Possibilities for modifying risk factors for the development of hospital-acquired pneumonia in intensive care patients: results of a retrospective, observational study

Radovan Uvizl^a, Milan Kolar^b, Tomas Herkel^a, Michaela Vobrova^a, Katerina Langova^c

Background. Hospital-acquired pneumonia (HAP) development is affected by a range of risk factors.

Methods. A retrospective, observational study processing data on all consecutive intensive care patients older than 18 years of age between 1 January 2011 and 31 December 2015. The aim was to determine the incidence of potential risk factors and their impact on the development of HAP.

Results. A total of 2229 patients. The overall mortality was 24.0%; the mean APACHE II score 21.4. The mean length of ICU stay was 5.9 days and the mean length of hospital stay was 20.5 days. The criteria for HAP were met by 310 patients (13.9%). Early- and late-onset HAP was diagnosed in 45 (14.5%) and 265 (85.5%) patients, respectively. The mean APACHE II score was 22.1, the mean length of ICU stay was 7.6 days and the mean length of hospital stay was 23.5 days. The most important non-modifiable factors increasing the risk of HAP were multiple organ failure (OR 13.733; $P<0.0001$), cardiac heart disease (OR 2.255; $P<0.0001$) and chronic renal failure (OR 2.194; $P<0.002$). The most common modifiable factors were intolerance to enteral nutrition (OR 3.055; $P<0.0001$), urgent tracheal intubation (OR 1.511; $P<0.024$), reintubation (OR 1.851; $P<0.001$), and bronchoscopy (OR 2.558; $P<0.0001$). Stress ulcer prophylaxis was administered to 83% of HAP patients and 68% of patients without HAP. Prophylaxis with famotidine was associated with a lower risk of HAP in 40.0% of patients (non-HAP in 49.9%), (OR 0.669; $P=0.001$) than prophylaxis with pantoprazol in 42.6% and 49.5% of patients, respectively (OR 0.756; $P=0.027$).

Conclusions. Factors associated with the highest risk of the development of HAP can be determined. Pharmacological prophylaxis of gastric and duodenal stress ulcers was identified as an independent risk factor for HAP. The study was registered in the ClinicalTrials.gov database under the number NCT02779933.

Key words: hospital-acquired pneumonia, mortality, intensive care, risk factor

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^aDepartment of Anesthesiology and Intensive Care Medicine, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Czech Republic

^bDepartment of Microbiology, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Czech Republic

^cDepartment of Medical Biophysics, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic
Corresponding author: Tomas Herkel, e-mail: juhdy@post.cz

INTRODUCTION

Early and correct identification of risk factors in the nursing process with respect to the development of nosocomial bacterial infections is a prerequisite for selecting rational and safe treatments in intensive care unit (ICU) patients. Moreover, effective preventive measures, together with adequate and early empirical antibiotic therapy, contribute to successful therapy, make it shorter and less expensive^{1,2}, and also lead to reduced mortality rates³. One of the most common infections associated with healthcare in ICU patients is hospital-acquired pneumonia (HAP). According to the American Thoracic Society and the Infectious Diseases Society of America, HAP includes ventilator-associated pneumonia (VAP) (ref.⁴). In ICU patients, HAP accounts for 10-47% of nosocomial infections⁵, with mortality rates ranging from 20% to 60% (ref.^{6,7}). Most frequently, HAP is associated with invasive airway management and mechanical ventilation, with

the latter being referred to as VAP (ref.⁸); this develops more than 48 h from endotracheal intubation. From an epidemiological perspective, two types of HAP are distinguished: early- and late-onset. The clinical and laboratory manifestations of early-onset HAP occur within 48 to 96 h from hospital admission; late-onset HAP develops from day 5 of a hospital stay but no later than 14 days after discharge⁹. The primary ways of transmission of etiological agents into the lower airways are most frequently microaspiration of microbes colonizing the oropharyngeal region or upper gastrointestinal tract⁷ or transmission of infection from the environment. The risk factors for the development of HAP may be either non-modifiable (patient-related) or modifiable (hospital-related).

The present study focused on assessing risk factors that may contribute to the development of HAP, determining their prevalence and proposing their modification in an effort to reduce the risk of developing HAP in intensive care patients.

