Prevention of ventilator-associated pneumonia or ventilator-associated complications: A worthy, yet challenging, goal

Marin H. Kollef, MD

Abstract: **Ventilator-associated pneumonia is a difficult diagnosis to establish in the critically ill patient because of the presence of underlying cardiopulmonary disorders (e.g., pulmonary contusion, acute respiratory distress syndrome, atelectasis) and the nonspecific radiographic and clinical signs associated with this infection. However, the escalating antimicrobial resistance of the bacterial pathogens associated with ventilator-associated pneumonia, as well as with other nosocomial infections, has created an imperative to reduce their occurrence and the unnecessary use of antibiotics. Hospital-based process improvement initiatives aimed at the prevention of ventilator-associated pneumonia, and other ventilator-associated complications, have been successfully used despite the limitations of clinical criteria for establishing the diagnosis of ventilator-associated pneumonia. Given current restrictions in hospital resources, absence of available new antimicrobial agents, and potential lack of reimbursement for patients with development of ventilator-associated pneumonia, hospitals need to develop and successfully implement programs aimed at reducing ventilator-associated pneumonia. The use of evidence-based bundles targeting ventilator-associated pneumonia seems to be a reasonable first step in addressing this important clinical problem. (Crit Care Med 2012; 40:000–000)**

Key Words: ●●●

Ventilator-associated pneumonia (VAP) is one of the most common infections managed by critical care physicians. Because VAP historically has been associated with excess morbidity and mortality in critically ill patients, it is an area of significant ongoing research. Although recent studies have challenged the association between VAP and increased mortality, there is greater consensus that VAP is associated with prolonged durations of mechanical ventilation, increased intensive care unit (ICU) length of stay, and increased hospital costs (1–3).

It is important to recognize that one of the major clinical issues related to the management of VAP, as well as other nosocomial infections, is the increasing occurrence of infection caused by multidrug-resistant or extremely drug-resistant pathogens (4). The available evidence suggests that the overall prevalence of nosocomial infections attributed to multidrug-resistant and extremely drug-resistant pathogens, as well as the global use of antibiotics in the hospital setting, and the ICU setting, are not diminishing despite local and national efforts to curb these infections (5). Disorders such as tracheobronchitis and sepsis, which often are diagnosed in the presence of nosocomial pneumonia, seem to be more common contributing, at least in part, to the increasing use of antibiotics in the ICU (6). VAP is recognized to be among the most common infections associated with multidrug-resistant and extremely drug-resistant bacteria including *Pseudomonas aeruginosa*, *Acinetobacter* species, and *Klebsiella pneumonia* carbapenemase containing *Enterobacteriaceae* (6, 7). The recent recognition of *Enterobacteriaceae* containing the *NDM1* gene in multiple continents raises the real possibility of endemic spread of common enteric bacteria possessing resistance to all currently available antibacterial agents (8).

The major concern related to the emergence of multidrug-resistant and extremely drug-resistant pathogens as a cause of nosocomial infections, including VAP, is the inability to empirically treat these infections when they are initially suspected. Inappropriate initial antimicrobial therapy, defined as an antimicrobial regimen that lacks *in vitro* activity against the isolated organism responsible for the infection, has been associated with excess mortality in patients with serious infections, including VAP and severe sepsis (9–13). This is largely related to increasing bacterial resistance to antibiotics as a result of their greater use and the limited availability of newer agents (4, 14). Escalating rates of antimicrobial resistance lead many clinicians to empirically treat critically ill patients with presumed infection with a combination of broad-spectrum antibiotics, which can further perpetuate the cycle of increasing resistance (14). Conversely, inappropriate initial antimicrobial therapy can lead to treatment failures and adverse patient outcomes (15). Furthermore, the limited diversity of available antimicrobial agents has created a clinical situation in which patients are repetitively exposed to the same class of antibiotic, or in some circumstances the exact same agent, resulting in an increased risk of treatment failures and mortality (16). Therefore, the broader concern for all intensivists is how to limit the emergence and spread of multidrug-resistant/extremely drug-resistant pathogens, as well as the infections associated with these pathogens.

