specific guidance regarding the "suspicion of infection" criteria may be required. On the other hand, quality improvement agents may be more interested in more standardized definitions for the local determination of cases. Changes in recognition and coding practices over time could profoundly impact the number of sepsis cases through a Hawthorne-like effect. If these groups have significantly different mortality rates, it may be difficult to gauge whether local interventions are truly successful or are simply the result of "diluting" the total number of sepsis patients with a less critically ill cohort. A detailed understanding of the number of sepsis cases also has significant implications for operations personal for the appropriate development of emergency department and ICU staffing plans and educational initiatives. Finally, accurate estimates of the incidence and mortality rate of sepsis are critical for guiding health policy. This includes both research funding priorities and national quality improvement initiatives.

In short, this study emphasizes the complexity of the seemingly simple problem of diagnosing sepsis. What is now needed is a better understanding of whether the differences highlighted here result from a simple reluctance to code for sepsis, a fundamental problem in the methodology of using administrative datasets for this purpose, or whether there is something unique about the 85% of patients who present to the hospital meeting criteria for sepsis who are seemingly missing from our datasets.

REFERENCES

1. Henriksen DP, Laursen CB, Jensen TG, et al: Incidence Rate of Community-Acquired Sepsis Among Hospitalized Acute Patients—A Population-Based Survey. *Crit Care Med* 2015; 43:13–21
2. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
3. Wilhelms SB, Huss FR, Granath G, et al: Assessment of incidence of severe sepsis in Sweden using different ways of abstracting International Classification of Diseases codes: Difficulties with methods and interpretation of results. *Crit Care Med* 2010; 38:1442–1449
4. Gaieski D, Edwards J, Kallan M, Carr B: Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 2013; 41:1167–1174
5. Wang HE, Shapiro NI, Angus DC, et al: National estimates of severe sepsis in United States emergency departments. *Crit Care Med* 2007; 35:1928–1936
6. Dombrovskiy VY, Martin AA, Sunderram J, et al: Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med* 2007; 35:1244–1250
7. Martin GS, Mannino DM, Eaton S, Moss M: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554

Ventilator-Associated Pneumonia and Ventilator-Associated Conditions: Apples Are Not Oranges (Mix Only in a *Salade de Fruits*!)*

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Ventilator-associated pneumonia (VAP) is the most frequent ICU-acquired infection among patients treated with mechanical ventilation (MV) (1, 2). Because VAP leads to considerable use of antibiotics and is associated with increased morbidity, longer hospital stays, increased healthcare costs, and higher mortality rates, its prevention is rightly viewed as imperative by all ICU healthcare workers (3, 4). However, establishing which preventive measures are really effective at preventing VAP and, thus, which one(s) should be implemented in the ICU is hampered by the difficulties that surround its diagnosis and the many confounding factors potentially impacting MV duration and mortality other than healthcare-associated infection in ICU patients (5, 6).

VAP-case definitions are complex, labor intensive, and frequently inaccurate and leave room for subjective interpretation, particularly regarding whether or not a new pulmonary infiltrate is present, which remains a prerequisite for VAP diagnosis according to the Centers for Disease Control and Prevention (CDC) criteria (5, 7–9). Low interrater reliability and poor correlation of usual clinical and microbiologic definitions with histopathology have also been described (10–12). As a consequence, all studies evaluating the potential efficacy of VAP-preventive measures, with unblinded ascertainment of VAP prevalence as the primary endpoint, are vulnerable to assessment bias and should be viewed with extreme caution (9, 11).

Considering the difficulties encountered in diagnosing VAP and that most currently described preventive measures are not easily amenable to blinding, VAP-prevention studies should focus on showing favorable effects on more tangible endpoints, such as ICU mortality and MV duration. However, although mechanically ventilated VAP patients in the ICU appear to have a two- to 10-fold higher risk of death than those without VAP, recent results obtained

*See also p. 22.

Key Words: quality indicator; subglottic-secretion suctioning; ventilator-associated condition; ventilator-associated pneumonia

Dr. Chastre consulted for Pfizer, Bayer, Cubist, Kenta, and Janssen-Cilag.

