Use of Quantitative Cultures and Reduced Duration of Antibiotic Regimens for Patients with Ventilator-Associated Pneumonia to Decrease Resistance in the Intensive Care Unit

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Ventilator-associated pneumonia is responsible for approximately half of the infections acquired in the intensive care unit and represents one of the principal reasons for the prescription of antibiotics in this setting. Invasive diagnostic methods, including bronchoalveolar lavage and/or protected specimen bronchial brushing, could improve the identification of patients with true bacterial pneumonia and facilitate decisions of whether to treat. These techniques also permit rapid optimization of the choice of antibiotics in patients with proven bacterial infection, once the results of respiratory tract cultures become available, based on the identity of the specific pathogens and their susceptibility to specific antibiotics, to avoid prolonged use of a broader spectrum of antibiotic therapy than is justified by the available information. Because unnecessary prolongation of antibiotic therapy for patients with true bacterial infection may lead to the selection of multidrug-resistant microorganisms without improving clinical outcome, efforts to reduce the duration of therapy for nosocomial infections are also warranted. An 8-day regimen can probably be standard for patients with ventilator-associated pneumonia. Possible exceptions to this recommendation include immunosuppressed patients, patients who are bacteremic or whose initial antibiotic therapy was not appropriate for the causative microorganism(s), and patients whose infection is with very difficult-to-treat microorganisms and show no improvement in clinical signs of infection.

In contrast to infections with susceptible strains, infections with antibiotic-resistant organisms in patients in intensive care units (ICUs)—and especially infections with nonfermenting gram-negative bacilli, such as Pseudomonas aeruginosa, Acinetobacter baumannii, and Stenotrophomonas maltophilia—are more likely to prolong hospitalization, to increase the risk of death, and to require treatment with more-toxic or more-expensive antibiotics [1–3]. Furthermore, such bacterial resistance limits the therapy options available to clinicians and forces the use of antibiotic regimens combining several broad-spectrum drugs for most patients in the ICU who are suspected of having a nosocomial infection, even if the pretest probability of having a disease caused by a multidrug-resistant strain is low, because initial inappropriate antibiotic therapy has been documented to be associated with poor prognosis [4–7]. Besides its economic impact, this practice of “spiraling empiricism” increasingly leads to the unnecessary administration of antibiotics to many patients in the ICU who are without true infection, paradoxically resulting in the emergence of infections with more–antibiotic-resistant bacteria that are, in turn, associated with increased rates of patient mortality and morbidity. Virtually all reports have emphasized that better antibiotic control programs to limit bacterial resistance are urgently needed in ICUs and that patients without true infection should not receive antibiotic therapy [1, 8, 9].
Ventilator-associated pneumonia (VAP) is responsible for approximately half of the infections acquired in the ICU and represents one of the principal reasons for the prescription of antibiotics in this setting [10]. Invasive diagnostic methods, including bronchoalveolar lavage (BAL) and/or protected specimen bronchial brushing (PSB) with quantitative cultures, could improve the identification of patients with true bacterial pneumonia and facilitate decisions of whether to treat [11, 12]. These techniques also permit a streamlined choice of antibiotics for patients with proven bacterial infection, once the results of respiratory tract cultures become available, based on the identity of the specific pathogens and their susceptibility to specific antibiotics, to avoid prolonged use of a broader spectrum of antibiotic therapy than is justified by the available information. Because unnecessary prolongation of antibiotic therapy for patients with true bacterial infection may lead to the selection of multidrug-resistant microorganisms without improving clinical outcome, efforts to reduce the duration of therapy for nosocomial infections are also warranted [7, 13]. In the present article, we review the potential advantages and drawbacks of using quantitative culture techniques and reduced duration of antibiotic regimens to decrease the emergence of resistant bacteria in the ICU, based on major additions to the literature that have appeared in recent years.

