

## Viewpoint

# The paradox of ventilator-associated pneumonia prevention measures

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## Abstract

There is a striking paradox in the literature supporting high-profile measures to reduce ventilator-associated pneumonia (VAP): many studies show significant reductions in VAP rates but almost none show any impact on patients' duration of mechanical ventilation, length of stay in the intensive care unit and hospital, or mortality. The paradox is largely attributable to lack of specificity in the VAP definition. The clinical and microbiological criteria for VAP capture a population of patients with an array of conditions that range from serious to benign. Many of the benign events are manifestations of bacterial colonization superimposed upon pulmonary edema, atelectasis, or other non-infectious processes. VAP prevention measures that work by decreasing bacterial colonization preferentially lower the frequency of these mislabelled, more benign events. In addition, misclassification obscures detection of an impact of prevention measures on bona fide pneumonias. Together, these effects create the possibility of the paradox where a prevention measure may have a large impact on VAP rates but minimal impact on patients' outcomes. The paradox makes changes in VAP rates alone an unreliable measure of whether VAP prevention measures are truly beneficial to patients and behooves us to measure their impact on patient outcomes before advocating their adoption.

## The paradox

Hospitals around the world are striving to reduce their rates of ventilator-associated pneumonia (VAP) in order to improve patient outcomes and minimize costs. Professional societies, legislators, quality improvement advocates, and medical product manufacturers are promoting an increasing array of interventions to reduce VAP rates. These include regular oral care, elevation of the head of the bed, continuous aspiration of subglottic secretions, silver-coated endotracheal tubes, and many other initiatives. Some jurisdictions now mandate hospitals to report adherence with a subset of these 'process measures'. Review of the literature supporting these interventions, however, reveals a striking paradox: each of

these strategies dramatically reduces VAP rates but almost none has any impact on patients' duration of mechanical ventilation, hospital length of stay, or mortality (Table 1).

Regular oral care with chlorhexidine, for example, reduces VAP rates by up to 37% to 66% but has no impact on duration of mechanical ventilation, intensive care unit (ICU) or hospital length of stay, or mortality [1-4]. Likewise, elevation of the head reduces the VAP rate by 78% [5], continuous aspiration of subglottic secretions reduces VAP rates by 50% to 55% [6,7], and silver-coated endotracheal tubes decrease VAP rates by 36% [8]. None of these investigations, though, showed an impact on patients' outcomes. Many of these studies were not primarily powered to detect a difference in length of stay or mortality, but it is striking that they did not even show trends toward improvements in these outcomes regardless of whether considered alone or in meta-analyses that included thousands of patients [4,9,10]. The failure of these studies to detect an impact on patient outcomes is conspicuous since the balance of research does show that VAP doubles the risk of dying and increases intensive care length of stay by a mean of 6 days [11].

## The explanation

The source of this paradox lies in the ambiguity and inaccuracy inherent in VAP diagnosis. VAP is typically defined as the presence of fever, abnormal white blood cell count, purulent sputum, and new radiographic infiltrates. On intensive investigation, however, only a fraction of patients with these signs truly have histological pneumonia [12]. Instead, up to two thirds of people who fulfill this definition have one or more alternative conditions that range from relatively benign, such as atelectasis and tracheobronchitis, to severe, such as acute respiratory distress syndrome or pulmonary infarction [13,14].

ICU = intensive care unit; VAP = ventilator-associated pneumonia.