Regarding these noted concerns, this review tries to clarify the limitations of current definitions of VAP, especially for assessing the impact of infection prevention programs. It also offers examples of new surveillance definitions and end

From the Department of Medicine, Washington University School of Medicine, St. Louis, MO.

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For information regarding this article, E-mail: mkollef@dom.wustl.edu

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points for quality improvement in the ICU as it relates to VAP and provides support for the use of directed approaches, including the use of bundled interventions, for the prevention of VAP.

Definition of VAP

Clinical criteria are known to be nonspecific for the diagnosis of nosocomial pneumonia, including VAP. Clinical findings such as fever, leukocytosis, and purulent secretions occur with other noninfectious pulmonary conditions, such as atelectasis, pulmonary contusion, and acute respiratory distress syndrome, and therefore lack specificity for the diagnosis of VAP (17–20). Similarly, chest radiographs can be nonspecific for the diagnosis of nosocomial pneumonia. Wunderink et al (21) found that no roentgenographic sign correlated well with the presence of pneumonia in mechanically ventilated patients. The presence of air bronchograms was the only roentgenographic sign that correlated with autopsy-verified pneumonia, correctly predicting 64% of cases. The most frequently used clinical diagnosis of VAP has traditionally required the presence of a new or progressive consolidation on chest radiology plus at least two of the following clinical criteria: fever >38°C, leukocytosis or leukopenia, and purulent secretions. This definition has been supported by several medical specialty groups (22, 23), despite the lack of specificity of these criteria (18–21).

The Centers of Disease Control and Prevention (CDC)/National Healthcare Safety Network has established a clinical definition for the presence of probable nosocomial pneumonia including VAP (24). Unfortunately, these diagnostic criteria have not been validated and at least one study found that decision-making using these criteria was less accurate, potentially resulting in the withholding of antibiotics in 16% of patients with VAP diagnosed by bronchoalveolar lavage (25). We recently compared the observed rates of VAP when utilizing the CDC/National Healthcare Safety Network surveillance method vs. the American College of Chest Physicians clinical criteria (26). Over the course of 1 year, 2060 patients required mechanical ventilation for >24 hrs and were prospectively evaluated. Of these, 83 patients (4%) had VAP according to the American College of Chest Physicians criteria, as compared to 12 patients (0.6%) using the CDC/National Healthcare Safety Network surveillance method. The corresponding rates of VAP were 8.5 vs. 1.2 cases per 1000 ventilator days, respectively. Agreement of the two sets of criteria was poor (κ statistic, 0.26). Quantitative lower respiratory tract cultures were positive in 88% of patients in the American College of Chest Physicians group and 92% in the National Healthcare Safety Network group (26).

Given the limitations of clinical criteria for establishing the diagnosis of VAP, alternative methods have been pursued. Several studies have evaluated the value of quantitative bacteriologic data in establishing the diagnosis of VAP compared to pathologic and clinical criteria. Torres et al (27) used quantitative cultures of respiratory specimens obtained by bronchoalveolar lavage, protected bronchoalveolar lavage, protected specimen brush, and tracheobronchial aspirate that were compared to histology of lung biopsy samples to establish the diagnosis of VAP. Sensitivities for the diagnosis of VAP ranged from 16% to 37% when only histologic reference tests were used, whereas specificity ranged from 50% to 77%. Corresponding positive predictive values ranged from 41% to 43% and negative predictive values ranged from 44% to 48%. When lung histology of guided or blind specimens and microbiology of lung tissue were combined, all quantitative diagnostic techniques achieved relatively higher, but still limited, diagnostic yields (sensitivity range, 43%–83%; positive predictive value range, 72%–83%; specificity range, 67%–91%; negative predictive value range, 61%–84%) (27). Similar diagnostic accuracy has been demonstrated by other investigators using histologic criteria as a reference standard (28–34). Fabregas et al (35) also showed that addition of the results of quantitative cultures to a clinical prediction rule for VAP called the clinical pulmonary infection score did not increase the accuracy of clinical pulmonary infection score in diagnosing VAP. However, Tejerina et al (18) found that the addition of microbiological data to clinical criteria for VAP, including clinical pulmonary infection score, increased the specificity and decreased the sensitivity for establishing the diagnosis of VAP.