**USE OF QUANTITATIVE TECHNIQUES**

Despite an enormous amount of research and several official statements, the diagnosis and treatment of VAP remain controversial. All experts interested in this field, however, agree that the major goals of any management strategy are the use of early, appropriate antibiotic therapy in adequate doses for patients with true VAP and the avoidance of both excessive antibiotic therapy and the emergence of multidrug-resistant strains [7, 11]. Failure to initiate prompt appropriate and adequate therapy (i.e., the etiologic organism is susceptible to the therapeutic agent, the dose is optimal, and the correct route of administration is used) has been a consistent factor associated with increased mortality [14–16]. However, most epidemiological investigations have clearly demonstrated that indiscriminate use of antibiotic agents for treatment of patients in ICUs may have immediate and long-term consequences, which contribute to emergence of multidrug-resistant pathogens and increase the risk of serious superinfections [1, 17].

Concern about the inaccuracy of clinical approaches to the recognition of VAP and the impossibility of using such a strategy to avoid overprescription of antibiotics in the ICU has led numerous investigators to postulate that “specialized” diagnostic methods, including quantitative cultures of specimens obtained by bronchoscopic or nonbronchoscopic techniques such as BAL and/or PSB, could improve the identification of patients with true VAP and facilitate decisions of whether to treat and, thus, clinical outcome [11, 18, 19].

By use of such a strategy, therapeutic decisions are tightly protocolized and are based on results of direct examination of distal pulmonary samples and results of quantitative cultures (figure 1). Briefly, antibiotic therapy is started immediately for...
patients with a positive result of direct examination of BAL fluid demonstrating the presence of bacteria, whereas it is withheld in patients with no bacteria on Gram-stained cytocentrifuged preparations and no signs of severe sepsis or septic shock. Furthermore, antibiotic therapy is discontinued when quantitative culture results are below the cutoff limit defining a positive result, except for patients with proven extrapulmonary infection and/or severe sepsis.

**ARGUMENT FOR QUANTITATIVE TECHNIQUES IN DIAGNOSIS OF VAP**

With the exception of decision-analysis studies [20–22] and 1 retrospective study [23], only 4 trials have thus far used a randomized scheme to assess the impact of a diagnostic strategy on antibiotic use and outcome for patients suspected of having VAP [19, 24–26]. One of the first studies to clearly demonstrate a benefit in favor of the bacteriologic strategy was a prospective cohort study conducted in 10 Canadian ICUs [23]. The authors compared 92 patients suspected of having pneumonia who underwent bronchoscopy and 49 patients who did not. Mortality among patients who underwent bronchoscopy was 19%, compared with 35% for control patients (P = .03). Furthermore, patients managed with a bacteriologic strategy received fewer antibiotics, and more patients had all of their antibiotic therapy discontinued, compared with the clinical strategy group, thereby confirming that the 2 strategies actually differed in their outcomes.

No differences in mortality and morbidity were found when either invasive (PSB and/or BAL) or noninvasive (quantitative cultures of endotracheal aspirates) techniques were used to diagnose VAP in 3 Spanish randomized studies [24–26]. However, those studies were based on relatively few patients (51, 76, and 88, respectively), and antibiotic therapy was continued for all patients despite negative culture results, thereby neutralizing one of the potential advantages of any diagnostic test for patients clinically suspected of having VAP. Concerning the latter, several prospective studies have concluded that antibiotic therapy can indeed be discontinued for patients with negative results of quantitative cultures with no adverse effects on the recurrence of VAP and mortality [18, 27].