Table 1

## Randomized controlled trials of interventions to prevent ventilator-associated pneumonia

	Impact on					
	Subjects	VAP rates	Ventilator LOS	ICU LOS	Hospital LOS	Mortality
Elevation of the head of the bed						
Drakulovic, <i>et al.</i> , 1999 [5]	86	78% ↓	NS	NS	-	NS
van Nieuwenhoven, <i>et al.</i> , 2006 [46]	221	NS	NS	NS	-	NS
Oral care						
Chlorhexidine						
DeRiso, <i>et al.</i> , 1996 [40]	353	NS	NS	-	NS	80% ↓
Fourrier, <i>et al.</i> , 2000 [1]	60	66% ↓	NS	NS	-	NS
Genuit, <i>et al.</i> , 2001 [2]	95	37% ↓	NS	NS	NS	-
Houston, <i>et al.</i> , 2002 [47]	561	NS	NS	-	-	-
Fourrier, <i>et al.</i> , 2005 [48]	228	NS	NS	NS	-	NS
Koeman, <i>et al.</i> , 2006 [3]	257	NS	NS	NS	NS	NS
Segers, <i>et al.</i> , 2006 [49]	954	50% ↓	-	NS	8% ↓	NS
Tantipong, <i>et al.</i> , 2008 [50]	207	NS	-	-	-	NS
Chan, <i>et al.</i> , 2007 [4] (meta-analysis)	2,144	44% ↓	NS	NS	-	NS
Oral topical antibiotics						
Laggner, <i>et al.</i> , 1994 [51] (gentamicin)	67	NS	NS	-	-	NS
Bergmans, <i>et al.</i> , 2001 [52] (gentamicin, colistin, vancomycin)	226	57%-68% ↓	NS	NS	NS	NS
Kollef, <i>et al.</i> , 2006 [53] (iseganan)	709	NS	-	-	-	NS
Chan, <i>et al.</i> , 2007 [4] (meta-analysis)	1,098	NS	NS	NS	-	NS
de Smet, <i>et al.</i> , 2009 [31] (tobramycin, colistin, amphotericin B)	3,894	-	NS	NS	NS	14% ↓
Deep vein thrombosis prophylaxis						
Samama, <i>et al.</i> , 1999 [54]	1,102	-	-	-	-	NS
Fraisse, <i>et al.</i> , 2000 [55]	223	-	-	-	-	NS
Leizorovicz, <i>et al.</i> , 2004 [56]	3,706	-	-	-	-	NS
Mahé, <i>et al.</i> , 2005 [57]	2,474	-	-	-	-	NS
Stress ulcer prophylaxis						
Prod'hom, <i>et al.</i> , 1994 [58]	248	NS	-	-	-	NS
Bonten, <i>et al.</i> , 1995 [59]	141	NS	-	-	NS	NS
Yildizdas, <i>et al.</i> , 2002 [60]	160	NS	-	-	-	NS
Kantorova, <i>et al.</i> , 2004 [61]	287	NS	NS	NS	-	NS
Cook, <i>et al.</i> , 1996 [10] (meta-analysis)	7,218	NS	-	-	-	NS
Continuous aspiration of subglottic secretions						
Valles, <i>et al.</i> , 1995 [6]	153	37% ↓	-	NS	-	NS
Kollef, <i>et al.</i> , 1999 [62]	343	39% ↓	NS	NS	NS	NS
Smulders, <i>et al.</i> , 2002 [63]	150	75% ↓	NS	NS	NS	NS
Lorente, <i>et al.</i> , 2007 [64]	280	64% ↓	NS	NS	-	NS
Bouza, <i>et al.</i> , 2008 [39]	690	NS	NS	NS	NS	NS
Silver-coated endotracheal tubes						
Kollef, <i>et al.</i> , 2008 [8]	2,003	36% ↓	NS	NS	NS	NS

ICU, intensive care unit; LOS, length of stay; NS, not statistically significant; VAP, ventilator-associated pneumonia; Ventilator LOS, duration of mechanical ventilation.

The addition of microbiological criteria does little to improve accuracy. Many studies define VAP as the presence of greater than 1,000 colony-forming units per milliliter on culture of bronchoalveolar lavage fluid. This definition is attractive because it is objective, but unfortunately it is no more accurate than clinical criteria alone [15]. The sensitivity and specificity of this definition relative to a histological gold standard are only 50%-70% and 40%-95%, respectively [16-19]. False positives are due to contamination of the lavage specimen by bacteria colonizing the patient's endotracheal tube and upper airway. This effect is particularly marked in patients with prolonged ventilation. False negatives arise from the failure to sample the correct lung segment, insufficient bacterial growth to cross the quantitative threshold, and damping of bacterial growth by prior antibiotic exposure.

Much of VAP misdiagnosis stems from bacterial colonization superimposed upon non-infectious pulmonary processes such as fluid shifts, barotrauma, atelectasis, inflammatory reactions, and exacerbations of patients' underlying lung disease. These factors wax and wane in ways that are difficult to discern at the bedside, leading to the transient appearance of clinical syndromes suggestive of VAP. As often as not, these processes spontaneously resolve in short order without definitive therapy. Clinical trials for early empiric treatment of suspected VAP followed by reassessment 48 to 72 hours later hint at this process. In many patients, the VAP syndrome is no longer present on reassessment and antibiotics can safely be stopped without discernible impact on patient outcomes [20-22].

Mislabelling benign events as VAP creates bias if prevention measures preferentially affect the more benign disorders over the more serious disorders present within the spectrum of conditions that look like VAP. This is particularly likely in studies that use a microbiological definition of VAP to assess interventions that work by decreasing bacterial colonization of the endotracheal tube. For example, the NASCENT (North American Silver-Coated Endotracheal Tube) study of silver-coated endotracheal tubes compared with conventional endotracheal tubes found a statistically significant 36% reduction in microbiologically confirmed VAP yet no difference in the rate of physician-suspected VAP (26% versus 31%,  $P=0.39$ ) or patients with radiographic infiltrates and suggestive clinical signs (53% versus 56%,  $P=0.74$ ) [8]. This discrepancy between rates of microbiologically defined VAP versus clinically defined VAP suggests that silver-coated tubes preferentially decrease colonization rather than infection. This is further borne out by identical durations of mechanical ventilation, ICU stay, hospital stay, and mortality between patients with silver-coated versus conventional tubes. Other interventions that decrease microbial colonization, such as oral chlorhexidine and continuous aspiration of subglottic secretions, might also be subject to this bias.

