Diagnostics and epidemiology in ventilator-associated pneumonia

Andrew F. Shorr, Chee M. Chan and Marya D. Zilberberg

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Abstract: Ventilator-associated pneumonia (VAP) represents a common nosocomial complication arising in the intensive care unit. Owing to concerns regarding the excess morbidity related to VAP, multiple interventions for preventing this syndrome exist. Despite controversy regarding the optimal diagnostic approach to VAP, clinicians now face many external pressures to try to reduce, if not eliminate, VAP. In fact, some organizations consider VAP an entirely preventable event. However, any dialog regarding the outcomes and burden of VAP must rest on an understanding and appreciation of both the diagnostic complexities surrounding VAP and the epidemiology of this condition. In addition, the issues of diagnostics and epidemiology are closely linked. The means employed for diagnosing VAP certainly affect the observed prevalence of VAP. Despite these concerns, several general themes emerge in the literature describing VAP epidemiology. First, VAP rates vary based on the diagnostic approach employed. Second, select cohorts of patients are at high risk for VAP, and patient case-mix clearly influences the epidemiology of VAP. Third, rates of VAP appear higher outside the US, irrespective of the diagnostic paradigm utilized.

Keywords: diagnosis, epidemiology, outcomes, ventilator-associated pneumonia

Introduction

Ventilator-associated pneumonia (VAP) remains a focus of both research and clinical care. Although traditionally VAP was thought to contribute to excess mortality in critically ill patients, strong evidence demonstrating an attributable mortality related to VAP has been limited [Nguile-Makao *et al.* 2010]. Greater consensus exists surrounding the notion that VAP leads to longer durations of ventilation and time in the intensive care unit (ICU) [Shorr *et al.* 2009; Warren *et al.* 2003]. This excess morbidity results in estimated costs per case of nearly US$15,000 [Shorr *et al.* 2009; Warren *et al.* 2003]. Other analysts have suggested that the costs of VAP are much higher. For example, Rello and coworkers estimated that the costs of VAP exceeded US$40,000 per occurrence [Rello *et al.* 2002]. This discordance in cost estimates reflects that some studies have used the concepts of 'charge' and 'cost' interchangeably. Often charge data are easy to obtain from medical billing records. In medicine 'charges', particularly in the US, rarely correlate with costs, when the term 'cost' is meant to describe the actual consumption of resources [Zilberberg and Shorr 2010a]. When charge data are employed rather than actual cost information, the estimated burden of a disease is almost uniformly increased.

Owing to the morbidity penalty associated with VAP, VAP prevention has become a major initiative in hospitals across the world. For example, in the US, some states require public reporting of rates of VAP. Similarly, third-party payers and national healthcare payers, such as the Centers for Medicare and Medicaid Services, are threatening to withhold reimbursement for the costs of VAP [Klompas and Platt, 2007]. As with the current situation revolving around catheter-associated bloodstream infections (CABSIs), these organizations suggest that VAP represents a relative 'medical error'. As such, these authorities claim that VAP should represent a 'never event'. Rates of VAP, as a corollary, are considered markers of hospital quality.

Any dialog about either the attributable burden of VAP, means for preventing VAP, or the

Correspondence to:
Andrew F. Shorr, MD, MPH
Pulmonary and Critical Care Medicine, Room 2A-68D, Washington Hospital Center, 110 Irving Street NW, Washington, DC 20010, USA
afshorr@dnamail.com

Chee M. Chan, MD, MPH
Section of Pulmonary and Critical Care Medicine, Washington Hospital Center, Washington, DC, USA

Marya D. Zilberberg, MD, MPH
EviMed Research Group, LLC, Goshen, MA and University of Massachusetts, Amherst, MA, USA

relationship between VAP and hospital quality presupposes some information regarding the epidemiology of VAP. In other words, one cannot discuss what VAP means for our patients and hospitals until one determines how to diagnose and to track VAP. The recent prominence of VAP has resulted in much confusion in the medical literature predominantly because of uncertainty about both diagnostics and epidemiology.

