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Original Article

Impact of evidence-based bundles on ventilator-associated pneumonia prevention: A systematic review

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Abstract

Introduction: This review aimed at investigating the impact of bundle components on the prevention of ventilator-associated pneumonia (VAP) in adults and the elderly.

Methodology: The databases consulted were PubMed, EBSCO, and Scielo. The terms Bundle and Pneumonia were searched in combination. The original articles were selected in Spanish and English; published between January 2008 and December 2017. After eliminating the duplicate papers, an analysis of the titles and the abstracts was performed in order to select the assessed articles. A total of 18 articles were included in this review that were evaluated according to the following criteria: research reference, country of data collection, type of study, characteristics of the studied patients, analysis and intervention performed, bundle items investigated and their results, and research outcome.

Results: Four bundle items were presented in all the investigated papers. 61% of those works were considered from seven to eight bundle items. Daily evaluation of sedation interruption and daily assessment for verifying extubation condition, head-of-bed elevation at 30 degrees, cuff pressure monitoring, coagulation prophylaxis, and oral hygiene were the most reported bundle items. One study described the increased mortality of patients under mechanical ventilation when omitted the bundle items of oral hygiene and stress ulcer prophylaxis. Head-of-bed elevation at 30 degrees was the item reported in 100% of the studied papers.

Conclusions: Existing research demonstrated that VAP reduction occurred when bundle items were performed for adults and the elderly. Four works showed the relevance of team education as a central approach to the event reduction related to the ventilator.

Key words: Elderly health; head-of-bed elevation; intensive care unit; mechanical ventilation; oral hygiene.

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Introduction

In the context of healthcare-related infections (HCRIs), pneumonia is the second most frequent and severe infection in hospital patients. It occurs from the inflammatory response of the pulmonary parenchyma and the uncontrolled penetration of infectious agents as multidrug-resistant microorganisms which lead to severe respiratory signs and symptoms [1,2].

Endotracheal intubation and mechanical ventilation are widely used for ensuring suitable oxygen supply and can save patient lives in the intensive care unit (ICU). However, these interventions can be deleterious since ventilator-associated pneumonia (VAP) can occur after 48 hours of intubation [3,4].

VAP has a high prevalence in ICU, representing one of the main infectious complications in severe patients, and is related to high mortality rates [5,6]. VAP incidence can rise when the days of mechanical ventilation increase. Rates in ICU ranging from 30 to 70% and from 8% to 33% for incidence and mortality associated with VAP are recorded, respectively. Previous studies demonstrated that VAP can delay the mechanical ventilation time by 7.6 to 11.5 days and can stay in the hospital for extended time intervals by 11.5 to 13.1 days. Moreover, the costs can increase by 40,000 U.S. dollars per episode [6,7].

In this scenario, improving care for ventilated patients has become a key concern for the national health systems of many countries. Prevention and control approaches are essential and priorities in order to avoid adverse events such as VAP. A basic set of interventions must be performed for preventing VAP and these strategies are widely recognized in literature as a care bundle [7,8]. In brief, the aim of care bundles is to improve health outcomes by facilitating and promoting changes in patient care and encouraging guideline compliance [6]. VAP bundle involves different care procedures such as the head-of-bed elevation, the daily sedation interruption protocols, the daily spontaneous breathing test, oral hygiene using mainly chlorhexidine, the aspiration of subglottic secretion, the cuff pressure verification, the coagulation prophylaxis, and the stress ulcer prophylaxis [9,10,11].

However, VAP represents a burden to health care, and previous studies have reported changes in their protocols and sets of interventions. In spite of the guidelines of VAP, bundles reveal some differences, these strategies substantially reduce morbidity and mortality rates when suitably implemented [6,7]. Taking all these into account, the present paper aimed to review the previous reports concerning the evidence-based bundles on ventilator-associated pneumonia prevention in adults and elderly patients admitted to the hospital ICUs.

Table 1. Search strategy used in the chosen databases.

Database	Search strategy
PubMed (Title and Abstract)	(pneumonia [Title/Abstract]) AND bundle [Title/Abstract])
EBSCO (Title)	Title (bundle) AND Title (pneumonia)
SciELO (Abstract)	bundle [Abstract] AND pneumonia [Abstract]

Methodology

The present study was carried out according to the PRISMA guideline (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes) [12].