Recently, Riaz et al (36) compared nonquantitative and quantitative cultures for the diagnosis of VAP. These investigators found that nonquantitative culture of bronchoalveolar lavage was fairly good at ruling out the presence of VAP but was poor at establishing the presence of VAP because of the low specificity of the test. Despite the limited overall accuracy of quantitative lower respiratory tract cultures for the diagnosis of VAP, the clinical use of such cultures has been associated with less overall antibiotic use (37–40). This presumably occurs because clinicians may have greater confidence in "ruling out" VAP with negative quantitative culture results. Similar reductions in the duration of antibiotic therapy prescribed for clinically suspected VAP have been demonstrated using serum procalcitonin thresholds, clinical pulmonary infection score values, and targeted protocols (41–43).

Given that VAP surveillance is time-consuming, potentially less accurate than clinical/microbiological criteria (25, 26), and the use of quantitative lower respiratory tract cultures for the establishment of VAP is not universally performed, the CDC Prevention Epicenters Program has recently supported efforts aimed at shifting ICU surveillance away from VAP. Instead, the CDC Prevention Epicenters Program has focused on the occurrence of "complications" in general that might circumvent subjectivity and inaccuracy of the definition of VAP, facilitate electronic assessment, make interfacility comparisons more meaningful, and encourage broader prevention strategies. Ventilator-associated complications (VAC) were selected as a more general marker and were defined by sustained increases in patient ventilator settings after a period of stable or decreasing support (Table 1).

The use of VAC as an outcome predictor was examined in a recent CDC Prevention Epicenters Program study of 597 mechanically ventilated patients (44). These investigators found that 9.3% of their study population had development of VAP (8.8 per 1000 ventilator days), whereas 23% had VAC (21.2 per 1000 ventilator days) (44). Compared to matched controls, both VAP and VAC prolonged days to extubation (5.8; 95% confidence interval [CI], 4.2–8.; 6.0; 95% CI, 5.1–7.1, respectively), days to ICU discharge (5.7; 95% CI, 4.2–7.7; 5.0; 95% CI, 4.1–5.9), and days to hospital discharge (4.7; 95% CI, 2.6–7.5; 3.0; 95% CI, 2.1–4.0). VAC was associated with increased mortality (odds ratio, 2.0; 95% CI, 1.3–3.2) but VAP was not (odds ratio, 1.1; 95% CI, 0.5–2.4). VAC assessment was also faster (mean 1.8 vs. 39 mins per patient). Both VAP and VAC events were predom-

Table 1. Criteria for ventilator-associated complications

An increase in the patient's daily minimum PEEP by 2.5 cm H_2O sustained for ≥2 days or an increase in the daily minimum F_{IO_2}) by ≥15 points sustained for ≥2 days after a minimum of 2 days of stable or decreasing daily minimum PEEPs and F_{IO_2}, respectively.
Patients with persistently elevated PEEP (≥7.5 cm H_2O) or F_{IO_2} (≥70%) during the first 3 days of mechanical ventilation (suggesting intubation for a severe, progressive respiratory disorder) were only eligible if they subsequently stabilized and only required minimal ventilator support (PEEP ≤5 cm H_2O and F_{IO_2} ≤40%) for ≥2 days.

PEEP, positive end-expiratory pressure.

