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Evaluation of a bundle approach for the prophylaxis of ventilator-associated pneumonia: A retrospective single-center Study

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Abstract: Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring after the first 48 hours of intubation and mechanical ventilation and is the most frequent hospital-acquired infection associated with intensive care unit (ICU) admissions. Herein, we defined a novel VAP bundle including 10 preventive items. We analyzed compliance rates and clinical effectiveness associated with this bundle in patients undergoing intubation at our medical center. A total of 684 consecutive patients who underwent mechanical ventilation were admitted to the ICU between June 2018 and December 2020. VAP was diagnosed by at least two physicians based on the relevant United States Centers for Disease Control and Prevention criteria. We retrospectively evaluated associations between compliance and VAP incidence. The overall compliance rate was 77%, and compliance generally remained steady during the observation period. Moreover, although the number of ventilatory days remained unchanged, the incidence of VAP improved statistically significantly over time. Low compliance was identified in four categories: head-of-bed elevation of 30-45º, avoidance of oversedation, daily assessment for extubation, and early ambulation and rehabilitation. The incidence of VAP was lower in those with an overall compliance rate of ≥ 75% than its incidence in the lower compliance group (15.8 *vs.* 24.1%, $p = 0.018$). When comparing low-compliance items between these groups, we found a statistically significant difference only for daily assessment for extubation (8.3 *vs.* 25.9%, $p = 0.011$). In conclusion, the evaluated bundle approach is effective for the prophylaxis of VAP and is thus eligible for inclusion in the Sustainable Development Goals.

***Keywords*:** intensive care unit, intratracheal intubation, mechanical ventilation

Introduction

Ventilator-associated pneumonia (VAP) is a preventable iatrogenic complication that can develop in patients undergoing mechanical ventilation. VAP is the most frequent hospital-acquired infection occurring in the intensive care unit (ICU) and has a high associated mortality rate (*1*). More specifically, the mortality rate for VAP ranges from 24-51% according to previously published findings (*2*).

The prevention of VAP has great value in the management of mechanical ventilation with intratracheal intubation. In addition to the personal, familial, and societal burden of this disease, past reports have demonstrated that VAP increases the length of hospital stay as well as costs associated with treatment and care and the usage of antibiotics in patients with longer hospital stays (*3-6*). It is therefore necessary to avert the risks of respiratory management in this setting and to prevent pathogens from entering the lower respiratory tract from both external and internal sources.

Preventive bundle approaches reduce the incidence of VAP. However, VAP prevention bundles are composed of different items and may vary substantially between institutions. Each item considered for the prevention of VAP (*i.e.*, included in the VAP prevention bundle) in the present study has been extensively studied in prior work (*7-9*). Some items in the VAP prevention bundle, including hand hygiene, oral care, and subglottic suctioning of secretions from the upper cuff, are effective in preventing the invasion of pathogens from outside the tube. Other measures aim to prevent pathogen invasion from inside the tracheal tube, including the use of closed suction circuits and the use of disposable breathing circuits.

For the above mentioned reasons, it is highly important to establish effective preventive strategies for VAP (*10*). However, the generalizability of prior work

and the effectiveness of the specific bundle approach presented herein remains unclear. In the present study, we comprehensively examined the preventive efficacy of a VAP prevention bundle consisting of ten items that had been implemented at our medical center.

Materials and Methods

This study was approved by the ethical review board at the National Center for Global Health and Medicine on September 10, 2021 (approval number: NCGM-S-004300-00). The requirement for written informed consent was waived due to the retrospective design of this study. This work was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013).

Patient selection and diagnosis of VAP

All patients who were admitted to the general ICU at our institution between June 2018 to December 2020, were older than 20 years of age, and received intubated mechanical ventilation for more than 48 hours were eligible for inclusion. We included 1,903 patients who were admitted to our ICU.

We use the following artificial respirators at our department: the Dräger Evita® Infinity V500 (Dräger, Lübeck, Germany) and the Nihon Kohden® HAMILTON-G5 (Nihon Kohden, Tokyo, Japan). In addition, was the Taper Guard® Evac (Medtronic, Dublin, Ireland) the tracheal intubation tube used herein; this tube uses subglottic suctioning.

