Cost-Effectiveness Issues in Ventilator-Associated Pneumonia

Joseph S Solomkin MD

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Summary

Ventilator-associated pneumonia has attracted considerable interest as a subject of clinical efficacy assessment research. This article summarizes recommendations made by the United States Public Health Service Panel on Cost-Effectiveness in Health and Medicine and by a panel convened by the American Thoracic Society to address economic analyses in critical care. The following recommendations are made for the performance of cost-efficacy studies in ventilator-associated pneumonia. For mortality-based studies, only data from prospective and blinded randomized trials are suitable for analysis. For cost-minimization studies, observational studies may be useful but should use rigorous matching schemes. Estimates for the quality of life of patients surviving an episode of ventilator-associated pneumonia should be based on the disease that required mechanical ventilation or compared to data available for survivors of the respiratory distress syndrome, whichever diagnosis provides a lessened quality of life. Within an individual intensive care unit the greatest cost savings come from constructing a cohesive and unified approach to many issues seen in the unit. *Key words: ventilator-associated pneumonia, cost-effectiveness, quality-adjusted life year, QALY.*
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Introduction

There is little doubt that ventilator-associated pneumonia (VAP), pulmonary infection complicating mechanical ventilation, is a major problem in critical care and a major cost item. Most physicians take an aggressive therapeutic approach to suspected infection because of a widely held belief that infection-related morbidity and mortality can be reduced by early empiric antimicrobial therapy. Under current algorithms requiring expensive and extraordinarily broad-spectrum therapy for many patients suspected of having VAP, a large number of patients are treated for

Joseph S Solomkin MD is affiliated with the Division of Trauma and Critical Care, University of Cincinnati Medical Center, Cincinnati, Ohio.

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Correspondence: Joseph S Solomkin MD, Division of Trauma and Critical Care, University of Cincinnati Medical Center, PO Box 670558, 231 Albert Sabin Way, Cincinnati OH 45267-0558. E-mail: solomkjs@uc.edu.

Table 1. Types of Cost-Efficacy Analyses

Study	Study Type	Numerator	Denominator	Examples	Comment
Singh et al[8]	Cost minimization	Dollars	None	Antibiotic therapy for intensive-care patients at low risk of nosocomial pneumonia. Drug acquisition costs for a 3-day course of ciprofloxin are $9,520 more than costs for unregulated antibiotic prescription.	No estimate of consequences on other health care elements. Clinical outcomes are assumed to be equivalent.
Bootman et al[9,10]	Cost/benefit	Dollars	Dollars	Aminoglycoside dose-monitoring program for burn patients with Gram-negative sepsis. Program led to $8.70 savings per dollar spent.	All costs and effects are expressed in monetary units. Converting clinical effects, such as lives lost or gained, into dollar amounts is controversial.
Mark et al[11]	Cost-effectiveness	Dollars	Clinical measure of effectiveness (lives saved)	Thrombolysis for acute myocardial infarction. Tissue plasminogen activator costs an additional $32,678 per additional life saved, compared to streptokinase.	It is not clear whether "lives saved" are equivalent to other lives saved in other settings and other diseases.
Stal et al[12]	Cost/utility	Dollars	QALYs	Prophylaxis against esophageal strictures. Omeprazole costs $49,600 more per additional QALY, compared to ranitidine.	Cost per QALY allows comparison with other therapies in other diseases.

QALY = quality-adjusted life year (Adapted from Reference 7.)

VAP with little evidence that they indeed have the disease. This approach has, however, become a driving force in the evolution of multiresistant bacterial pathogens in the intensive care unit (ICU).[1] These organisms themselves have become an important cause of morbidity and mortality, and the suggestion has even been made that survival from ICU residence would improve if VAP were *not* treated.[2]

Because of these issues, VAP has attracted considerable interest as a subject of clinical efficacy assessment research. Assessment of cost efficacy for VAP is, nonetheless, a difficult task. The problems relate to center-by-center variations in criteria for (1) diagnosis, (2) microbiologic techniques for organism identification (highly specific bronchoalveolar lavage [BAL] vs endotracheal aspirate), (3) agents selected for empiric therapy, and (4) criteria for terminating treatment. Subspecialty critical care units (surgical vs medical vs pulmonary vs cardiac) see patients with marked differences in well known risk factors for adverse outcome, including age, background disease, severity, and immune status.

Furthermore, data on the effectiveness of ICU interventions are often lacking; ICU patients are complex, with multiple concurrent problems and interventions; most ICU therapies are only supportive and therefore may not individually result in improved outcome expressed as survival; and accurate cost data are not commonly available. A truly major hurdle is that typical outcomes measures in ICU studies (eg, short-term mortality) are not ideal for cost-effectiveness analyses, while preferred outcomes for cost-effectiveness analyses (eg, long-term quality-adjusted survival) are rarely collected.