Table 2. A new streamlined surveillance defintion for ventilator-associated pneumonia

Any one of the following
1. Opacity, infiltrate, or consolidation that appears, evolves, or persists over ≥72 hrs
2. Cavitation
Any one of the following
1. Temperature >100.4°F within past 24 hrs
2. White blood cell <4,000 or >12,000 white blood cells/mm^3 within past 24 hrs
Both of the following
1. Two days of stable or decreasing daily minimum F_{IO_2} followed by increase in daily minimum F_{IO_2} ≥15 points sustained for ≥2 calendar days OR 2 days of stable or decreasing daily minimum positive end-expiratory pressure followed by increase in daily minimum positive end-expiratory pressure by ≥2.5 cm H_2O sustained for ≥2 calendar days
and
1. Gram-negative stain of respiratory secretions with moderate (2+) or more neutrophils per low-power field within 72 hrs

inantly attributable to pneumonia, pulmonary edema, acute respiratory distress syndrome, and atelectasis. The authors concluded that screening for VAC captures a similar set of complications to traditional VAP surveillance but is faster, more objective, and potentially a superior predictor of clinical outcomes.

Building on their experience with VAC, the CDC Prevention Epicenters Program has begun to evaluate a new streamlined surveillance definition for VAP (sVAP) (Table 2) based on their experience with VAC (45). This proposed study attempts to validate sVAP as a clinical marker of outcomes in the ICU setting. Additionally, these investigators hope to perform an intervention study aimed at optimizing sedation practices in the ICU that will use sVAP as the primary outcome variable. Although sVAP does not necessarily reflect the presence of bacterial pneumonia, it is hoped that this marker will allow quality-improvement efforts to be more accurately assessed across time periods and institutions compared to the traditional use of VAP as an indicator of the quality of medical care (46). However, it is important to note that neither VAC nor sVAP has been evaluated in terms of potentially modifying antibiotic consumption or reducing the emergence of antibiotic-resistant bacteria in the ICU setting.

Bundles for Quality Improvement and the Prevention of VAP

Almost a decade ago, an education-based program at Barnes-Jewish Hospital directed toward respiratory care practitioners and ICU nurses was developed by a multidisciplinary task force to highlight correct practices for the prevention of VAP (47). Each participant was required to complete a preintervention test before reviewing a study module and an identical postintervention test after completion of the study module. After implementation of the education module, the rate of VAP decreased to 5.7 per 1000 ventilator days from 12.6 per 1000 ventilator days (47). The cost-savings secondary to the decreased rate of VAP for the 12 months after the intervention was estimated to be >$400,000. This educational protocol was then implemented across the four largest hospitals in the local healthcare system (48). VAP rates for all four hospitals combined declined by 46%, from 8.75 of 1000 ventilator days in the year before the intervention to 4.74 of 1000 ventilator days in the 18 months after the intervention ($p < .001$). Statistically significant decreased rates were observed at the pediatric hospital and at two of the three adult hospitals. No significant change in VAP rates was seen at the community hospital with the lowest rate of study module completion among respiratory therapists (56%). In addition to showing the effectiveness of a bundle for VAP prevention, these studies highlight the importance of compliance with the elements of the bundle to insure its success. This same education-based bundle package also has been successfully used in the ICUs of a hospital in Thailand (49).

Lansford et al (50) also developed a simple bundle for the prevention of VAP in trauma patients, focusing on head of bed elevation, oral cleansing with chlorhexidine, a once-daily respiratory therapist-driven weaning attempt, and conversion of nasogastric to orogastric feeding tubes. They found that implementation of this bundle was associated with a significant reduction in the rate of VAP. Elements of this bundle also have been shown to be effective in other surgical/trauma units at Barnes-Jewish Hospital (51). However, compliance with infection-control protocols often wane over time and can be significantly influenced by staffing levels in the ICU (52). Some institutions have used computerized flow sheets and quality rounding checklists in the ICU to improve compliance with care measures involved in the prevention of VAP, as well as other complications (e.g., deep vein thrombosis, stress ulcer formation) (53, 54).