A large, prospective, randomized trial compared clinical and bacteriologic strategies for the management of 413 patients suspected of having VAP [19]. In the noninvasive group (n = 209), empirical antibiotic therapy was based on the presence of bacteria in Gram-stained endotracheal aspirates, and therapy could be adjusted or discontinued according to the results of qualitative cultures. In the case of severe sepsis, empirical therapy was started without the laboratory result. With this schedule, which resembles clinical practice in most ICUs, 91% of patients (191/209) received empirical therapy for suspected VAP, and only 7% did not. The decision algorithm for withholding or withdrawing antibiotics by use of the bacteriologic strategy was as shown in figure 1 [19]. Compared with patients managed clinically, those receiving bacteriologic management had a lower mortality rate on day 14 (25% vs. 16%; P = .02), lower sepsis-related organ failure assessment scores on day 3 and 7 (P = .04), and less antibiotic use (mean ± SD number of antibiotic-free days, 2 ± 3 vs. 5 ± 5; P < .001). Multivariate analysis showed a significant difference in mortality on day 28 in favor of bacteriologic management, associated with a significant reduction in antibiotic consumption (figure 2). Thus, implementation of bacteriologic techniques in the diagnosis of VAP reduces antibiotic use and improves outcome for patients.

Once the results of respiratory tract and blood cultures become available, therapy can often be focused or narrowed on the basis of the identity of specific pathogens and their susceptibility to specific antibiotics, to avoid prolonged use of a broader spectrum of antibiotic therapy than is justified by the available information [7, 28, 29]. For many patients, including those with late-onset infection, therapy can be narrowed because an anticipated organism (such as *P. aeruginosa*, *Acinetobacter* species, or methicillin-resistant *S. aureus*) was not recovered or because the organism isolated is susceptible to a more narrow-spectrum antibiotic than was used in the initial regimen. For example, vancomycin and linezolid therapy should be discontinued if no methicillin-resistant *S. aureus* is identified, unless the patient is allergic to β-lactams and has developed an infection with a gram-positive microorganism. Very-broad-spectrum agents, such as carbapenems, piperacil-

![Figure 2](cid2006:43/suppl2/s77)
lin-tazobactam, and/or cefepime, should also be restricted to patients infected with pathogens only susceptible to these agents. In the case of infection with a piperacillin-susceptible P. aeruginosa strain, antibiotic therapy should be streamlined to this specific drug. Similarly, in the absence of infection with a nonfermenting gram-negative bacillus or an extended-spectrum β-lactamase–producing Enterobacteriaceae species, the β-lactam should be changed to a nonantipseudomonal antibiotic, such as ceftiraxone or cefotaxime. Clinicians must be aware, however, that emergence of stable derepressed antibiotic-resistant mutants may lead to therapy failure when third-generation cephalosporins are chosen in the case of infection with Morganella morganii, Enterobacter species, Citrobacter species, Serratia species, or indole-positive Proteus species, even if the isolate appears to be susceptible on initial testing [30]. Because fluoroquinolones may particularly lead to selection of multidrug-resistant strains, their use should be carefully restricted to cases in which no other agent can be used [31, 32]. Although a de-escalating approach to antibiotic therapy (i.e., culture-guided therapy) may not help individuals, it could benefit the ICU as a whole by reducing the selection pressure for resistance. Every possible effort should therefore be made to obtain, before new antibiotics are administered, reliable specimens for direct microscope examination and cultures from each patient clinically suspected of having developed nosocomial infection.

POTENTIAL LIMITATIONS OF BRONCHOSCOPIC TECHNIQUES

It should be remembered, however, that several constraints specific to any microbiological procedure should be respected when using a quantitative culture technique for diagnosing pulmonary infection. First of all, pulmonary secretions need to be obtained before new antibiotic therapy is started, since performing quantitative cultures for diagnostic purposes after the initiation of new antibiotic therapy in patients suspected of having developed pneumonia leads to a high rate of false-negative results [33]. A negative finding could indicate either that the patient has been successfully treated for pneumonia and the bacteria are eradicated or that the patient had no lung infection to begin with. Second, as with all diagnostic tests, borderline results of PSB and/or BAL quantitative culture should be interpreted cautiously, and the clinical circumstances should be considered before reaching any therapeutic decision [34, 35]. Finally, several technical factors, including the need to have adequate resources (e.g., someone to perform the bronchoscopy and a microbiologist to examine the specimens fast enough) may render difficult the implementation of these procedures in many hospitals [12, 36].