VAP diagnostics

Two broad strategies exist for the diagnosis of VAP. One relies essentially on clinical criteria while the other requires evidence of a pathogen in the lower airways. Confusing all research into the diagnosis of VAP is the lack of an accepted gold standard [American Thoracic Society and the Infectious Diseases Society of America, 2005]. Unlike the diagnosis of acute myocardial infarction or pulmonary embolism where there are clear, easy to apply, and validated diagnostic criteria, this is not the case in VAP. As a consequence, varying findings in epidemiologic studies dealing with VAP occurrence, in part, reflect the differing diagnostic criteria employed. Put simply, when contrasting VAP epidemiology studies, it is unclear whether one is actually comparing 'apples with apples'.

Clinical approaches

The most routinely utilized clinical criteria for VAP were developed by the US Centers for Disease Control and Prevention. Direct application of these clinical criteria is relatively easy, does not require extensive, specialized training, and does not necessitate expensive diagnostic tools. Despite these strengths of this paradigm, this clinical approach likely over-diagnoses VAP [American Thoracic Society and the Infectious Diseases Society of America, 2005; Baughman 2005]. This is particularly concerning given the relatively nonspecific findings seen in pneumonia in the critically ill patient. Many of the findings seen in true VAP, such as fever, elevated white blood cell counts (WBCs), and the presence of a new or evolving infiltrate can often be explained by processes other than VAP. Some of these possible alternate diagnoses even encompass the broad day-to-day intrapatient fluctuations seen within ICU subjects.

The current CDC definition has three specific components: radiologic evidence of infection, systemic findings of inflammation, and specific pulmonary signs of organ compromise [Edwards *et al.* 2009]. Again, these criteria do not require microbiologic evidence of infection. Thus they likely lead to misdiagnosis and overdiagnosis even when not properly applied. Proof of this point can be found in initiatives to revise the clinical criteria. For example, new more stringent clinical criteria for VAP have been implemented as part of the National Healthcare Safety Network (NHSN) [Edwards *et al.* 2009]. The NHSN is a follow-on national surveillance system in the US evolving from the original National Nosocomial Infections Network. The new NHSN definition does require isolation of a pathogen [Edwards *et al.* 2009]. This can derive from blood, pleural, sputum, or lower airway cultures. Although modern culturing strategies are not perfect and may certainly fail to detect a pathogen when one is likely present, the requirement of pathogen isolation has major implications for how one evaluates the epidemiology of VAP. Edwards and colleagues recently reported the findings from NHSN surveillance covering 2006–2009 [Edwards *et al.* 2009]. The median rate of VAP based on clinical criteria was approximately 3 per 1000 ventilator days. The rate varied based on ICU type ranging from more than 10 per 1000 ventilator days in burn ICUs to less than 1 case per 1000 ventilator days in pediatric cardiothoracic ICUs [Edwards *et al.* 2009]. When the rate of VAP was calculated based on the modified CDC criteria and requiring microbiologic confirmation of infection, the rate fell by more than 40% [Edwards *et al.* 2009]. This fall in VAP rates was evident in all types of ICUs. However, this impact on VAP prevalence was most evident in those ICUs where the patient case mix was such that there were likely to be many clinical conditions which can confound the diagnosis of VAP.

Furthermore, until recently little research addressed the interobserver variability in the clinical criteria for VAP diagnosis. Diagnostic criteria for any condition that are prone to substantial interobserver variability undermine efforts to correctly assess epidemiology and to initiate protocols for treatment and prevention. Substantial interobserver variability in the clinical criteria for VAP diagnosis is particularly concerning given the way VAP incidence is being utilized as a surrogate for hospital quality. Despite this concern and the attendant incentive it provides to undercount VAP, few analyses have systematically compared the agreement among

differing adjudicators for VAP determination. Klompas had three observers apply the clinical diagnostic criteria for VAP to 50 patients suspected of having VAP. The kappa statistic measured 0.40, indicating weak agreement [Klompas, 2010]. In fewer than two-thirds of cases did all of the assessors agree as to either the presence of absence of VAP. In examining the sources of the disagreement, there was very poor agreement as to whether (1) a change in sputum quality or quantity had transpired and (2) if impaired gas exchange had developed [Klompas, 2010]. However, even with respect to something that should be fairly objective, such as the presence of fever, there was still major discordance among the various clinician reviewers.