Boudama et al (55) recently published a multimodal intervention strategy for VAP prevention with a strong emphasis on process control. This French intervention included a multidisciplinary task force, an educational session, and direct observations with performance feedback, technical improvements, and scheduled reminders. Eight evidence-based bundled interventions were systematically started and used, including: hand hygiene, preferably alcohol-based hand-rubbing; glove and gown use for endotracheal tube manipulation; back-rest elevation of 30 to 45 degrees; tracheal cuff pressure maintenance >20 cm H_2O; use of orogastric tubes; avoidance of gastric overdistension; oral hygiene with chlorhexidine; and elimination of nonessential tracheal suction. The authors carefully monitored compliance with process indicators and VAP rates over the study period. Compliance assessment consisted of five 4-week periods (before the intervention and 1, 6, 12, and 24 months thereafter). Compliance with procedures such as hand hygiene or wearing gloves and gowns for endotracheal tube handling were already

high at study entry and remained so. Other procedures such as back-rest elevation or correct tracheal cuff pressure maintenance were low and did not increase until the introduction of two prompts. Overall quality improvement, measured by a continuous increase in compliance with the eight prevention measures, resulted in a 51% reduction of VAP rates. These investigators focused on process control rather than outcome measure for sustained practice improvement and benchmarking, which is a compelling approach in the light of the unsettled dilemma of VAP definitions and the impact of case-mix (56).

Choosing Elements for Inclusion in VAP Prevention Bundles

The Institute for Healthcare Improvement has put forward the simplest "ventilator bundle," consisting of four evidence-based practices to improve the outcomes of mechanical ventilation: peptic ulcer disease prophylaxis; deep venous thrombosis prophylaxis; elevation of head of the bed; and daily sedation "vacation" and assessment of readiness to wean (57). Interestingly, only two of these bundle elements (elevation of the head of the bed and sedation vacations) have been specifically evaluated as VAP prevention measures. Despite methodologic flaws, a recent systematic review identified four peer-reviewed studies that assessed in various degrees the effect of implementing the Institute for Healthcare Improvement ventilator bundle on the incidence of VAP (58). In these studies, the incidence of VAP decreased from the range of 2.7 to 13.3 cases to 0.0 to 9.3 cases per 1000 ventilator days. In addition, two of the four studies noted a directional decline in the average ICU length of stay. The Institute for Healthcare Improvement bundle approach to VAP prevention, although attractively simple on the surface, may represent only an incremental first, and seemingly sensible, step to translating evidence into practice with an impact that nevertheless remains unknown. The authors of this review also concluded that the Institute for Healthcare Improvement VAP bundle, and other seemingly sensible approaches to VAP prevention, need to be examined for their clinical effectiveness and cost-effectiveness, particularly as new technologies or prevention strategies coming to the market will require evaluation of their comparative effectiveness (59, 60).

Other investigations have used more targeted elements in their bundles specifically aimed at the prevention of VAP (47–49). As previously noted, Bouadma et al (55) implemented a rigorous bundle with eight evidence-based elements directly linked to the prevention of VAP. More recently, Heimes et al (61) performed a retrospective study examining 696 consecutive ventilated patients in a level one trauma center to evaluate a VAP prevention bundle with seven elements (elevate head of bed 30 degrees or higher unless contraindicated; twice-daily oral cleansing with chorhexidine; daily respiratory therapy-driven attempt to liberate from mechanical ventilation; nasogastric tubes replaced with orogastric tubes; sedation held and monitored daily to allow patients to follow commands; stress gastritis prophylaxis with H_2 blockers or proton pump inhibitors; hand washing by healthcare personnel). Three time periods were assessed: pre-VAP bundle implementation; VAP bundle implementation; and a subsequent time period of VAP bundle enforcement. During the pre-VAP bundle period, 5.2 cases of VAP occurred per 1000 days of ventilator support compared to 2.4 per 1000 days ($p = 0.172$) and 1.2 per 1000 days ($p = 0.085$) in the implementation and enforcement periods, respectively. However, when including all trauma patients, regardless of head abbreviated injury score, the difference in the rate of VAP was statistically significant in the enforcement period, but not in the implementation period, compared with the pre-VAP bundle period ($p = 0.014$ and 0.062, respectively). This study supports the need for strict enforcement or compliance with VAP bundles to maximize their successful implementation (48, 55).