NONBRONCHOSCOPIC TECHNIQUES

Compared with conventional PSB and/or BAL, nonbronchoscopic techniques using various types of endobronchial catheters for sampling distal lower respiratory tract secretions are less invasive, can be performed by clinicians not qualified to perform bronchoscopy, have lower initial costs than bronchoscopy, are associated with less compromise of gas exchange during the procedure, and can be performed even for patients intubated with small endotracheal tubes. Disadvantages include the potential sampling errors inherent in a blind technique and the lack of airway visualization. Although autopsy studies indicate that pneumonia in ventilator-dependent patients has often spread into every pulmonary lobe and predominantly involves the posterior portion of the lower lobes, several clinical studies of patients with pneumonia undergoing ventilation contradict those findings, because, for some patients, culture of specimens obtained by PSB from the noninvolved lung have yielded negative results [37, 38]. Furthermore, although the authors of most studies have concluded that the sensitivities of nonbronchoscopic and bronchoscopic techniques are comparable [39], the overall concordance has been only ∼80%, emphasizing that, for some patients, the diagnosis could be missed by a blind technique, especially in the case of pneumonia involving the left lung, as was demonstrated by Meduri et al. [38].

SHORTENING THE DURATION OF THERAPY

Experts usually recommend that nosocomial pulmonary infections be treated for 14–21 days in most cases [40]. This recommended duration is based on the high theoretical risk of infection relapse after a shorter duration of antibiotic therapy. Although the risk is likely to be low for bacteria considered highly susceptible to antibiotic agents, such as methicillin-susceptible Staphylococcus aureus or Haemophilus influenzae, it could be high for certain species, particularly P. aeruginosa, which is difficult to eliminate from the respiratory tract [41]. As a result, clinicians often opt for a prolonged course of broad-spectrum antibiotics, trading the potential risk of promoting antibiotic resistance or superinfection for the presumptive security of the patient being adequately treated.

Efforts to reduce the duration of therapy for VAP are, however, justified by studies of the natural history of the response to therapy. Dennesen et al. [42] demonstrated that when VAP was adequately treated, significant improvements were observed for all clinical parameters, generally within the first 6 days of antibiotic therapy. The consequence of prolonging therapy to 14 days was newly acquired colonization, especially with P. aeruginosa and Enterobacteriaceae species, generally during the second week of therapy. These data support the premise that
most patients with VAP who receive appropriate antibiotic therapy have a good clinical response within the first 6 days [42–44]. Prolonged therapy simply leads to colonization with antibiotic-resistant bacteria, which may precede a recurrent episode of VAP.

Reducing the duration of therapy in patients with VAP has led to good outcomes with less antibiotic use by means of a variety of different strategies. Singh et al. [45] used a modification of the clinical pulmonary infection score to identify low-risk patients (score of ≤6) with suspected VAP who could be treated with antibiotics for 3 days, as opposed to the conventional practice of antibiotic therapy for 10–21 days. Patients receiving the shorter course of antibiotic therapy had better clinical outcomes than did patients receiving more-prolonged therapy, with fewer subsequent superinfections attributed to antibiotic-resistant pathogens, although many of these patients may not have had pneumonia.

A recent multicenter, randomized, controlled trial with a large series of 413 patients with microbiologically proven VAP demonstrated that patients who received appropriate, initial empirical therapy for 8 days had outcomes similar to those of patients who received therapy for 15 days [13]. Compared with patients who received a long course of therapy, patients who received a short course had neither excess mortality (18.8% vs. 17.2%; 90% CI for the difference, −3.7 to +6.9 percentage points) nor excess pulmonary infection recurrence (28.9% vs. 26.0%; 90% CI for the difference, −3.2 to +9.1 percentage points). There were also no statistically significant differences between patients receiving a short course and those receiving a long course of antibiotics with regard to the numbers of days alive without mechanical ventilation (mean ± SD, 8.7 ± 9.1 vs. 9.1 ± 9.4 days) or without organ failure (7.5 ± 8.7 vs. 8.0 ± 8.9 days); the combined outcome of death, infection recurrence, or new antibiotic therapy during the study period (45.7% vs. 43.1%); the duration of ICU stay (30.0 ± 20.0 vs. 27.5 ± 17.5 days); or the mortality rate at day 60 (25.4% vs. 27.9%).

