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Review Article

Effectiveness of a Ventilator Care Bundle to Prevent Ventilator-Associated Pneumonia at the PICU: A Systematic Review and Meta-Analysis

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Objectives: Ventilator-associated pneumonia is one of the most frequent hospital-acquired infections in mechanically ventilated children. We reviewed the literature on the effectiveness of ventilator care bundles in critically ill children.

Data Sources: Embase, Medline OvidSP, Web-of-Science, Cochrane Library, and PubMed were searched from January 1990 until April 2017.

Study Selection: Studies were included if they met the following criteria: 1) implementation of a ventilator care bundle in PICU setting; 2) quality improvement or multicomponent approach with the (primary) objective to lower the ventilator-associated pneumonia rate (expressed as ventilator-associated pneumonia episodes/1,000 ventilator days); and 3) made a comparison, for example, with or without ventilator care bundle, using an experimental randomized or nonrandomized study design, or an interrupted-times series. Exclusion criteria were (systematic) reviews, guidelines, descriptive studies, editorials, or poster publications.

Data Extraction: The following data were collected from each study: design, setting, patient characteristics (if available), number of ventilator-associated pneumonia per 1,000 ventilator days, ventilator-associated pneumonia definitions used, elements of the ventilator care bundle, and implementation strategy. Ambiguities about data extraction were resolved after discussion and consulting a third reviewer (M.N., E.I.) when necessary. We quantitatively pooled the results of individual studies, where suitable. The primary outcome, reduction in ventilator-associated pneumonia per 1,000 ventilator days, was expressed as an incidence risk ratio with a 95% CI. All data for meta-analysis were pooled by using a DerSimonian and Laird random effect model.

Data Synthesis: Eleven articles were included. The median ventilator-associated pneumonia incidence decreased from 9.8 (interquartile range, 5.8–18.5) per 1,000 ventilator days to 4.6 (interquartile range, 1.2–8.6) per 1,000 ventilator days after implementation of a ventilator care bundle. The meta-analysis showed that the implementation of a ventilator care bundle resulted in significantly reduced ventilator-associated pneumonia incidences (incidence risk ratio = 0.45; 95% CI, 0.33–0.60; $p < 0.0001$; $I^2 = 55\%$).

Conclusions: Implementation of a ventilator-associated pneumonia bundle has the potential to reduce the prevalence of ventilator-associated pneumonia in mechanically ventilated children. (*Pediatr Crit Care Med* 2019; 20:474–480)

Key Words: care bundle; children; evidence-based practice; implementation; pediatric intensive care; ventilator-associated pneumonia

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Ventilator-associated pneumonia (VAP) is one of the most frequent hospital-acquired infections in mechanically ventilated patients in critical care settings (1). VAP manifests in two ways: colonization of the respiratory and digestive tracts or microaspiration of secretions of the upper and lower parts of the airway. As the stomach may be a reservoir for bacteria, aspiration is a potential cause for VAP. This nosocomial infection is associated with prolonged mechanical ventilation and hospital stay, increased use of broad-spectrum antibiotics,

increased morbidity and considerable healthcare costs (2–4). The National Nosocomial Infections Surveillance (NNIS) System Report mentioned a pooled mean incidence of 2.9 VAP per 1,000 ventilator days in adults ICUs in the United States versus 7.9 in Latin America, Asia, Africa, and Europe (5, 6). The reported incidence of VAP in the PICU setting ranges from 2.9 to 11.6 VAP per 1,000 ventilator days (3). Risk factors for VAP in this setting include genetic syndromes, steroid use, reintubation or self-extubation, bloodstream infection, prior antibiotic therapy, and bronchoscopy (7). What are known as "care bundles" are emerging in healthcare quality improvement (8). These comprise a set of evidence-based clinical practices to improve patient outcomes—implemented as a single intervention (9, 10). In the "100,000 Lives Campaign" four key components of the ventilator care bundle (VCB) with pediatric modifications are described: 1) elevation of the head of the bed to between 15–30° for neonates and 15–30° for neonates and 30–45° for infants or older children; 2) daily assessment of readiness to extubate; 3) peptic ulcer disease prophylaxis (unless contraindicated); and 4) deep venous thrombosis prophylaxis, unless contraindicated (11). Additional interventions described in the literature include staff education and good hand hygiene among other things (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/A880) (3, 12, 13). A pediatric modification is the advice against "sedation vacation" in view of the high risk of accidental extubation in young children.

