

Prevention of ventilator-associated pneumonia

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Michael Klompas

Infection Control Department,
Brigham and Women's Hospital,
Boston, MA 02115, USA
and
Department of Population Medicine,
Harvard Medical School and Harvard
Pilgrim Health Care Institute,
133 Brookline Avenue, 6th Floor,
Boston, MA 02115, USA
Tel.: +1 617 509 9991
Fax: +1 617 859 8112
mklompas@partners.org

Ventilator-associated pneumonia (VAP) is an important source of morbidity and mortality in critically ill patients. Many interventions are touted to prevent VAP but studies supporting these interventions are difficult to interpret owing to an exceedingly poor correlation between clinical diagnosis of VAP and the presence of an invasive pneumonia. There is consequently a risk that purported decreases in VAP rates may reflect decreases in oropharyngeal colonization rates more than reductions in invasive disease. To circumvent this source of error, it is critical to assess the impact of intervention measures on patient outcomes rather than on VAP rates alone. This article will review selected VAP prevention methods using this framework and advocate for the development of a new surveillance definition that will more reliably predict patient outcomes.

KEYWORDS: healthcare-acquired infections • infection prevention • infection surveillance • quality improvement • ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is the most complicated and morbid of healthcare-acquired infections. The crude mortality of patients with VAP ranges from 30 to 50% [1–3]. Calculation of the attributable mortality is a challenge since VAP tends to afflict the sickest and most vulnerable of hospitalized patients, but it is estimated to be between 5 and 25% [4–7]. VAP prolongs the duration of mechanical ventilation, increases lengths of stay in the intensive care unit (ICU) and extends hospitalizations [8,9]. Treatment of suspected and confirmed VAP is estimated to account for approximately 50% of antibiotic dispensing in ICUs [10–12]. These factors make VAP a potent driver of morbidity, cost and the cultivation of antibiotic-resistant bacteria.

Given the weight of morbidity associated with VAP, clinicians, policy makers, patient advocates and legislators have targeted VAP for elimination. High-profile organizations such as the Institute for Healthcare Improvement, the National Quality Forum, the Center for Medicare and Medicaid Services, the Joint Commission and many state legislatures variously advocate specific VAP prevention measures, rigorous hospital surveillance and, in some states, mandatory reporting of VAP rates.

Hospitals galvanized to address VAP, however, are confronted by an increasing set of options to prevent VAP ranging from probiotics to hand hygiene. Many organizations promote the adoption of 'ventilator bundles', which

include an array of measures that target VAP. The most famous bundle, that of the Institute for Healthcare Improvement, includes elevating the head of the bed, thromboembolism prophylaxis, stress ulcer prophylaxis, daily sedative interruption and daily assessment of patients' readiness to wean from mechanical ventilation. Some institutions, however, take issue with specific components of the bundle (stress ulcer prophylaxis, for example, is associated with an increased risk of hospital-acquired pneumonia and *Clostridium difficile* infections [13,14]), add additional components (such as frequent oral care with chlorhexidine) or embrace complementary interventions such as selective oral or digestive decontamination, continuous aspiration of subglottic secretions or silver-coated endotracheal tubes [15–21].

Rational selection of interventions for a VAP prevention program requires an appreciation of the clinical complexity of VAP. One cannot simply take the risk reductions reported in clinical trials and assume that implementation of these measures will lead to a clinical benefit for patients. Many if not most patients labeled with VAP do not have a diagnosis of pneumonia on biopsy [22]. Additionally, reported VAP rates are exquisitely dependent upon the mode of diagnosis [23]. The relative risk reductions reported in trials are thereby limited by imperfections in the VAP definition, which make it possible to substantially decrease apparent VAP rates without necessarily impacting clinically meaningful disease.

Difficulty in the interpretation of VAP rates is a consequence of the poor sensitivity and specificity of clinical signs used to diagnose the disease [22]. VAP is typically suspected if patients manifest some combination of the following cardinal signs: new or progressive infiltrates on portable chest radiographs, fever, abnormal white blood cell count and purulent sputum. These findings are all very nonspecific in critically ill, ventilated patients. Some patients come to the ICU with underlying pulmonary disease such as pulmonary contusion, interstitial lung disease, pulmonary vasculitis, sarcoidosis or cancer that in and of themselves might generate pulmonary infiltrates, fever and abnormal white blood cell counts [24]. Intubation compounds uncertainty by interfering with the body's clearance of normal, constitutive pulmonary secretions – leading to frequent variation in the quantity and quality of sputum suctioned from the endotracheal tube [25]. Ventilated patients are then at risk of a panoply of complications that alone or in combination can perfectly mimic the clinical picture of VAP. These include acute respiratory distress syndrome, pulmonary embolism, barotrauma, atelectasis, pulmonary edema and pneumonitis [24,26]. Sometimes, two or more conditions, such as pulmonary edema and central line-associated bloodstream infection, might combine to mimic the clinical picture of VAP. Autopsy series of patients clinically suspected of having VAP affirm that only approximately half truly have pneumonia [27–30].

Unfortunately, addition of microbiological criteria does not significantly enhance accuracy. Quantitative culture of bronchoalveolar lavage fluid is only approximately 50–75% sensitive and 50–90% specific [31–35]. Protected specimen brush cultures likewise only have a sensitivity of 30–60% and a specificity of 50–90% [31–36]. Not surprisingly, reported VAP rates depend heavily upon diagnostic technique. Researchers who use a purely clinical definition are apt to report VAP rates five-times higher than those who require positive quantitative bronchoalveolar lavage in addition to clinical signs [23].

In theory, these sources of inaccuracy should not alter the internal validity of clinical trials so long as the same diagnostic criteria are used for the intervention and control arms. In practice, however, there is circularity between the diagnostic criteria for VAP and the targets of most intervention measures that make it possible to show significant decreases in VAP rates in the intervention arm relative to the control arm that do not necessarily reflect reductions in clinically impactful disease [37].

For example, many VAP prevention measures target bacterial colonizers of the oropharynx and endotracheal tube on the reasonable rationale that they are critical antecedents on the pathway to VAP. There is an inherent risk that intervention measures directed against colonizers (oral antimicrobials, antiseptics and silver-coated endotracheal tubes) will disproportionately reduce false-positive VAP misdiagnoses relative to clinically morbid invasive infections by decreasing contamination of diagnostic specimens. These interventions might show apparent decreases in VAP rates that better reflect a decrease in colonization and lack of specificity of the VAP definition than clinically meaningful benefits for patients. Aspiration of

subglottic secretions and elevation of the head of bed may also be subject to circularity between intervention target and diagnostic criteria since these interventions are designed to decrease the patient's volume of secretions at the head of the respiratory tract, an important source of 'purulent'-looking secretions and contamination of microbiological specimens.