The PICOS approach was used in order to formulate the guiding question [13,14], where "P" refers to the population or patient; "I" to the intervention; "C" to the comparison; "O" to outcome; and "S" to study design. Considering these parameters, this systematic review was based on: P: adult and elderly patients; I: to have received the bundle care package on PAV prevention; C: have not received the care bundle on PAV prevention; O: intervention efficacy; and S: observational studies and clinical trials.

Table 2. Data extraction from included articles.

Reference	COUNTRY	KIND OF STUDY	SAMPLE CHARACTERIZATION	INTERVENTION	OUTCOME
(Maldonado, Robledo, Sabido, 2013) [27]	Mexico	Cohort	232 patients; Cohort age from 2010 to 2011: 47 ± 17 yr.; Cohort age from 2012 to 2013: 49 ± 18 yr.; Comorbidities: ABI, ARI, AHF, postoperative thoracic surgery, sepsis, septic shock, neurological disorders, and cancer.	The patients were evaluated regarding to the Richmond Confusion/Randomness Scale/Agitation Scale (RASS). It was studied the fulfillment of three quality indicators: NPE, re-intubation, and VAP.	It occurred reduction in the indicators: 1.6% *vs.* 7% in re-intubation rate ($p = 0.02$) and 8.1 *vs.* 17 episodes per 1,000 days of mechanical ventilation for NPE ($p = 0.04$) within the multi-professional work, team education, and feedback. The VAP indicator was 18.4 *vs.* 15.1 episodes per 1,000 days of mechanical ventilation ($p = 0.5$).
(Shitrit *et al.*, 2015) [43]	Israel	Case-control	128 elderly patients; Age before and after intervention: 78.8 ± 11.0 yr. and 81.1 ± 10.8 yr.; Comorbidities: CHF, RI, CVA, DM, COPD, dementia, and malnutrition.	Evaluation of the package implementation of the VAP preventive measures in long-term health institutions for elderly people. The VAP criteria were defined according to the National Health Care Safety Network: ventilated patients for at least 48 h.	The total VAP rate decreased from 5.97 before implementation of the package to 2.34 after implementation ($p < 0.001$). The highest adhesion rates were related to cuff pressure (95.7%) and oral hygiene (80.5%) from the five bundle items.
(Parisi, 2016) [6]	Greece	Case-control	362 patients; Mean age before and after intervention: 59 yr. (41-73 yr.) and 58 yr. (42-72 yr.); Comorbidities: ResI, neurological disease, cardiovascular disease, neurotrauma, multiple injury, sepsis, and gastrointestinal diseases.	Before intervention: all VAP cases were recorded on structured forms. Intervention was carried out by the staff education on VAP preventive measures and the fixed posters at the bedside.	VAP density was reduced from 21.6 to 11.6 events per 1,000 days of ventilation ($p = 0.01$), as well as the reduction in mean time of mechanical ventilation from 26 to 21 days and in ICU stay from 36 to 27 days ($p = 0.04$) were achieved.
(Mogyoródi *et al.*, 2016) [32]	Hungary	Case-control	535 patients; Age before and after bundle VAP implantation: 68.74 ± 14.04 yr. and 69.75 ± 14.32 yr.; Comorbidities: COPD, AH, DM, ARDS, gastroesophageal reflux disease, RI, CT, immunosuppression, surgery of thorax, abdominal surgery, and dementia.	535 hospital patients: 275 patients before and 260 patients after bundle implantation on VAP, respectively. Nurses were trained on the relevance of the VAP bundle.	The VAP incidence was 21.5 per 1,000 days of ventilation (95% CI: 14.17-31.10) and 12.0 per 1,000 days (95% CI: 7.2-19.49) in before-after analysis. The relative risk reduction was 44% (95% CI 0.50-0.98). Significant parameters: head-of-bed elevation ($p = 0.004$), oral care ($p = 0.01$), hand hygiene ($p < 0.001$), endotracheal suction ($p = 0.004$), and condensate removal from ventilator connections ($p = 0.043$).
(Pérez-Granda (Mogyoródi *et al.*, 2014) [15]	Spain	Case-control	1935 patients; Mean age: 66.45 ± 12.0 yr. before and 67.36 ± 30.6 yr. after intervention; Comorbidities: AMI, CHF, RI, DM, PVD, PU, and CNSD.	The first measure was the training of ICU team; the second measure was the systematic aspiration of subglottic secretions using TaperGuard Evac endotracheal tube; the third measure was the application of PAV bundle items by a nurse.	The incidence of VAP per 1,000 days of ventilation was 23.9 *vs.* 13.5 ($p = 0.005$). Mean of mechanical ventilation days per 1,000 days was 507 *vs.* 375 ($p = 0.001$). Reduction on VAP rate of 41%, IRR = 0.41 (95% CI: 0.28-0.62). Mortality before and during the intervention was 13.0 and 10.2%.
(Rosenthal (Mogyoródi *et al.*, 2012) [33]	Argentina, Brazil, China, Colombia, Costa Rica, Cuba, India, Lebanon, Macedonia, Mexico, Morocco, Panama, Peru, and Turkey	Cohort	55,507 patients admitted to 44 ICUs from 38 hospitals in several countries; Mean age: initial period: 57.2 ± 19.5 yr.;intervention period: 57.6 ± 19.9 yr.; Comorbidities: endocrine diseases, cardiac failure, cardiac surgery, thoracic surgery, and trauma.	The time interval of this study was 12 years and 8 mos. In the intervention period were included: 1) set of infection control measures; 2) education; 3) surveillance result; 4) process monitoring; 5) feedback of VAP rates; and 6) performance feedback of team members' adherence to infection prevention.	The incidence of PAV per 1,000 days of ventilation was 22.0 *vs.* 17.2. The The linear regression model demonstrated a 55.83% reduction in the VAP rate at the end of the study period.
(Dubose (Mogyoródi *et al.*, 2010) [8]	USA	Cohort	1147 patients; Mean age: 39.4 ± 20.6 yr. (before) and 39.0 ± 21.1 (after); Comorbidities: spinal fracture, cervical fracture, lumbar thoracic fracture, spinal cord injury, CT, abdomen trauma, and thoracic trauma.	The Quality Rounds Checklist included preventive measures: VAP bundle, central venous catheter, glucose control, nutrition, and antibiotic prescription.	The VAP incidence was lower among the patients who received the total care of the package 13.4% *vs.* 3.5% ($p = 0.04$) and reductions in VAP time interval: 6.2 ± 4.5 days *vs.* 14.8 ± 13.5 days ($p < 0.001$), ICU stay: 9.4 ± 7.7 days *vs.* 18.0 ± 12.5 days ($p < 0.001$), hospital stay: 16.1 ± 11 days *vs.* 34.1 ± 31.7 days ($p < 0.001$) and also reduced hospital expenses: US$