In order to minimize the subjectivity in a purely clinical diagnostic standard, some have advocated broader utilization of the Clinical Pulmonary Infection Score (CPIS). Pugin and colleagues developed the CPIS in a cohort of medical patients and relied on pulmonary pathology as the gold standard for the diagnosis of VAP [Pugin *et al.* 1991]. The CPIS assigns points based on the extent of fever, the magnitude of the WBC change, the degree of hypoxemia, the change in tracheal secretions, and the distribution of chest infiltrates. A score of >6 is thought to indicate a diagnosis of VAP [Zilberberg and Shorr, 2010b]. Reflecting a desire to make VAP diagnostics more objective, both US and European drug regulatory authorities essentially require computation of the CPIS as part of the assessment for eligibility in randomized, controlled trials (RCTs) of therapeutic agents for VAP. Furthermore, RCTs in other areas of critical care have embraced CPIS as a diagnostic tool.

Unfortunately it remains unclear whether CPIS represents an improvement [Zilberberg and Shorr, 2010b]. First, the CPIS has mainly been evaluated in medical ICU patients. Studies in surgical and trauma patients reveal that the CPIS performs poorly. In nearly 250 trauma patients, Croce and colleagues observed that the CPIS had a sensitivity and specificity of only 61% and 43%, respectively, compared with bronchoalveolar lavage (BAL) [Croce *et al.* 2006]. Second, a meta-analysis of all of the studies of CPIS that relied on an independent definition of VAP identified only two well done studies and determined that the CPIS alone was inadequate for the diagnosis of VAP [Klompas, 2007]. Third, as with pure clinical criteria for VAP the CPIS remains prone to interobserver variability. Schurink and colleagues assessed the interobserver variability of the CPIS and calculated that the kappa statistic measured only 0.16 [Schurink *et al.* 2004]. This low extent of correlation underscores that the CPIS alone has many limitations.

One theoretical means for improving on clinical criteria along with sputum cultures and/or tracheal aspirates is to utilize quantitative and semiquantitative approaches to the culture. This is routinely a component of lower airway culturing (as described in the following). Via an objective assessment of the organism burden in the upper airway, one potentially can limit the impact of colonization. Colonizing organisms tend to be present but in lower numbers relative to the true infecting pathogen. Although intellectually attractive as a way to balance the need for a more specific means for determining the presence of actual infection against the issues related to lower airway culturing, few data support this approach [Chastre *et al.* 2010]. Studies that have examined quantitative tracheal aspirates relative to lower airway culturing as a tool to guide antibiotic management indicate that the lower airway approach is superior [Giantsou *et al.* 2007]. In a recent analysis of quantitative tracheal aspirates, Giantsou and colleagues noted that lower airway culturing proved superior at facilitating de-escalation of antibiotics [Giantsou *et al.* 2007]. Tetenta and Metersky further documented that quantitative tracheal aspirates proved unhelpful when the pathogen of concern was *Staphylococcus aureus*, a notorious upper airway colonizer in mechanically ventilated subjects [Tetenta and Metersky, 2010]. Those advocating for the use of either semiquantitative or quantitiave tracheal aspirates and sputa cultures in the diagnosis of VAP argue that this approach has acceptable sensitivity and specificity [Niederman, 2010]. Such arguments are specious since they fail to acknowledge that there is no accepted gold standard for the diagnosis of VAP. Hence, discussions of sensitivity and specificity are necessarily limited, if not misdirected. The key issue, therefore, becomes one of how diagnostics affect outcomes, and few studies have even approached this topic in terms of the role for quantitative and semiquantitative tracheal aspirates.

Invasive approaches

Reliance on isolation of a lower airway pathogen represents an alternative approach to the diagnosis of VAP. The theory here is that samples from the lower airways are less likely to represent upper airway colonization and rather indicate a true infectious process. In addition, recovery of an organism in sufficient quantity from the lower airways helps limit the lack of specificity associated with a pure clinical approach to VAP. Confirming this notion are studies demonstrating no excess mortality among patients in whom antibiotics are withheld as a consequence of negative lower airway cultures [Baughman, 2005].

