Bundles to prevent ventilator-associated pneumonia: how valuable are they?
Charity Wip and Lena Napolitano

Introduction
Ventilator-associated pneumonia (VAP) is a common nosocomial infection in critically ill patients that is associated with poor clinical and economic outcomes, including longer duration of mechanical ventilation, longer ICU and hospital stay, increased mortality, and increased hospital charges [1–3]. It is the leading cause of death among nosocomial infections, exceeding rates of death secondary to central line infections, severe sepsis, and respiratory tract infections in nonintubated patients. The impact of VAP on our healthcare systems is considerable, with estimates that VAP accounts for approximately 17,000 ICU days per year (2% of all ICU days) and 46 million dollars per year in the Canadian healthcare system [4*]. Eradication of this preventable nosocomial infection would save lives and conserve scarce health-care resources. Given these findings, strategies that effectively prevent VAP are urgently needed, and streamlined methods for universal implementation are necessary.

Ventilator-associated pneumonia prevention guidelines
VAP is preventable, and many practices have been demonstrated to reduce the incidence of VAP and its associated burden of illness. We should therefore first review the published evidence-based guidelines for VAP prevention. The Canadian Critical Care Trials group initially published comprehensive evidence-based clinical practice guidelines for VAP prevention in 2004, with an update published in 2008 [5**]. Table 1 provides the summary of recommendations for VAP prevention from this group.
The Centers for Disease Control (CDC) guidelines for preventing healthcare-associated pneumonia provide recommendations of the CDC and the Healthcare Infection Control Practices Advisory Committee, updated from the previously published guideline in 1997 [6,7].

**Bundles**

Bundles are a method used to implement evidence-based clinical practice guidelines. Bundles are a grouping of best practices that, when used individually, are found to be effective. The Institute for Healthcare Improvement (IHI) advocated the use of bundles, defined as ‘a small, straightforward set of practices – generally three to five – that, when performed collectively and reliably, have been proven to improve patient outcomes’ [8]. The IHI developed the ‘Ventilator Bundle’ consisting of four evidence-based practices to improve the outcomes of patients requiring mechanical ventilation and provided the methodology for bundle implementation and measurement of compliance. The Ventilator Bundle components are as follows:

1. Elevation of the head of the bed to 30–45°.
2. Daily ‘sedation vacation’ and daily assessment of readiness to extubate.
3. Peptic ulcer disease prophylaxis.

When hospitals using the IHI Ventilator Bundle saw significant reductions in VAP rates, it was promoted as a tool for VAP prevention. Many institutions have modified the IHI Ventilator Bundle and call it the ‘VAP Bundle’.

Although the IHI has published positive results of Ventilator Bundle implementation and VAP prevention from specific ICU teams on their website, a recent systematic literature review on the effectiveness of the IHI Ventilator Bundle to prevent VAP revealed major methodologic flaws in the design, reporting, and results of the four published studies (Table 2) that were reviewed [9**]. The methodologic flaws of the studies included bias, confounding, and lack of generalizability and precluded any conclusive statements about the bundle’s effectiveness or cost-effectiveness. These authors concluded that, to ensure efficient allocation of the limited healthcare resources, rigorous evaluation of optimal strategies for VAP prevention is needed to establish best practices and create a benchmark against which new technologies’ value can be assessed. The Ventilator Bundle is not a viable quality measure in the ICU at this time.

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**Table 1 Summary of recommendations for ventilator-associated pneumonia prevention**