In 1996 the United States Public Health Service Panel on Cost-Effectiveness in Health and Medicine published guidelines for the conduct and reporting of economic analyses.[3–6] The American Thoracic Society convened a panel to address economic analyses in critical care. The goals were to interpret the Panel's guidelines in the context of caring for critically ill patients, to recommend a standardized approach to the conduct and interpretation of cost-effectiveness analyses in critical care, and to highlight areas for future research.[7] The report endorsed use of the guidelines for critical care.

This article will summarize the material presented in those 2 sets of documents. Finally, recommendations will be made regarding the conduct of such studies, with particular regard to VAP and mechanisms for application of these data to the ICU environment.

Types of Economic Analyses

There are 4 types of economic analyses used to compare alternative technologies: cost minimization, cost/benefit, cost-effectiveness, and cost/utility (Table 1). Each compares the costs and clinical outcomes associated with alternative interventions, but each uses a different approach to measure the effects. *Cost minimization* is often used as

the basis for decisions in the ICU. It assumes each technology is equally effective and identifies the option associated with least cost.[8] *Cost/benefit* measures costs and consequences in the same units (eg, expresses a life saved as a monetary gain), is difficult to conduct, and is now rarely used. *Cost-effectiveness* and *cost/utility* analyses are the preferred approaches to evaluate medical care technologies today. A cost-effectiveness analysis produces a ratio, such as the cost per year of life gained, where the denominator reflects the gain in health from a specific intervention (eg, life years gained, number of additional survivors, or number of pneumonias averted) and the numerator reflects the cost in dollars of obtaining that gain. Cost/utility is a type of cost-effectiveness analysis, where effects are expressed as utilities, such as quality-adjusted survival, facilitating comparisons across different diseases and interventions (eg, quality-adjusted life years [QALYs]). Cost-effectiveness analysis refers to both cost-effectiveness and cost/utility analyses.

What Is a Reasonable Price for a QALY?

A central issue in any analysis becomes previous experience with other interventions and the cost/QALY. This provides some sense of acceptable boundaries. Tables 1 and 2 provide data from representative cost-effectiveness analyses across different areas.[13–15] If one looks at the intervention and its consequences, and recognizes that it seems appropriate, most analyses come in between $25,000 and $50,000 United States dollars. Above that, acute care interventions are not widely supported.

Standardization of Reporting Across Different Cost-Effectiveness Analyses

One key contribution of the Public Health Service Panel on Cost-Effectiveness in Health and Medicine was to recommend that future cost-effectiveness analyses at a minimum produce a *reference case*, where the cost-effectiveness ratio is generated by a standardized approach to important elements of the analysis, including the perspective chosen, the determination of costs and effects, the study time horizon, and the assessment of uncertainty and sensitivity analyses. This standardized approach facilitates comparability among cost-effectiveness analyses. For example, by comparing the reference cases from different cost-effectiveness analyses, one can make inferences about whether one therapy for one disease has a better or worse cost-effectiveness ratio than another therapy used in another field of medicine.

Problems With Available Data on Outcomes From VAP

Because the purpose of a cost-effectiveness analysis is to provide insight into the cost incurred per effect gained, a lack of evidence regarding effect diminishes the value of a cost-effectiveness analysis. ICU outcome measurements are often physiological variables (eg, arterial oxygenation or cardiac ejection fraction), which are types of outcomes that are not well suited for efficacy analyses. Furthermore, ICU care is often supportive rather than curative. The goals of many ICU interventions are to stabilize and support patients (eg, mechanical ventilation), rather than to cure or improve an underlying condition. In such instances, isolating the clinical and economic consequences of individual interventions can be difficult.

There are other confounding variables. ICU interventions are often applied to heterogeneous patient populations with different underlying comorbidities and probabilities of survival. ICU patients can also develop complications, which themselves have multisystem manifestations. Determining the effect of a particular therapy in such situations is difficult, complicating both clinical trials and cost-effectiveness analyses.

In regards to VAP, making a definitive diagnosis of VAP is often quite difficult. While many believe that quantitative cultures of BAL or brush specimens provide a high degree of diagnostic certainty, this remains an area of great controversy. The diagnostic picture is confusing because the disease states requiring mechanical ventilation typically are associated with abnormalities of plain chest radiographs, an imprecise if commonly used indicator of pulmonary infection.[16] Patients at risk for such infections typically have multiple reasons for fever and leukocytosis, including extra-pulmonary infection, and noninfectious diseases that elicit an inflammatory response, such as major trauma, pancreatitis, or thrombophlebitis. Mechanical ventilation by itself is now recognized as an inducer of intra-pulmonary inflammation.[17]

The Case for Careful Matching in Case-Controlled (Observational or Record Review) Studies