These sources of inaccuracy make interpretation of reported impacts on VAP rates very difficult [38]. They make it impossible to meaningfully assess the validity of reported risk reductions or to compare risk reductions from trial to trial, and from intervention to intervention. Instead, VAP prevention measures should be assessed by their impact on patient outcomes. Reasonable outcomes to assess include duration of mechanical ventilation, ICU and hospital length-of-stay, mortality, and antibiotic use. Assessing outcomes rather than VAP rates make assessment more reliable (by obviating the unreliability of VAP rates) and more meaningful (by replacing a proxy measure with a direct measure of patient prognoses).

Professional societies from North America and Europe have published extensive guidelines on the diagnosis, management and prevention of VAP [39–41]. These guidelines are important sources of summary information on VAP and provide essential guidance on the design of comprehensive infection prevention programs. The guidelines emphasize the importance of conducting active VAP surveillance, encouraging fastidious hand hygiene, avoiding intubation whenever possible, minimizing the duration of mechanical ventilation and the frequency of ventilator circuit changes, and providing staff with ongoing education about VAP. The guidelines then review specific VAP prevention measures but tend to accept reported reductions in VAP rates at face value despite their many inaccuracies and variable correlation with patient outcomes. This article will therefore focus on reviewing a selection of the most frequently cited VAP prevention measures with particular regard to their impact upon patient outcomes (summarized in TABLE 1). The measures to be assessed will include elevation of the head of the bed, endotracheal tubes with subglottic secretion aspiration ports, silver-coated endotracheal tubes, oral antiseptics and antibiotics, ventilator weaning protocols and ventilator care bundles.

Elevation of the head of the bed

Elevation of the head of the bed is hypothesized to decrease the frequency of gastroesophageal reflux, aspiration and hence pneumonia [42]. In a multivariate analysis of a prospective cohort of 277 ventilated patients, supine positioning during the first 24 h of intubation was independently associated with developing VAP (odds ratio [OR]: 2.9; 95% CI: 1.3–6.8) and increased mortality (OR: 3.1; 95% CI: 1.2–7.8) [43]. These associations have not been consistently borne out in interventional controlled trials, however, this is possibly because there are very few rigorous studies of this intervention. Drakulovic *et al.* randomized 86 patients to semi-recumbent positioning at 45° versus fully supine at 0° elevation of the head of the bed [44]. They found a statistically significant reduction in

both clinical and microbiological diagnoses of VAP but no difference in duration of mechanical ventilation, ICU length of stay or mortality. The trial was, however, underpowered to assess these outcomes, therefore their findings do not preclude an effect. There was a strong association in this trial between supine positioning, enteral nutrition and VAP; 14 of 28 supine patients on enteral nutrition developed VAP versus only two of 22 semi-recumbent patients (adjusted OR: 5.7; 95% CI: 1.5–22.8).

Researchers in The Netherlands attempted to replicate the findings of this study in a larger, multicenter evaluation that included 221 patients from three hospitals [45]. Patients were randomized to 45° elevation of the backrest versus 10° rather than 0° given the very high rate of VAP in completely supine patients on enteral nutrition. There was no difference in VAP rates, duration of ventilation, intensive care length of stay or mortality between the semi-recumbent patients versus the supine patients. Notably, however, the study protocol included continuous measurement of the backrest angle of elevation. Despite employing a research nurse who assessed and corrected patients' bed position 2–3 times per day, the average backrest elevation in the intervention arm of the trial was only 22.6° versus 16.1° in the control arm. This small difference in elevation may explain the negative findings in this trial but it also highlights the practical challenge in continuously maintaining backrest elevation above 30°.

Endotracheal tubes with subglottic secretion aspiration ports

Endotracheal tubes disrupt normal clearance of constitutively produced pulmonary secretions. This can lead to pooling of secretions above the endotracheal cuff in the lower trachea. These rapidly become colonized by pathogenic bacteria and fungi [46,47]. Researchers hypothesize that leakage of contaminated secretions around the cuff is an important cause of VAP [48]. Specialized endotracheal tubes equipped with a suction port immediately above the cuff are thought to mitigate the risk of aspiration around the cuff by permitting intermittent or continuous aspiration of subglottic secretions pooling above the cuff [49].

Endotracheal tubes with subglottic suction ports have been assessed in at least eight randomized trials with mixed results [50–57]. Of the five trials written in English that report on patients' outcomes, three found that aspiration of subglottic secretions reduced VAP rates while two did not. None of

Table 1. Selected ventilator-associated pneumonia prevention measures and their impact on patients' outcomes.

Intervention	VAP rates	Ventilator days	Intensive care days	Hospital days	Mortality	Ref.
Elevation of the head of the bed	Decrease	No impact	No impact	No impact	No impact	[44,45]
Continuous aspiration of subglottic secretions	Decrease	No impact	No impact	No impact	No impact	[49,55]
Silver-coated endotracheal tubes	Decrease	No impact	No impact	No impact	No impact	[59]
Oral care with chlorhexidine	Variable	No impact	No impact	No impact	No impact	[64–74]
Selective oral and digestive decontamination	Decrease	Variable	Variable	Variable	Probable decrease	[78–80]
Daily assessment of readiness to wean	Decrease	Decrease	Decrease	Decrease	Possible decrease	[82]
Daily interruption of sedation	Possible decrease	Decrease	Decrease	Decrease	Possible decrease	[83,84]
Ventilator bundles	Unknown [†]	Unknown [†]	Unknown [†]	Unknown [†]	Unknown [†]	NA

[†]All extant trials of ventilator bundles use historical controls; no randomized controlled trials to date. NA: Not applicable; VAP: Ventilator-associated pneumonia.

the studies, however, showed any impact upon duration of mechanical ventilation, intensive care length of stay, hospital length of stay or mortality.

