intubation or tracheotomy was present. MV was not associated with the occurrence of TC. However, we found a connection with previous use of first-generation cephalosporins. In these patients, the incidence of colonization was lower than in those without having previously taken cephalosporins. In patients with MV, CP represented a risk factor for 'early pneumonia', while previous use of broad-spectrum antibiotics a risk factor for "late pneumonia"^{5,39}. Previous use of antibiotics in some trials increased the likelihood of HAP⁴⁰⁻⁴³. We found that patients having taken first-generation cephalosporins prior to inclusion in the study developed HAP significantly later than those having used no antibiotics.

Feldman *et al.*⁴³ investigated colonization of upper and lower respiratory tract and concluded that colonization occurred very fast with microorganisms that later caused pneumonia. In our study, we recorded similar results. CS occurred between days 2 and 3 (mean 3.2 days), CP between days 2 and 3 (mean 4.2 days), and TC between days 2 and 5 (mean 4.95 days). Regarding LAT, we could conclude that stomach or pharynx were an important source of TC. The CP by *Acinetobacter* and *Pseudomonas* was often associated with TC ($p=0.05$). We also found that TC with *Acinetobacter* and *Pseudomonas* occurred later ($p=0.003$). TC was significantly more common in patients that had oropharyngeal colonization for more than 2 days, meaning that CP was an independent risk factor for late TC ($p=0.04$). The same was confirmed by Ewig *et al.*⁴⁴ and Safdar *et al.*⁴⁵, who concluded that colonization of the upper respiratory system was an independent risk factor for TC, and had greater probability for the occurrence of early HAP.

Oropharyngeal colonization by the gram-negative bacteria *Pseudomonas* and *Acinetobacter* has been proven to be an independent risk factor for TC^{28,46,47}. When comparing correlation of CP with microorganisms, the incidence of TC was significantly higher when the pharynx was colonized by *Enterobacteriaceae*, *Pseudomonas* and *Acinetobacter* ($p=0.022$). Chastre and Fagon⁴⁷ emphasized the great importance of microorganisms that colonized the upper respiratory tract for the emergence of HAP in patients on MV. In the

early period (the first week), the microorganisms involved were *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. Later, these microorganisms were replaced by resistant microorganisms such as *Pseudomonas aeruginosa*, MRSA and *Acinetobacter baumannii*. These microorganisms are probably the main cause of higher mortality. Similar findings were observed by Brusich *et al.*⁴⁸, who found that gram-negative bacteria were the leading causative agents (82.03%) of VAP and were even multidrug-resistant. Thus, we must also consider fungi, especially in immunocompromised patients⁴⁹. Bonten *et al.*³⁸ found shorter LAT in patients that had previous TC than in those that previously had only CP. Accordingly, pneumonia occurred later in infections by *Pseudomonas aeruginosa* than by other gram-negative bacteria. In the present study, we found a significantly longer LAT for *Acinetobacter* infections ($p=0.01$) and slightly longer LAT for *Pseudomonas aeruginosa* ($p=0.08$) compared to other pathogens. The difference could be clinically relevant. However, LAT was shorter when the same bacteria had previously colonized the trachea compared to previous CP. Although the results showed significantly longer LAT in patients with APACHE II >18 , clinically significantly longer LAT in tracheotomized *versus* intubated patients ($p=0.09$), and clinically shorter LAT in patients with higher pH of the stomach contents ($p=0.07$), logistic regression analysis showed that the independent risk factors affecting LAT were only pH of gastric contents ($p=0.01$) and previous antibiotic treatment ($p=0.020$). Higher pH of gastric contents was associated with shorter LAT, and secondly taking first-generation cephalosporins extended LAT. The use of broad-spectrum antibiotics affected the initial CP and thus prevented the development of pneumonia in the first 4 days, thus enabling late (generally after 4 days) colonization and infection by gram-negative pathogens. This could be in line with the fact that these patients usually acquired HAP caused by microorganisms that extend LAT. Moreover, our study found the rate of TC to be statistically lower in patients with gastric pH <4.0 , suggesting that the beneficial effect of sucralfate is essentially obtained in the group of patients able to maintain low gastric pH. Our results also agree with the results of a study² that showed correlation between the microorganisms recovered from the lower respiratory tract and those from the stomach, but not with those found in the pharynx.