It becomes apparent that the technique of "matched" case control studies to determine attributable mortality results in highly variable control groups from study to study, and may substantially overestimate the effect of an acute event such as VAP. The problem becomes even more complicated because the degree of acute physiologic derangement varies greatly across patient populations at risk for VAP (eg, trauma/surgical ICU patients vs medical ICU patients). Finally, most studies have utilized data from single centers and have therefore introduced both recognized and unrecognized unit-specific and hospital-specific determinants into their findings and conclusions. There is considerable variation from center to center in such important variables as the affected patient population, diagnostic strategies employed, causative organisms, and therapeutic approaches. These issues may well preclude translating conclusions from one study into clinical prac-

Table 2. Various Cost Estimates With Different Interventions and Diseases

Study	Objective	Design	Data Sources	Target Population	Time Horizon	Perspectives	Interventions	Outcome Measures	Results of Base-Case Analysis	Results of Sensitivity Analysis	Conclusions
Herman et al[13]	Evaluate the relative cost-effectiveness of radiofrequency ablation and hepatic resection in patients with metachronous liver metastases from colorectal carcinoma	State-transition decision model. Survival, quality of life, and cost were predicted on the basis of disease extent.	NR	NR	NR	NR	NR	NR	Hepatic resection is more effective (in terms of QALYs gained) than radiofrequency ablation and has an incremental cost-effectiveness ratio of less than $35 000 per QALY.	NR	Radiofrequency ablation is a cost-effective treatment option for patients with colorectal cancer liver metastases.
Beck et al[14]	Diabetes prevention program	Markov simulation model	Diabetes prevention program and published reports	Members of the diabetes prevention program cohort ≥ 25 years old, with impaired glucose tolerance	Lifetime	Health system and societal	Intensive lifestyle, metformin, and placebo interventions	Cumulative incidence of diabetes, microvascular and neuropathic complications, cardiovascular complications, survival, direct medical and direct nonmedical costs, QALYs, and cost per QALY	Intensive lifestyle interventions: $8,800 per QALY Metformin: $29,900 per QALY	Metformin intervention did not represent good use of resources for persons > 65 years old	Health policy should promote diabetes prevention in high-risk individuals.
Shorr et al[15]	Estimate the cost-effectiveness ratio of HAART in Canada	Before-and-after analysis to calculate incremental cost of life-year gained between 1991 and 1995 (pre-HAART period) and between 1997 and 2001 (HAART period)	Two Quebec HIV hospital clinics	For non-AIDS and AIDS groups (Centers for Disease Control definition)	NR	NR	HAART	In-patient days; outpatient visits; direct health-care costs (drugs, tests)	Total cost was U.S. $4,265 in the pre-HAART period, and U.S. $9,445 per person per year in the HAART period. Cost per life year gained between periods was U.S. $14,587.	NR	HAART appeared to be a cost-effective intervention in Canada.

QALY = quality-adjusted life-year
HIV = human immunodeficiency virus
AIDS = acquired immune deficiency syndrome
HAART = highly active antiretroviral therapy
NR = not reported

tice at another facility. This is not for lack of trying. Heyland et al screened 4,167 papers manually and > 450 abstracts and titles in a computer search.[18] One hundred fifty-one papers were retrieved for further evaluation; 29 papers met their inclusion criteria. Of these 29 papers, only 14 (48%) adequately described competing healthcare interventions, 17 (59%) provided sufficient evidence of clinical efficacy, 6 (21%) identified, measured, and valuated costs appropriately, and 3 (10%) performed a sensitivity analysis. None of the papers met all 4 of these criteria for a minimum level of methodologic soundness. Four (14%) of 29 studies that adequately dealt with issues of cost and efficacy were evaluated using our generalizability criteria.[19–22] Different costing methods precluded the application of the results of 3 of the 4 studies to their intensive care unit.[12,18]

Can Mortality Be Used As an End Point for Cost Efficacy Analysis of Treatments for VAP?

It is difficult, if indeed not impossible, to define the impact of an episode of VAP on mortality from intensive care. It therefore follows that it is equally difficult to identify an improvement in mortality with a specific therapy. The reasons for this have to do with the intertwining of variables predicting risk of death and also risk of developing VAP. Patients who die in the ICU typically do so after a protracted illness and with progressive organ failure. Such patients have often suffered prior infection, and it is not obvious whether infection accompanies or causes death. The standard approach to this problem is to attempt to define an "attributable" mortality figure. This is arrived at by comparing a cohort of patients diagnosed as having (in this case) VAP, and then comparing their outcomes to those of other patients matched in various and varying ways from the same historical cohort. Diverse study designs, modest sample sizes, and different definitions of VAP have made interpretation of this literature challenging.