VAP was evaluated based on the diagnostic criteria for clinically defined pneumonia delineated by the United States (US) Centers for Disease Control and Prevention (*1*). The infection control team, radiology department, and ICU physicians at our medical center screened suspected cases of VAP, and the supervising ICU specialist made a final diagnosis of VAP based on chest imaging test results, clinical signs/symptoms, and laboratory findings. We evaluated the severity of all VAP patients using sequential organ failure assessment (SOFA) scores at ICU admission and on ICU discharge (*11*).

Bundle implemented at our institution

The VAP prevention bundle evaluated in the current study consisted of the following ten items (Supplemental Figure S1); *i*) hand hygiene, *ii*) head-of-bed elevation (30-45º), *iii*) oral care with cetylpyridinium chloride (CPC), *iv*) avoidance of oversedation, *v*) proper breathing circuit management, *vi*) appropriate maintenance of endotracheal tube cuff pressure, *vii*) closed system and subglottic suctioning, *viii*) daily assessment for extubation, *ix*) early ambulation and rehabilitation, and *x*) peptic ulcer and deep vein thrombosis (DVT) prophylaxis. We modified the bundles implemented in studies conducted by the US Institute for Healthcare Improvement (IHI) and the Japanese Society of Intensive Care Medicine (*12,13*) based on the current evidence base and an evolving clinical situation (*14,15*). For example, we added "maintenance of adequate cuff pressure (20-30 cmH_2O)", "use of a tracheal tube with aspiration of subglottic secretions", and "early ambulation and rehabilitation" items to the bundle.

Bundle compliance rates were calculated using the VAP care bundle sheet included in patients' medical records and were entered into database software (FileMaker Pro, version 19, Claris International Inc. Cupertino, CA, USA) for subsequent analyses.

Statistical analyses

Differences in categorical variables were analyzed using Chi-square tests, whereas continuous variables were analyzed using *t*-tests. All cumulative survival curves were estimated using the Kaplan-Meier method. Intergroup differences were evaluated using log-rank tests.

The VAP incidence was calculated by dividing the number of VAP cases by the total number of ventilator-days and multiplying the result by 1,000 (*1*). Hypothesis testing regarding differences in the incidence of VAP was conducted to compare the pre- and post-intervention VAP incidence rates using z-scores. We considered two-sided *p*-values of < 0.05 as the threshold for statistical significance. All statistical analyses were performed using the R statistical software (ver. 3.0.2, The R Project for Statistical Computing, Vienna, Austria. *http://www.r-project.org*).

Results

Among the 1,903 included patients, 684 (36%) received mechanical ventilation. The clinical characteristics of the patients in the intubation and non-intubation groups are shown in Table 1. The intubation group included 406 (59%) men and the median age at the time of admission was 64 years (standard deviation, ± 17 years). The patients in the intubation group had mean SOFA scores of 7.1 ± 3.4 on admission and 4.9 ± 3.8 at discharge, respectively. The median length of patients' ICU stays was 8.2 ± 7.0 days. Forty-eight patients died in the ICU in the intubation group and the overall mortality rate was 7.0%.

The reasons for ICU admission are described in Table 1. In the intubation group, gastrointestinal surgery exhibited the highest frequency (181 patients, 26.5%), followed by cardiovascular surgery (114 patients, 16.7%). In terms of types of admission, emergency surgery exhibited the highest frequency (369 patients, 53.9%), followed by scheduled surgery (184 patients, 26.9%).

Compliance rates for the VAP bundle and the VAP incidence

The compliance rate for each item is shown in Figure 1. In our ICU, we routinely implement several items as part of our standard of care: hand hygiene (*i*), oral care with CPC (*iii*), proper breathing circuit management (*v*), appropriate maintenance of endotracheal tube cuff pressure (*vi*), and peptic ulcer and DVT prophylaxis (*x*). The compliance rate was 100% for each item.