There are several means for obtaining lower airway samples. These include traditional brochoscopic methods such as BAL and bronchoscopic brush (BB). Because there is always the potential for contamination of the bronchoscope from upper airway secretions, and given the fact that bacteria reside in the lung naturally, invasive approaches usually rely on a quantitative assessment of organism burden. For these reasons, the quantitative approach with respect to the lung is similar to the situation surrounding the diagnosis of urinary tract infections. For BAL traditionally a culture is considered positive when there are 10^4 colony forming units (CFUs) isolated per milliliter while for BB fewer organisms ($>10^3$ CFUs/ml) defines a positive culture [American Thoracic Society and the Infectious Diseases Society of America, 2005; Baughman 2005]. One concern with any quantitative threshold is that it is necessarily arbitrary and in some ways trades specificity for sensitivity. Several studies have detailed the relationship between quantitative colony counts noted in the lower airways of persons with a clearly defined clinical pneumonia versus those lacking pneumonia [Cantral *et al.* 1993; Thorpe *et al.* 1987].

Nonbronchoscopic approaches to obtaining lower airway samples include blind BB and mini-BAL. Both of these alternatives have the advantage of not requiring a formal bronchoscopy and its attendant risks. Moreover, these less-invasive options can be easily performed during nonstandard duty hours by respiratory therapists. Hence, the culture can be obtained soon after there is a clinical suspicion for VAP, rather than waiting until some time when a bronchoscopist is available. Studies comparing both mini-BAL and blind BB with traditional bronchoscopic strategies demonstrate that these techniques perform similarly [Kollef and Ward, 1998; Papazian, *et al.* 1995]. One key caveat is that these comparisons have been conducted in immunocompetent subjects.

The main limitation of all lower airway approaches is cost. Any method employing bronchoscopy results in greater expense. Although nonbronchoscopic techniques are less expensive than traditional bronchoscopy with either BAL or brush, mini-BAL and BB kits costs approximately US$20–50. Quantitative (or even semi-quantitative) cultures which are required with lower airway sampling are also more expensive than standard cultures.

With respect to patient outcomes several protocols have randomized patients to diagnostic algorithms relying on lower airway sampling with either bronchoscopic or nonbronchoscopic cultures or to diagnosis based on sputum cultures/endotracheal aspirate [Ruiz *et al.* 2000; Solé Violán *et al.* 2000; Sanchez-Nieto *et al.* 1998]. These reports and a subsequent meta-analysis show that the diagnostic strategy does not alter mortality [Shorr *et al.* 2005]. However, antibiotic management is more often altered in persons undergoing lower airway culturing [Shorr *et al.* 2005]. Part of the shift in antibiotic utilization with lower airway approaches can be attributed to an increase in physicians' comfort with discontinuing antibiotics if these cultures are negative. The combination of similar mortality rates coupled with less antibiotic use suggests that lower airway culturing as a strategy does correctly identify subjects without a clinically significant pneumonia. As such, for epidemiologic purposes, analyses that employ lower airway culturing likely better capture the true incidence and burden of VAP.

Epidemiology

With an appreciation of the complex issues surrounding diagnosis one can better comprehend the epidemiology of VAP. Epidemiologic information describing VAP derives from two main sources. First are reports specifically focusing on either the epidemiology or microbiology of VAP as part of surveillance programs for nosocomial infection. Some of these analyses are retrospective while others are prospective. The definition of VAP is often not consistent across these studies. Second, important insights into the shifting epidemiology of VAP come from

interventional efforts to reduce VAP prevalence. Some of these prevention trials describe single interventions while other look at bundles of care which contain various components. The control arm of these prevention trials provides baseline information regarding the initial rate of VAP.

Surveillance studies

Most surveillance studies of VAP prevalence are directed by either national or international organizations focused on infection control. Owing to their large sample size and the differing types of institutions participating, these reports provide crucial information across a range of hospitals and ICUs.

