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Compliance to ventilator care bundles and its association with ventilator-associated pneumonia

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Abstract

Purpose Ventilator care bundles are effective in the prevention of ventilator-associated pneumonia (VAP). However, the compliance of these bundles in intensive care units (ICUs) remains poorly studied. This study investigates the Medical Information Mart for Intensive Care (MIMIC)-IV cohort's compliance with the Institute for Healthcare Improvement (IHI) bundle and its resulting association with VAP incidence.

Methods This is a retrospective cohort study of the MIMIC-IV database. Patients with > 48 h of invasive mechanical ventilation (IMV) were included. Diagnosis of VAP was identified with the International Classification of Diseases (ICD)-9 and ICD-10 codes. Compliance rates to the IHI bundle were extracted. The association of the IHI bundle and its individual interventions with VAP incidence was analyzed with univariate and multivariate analysis.

Results 8270 patients were included, of which 1328 (16.1%) had VAP. 25 patients (0.3%) had full compliance to the IHI bundle. 137 patients (1.7%) received no interventions from the bundle. Gastroprophylaxis had the lowest (2.1%) while head elevation had the highest (89.3%) compliance rates. In patients receiving the IHI bundle, each additional intervention was associated with lower VAP incidence (OR [odds ratio] = 0.906, 95% CI [confidence interval] 0.847–0.969). Appropriate sedation levels (OR = 0.765, 95% CI 0.661–0.885) and the use of heat and moisture exchanger (HME) filters (OR = 0.862, 95% CI 0.745–0.998) were individually associated with reduced VAP incidence, while active humidification was individually associated with increased VAP incidence (OR = 1.139, 95% CI 1.001–1.296).

Conclusion The use of the IHI bundle was associated with a lower incidence of VAP, but compliance with the bundle was poor. Appropriate sedation and HME filters were individually associated with reduced VAP incidence. Better compliance with the IHI bundle may reduce VAP rates in mechanically ventilated patients.

Keywords Ventilator-associated pneumonia, Compliance, Intensive care unit, Infection control, Ventilator care bundles

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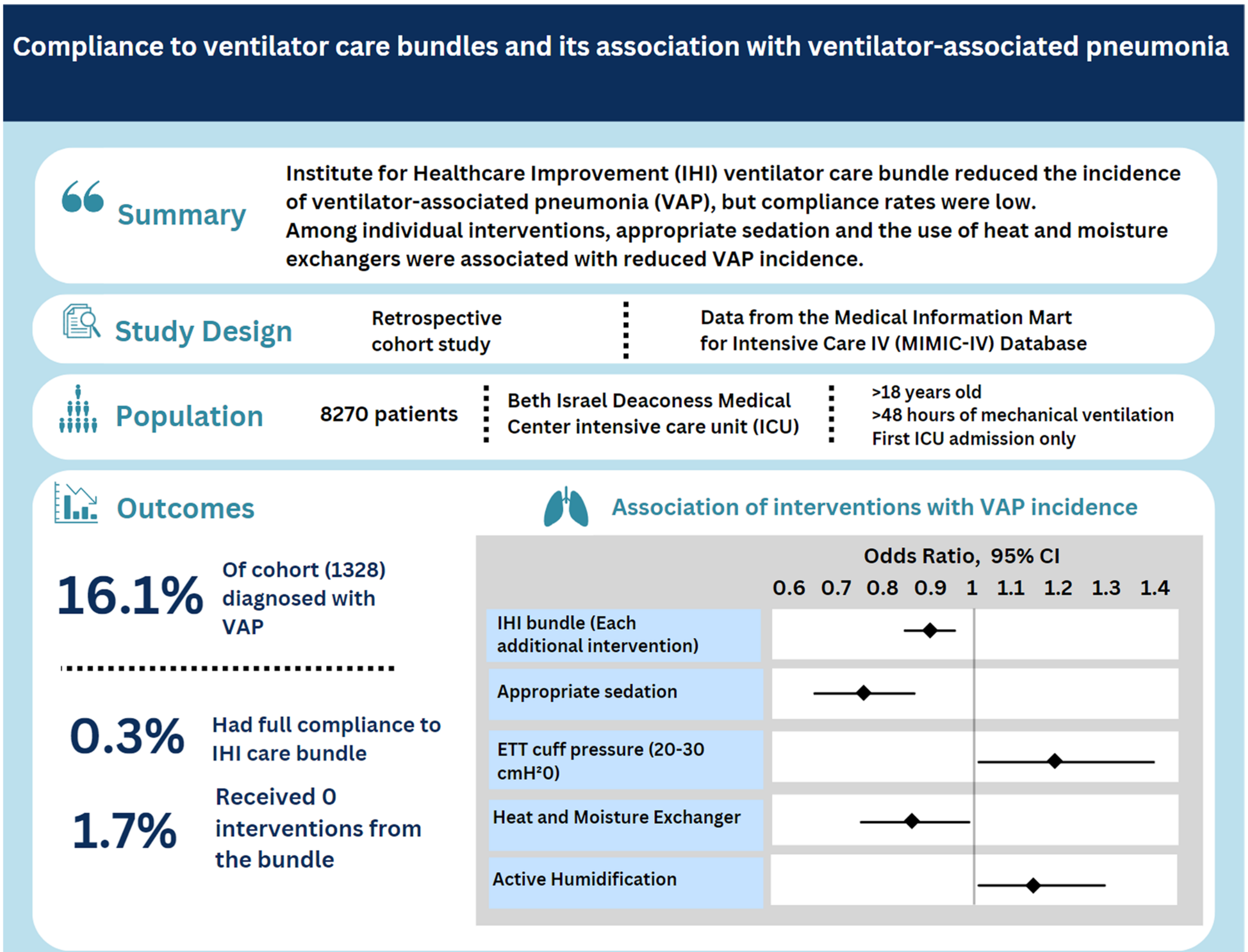
Graphical Abstract



1 Introduction

Ventilator-associated pneumonia (VAP), defined as infection of the lung parenchyma in patients after at least 48 h of exposure to invasive mechanical ventilation (IMV), is a common and serious nosocomial infection in intensive care units (ICUs). VAP has been shown to affect up to 40% of patients on mechanical ventilators [1], making it one of the most prevalent ICU-acquired infections. Many previous studies have linked VAP to poorer outcomes like longer IMV durations and ICU stays, higher antibiotic use [2] as well as increased average hospitalization cost of patients [3]. The mortality rate of ICU patients with VAP is also higher, with studies showing increased 90 and 180-day mortality when compared to patients without VAP [4].