<table>
<thead>
<tr>
<th>Physical strategies</th>
<th>Pharmacological strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of endotracheal intubation</td>
<td>We recommend that the orotracheal route of intubation should be used when intubation is necessary</td>
</tr>
<tr>
<td>Systematic search for maxillary sinusitis</td>
<td>We make no recommendation</td>
</tr>
<tr>
<td>Frequency of ventilator circuit changes</td>
<td>We recommend new circuits for each patient, and changes if the circuits become soiled or damaged, but no scheduled ventilator circuit changes</td>
</tr>
<tr>
<td>Type of airway humidification</td>
<td>We make no recommendation</td>
</tr>
<tr>
<td>Frequency of change of airway humidification</td>
<td>We recommend changes of heat and moisture exchangers with each patient every 5–7 days and as clinically indicated</td>
</tr>
<tr>
<td>Type of endotracheal suctioning system (open vs. closed)</td>
<td>We recommend the use of closed endotracheal suctioning system</td>
</tr>
<tr>
<td>Frequency of change of endotracheal suctioning system</td>
<td>We recommend that closed endotracheal suctioning system should be changed for each patient and as clinically indicated</td>
</tr>
<tr>
<td>Subglottic secretion drainage</td>
<td>We recommend the use of subglottic secretion drainage in patients expected to be mechanically ventilated for &gt;72 h.</td>
</tr>
<tr>
<td>Timing of tracheostomy</td>
<td>We make no recommendation</td>
</tr>
<tr>
<td>Bacterial filters</td>
<td>We do not recommend</td>
</tr>
<tr>
<td>Positional strategies</td>
<td>The use of rotating beds should be considered</td>
</tr>
<tr>
<td>Rotating beds</td>
<td>We recommend that the head of the bed should be elevated to 45°. When this is not possible, attempts to raise the head of the bed as much as possible should be considered</td>
</tr>
<tr>
<td>Semirecumbent positioning</td>
<td>We make no recommendation</td>
</tr>
<tr>
<td>Prone positioning</td>
<td>We make no recommendation</td>
</tr>
<tr>
<td>Prophylactic antibiotics</td>
<td>We make no recommendation</td>
</tr>
<tr>
<td>Aerosolized antibiotics</td>
<td>We make no recommendation</td>
</tr>
<tr>
<td>Nasal antibiotics</td>
<td>We make no recommendation</td>
</tr>
<tr>
<td>Intravenous antibiotics alone</td>
<td>We make no recommendation</td>
</tr>
<tr>
<td>Topical/topical and intravenous antibiotics</td>
<td>We make no recommendation</td>
</tr>
<tr>
<td>Oral antiseptic</td>
<td>The use of the oral antiseptic, chlorhexidine, should be considered</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>The use of the oral antiseptic, povidone–iodine, should be considered in patients with severe head injury</td>
</tr>
<tr>
<td>Povidone–iodine</td>
<td>We do not recommend</td>
</tr>
<tr>
<td>Iseganan</td>
<td>We make no recommendation</td>
</tr>
</tbody>
</table>

Adapted with permission from [5**].
Evidence supporting Ventilator Bundle components

It is important to review the level of evidence supporting each of the Ventilator Bundle components recommended by the IHI.

Elevation of the head of the bed to 30–45°

The semirecumbent position, achieved by elevation of the head of the bed, is an integral portion of the VAP bundle. It has been speculated that the semirecumbent position may decrease VAP by reduction in gastroesophageal reflux and subsequent aspiration of gastrointestinal, oropharyngeal, and nasopharyngeal secretions.

Which studies have demonstrated reductions in VAP associated with the semirecumbent position? Drakulovic et al. [14] reported the results of a randomized trial of supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients. Patients from one medical and one respiratory ICU at a tertiary care university hospital were randomized to the ‘semi-recumbent’ (n = 39) or ‘supine’ (n = 47) body position (supine was complete horizontal position, 0°). The frequency of clinically suspected and microbiologically confirmed nosocomial pneumonia (clinical and quantitative bacteriological criteria) was assessed in both groups. Body position was analyzed together with known risk factors for nosocomial pneumonia. The frequency of ‘clinically suspected’ (on the basis of CDC criteria) nosocomial pneumonia was lower in the semirecumbent group than in the supine group [three of 39 patients (8%) vs. 16 of 47 patients (34%)]. This was also true for ‘microbiologically confirmed’ pneumonia. The frequency of clinically suspected pneumonia was 14/28 (50%). Mechanical ventilation for 7 days or more (OR 10.9, 95% CI 3.0–40.4, P = 0.001) and a Glasgow coma scale score of less than 9 were additional risk factors. The authors concluded that the semirecumbent position reduces the frequency and risk of nosocomial pneumonia, especially in patients who receive enteral nutrition. Interestingly, this study was terminated at a scheduled interim analysis after only 86 patients had been recruited. Mortality did not differ significantly between patients in the supine and those in the semirecumbent position.