Although implementation of a VCB has shown to be an effective preventive strategy to decrease the incidence of VAP in the adult intensive care, evidence for the efficacy of these strategies in the PICU setting is lacking (3, 12, 13). With this systematic review and meta-analysis, we aimed to assess to what extent the VCB is effective in reducing the VAP rate in the PICU setting.

METHODS

This systematic review and meta-analysis were performed according to the guidelines on reporting systematic reviews as described in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (14).

Literature Search Methodology

We searched in the PubMed, Embase, Medline, OvidSP, Web-of-Science, Cochrane, and Google Scholar databases for relevant studies published from January 1990 until April 2017. The search terms included "VAP," "bundle," "prevention and control," and "pediatric." An information specialist devised and executed the search strategy; the full search strategy is presented in **Supplemental File 1** (Supplemental Digital Content 2, http://links.lww.com/PCC/A881). No limitations were imposed on language, country, study design methodology, or patient characteristics.

Study Selection

Studies that met the following criteria were included: 1) implementation of a VCB in PICU setting; 2) quality improvement or multicomponent approach with the primary objective to lower the VAP rate (expressed as VAP episodes/1,000 ventilator days); and 3) made a comparison, for example, with or without VCB, using an experimental randomized or nonrandomized study design, or an interrupted-times series. Excluded were (systematic) reviews, guidelines, descriptive studies, editorials, or poster publications. The titles and abstracts of the retrieved citations were screened on eligibility on the basis of these criteria.

This selection was followed by full-text review. All identified records were independently reviewed for relevance by two investigators (M.N., L.B., S.D., P.R.-J., A.V., E.I.); disagreement was solved by discussion (M.N., E.I.). We included one article in Spanish, which was translated into Dutch by a Spanish-speaking nurse.

Outcome Measures

The primary outcome of this study was the difference in incidence rate of VAPs per 1,000 days of ventilation before-and-after the implementation of a VCB. Secondary outcomes were compliance to the VCB and applied implementation strategies. Compliance was defined as the percentage of intensive care patients on mechanical ventilation for whom all components of the VCB were documented on daily goals sheets and/or another place in the medical record.

Data Extraction

The following data were collected from each study: design, setting, patient characteristics (if available), number of VAP per 1,000 ventilator days, VAP definitions used, components of the VCB, and implementation strategy. Ambiguities about data extraction were resolved after discussion and consulting a third reviewer (M.N., E.I.) when necessary. Extracted data were sent to the corresponding author of the original article with the requests to verify whether the data were extracted correctly and, if needed, to provide missing information.

Quality Assessment

The methodological quality of the studies was assessed with the 27-item scoring system of Downs and Black (15). Scores below 12 were considered to reflect low quality; scores 12 and 13 moderate quality; and score of 14 high or higher quality (15). Level of quality was no exclusion criterion.

Statistical Analysis

Study characteristics are summarized as frequencies and percentages. We quantitatively pooled the results of individual studies on the basis of the number of VAPs and number of ventilation days described in the original study or provided by the authors. In case of multiple study periods, for example, intervention period, we used data of the preintervention period and the postintervention period. The primary outcome, difference in incidence of VAPs per 1,000 ventilator days, was expressed as an incidence risk ratio (IRR) with a 95% CI. All data for meta-analysis were pooled by using a DerSimonian and Laird (16) random effect model. The heterogeneity among studies was tested using the Cochrane Q test and the inconsistency index (I^2). Heterogeneity was categorized as low (I^2 = 25–50%), moderate (I^2 = 50–75%), or high ($I^2 > 75\%$) (17). We did subgroup analysis for studies of low/middle income versus high-income