Many interventions and strategies have been proposed for VAP prevention. In particular, the Institute for Healthcare Improvement (IHI) introduced the concept of a ventilator care (VC) bundle comprising five interventions: head of the bed elevation to 30–45 degrees, daily sedation interruption and daily assessment of readiness to extubate, peptic ulcer prophylaxis, deep vein thrombosis (DVT) prophylaxis, and daily oral care with chlorhexidine. While the care bundle approach has been shown to be effective in reducing VAP incidence [5], there have been conflicting results on the impact of each individual intervention in reducing VAP incidence [6–12]. Therefore, all interventions in the bundle need to be implemented collectively and reliably, making on-the-ground compliance to the interventions of vital importance. Previous studies looking at bundle compliance rates have shown a wide range of compliance rates ranging from as low as 16.2% to 90%. These studies were often also small in scale and combined with educational interventions [13, 14].

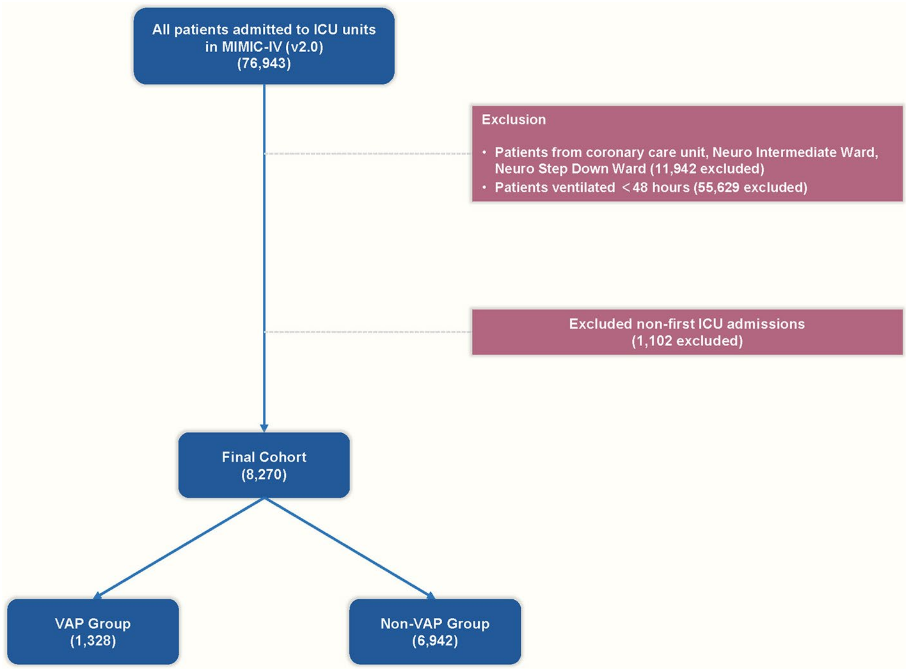


Fig. 1 Study flow diagram

The Medical Information Mart for Intensive Care (MIMIC) database is the largest open-source and free clinical database in the critical care and emergency department based on Beth Israel Deaconess Medical Center's (BIDMC) intensive care inpatient system. Using the MIMIC dataset provides a unique opportunity to perform a large retrospective cohort study on patients with VAP. There are no previous studies analyzing the compliance to the IHI bundle and its association with VAP using this dataset.

The primary objective of this study is to investigate the compliance with the IHI ventilator care bundle within this large, single-center patient cohort. In our secondary analysis, we aim to investigate the association of the IHI bundle as well as its individual components on the incidence of VAP. As part of an exploratory analysis, we also examined the effects of several ventilator-related interventions/factors that are not part of the IHI bundle.

2 Materials and Methods

2.1 Study design and setting

This was a retrospective cohort study based on a large US-based database called the MIMIC-IV. MIMIC-IV is the largest open source and free clinical database in critical care containing comprehensive and high-quality data of patients admitted to ICUs at the BIDMC. We used MIMIC-IV (version 2.0) for the data analysis, which contained data from 2008 to 2019 [15]. We completed the courses required to use the database and obtained the corresponding certificate on 30th November 2022, allowing us to access the database for data extraction. The requirement for individual patient consent was waived as all protected health information was anonymized. We used the STROBE cohort checklist when writing our report [16].

2.2 Selection of participants

Patients in the MIMIC-IV database who were 18 years or older at the time of admission to the ICU and had a longer than 48 h stay in the ICU were eligible for the study. International Classification of Diseases (ICD)-9 codes (4957 and 99,731) and ICD-10 codes (J95851) were used to identify patients with VAP. We excluded patients who received less than 48 h of mechanical ventilation from the time of initiation to the time of discharge from the ICU, as this duration was deemed insufficient for a thorough analysis of the effects of ventilation on patient outcomes. Only the first admission to ICU was analyzed if a patient had multiple admissions to the ICU. No sample size calculation was done as this was a retrospective study with a large cohort size. The patient enrollment flow diagram is illustrated in Fig. 1.

2.3 Variables and data extraction

We extracted data from the MIMIC-IV study database using PostgreSQL (version 13.0, PostgreSQL Global Development Group). Structured Query Language was used to extract the data of the patients, which included demographic characteristics, laboratory measurements, complications, medications, and interventions.

Baseline characteristics of the patients were extracted including demographics, ICU admission details, medical comorbidities, Charlson's comorbidity index (CCI), Sequential Organ Failure Assessment (SOFA) Score, and Glasgow Coma Scale (GCS) score. Patients who were admitted to the Cardiovascular Intensive Care Unit, Neurosurgical Intensive Care Unit, Surgical Intensive Care Unit (SICU), and Trauma SICU were all classified under "SICU". Interventions within the first 48 h from the start of ventilation were extracted. These include nursing interventions, medications, and ventilation details. Where there were multiple readings in the first 48 h, the most common value was taken for interventions and the first value was taken from blood tests such as hemoglobin and total white cell count.

The primary exposure was the patients' exposure to the IHI bundle interventions. These included the five interventions from the IHI bundle: head elevation [9, 17], appropriate sedation [18, 19], chlorhexidine oral care [7], DVT prophylaxis [20], and gastroprophylaxis [21]. Head elevation refers to maintaining the head of the bed at an angle of 30 to 45 degrees. Appropriate sedation is defined as maintaining patients at a Richmond Agitation Sedation Scale (RASS) score of 0 to −1. Chlorhexidine oral care was identified as a significant intervention based on the administration of this particular medication. DVT prophylaxis involves administering medications such as heparin, clexane, or enoxaparin within 48 h of ICU admission. Gastroprophylaxis refers to the administration of proton pump inhibitors or H2 antagonists within 48 h of ICU admission. Patients were then grouped to analyze compliance rates to the IHI bundle. This was represented using a 0–5 scale, where 0 meant that none of the interventions were carried out while 5 indicated that all five interventions from the IHI bundle were carried out.

In addition, other ventilator-related interventions were identified and extracted based on previous literature reviews as part of an exploratory analysis. These included data on endotracheal tube (ETT) cuff pressure [22], ventilation mode, the use of a heat and moisture exchanger (HME), active humidification, frequency of oral care, and frequency of subglottic suctioning. Adequate ETT cuff pressure was defined as maintaining a cuff pressure between 20–30 cmH_2O.