Subglottic suction (*vii*) was not implemented in only a few emergency surgery cases, and hence this preventive measure achieved a compliance rate of 92.6%. Conversely, we could not implement early ambulation and rehabilitation (*ix*) effectively, and the compliance rate for this preventive measure reached only 5.8%. The compliance rates for the remaining three measures (*ii*, *iv*, and *viii*) were each approximately 50%. Reasons for these findings included restrictions on therapeutic management, decreased levels of consciousness, and unstable vital signs. The total compliance rate for the ten measures comprising the VAP prevention bundle was 77.0%.

Ventilator-days and VAP incidence in the intubation group are shown in Figure 2. In Japan, ventilator-days increased considerably in April 2020 due to the coronavirus disease 2019 pandemic. This time period represented the start of the pandemic in Japan and the uptick in this metric might have occurred due to evolving surveillance and treatment methods. However, the number of ventilator-days was almost unchanged in every other month, and the median number of ventilator-days was 6.17 days (Figure 2A).

Although VAP incidence varied each month (ranging from 0.0 to 96.2 per 1,000 ventilator-days), it gradually decreased from 2018 to 2020. The total VAP incidence was 31.5 per 1,000 ventilator-days during the observation period (Figure 2B).

Prophylaxis effects based on compliance rates for the VAP bundle

Table 1. Characteristics of ventilated and non-ventilated patients, June 2018 to December 2020

Variable	Intubated	Non-intubated
Patients receiving MV, *n*	684	1,219
Male sex, *n* (%)	406 (59.3)	779 (63.9)
Age, mean ± SD	63.9 ± 17.2	66.9 ± 14.5
SOFA score on ICU admission, mean ± SD	7.1 ± 3.4	2.3 ± 2.1
SOFA score at ICU discharge, mean ± SD	4.9 ± 3.8	1.6 ± 1.9
ICU length of stay (days), mean ± SD	8.2 ± 7.0	2.7 ± 1.6
ICU mortality (%)	48 (7.0)	7 (0.6)
Underlying disease, *n* (%)		
Gastrointestinal surgery	181 (26.5)	484 (39.7)
Cardiovascular surgery	114 (16.7)	105 (8.6)
Respiratory surgery	5 (0.7)	294 (24.1)
Neurosurgery	240 (35.1)	144 (11.8)
Other surgery	13 (1.9)	24 (2.0)
Emergency and critical care medicine	26 (3.8)	2 (0.2)
Internal medicine	51 (7.5)	24 (2.0)
Cardiovascular medicine	51 (7.5)	142 (11.6)
Pediatrics	3 (0.4)	0 (0)
Type of admission, *n* (%)		
Scheduled surgery	184 (26.9)	934 (76.6)
Emergency surgery	369 (53.9)	117 (9.6)
Coronary intervention	21 (3.1)	104 (8.5)
Medical	110 (16.1)	64 (5.3)
Trauma	41 (6.0)	15 (1.2)

ICU, intensive care unit; MV, mechanical ventilation; SD, standard deviation; SOFA, sequential organ failure assessment.

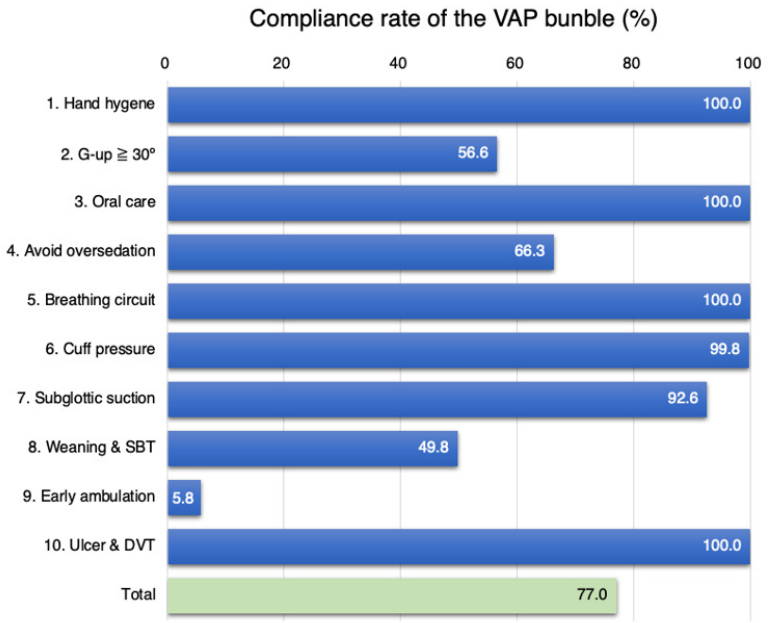

Figure 1. Compliance rate of the VAP bundle. SBT, spontaneous breathing trial; DVT, deep vein thrombosis.