					143,554 ± 100,971 *vs.* US$ 311,930 ± 268,221 ($p <$ 0.001).
(Akdogan (Mogyoródi *et al.*, 2016) [39]	Turkey	Case-control	133 patients, 37 cases and 96 controls; The mean age was 60.32 ± 21.6 yr. for cases and 61.34 ± 19.8 yr. for control patients (p = 0.7); Comorbidities: respiratory disease, cardiac disease, and trauma.	Control group was carried out during the first 6 mos; patients intubated with endotracheal tube with subglottic secretion drainage were included as cases. Health professionals have had training.	VAP per 1,000 days was significantly higher for controls (40.8) than for cases (22.1) ($p < 0.05$). There was a significant increase in adherence of cuff pressure measurement, use of subglottic drainage, and oral care with chlorhexidine for cases compared to controls.
(Rello (Mogyoródi *et al.*, 2012) [36]	Spain	Cohort	149 patients in the initial period and 855 in the intervention one; Mean age: initial phase: 59 ± 18 yr. and intervention phase: 66 ± 18 yr.; Comorbidities: COPD, CRF, and cardiopathy.	An Intensive Care Society invited five hospitals to implement the bundle care package after an initial period of 3 mos. This package was registered prospectively for 16 mos.	VAP incidence decreased from 15.5% (23/149) to 11.7% (104/885) ($p < 0.05$), associated to hand hygiene (OR = 0.35), cuff pressure (OR = 0.21), oral hygiene (OR = 0.23), and sedation control (OR = 0.51).
(Roquilly (Mogyoródi *et al.*, 2013) [29]	France	Cohort	499 patients; Mean age in control phase: 50 yr. and in the intervention phase: 52 yr.; Comorbidities: CT, subarachnoid hemorrhage, cancer, cerebellar lesion, and external ventricular drain in decompressive craniectomy.	The control phase consisted of 299 patients with severe brain injury admitted to the ICU 3 yr. before the beginning of the educational program. The intervention phase consisted of 200 patients with severe brain injury during a period of 22 mos.	Intervention phase was associated with a lower tidal volume ($p < 0.01$), expiratory pressure ($p < 0.01$), and higher enteral intake in the first seven days ($p = 0.01$). The mean duration of mechanical ventilation was 14.9 ± 11.7 days in the control phase and 12.6 ± 10.3 days in the intervention ($p = 0.02$). The adjusted risk index was 1.40 (95% CI: 1.12-1.76, $p < 0.01$) and it was 1.34 (95% CI: 1.03-1.74) for the multivariate analysis.
(Klompas (Mogyoródi *et al.*, 2016) [11]	USA	Cohort	5539 patients on mechanical ventilation; Mean age: 61.2 ± 16.1 yr.; Comorbidities: CAD, CHF, PVD, COPD, DM, CRF, HD, and solid lymphoma.	Six ICUs were evaluated regarding to the associations among VAP prevention package components, risk factors related to ventilator use, and risk of death.	Sedative infusion interruptions were associated with less time to extubation (HR: 1.81; 95% CI: 1.54-2.12; $p < 0.001$) and a lower hazard for ventilator mortality (HR: 0.51, 95% CI: 0.38-0.68; $p < 0.001$). Similar associations were found for spontaneous breathing trials (HR for extubation: 2.48; 95% CI: 2.23-2.76; $p <$ 0.001; HR for mortality: 0.28; 95% CI: 0.20-0.38; p = 0.001). Spontaneous breathing trials were also associated with lower hazards for ventilator-associated events (HR: 0.55; 95% CI: 0.40-0.76; $p < 0.001$). Associations with less time to extubation were found for head-of-bed elevation (HR: 1.38, 95% CI: 1.14-1.68; $p = 0.001$) and coagulation prophylaxis (HR: 2.57; 95% CI: 1.80-3.66; $p < 0.001$) but not for ventilator mortality. Oral care with chlorhexidine was associated with an increased risk for ventilator mortality (HR: 1.63; 95% CI: 1.15-2.31; $p = 0.006$), and stress ulcer prophylaxis was associated with an increased risk for VAP (HR: 7.69; 95% CI: 1.44-41.10; $p = 0.02$).
(Deluca (Mogyoródi *et al.*, 2016) [25]	USA	Cohort	540 patients; Ages at pre-1 phase: 35 yr. (23-55 yr.); pre-2 phase: 47 yr. (24-63 yr.), and post-3 phase: 55 yr. (36-63 yr.); Comorbidities: respiratory conditions: pneumonia, pulmonary edema, and pulmonary contusion.	Pre-1 phase occurred before the implantation of the VAP bundle in ICU; pre-2 phase: implantation of VAP package in ICU; post-3 phase: included patients who received VAP prevention from intubation in the emergency room and ICU.	VAP rates were 22 (11.3%), 11 (5.7%), and 6 (3.9%). Log-rank test showed a VAP significant reduction (χ^2 = 9.16, $p = 0.0103$). Bundle compliance was greater than 50% for head-of-bed elevation, oral care, subglottic suctioning, and titrated sedation.