2.4 Statistical Analysis

Descriptive statistics were calculated for the entire dataset and were further stratified based on the presence or absence of VAP diagnosis amongst the patients. Continuous variables were expressed as median and interquartile range (IQR, 25–75th percentile) and their *p*-values evaluated using the Kruskal-Wallis test. Categorical variables were expressed as numbers and proportions and evaluated using the Chi-square test.

Features with > 15% missing values were discarded. These included frequency of incentive spirometry, minimum and maximum ETT size, and feeding status. The rest were imputed using the median for continuous variables and mode for categorical ones.

To investigate the association between the ventilator care bundles and VAP, both univariate and multivariate logistic regression models were performed. The effect size was reported as an odds ratio (OR) and its 95% confidence interval (CI). Potential confounders for VAP were identified based on pre-existing literature and included age, gender, race, CCI, SOFA score, GCS score, admission unit, history of smoking, and pre-existing lung disease [23]. These confounders were then adjusted for in the multivariate logistic regression models. Bonferroni correction was used to adjust for *p*-value in multivariate logistic regression models.

Analysis was conducted in Python 3.9.7 (Anaconda 3 distribution). Exploratory data visualization was done using the Seaborn package (0.11.2) and statistical analysis was done using Statsmodels (0.13.5). All the codes for the analysis are publically available at https://github.com/youliangggg/VAP.git.

3 Results

3.1 Baseline characteristics

A total of 76,943 patients were screened in the database and 8270 patients were included in our study. There were 1328 (16.1%) patients who were diagnosed with VAP (Fig. 1). Amongst all patients, the median age was 64.0 years, 4728 (57.2%) were male, 5010 (60.6%) were white and 7592 (91.8%) were emergency admissions. There were 1113 (13.5%), 1701 (20.6%), and 5456 (65.9%) patients who had a CCI score of mild, moderate, and high respectively, as well as 7908 (95.5%), 287 (3.5%) and 75 (0.9%) patients who had a SOFA score of 0–6, 7–9 and > 9 respectively. The baseline characteristics of the VAP and non-VAP groups are summarized in Table 1.

3.2 Comparison of Characteristics between VAP group and Non-VAP Group

Patients in the VAP group had a lower median age (63 vs 65, $p = 0.011$), a higher percentage of male patients (62.4% vs 56.2%, $p < 0.001$) but a lower percentage of white ethnicity (56.7% vs 61.3%, $p = 0.002$). The VAP group also had a lower percentage of patients admitted to the combined Medical Intensive Care Unit (MICU)/SICU (13.9% vs 17.4%, $p = 0.002$) and MICU units (25.5%

Table 1 Baseline characteristics of study population ($N = 8270$)

Demographics and outcomes	Overall ($N = 8270$)	Non-VAP ($N = 6942$)	VAP ($N = 1328$)	*p*-values
Age	64.0 [53.0,75.0]	65.0 [53.0,75.0]	63.0 [52.0,73.0]	**0.011**
Gender				**< 0.001**
Male	4728 (57.2%)	3899(56.2%)	829 (62.4%)	
Female	3542 (42.8%)	3043 (43.8%)	499 (37.6%)	
Race				**0.002**
White	5010 (60.6%)	4257 (61.3%)	753 (56.7%)	
Others	3260 (39.4%)	2685 (38.7%)	575 (43.3%)	
Admission type				0.421
Elective	678 (8.2%)	577 (8.3%)	101 (7.6%)	
Emergency	7592 (91.8%)	6365 (91.7%)	1227 (92.4%)	
Admission Unit				**0.002**
Combined	1389(16.8%)	1205 (17.4%)	184 (13.9%)	
MICU/SICU	2173(26.3%)	1834 (26.4%)	339 (25.5%)	
MICU/SICU	4708(56.9%)	3903 (56.2%)	805 (60.6%)	
History of alcohol use				0.238
No	8216 (99.3%)	6893 (99.3%)	1323 (99.6%)	
Yes	54 (0.7%)	49 (0.7%)	5 (0.4%)	
History of smoking				0.476
No	5936 (71.8%)	4994 (71.9%)	942 (70.9%)	
Yes	2334 (28.2%)	1948 (28.1%)	386 (29.1%)	
Pre-existing lung disease				0.374
No	8037 (97.2%)	6741 (97.1%)	1296 (97.6%)	
Yes	233 (2.8%)	201 (2.9%)	32 (2.4%)	
History of cancer				0.153
No	6611 (79.9%)	5569 (80.2%)	1042 (78.5%)	
Yes	1659 (20.1%)	1373 (19.8%)	286 (21.5%)	
Gag reflex[a]				**< 0.001**
Impaired	5614 (67.9%)	4651 (67.0%)	963 (72.5%)	
Intact	2656 (32.1%)	2291 (33.0%)	365 (27.5%)	
Cough reflex[a]				> 0.999
Impaired	4693 (56.7%)	3939 (56.7%)	754 (56.8%)	
Strong	3577 (43.3%)	3003 (43.3%)	574 (43.2%)	
Cough type[a]				0.156
Non-productive	3568 (43.1%)	3019 (43.5%)	549 (41.3%)	
Productive	4702 (56.9%)	3923 (56.5%)	779 (58.7%)	
ICU length of stay (hours)	209 [132, 341]	190.0 [123.2, 305]	360 [229.2,548.2]	**< 0.001**
Total duration of mechanical ventilation (hours)	138 [82.0, 260.2]	121.9 [76.0, 221.0]	284.0 [175, 459.5]	**< 0.001**
Average Inspired FiO_2	48.8 [42.5, 56.2]	48.8 [42.7, 56.2]	48.9 [42.0, 55.9]	0.198
Average Tidal Volume(ml)	467.7 [413.2, 524.6]	466.9 [412.1, 523.8]	470.7 [420.2, 529.4]	**0.038**
Mortality				**< 0.001**
1-month	1186 (14.3%)	969 (14.0%)	217 (16.3%)	
3-months	159 (1.9%)	118 (1.7%)	41 (3.1%)	
Charlson Comorbidity Index Score[a]				0.069
Mild (1–2)	1113 (13.5%)	931 (13.4%)	182 (13.7%)	
Moderate (3–4)	1701 (20.6%)	1373 (19.8%)	328 (24.7%)	
Severe (≥ 5)	5456 (65.9%)	4638 (66.8%)	818 (61.6%)	
SOFA score[a]				0.181
0–6	7908 (95.5%)	6626 (95.4%)	1282 (96.5%)	
7–9	287 (3.5%)	252 (3.6%)	35 (2.6%)	

Table 1 (continued)