METHODS

Setting and Study design

A retrospective, observational study was proposed, to obtain clinical and epidemiological data on ICU patients. The sample was divided into patients who developed HAP and a subgroup of those who did not. In both subgroups, the frequency of potential risk factors for therapy and nursing care was investigated. The study was approved by the University Hospital Olomouc Ethics Committee (No. 63/16). Informed consent from patients enrolled in the study was not required. The study was registered in the ClinicalTrials.gov database under the number NCT02779933. The enrolment was influenced by neither the type of lower airway management (invasive/non-invasive) nor the result (positive/negative) of microbiological testing of samples collected from the lower airways (endobronchial aspirate or bronchoalveolar lavage) as it has been demonstrated that approximately one-third of collected samples may be microbiologically negative even if pneumonia is clinically manifested¹⁰.

Participants

Enrolled in the study were patients staying at the ICU of the Department of Anesthesiology and Intensive Care Medicine, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, between 1 January 2011 and 31 December 2015. The participants were all patients older than 18 years of age consecutively admitted to the ICU.

Definitions

Pneumonia is acute inflammation of the respiratory bronchioles, alveolar structures and pulmonary interstitium. Clinically it is defined as the presence of newly developed or progressive infiltrates on chest radiographs plus at least two other signs of respiratory tract infection: temperature $>38^{\circ}\text{C}$, chest pain, purulent sputum, leukocytosis or leukopenia, signs of inflammation on auscultation, cough and/or respiratory insufficiency¹¹. HAP is defined as pneumonia that occurs 48 h or more after admission, which was not incubating at the time of admission⁴.

Outcome Assessment

The primary outcome was investigation of the relationship between individual risk factors and the development of early- and late-onset HAP. The risk factors were assessed based on their presence in the time interval between hospital admission and the moment of fulfilling the criteria for pneumonia. The risk factors were classified into two subgroups: patient-related (non-modifiable) or hospital-related (modifiable). The patient-related factors were gender (male/female), age at enrolment (years), multiple organ failure (MOF), hypertension (HN), coronary heart disease (CHD), chronic renal failure (CRF), continuous renal replacement therapy (CRRT), acute kidney injury (AKI), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), immunosuppression (immune) or leukopenia ($\text{WBC} < 1.5 \times 10^9/\text{L}$), impaired consciousness ($\text{GCS} < 8$) and craniocerebral trauma (CCT).

The hospital-related factors were thoracotomy (thor), aspiration into the lower airways (aspir), urgent tracheal intubation (urg TI), reintubation (re TI), bronchoscopy (BSC), gastric tube (GT), intolerance of enteral nutrition (intol EN), transport outside the ICU (trans) and physiotherapy (phys).

Statistical Methods

No replacement of missing values or outliers was performed in order to minimize bias due to changed content of retrospective clinical records. Standard descriptive statistics were applied to summarize the primary data; continuous variables as means and 95% confidence intervals or median and range; categorical variables by absolute and relative frequencies. Multivariate logistic regression was adopted for adjusting univariate results for age and for defining the final multivariate model. The selection of variables for the multivariate model was based on univariate $P < 0.1$ and redundancy analysis of these preselected predictors. $P \leq 0.05$ was adopted as the level of statistical significance for all analyses. In the tables, the odds ratio (OR) with 95% confidence interval was calculated. The statistical significance (P -value) was assessed with Fisher's exact test. Factors with OR and P -value in bold type are statistically significant (the confidence interval does not include 1). The association of risk factors with HAP was also verified with multivariate logistic regression. As independent predictors, the model included variables with decreased P -value ($P < 0.2$) and risk factors present in both subgroups. The independent predictors were proton pump inhibitor (PPI), H₂ antagonist (H₂ antagon), MOF, HN, CHD, CRF, CRRT, AKI, DM, immuno, COPD, $\text{GCS} < 8$, tracheostomy (TS), CCT, thor, aspir, urg TI, re TI, BSC, GT, intol EN, trans and phys. The dependent variable was HAP (early-/late-onset). The model was constructed using the forward stepwise method involving 4 steps. SPSS 21 (IBM Corporation, 2012) was the software used.