TABLE 1. Study Characteristics and Ventilator-Associated Pneumonia Rates

References (Country)	Study Design	Responsible for Adjudicating VAP[a]	Site Characteristics		
			No. of Beds	Patients Pre	Patients Post
Babcock et al (20) (United States)	Pre- and postinterventional study	1 + 2	Four hospitals including a 26-bed PICU	NA	NA
Bigham et al (2) (United States)	Pre- and postinterventional study	2	Twenty-five bed PICU	*n* = 617; age: 74.1 mo (80.6 mo)[c]	*n* = 1,782; age: 81.5 mo (82.4 mo)[c]
De Cristofano et al (21) (Argentina)	Quasi experimental time series study	1 + 2 + 3	One PICU, developing country	*n* = 348	*n* = 365
Esteban et al (22) (Spain)	Pre- and postinterventional study	2	Fourteen-bed PICU	*n* = 851; age: 70.9 mo (73.5 mo)[c]	*n* = 851; age: 64.2 mo (71.3 mo)[c]
Gan et al (23) (Malaysia)	Pre- and postinterventional study	1 + 2	One PICU	NA	NA
Gurskis et al (24) (Lithuania)	Pre- and postinterventional study	1	Three PICUs	*n* = 270; age: 4.01 yr (10.0 yr)[d]	*n* = 322; age: 3.74 yr (11.26 yr)[d]
Hernández-Orozco et al (25) (Mexico)	Pre- and postinterventional study	1 + 2	One PICU	NA	NA
Hill (26) (United Kingdom)	Pre- and postinterventional study	1	One PICU	NA	NA
Muszynski et al (27) (United States)	Pre- and postinterventional study	1 + 3	Thirty-bed PICU	*n* = 338; age: 18.8 mo (3.6–109 mo)[d]	*n* = 387; age: 27.8 mo (5.2–144 mo)[d]
Peña-López et al (28) (Spain)	Pre- and postinterventional study	1	Sixteen-bed PICU	*n* = 95; age: 2.9 yr (4.2 yr)[c]	*n* = 108; age: 4.0 yr (5.1 yr)[c]
Rosenthal et al (29) (Colombia, El Salvador, India, the Philippines, and Turkey)	Pre- and postinterventional study	1 + 2	Eight PICUs in five developing countries	*n* = 1,272; age: 7 mo	*n* = 3,067; age: 21.1 mo (range. 7–52; SD, 15.1)

NA = not available, VAP = ventilator-associated pneumonia.
[a]1: PICU team; 2: infection control team; and 3: respiratory care team.
[b]Incidence of VAP/1,000 ventilation days.
[c]Mean (SD) and
[d]median (interquartile range).

countries. Funnel plots were constructed as a visual aid to detect publication bias. A symmetric funnel arises from a well-balanced dataset; an asymmetric plot suggests publication bias (18, 19). Results with two-sided *p* values of less than 0.05 were considered statistically significant. Analyses were performed with Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA) and IBM SPSS 22.0 (Armonk, NY).

RESULTS

The literature search identified 839 studies. Screening of titles and abstracts resulted in the exclusion of 515 duplicates and 479 ineligible studies. We read the full text of the remaining 39 studies (**Supplemental Fig. 1**, Supplemental Digital Content 3, http://links.lww.com/PCC/A882; legend: search results). Eleven of these, involving 20 PICUs, met the eligibility criteria. Ten studies were pre- and postinterventional studies, one study had an interrupted time series study design (2, 20–29). Two studies were multicenter studies (24, 29). Nine (82%) corresponding authors returned the data abstraction form with approval or provided supplemental or missing data (**Table 1**).