Rosenthal and co-workers recently reported the findings of the International Nosocomial Infection Control Consortium (INICC) [Rosenthal *et al.* 2010]. The INICC models itself after the NHSN from the US and includes hospitals from across the globe. Mainly, though, participating hospitals are found in South America, Southeast Asia, Eastern Europe, and the Middle East. Both pediatric and adult ICUs contribute to the INICC. In its latest publication regarding VAP, 173 ICUs were involved with approximately half being mixed medical–surgical ICUs [Rosenthal *et al.* 2010]. The INICC directly adopts the CDC definitions of VAP and does not require microbiologic evidence of infection. The authors estimated that the pooled rate of VAP was 13.6 cases per 1000 ventilator days [Rosenthal *et al.* 2010]. Rates of VAP were highest in trauma and neurosurgical ICUs (51.7 cases per 1000 ventilator days and 25.3 cases per 1000 ventilator days, respectively). In cardiothoracic ICUs, the rate was only 9.3 cases per 1000 ventilator days [Rosenthal *et al.*, 2010]. Of note these rates are remarkably higher than those noted in studies from the US and from Europe. Beyond the concerns noted above with overdiagnosis based on clinical criteria, the data from the INICC does not appear to undergo quality control efforts or random auditing for accuracy.

In comparison, the NHSN incorporates data from over 1500 US hospitals in 48 states [Edwards *et al.* 2009]. The data from the NHSN undergo periodic auditing. In most instances, the information reported to the NHSN is provided by a trained infection control practitioner. Rates of VAP were less than a quarter of what was seen internationally in the INICC (approximately 3 per 1000 ventilator days) [Edwards *et al.* 2009]. As with the INICC study, the prevalence of VAP varied based on ICU type [Edwards *et al.* 2009]. Again, VAP was most prevalent in trauma and burn ICUs (8.0 and 10.7 cases per 1000 ventilator days). VAP appeared least often in mixed medical/surgical ICUs at nonteaching hospitals (two cases per 1000 ventilator days). The rate in cardiothoracic ICUs equaled 3.9 episodes per 1000 ventilator days [Edwards *et al.* 2009]. When microbiologic evidence of a pathogen (e.g. tracheal aspirate) was required for the definition of VAP, rates fell across the board and across ICU types by approximately half [Edwards *et al.* 2009]. Nonetheless, even with these more stringent criteria these results highlight that no single type of ICU in the US appears to have successfully eliminated VAP. The variability in rates based on case mix and on diagnostic criteria underscores the need to be cautious when interpreting publicly reported quality data about VAP. Who and how VAP is counted clearly confounds efforts to assess the true impact of VAP on the healthcare system.

Confirming the importance of case definitions as part of the process for estimating the morbidity and mortality burden of VAP, Muscedere and colleagues evaluated the Canadian experience with VAP [Muscedere *et al.* 2008]. Based on an estimated VAP rate of 10.6 cases per 1000 ventilator days, these investigators estimated that VAP accounted for 2% of all ICU days in Canada and cost the healthcare system CAN$46 million [Muscedere *et al.* 2008]. However, when these researchers applied a more stringent definition for VAP and concluded that the true VAP rate in Canada might approximate 5.1 cases per 1000 ventilator days (half the baseline estimate of VAP prevalence), the economic implications of VAP fell significantly [Muscedere, *et al.* 2008]. In this situation, VAP added only approximately CAN$10 million to the Canadian healthcare expenditures.

One population that often receives disproportionate attention with respect to VAP consists of patients who have undergone cardiothoracic surgery. Cardiothoracic surgery is performed commonly in the US. Because many of these surgeries are covered by Medicare, the CMS has directed substantial resources towards quality control in this field. Complication and mortality rates are followed closely. Moreover, VAP following cardiothoracic surgery may contribute to

excess mortality, as those undergoing this form of surgery are often otherwise healthy. Hortal and co-workers prospectively attempted to gage the incidence of and risk factors for VAP following cardiothoracic surgery [Hortal *et al.* 2009a]. They calculated a VAP rate of 22.2 episodes per 1000 ventilator days (nearly 6% of all patients) [Hortal *et al.* 2009a]. Confirming the nexus between duration of mechanical ventilation and VAP, the median duration of ventilation prior to the diagnosis of VAP was 9 days. Although these authors prospectively applied their case definition, they did not require lower airway confirmation of infection. Rather they potentially overestimated the prevalence of VAP via use of the CPIS along with endotracheal aspirates. The high rate of VAP also stands in contradistinction to the rate reported in the NHSN for US centers [Edwards *et al.* 2009]. This discordance may, in part, reflect the fact that this study reported the experience of a single center.