RESULTS

Patients and descriptive data

During the above period, a total of 2229 patients, of whom 761 (34.1%) were females and 1468 (65.9%) were males, were admitted to an ICU for a total of 13,139 days. Their mean age was 58.7 ± 17.2 years (median, 63 years), specifically 62.9 ± 18.1 years (median, 67 years) for females and 57.5 ± 17.4 years (median, 62 years) for males. Their mean APACHE II score was 21.4. The mean length of ICU stay was 5.9 days and the mean length of hospital stay was 20.5 days. Based on their admission diagnosis, the participants were classified as non-surgical (1195 patients; 53.6%) or surgical (1034 patients; 46.4%). The overall mortality was 24.0% (535 patients irrespective of their diagnosis), of whom 170 were females and 365 were males.

The criteria for HAP were met by 310 patients (13.9%), 108 females and 202 males. Their mean age was 60.7 ± 17.2 years (median, 64 years), specifically 64.9 ± 17.8 years (median, 68 years) for females and 59.5

Table 1. Incidence of modifiable/non-modifiable factors for therapy and nursing care with respect to early- and late-onset HAP.

	HAP				OR	95% CI for OR		P
	early-onset (n = 45)		late-onset (n = 265)					
	n	%	n	%				
PPI	7	15.6%	125	47.2%	0.206	0.089	0.479	<0.0001
H2 antag	26	57.8%	98	37.0%	2.332	1.227	4.431	0.013
MOF	31	68.9%	179	67.5%	1.064	0.538	2.103	1.000
HN	27	60.0%	178	67.2%	0.733	0.383	1.403	0.395
CHD	39	86.7%	135	50.9%	6.259	2.564	15.282	<0.0001
CRF	9	20.0%	33	12.5%	1.758	0.777	3.976	0.236
CRRT	0	0.0%	66	24.9%				<0.0001
AKI	0	0.0%	60	22.6%				<0.0001
DM	7	15.6%	66	24.9%	0.555	0.237	1.303	0.189
Immune	0	0.0%	27	10.2%				0.020
COPD	18	40.0%	36	13.6%	4.241	2.122	8.474	<0.0001
GCS<8	3	6.7%	52	19.6%	0.293	0.087	0.981	0.035
TS	0	0.0%	49	18.5%				0.0003
CCT	0	0.0%	34	12.8%				0.008
Thor	1	2.2%	30	11.3%	0.178	0.024	1.340	0.062
Aspir	0	0.0%	45	17.0%				0.001
urg TI	36	80.0%	189	71.3%	1.608	0.739	3.500	0.280
re TI	13	28.9%	58	21.9%	1.450	0.715	2.941	0.338
BSC	7	15.6%	40	15.1%	1.036	0.433	2.482	1.000
GT	16	35.6%	106	40.0%	0.828	0.429	1.598	0.623
intol EN	0	0.0%	45	17.0%				0.001
Trans	12	26.7%	58	21.9%	1.298	0.630	2.672	0.563
Phys	22	48.9%	44	16.6%	4.804	2.463	9.371	<0.0001

The presence of factors in the last 7 days prior to the onset of HAP: MOF – multiple organ failure, HN – hypertension, CHD – coronary heart disease, CRF – chronic renal failure, CRRT – continuous renal replacement therapy, AKI – acute kidney injury, DM – diabetes mellitus, immuno – immunosuppression, COPD – chronic obstructive pulmonary disease, GCS < 8 – Glasgow Coma Scale < 8, TS – tracheostomy, CCT – craniocerebral trauma, thor – thoracotomy, aspir – aspiration into the lower airways, urg TI – urgent tracheal intubation, re TI – reintubation, BSC – bronchoscopy, GT – gastric tube, intol EN – intolerance of enteral nutrition, trans – transport outside the ICU, phys – physiotherapy

± 16.5 years (median, 63 years) for males. Females were statistically significantly older than males ($P=0.022$). Early- and late-onset HAP was diagnosed in 45 (14.5%) and 265 (85.5%) patients, respectively. The flow chart is shown in Figure 1. No statistically significant relationship was found between the HAP type and patient gender ($P=1.000$). There was a statistically significant

association between the HAP type and patient age, with mean ages of 55.3 and 61.9 years for patients with early- and late-onset HAP, respectively ($P=0.049$). The mean APACHE II score was 22.136 (range, 8-43; median, 21.0), specifically 23.706 (range, 8-43; median, 24.0) for females and 21.704 (range, 8-40; median, 21.0) for males. The difference between gender was not statistically sig-

Fig. 1. Study flow chart.