Demographics and outcomes	Overall (*N* = 8270)	Non-VAP (*N* = 6942)	VAP (*N* = 1328)	*p*-values
> 9	75 (0.9%)	64 (0.9%)	11 (0.8%)	
GCS[a]				0.682
3–7	299 (3.6%)	255 (3.7%)	44 (3.3%)	
8–13	559 (6.8%)	464 (6.7%)	95 (7.2%)	
14–15	7412 (89.6%)	6223 (89.6%)	1189 (89.5%)	
Hemoglobin (g/dL)[a]				
0 h	10.3 [8.9,12.0]	10.3 [8.8,11.9]	10.6 [9.1,12.4]	**< 0.001**
24 h	9.8 [8.6,11.1]	9.8 [8.6,11.1]	9.9 [8.7,11.3]	**0.002**
48 h	9.6 [8.5, 10.9]	9.6 [8.5, 10.8]	9.7 [8.6, 11.1]	**0.001**
Total white blood cell count (g/dL)[a]				
0 h	12.2 [8.4,17.2]	12.2 [8.3,17.4]	12.2 [8.8,16.6]	0.825
24 h	11.7 [8.4,16.1]	11.7 [8.3,16.2]	11.7 [8.8,15.8]	0.649
48 h	11.4 [8.3, 15.8]	11.4 [8.2, 15.8]	11.5 [8.5, 15.6]	0.496

Median (IQR) or N (%)

[a] Where there are multiple readings in the 48 h, the most common value is taken for interventions and the first value is taken from blood tests such as hemoglobin and total white

VAP Ventilator Associated Pneumonia, *MICU* Medical Intensive Care Unit, *SICU* Surgical Intensive Care Unit, *FiO_2* Fraction of Inspired Oxygen, *ICU* Intensive Care Unit, *IQR* Interquartile Range, *SOFA* Sequential Organ Failure Assessment, *GCS* Glasgow Coma Scale

vs 26.4%, $p = 0.002$) but a higher percentage of patients admitted to SICU (60.6% vs 56.2%, $p = 0.002$). VAP patients had higher impaired gag reflex (72.5% vs 67%, $p < 0.001$), increased ICU length of stay (360 vs 190 h, $p < 0.001$), and total duration of mechanical ventilation (284 vs 121.9 h, $p < 0.001$). The 1- and 3-month mortality rates were higher in the VAP group (16.3% vs 14.0%; 3.1% vs 1.7%, $p < 0.001$). Both groups did not show a statistically significant difference in terms of their CCI, SOFA, and GCS scores.

3.3 Overall compliance with the IHI Ventilator Care Bundle

Out of the 8270 patients studied, only 25 patients (0.3%) had full compliance with the IHI ventilator care bundle, with 137 patients (1.7%) not having received a single intervention from the bundle. When the individual components were examined, the lowest compliance rates lie in the gastroprophylaxis component of the bundle, with only 177 (2.1%) of patients having received this intervention, while the highest compliance was found to be in providing head elevation, with 7383 (89.3%) receiving this intervention. The full results are shown in Table 2.

3.4 Association of IHI bundle and individual interventions with VAP incidence

The adjusted analysis of the IHI bundle showed that each additional IHI bundle intervention that patients received was associated with lower VAP incidence (OR = 0.906, 95% CI 0.847–0.969, $p = 0.004$). When individual components of the IHI bundle were analyzed, only appropriate sedation levels were associated with reduced VAP incidence after adjusting for confounders (OR = 0.765, 95% CI 0.661–0.885, $p = < 0.001$).

When interventions outside the IHI bundle were analyzed, an HME filter was also associated with reduced VAP incidence (OR = 0.862, 95% CI 0.745–0.998, $p = 0.047$). Conversely, ETT cuff pressure levels of 20–30 cmH_2O were associated with an increased incidence of VAP (OR = 1.187, 95% CI 1.016–1.388, $p = 0.031$). Active humidification also showed an increase in VAP incidence (OR = 1.139, 95% CI 1.001–1.296, $p = 0.048$). The full results can be seen in Table 3.

A further breakdown of VAP incidence in different groups of ETT cuff pressure is also presented in Fig. 2, with the highest incidence of VAP being in the 26–30 cmH_2O subgroup while the lowest incidence of VAP is in the < 20 cmH_2O subgroup. All other individual interventions studied did not show a statistically significant association with VAP incidence.

We further looked at the feature importance of the five components that made up the IHI ventilator bundle (Fig. 3). Feature importance was calculated by taking each component's coefficient from the logistic regression, multiplied by their respective standard error. Gastroprophylaxis had the greatest weightage in the ventilator bundle scores in affecting VAP diagnosis.

4 Discussion

4.1 Compliance to the IHI Bundle

This study highlights an overall low compliance rate of 0.3% to the full IHI ventilator care bundle. There are a few

Table 2 Comparison of interventions between Non-VAP and VAP groups—Study population (*N* = 8270)

IHI bundle Interventions[a]	Overall (*N* = 8270)	Non-VAP (*N* = 6942)	VAP (*N* = 1328)	*p-values*
Head elevation				0.065
No (all other values)	887 (10.7%)	725 (10.4%)	162 (12.2%)	
Yes (30–45 degrees)	7383 (89.3%)	6217 (89.6%)	1166 (87.8%)	
Appropriate sedation				< 0.001
No (all other values)	6248 (75.6%)	5188 (74.7%)	1060 (79.8%)	
Yes (RASS 0 to −1)	2022 (24.4%)	1754 (25.3%)	268 (20.2%)	
Chlorhexidine oral care				0.507
No	2524 (30.5%)	2108 (30.4%)	416 (31.3%)	
Yes	5746 (69.5%)	4834 (69.6%)	912 (68.7%)	
DVT prophylaxis				0.754
No	4199 (50.8%)	3519 (50.7%)	680 (51.2%)	
Yes	4071 (49.2%)	3423 (49.3%)	648 (48.8%)	
Gastroprophylaxis				0.068
No	8093 (97.9%)	6783 (97.7%)	1310 (98.6%)	
Yes	177 (2.1%)	159 (2.3%)	18 (1.4%)	
IHI bundle				0.015
0	137 (1.7%)	108 (1.6%)	29 (2.2%)	
1	1209 (14.6%)	986 (14.2%)	223 (16.8%)	
2	3297 (39.9%)	2764 (39.8%)	533 (40.1%)	
3	2937 (35.5%)	2487 (35.8%)	450 (33.9%)	
4	665 (8.0%)	573 (8.3%)	92% (6.9%)	
5	25 (0.3%)	24 (0.3%)	1 (0.1%)	
Other Interventions[a]				
ETT cuff pressure				0.024
No (all other values)	1589 (19.2%)	1364 (19.6%)	225 (16.9%)	
Yes (20–30 cmH_2O)	6681 (80.8%)	5578 (80.4%)	1103 (83.1%)	
Main ventilation mode				0.655
APRV	1496 (18.1%)	1239 (17.8%)	257 (19.4%)	
CMV	4458 (53.9%)	3751 (54.0%)	707 (53.2%)	
CPAP	1928 (23.3%)	1628 (23.5%)	300 (22.6%)	
PSV	362 (4.4%)	301 (4.3%)	61 (4.6%)	
HME filter				0.044
No	1642 (19.9%)	1351 (19.5%)	291 (21.9%)	
Yes	6628 (80.1%)	5591 (80.5%)	1037 (78.1%)	
Active humidification				0.025
No	2866 (34.7%)	2442 (35.2%)	424 (31.9%)	
Yes	5404 (65.3%)	4500 (64.8%)	904 (68.1%)	
Frequency of oral care	13.0 [11.0, 15.0]	13.0 [11.0, 15.0]	13.0 [11.0, 16.0]	0.069
Frequency of subglottic suction	8.0 [5.0, 10.0]	8.0 [5.0, 10.0]	8.0 [5.0, 11.0]	0.032