One trial assessed the impact of subglottic secretion drainage tubes on antibiotic usage. Bouza *et al.* found patients randomized to continuous aspiration of subglottic secretions were prescribed almost 30% fewer defined daily doses of antibiotics despite no difference in measured VAP rates, days of mechanical ventilation or duration of intensive care stay [54]. This curious mismatch between antibiotic prescribing and patients' outcomes may hint at the phenomenon described earlier: prevention measures that target bacterial colonization and pulmonary secretions may preferentially decrease false-positive diagnoses of VAP in intervention arms relative to control arms without necessarily impacting the frequency of invasive, morbid disease. Patients with continuous aspiration of subglottic secretions may have been prescribed fewer antibiotics owing to lower volume and variability in their pulmonary secretions, but the identical outcomes for intervention and control patients in these trials argue against clinically meaningful differences between these populations.

A meta-analysis of subglottic secretion drainage trials published in 2005 suggested an impact upon ventilator days and ICU days. This result was achieved, however, by excluding the largest (and arguably most rigorous) study [52], and by analyzing

the results per-protocol rather than by intention-to-treat [58]. When the meta-analysis was run including all available studies and all enrolled patients on an intention-to-treat basis, there was no discernable impact on patient outcomes.

The contradictory results between the per-protocol versus intention-to-treat analyses and the different impacts on VAP rates reported by different trials may be due to differences in enrollment strategies amongst trials. The three trials that found a significant impact on VAP rates all had strict inclusion criteria: only patients expected to be on mechanical ventilation for greater than 1 day [52] or greater than 3 days [51,53] were enrolled, whereas the negative trials enrolled consecutive patients [52,54]. Limiting the trials to patients ventilated for longer periods and therefore at greater risk for VAP increased their power but limits their generalizability to routine clinical practice where the majority of intubated patients require less than 48 h of mechanical ventilation.

Prospectively identifying the subset of patients who will require prolonged ventilation is very challenging. Indeed, despite attempting only to enroll patients expected to require extended mechanical ventilation, 20–30% of enrolled patients were extubated in less than 3 days [51,53]. These patients were excluded from the trials analyzed per-protocol. Doing so decreased the denominator of patients at risk for VAP and again increased the studies' power but further reduced generalizability. These trialists' difficulty in prospectively identifying patients likely to need prolonged ventilation underscores the operational difficulty in identifying patients in advance who are most likely to benefit from VAP prevention measures. Practical considerations compel most intensivists to apply VAP prevention measures to all patients. Therefore, assessment of the impact of prevention measures should consider their impact for all patients and not just the limited subset ultimately found to have required prolonged ventilation.

In summary, there may be a small subset of patients ventilated for intermediate lengths of time who benefit from endotracheal tubes equipped with subglottic secretion aspiration ports but prospectively identifying these patients is elusive. Overall, there is negligible benefit for unselected populations of intubated patients.

Silver-coated endotracheal tubes

Silver coating is designed to decrease microbial colonization of endotracheal tubes and thereby decrease the likelihood of pulmonary inoculation if and when patients aspirate secretions around the endotracheal tube cuff. The impact of silver coating of endotracheal tubes has been evaluated in a large, multicenter trial with 2003 participants [59]. As with the studies of continuous aspiration of subglottic secretions, these investigators also tried to only enroll patients expected to require greater than 24 h of mechanical ventilation. Despite screening 9417 patients to enroll 2003 individuals, more than 20% of participants were extubated in less than 24 h. This again highlights the difficulty of prospectively selecting patients for focused prevention measures.

Patients in this trial underwent bronchoalveolar lavage if physicians clinically suspected VAP, or if patients had radiographic infiltrates and typical signs of VAP. VAP was defined as

a bronchoalveolar lavage culture with 10^4 CFU/ml or more. The investigators reported a 34% decrease in the relative risk of VAP ($p = 0.03$). However, the VAP counts included patients with bronchoalveolar lavages that grew organisms not typically considered to be pulmonary pathogens, such as yeast, enterococcus, coagulase-negative *Staphylococcus* and normal flora. Excluding these nonpathogens from the analysis eliminated the observed difference in VAP rates between silver-coated and conventional endotracheal tubes ($p = 0.08$) [60].

As with continuous aspiration of subglottic secretion studies, silver coating appeared to preferentially decrease the prevalence of clinically benign events (such as colonization with nonpathogens). When the investigators considered the study population as a whole without regard to treatment assignment, those with VAP were ventilated for significantly more days and had longer intensive care and hospital lengths of stay. Yet when the investigators compared these outcomes for patients randomized to silver-coated versus conventional tubes, the median durations of intubation, intensive care length of stay and hospital length of stay were identical. This paradox of an apparent decrease in VAP rates yet identical outcomes (despite the apparently deleterious consequences of a diagnosis of VAP) suggests that silver-coated tubes preferentially decrease colonization rather than invasive infections.

Oral antiseptics & antibiotics

Oral antiseptics and antibiotics are intended to prevent VAP by decreasing bacterial contamination of the lungs when patients microaspirate oral secretions around the cuff of the endotracheal tube. Researchers have assessed a range of strategies that target the oral and gastrointestinal bacterial reservoirs. These include oral antiseptic or antibiotic washes to the mouth alone, antibiotics administered to mouth and stomach for oral decontamination, and antibiotics administered by mouth, stomach and intravenous for digestive decontamination. There is also a small body of literature assessing aerosolized antibiotics administered to the respiratory tract [61].

The major antiseptics that have been assessed in randomized controlled trials that include data on patient outcomes are providone-iodine, iseganan and chlorhexidine. Providone-iodine and iseganan have only been evaluated in one trial each. The providone-iodine trial showed a decrease in VAP rates but no impact on patient outcomes [62]. The trial of iseganan showed no impact on either VAP rates or patient outcomes [63]. Chlorhexidine at varying concentrations, however, has been evaluated in more than 11 trials. Impacts on VAP rates have been variable: three reported decreases [64–66] while the other eight did not [67–74]. One trial reported a decrease in antibiotic usage for patients treated with chlorhexidine [67]. Impacts on other outcomes, however, have been more uniformly disappointing. One trial did report a decrease in mortality [67] and one reported a decrease in duration of hospitalization [66], but these findings were not borne out by the other nine studies. A meta-analysis including the six trials published through 2007 suggested a net 44% decrease in VAP rates but no decreases in patients' ventilator days, hospital days or mortality [75].