In our study, several limitations were observed. Our sample size was too small to make definite conclusions on the predictive values of specific risk factors for TC or HAP. Moreover, the selection of patients included in the study could be more representative, but it is difficult to gather a larger sample of appropriate and comparable patients for three test groups. Patients that are on MV, intubated or tracheotomized have already been staying at the ICU for quite a long time. However, our analysis of LAT between TC and HAP is a valuable add to the existing literature. To our knowledge, this is one of the rare studies to assess correlation between different steps of infection in respiratory system, especially in recent literature. Therefore, our study represents an important update on this subject. We observed several steps of colonization which could be evaluated further in future studies in a larger sample size.

Conclusions

The problem of correlation between TC and HAP in this manner was processed for the first time and presented in this study. Risk factors that influenced HAP did not always influence TC. Risk factors that significantly worsened disease outcome (increased mortality) were identified as APACHE II >18 , presence of heart and circulatory system disease as primary disease, previous use of antibiotics, and presence of MV. In most cases, HAP was preceded by TC. Higher gastric content pH was related to shorter LAT, and antibiotic therapy was an independent risk factor for longer LAT. The results of this trial deepen the knowledge about HAP pathogenesis and suggest some possibilities for early prevention of hospital infections and rational use of antibiotics.

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Sažetak

**PROFILAKSA STRESNOG ULKUSA KAO ČIMBENIK RIZIKA
ZA KOLONIZACIJU TRAHEJE I BOLNIČKI STEČENU PNEUMONIJU
KOD BOLESNIKA U JEDINICI INTENZIVNOG LIJEĆENJA:
UTJECAJ NA VRIJEME LATENCIJE ZA PNEUMONIJU**

I. Muzlović i D. Štubljar

Profilaksa stresnog ulkusa povezana je s bakterijskom kolonizacijom respiratornog trakta. Cilj našega istraživanja bio je utvrditi čimbenike rizika za kolonizaciju traheje (KT), ždrijela (KŽd) ili želuca (KŽe) i bolnički stečenu pneumoniju (BSP) te podijeliti čimbenike na one s visokim rizikom i niskim rizikom. Ispitivana populacija (bolesnici u jedinici intenzivnog liječenja (JIL) s ventilacijom koji imaju pravo na profilaksu stresnog ulkusa) randomizirani su za primjenu jedne od tri različite vrste liječenja: ranitidin, sukralfot i kontrolnu skupinu. Zabilježeni su klinički podaci u odnosu na unaprijed određene čimbenike rizika za kolonizaciju traheje ili BSP te APACHE II (drugi čimbenik rizika), trajanje intubacije ili traheotomija (treći čimbenik rizika), trajanje mehaničke ventilacije (četvrti čimbenik rizika) i trajanje hospitalizacije u JIL-u (peti čimbenik rizika). Zabilježeni su želučani pH i prikupljeni su mikrobiološki podaci o želucu, ždrijelu i dušniku 1., 2., 3. i 5. dana. Od 81 bolesnika BSP se razvila u njih 58 (uključujući upalu pluća povezanu s ventilatorom), i to kasnije u bolesnika s pH želučanog sadržaja <4 ili onih koji su traheotomizirani. Profilaksa stresnog ulkusa nije bila povezana s BSP-om, no dokazana je kao čimbenik rizika za kolonizaciju traheje. Kolonizacija traheje je otkrivena kod bolesnika s traheotomijom, a bila je uzrokovana gram-negativnim patogenima. Kolonizacija ždrijela bila je povezana s kolonizacijom traheje, jer je većina bolesnika imala kolonizaciju ždrijela prije kolonizacije traheje. Kombinacija čimbenika rizika (APACHE II >18, dob >65 godina, mehanička ventilacija i sedacija) uzrokovala je veću učestalost BSP-a i manju učestalost kolonizacije traheje. BSP je bila češća u bolesnika koji su boravili u JIL-u >10 dana i onih s kardiovaskularnim bolestima kao temeljnim poremećajem. Sedacija i prethodna antibiotička terapija bile su u korelaciji s dužim latentnim razdobljem (LAT), dok su veće vrijednosti pH sadržaja želuca bile povezane s kraćim LAT. Najduži LAT pronađen je u bolesnika koloniziranih bakterijom *Acinetobacter* spp. Utvrđeno je da su čimbenici rizika koji su ubrzali pojavu BSP-a uzrokovali prethodnu kolonizaciju. Kombinacija čimbenika rizika povećala je vjerojatnost kolonizacije traheje i BSP-a te skratila LAT između kolonizacije traheje i BSP-a.

Ključne riječi: *Želudac, ulkus; Bakterije – rast i razvoj; Bolnički stečena upala pluća; Jedinice za intenzivnu skrb; Rizični čimbenici; Traheotomija*