Building on this project and in an effort to obtain more generalizable results, several of these researchers conducted a multicenter prevalence study in Western European cardiothoracic ICUs [Hortal *et al.* 2009b]. They used a definition similar to the one applied in the previous study [Hortal *et al.* 2009a]. They also specifically recorded rates of tracheobronchitis as distinct from VAP. The definitions for VAP and tracheobronchitis were similar except that if there was no new or evolving infiltrate, the investigators categorized that as tracheobronchitis. Twenty-five ICUs contributed patients during a 1-month period, and the total population included 971 subjects. VAP arose in 2.1% of subjects [Hortal *et al.* 2009b]. The actual rate of VAP measured 13.9 cases per 1000 ventilator days [Hortal *et al.* 2009b]. This prevalence of VAP was significantly lower than that reported in the original report by Hortal and colleagues [Hortal *et al.* 2009a]. This reinforces the conclusion that VAP rates range substantially from institution to institution, even when exploring a relatively homogeneous population (cardiothoracic surgery patients). Interestingly, the rate of VAP in Western Europe appears higher than that seen in both the INICC participants and the NHSN hospitals. For example, in INICC cardiothoracic ICUs, the prevalence of VAP is less than 10 cases per 1000 ventilator days, and this is likely an overestimate since the INICC, as mentioned earlier, did not require microbiologic confirmation of the diagnosis.

Prevention trials

Most prevention trials examine one or several interventions for preventing VAP. Thus, to measure the impact of the intervention, it is necessary to establish some baseline rate of VAP for comparison. Although VAP prevention studies have limitations in terms of generalizability, they often employ more stringent definitions of VAP than those used in surveillance reports. Well-performed prevention trials, furthermore, are nearly all prospective rather than before-and-after studies. Some prevention projects actually take the form of blinded RCTs, thus limiting confounding due to the Hawthorne effect and secular trends in the outcome. The Hawthorne, or observation, effect is particularly concerning in surveillance studies given the outside pressures to report lower rates of VAP [Zuschneid *et al.* 2007; Gastmeier *et al.* 2006]. In other words, given the external incentives to find fewer VAP cases, rates of VAP fall because people are paying more attention to the concept of VAP. One recent analysis of centers just joining public reporting networks for nosocomial infection concluded that the Hawthorne effect explains a substantial component of decreasing VAP rates [Zuschneid *et al.* 2007]. As such, one must rely on more than just surveillance data to appreciate the epidemiology of VAP.

Many early studies of 'ventilator bundles' for VAP prevention were flawed [Zilberberg *et al.* 2009]. Aside from the before-and-after design, they often failed to describe precisely which interventions for VAP prevention were applied, how compliance with the bundle was assessed, or even the means for the diagnosis of VAP [Zilberberg *et al.* 2009]. Most early ventilator bundle reports were also retrospective and prone to many forms of bias. The quality of the ventilator bundle literature, though, has improved recently. For example, Hawe and colleagues prospectively recorded rates of VAP prior to the implementation of a prevention bundle [Hawe *et al.* 2009]. The diagnosis of VAP did not require lower airway culturing, which limits this study. However the authors did assess rates of bundle compliance. In the pre-intervention time frame the rate of VAP was 19.1 cases per 1000 ventilator days and fell to 7.5 cases per 1000 ventilator days after the bundle was applied. Rates of compliance with various preventive options, such as head of the bed elevation, increased significantly [Hawe *et al.* 2009]. The pre-intervention high rate of VAP is consistent with other reports from

Europe and adds credence to the notion that VAP is more of a challenge there than in the US.

A similar report from the US confirms that in VAP bundle projects, baseline rates of VAP seem comparable to those described in surveillance studies. Bird and colleagues prospectively examined VAP rates before and after the addition of a ventilator bundle to routine care in a surgical ICU [Bird *et al.* 2010]. As with the report by Hawe and coworkers, these investigators employed a modified clinical definition for VAP which did not require lower airway culturing. The VAP rate prior to the bundle's adoption measured 10.2 cases per 1000 ventilator days and was reduced to 3.4 cases per 1000 ventilator days subsequently. Even with the bundle VAP was not eliminated [Bird *et al.* 2010].