Median (IQR) or N (%)

[a] Where there are multiple readings in the 48 h, the most common value is taken for interventions

RASS Richmond Agitation Sedation Scale, *DVT* Deep Vein Thrombosis, *IHI* Institute for Healthcare Improvement, *ETT* Endotracheal Tube, *APRV* Airway Pressure Release Ventilation, *CMV* Continuous Mandatory Ventilation, *CPAP* Continuous Positive Airway Pressure, *PSV* Pressure Support Ventilation, *HME* Heat and Moisture Exchanger

possible reasons for these results. Firstly, conflicting evidence and uncertainty surrounding certain components of the IHI bundle might have led to an unwillingness to implement some of these interventions. For example, the use of gastroprophylaxis has been shown to potentially increase the incidence of VAP in previous studies [10] [11], but this has not been consistently proven. It is also unclear if there is any association between DVT prophylaxis and decreasing rates of VAP [12]. This uncertainty might explain the low level of compliance to

Table 3 Univariate and multivariate analysis of the effect of the ventilator care bundle and individual interventions on incidence of VAP

Interventions	Univariate			Multivariate[a]		
	Odds Ratio	95% CI	*p-value*	Odds Ratio	95% CI	*p-value*
IHI Bundle (Each additional intervention)	0.891	0.834–0.951	**0.001**	0.906	0.847–0.969	**0.004**
Head elevation	0.839	0.700–1.006	0.059	0.909	0.753—1.097	0.319
Appropriate Sedation	0.748	0.647–0.864	**< 0.001**	0.765	0.661–0.885	**< 0.001**
Chlorhexidine oral care	0.956	0.842–1.085	0.487	0.955	0.840–1.085	0.476
DVT prophylaxis	0.980	0.871–1.102	0.732	0.987	0.876–1.113	0.836
Gastroprophylaxis	0.586	0.359–0.958	**0.033**	0.628	0.384–1.029	0.065
ETT Cuff Pressure	1.199	1.027–1.400	**0.022**	1.187	1.016–1.388	**0.031**
Main Ventilation mode						
APRV	1.105	0.951–1.282	0.192	1.097	0.944–1.276	0.228
CMV	0.969	0.861–1.089	0.594	0.975	0.866–1.097	0.672
CPAP	0.953	0.828–1.096	0.497	0.942	0.818–1.085	0.407
PSV	1.062	0.801–1.408	0.674	1.098	0.827–1.458	0.516
HME filter	0.861	0.746–0.993	**0.040**	0.862	0.745–0.998	**0.047**
Active humidification	1.157	1.021–1.312	**0.023**	1.139	1.001–1.296	**0.048**
Frequency of oral care	1.009	1.000–1.019	0.054	1.008	0.998–1.017	0.117
Frequency of subglottic suctioning	1.010	0.999–1.021	0.077	1.007	0.996–1.018	0.221

[a] Confounders adjusted for includes: Age, gender, race and CCI, SOFA score, GCS score, admission unit, history of smoking, pre-existing lung disease

CCI Charlson's Comorbidity Index, *CI* Confidence Interval

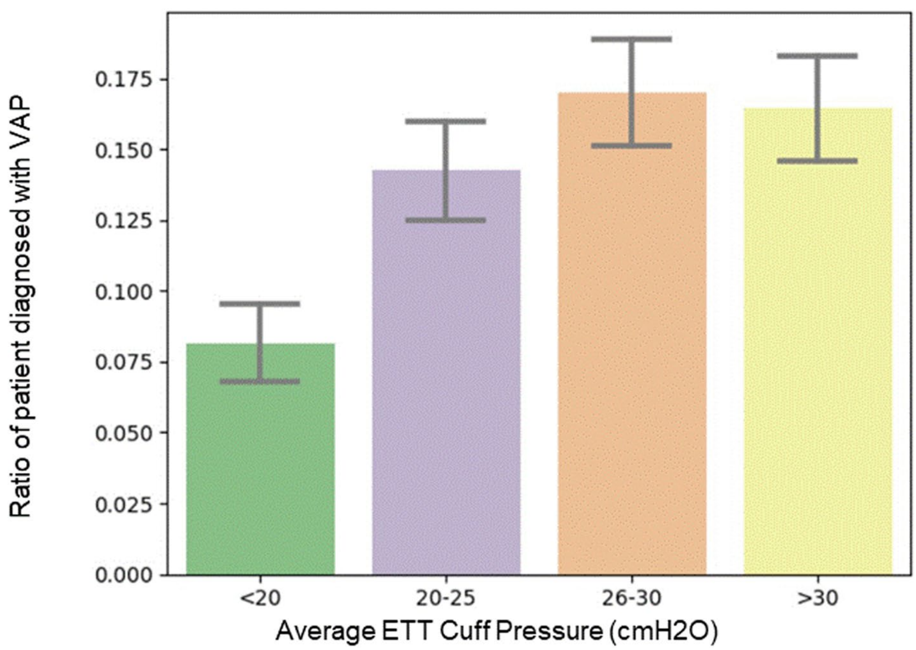


Fig. 2 Barplot with different groups of ETT cuff pressure (cmH_2O) (Most frequent cuff pressure documented in the 48 h) and the ratio of patients diagnosed with ventilator associated pneumonia. Errors bars are presented

gastroprophylaxis (2.1%) and DVT prophylaxis (49.2%) in this study.