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with multistate progressive disability models, which appropriately handled VAP as a time-dependent event, demonstrated that VAP-attributable mortality was up to 10% (13–15). Furthermore, VAP increased mortality only in the subset of patients with intermediate disease severity, when initial treatment was inappropriate, and/or in patients with VAP caused by high-risk pathogens, for example, *Pseudomonas aeruginosa.* Patients with very low disease severity and early-onset VAP caused by microorganisms, such as *Haemophilus influenzae* or *Streptococcus pneumoniae*, have excellent prognoses with or without VAP, whereas very ill patients in a quasiterminal state developing late-onset VAP would be unlikely to survive under any circumstances. Therefore, to be sufficiently powered to demonstrate beneficial effects on mortality, VAP-prevention studies must include several thousand patients, thereby rendering them extremely difficult to conduct in practice.

MV duration and ICU length of stay may be more attainable endpoints, since VAP appears to consistently prolong the MV duration and ICU stay by more than or equal to 4 days, with the VAP-attributable ICU length of stay being longer for medical than surgical patients and those infected with "high-risk" as opposed to "low-risk" microbes (4, 16–18). However, many factors can interfere with MV and ICU stay durations, including ventilator settings, nurse/ventilated-patient ratio, fluid management and sedation, and weaning protocols, making such endpoints difficult to use in large, multicenter trials, which are inherently difficult to control.

In September 2011, the CDC convened leaders and experts of key professional organizations to propose new approaches to VAP surveillance and diagnosis in adult patients. This group proposed abandoning the conventional VAP definition and creating new constructs termed ventilator-associated conditions (VAC) and infection-related VAC (IVAC), using routine objective clinical data, readily amenable to electronic data capture (19). Although the VAC definition has changed several times, all of its forms primarily measure changes made to MV settings, that is, positive end-expiratory pressure (PEEP) and FIO_2 levels, aiming to identify patients with deteriorating respiratory status after a period of stability or improvement. Specifically, VAC diagnosis requires an increase of the daily minimum PEEP of at least 3 cm H_2O and/or the daily minimum FIO_2 of at least 20 points sustained, respectively, for at least 2 days after at least 2 days of stable or decreasing daily minimum PEEP and/or FIO_2. Similarly, IVAC requires an abnormal temperature or WBC count within 2 days of VAC onset and clinically suspected infection, defined as the initiation of new antibiotics for at least 4 days. However, whether or not VAC and/or IVAC events are preventable and that their prevention leads to fewer patient-centered outcomes is presently mostly unknown and, to my knowledge, had never been examined in a randomized-controlled trial evaluating a preventive measure specifically targeting VAP.

That is exactly what Damas et al (20) did in their study whose findings are reported in this issue of *Critical Care Medicine*, that is, 352 adult patients intubated with a tracheal tube allowing subglottic-secretion suctioning were randomly assigned to undergo suctioning of oropharyngeal secretions ($n = 170$) or not ($n = 182$), while VAP, VAC, and IVAC prevalences and mortality, MV duration, and antibiotic exposure were determined for the two groups. As recognized by the authors, this suctioning was previously shown to substantially decrease VAP rates in several studies: when the results of the 13 randomized trials that evaluated subglottic-secretion drainage for a total of 2,442 patients were combined in a meta-analysis, the overall risk ratio for VAP was 0.55 (95% CI, 0.46–0.66; $p < 0.00001$), with no heterogeneity (21). Nonetheless, some doubt persists regarding its real efficacy for two major reasons. First, in most previous studies, VAP diagnosis was established using a clinical definition based on the CDC criteria, rather than a more stringent and objective diagnostic tool based on quantitative cultures of distal respiratory specimens obtained with bronchoscopic or nonbronchoscopic techniques, for example, bronchoalveolar lavage. Second, and more worrisome, shorter ICU stay and MV duration could be discerned only when the results of the 13 studies were pooled; no single study was able to demonstrate such a clinical benefit on its own. Regrettably, antimicrobial consumption was not assessed in any of those trials, although a lower VAP prevalence should mean less antibiotic use.