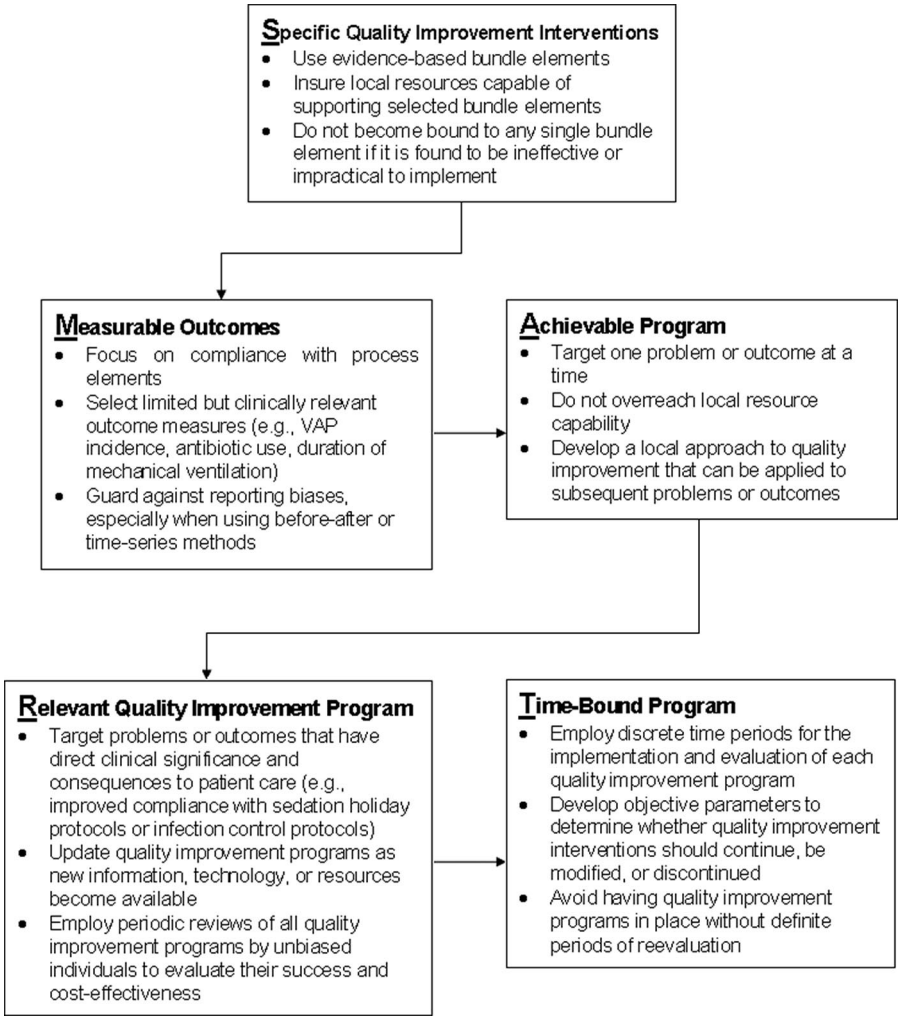

Figure 1. A specific, measurable, achievable, relevant, time-bound (*SMART*) program for process improvement and quality control. *VAP*, ventilator-associated pneumonia.