The limited success of chlorhexidine may be due to a number of factors. Subgroup analysis of chlorhexidine trials suggest that it has less activity against Gram-negatives compared with Gram-positives [70,74]. This may be due to a differential effect of the antiseptic or it may suggest an unaddressed reservoir of bacteria in the stomach and GI tract where Gram-negatives predominate. Some also speculate that patients require mechanical brushing of their teeth to dislodge bacteria rather than surface application of liquid antiseptic alone. Studies attest to frequent genetic homology between bacterial isolates from the dental plaque and lungs of patients with VAP [76] but clinicians have thus far been reluctant to assess an aggressive brushing regimen, perhaps for fear that it will promote bacterial translocation and bacteremia [64,74].

European trialists have taken the lead in assessing antibiotic-based regimens designed to suppress gastric and intestinal flora in addition to oral colonizers. Strategies that include both parenteral and enteral antibiotics are known as selective digestive decontamination whereas those with enteral antibiotics alone are known as selective oral decontamination. These regimens are called selective because they are designed to preferentially target fungi and aerobic bacteria in the digestive system while sparing anaerobes. They usually consist of nonabsorbable oral antibiotics (e.g., colistin, polymixin, tobramycin and/or amphotericin) and intravenous agents (e.g., cefotaxime or ciprofloxacin). Some have also proposed the use of probiotics to favorably alter intestinal flora [77].

There have been many trials of decontamination regimens over the past 20 years. Van Nieuwenhoven and colleagues thoughtfully analyzed this literature approximately 10 years ago and demonstrated an inverse relationship between methodological quality and impact upon VAP rates [78]. Nonetheless, a meta-analysis of more than 30 such trials published in 2007 found a statistically significant decrease in the incidence of VAP, bacteremia and mortality [79].

The nuanced but positive findings of these analyses are mirrored by the most rigorous decontamination trial to date, a cluster randomized trial involving 13 ICUs and almost 6000 patients in The Netherlands [80]. Participating units were assigned to a random sequence of 6-month periods of standard care, selective oral decontamination and selective digestive decontamination. Selective oral decontamination consisted of topical tobramycin, colistin and amphotericin B to the oropharynx and stomach for 4 days. Selective digestive decontamination entailed the same oral and gastric formula along with 4 days of intravenous cefotaxime. There was no difference between the treatment arms in crude mortality rates or time to cessation of mechanical ventilation, intensive care discharge or hospital discharge. However, at the end of the trial the investigators noted that patients enrolled during oral and digestive decontamination periods were significantly older and had higher Acute Physiology and Chronic Health Evaluation (APACHE) scores compared with those enrolled during standard care periods. Adjusting for this enrollment bias lowered the relative mortality of decontamination patients compared

with standard care patients. The 28-day adjusted odds of mortality was 0.86 (95% CI: 0.74–0.99) for patients assigned to selective oral decontamination, and 0.83 (95% CI: 0.72–0.97) for those assigned to selective digestive decontamination. Additionally, clinicians prescribed fewer antibiotics overall during decontamination periods relative to standard care periods, despite the large amount of antimicrobials dispensed for decontamination itself.

Notwithstanding the laudable mortality benefit suggested by this trial, North American clinicians have been reluctant to adopt antibiotic-based decontamination regimens. Enthusiasm for the Dutch trial has been tempered by the failure of randomization (requiring multivariate analysis to detect a significant impact on mortality with consequent concern that residual undetected confounders might still be present) and ongoing concerns that decontamination antimicrobial regimens might promote antibiotic resistance and *C. difficile* infections. Surveillance cultures from The Netherlands during decontamination periods had very low rates of antibiotic resistance, with fewer than 5% of isolates resistant to aminoglycosides, ciprofloxacin or ceftazidime [80]. A follow-up study did show a rebound in the prevalence of antibiotic resistant flora after the trial to approximately 10–15% of isolates, but this was similar to rates of resistance prior to decontamination periods [81].

North American clinicians continue to wonder about the applicability of this trial to their hospitals, however, where the baseline rates of antibiotic resistance are much higher compared with The Netherlands, this remains an unresolved question. Many clinicians have embraced chlorhexidine-based oral regimens for the interim despite the paucity of data showing an impact upon outcomes.

Ventilator weaning & extubation protocols

In contrast to the plurality of VAP prevention trials that have failed to show significant impacts on patient outcomes, studies of ventilator weaning protocols have been strikingly successful in decreasing patients' ventilator and ICU days. For example, Ely and colleagues showed that daily, structured evaluations of patients' readiness to wean decreased the median duration of mechanical ventilation by 1.5 days compared with usual care [82]. Likewise, daily interruption in continuous infusion sedatives (titrated to patient wakefulness) shortened the median duration of mechanical ventilation by 2.4 days and the median intensive care length of stay by 3.5 days [83]. Combining these two interventions appears even more potent. Girard and colleagues found that the combination of daily assessment of readiness to wean and daily sedative interruption together versus daily assessment of readiness to wean alone reduced the median duration of mechanical ventilation by 3.1 days, intensive care length of stay by 3.8 days and hospital length of stay by 4.1 days [84]. Patients randomized to the combination arm may also have realized a mortality benefit, although this was not entirely clear as there was no difference between mortality rates at 28 days but there was a statistically significant reduction in mortality rates at 1 year.

Bundles

Quality-of-care proponents advocate combining multiple prevention measures into defined bundles. This not only makes them easier to 'market' to practitioners but may offer synergies beyond any one intervention alone or the simple sum of their components. Indeed, the study by Girard *et al.* showing an additive benefit to performing both daily assessment of readiness to wean and daily sedative interruption may hint at the benefit of combining multiple interventions [84]. There is no consensus on the ideal set of interventions to include in VAP prevention bundles [85–87]. Different institutions have developed their own protocols [15–21].

To date, there are no high-quality trials assessing the benefits of VAP prevention bundles [87]. Many institutions have reported dramatic decreases in VAP rates by implementing bundles but these studies all suffer significant methodological flaws, including lack of blinding and absence of concurrent control groups. Instead, these studies use their institutions' historical VAP rates as the comparator. Without blinding (which may be impossible in these studies) and concurrent control groups, it is impossible to disassemble a bundle-specific effect from secular trends, concurrent interventions and subconscious measurement biases (the Hawthorne effect). The latter is a particular concern for VAP studies given the inherent subjectivity of the diagnostic definition [88]. Nonetheless, some institutions have not only reported decreases in VAP rates, but also decreases in ventilator days, intensive care length of stay and hospital length of stay compared with their historic rates [89–92]. One acute hospital trust has also reported a decrease in hospital mortality after implementing a global care improvement program incorporating eight care bundles targeting 13 high-morbidity diagnoses (but with insufficient data to assess the specific contribution of the ventilator bundle to their overall success) [93]. Definitive assessment of the benefit of bundles to improve outcomes for ventilated patients awaits a well-designed and controlled trial.