The average number of antibiotic-free days from day 1 to day 28 was 50% higher for patients receiving the 8-day regimen than for patients receiving the 15-day regimen (figure 3). This finding strongly indicates that such a strategy could effectively lower the exposure of patients in ICUs with VAP to unnecessary antibiotic therapy after randomization. Pathogens resistant to many drugs emerged more frequently for patients with recurrence of pulmonary infection who had received antibiotics for 15 days (62% vs. 42%). Nearly one-third of patients enrolled in this trial had VAP caused by nonfermenting gram-negative bacilli, such as *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*. Interestingly, these patients did not have more adverse outcomes when the duration of antibiotic therapy was only 8 days, although a slightly higher percentage of pulmonary infections recurred in this group (40% vs. 25%).

These findings are consistent with those of other prospective studies evaluating the possibility of reducing the duration of antibiotic therapy among patients in ICUs [46, 47]. In a recent cohort study [46], 102 consecutive patients with VAP were prospectively evaluated before and after the application of a clinical guideline restricting the total duration of antibiotic therapy to 7 days for selected patients (those who were neither bacteremic nor neutropenic and who became afebrile while undergoing therapy). The investigators found no statistically significant differences in hospital-associated mortality rates and duration of hospitalization between the 2 study groups; however, patients in the group treated before the guidelines were applied whose mean duration of therapy was 15 days were more likely to develop a second episode of VAP. Recently, the same group of investigators was able to demonstrate, in a prospective, randomized trial with 290 patients [47], that an antibiotic discontinuation policy directed at the treatment of clinically suspected VAP was associated with the administration of statistically shorter durations of antibiotic therapy. On average, patients treated under the antibiotic discontinuation policy received antibiotic therapy for 2 fewer days than did patients in the conventional group. No differences in hospital-associated mortality or in the durations of intensive care and hospitalization were observed between the 2 treatment groups. The occurrence of a second episode of VAP was also similar in both treatment groups.

On the basis of these data, an 8-day regimen can probably be standard for patients with VAP. Possible exceptions to this

![Figure 3](cid2006:43 (suppl 2) s79)

**Figure 3.** Numbers of days alive without antibiotic therapy according to duration of therapy for 197 patients who received antibiotics for 8 days and 204 patients who received antibiotics for 15 days (data are from [13]). Box plots represent the 25th and 75th percentiles, with the internal horizontal dotted and dashed lines showing the mean and the median, respectively. T bars represent the 10th percentiles, and circles represent outliers.
recommendation include immunosuppressed patients, patients who are bacteremic or whose initial antibiotic therapy was not appropriate for the causative microorganism(s), and patients whose infection was with very-difficult-to-treat microorganisms and who had no improvement in clinical signs of infection. This approach, however, must be combined with extreme vigilance after antibiotic therapy is discontinued. Fiberoptic bronchoscopy should be performed as soon as possible when relapse is suspected, so as to detect and immediately treat a recurrence of pulmonary infection.

CONCLUSION

In summary, the rapid emergence and dissemination of antibiotic-resistant microorganisms in hospitals worldwide is a problem of crisis dimensions. The root causes of this problem are multifactorial, but the core issues are clear. The emergence of antibiotic resistance is highly correlated with selective pressure that results from inappropriate use of antibiotic agents. Appropriate antibiotic stewardship includes not only the limitation of use of inappropriate agents for patients with VAP but also improving our ability to diagnose and exclude infection in the ICU setting to avoid administering unnecessary antibiotics to patients without infection. Furthermore, patients with proven bacterial infection should be treated only for the period that is mandatory to eradicate the responsible microorganism.

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References