(Viana (Mogyoródi *et al.*, 2013) [44]	Brazil	Uncontrolled clinical trial	518 patients; Mean age at the intervention group: 77 yr. (65-85 yr.) and at the control group: 76 yr. (61-83 yr.); Comorbidities: pulmonary, cardiac, neurological diseases, and sepsis.	224 patients in intervention group and 294 in the control one. An educational module was developed for all ICU professionals and a pre-test was performed and followed by a post-test.	The mean monthly VAP rate observed before the intervention was 18.6 ± 7.8 per 1,000 days of ventilation (95% CI: 8.7-14.9), decreasing to 11.8 ± 7.8 per 1,000 days of ventilation (95% CI: 15.5-27.7) ($p = 0.002$) after the intervention and the mean difference corresponded to a 38% reduction in the VAP risk compared to the mean risk prior to the interventions.
(Leblebicioglu (Mogyoródi *et al.*, 2013) [24]	Turkey	Cohort	4312 patients; Mean age at initial phase: 52.37 ± 22.5 yr. and at intervention phase: 49 ± 21.6 yr.; Comorbidities: surgical patients, trauma, abdominal surgery, and liver failure.	A before-after prospective surveillance study was performed in 11 adult ICUs from ten INICC member hospitals in ten cities in Turkey. In the initial phase, the multidimensional approach was used.	In the initial period, the VAP rate was 31.14 per 1,000 days of ventilation and the VAP intervention rate was 16.82 per 1,000 days of ventilation (RR: 0.54, 95% CI: 0.42-0.70, $p = 0.0001$). VAP rates were 33% lower in the second year, 25% in the third year, 30% in the fourth year, and 56% in the fifth and sixth year.
(Stone (Mogyoródi *et al.*, 2011) [38]	USA	Experimental	366 trauma patients hospitalized in ICU; Pre-round age: 44.4 ± 19.7 yr. and post round: 47.3 ± 23.7 yr.; Comorbidities: fractures due to collision of motor vehicles, motorcycle collision, and others, such as: penetrating trauma and thorax injury.	Implantation of Multidisciplinary Daily Rounds in which a checklist of integrated care by the health team was carried out. It occurred in two periods of ten mos: before the conception of the pre-round group and after the post-round group.	There was a 67% decrease in the number of VAPs after round implantation: 15 (17.6%) in the pre-round group and five (5.6%) in the post-round group (p = 0.02). It corresponded to a decrease in the VAP incidence rate from 26.8 to 7.0 per 1,000 days of ventilation ($p = 0.001$, RR: 0.26, 95% CI: 0.07-0.75).
(Guanche-Garcell, Morales-Perez; Rosenthal, 2013) [3]	Cuba	Cohort	1075 patients; mean age at initial phase: 60.0 ± 19 yr. and 61.4 ± 17.6 yr. at intervention phase; Comorbidities: RI, CVA, lung disease, trauma, endocrine disease, liver failure, thoracic surgery, and abdominal surgery.	A prospective study of patient surveillance in an adult ICU. During the initial period, an active prospective surveillance on VAP was performed. In the intervention period, the multidimensional approach of INICC to VAP was carried out.	During the initial phase, the VAP rate was 52.63 per 1,000 days of mechanical ventilation, while the VAP rate was 15.32/ per 1,000 days of mechanical ventilation during the intervention (RR: 0.3, 95% CI: 0.12-0.70, $p = 0.003$). These results showed a reduction of the VAP rate of 70%, thus demonstrating that this type of infection control (bundle) approach is successful.
(Croce (Mogyoródi *et al.*, 2013) [10]	USA	Cohort	630 trauma patients; Mean age: 47 yr.; Comorbidities: rib fracture, pulmonary contusion, blunt injury, and bone marrow lesion.	This study included six level I trauma centers over a 16-mos. period. Compliance for each bundle component was recorded daily by evaluating the patient risk factors.	226 patients (36%) evolved with the VAP diagnosis, and 16 patients (7.0%) developed late VAP with 15% of mortality. Regression identified male gender and pulmonary contusion as independent VAP predictors.
(Hudson *et al.*, 2015) [5]	Canada	Case-control	4880 patients undergoing cardiac surgery; Mean age at control group: 65.6 ± 11.9 yr. and mean age at CASS group 65.0 ± 11.9 yr.; Comorbidities: myocardial revascularization and heart valve.	Control group: 2430 patients showing standard subglottic aspiration; intervention group or CASS: 2450 patients with continuous subglottic aspiration.	The unadjusted VAP incidence was 1.9% in the CASS group and 5.6% in the control group ($p < 0.0001$). The CASS group also had lower hospital mortality rates in the 30 days (2.1% *vs.* 3.3%, $p = 0.007$), mean ventilation time (7.3 *vs.* 8.4 hours, $p < 0.0001$), and ICU stay (1.17 *vs.* 1.77 days, $p < 0.0004$) compared to the control group.