Expert commentary & five-year view

From the point of view of patient outcomes rather than changes in VAP rates, most extant VAP prevention measures have had disappointingly little impact. Studies investigating silver-coated endotracheal tubes, continuous aspiration of subglottic secretions and oral care with chlorhexidine have not shown an impact upon ventilator days, length of stay or mortality. Elevation of the head of the bed still awaits a large, well-organized trial to assess its true impact upon outcomes. Selective oral and digestive decontamination may well decrease mortality, but North American clinicians will likely need to see the results of the Dutch trial duplicated in their hospitals to reassure them that this strategy is generalizable to their institutions without exacerbating their higher baseline rates of multidrug-resistant flora.

The one consistently positive theme in trying to improve outcomes for ventilated patients is ventilator weaning protocols. These have repeatedly shown decreases in ventilator days, hospital days and perhaps even mortality. It is striking that weaning

protocols have yielded significant results on these outcomes, despite studying relatively few patients, often far fewer than those enrolled in VAP prevention studies. On this basis, hospitals are well advised to make ventilator weaning protocols the bedrock upon which to build their VAP prevention programs.

The failure of many interventions to show an impact on patient outcomes does not preclude all possibility of benefit from these interventions. Many studies are simply underpowered to meaningfully assess outcomes, particularly mortality [94]. Assessing outcomes rather than VAP rates is a methodologically rigorous but more difficult standard for VAP prevention measures to meet. Very low VAP prevalence rates in most contemporary series limit studies' power to detect impacts on outcomes since even large improvements for a tiny fraction of a population translate into minimal impacts for the population at large. Interventions that directly target VAP (such as continuous aspiration of subglottic secretions) rather than ventilator care in general (such as weaning protocols) suffer a disadvantage when evaluating outcomes since only a small target group of patients stand to benefit (i.e., those at highest risk for VAP). In some recent series, only 5% of patients ultimately developed VAP [59].

The difficulty in the assessment of VAP prevention measures using outcomes alone is one of many important arguments for a new measure for complications of mechanical ventilation that more tightly predicts patients' outcomes in order to better assess quality of care and drive improvements for ventilated populations. Other interrelated arguments include the predilection for current VAP definitions to miss patients with true pneumonias, to mislabel patients with other benign and serious conditions as having pneumonia, and low VAP incidence rates in many contemporary series that make it a vanishing target upon which to focus care improvement programs.

A new measure should shift our emphasis from pneumonia in particular to complications of mechanical ventilation in general. Such a shift would have the advantage of simultaneously circumventing the inaccuracies of all extant VAP definitions and emphasizing the importance of preventing all complications of mechanical ventilation rather than just pneumonia alone. Approaches to surveillance using this rubric are under development [95]. If the field moves in this direction, we can expect augmented bundles in the future that will not only target pneumonia, but also pulmonary edema, atelectasis, barotrauma and thromboembolism.

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Key issues

- Ventilator-associated pneumonia (VAP) is an important source of morbidity and mortality for ventilated patients.
- Clinical and microbiological assessment of VAP is frequently prone to both false-positive and false-negative diagnoses.
- There is circularity between the way VAP is measured and the way prevention measures target VAP – this makes it possible to decrease the apparent VAP rate without necessarily impacting clinically meaningful invasive disease.
- Difficulty interpreting changes in VAP rates compels one to look at patient outcomes rather than VAP rates to assess the impact of VAP prevention measures.
- Daily assessment of readiness to extubate and daily interruption of sedation consistently decrease patient's ventilator days, hospital days and perhaps mortality. Ventilator weaning protocols should be the core constituent of hospitals' VAP prevention programs.
- There is a paucity of studies assessing head-of-bed elevation; there appears to be a strong correlation between supine position, enteral feeding and aspiration pneumonia but insufficient data to assess the impact of head-of-bed elevation on patient outcomes.
- Continuous aspiration of subglottic secretions decreases VAP rates and antibiotic usage but does not improve patient outcomes.
- Silver coating on endotracheal tubes decreases colonization rates but has a questionable impact on VAP rates and no impact upon patient outcomes.
- Selective oral and digestive decontamination regimens lower mortality but their applicability to settings with high endemic rates of antibiotic resistance is still questioned.
- Grouping prevention measures into 'bundles' has led to dramatic reductions in VAP rates and improved patient outcomes for some hospitals; however, no trial data to date include a concurrent control group to enable rigorous evaluation of the true impact of bundles.