Nevertheless, this study provides compelling evidence that the implementation of the IHI bundle does lead to a significant reduction in VAP incidence and should be actively used in the management of patients on mechanical ventilation. It is noteworthy that while many interventions did not show statistically significant results when

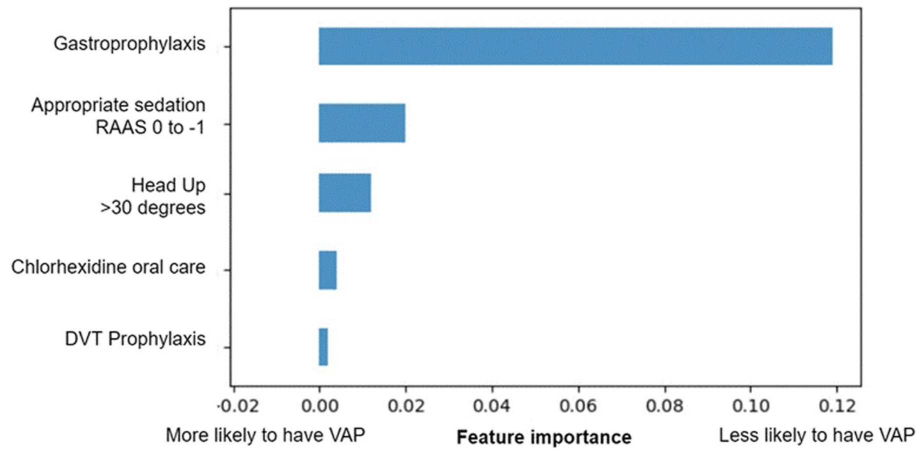


Fig. 3 Features importance of interventions under the ventilator bundle and the diagnosis of VAP

examined in isolation, the collective implementation of the bundle yielded substantial benefits in this study. These results align with existing literature emphasizing the effectiveness of "care bundles", which encompass a concise set of interventions implemented as a standardized protocol. Such an approach has been shown to improve patient outcomes [5, 24–26].

Secondly, it is important to acknowledge that the dissemination of care bundle guidelines might not always translate to changed behaviors in actual clinical practice. Nurses play a critical role in ensuring the successful implementation of ventilator care bundles, but may not consistently and uniformly implement these measures [27].

This is especially worrying as existing literature suggests that nursing compliance with VAP prevention guidelines needs to be at least 95% to effectively reduce VAP incidence [28]. One reason for this could be inadequate education and staff training, which is one of the major barriers to nursing adherence to care bundles [29]. Educational interventions that can potentially improve compliance with care bundles should be actively and regularly conducted in ICU units [14]. Another potential reason for suboptimal compliance could be the increasing complexity of ventilator care bundles. Many interventions, like the maintenance of endotracheal tube cuff pressures between 20–30 cmH_2O [30, 31] and the use of subglottic suctioning have both been proposed to reduce the incidence of VAP [32] and are commonly added to existing ventilator care bundles. The difficulty of adhering to increasingly complex bundles, combined with the high workload of ICU staff members, can overwhelm healthcare professionals and lead to inconsistent implementation of ventilator care bundles [33]. A recent systematic review studying ventilator care bundles in pediatric and neonatal ICUs revealed that there were significant variations in care bundle elements between ICUs and emphasized the need for further research to standardize the components of pediatric ventilator bundles [34]. Similarly, for adults, there is a need for further high-quality studies to determine an optimal, evidence-based combination of interventions that can be easily adhered to in a practical, real-world setting.

4.2 Individual components of the IHI bundle

Despite the association of appropriate sedation (RASS 0 to −1) with lower VAP incidence, the overall compliance rates were low. Avoiding over-sedation often helps to preserve protective airway reflexes and previous studies have shown that the utilization of daily sedation vacations is an effective way of reducing VAP incidence [18, 35]. Conversely, mechanical ventilation can be uncomfortable for patients and under-sedation might lead to hypertension, tachycardia, discomfort, and even self-extubation [36]. This raises the question of the appropriate duration of a "sedation break" that would maximize patient outcomes. Previous studies often considered patients to be "awake" on a given day as long as they were "awake" at any time during the day. This is in contrast to our study, in which only patients who had an RASS score of 0 to −1 for a majority of the first 48 h of mechanical ventilation were considered to have appropriate sedation levels. While both methods of the analysis show a reduction in VAP incidence, further studies can be done to evaluate the optimum duration of “sedation vacations” that would best minimize the negative effects of both under and over-sedation during mechanical ventilation.

4.3 Other VAP prevention interventions

In our study, the use of an HME filter was also found to be associated with a lower VAP incidence while conversely, active humidification was associated with a higher VAP incidence. In mechanically ventilated patients, the natural mechanisms of air humidification are suppressed due to the bypassing of the upper airway. Humidification can mainly be achieved by active methods like heated humidifiers or passively via heat and moisture exchangers. Active heating and humidification can cause condensation of water in the ventilator circuit, which can theoretically serve as a nidus for infection and increase the risk of VAP [37]. On the other hand, HME filters cause less condensation of water and have a microbe filter that could reduce the entry of exogenous bacteria into the patient's respiratory system, potentially reducing VAP risk [38]. Previous studies have not shown any conclusive difference between the rates of VAP among patients undergoing active or passive humidification, with an overall low quality of evidence [39, 40]. In addition, a recent meta-analysis in 2014 showed insufficient evidence to exclude the association of HME filters and VAP due to methodological limitations found in selected trials [41]. Our study provides additional evidence in this area with one of the largest retrospective cohort studies done to date and could help to further conclusions in this field in the future.

Interestingly, the maintenance of ETT cuff pressures at 20–30 cmH_2O was found to increase the incidence of VAP in our study. Subgroup analysis was performed to further understand the differences in the breakdown between the average cuff pressures. The average cuff pressure of < 20 cmH_2O had the least amount of patients diagnosed with VAP. This was in contrast to Rello et al. where a study of 83 consecutive patients who were intubated with continuous subglottic suctioning of secretions had a trend of higher risk of pneumonia when their tracheal cuff pressure was < 20 cmH_2O in the first 8 days [30]. One could propose that underinflation of tracheal cuffs could be a risk factor for the microaspiration of contaminated secretions and may increase the risk of VAP. However, a literature review and survey of intensivists in Queensland has shown that there has been no consensus on the optimal cuff pressure [42]. Some studies have even suggested using only clinical assessments like bedside minimal leak techniques to adjust ETT cuff inflation, while others have shown potential inadequacies with the traditional methods of cuff pressure measurement [43, 44]. These findings may prompt further investigations on the optimal methods of measurement as well as the optimal cuff pressure range in the prevention of VAP.

When the frequency of subglottic suctioning for patients with subglottic suction endotracheal tubes was analyzed, it was not found to have any significant impact on VAP incidence. Previous studies done comparing continuous and intermittent subglottic suctioning have also shown conflicting results on VAP incidence [45, 46]. These inconsistencies emphasize the lack of clarity surrounding the optimal frequency of subglottic suctioning.

4.4 Limitations

Several limitations in the present study should be considered. Our study was a retrospective cohort study from a single center and hence carries the inherent limitations of the study type. The cohort and data also span over a decade, where standards of care and interventions may have shifted. The different types of surgical ICU (e.g., Cardiothoracic, Neurosurgery, Trauma ICU) were combined for ease of analysis and presentation, which may result in losses in the granularity of the data. Furthermore, innate heterogeneity across the different types of surgical ICUs may lead to selection bias. The presence of subglottic suctioning was also not included in the analysis even though it was a common intervention in many ventilator care bundles worldwide due to missing data within MIMIC.