Although some assessment bias cannot be totally excluded in the present study (20), the authors did their best to avoid most of the caveats that were present in the earlier ones concerning VAP diagnosis. All randomized patients were screened daily for VAP onset, and the diagnosis was confirmed by quantitative bacterial culture of at least 10^6 CFU/mL of a true pathogen from an endotracheal specimen or at least 10^4 CFU/mL from bronchoalveolar lavage fluid. After study completion, all cases with suspected or confirmed VAP were reviewed by an infectious disease specialist unaware of the patient's randomized allocation, who ultimately decided whether or not VAP was present. Using that methodology, the researchers were able to confirm undisputedly the subglottic-suctioning impact on VAP prevention and less antibiotic use. VAP was microbiologically confirmed for 15 patients (8.8%) who underwent subglottic-secretion drainage and 32 controls (17.6%) ($p = 0.018$). Their respective VAP rates were 9.6 and 19.8 per 1,000 MV days ($p = 0.0076$). Total antibiotic days were 1,696 for the subglottic-suctioning group, representing 61.6% of the 2,754 ICU days, and 1,965 for the controls, representing 68.5% of the 2,868 ICU days ($p < 0.0001$) (20).

As previously reported (22–25), VAC was diagnosed more frequently than VAP, affecting 78 of the 352 enrolled patients (22.2%), and it was clearly associated with higher mortality (59% and 32.9% of patients with and without VAC, respectively, $p < 0.0001$) and longer MV duration (median, 14 vs 6 d, $p < 0.0001$), also in accordance with a growing body of literature (22–24, 26, 27). However, no difference was observed between the experimental and control groups regarding the percentages of patients who developed VAC (22% and 22.9%, respectively; $p = 0.84$), casting some doubt on the sensitivity and specificity of this construct for diagnosing true VAP episodes. Furthermore, VAC surveillance missed a substantial number of microbiologically documented VAP episodes. Among the 47 patients with VAP, only 25 experienced a concomitant VAC episode (53.2%) and 24 a concomitant IVAC episode (51.1%). Clearly, VAC and IVAC differ from VAP, and as concluded by Damas et al (20), VAC appears to more closely cover other medical entities than

VAP and cannot be used to assess the potential value of measures specifically targeting in-hospital bacterial infection in mechanically ventilated patients. Indeed, their finding is not surprising, since VAC, by construction, was intended to identify additional morbid complications of MV that could trigger clinical deterioration beyond nosocomial pneumonia, such as pulmonary edema, acute respiratory distress syndrome, and atelectasis (19).

Like all studies, this one has some limitations, which were frankly acknowledged by the authors. First, it could not be blinded to physicians and nurses, and thus, as indicated above, an assessment bias cannot be totally excluded. Second, because many patients were intubated outside the ICU or hospital with an endotracheal tube not permitting subglottic-secretion drainage, only a fraction of those admitted to the ICU who required MV could be enrolled, thereby limiting the study's external validity. Finally, because a relatively low number of patients were randomized, we cannot exclude that the absence of a subglottic-suctioning benefit on VAC merely reflected a lack of power. Because VAP leads to VAC in approximately half of the patients, VAP prevention should in fine also decrease VAC.

What lessons, then, can be learned from this study? First, in view of Damas et al's (20) findings, it now seems clear that aspiration of subglottic secretions should be on the list of measures effectively decreasing VAP prevalence and, as such, should be implemented whenever possible in ICU patients requiring prolonged MV. Second, their observations add to a growing body of evidence showing that VAC and VAP definitions are not interchangeable, targeting different morbid conditions, with different prevalences and attributable morbidity and mortality (25, 27). Clearly, the VAC construct cannot replace the usual VAP definition when the objective is to assess the clinical utility of a measure designed to prevent VAP and/or for deciding whether or not an ICU patient should receive antibiotics. However, many arguments favor the application of this construct in an ICU quality-improvement program based on its robustness and objectivity for identifying severe complications that can affect mechanically ventilated patients beyond nosocomial pneumonia (24). Unfortunately, for the time being, which interventions and improvements of care are indeed able to lower VAC rates remain elusive and warrant being the focus of future investigations.