ABI: Acute Breathing Insufficiency; AH: Arterial Hypertension; AHF: Acute Heart Failure; AMI: Acute Myocardial Infarction; ARDS: Acute Respiratory Disorder Syndrome; ARI: Acute Renal Insufficiency; CAD: Coronary Artery Disease; CASS: Continuous Aspiration Of Subglottic Secretions; CHF: Congestive Heart Failure; CI: Confidence Interval; CNSD: Central Nervous System Disease; COPD: Chronic Obstructive Pulmonary Disease; CRF: Chronic Renal Failure; CT: Cranial Trauma; CVA: Cerebrovascular Accident Or Stroke; DM: Diabetes Mellitus; HD: Hepatic Disease; HR: Hazard Ratio; HT: Head Trauma; ICU: Intensive Care Unit; IHD: Ischemic Heart Disease; INICC: International Nosocomial Infection Control Consortium; IRR: Incidence Rate Ratio; NPE: Non-Programmed Extubation; OR: Odds Ratio; PU: Peptic Ulcer; PVD: Peripheral Vascular Disease; RASS: Richmond Agitation-Sedation Scale; RESI: Respiratory Insufficiency; RI: Renal Insufficiency; RR: Relative Risk; SAH: Subarachnoid Hemorrhage; VAP: Ventilator-Associated Pneumonia