The most frequent value within the first 48 h was extracted from the interventions, such as the "Head Elevation". However, the periods of supine and head down are not captured and may result in micro-aspirations even though they are only performed infrequently. In addition, indirect factors unrelated to interventions may also influence the rate of VAP, such as hospital funding, nursing-to-patient ratio, antibiotics stewardship, and compliance with hand hygiene. Lastly, this study does not analyze the effect of ventilator care bundles on other ventilator-associated events, and thus any conclusions made in this study regarding the effectiveness of the VC bundles are only limited to its impact on VAP.

5 Conclusion

The overall compliance with the IHI bundle was poor, with the gastroprophylaxis component being the lowest. When performed collectively, each additional intervention of the IHI bundle is associated with a lower incidence of VAP. When examined individually, only appropriate sedation and the use of an HME filter were associated with reduced VAP incidence. Better compliance with the IHI bundle may reduce VAP rates in mechanically ventilated patients. Prospective studies should be conducted to determine an optimal combination of interventions in a VC bundle that is both practical and evidence-based.

Abbreviations

APRV	Airway pressure release ventilation
BIDMC	Beth Israel Deaconess Medical Center
CCI	Charlson's comorbidity index
CI	Confidence interval
CMV	Continuous mandatory ventilation
CPAP	Continuous positive airway pressure
DVT	Deep vein thrombosis

ETT	Endotracheal tube
FiO_2	Fraction of inspired oxygen
GCS	Glasgow Coma Scale
HME	Heat and moisture exchanger
ICD	International Classification of Diseases
ICU	Intensive care unit
IHI	Institute for Healthcare Improvement
IMV	Invasive mechanical ventilation
MICU	Medical Intensive Care Unit
PSV	Pressure support ventilation
RASS	Richmond Agitation Sedation Scale
SICU	Surgical Intensive Care Unit
SOFA	Sequential Organ Failure Assessment Score
VAP	Ventilator-associated pneumonia
VC	Ventilator care

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Authors' contributions
Leong Yun Hao and Ke Yuhe: Conceptualization (initiated the study) and Methodology (participated in the study design). Leong Yun Hao: Writing—Original Draft (drafted the manuscript with critical appraisal and further development by Ke Yuhe). Ke Yuhe and Hairil Rizal Abdullah: Writing—Review and Editing (provided critical appraisal and further development to the original draft). Khoo You Liang: Formal Analysis (advised regarding statistical and data analyses). All authors: Writing—Review and Editing (contributed to the revision of the manuscript) and Supervision (approved the final version).

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA), and consent was obtained for the original data collection. Therefore, ethical approval and the need for informed consent was waived for this manuscript.

Consent for publication
All authors gave their consent for publication.

Competing interest
The authors declare no conflict of interest in this manuscript.

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References

1. Papazian L, Klompas M, Luyt C-E. Ventilator-associated pneumonia in adults: a narrative review. Intensive Care Med. 2020;46(5):888–906.
2. Hayashi Y, Morisawa K, Klompas M, Jones M, Bandeshe H, Boots R, et al. Toward improved surveillance: the impact of ventilator-associated complications on length of stay and antibiotic use in patients in intensive care units. Clin Infect Dis. 2013;56(4):471–7.
3. Restrepo MI, Anzueto A, Arroliga AC, Afessa B, Atkinson MJ, Ho NJ, et al. Economic burden of ventilator-associated pneumonia based on total resource utilization. Infect Control Hosp Epidemiol. 2010;31(5):509–15.
4. Luo W, Xing R, Wang C. The effect of ventilator-associated pneumonia on the prognosis of intensive care unit patients within 90 days and 180 days. BMC Infect Dis. 2021;21(1):684.
5. Okgün Alcan A, Demir Korkmaz F, Uyar M. Prevention of ventilator-associated pneumonia: Use of the care bundle approach. Am J Infect Control. 2016;44(10):e173–6.
6. Pozuelo-Carrascosa DP, Cobo-Cuenca AI, Carmona-Torres JM, Laredo-Aguilera JA, Santacruz-Salas E, Fernandez-Rodriguez R. Body position for preventing ventilator-associated pneumonia for critically ill patients: a systematic review and network meta-analysis. J Intensive Care Med. 2022;10(1):9.
7. Dai W, Lin Y, Yang X, Huang P, Xia L, Ma J. Meta-analysis of the efficacy and safety of chlorhexidine for ventilator-associated pneumonia prevention in mechanically ventilated patients. Evid Based Complement Alternat Med. 2022;2022:5311034. Retraction in: Dai W, Lin Y, Yang X, Huang P, Xia L, Ma J. Evid Based Complement Alternat Med. 2023:9873478
8. Chen T-J, Chung Y-W, Chen P-Y, Hu SH, Chang C-C, Hsieh S-H, et al. Effects of daily sedation interruption in intensive care unit patients undergoing mechanical ventilation: A meta-analysis of randomized controlled trials. Int J Nurs Pract. 2022;28(2):e12948.
9. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogué S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet. 1999;354(9193):1851–8.
10. Klompas M, Li L, Kleinman K, Szumita PM, Massaro AF. Associations between ventilator bundle components and outcomes. JAMA Intern Med. 2016;176(9):1277–83.
11. Miano TA, Reichert MG, Houle TT, MacGregor DA, Kincaid EH, Bowton DL. Nosocomial pneumonia risk and stress ulcer prophylaxis: a comparison of pantoprazole vs ranitidine in cardiothoracic surgery patients. Chest. 2009;136(2):440–7.
12. Lewis SC, Li L, Murphy MV, Klompas M, CDC Prevention Epicenters. Risk factors for ventilator-associated events: a case-control multivariable analysis. Crit Care Med. 2014;42(8):1839–48.
13. Sachetti A, Rech V, Dias AS, Fontana C, Barbosa Gda L, Schlichting D. Adherence to the items in a bundle for the prevention of ventilator-associated pneumonia. Rev Bras Ter Intensiva. 2014;26(4):355–9.
14. Mogyoródi B, Skultéti D, Mezőcsáti M, Dunai E, Magyar P, Hermann C, et al. Effect of an educational intervention on compliance with care bundle items to prevent ventilator-associated pneumonia. Intensive Crit Care Nurs. 2023;75:103342.
15. Johnson A, Bulgarelli L, Pollard T, Horng S, Celi L A, Mark R. MIMIC-IV (version 0.4). PhysioNet. 2020. Available from: https://doi.org/10.13026/a3wn-hq05.
16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12(12):1495–9.
17. Kong X, Wu Y, Wen B, Meng D, Wei L, Yu P. Effect of stress ulcers prophylaxis, sedative and statin on ventilator-associated pneumonia: a retrospective analysis based on MIMIC database. Front Pharmacol. 2022;13:921422.
18. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000;342(20):1471–7.
19. Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet. 2010;375(9713):475–80.
20. Wang M, Wang W, Jia X, He Q, Zhu S, Kang Y, et al. Associations between antithrombosis and ventilator-associated events, ICU stays, and mortality among mechanically ventilated patients: a registry-based cohort study. Front Pharmacol. 2022;13:891178.
21. Navab F, Steingrub J. Stress ulcer: is routine prophylaxis necessary? Am J Gastroenterol. 1995;90(5):708–12.
22. Grap MJ, Munro CL, Unoki T, Hamilton VA, Ward KR. Ventilator-associated pneumonia: the potential critical role of emergency medicine in prevention. J Emerg Med. 2012;42(3):353–62.