Mislabelling benign events as VAP further contributes to the paradox by obscuring faint but true signals from bona fide pneumonias. Some interventions designed to prevent VAP may well reduce the frequency of bona fide pneumonias (and truly improve outcomes for this subset of patients), but the plethora of alternative conditions captured by the VAP definition dilute the signal coming from the subset of patients with true pneumonias. Generally low event rates in both the intervention and control groups of many studies compound the challenge of detecting significant impacts on outcomes. These effects may also explain some of the conflicting results in studies evaluating the attributable mortality of VAP: the failure of some studies to detect an impact on mortality [23-26] despite a statistically significant impact in other studies [27-29] and on meta-analysis [11] may be due to damping of the 'true' VAP morbidity signal by misclassifying relatively benign conditions as VAP. Alternatively, VAP may be more of a marker for severity of illness in intubated patients rather than an independent source of morbidity in and of itself. Either way, the failure of multiple clinical trials to detect an impact of VAP prevention measures on patient outcomes suggests that the net benefit of these interventions on the population level is small.

### The implication

The near impossibility of accurate VAP diagnosis compels us to exert great caution when interpreting trial data and hospital surveillance data showing decreases in VAP rates. Lower rates in the intervention arm of clinical trials may reflect disproportionate decreases in benign mimickers of VAP rather than VAP itself. Similarly, observational reports of markedly reduced VAP rates in some hospitals may reflect measurement artefact more than true reductions in serious disease [14]. Before advocating their adoption, we need to see that new interventions and quality improvement programs impact meaningful outcomes rather than just VAP rates.

Likewise, legislators considering mandatory reporting of VAP prevention process measures should consider their impact on outcomes before compelling implementation. Due to the inaccuracy and ambiguity in surveillance definitions, many jurisdictions have shied away from requiring VAP reporting [14,30]. It will be a great irony if these jurisdictions now compel hospitals to report VAP prevention process measures validated by studies that used the same imperfect VAP definitions to prove their value yet failed to show any impact on patient outcomes.

Clinicians and patients can take heart that some interventions have been shown to improve hard outcomes and do merit adoption. Selective oropharyngeal decontamination reduces ICU patients' mortality [31]. Likewise, daily sedative interruptions and daily assessments of readiness to extubate consistently reduce patients' duration of mechanical ventilation and possibly lower mortality (Table 2) [32-38]. Other

Table 2

## Randomized controlled trials of ventilator weaning strategies

	Subjects	VAP rates	Impact on			
			Ventilator LOS	ICU LOS	Hospital LOS	Mortality
Daily spontaneous breathing trial						
Esteban, <i>et al.</i> , 1995 [35]	546	-	40% ↓ (-2 days)	-	-	-
Ely, <i>et al.</i> , 1996 [34]	300	-	25% ↓ (-1.5 days)	NS	NS	NS
Kollef, <i>et al.</i> , 1997 [33]	357	-	20% ↓ (-0.4 days)	-	NS	NS
Marelich, <i>et al.</i> , 2000 [32]	385	NS	45% ↓ (-2.3 days)	-	-	NS
Lellouche, <i>et al.</i> , 2006 [36]	144	NS	38% ↓ (-4.5 days)	22.6% ↓ (-3.5 days)	NS	NS
Daily sedative interruption						
Kress, <i>et al.</i> , 2000 [37] and Schweickert, <i>et al.</i> , 2004 [65]	128	NS	33% ↓ (-2.4 days)	35% ↓ (-3.5 days)	NS	NS
Daily spontaneous breathing trial and sedative interruption						
Girard, <i>et al.</i> , 2008 [38]	336	-	19% ↓ (-3.1 days)	29% ↓ (-3.8 days)	22% ↓ (-4.3 days)	28 days: NS 1 year: 32% ↓

ICU, intensive care unit; LOS, length of stay; NS, no statistically significant impact; VAP, ventilator-associated pneumonia; Ventilator LOS, duration of mechanical ventilation.

VAP prevention measures may decrease antibiotic usage [39,40] but this outcome has not yet been widely studied.

There is also tentative evidence that combining interventions into bundles may impact patient outcomes even when the component interventions alone do not. Ventilator bundles typically include elevating the head of the bed, stress ulcer prophylaxis, thromboembolism prophylaxis, and a daily weaning assessment. None of these measures in isolation has been shown to decrease patients' length of stay, yet three centers implementing these measures as a bundle reported shorter ICU lengths of stay [41-43] and a fourth center found shorter hospital length of stay [44] compared with historical rates. These studies, while promising, need to be interpreted with great caution since they suffer many methodological limitations, including the use of historical rather than concurrent controls [45].

For too long, we have accepted VAP as a surrogate marker for the outcomes we really care about, namely patients' duration of mechanical ventilation, hospital length of stay, and mortality. The disparity between prevention measures' impact on VAP rates and their lack of impact on patient outcomes underscores the inadequacy of VAP as a surrogate marker. We need to directly assess the impact of VAP prevention measures on patient outcomes before advocating or compelling their adoption.

## Competing interests

The author declares that they have no competing interests.

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