All included studies were of moderate to good methodological quality. The Downs and Black score ranged from 10 to 20, with a median of 18.5 (interquartile range [IQR], 16.0–19.0)

Preintervention Period			Postintervention Period				
Observation Time	*n*	VAP Rate[b]	Observation Time	*n*	VAP Rate[b]	*p*	Quality Score
12 mo	NA	7.9	18 mo	NA	4.9	< 0.001	22
12 mo	617	5.6	28 mo	1,782	0.3	< 0.0001	22
24 mo	348	6.3	24 mo	365	2.4	0.005	16
12 mo	851	28.3	12 mo	822	10.6	0.005	23
3	NA	15.6	18 mo	NA	13.2		17
12 mo	270	21.8	12 mo	322	8.8	0.05	20
12 mo	NA	13.85	24 mo	NA	4.3	0.009	15
12 mo		19.5	24 mo		7.6	NA	15
14 mo	338	3.9	19 mo	387	1.8	0.04	21
12 mo	95	4.14	12 mo	108	1.05	0.088	19
NA	1,272	11.7	NA	3,067	8.1	0.029	18

(**Supplemental Table 2**, Supplemental Digital Content 4, http://links.lww.com/PCC/A883).

In all studies, VAP was defined in accordance with criteria established by the Centers for Disease Control and Prevention (CDC), sometimes supplemented by other criteria (such as the NNIS System [30]). The teams that made the diagnosis VAP consisted of representatives of different professions, such as epidemiologists, physician on duty, investigators, or "infection committees" of which the composition was not always clear.

Elevation of the head of the bed, daily assessment readiness to extubate, oral hygiene, and hand hygiene were the most represented components of the VCB. Hill and Muszynski (26, 27) added peptic ulcer prophylaxis to the VCB. Babcock and Gurskis added the avoidance of peptic ulcer prophylaxis to the VCB (**Supplemental Table 3**, Supplemental Digital Content 5, http://links.lww.com/PCC/A884) (20, 24).

Outcomes

The baseline VAP incidence ranged from 3.9 to 28.3 per 1,000 ventilator days (median, 9.8; IQR, 5.8–18.5) and decreased to a median of 4.6 (IQR, 1.2–8.6) per 1,000 ventilator days with a range of 0.3–13.2 after implementation of the VCB (Table 1).

All 11 studies were included in the meta-analysis. Overall, the pooled IRR was consistent with effectiveness of the

implementation of a VCB in reducing the VAP incidences (IRR = 0.45; 95% CI, 0.33–0.60; $p < 0.0001$; $I^2 = 55\%$) (**Fig. 1**). The risk reduction in studies of low-income and middle-income countries ($n = 5$; IRR = 0.48; 95% CI, 0.30–0.78) did not significantly differ from that in studies of high-income countries ($n = 6$; IRR = 0.40; 95% CI, 0.26–0.63; $p = 0.56$). The funnel plot showed asymmetry suggesting reporting bias, in all probability, caused by heterogeneity due to the inclusion of small studies with large effects and large studies with small effects (**Supplemental Fig. 2**, Supplemental Digital Content 6, http://links.lww.com/PCC/A885).

Compliance and Implementation Strategies

Only two studies described the compliance with all parts of the VCB (2, 21). Three studies did not describe compliance rates (20, 24, 28). Compliance was described in part in half of the studies (**Supplemental Table 4**, Supplemental Digital Content 7, http://links.lww.com/PCC/A886) (22, 23, 25–27, 29). Described compliance rates were high for the head of bed elevation (seven studies, median 99%, IQR, 95–100%). Low compliance was reported with interruption of sedatives and the assessment of readiness to extubate. Babcock et al (20) defined compliance as the percentage of staff that completed the education module.

The most used implementation strategies were education (83%), performance feedback (58%), and debriefing and result feedback (67%) The median number of implementation strategies per study was 4.0 (IQR, 2.5–5.0) (Supplemental Table 4, Supplemental Digital Content 7, http://links.lww.com/PCC/A886).