23. Oliveira J, Zagalo C, Cavaco-Silva P. Prevention of ventilator-associated pneumonia. Rev Port Pneumol. 2014;20(3):152–61.
24. Burja S, Belec T, Bizjak N, Mori J, Markota A, Sinkovič A. Efficacy of a bundle approach in preventing the incidence of ventilator associated pneumonia (VAP). Bosn J Basic Med Sci. 2018;18(1):105–9.
25. Mastrogianni M, Katsoulas T, Galanis P, Korompeli A, Myrianthefs P. The impact of care bundles on ventilator-associated pneumonia (VAP) prevention in adult ICUs: a systematic review. Antibiotics (Basel). 2023;12(2):227. https://doi.org/10.3390/antibiotics12020227
26. de Neef M, Bakker L, Dijkstra S, Raymakers-Janssen P, Vileito A, Ista E. Effectiveness of a ventilator care bundle to prevent ventilator-associated pneumonia at the PICU: a systematic review and meta-analysis. Pediatr Crit Care Med. 2019;20(5):474–80.
27. Al-Sayaghi KM. Critical care nurses' compliance and barriers toward ventilator-associated pneumonia prevention guidelines: cross-sectional survey. J Taibah Univ Med Sci. 2021;16(2):274–82.
28. Pogorzelska M, Stone PW, Furuya EY, Perencevich EN, Larson EL, Goldmann D, et al. Impact of the ventilator bundle on ventilator-associated pneumonia in intensive care unit. Int J Qual Health Care. 2011;23(5):538–44.
29. Aloush SM, Al-Rawajfa OM. Prevention of ventilator-associated pneumonia in intensive care units: Barriers and compliance. Int J Nurs Pract. 2020;26(5):e12838.
30. Rello J, Soñora R, Jubert P, Artigas A, Rué M, Vallés J. Pneumonia in intubated patients: role of respiratory airway care. Am J Respir Crit Care Med. 1996;154(1):111–5.
31. Touat L, Fournier C, Ramon P, Salleron J, Durocher A, Nseir S. Intubation-related tracheal ischemic lesions: incidence, risk factors, and outcome. Intensive Care Med. 2013;39(4):575–82.
32. Damas P, Frippiat F, Ancion A, Canivet J-L, Lambermont B, Layios N, et al. Prevention of ventilator-associated pneumonia and ventilator-associated conditions: a randomized controlled trial with subglottic secretion suctioning. Crit Care Med. 2015;43(1):22–30.
33. Almenyan AA, Albuduh A, Al-Abbas F. Effect of nursing workload in intensive care units. Cureus. 2021;13(1):e12674.
34. Niedzwiecka T, Patton D, Walsh S, Moore Z, O'Connor T, Nugent L. What are the effects of care bundles on the incidence of ventilator-associated pneumonia in paediatric and neonatal intensive care units? A systematic review. J Spec Pediatr Nurs. 2019;24(4):e12264.
35. Shahabi M, Yousefi H, Yazdannik AR, Alikiaii B. The effect of daily sedation interruption protocol on early incidence of ventilator-associated pneumonia among patients hospitalized in critical care units receiving mechanical ventilation. Iran J Nurs Midwifery Res. 2016;21(5):541–6.
36. Garrett KM. Best practices for managing pain, sedation, and delirium in the mechanically ventilated patient. Crit Care Nurs Clin North Am. 2016;28(4):437–50.
37. Craven DE, Goularte TA, Make BJ. Contaminated condensate in mechanical ventilator circuits. A risk factor for nosocomial pneumonia? Am Rev Respir Dis. 1984;129(4):625–8.
38. Kola A, Eckmanns T, Gastmeier P. Efficacy of heat and moisture exchangers in preventing ventilator-associated pneumonia: meta-analysis of randomized controlled trials. Intensive Care Med. 2005;31:5–11.
39. Gillies D, Todd DA, Foster JP, Batuwitage BT. Heat and moisture exchangers versus heated humidifiers for mechanically ventilated adults and children. Cochrane Database Syst Rev. 2017;9(9):CD004711.
40. Oğuz S, Değer I. Ventilator-associated pneumonia in patients using HME filters and heated humidifiers. Ir J Med Sci. 2013;182(4):651–5.
41. Menegueti MG, Auxiliadora-Martins M, Nunes AA. Effectiveness of heat and moisture exchangers in preventing ventilator-associated pneumonia in critically ill patients: a meta-analysis. BMC Anesthesiol. 2014;14:115.
42. Talekar CR, Udy AA, Boots RJ, Lipman J, Cook D. Tracheal cuff pressure monitoring in the ICU: a literature review and survey of current practice in Queensland. Anaesth Intensive Care. 2014;42(6):761–70.
43. Shaikh F, Janaapureddy YR, Mohanty S, Reddy PK, Sachane K, Dekate PS, et al. Utility of endotracheal tube cuff pressure monitoring in mechanically ventilated (MV) children in preventing post-extubation stridor (PES). Indian J Crit Care Med. 2021;25(2):181–4.
44. Huang L, Zhang L, Meng L, Zhou C, Lin J, Li Y, et al. [Application study on improving the methods of endotracheal cuff pressure measurement to prevent ventilator-associated pneumonia]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2019;31(8):1024–7. Chinese.
45. Fujimoto H, Yamaguchi O, Hayami H, Shimosaka M, Tsuboi S, Sato M, et al. Efficacy of continuous versus intermittent subglottic secretion drainage in preventing ventilator-associated pneumonia in patients requiring mechanical ventilation: A single-center randomized controlled trial. Oncotarget. 2018;9(22):15876–82.
46. Anand R, Singh S, Prasoon A, Kumar S, Singh R, Nayan SK. Comparative study of effect of continuous versus intermittent subglottic suctioning by the suction above the cuff endotracheal tube (SACETT) on tracheal mucosa and incidence of VAP in intensive care unit. J Card Crit Care TSS. 2021;5(3):196–200. https://doi.org/10.1055/s-0041-1741524.

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