According to the total compliance rate of 77.0% reported above, the 684 patients who required mechanical ventilation were divided into two groups using a cut-off value of 75%. The evaluated clinical outcomes included the incidence of VAP, as shown in Table 2, as well as associated mortality rates.

Regarding total compliance rates, the high compliance group comprised 385 patients (56%) with a compliance rate of ≥ 75%, whereas the low compliance group comprised 299 (44%) with a compliance rate of < 75%; 61 (15.8%) developed VAP in the high compliance group, in contrast with 72 (24.1%) in the low compliance group. We observed statistically significant differences in the proportion of VAP occurrence between the two groups ($p = 0.02$, Figure 3A).

Moreover, 11 patients (2.9%) died in the high compliance group, in contrast with 37 (12.4%) who died in the low compliance group ($p < 0.001$, Figure 3B). Relationships between the incidence of VAP and the bundle items with low compliance rates (*ii*, *iv*, *viii*, and *ix*) are presented in Figure 4.

Only daily assessment for extubation (*viii*) demonstrated statistically significant differences with regard to the proportion of VAP cases; the high compliance group included 252 patients (37%) and the low compliance group included 432 (63%). A total of 21 patients (8.3%) developed VAP in the high compliance group, whereas 112 (25.9%) developed VAP in the low compliance group ($p = 0.011$, Figure 4C, Table 2). No other items exhibited statistically significant differences.

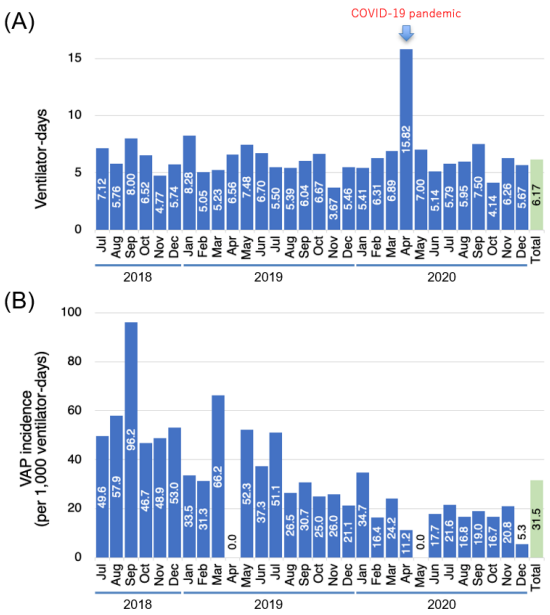

Figure 2. Number of ventilator-days and VAP incidence during the observation period. (A) The number of ventilator-days, **(B)** VAP incidence (per 1,000 ventilator-days). VAP, ventilator-associated pneumonia.

Discussion

In the present study, patients with high compliance rates for the evaluated VAP prevention bundle demonstrated a lower incidence of VAP than the VAP incidence of those with low compliance rates (Figure 3). Daily assessment for extubation (*viii*) affected the incidence of VAP, such that those with high compliance showed a lower incidence of VAP than those in the low compliance group (Figure 4C). However, no other items showed statistically significant differences.

In this study, the intubation group included patients with various risk factors and profiles, such as high SOFA scores, an increased length of hospital stay, and high mortality rates (Table 1). Risk factors increasing the incidence of VAP have been reported in many prior reports, and include long-term intubation, disorders of

Table 2. Clinical outcomes as relevant to the ventilator-associated pneumonia (VAP) prevention bundle evaluated at our medical center