Literature search strategy

The studies were identified using search strategies provided by the given databases (PubMed, EBSCO and SciELO) as described in Table 1.

Inclusion/exclusion criteria

Inclusion criteria for the studies were: clinical trials based on observational and interventional studies which were performed involving adult and/or elderly populations and were published in English and in Spanish between January 2008 and December 2017. After identifying the studies from these databases, two researchers carefully assessed if they fulfilled the inclusion criterion for this study. Duplicate papers were excluded. Titles and abstracts were then examined. The papers that did not fit to the PICOS parameters and those that did not describe the patients' comorbidities were also excluded.

Literature identification

The data collected were summarized according to the following information: population, country, type of study, patients' characterization as age and comorbidities, analysis and intervention performed, recorded bundle items, main results, and outcome (Table 2).

Results

Figure 1 shows the flowchart of the methodology used for identifying research work for this study. Considering the inclusion and exclusion criteria, a total of 18 papers were included for an in-depth review. Regarding the clinical trials investigated, ten papers were cohort studies, six articles were devoted to reporting case-control studies, and two works were experimental studies. Considering the comorbidities related to the samples evaluated, cardiovascular diseases were the most prevalent ones followed by respiratory disorders, bone fractures, trauma, and renal insufficiency.

The bundle items described in these papers for VAP prevention are shown in Table 3. Four bundle items were reported in all the investigated papers. A maximum of nine bundle items were recorded and 61% of the studies considered from seven to eight bundle items. The five main items assessed were: (a) daily evaluation of sedation interruption and daily assessment for verifying extubation condition, (b) head-of-bed elevation at 30 degrees, (c) cuff pressure monitoring, (d) coagulation prophylaxis, and (e) oral hygiene. One study described the increased mortality of patients

Figure 1. Flow through the different phases of systematic review.

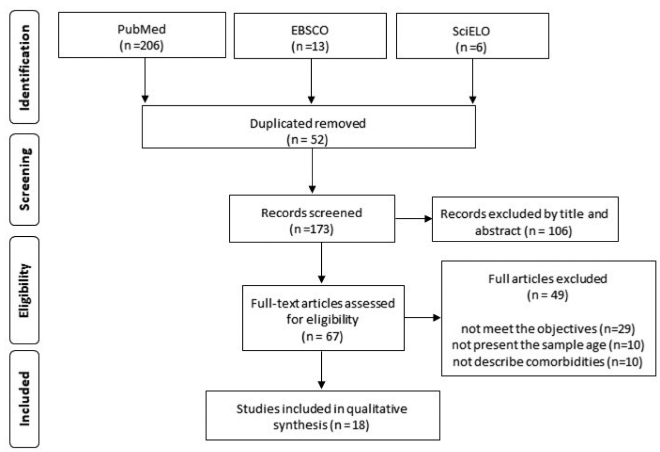

Table 3. Description of PAV bundle items extracted from included papers.