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest

- 1 Rello J, Quintana E, Ausina V *et al.* Incidence, etiology, and outcome of nosocomial pneumonia in mechanically ventilated patients. *Chest* 100(2), 439–444 (1991).
- 2 Tejerina E, Frutos-Vivar F, Restrepo MI *et al.* Incidence, risk factors, and outcome of ventilator-associated pneumonia. *J. Crit. Care* 21(1), 56–65 (2006).
- 3 Fagon JY, Chastre J, Vuagnat A, Trouillet JL, Novara A, Gibert C. Nosocomial pneumonia and mortality among patients in intensive care units. *JAMA* 275(11), 866–869 (1996).
- 4 Nguile-Makao M, Zahar JR, Francois A *et al.* Attributable mortality of ventilator-associated pneumonia: respective impact of main characteristics at icu admission and vap onset using conditional logistic regression and multi-state models. *Intensive Care Med.* 36(5), 781–789 (2010).
- 5 Heyland DK, Cook DJ, Griffith L, Keenan SP, Brun-Buisson C. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials group. *Am. J. Respir. Crit. Care Med.* 159(4 Pt 1), 1249–1256 (1999).
- 6 Muscedere JG, Martin CM, Heyland DK. The impact of ventilator-associated pneumonia on the canadian health care system. *J. Crit. Care* 23(1), 5–10 (2008).
- 7 Melsen WG, Rovers MM, Bonten MJ. Ventilator-associated pneumonia and mortality: a systematic review of observational studies. *Crit. Care Med.* 37(10), 2709–2718 (2009).
- 8 Safdar N, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit. Care Med.* 33(10), 2184–2193 (2005).
- 9 Beyersmann J, Gastmeier P, Grundmann H *et al.* Use of multistate models to assess prolongation of intensive care unit stay due to nosocomial infection. *Infect. Control Hosp. Epidemiol.* 27(5), 493–499 (2006).
- 10 Warren MM, Gibb AP, Walsh TS. Antibiotic prescription practice in an intensive care unit using twice-weekly collection of screening specimens: a prospective audit in a large UK teaching hospital. *J. Hosp. Infect.* 59(2), 90–95 (2005).
- 11 Bergmans DC, Bonten MJ, Gaillard CA *et al.* Indications for antibiotic use in icu patients: a one-year prospective surveillance. *J. Antimicrob. Chemother.* 39(4), 527–535 (1997).
- 12 Roder BL, Nielsen SL, Magnussen P, Engquist A, Frimodt-Moller N. Antibiotic usage in an intensive care unit in a danish university hospital. *J. Antimicrob. Chemother.* 32(4), 633–642 (1993).
- 13 Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA* 301(20), 2120–2128 (2009).
- 14 Dubberke ER, Reske KA, Yan Y, Olsen MA, McDonald LC, Fraser VJ. *Clostridium difficile*-associated disease in a setting of endemicity: identification of novel risk factors. *Clin. Infect. Dis.* 45(12), 1543–1549 (2007).
- 15 Berriel-Cass D, Adkins FW, Jones P, Fakhri MG. Eliminating nosocomial infections at Ascension Health. *Jt Comm. J. Qual. Patient Saf.* 32(11), 612–620 (2006).
- 16 Apisarnthanarak A, Pinitchai U, Thongphubeth K *et al.* Effectiveness of an educational program to reduce ventilator-associated pneumonia in a tertiary care center in Thailand: a 4-year study. *Clin. Infect. Dis.* 45(6), 704–711 (2007).
- 17 Zilberberg MD, Shorr AF, Kollef MH. Implementing quality improvements in the intensive care unit: ventilator bundle as an example. *Crit. Care Med.* 37(1), 305–309 (2009).
- 18 Blamoun J, Alfakir M, Rella ME *et al.* Efficacy of an expanded ventilator bundle for the reduction of ventilator-associated pneumonia in the medical intensive care unit. *Am. J. Infect. Control* 37(2), 172–175 (2009).
- 19 Cocanour CS, Peninger M, Domonoske BD *et al.* Decreasing ventilator associated pneumonia in a trauma ICU. *J. Trauma* 61(1), 122–129; discussion 129–130 (2006).
- 20 Hawe CS, Ellis KS, Cairns CJ, Longmate A. Reduction of ventilator-associated pneumonia: active versus passive guideline implementation. *Intens. Care Med.* 35(7), 1180–1186 (2009).

- 21 Rello J, Lode H, Cornaglia G, Masterton R. A European care bundle for prevention of ventilator-associated pneumonia. *Intens. Care Med.* 36(5), 773–780 (2010).
- 22 Klompas M. Does this patient have ventilator-associated pneumonia? *JAMA* 297(14), 1583–1593 (2007).
- **Assessment of the accuracy of clinical signs to diagnose ventilator-associated pneumonia relative to histology as the reference standard.**
- 23 Morris AC, Kefala K, Simpson AJ *et al.* Evaluation of the effect of diagnostic methodology on the reported incidence of ventilator-associated pneumonia. *Thorax* 64(6), 516–522 (2009).
- 24 Petersen IS, Aru A, Skodt V *et al.* Evaluation of pneumonia diagnosis in intensive care patients. *Scand. J. Infect. Dis.* 31(3), 299–303 (1999).
- 25 Louthan FB, Meduri GU. Differential diagnosis of fever and pulmonary densities in mechanically ventilated patients. *Semin. Respir. Infect.* 11(2), 77–95 (1996).
- 26 Meduri GU, Mauldin GL, Wunderink RG *et al.* Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. *Chest* 106(1), 221–235 (1994).
- 27 Rouby JJ, Rossignon MD, Nicolas MH *et al.* A prospective study of protected bronchoalveolar lavage in the diagnosis of nosocomial pneumonia. *Anesthesiology* 71(5), 679–685 (1989).