VAP bundle items	Patients (*n*)	VAP (*n*)	ICU-days	Ventilator-days	VAP (%)	VAP incidence (per 1,000 MV days)	*p*-value*
Total compliance							
High (compliance ≥ 75%)	385	61	9.13	6.49	15.8	24.4	0.018
Low (compliance < 75%)	299	72	6.91	5.74	24.1	42.0	
Gatching up the bed to 30-45º							
High (compliance ≥ 75%)	330	60	9.34	6.59	18.2	27.6	0.545
Low (compliance < 75%)	354	73	7.06	5.77	20.6	35.7	
Avoidance of oversedation							
High (compliance ≥ 75%)	378	61	7.89	5.59	16.1	28.9	0.217
Low (compliance < 75%)	306	72	8.49	6.88	23.5	34.2	
Daily assessments for extubation							
High (compliance ≥ 75%)	252	21	6.65	4.10	8.3	20.3	0.011
Low (compliance < 75%)	432	112	9.04	7.37	25.9	35.2	
Early ambulation and rehabilitation							
High (compliance > 0%)	76	27	16.17	13.67	35.5	26.0	0.900
Low (0% compliance)	608	106	7.16	5.23	17.4	33.3	
Total	684	133	8.16	6.17	19.4	31.5	

ICU, intensive care unit; MV, mechanical ventilation. *Generalized Wilcoxon test.

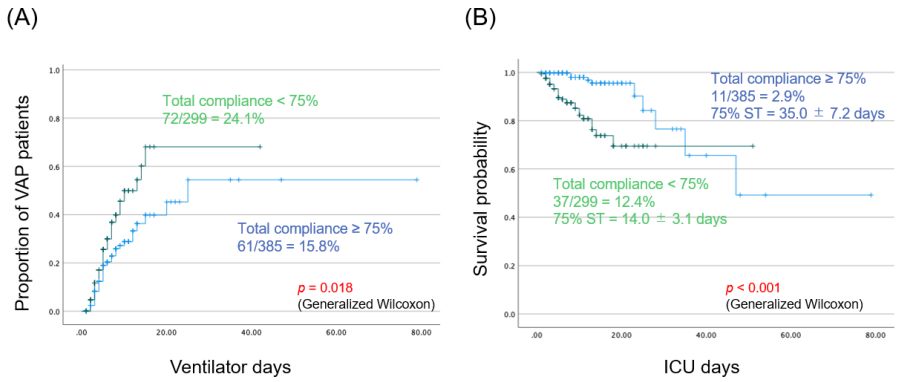

Figure 3. Proportion of VAP occurrence according to the compliance rate. (A) Proportion of VAP patients, **(B)** Survival probability. VAP, ventilator-associated pneumonia.

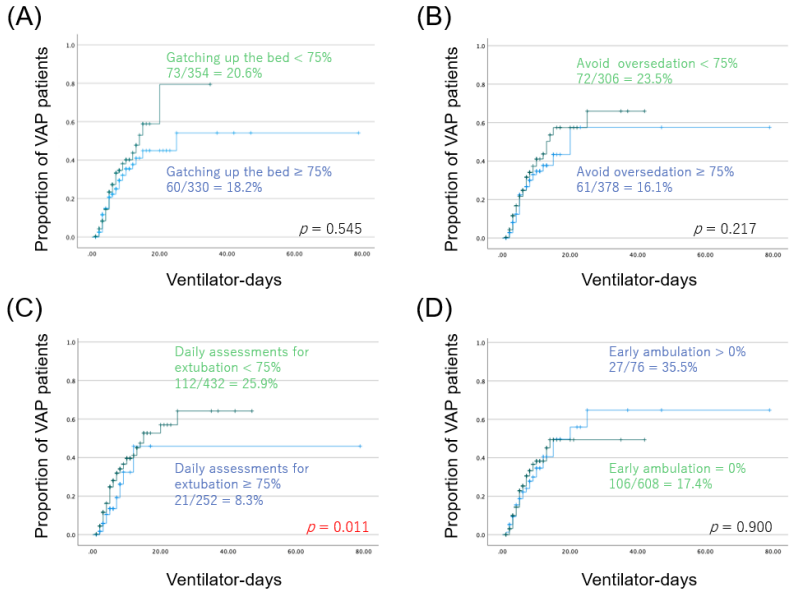

Figure 4. Proportion of VAP occurrence according to the preventive item. (A) Gatching up the bed, **(B)** Avoid oversedation, **(C)** Daily assessments for extubation, **(D)** Early ambulation. VAP, ventilator-associated pneumonia.

consciousness, and various comorbidities (*16-18*). We introduced the bundle approach described herein to at-risk patients with the aim of preventing VAP.