Table 2. Incidence of modifiable/non-modifiable factors for therapy and nursing care with respect to the presence/absence of HAP.

	HAP				OR	95% CI for OR		P
	yes (n = 310)		no (n = 1919)					
	n	%	n	%				
PPI	132	42.6%	650	33.8%	0.756	0.594	0.964	0.027
H2 antag	124	40.0%	658	34.3%	0.669	0.524	0.854	0.001
MOF	210	67.7%	319	16.6%	10.533	8.067	13.753	<0.0001
HN	205	66.1%	1252	65.2%	1.040	0.807	1.340	0.797
CHD	174	56.1%	718	37.4%	2.140	1.679	2.728	<0.0001
CRF	42	13.5%	206	10.7%	1.303	0.913	1.860	0.145
CRRT	66	21.3%	435	22.7%	0.923	0.689	1.236	0.660
AKI	60	19.4%	368	19.2%	1.012	0.746	1.371	0.938
DM	73	23.5%	387	20.2%	1.219	0.917	1.622	0.174
Immune	27	8.7%	145	7.6%	1.167	0.760	1.794	0.491
COPD	54	17.4%	282	14.7%	1.224	0.890	1.686	0.231
GCS<8	55	17.7%	281	14.6%	1.257	0.915	1.727	0.171
TS	49	15.8%	286	14.9%	1.072	0.771	1.491	0.669
CCT	34	11.0%	179	9.3%	1.197	0.812	1.765	0.350
Thor	31	10.0%	157	8.2%	1.247	0.831	1.870	0.272
Aspir	45	14.5%	95	5.0%	3.260	2.236	4.755	<0.0001
urg TI	225	72.6%	1149	59.9%	1.774	1.360	2.314	<0.0001
re TI	71	22.9%	321	16.7%	1.479	1.106	1.978	0.010
BSC	47	15.2%	119	6.2%	2.703	1.883	3.881	<0.0001
GT	122	39.4%	629	32.8%	1.331	1.040	1.704	0.028
intol EN	45	14.5%	159	8.3%	1.880	1.318	2.681	0.001
Trans	70	22.6%	383	20.0%	1.170	0.876	1.561	0.287
Phys	66	21.3%	467	24.3%	0.841	0.629	1.125	0.252

The presence of factors in the last 7 days prior to the onset of HAP: PPI – administration of the proton pump inhibitor pantoprazole in therapeutic doses, H2 antag – the H2 antagonist famotidine at therapeutic doses, MOF – multiple organ failure, HN – hypertension, CHD – coronary heart disease, CRF – chronic renal failure, CRRT – continuous renal replacement therapy, AKI – acute kidney injury, DM – diabetes mellitus, immuno – immunosuppression, COPD – chronic obstructive pulmonary disease, GCS < 8 – Glasgow Coma Scale < 8, TS – tracheostomy, CCT – craniocerebral trauma, thor – thoracotomy, aspir – aspiration into the lower airways, urg TI – urgent tracheal intubation, re TI – reintubation, BSC – bronchoscopy, GT – gastric tube, intol EN – intolerance of enteral nutrition, trans – transport outside the ICU, phys – physiotherapy

nificant ($P=0.062$). No association was found between the APACHE II score and HAP type. The mean length of HAP patients' stay in the ICU was 7.6 days and their mean hospital stay was 23.5 days.

Main results

The absolute and relative frequencies of modifiable/non-modifiable factors for therapy and nursing care with respect to the risk of developing early- and late-onset HAP are shown in Table 1.

Stress ulcer prophylaxis was administered to 83% of HAP patients and 68% of patients without HAP.

The absolute and relative frequencies of modifiable/non-modifiable factors for therapy and nursing care with respect to the presence/absence of HAP are shown in Table 2.

After the relationships between therapy / nursing care factors and the risk of the development of HAP were assessed by multivariate logistic regression, statistically significant predictors for the development of HAP were identified as shown in Table 3.

Table 3. Statistically significant independent predictors for the development of HAP.