Aspiration of colonized or infected oropharyngeal or gastrointestinal contents is a potential contributing cause of VAP, and evidence that aspiration of the gastric contents occurs to a greater degree when patients are in the supine position has been confirmed in clinical studies. In a randomized crossover trial of semirecumbent (backrest position at 45°) vs. supine position, gastric contents were labeled with technetium-99m sulphur colloid, and the radioactivity of endobronchial secretions was measured in mechanically ventilated patients [15]. Mean radioactive counts in endobronchial secretions were higher in samples obtained while patients were in the supine position. Furthermore, the same organisms were isolated from gastric juice, pharynx, and endobronchial samples from 68% of patients in the supine position compared with only 32% of patients in the semirecumbent position. Similar results were reported by Orozco-Levi et al. [16] in a randomized study of 15 patients in the supine or the semirecumbent position. Other studies have shown that the presence and size of the nasogastric tube also influence the frequency of aspiration, presumably by compromising the action of the lower esophageal sphincter [17].

In the study by Drakulovic et al. [14], patients allocated to the supine position were more likely to have a large-bore nasogastric tube in place and an ultimately fatal disease status and a higher Acute Physiology and Chronic Health Evaluation II score. Although for each of these variables, the differences between the groups did not reach statistical significance, all P values were less than 0.08. Combination of all these factors may have led to an
inadvertent bias in the patients assigned to the supine group.

Other important criticisms raised against this study were
the applicability of this intervention ‘in the real world’;
the lack of strict control of the 45° bed angle for patients
in the semirecumbent group (checked only once a day);
the exclusion of three patients in the semirecumbent
group due to protocol violation, implying that the analysis
was not conducted in an intention-to-treat fashion; and
the unusually high frequency of VAP in control patients
receiving enteral nutrition, which was largely responsible
for the significant difference observed in the study.

More recently, van Nieuwenhoven et al. [18] published
the results of a multicenter prospective trial of ICU
patients randomly assigned to receive mechanical venti-
lation in the semirecumbent position (with a target
backrest elevation of 45°) or in the supine position (with
initial backrest elevation set at 10°, the observed standard
care in their ICUs). The objectives of this study were
to assess the feasibility of the semirecumbent position in
mechanically ventilated ICU patients and determine,
in an intention-to-treat analysis, the effectiveness of
the measure in the prevention of microbiologically
proven VAP. Mean backrest elevation was measured
every minute by means of an ingenious system placed
on the bed frame consisting of a pendulum and a
transducer connected to a computer.

Importantly, the target semirecumbent position of 45°
was not achieved in 85% of the study time in the inter-
vention group, being only 28.1 and 22.6° on average at
days 1 and 7, respectively. This is similar to findings in
other studies, in which the semirecumbent position was
reached for only a minority (<30%) of mechanically
ventilated ICU patients, despite a comprehensive pro-
gram combining education of nurses and physicians and
the systematic addition of a standardized order for placing
patients in the 45° position [19]. On the contrary, mean
backrest elevation rose in the standard group (9.8 to 16.1°
from day 1 to 7). The other important result is that no
significant difference was detected regarding the second
major endpoint of the study, the incidence of microbio-
logically proven VAP, which was 6.5% in the supine
group and 10.7% in the semirecumbent group.

Diagnosis of VAP was made by quantitative cultures of
samples obtained by bronchoscopic techniques in this
study, whereas the prior study by Drakulovic et al. [14]
used clinical criteria and nonquantitative cultures. This
study also had a significantly larger sample size than the
prior study (n = 221). Despite these improvements,
there are a number of limitations of this study as well
[20]. The major problem with this study is that it does not
provide a definitive answer on the efficacy of semirecum-

bency because of a failure to reach the targeted 45°
backrest position in the intervention group. Another
limitation of the study is the erroneous hypothesis regard-
ing VAP incidence in the control group. On the basis of
previous data from their groups, they hypothesized a 25% 
VAP rate in the control group, whereas the observed rate
was less than 10%. This wrong assumption may have
markedly decreased the power of the study to detect a
significant difference between groups.