- 28 Balthazar AB, Von Nowakowski A, De Capitani EM, Bottini PV, Terzi RG, Araujo S. Diagnostic investigation of ventilator-associated pneumonia using bronchoalveolar lavage: comparative study with a postmortem lung biopsy. *Braz. J. Med. Biol. Res.* 34(8), 993–1001 (2001).
- 29 Bregeon F, Papazian L, Thomas P *et al.* Diagnostic accuracy of protected catheter sampling in ventilator-associated bacterial pneumonia. *Eur. Respir. J.* 16(5), 969–975 (2000).
- 30 Tejerina E, Esteban A, Fernandez-Segoviano P *et al.* Accuracy of clinical definitions of ventilator-associated pneumonia: comparison with autopsy findings. *J. Crit. Care* 25(1), 62–68 (2010).
- 31 Kirtland SH, Corley DE, Winterbauer RH *et al.* The diagnosis of ventilator-associated pneumonia: a comparison of histologic, microbiologic, and clinical criteria. *Chest* 112(2), 445–457 (1997).
- 32 Fabregas N, Ewig S, Torres A *et al.* Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. *Thorax* 54(10), 867–873 (1999).
- 33 Papazian L, Thomas P, Garbe L *et al.* Bronchoscopic or blind sampling techniques for the diagnosis of ventilator-associated pneumonia. *Am. J. Respir. Crit. Care Med.* 152(6 Pt 1), 1982–1991 (1995).
- 34 Marquette CH, Copin MC, Wallet F *et al.* Diagnostic tests for pneumonia in ventilated patients: prospective evaluation of diagnostic accuracy using histology as a diagnostic gold standard. *Am. J. Respir. Crit. Care Med.* 151(6), 1878–1888 (1995).
- 35 Torres A, El-Ebiary M, Padro L *et al.* Validation of different techniques for the diagnosis of ventilator-associated pneumonia. Comparison with immediate postmortem pulmonary biopsy. *Am. J. Respir. Crit. Care Med.* 149(2 Pt 1), 324–331 (1994).
- 36 Chastre J, Viau F, Brun P *et al.* Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections in ventilated patients. *Am. Rev. Resp. Dis.* 130(5), 924–929 (1984).
- 37 Klompas M. The paradox of ventilator-associated pneumonia prevention measures. *Crit. Care (London, England)* 13(5), 315 (2009).
- 38 Klompas M, Platt R. Ventilator-associated pneumonia – the wrong quality measure for benchmarking. *Ann. Intern. Med.* 147(11), 803–805 (2007).
- 39 American Thoracic Society and Infectious Diseases Society of America: guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am. J. Respir. Crit. Care Med.* 171(4), 388–416 (2005).
- 40 Coffin SE, Klompas M, Classen D *et al.* Strategies to prevent ventilator-associated pneumonia in acute care hospitals. *Infect. Control Hosp. Epidemiol.* 29(Suppl. 1), S31–S40 (2008).
- **Concise summary of consensus strategies to prevent ventilator-associated pneumonia, endorsed by many professional societies.**
- 41 Torres A, Ewig S, Lode H, Carlet J. Defining, treating and preventing hospital acquired pneumonia: European perspective. *Intensive Care Med.* 35(1), 9–29 (2009).
- 42 Torres A, Serra-Batlles J, Ros E *et al.* Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. *Ann. Intern. Med.* 116(7), 540–543 (1992).
- 43 Kollef MH. Ventilator-associated pneumonia. A multivariate analysis. *JAMA* 270(16), 1965–1970 (1993).
- 44 Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet* 354(9193), 1851–1858 (1999).
- 45 Van Nieuwenhoven CA, Vandenbroucke-Grauls C, Van Tiel FH *et al.* Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: a randomized study. *Crit. Care Med.* 34(2), 396–402 (2006).
- 46 Johanson WG, Pierce AK, Sanford JP. Changing pharyngeal bacterial flora of hospitalized patients. Emergence of Gram-negative bacilli. *N. Engl. J. Med.* 281(21), 1137–1140 (1969).
- 47 Johanson WG Jr, Pierce AK, Sanford JP, Thomas GD. Nosocomial respiratory infections with Gram-negative bacilli. The significance of colonization of the respiratory tract. *Ann. Intern. Med.* 77(5), 701–706 (1972).
- 48 Johanson WG, Dever LL. Nosocomial pneumonia. *Intens. Care Med.* 29(1), 23–29 (2003).
- 49 Mahul P, Auboyer C, Jospe R *et al.* Prevention of nosocomial pneumonia in intubated patients: respective role of mechanical subglottic secretions drainage and stress ulcer prophylaxis. *Intens. Care Med.* 18(1), 20–25 (1992).
- 50 Mahul P, Auboyer C, Jospe R *et al.* Prevention of nosocomial pneumonia in intubated patients: respective role of mechanical subglottic secretions drainage and stress ulcer prophylaxis. *Intensive Care Med.* 18(1), 20–25 (1992).
- 51 Valles J, Artigas A, Rello J *et al.* Continuous aspiration of subglottic secretions in preventing ventilator-associated pneumonia. *Ann. Intern. Med.* 122(3), 179–186 (1995).
- 52 Kollef MH, Skubas NJ, Sundt TM. A randomized clinical trial of continuous aspiration of subglottic secretions in cardiac surgery patients. *Chest* 116(5), 1339–1346 (1999).
- 53 Smulders K, Van Der Hoeven H, Weers-Pothoff I, Vandenbroucke-Grauls C. A randomized clinical trial of intermittent subglottic secretion drainage in patients receiving mechanical ventilation. *Chest* 121(3), 858–862 (2002).
- 54 Bouza E, Perez MJ, Munoz P, Rincon C, Barrio JM, Hortal J. Continuous aspiration of subglottic secretions in the prevention of