REFERENCES

1. American Thoracic Society; 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* 2005; 171:388–416
2. Chastre J, Fagon JY: Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002; 165:867–903
3. Klevens RM, Edwards JR, Richards CL Jr, et al: Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep* 2007; 122:160–166
4. Zimlichman E, Henderson D, Tamir O, et al: Health care-associated infections: A meta-analysis of costs and financial impact on the US health care system. *JAMA Intern Med* 2013; 173:2039–2046
5. Klompas M: Does this patient have ventilator-associated pneumonia? *JAMA* 2007; 297:1583–1593
6. Bonten MJ, Gaillard CA, Wouters EF, et al: Problems in diagnosing nosocomial pneumonia in mechanically ventilated patients: A review. *Crit Care Med* 1994; 22:1683–1691
7. Uçkay I, Ahmed QA, Sax H, et al: Ventilator-associated pneumonia as a quality indicator for patient safety? *Clin Infect Dis* 2008; 46:557–563
8. Skrupky LP, McConnell K, Dallas J, et al: A comparison of ventilator-associated pneumonia rates as identified according to the National Healthcare Safety Network and American College of Chest Physicians criteria. *Crit Care Med* 2012; 40:281–284
9. Lin MY, Bonten MJ: The dilemma of assessment bias in infection control research. *Clin Infect Dis* 2012; 54:1342–1347
10. Fagon JY, Chastre J, Hance AJ, et al: Evaluation of clinical judgment in the identification and treatment of nosocomial pneumonia in ventilated patients. *Chest* 1993; 103:547–553
11. Klompas M: Interobserver variability in ventilator-associated pneumonia surveillance. *Am J Infect Control* 2010; 38:237–239
12. Fàbregas N, Ewig S, Torres A, et al: Clinical diagnosis of ventilator associated pneumonia revisited: Comparative validation using immediate post-mortem lung biopsies. *Thorax* 1999; 54:867–873
13. Bekaert M, Timsit JF, Vansteelandt S, et al; Outcomerea Study Group: Attributable mortality of ventilator-associated pneumonia: A reappraisal using causal analysis. *Am J Respir Crit Care Med* 2011; 184:1133–1139
14. Melsen WG, Rovers MM, Groenwold RH, et al: Attributable mortality of ventilator-associated pneumonia: A meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect Dis* 2013; 13:665–671
15. Nguile-Makao M, Zahar JR, Français 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* 2010; 36:781–789
16. Kollef MH, Hamilton CW, Ernst FR: Economic impact of ventilator-associated pneumonia in a large matched cohort. *Infect Control Hosp Epidemiol* 2012; 33:250–256
17. Rello J, Ollendorf DA, Oster G, et al; VAP Outcomes Scientific Advisory Group: Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest* 2002; 122:2115–2121
18. Warren DK, Shukla SJ, Olsen MA, et al: Outcome and attributable cost of ventilator-associated pneumonia among intensive care unit patients in a suburban medical center. *Crit Care Med* 2003; 31:1312–1317
19. Magill SS, Klompas M, Balk R, et al: Developing a new, national approach to surveillance for ventilator-associated events. *Crit Care Med* 2013; 41:2467–2475
20. Damas P, Frippiat F, Ancion A, et al: Prevention of Ventilator-Associated Pneumonia and Ventilator-Associated Conditions: A Randomized Controlled Trial With Subglottic Secretion Suctioning. *Crit Care Med* 2015; 43:22–30
21. Muscedere J, Rewa O, McKechnie K, et al: Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: A systematic review and meta-analysis. *Crit Care Med* 2011; 39:1985–1991
22. Klein Klouwenberg PM, van Mourik MS, Ong DS, et al; MARS Consortium: Electronic implementation of a novel surveillance paradigm for ventilator-associated events. Feasibility and validation. *Am J Respir Crit Care Med* 2014; 189:947–955
23. Klompas M, Khan Y, Kleinman K, et al; CDC Prevention Epicenters Program: Multicenter evaluation of a novel surveillance paradigm for complications of mechanical ventilation. *PLoS One* 2011; 6:e18062
24. Muscedere J, Sinuff T, Heyland DK, et al; Canadian Critical Care Trials Group: The clinical impact and preventability of ventilator-associated conditions in critically ill patients who are mechanically ventilated. *Chest* 2013; 144:1453–1460
25. Lilly CM, Landry KE, Sood RN, et al; UMass Memorial Critical Care Operations Group; UMass Memorial Critical Care Operations Group: Prevalence and test characteristics of national health safety network ventilator-associated events. *Crit Care Med* 2014; 42:2019–2028
26. Klompas M, Magill S, Robicsek A, et al; CDC Prevention Epicenters Program: Objective surveillance definitions for ventilator-associated pneumonia. *Crit Care Med* 2012; 40:3154–3161
27. Hayashi Y, Morisawa K, Klompas M, et al: Toward improved surveillance: The impact of ventilator-associated complications on length of stay and antibiotic use in patients in intensive care units. *Clin Infect Dis* 2013; 56:471–477