PAV BUNDLE items	REFERENCES (Maldonado *et al.*, 2013) [27]	(Shitrit *et al.*, 2015) [43]	(Parisi *et. al.*, 2016) [6]	(Mogyoródi *et al.*, 2016) [32]	(Pérez-Granda *et al.*, 2014) [15]	(Rosenthal *et al*, 2012) [33]	(Dubose *et al.*, 2010) [8]	(Akdogan *et al.*, 2016) [39]	(Rello *et al.*, 2012) [36]	(Roquilly *et al*, 2013) [29]	(Klompas *et al.*, 2016) [11]	(Deluca *et al.*, 2016) [25]	(Viana *et al.*, 2013) [44]	(Leblebicioglu *et al*, 2013) [24]	(Stone *et al.*, 2011) [38]	(Guanche-Garcell *et al.*, 2013) [3]	(Croce *et al.*, 2013) [10]	(Hudson *et al*, 2015) [5]
Daily evaluation of sedation interruption	x		x			x	x	x	x	x	x	x	x	x	x	x	x	x
Daily assessment for verifying extubation condition	x		x	x			x	x		x	x	x	x	x	x	x	x	x
Head-of-bed elevation at 30 degrees	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Oral hygiene	x	x	x	x	x	x		x	x		x	x	x	x		x		x
Hand hygiene	x		x						x				x	x		x		
Cuff pressure monitoring	x	x		x	x	x		x	x		x		x	x				
Coagulation prophylaxis	x		x	x			x	x			x	x	x		x		x	
Stress ulcer prophylaxis	x		x			x	x	x			x	x	x		x		x	
Aseptic endotracheal aspiration				x	x		x	x	x	x		x				x		x
Evaluation of gastric/enteral catheter position		x						x		x								
Droplets removal in breathing circuits						x			x	x				x				
Replacement of ventilator circuits when visible dirty or malfunctioning				x			x							x		x		
Optimization of antibiotic therapy							x			x								
All items contributed to PAV reduction	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x

under mechanical ventilation when omitted the bundle items of oral hygiene and stress ulcer prophylaxis. In particular, head-of-bed elevation at 30 degrees was the item reported in 100% of the studied papers.

Discussion

The care bundle to prevent VAP is a priority in hospital ICU services due to these patients show high morbidity and mortality rates [15,16]. Risk factors that lead to the VAP evolution are commonly classified as non-modifiable, including age, patient severity score at ICU admission, and presence of comorbidities. In contrast, the modifiable factors are associated with mechanical ventilation, previous use of antimicrobial agents, colonization and biofilm formation in the buccal cavity and endotracheal tube, patient position in bed, and other invasive procedures [17,18].

Regarding the main non-modifiable risk factors, 15 studies (83.33%) investigated patients with a mean age of 47 to 66 years, two papers (11.11%) examined patients over 65 years (77 to 78.8 years), and one work evaluated adults with a mean age of 35 years. These clinical trials demonstrated that elderly patients are more vulnerable to acquiring HCRIs compared to young adults because there are physiological changes concerning aging, the declining immune response, the number of invasive procedures, and a higher predisposition to chronic diseases [19,20,21]. Comorbidities were remarkable elements for patients' admission to ICU services due to complications related to cardiovascular, respiratory, renal, and hepatic disorders [15,22,23], and these findings were similar among the 18 papers here investigated.

In this perspective, the care bundle was described as a suitable approach for ICU patients to reduce the incidence of VAP considering the 18 articles studied. Among the bundle items for VAP prevention, five of them demonstrated the highest level of evidence for supporting a prevention action plan against events associated with the ventilator: (1) head-of-bed elevation at 30 degrees, (2) daily evaluation of sedation interruption, and daily assessment for verifying extubation condition, (3) oral hygiene, (4) cuff pressure monitoring, and (5) coagulation prophylaxis. The head-of-bed elevation between 30 and 45 degrees is one of the main recommended care procedures to decrease the gastroesophageal pressure and the succeeding bronchial aspiration. This simple procedure ensures increased inspired tidal volume and muscular effort reduction. In addition, the findings from randomized clinical trials showed that head-of-bed elevation is related to the reduction of days spent in mechanical ventilation, which reinforces that this no-cost procedure has a positive effect on mechanically ventilated patients [10]. Two studies involving VAP prevalence in mechanically ventilated patients revealed appropriate results concerning the reduction of VAP rates by 60% when the head-of-bed elevation was associated with other care procedures [24,25].

It is well known that suitable sedation is essential in the intensive care of critically ill patients with respiratory problems and under mechanical ventilation. The obtained results from a retrospective review of the VAP incidence in mechanically ventilated patients were lower in the group of patients with daily sedation interruption when compared to the continuous sedative infusion [26,27,28]. Another study devoted to evaluating the association among bundle items for VAP prevention reported a high team adherence to daily sedative infusion interruptions (94%). This care procedure led to a decreased extubation time [hazard ratio (HR), 1.81; 95% confidence interval (CI), 1.54–2.12, $p < 0.001$) and to a low risk for mortality in ventilated patients (HR, 0.51; 95% CI, 0.38–0.68; $p < 0.001$) [29,30].