- ventilator-associated pneumonia in the postoperative period of major heart surgery. *Chest* 134(5), 938–946 (2008).
- 55 Lorente L, Lecuona M, Jimenez A, Mora ML, Sierra A. Influence of an endotracheal tube with polyurethane cuff and subglottic secretion drainage on pneumonia. *Am. J. Respir. Crit. Care Med.* 176(11), 1079–1083 (2007).
 - 56 Yang CS, Qiu HB, Zhu YP *et al.* [Effect of continuous aspiration of subglottic secretions on the prevention of ventilator-associated pneumonia in mechanically ventilated patients: a prospective, randomized, controlled clinical trial]. *Zhonghua Nei Ke Za Zhi* 47(8), 625–629 (2008).
 - 57 Zheng RQ, Lin H, Shao J *et al.* [A clinical study of subglottic secretion drainage for prevention of ventilation associated pneumonia]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 20(6), 338–340 (2008).
 - 58 Dezfulian C, Shojania K, Collard HR *et al.* Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis. *Am. J. Med.* 118(1), 11–18 (2005).
 - 59 Kollef MH, Afessa B, Anzueto A *et al.* Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: the nascent randomized trial. *JAMA* 300(7), 805–813 (2008).
 - 60 Klompas M. Silver-coated endotracheal tubes and patient outcomes in ventilator-associated pneumonia. *JAMA* 300(22), 2605; author reply 2605–2606 (2008).
 - 61 Falagas ME, Siempos II, Bliziotis IA, Michalopoulos A. Administration of antibiotics via the respiratory tract for the prevention of icu-acquired pneumonia: a meta-analysis of comparative trials. *Crit. Care (London, England)* 10(4), R123 (2006).
 - 62 Seguin P, Tanguy M, Laviolle B, Tirel O, Malledant Y. Effect of oropharyngeal decontamination by povidone–iodine on ventilator-associated pneumonia in patients with head trauma. *Crit. Care Med.* 34(5), 1514–1519 (2006).
 - 63 Kollef M, Pittet D, Sanchez Garcia M *et al.* A randomized double-blind trial of isegagan in prevention of ventilator-associated pneumonia. *Am. J. Respir. Crit. Care Med.* 173(1), 91–97 (2006).
 - 64 Fourrier F, Cau-Pottier E, Boutigny H, Roussel-Delvallez M, Jourdain M, Chopin C. Effects of dental plaque antiseptic decontamination on bacterial colonization and nosocomial infections in critically ill patients. *Intensive Care Med.* 26(9), 1239–1247 (2000).
 - 65 Genuit T, Bochicchio G, Napolitano LM, Mccarter RJ, Roghman MC. Prophylactic chlorhexidine oral rinse decreases ventilator-associated pneumonia in surgical ICU patients. *Surg. Infect.* 2(1), 5–18 (2001).
 - 66 Segers P, Speekenbrink RG, Ubbink DT, Van Ogtrop ML, De Mol BA. Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate: a randomized controlled trial. *JAMA* 296(20), 2460–2466 (2006).
 - 67 Deriso AJ 2nd, Ladowski JS, Dillon TA, Justice JW, Peterson AC. Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. *Chest* 109(6), 1556–1561 (1996).
 - 68 Houston S, Hougland P, Anderson JJ, Larocco M, Kennedy V, Gentry LO. Effectiveness of 0.12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery. *Am. J. Crit. Care* 11(6), 567–570 (2002).
 - 69 Fourrier F, Dubois D, Pronnier P *et al.* Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit: a double-blind placebo-controlled multicenter study. *Crit. Care Med.* 33(8), 1728–1735 (2005).
 - 70 Koeman M, Van Der Ven AJ, Hak E *et al.* Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. *Am. J. Respir. Crit. Care Med.* 173(12), 1348–1355 (2006).
 - 71 Tantipong H, Morkhareonpong C, Jaiyindee 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.* 29(2), 131–136 (2008).
 - 72 Bellissimo-Rodrigues F, Bellissimo-Rodrigues WT, Viana JM *et al.* Effectiveness of oral rinse with chlorhexidine in preventing nosocomial respiratory tract infections among intensive care unit patients. *Infect. Control Hosp. Epidemiol.* 30(10), 952–958 (2009).
 - 73 Panchabhai TS, Dangayach NS, Krishnan A, Kothari VM, Karnad DR. Oropharyngeal cleansing with 0.2% chlorhexidine for prevention of nosocomial pneumonia in critically ill patients: an open-label randomized trial with 0.01% potassium permanganate as control. *Chest* 135(5), 1150–1156 (2009).
 - 74 Scannapieco FA, Yu J, Raghavendran K *et al.* A randomized trial of chlorhexidine gluconate on oral bacterial pathogens in mechanically ventilated patients. *Crit. Care (London, England)* 13(4), R117 (2009).
 - 75 Chan EY, Ruest A, Meade MO, Cook DJ. Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis. *Br. Med. J. (Clin. Res. Ed.)* 334(7599), 889 (2007).
 - 76 Heo SM, Haase EM, Lesse AJ, Gill SR, Scannapieco FA. Genetic relationships between respiratory pathogens isolated from dental plaque and bronchoalveolar lavage fluid from patients in the intensive care unit undergoing mechanical ventilation. *Clin. Infect. Dis.* 47(12), 1562–1570 (2008).
 - 77 Siempos II, Ntaidou TK, Falagas ME. Impact of the administration of probiotics on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials. *Crit. Care Med.* 38(3), 954–962 (2010).
 - 78 Van Nieuwenhoven CA, Buskens E, Van Tiel FH, Bonten MJ. Relationship between methodological trial quality and the effects of selective digestive decontamination on pneumonia and mortality in critically ill patients. *JAMA* 286(3), 335–340 (2001).
 - 79 Silvestri L, Van Saene HK, Milanese M, Gregori D, Gullo A. Selective decontamination of the digestive tract reduces bacterial bloodstream infection and mortality in critically ill patients. Systematic review of randomized, controlled trials. *J. Hosp. Infect.* 65(3), 187–203 (2007).
 - 80 De Smet AM, Kluytmans JA, Cooper BS *et al.* Decontamination of the digestive tract and oropharynx in icu patients. *N. Engl. J. Med.* 360(1), 20–31 (2009).
- **Large cluster randomized trial assessing the benefit of selective oral decontamination versus selective digestive decontamination versus standard care.**
- 81 Oostdijk EA, De Smet AM, Blok HE *et al.* Ecological effects of selective decontamination on resistant Gram-negative bacterial colonization. *Am. J. Respir. Crit. Care Med.* 181(5), 452–457 (2010).
 - 82 Ely EW, Baker AM, Dunagan DP *et al.* Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N. Engl. J. Med.* 335(25), 1864–1869 (1996).
 - 83 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.* 342(20), 1471–1477 (2000).
- 84 Girard TD, Kress JP, Fuchs BD *et al.* Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): a randomised controlled trial. *Lancet* 371(9607), 126–134 (2008).
- **Well-designed trial showing the additive benefit of daily assessment of readiness to wean and daily sedative interruptions in improving patients' outcomes.**
- 85 Wip C, Napolitano L. Bundles to prevent ventilator-associated pneumonia: how valuable are they? *Curr. Opin. Infect. Dis.* 22(2), 159–166 (2009).
- 86 Van Saene HK, Silvestri L, De La Cal MA, Baines P. The emperor's new clothes: the fairy tale continues. *J. Crit. Care* 24(1), 149–152 (2009).
- 87 Zilberberg MD, Shorr AF, Kollef MH. Implementing quality improvements in the intensive care unit: ventilator bundle as an example. *Crit. Care Med.* 37(1), 305–309 (2009).
- 88 Klompas M. Interobserver variability in ventilator-associated pneumonia surveillance. *Am. J. Infect. Control* 38(3), 237–239 (2010).
- 89 Burger CD, Resar RK. "Ventilator bundle" approach to prevention of ventilator-associated pneumonia. *Mayo Clin. Proc.* 81(6), 849–850 (2006).
- 90 Lansford T, Moncure M, Carlton E *et al.* Efficacy of a pneumonia prevention protocol in the reduction of ventilator-associated pneumonia in trauma patients. *Surg. Infect.* 8(5), 505–510 (2007).
- 91 Bloos F, Muller S, Harz A *et al.* Effects of staff training on the care of mechanically ventilated patients: a prospective cohort study. *Br. J. Anaesth.* 103(2), 232–237 (2009).
- 92 Crunden E, Boyce C, Woodman H, Bray B. An evaluation of the impact of the ventilator care bundle. *Nurs. Crit. Care* 10(5), 242–246 (2005).
- 93 Robb E, Jarman B, Suntharalingam G, Higgins C, Tennant R, Elcock K. Using care bundles to reduce in-hospital mortality: quantitative survey. *Br. Med. J. (Clin. Res. Ed.)* 340, c1234 (2010).
- 94 Falagas ME, Kouranos VD, Michalopoulos A, Rodopoulou SP, Athanasoulia AP, Karageorgopoulos DE. Inadequate statistical power of published comparative cohort studies on ventilator-associated pneumonia to detect mortality differences. *Clin. Infect. Dis.* 50(4), 468–472 (2010).
- 95 Klompas M, Khan Y, Kleinman K *et al.* Multicenter evaluation of a novel surveillance definition for complications of mechanical ventilation (abstract 741). Presented at: *Society for Healthcare Epidemiology of America and the Association of Professionals in Infection Control, Fifth Decennial Meeting*. GA, USA, 18–22 March 2010.