Table 3. Potential bundle elements and enforcement measures for a ventilator-associated pneumonia prevention program

Bundle elements
Use of noninvasive mask ventilation
Avoid reintubation
Avoid patient transports
Orotracheal intubation preferred
Orogastric intubation preferred
Avoid routine ventilator circuit changes
Use of closed endotracheal suctioning
Subglottic secretion drainage
Shortening the duration of mechanical ventilation
Adequate intensive care unit staffing
Silver-coated or endotracheal tubes with polyurethrane cuffs
Semi-erect positioning
Rotational beds for specific high-risk populations
Use of protocols/bundles
Oro-digestive decontamination (topical/topical plus intravenous antibiotics)
Oral chlorhexidine
Enforcement measures
Computerized order sets for bundle elements
Use of rounding checklists
Compliance assessments using random surveillance or observation periods
Distribution of report cards and infection rates
Involvement of hospital leadership in the review of prevention program outcomes
Scheduled in-services, educational briefings, and town hall sessions to review processes, outcomes, and barriers to successful bundle implementation

SMART Approaches for Quality Improvement and the Prevention of Complications in the ICU

Evidence-based interventions are available to reduce the occurrence of VAP, especially when these interventions are bundled together (47–49, 62). To increase the likelihood of success, clinicians and administrators should follow a "SMART" (specific, measurable, achievable, relevant, time-bound) approach for the implementation of such quality improvement efforts (Fig. 1) (63). Process improvement initiatives in the hospital should choose specific objectives that precisely define and quantify desired outcomes, such as reducing the rate of VAP by 25% or improving compliance with specific processes (e.g., compliance with identifiable VAP prevention interventions to a predetermined goal level). Similarly, such efforts should avoid unrealistic objectives, such as attempting to completely eliminate VAP. This could result in biased underreporting of VAP, or other complications, to meet the desired goal. A practical process improvement should be implemented in a way that will allow both measurement of the outcome (VAP, VAC, sVAP) and staff adherence to the elements comprising the bundle for the process improvement project. All objectives should be achievable and relevant by engaging stakeholders and empowering them to select specific tactics and steps for implementation. Nurses, respiratory therapists, and other stakeholders are in the best position to identify the preventive tactics that are achievable within their busy ICUs. Begin with simple, cost-effective tactics. Anticipate the need to add more tactics or bundle elements to achieve the desired process implementation and targeted infection/complication rates (55), and consider the use of certain measures aimed at "enforcing" the use of the prevention or quality improvement program (Table 3) (61).

All process improvement efforts should be periodically reviewed to assess compliance with their elements and sustained ability to achieve targeted goals, and to introduce advances in technology or behavioral science techniques. Bouadma et al (64) demonstrated the ability of such rigorous methods to produce sustained VAP rate decreases in the long-term. However, these authors also showed that VAP rates remained substantial at their institution despite high compliance with preventive measures, suggesting that elimination of VAP or other VACs may be an unrealistic goal. Therefore, the focus on such quality-improvement efforts should be process-driven to maximize the benefits of available hospital resources for the desired goal (e.g., reduced occurrence of VAP or VACs).

CONCLUSIONS

Given the increasing costs of health care and limited government budgets, process improvement, safety, and quality should be hard-wired into the culture of hospitals. This is becoming increasingly evident as more institutions are adopting Toyota-inspired quality-management strategies to improve quality as well as to reduce hospital costs (65). Furthermore, until we develop and validate more objective surveillance end points, such as potentially sVAP, it will be difficult to compare quality-improvement efforts across sites or to know what ultimate levels of improved medical care (e.g., zero VAP rates) actually can be achieved (66).

Antibiotic use in ventilated patients also seems inevitable given the nonspecific nature of the diagnostic criteria for VAP and the difficulty in differentiating airway colonization from true infection. Furthermore, current evidence does not suggest that VAP prevention bundles reduce antimicrobial use or the occurrence of antibiotic resistance. However, a number of clinical approaches in patients with microbiologically documented or suspected VAP have been associated with decreased antibiotic use (37, 39–43, 67) and subsequent emergence of antibiotic resistance (39, 67). Similarly, at least one VAP prevention intervention has been associated with significant reductions in overall antibiotic utilization (68). Given the increasing rates and clinical importance of antibiotic resistance, it seems reasonable to incorporate strategies aimed at minimizing their use in VAP bundles. Future studies are needed to address these important clinical issues.

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