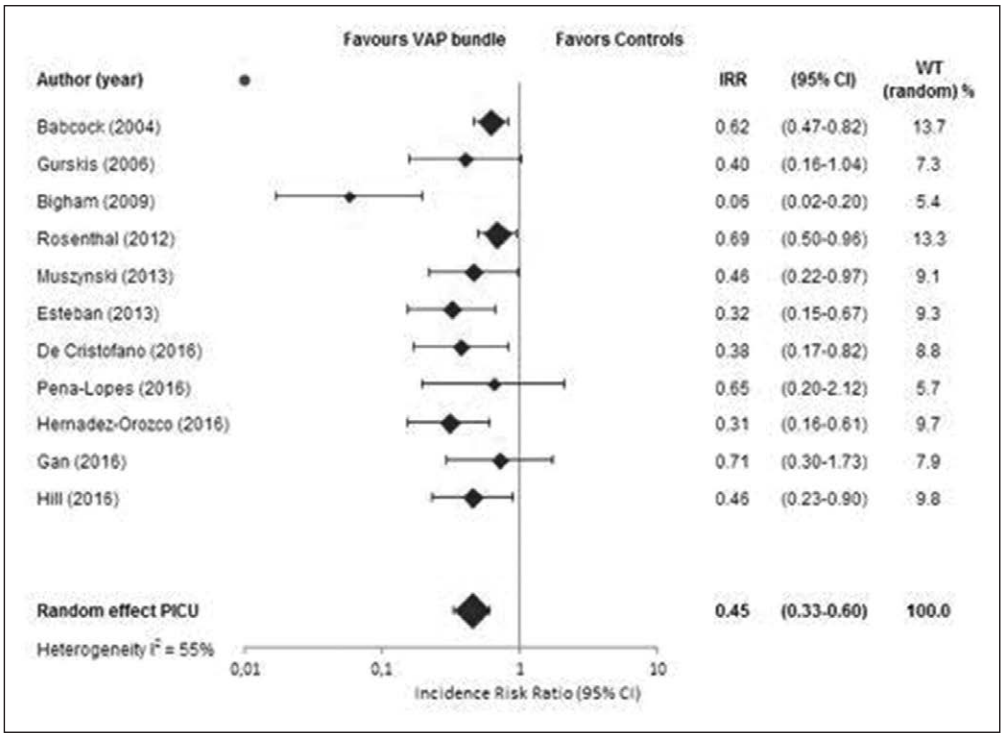

Figure 1. Forest plot for the effectiveness of a ventilator care bundle in the PICU.

DISCUSSION

This systematic review and meta-analysis demonstrate that the implementation of a VCB can help reduce the incidence of VAPs in critically ill children. This finding is in line with similar studies in adults (12, 13). The VCBs studied consists of quality improvement interventions for which the evidence separately is low to average; strength is provided by the synergy of the separate components. The VCB developed by the Institute for Healthcare Improvement (IHI) has five components. First, elevation of the head of the bed, which was included in all studies in this review. Second, to determine readiness for extubation. Although the IHI does not recommend daily interruption of sedation in pediatrics due to high risk of accidental extubation, Vet et al (31) found no safety issues during daily sedation interruption. Further, daily interruption of sedation in addition to protocolized sedation did not improve clinical outcomes (31). Third, prevention of peptic ulcer disease. The use of this component differed between the included studies. Two studies had a component avoidance of peptic ulcer prophylaxis; two studies included peptic ulcer prophylaxis in the VCB; and four studies did not use peptic ulcer prophylaxis, without explanation (Table 1). Peptic ulcer prophylactics (H2 antagonists and antacids) raise the gastric pH and may increase colonization with pathogenic organisms and therefore increase the risk of VAP. In adults, the use of sucralfate as peptic ulcer prophylaxis, which does not alter the gastric pH, was associated with a significant reduction in the incidence of VAP compared with the use of H2 antagonists (7, 32). A recent study of Albert et al (33) found a significant increase of VAP rates with the use of the use of acid-suppressive medication (odds ratio, 2.0; 95% CI, 1.2–3.6; $p = 0.011$). Fourth, to prevent deep venous thrombosis prophylaxis (unless contra-indicated). The IHI does not recommend this for use in children (11). One study included in this review made use of deep venous thrombosis prophylaxis as a component of the VCB (26). Last, oral care with chlorhexidine as a preventive measure was added in 2012. In all studies this intervention was applied, but with different concentrations of chlorhexidine (0.1–2%).