A cohort study involving seven bundle components for VAP prevention presented that the daily sedation interruption and the management of breathing patterns in order to attempt to discourage mechanical ventilation support showed a reduction in VAP rates (from 8.6 per 1,000 days to 2.0 per 1,000 days ($p < 0.0001$). However, there was no change in the mean mechanical ventilation time (6.8 ± 9.0 days *vs*. 6.9 ± 14.1 days, $p = 0.78$) [31]. A case-control study with 535 patients achieved suitable results after the team education as a decreased PAV incidence rate from 21.6 to 11.6 per 1,000 days of ventilation, a lower mean ICU stay from 36 to 27 days, and a lower value of mechanically ventilated days from 26 to 21 days [32]. As well, the PAV incidence before and after educational workshops was 22.0 *vs.* 17.2. The linear regression model demonstrated a reduction of 55.83% in the VAP rate at the end of the study time interval [33].

Concerning oral hygiene, biofilm formation in critical patients can worsen their health status. Several studies demonstrated intense colonization in the oropharynx after 48 hours of patient admission, mainly in those with endotracheal tube [34]. Previous papers reported the presence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Streptococcus pneumoniae* in hospital patients, which differed from normal buccal microbiota [35].

A retrospective cohort study was performed for investigating four bundle components for VAP prevention in mechanically ventilated adults and found that oral care using chlorhexidine decreased the ventilator-associated events (HR, 0.44; 95% CI, 0.26-0.77, $p < 0.05$) [36,37]. However, only one paper demonstrated dissimilar results, in which oral care using chlorhexidine was associated with an increased risk of mortality in ventilated patients (HR, 1.63; 95% CI, 1.15-2.31; $p = 0.006$) [11]. A cohort study including nine bundle components for VAP prevention revealed that the highest team adherence was observed for oral hygiene. This procedure when added to other performed care as daily sedation interruption achieved a significant reduction in VAP ($\chi^2 = 9.16$, $p = 0.0103$) [38,39].

Endotracheal tube (ETT) cuff pressure is one of the main components of the VAP prevention package due to this procedure avoids the secretion spread from the upper airways to the lower airways and lungs [40,41]. Therefore, it is recommended that the inflated cuff pressure remains between 20 and 25 mmHg and should be checked every 4 hours. Excessive pressure can compromise the tracheal mucosa microcirculation and can cause ischemic lesions. However, if the pressure is lacking, a ventilation problem with positive pressure can occur and leakage of subglottic secretion between the tube and the trachea can arise [42,43]. According to a non-controlled clinical trial, the VAP incidence rate reduced from 18.6 ± 7.8 per 1,000 days of ventilation (95% CI 8.7–14.9) to 11.8 ± 7.8 per 1,000 days of ventilation (95% CI 15.5–21.7) ($p = 0.002$) before and after an educational module for VAP prevention, respectively. In brief, this intervention consisted of a daily bundle checklist, daily oral care, and measurements at least twice a day of the ETT cuff pressure that was kept between 20 and 30 cm H_2O [44].

Critically ill patients with respiratory problems have a high risk of presenting venous thromboembolism (VTE) and consequently account for more days spent in mechanical ventilation, ICU stays, and hospitalization [45]. A retrospective study based on prediction scores found that 65.2% of patients did not receive suitable coagulation prophylaxis ($p < 0.001$). Hence, it was concluded that coagulation prophylaxis is underused in hospital patients with pulmonary diseases by taking into consideration the scoring system used [46,47]. Severe patients, mechanical ventilation, and medications such as sedatives were the main risk factors that contributed to the high risk of VTE.

Conclusions

In summary, this systematic review identified that the care bundle implementation was suitable for preventing VAP incidence in adults and the elderly. The success of the care bundle on VAP prevention demanded three key points: (a) regular training of health professionals, (b) teamwork, and (c) continuous feedback. Moreover, the VAP bundle implementation and maintenance required the regular effort of all ICU staff. In this context, the results demonstrated that the training ensured high adherence to the ICU care protocols and suitable prevention of the VAP incidence as evidenced by the decrease in both the ICU days and the mechanical ventilation days.

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Authors’ Contributions

MDRG and ECAR: the work conception and the systematic review planning. RGM and MDRG: searched the literature in the chosen databases and performed the data extraction. ECAR and LPAC: data collection. MDRG and FAS: data analysis and interpretation. PVF and JMN: elaborated the manuscript and provided insights on discussion topics. PVF and JMN: English editing. FAS and RGM: the manuscript critical revision. All authors discussed the results and contributed to the final manuscript.

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