In consideration of such risk factors, the US IHI and the Japanese Society of Intensive Care Medicine have included item x (*i.e.*, the peptic ulcer and DVT prophylaxis item) in their protocols. In Japan, the incidence rates of obesity and pulmonary embolism are lower than the respective incidence of each condition in the US (*12,13*). Hence, DVT prophylaxis has less clinical importance in Japan than it does in the US, and we conclude that preventive measures should be modified based on the clinical situation specific to each institution. The incidence of VAP gradually decreased after the introduction of our modified bundle (Figure 2). We emphasize that our selected measures led to good clinical outcomes overall.

The favorable consequences of including an educational program were proven in a past study, in which the resulting incidence of VAP was reduced by 51% (*2*). In this study, the incidence of VAP has decreased over time due to better management (overall and for each preventive measure included in the bundle) as compared with our management capabilities immediately after the introduction of the preventive bundle. One potential reason for this may be that the level of nursing care has improved over time because nurses' awareness of and training regarding VAP care has increased.

Our department was able to comply with many of the measures implemented in the evaluated preventive bundle, hence yielding a median compliance rate of

77%. This higher compliance rate led to a lower VAP incidence. Moreover, a subgroup analysis of the four measures with the lowest compliance rates showed that only daily assessment for extubation (item *viii*) was statistically significantly different between compliance groups. Prior studies have reported that early extubation is difficult in older patients as well as in patients in poor general condition and/or with consciousness disorders due to brain injury (*19,20*). Invasive surgery for older patients and those with cerebrovascular disease may lead to prolonged intubation, even at our institution. In these cases, tracheostomy and aggressive nutritional management may reduce the occurrence of VAP (*21,22*). We would also like to consider tracheostomy for long-term management in future research.

In the preventive bundle evaluated herein, "early ambulation and rehabilitation" was the only item that showed low compliance rates. The clinical effects of early ambulation and rehabilitation have been proven (*23,24*). We aim to identify the factors contributing to inadequate management as well as to improve management methods in future work. We also note that our medical staff has experienced some difficulty implementing ambulation and rehabilitation programs in normally intubated patients (other than tracheostomy patients) due to bucking and blood pressure fluctuations, which may occur given inadequate sedation. In our ICU, we try to achieve a 90° gatch-up position or a standing position using a Sara® Combilizar device (Arjo, Stockholm, Sweden) under mild sedation. We hope to increase the number of cases undergoing therapeutic ambulation and rehabilitation protocols in the future.

Our study had several limitations. First, this was a retrospective study that only included Japanese patients from a single institution. However, our database is large and has been continuously updated based on uniform follow-up protocols. Second, although a general rule was similarly applied to all patients when diagnosing VAP, the diagnostic criteria for VAP are somewhat controversial. For example, criteria that have been considered for VAP diagnoses (and remain controversial) include evaluation of the patient's respiratory condition (*i.e*., based on the fraction of inspired oxygen and positive-end-expiratory pressure findings) (*1*). Third, according to the diagnostic criteria for VAP described above, we evaluated respiratory function and symptoms in reaching VAP diagnoses; however, the data for bacterial composition in mechanical ventilation patients' sputum tests included many missing values. Fourth, we could not identify survival effects for VAP. No patient died from VAP in this study; the main cause of death in our ICU was primary disease or other severe complications thereof. A multicenter prospective study is required for confirming the efficacy of the VAP bundle approach in intubated patients admitted to the ICU.

In conclusion, an observed decreased incidence of VAP was a critically important outcome of the VAP bundle approach in the intubated patients evaluated herein. We plan to enact these preventive measures at our medical center using this VAP bundle. This approach was effective for the prophylaxis of VAP and is hence eligible for inclusion in our Sustainable Development Goals.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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Supplementary Data

Supplemental Figure S1. Graphic symbol of ten items in VAP bundle. VAP, ventilator-associated pneumonia.