	OR	95% CI for OR		P
PPI	0.010	0.005	0.022	<0.0001
H2 antag	0.012	0.006	0.027	<0.0001
MOF	13.733	9.966	18.923	<0.0001
CHD	2.255	1.645	3.092	<0.0001
CRF	2.194	1.344	3.580	0.002
urg TI	1.511	1.056	2.160	0.024
re TI	1.851	1.273	2.690	0.001
BSC	2.558	1.610	4.065	0.0001
intol EN	3.055	1.962	4.757	<0.0001

The presence of factors in the last 7 days prior to the onset of HAP: MOF – multiple organ failure, CHD – coronary heart disease, CRF – chronic renal failure, urg TI – urgent tracheal intubation, re TI – reintubation, BSC – bronchoscopy, intol EN – intolerance of enteral nutrition

DISCUSSION

Data are presented from a long-term study of a large sample of ICU patients comparing the risk posed by individual factors of therapy and nursing care with respect to the development of early- and late-onset HAP; the impact that the two most common types of stress ulcer prophylaxis have on the incidence of HAP is also documented. The study showed that certain factors, both modifiable and non-modifiable, significantly increase the risk of HAP. The most important non-modifiable factors increasing the risk of developing HAP are MOF, CHD and, at a lower level of statistical significance, the presence of CRF. Patient-related risk factors were investigated, among others, in a large study of 8657 ICU patients which identified atrial fibrillation as a significant risk factor for the development of HAP. However, gender, smoking, CHD, DM, rheumatic heart disease, non-rheumatic valvular disease, myocardiopathy/myocarditis, hyperlipidemia, electrolyte disturbance and congenital heart disease were not significant risk factors for HAP (ref.¹²). Another study of ICU patients with HAP in association with *Staphylococcus aureus* showed that significant risk factors are diseases such as liver cirrhosis or DM. On the other hand, the study failed to show a relationship to COPD, hypertension or CRF (ref.¹³). Consistent with the present study, Vardakas et al. did not identify DM as a risk factor for HAP (ref.¹⁴). Finally, monitoring of residual gastric volume was not a factor significantly reducing the risk of developing HAP (ref.¹⁵).

Among hospital-related, or modifiable, factors included in the present study, intolerance of enteral nutrition was the most significant, with urgent tracheal intubation, reintubation and bronchoscopy showing a lower level of statistical significance. If well-tolerated, enteral nutrition is not a risk factor. This was documented, for example, in a study of polytrauma patients showing that enteral nutrition can decrease the incidence of nosocomial pneumonia¹⁶. By contrast, the presence of an inserted GT is considered as a significant risk factor, as seen from a recent large study of 4427 patients documenting that mechanical ventilation and the use of a GT were the most significant risk factors for the development of HAP (ref.¹⁷). Apart from the insertion of a GT, patient immobility is a stronger risk factor for HAP than dysphagia, as shown by Brogan et al.¹⁸. Also consistent with the present study are the results of a Polish study of 1227 ICU patients showing a statistically significant correlation between the development of HAP and incidence of reintubation, tracheostomy and bronchoscopy¹⁹. Another study showed the effect of a history of pre-hospital aspiration or the presence of blood and emesis in the airways after intubation on the development of HAP (aspiration 16% vs. no aspiration 4%) (ref.²⁰). In the HAP group 10% of patients and in the non-HAP group 8% of patients had undergone thoracic surgery; the difference was not statistically significant and therefore the present study failed to identify thoracic surgery as a risk factor for HAP. Some studies referred to the incidence of pneumonia and