So what is the ideal head elevation for mechanically
ventilated patients that we should include in the VAP
bundle? Although there is strong evidence to suggest that
a strict 0° supine position is deleterious to patients placed
on mechanical ventilation, especially when they are being fed
by a nasogastric tube, this question remains unanswered.
Additional studies are warranted to compare the recom-
ended 30–45° semirecumbent position advocated in the
current Ventilator Bundle to a more feasible 10–30° semi-
recumbent position that may be achieved in our ICUs.

Daily ‘sedation vacation’ and daily assessment of
readiness to extubate

‘Sedation vacations’ are an integral component of the
VAP bundle and can have major implications in that
patients who are extubated early are at decreased risk
of VAP. Sedation vacations are daily scheduled interrup-
tions of sedation based on criteria. If patients meet these
criteria, their sedation is decreased or turned off in order
to assess whether extubation criteria are met. If criteria
are met, patients are extubated.

In many ICUs, patients are inconsistently evaluated for
extubation on the basis of subjective assessment by care-
takers. Many patients are therefore inadvertently left
intubated when they could have been extubated, thereby
increasing their risk of VAP. Schweickert et al. [21] evalu-
ated 128 mechanically ventilated patients receiving con-
tinuous sedative infusions. Patients were randomized to
either daily interruption of sedative infusions (n = 66) or
sedation directed by the medical ICU team without this
strategy (n = 60). Daily sedation interruptions reduced
ICU length of stay (6.2 vs. 9.9 days, P < 0.01), duration
of mechanical ventilation (4.8 vs. 7.3 days, P < 0.005), and
the incidence of complications.

Dries et al. [22] conducted a study in which they used a
standardized weaning protocol to study reduction in the
days of mechanical ventilation. They found that utilizing
this standard protocol, they reduced the number from
0.47 to 0.33 ventilator days/ICU days. They also found
that they had reduced rates of VAP (15% in control
patients vs. 5% in protocol patients).

The use of a peer network to facilitate implementation of
a standardized evidence-based spontaneous breathing
trial (SBT) protocol provided important information regarding this strategy [23]. Six medical, two surgical, and two combined medical/surgical adult ICUs among eight academic medical centers participated. Patients initiating mechanical ventilation through an endotracheal tube during a 12-week interval formed the study population. Adoption and implementation of a common SBT protocol across these ICUs was assessed. Seven hundred and five patients had 3486 safety screens for conducting a SBT; 2072 (59%) patients failed the safety screen. Another 379 (11%) patients failed a 2-min tolerance screen, and 1122 (34%) patients had a full 30–120 min SBT performed. Seventy percent of eligible patients were enrolled. Only 55% of passing SBTs resulted in liberation from mechanical ventilatory support before another SBT was performed. This study documented that peer networks can be effective in promoting and implementing evidence-based best practices. Implementation of a best practice (SBT) may be necessary for, but by itself insufficient to achieve, consistent and timely liberation from ventilator support.

Most recently, a protocol that pairs spontaneous awakening trials (SATs), with SBTs has been confirmed to be effective [24]. The Awakening and Breathing Controlled trial was a clinical trial in four tertiary care hospitals that randomly assigned 336 mechanically ventilated patients in the ICU to management with a daily SAT followed by an SBT or with sedation per usual care and a daily SBT. The primary endpoint was breathing without assistance. Patients in the intervention group spent more days breathing without assistance during the 28-day study period than those in the control group (14.7 vs. 11.6 days, mean difference 3.1 days, 95% CI 0.7–5.6, \( P = 0.02 \)) and were discharged from ICU (median time in ICU 9.1 vs. 12.9 days, \( P = 0.01 \)) and the hospital earlier (median time in the hospital 14.9 vs. 19.2 days, \( P = 0.04 \)). More patients in the intervention group self-extubated than in the control group (16 vs. six patients, 6.0% difference, 95% CI 0.6–11.8, \( P = 0.03 \)), but the number of patients who required reintubation after self-extubation was similar (five vs. three patients, 1.2% difference, 95% CI −5.2–2.5, \( P = 0.47 \)), as were total reintubation rates (13.8 vs. 12.5%, 1.3% difference, 95% CI −8.6–6.1%, \( P = 0.73 \)). At any instant during the year after enrolment, patients in the intervention group were less likely to die than patients in the control group (hazard ratio 0.68, 95% CI 0.50–0.92, \( P = 0.01 \)). For every seven patients treated with the intervention, one life was saved (number needed to treat was 7.4, 95% CI 4.2–35.5). These results suggest that a wake up and breathe protocol that pairs daily SATs (interruption of sedatives) with daily SBTs results in better outcomes for mechanically ventilated patients than current standard approaches and should become routine practice. On the basis of the evidence presented above, we suggest that this component of the ventilator bundle should be modified to advocate for daily SAT and SBT for all mechanically ventilated patients.