Overall, the evidence of the different VCB components in pediatrics is scarce. Further, given the heterogeneity in the VCB components used we were unable to identify components that affect the effectiveness of the bundle. A recent meta-analysis showed that ventilator bundles are indeed beneficial in adult ICU

patients. The implementation of a VCB was associated with a 10% relative reduction in mortality (34). Also, a combination of the bundle components elevation of head of bed, daily assessment of readiness to extubate, daily oral care, and sedation vacation was found the most beneficial (34). The optimal composition of the bundle is not known (32).

Compliance is highly important for the VCB to be successful. A well-thought-out implementation plan, with an important role for education and the use of checklists, is essential to achieve good compliance. Achieving compliance with evidence-based interventions and bundles is still a challenge in healthcare (35). It requires changes in healthcare professionals' behavior, education, and training, which in this review were the most frequently applied strategies. Gaining insight in all influencing factors (e.g., human behavioral, organizational, provider characteristics) is a crucial first step to develop strategies, which are more effective than the "one size fits all" strategy. Further, quality improvement and implementation will be more successful with understanding of the complexity of the innovation and a setting's culture (36, 37). Ongoing attention must be given to sustaining compliance and the positive effects in the post-implementation phase. It is equally important to pay attention to compliance with the separate components; this gives information about compliance failure and changes for improvement (10, 38).

VAP is associated with high costs. Economic studies described that the additional healthcare costs of an ICU-patient with VAP were 1.66–2.9 times higher than those of a patient without VAP (39). For PICU patients, additional costs of $ 50,000 for each event have been described (4). The results of our study should be interpreted with respect to the following limitations. First, a methodological and clinical heterogeneity were present as the result of a moderate variability in bundle compositions. To account for these variations, data were analyzed with a random-effects model rather than a fixed effects model (40). Second, studies differed with regard to setting (developing vs nondeveloping countries), study design, characteristics of the population, and baseline measurements. None of the trials had a randomized or controlled study design. Most studies applied a before-and-after design, which is a weaker model prone to bias by secular trends and overestimation of the true effect of the VCB (41, 42). These studies should have reported the proportion of ventilated patients and duration of ventilation of the study population because the higher the proportion and the shorter the duration, the greater the probability of effect overestimation. Additionally, analysis of IRR in these studies was based on crude estimates of infections, which could have resulted in an overestimation of treatment effects. Third, the researchers did not succeed in getting a full basic description of the study population from all studies. This limits the generalizability of the results. Last, a major problem in investigating VAP is the absence of an accepted definition and the lack of an accurate diagnostic test for VAP. The CDC identified a number of criteria on which the diagnosis is made; some of these seem subjective and nonspecific (43). For example, criteria such as "apnea" or "coughing" are hard to apply to a mechanically ventilated patient. Further, the definitions varied in the studies, because the CDC criteria for VAP have been changed over time. This could have affected the VAP incidence, but criteria used within the studies were similar.

The CDC recently concluded the VAP definition was not valid, not reliable and included subjective elements. For adult locations, a new VAP surveillance approach was proposed, the ventilator-associated event (VAE).

VAE is a collective name for a broader range of VAEs: ventilator-associated condition, infection-related ventilator-associated condition, possible pneumonia, and probable pneumonia. VAE are defined as a combination of objective criteria: deterioration in respiratory status after a period of stability or improvement on the ventilator, evidence of infection or inflammation, and laboratory evidence of respiratory infection (44, 45) Research for the use of VAE definitions in a pediatric population is upcoming (46–48). At the time of this systematic review, research to identify ventilator-associated infections made use of VAP definitions.

CONCLUSIONS

The results of this systematic review and meta-analysis suggest that the implementation of a VAP bundle in PICU patients has the potential to prevent VAP. Still, as all but one study used a before-after design, the results of the meta-analysis should be interpreted with caution. For research purposes, it would be interesting to explore which elements of the VCB are most effective and which implementation strategies in combination with education would increase compliance with the bundle in daily practice.

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