subsequently of thoracic surgery in 3.3-25%. Similarly, a study of 604 patients undergoing resection of bronchogenic carcinoma showed 5% incidence of HAP (ref.²¹). In a group of major heart surgery patients, however, the incidence of HAP was 46% in those requiring more than 48 h of mechanical ventilation. The independent risk factors for HAP were age older than 70 years, perioperative transfusions, days of mechanical ventilation, reintubation, previous cardiac surgery, emergent surgery and intraoperative inotropic support²². In the present study, previous aspiration was only a risk factor at a low level of statistical significance. Craniocerebral trauma or neurosurgical intervention were associated with the development of HAP in 13% of patients in the present study. In neurosurgery patients, univariate analysis demonstrated that a low GCS, long hospital stay, use of wide-spectrum antibiotics, mechanical ventilation, total parenteral nutrition and reoperation were risk factors for nosocomial infections²³. Similarly, in abdominal surgery patients, an ICU stay longer than or equal to 7 days and a postoperative hospital stay of 15 days or more were the predictive factors most strongly associated with lung infection²⁴. The varied results for individual risk factors may also be documented by one study on the incidence of HAP in non-ICU patients. Malnutrition, CRF, anemia, depression of consciousness, previous hospitalization and thoracic surgery were significant risk factors for HAP in these patients²⁵. There were lower mean ages of 55.3 and 61.9 years for patients with early- and late-onset HAP, respectively. We explain that the late-onset HAP affects more weakened patients with polymorbidity, who are more susceptible to infections caused by MDR pathogens. Further, in the presented study bronchoscopy was associated with a higher incidence of HAP, but bronchoscopy cannot be considered as a risk factor for HAP, because risk factors are the reasons which led to its implementation. These were most commonly: massive congestion, aspiration into the lungs, chronic lung disease or esophagotracheal fistula. Also intolerance of enteral nutrition is associated with higher incidence of HAP more due to capillar action from around the gastric tube and more frequent gastric fluid retention in the space above the obturation balloon of the tracheal tube causes silent microaspiration.

An important outcome of the present study is assessment of the impact of the two most common types of stress ulcer prophylaxis on the incidence of HAP. Stress ulcer prophylaxis was administered to 83% of HAP patients and 68% of patients without HAP. Prophylaxis with famotidine used to prevent stress ulcer was associated with a lower risk of HAP in 40% of patients (OR 0.669; $P=0.001$) than pantoprazol prophylaxis in 43% of patients (OR 0.756; $P=0.027$), but the results are not as significant as in another similar study. The rate of HAP was lower for an H2 antag (10%) than for a PPI (30%). Administration of the H2 antag was also associated with fewer hospital days (5.6 vs. 17.6) (ref.²⁶). A statistically significant difference in the incidence of HAP was found in a study comparing the effects of sucralfate (14%) and

a PPI (36%) (ref.²⁷). Similar findings were also reported by authors of a large retrospective study of 21,214 cardiac surgery ICU patients, with the incidence of HAP being higher in patients receiving a PPI as compared to an H2 antag²⁸. However, the administration of stress ulcer prophylaxis itself is linked to a higher risk of HAP, as documented, for example, by a large study of 63,878 patients showing that acid-suppressive medication was associated with a higher incidence of HAP, the association being significant for a PPI and non-significant for H2 antag²⁹.

The present study found differences in the incidence of certain modifiable/non-modifiable factors for early- and late-onset HAP (Table 1). In early-onset HAP, the statistically significantly more frequent factors were CHD, COPD and phys, while in late-onset HAP, AKI, CRRT and TS were statistically significantly more common. However, the presence of physiotherapy in early-onset HAP is not considered a factor increasing its incidence. This is rather associated with physiotherapy provided to at-risk patients who subsequently develop HAP. Similarly, higher TS rates in patients with late-onset HAP is considered a sign of more severe pneumonia requiring longer ventilator use. TS was performed in patients prior to randomization, prior to formation of HAP and the reason for its implementation was different than the current HAP attack. Most often it was long-term impairment of consciousness, respiratory insufficiency after previous severe pneumonia or long term ventilator dependence in chronic pulmonary disease patients. The presence of TS increases the HAP incidence probably due to the bypassed upper airway, as a natural bacterial filter.

CONCLUSION

Epidemiological data on ICU patients obtained over the five-year period show that the highest risk of HAP is associated with the patient-related factors MOF, CHD and CRF and the following hospital-related factors: urgent tracheal intubation, reintubation, bronchoscopy and intolerance of enteral nutrition. Additionally, stress ulcer prophylaxis was found to be an independent risk factor for the development of HAP. Prophylaxis with famotidine was associated with a lower risk than pantoprazol prophylaxis.

ABBREVIATIONS

AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; BSC, bronchoscopy; ICU, intensive care unit; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; DM, diabetes mellitus; EN, enteral nutrition; GCS, Glasgow Coma Scale; GT, gastric tube; HAP, hospital-acquired pneumonia; HN, hypertension; CRF, chronic renal failure; CRRT, continuous renal replacement therapy; ICU, intensive care unit; MOF, multiple organ failure; PPI, proton pump inhibitor; TI, tracheal intubation; TS, tracheostomy; VAP, ventilator-associated pneumonia; WBC, white blood cell count.

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