The most rigorously designed trial of bundles for VAP prevention was reported by Bouadma and coworkers [Bouadma *et al.* 2010]. These researchers developed a VAP bundle based on a multidisciplinary team that explored local issues with VAP education and ventilator care. Rather than advocating for some broad bundle they focused on eight specific interventions for VAP prevention and assessed compliance with these both before and after the intervention. All data were collected prospectively. Unlike earlier analyses of bundles, they measured outcomes an extended period after the intervention was in place (2 years). For the diagnosis of VAP, lower airway culturing with quantitative cultures was required. This aspect of the study alone reinforces the quality of the epidemiologic information one can glean from this report. Baseline VAP prevalence appeared similar to the rate described across Europe (23.5 cases per 1000 ventilator days) [Bouadma *et al.* 2010]. In the first year after the bundle's implementation VAP rates fell to 14.9 cases per 1000 ventilator days while the burden of VAP continued to fall at year two after the study (11.5 cases per 1000 ventilator days) [Bouadma *et al.* 2010].

The reason for the high rate of VAP in Europe compared with the US, irrespective of the diagnostic approach, is unclear. The difference cannot be explained by case mix alone given that the trend is seen both in mixed populations and also within specific ICU subtypes. The use and duration of ventilation also appears similar between the US and Europe. Possibly other features of ICU organization may explain these findings. Irrespective of the reason for the variability, these results reinforce the need to avoid generalizing across the globe as to either the epidemiology or outcomes associated with VAP.

Unlike studies of bundles, RCTs for preventative options for VAP are not confounded by observation bias. Even in the more rigorous, prospective observational analyses of ventilator bundles, one cannot exclude that the rate of VAP is affected by the Hawthorne effect. Thus, the final reported VAP rate may be suppressed artificially. This tends not to be a concern in randomized trials. The limitations of RCTs, though, relate to confounding due to temporal trends in the rate of VAP (e.g. the VAP rate was falling prior to and during the study despite the intervention under evaluation). In addition, the results may lack generalizability due to the myriad exclusion criteria for entry into the RCT.

Caruso and coworkers hypothesized that the instillation of saline prior to suctioning would decrease the rate of VAP in their ICU [Caruso *et al.* 2009]. To assess this, they randomized patients to either saline installation or placebo. Unfortunately, the authors failed to describe in detail the standard measures they employed in their ICU for VAP prevention. Despite this, the population appeared well matched as to VAP risk factors. As with the bundle study by Bouadma and colleagues, these authors relied on lower airway cultures to confirm the diagnosis of VAP. The rate of VAP declined with the saline approach from 21 cases per 1000 ventilator days to approximately 10 VAPs per 1000 ventilator days [Caruso *et al.* 2009]. Again, these data from Western Europe reinforce the proposition that the baseline rate of VAP there is approximately 20 cases per 1000 days of ventilation exposure.

Bouza and colleagues conducted a single-center RCT limited to cardiac surgery patients [Bouza *et al.* 2008]. In their study they randomized patients to an endotracheal tube capable of continuous subglottic suctioning relative to a traditional endotracheal tube. Lower airway culturing was not required. The rate of VAP in the control arm equaled 27.6 cases per 1000 ventilator days [Bouza *et al.* 2008]. The novel endotracheal tube did not alter rates of VAP significantly (17.9 cases per 1000 ventilator days) [Bouza *et al.* 2008]. Again, these findings suggest that VAP rates following major heart

surgery are relatively stable in Europe (in contrast to the US) and consistent across varying study populations and design types. Put another way, irrespective of how one appears to diagnose VAP or how one chooses to evaluate the incidence of VAP, the rate in Europe, at least, appears rather consistent. Conversely, variability in the estimated incidence of VAP in observational studies does suggest potential underreporting.