**Peptic ulcer disease prophylaxis**

Although included within the Ventilator Bundle, this is not a specific strategy for VAP prevention. It was included in the Ventilator Bundle as a strategy to prevent stress-related mucosal disease, as mechanical ventilation is a significant risk factor. A prospective multicenter cohort study evaluated potential risk factors for stress ulceration in ICU patients and documented the occurrence of clinically important gastrointestinal bleeding (defined as overt bleeding in association with hemodynamic compromise or the need for blood transfusion) [25]. Of 2252 patients, 33 (1.5%; 95% CI, 1.0–2.1) had clinically important bleeding. Two strong independent risk factors for bleeding were identified: respiratory failure (OR 15.6) and coagulopathy (OR 4.3). Of 847 patients who had one or both of these risk factors, 31 (3.7%, 95% CI 2.5–5.2) had clinically important bleeding. Of 1405 patients without these risk factors, two (0.1%; 95% CI 0.02–0.5) had clinically important bleeding. The mortality rate was 48.5% in the group with bleeding and 9.1% in the group without bleeding (\( P < 0.001 \)). In this study, coagulopathy and the need for mechanical ventilation were definitively identified as the two specific risk factors that warrant stress ulcer prophylaxis. On the basis of this evidence, this component of the Ventilator Bundle should be retained; however, it must be clearly noted that this is not related to VAP prevention.

**Deep venous thrombosis prophylaxis**

Sedated ventilated patients are at significantly increased risk for DVT. Hence, DVT prophylaxis is an important component of standard care of these patients. Similar to stress ulcer prophylaxis, DVT prophylaxis has not been demonstrated to reduce the risk of VAP. It remains part of the Ventilator Bundle in order to prevent other serious complications that could increase the morbidity and mortality of these patients and should be retained.

**Problems with ventilator-associated pneumonia bundles**

A number of studies have demonstrated the positive impact of implementation of the Ventilator Bundle or a modified VAP bundle on the reduction of VAP in ICUs. As stated earlier, many of these are difficult to interpret as they do not report bundle compliance rates, do not control for other specific VAP risk factors, and use the clinical definition of VAP [10,12,26,27]. Without a robust method to collect data on prevalence of VAP with all associated risk factors and specific VAP definitions [28], the impact of the care bundles on improving outcomes for this aspect of care is still unknown. Furthermore, the
quantification of the use of other practices to prevent VAP (chlorhexidine and subglottic secretion drainage) in the ICUs is not routinely performed in these quality improvement studies, and these concurrent efforts may have a substantial impact on the results [29].

**Potential additions to Ventilator Bundle**

Other evidence-based recommendations included in the VAP prevention clinical practice guideline, but not the bundle, may impart a greater magnitude of VAP prevention, including the importance of educational programs and other pharmacologic and physical strategies [30*,31,32]. Other effective evidence-based strategies for VAP prevention should therefore be considered in addition to the Ventilator Bundle or the development of a VAP bundle more specifically aimed at VAP prevention. Implementation of such expanded or revised VAP bundles has been associated with VAP reduction in published studies [33–35]. We advocate serious consideration of the following two additions to the Ventilator Bundle:

1. chlorhexidine antiseptic,
2. subglottic secretion drainage.