The insights one gleans from prevention trials in the US, though, appear different. Morrow and colleagues, for instance, evaluated the efficacy of probiotic prophylaxis for VAP prevention [Morrow *et al.* 2010]. In this single-center study, the authors described a detailed background approach to VAP prevention and adopted a rigorous definition for VAP that required mini-BAL. Unlike nearly all other studies of VAP, this effort was blinded, which substantially limits the impact of many forms of bias. The prevalence of VAP in the control arm was approximately 7 cases per 1000 ventilator days and was reduced by 50% with the probiotic [Morrow *et al.* 2010]. Although the rate of VAP with either intervention or control was lower than that seen in the European or international reports, the control arm VAP frequency approximates the rate seen in mixed ICUs from teaching hospitals in the NHSN [Edwards *et al.* 2009]. One would have predicted the rate in the control arm of this trial to be lower given the use of lower airway culturing as opposed to the clinical criteria utilized by the NHSN. The somewhat high rate likely reflects the study's entry criteria and the investigators efforts to enroll subjects considered to be at high risk for VAP. Again, despite this fact, the data help to bracket the true rate of VAP seen in US ICUs when one employs a diagnostic method with substantial precision.

Confirming that rates of microbiologically proven VAP remain lower in North America as opposed to elsewhere, Kollef and colleagues conducted a multicenter, single-blind trial of a silver-coated endotracheal tube for VAP prevention [Kollef *et al.* 2008]. Sites for this analysis were selected because they had VAP prevention efforts in place and agreed to continue them during the course of the trial. This factor likely limited the effect of parallel temporal trends in the prevalence of VAP on outcomes. In other words, given that VAP rates have been declining in the US, attempts were made to control for this phenomenon during the study's execution via careful site selection. Block randomization by site also helped further limit the impact of preventive efforts at any one center from skewing the results. Among subjects intubated for more than 24 hours, VAP occurred in 7.5% of patients with a conventional endotracheal tube as compared with 4.8% of those intubated with the silver-coated endotracheal tube [Kollef *et al.* 2008]. Based on the median duration of ventilation, the incidence of VAP in the control arm was approximately seven events per 1000 ventilator days [Kollef *et al.* 2008]. The population studied consisted of mixed patient types including medical patients, those suffering trauma, and those undergoing major surgery. Strikingly, this estimated VAP prevalence equals that seen in the trial of probiotics.

Conclusions

The epidemiology of VAP remains a contentious yet important issue. Unlike the scenario surrounding the diagnosis of CABSIs, the case definition for VAP remains controversial. Differing diagnostic algorithms clearly affect estimated rates of VAP. As such, one cannot simply compare rates noted in one report to those described in another without carefully reviewing the diagnostic criteria and the definitions utilized. Similarly, one must examine carefully studies claiming to have eliminated VAP, as simply changing the case definition will alter the prevalence of VAP irrespective of any quality improvement project.

Much effort continues to be directed at VAP prevention. Although prevention generally is a major theme in ICU care, efforts at VAP prevention seem driven by a misperception that there is an epidemic of VAP. This seems particularly true in the US. However, compared with the rest of the world, VAP rates are already significantly lower. Furthermore, this lower rate of VAP is not a reflection of differing diagnostic approaches to the syndrome. Rather, the observation that VAP is less common in the US is a consistent theme irrespective of both (1) the study designs utilized to assess VAP epidemiology and (2) the diagnostic means employed.

Even with lower rates of VAP in the US, the prevalence of VAP differs among ICU types. Select groups appear to be at exceedingly high risk for VAP. Namely, trauma and cardiothoracic surgery patients face a disproportionate risk for VAP. This excess VAP burden again appears whether

the diagnosis is made based purely on clinical criteria or via invasive lower airway culturing. The disproportionate prevalence of VAP in these settings indicates that preventive efforts might be best employed in selected areas rather than diffusely throughout the hospital. As a corollary, no well-performed epidemiologic or preventive analyses indicate that VAP can be eliminated. Rather, when one is consistent in their case finding and diagnostic paradigm and when one extends the period of observation beyond the short term, VAP still occurs. In one sense this is understandable given the natural variability in patients, their disease severity, and compliance with efforts at prevention. Natural systems tend to have too much variability to be entirely predictable. Although one cannot eliminate VAP, it does not necessarily follow, though, that we should abandon attempts to contain and limit VAP.

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