**Chlorhexidine antiseptic**

The use of the oral antiseptic chlorhexidine gluconate has been definitively demonstrated to be an effective VAP prevention strategy, and its use has been advocated in the most recent evidence-based VAP prevention clinical practice guidelines. Furthermore, safety, feasibility, and cost considerations for this intervention are all very favorable. A recent systematic review and meta-analysis evaluated the effect of oral decontamination on the incidence of VAP and mortality in mechanically ventilated adults. In seven trials with 2144 patients, oral application of antiseptics significantly reduced the incidence of VAP [relative risk (RR) 0.56, 95% CI 0.39–0.81] but was not associated with reduced mortality, duration of mechanical ventilation, or stay in the ICU [36**].

Another meta-analysis documented that topical chlorhexidine resulted in a reduced incidence of VAP (RR 0.74, 95% CI 0.56–0.96, P = 0.02) using a fixed effects model. Subgroup analysis showed that the benefit of chlorhexidine was most marked in cardiac surgery patients (RR 0.41, 95% CI 0.17–0.98, P = 0.04) [37**]. There was no mortality benefit with chlorhexidine although the sample size was small. This analysis showed that topical chlorhexidine is beneficial in preventing VAP; the benefit was most marked in cardiac surgery patients. Most recently, another randomized controlled trial documented that oral decontamination with 2% chlorhexidine solution is an effective and well tolerated method for preventing VAP in patients who receive mechanical ventilation (n = 207) [38*]. A large randomized trial is, however, needed to determine the impact of topical chlorhexidine on mortality.

Figure 1 Risk ratios of meta-analysis for overall ventilator-associated pneumonia, early-onset ventilator-associated pneumonia, and mortality

VAP, ventilator-associated pneumonia. Adapted from [39].
Subglottic secretion drainage
Continuous aspiration of subglottic secretions (CASS) has been demonstrated to be effective in the prevention of VAP. A recent meta-analysis, including five studies and 896 patients, confirmed that subglottic secretion drainage was effective in the prevention of early-onset VAP among patients expected to require more than 72-h duration of mechanical ventilation (Fig. 1) [39]. The recent VAP prevention guidelines advocate CASS use in patients expected to be mechanically ventilated for more than 72 h.

A recent randomized study (*n* = 714) was performed on cardiac surgery patients [40**]. In patients who had received mechanical ventilation for more than 48 h, the comparisons of CASS patients and control individuals were as follows: VAP incidence, 26.7 vs. 47.5% (*P* < 0.04); incidence density, 31.5 vs. 51.6 episodes per 1000 days of mechanical ventilation (*P* = 0.03); median length of ICU stay, 7 vs. 16.5 days (*P* = 0.01); hospital antibiotic use, 1206 vs. 1877 defined daily dose (DDD) (*P* < 0.001); and overall mortality rate, 44.4 vs. 52.5% (*P* = 0.3), respectively. Reintubation increased the risk of VAP (RR 6.07, 95% CI 2.20–16.60, *P* < 0.001), whereas CASS was the only significant protective factor (RR 0.40, 95% CI 0.16–0.99, *P* = 0.04). No complications related to CASS were observed. The cost of the CASS tube was 9 euro compared with 1.5 euro for the conventional tube. The authors concluded that CASS is a well tolerated procedure that reduced the use of antimicrobial agents in the overall population and the incidence of VAP in patients who are at risk.

Conclusion
VAP represents a large percentage of ICU-acquired infections and is associated with significant antibiotic utilization in the ICU and substantial morbidity, mortality, and costs. VAP cases are potentially preventable. The Ventilator Bundle has been an effective intervention for VAP prevention in some institutions. Information from evidence-based VAP prevention guidelines suggests that the Ventilator Bundle should be modified to include additional effective VAP preventive strategies or a specific VAP bundle created to focus on VAP prevention.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
** of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 206).


28 Berton DC, Kall DC, Cavalcanti M, Teixeira PJ. Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator-associated pneumonia. Cochrane Database Syst Rev 2008:CD006482. Systematic review of published data regarding the use of quantitative vs. qualitative cultures to make a diagnosis of VAP, but only three studies compared invasive vs. noninvasive methods.


38 Tantipong H, Mokchareonpong C, Jayinda S, Thamlikitkul V. Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia. Infect Control Hosp Epidemiol 2008; 29:131–136. Most recent study of topical chlorhexidine in posterior pharynx for VAP prevention demonstrating that it was effective and its addition to meta-analysis of all prior studies.