The central issue is what criteria for matching patients are used in a given study. Typically, these include age, sex, diagnosis, and duration of hospitalization. In many studies, patients are not, however, matched for such key issues as duration of mechanical ventilation or antecedent infection and antimicrobial treatment. In some cases, matching does not even include residence in the intensive care unit.

The Canadian Critical Care Study Group performed a careful study of attributable mortality in VAP.[23] They analyzed case records from a multicenter trial examining the effect of ranitidine versus sucralfate on the incidence of VAP.[24] These therapies had no effect, so the patient populations were pooled. Of 1,014 patients, 250 (24.7%) developed clinically suspected VAP. Of these, 186 (74.4%) underwent bronchoscopy and had a specimen collected with protected-specimen-brush technique or underwent BAL. After a review of pertinent patient data by an expert panel, 177 patients were judged to have VAP. The median duration from admission to the onset of VAP was 7 days.

To determine attributable mortality and length of stay, 10 criteria were used to determine the best match for a case. This will be described in some detail because it is an outstanding model of how case-matched studies should be performed. It is important to note that all observational studies are effectively case-matched studies. A control had to match a patient in 4 of the following 6 criteria to be considered a possible match: mortality status, medical/surgical status, time in ICU prior to the development of VAP, duration of mechanical ventilation prior to VAP, day-1 Acute Physiology and Chronic Health Evaluation (APACHE II) score (±4 points), and multiple organ dysfunction (MOD) score on the day prior to development of VAP (±3 points).

For each possible matched control, the remaining 4 criteria were weighted with regard to their importance in influencing outcome: (1) ICU admitting diagnosis: 8 points; (2) age ±15 years: 4 points; (3) center at which treated: 2 points; and (4) gender: 1 point. The overall score was the sum of the points for which the control matched the characteristics of the case. Among the potential control subjects who met the "must match" criteria, the subject with the highest score was matched to the case. Thus, if one potential control subject had the same admission diagnosis as a case (8 points) and another matched the case on all the less important criteria (a total of 7 points), the control subject matching by admission diagnosis status had the higher score. In the case of a tie, the control subject with the closest APACHE II score was chosen. If there was still a tie, the control closest in age to the case was chosen.

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Pertinent outcomes data are presented in Table 2, and they demonstrate an absence of attributable mortality in either medical or surgical ICU populations. There was a significant increase in length of stay for medical patients with infection, but not for a smaller cohort of surgical patients.

The findings of that study were supported by an analysis of a large United States multi-hospital database.[25] The MediQual-Profile database contains information on approximately 750,000 in-patient admissions annually, to more than 100 United States acute-care hospitals. Of 9,080 patients meeting study entry criteria, VAP developed in 842 patients (9.3%). Patients with VAP were matched with 2,243 control subjects without VAP. Hospital mortality did not differ significantly between cases and matched control subjects (30.5% vs 30.4%). Nevertheless, patients

with VAP had a significantly longer duration of mechanical ventilation (14.3 ± 15.5 d vs 4.7 ± 7.0 d), ICU stay (11.7 ± 11.0 d vs 5.6 ± 6.1 d), and hospital stay (25.5 ± 22.8 d vs 14.0 ± 14.6 d). Development of VAP was also associated with an increase in mean hospital charges per patient ($104,983 ± $91,080 vs $63,689 ± $75,030).

More likely, there is a mortality effect, but the statistical techniques used may be insufficiently robust. In published models that consider mortality and nosocomial infections and the risks for both, each event—death and infection—undergoes separate statistical analysis; infections are most often treated as an adjustment factor or as a variable for subgroup analyses.[26–29] These studies have all used standard statistical analyses such as Cox or logistic regression model fitting. However, the relationship between death in the ICU and nosocomial infection acquired there is closely linked, and many variables may be risk factors for both. It is therefore difficult to evaluate the fraction of ICU mortality rate that is attributable to nosocomial infections. These questions can be addressed only by more complex modeling that takes into account the various events of a patient's ICU stay.[30]

An Example Study of Cost-Efficacy Analysis for Respiratory Failure/Pneumonia in the ICU

Recently, Hamel et al reported a cost-effectiveness study of aggressive ICU/ventilator care for patients with respiratory failure and pneumonia. The patients were identified from a multicenter study of outcomes, preferences, and decision making for seriously ill adult patients.[31]

Using a prognostic model based on the entire phase I SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment) cohort of 4,301 patients, the authors estimated the probability of surviving at least 2 months from the time of diagnosis with acute respiratory failure for each patient. The model is based on patient age, diagnoses, comorbid illnesses, and 11 physiologic variables.[32] High-risk patients were defined as those with ≤ 50% probability of surviving at least 2 months, medium-risk patients as those with 51–70% probability of surviving at least 2 months, and low-risk patients as those with > 70% probability of surviving at least 2 months. We also determined actual 2-month survival for each of these 3 groups. The actual mortality curves for these groups are provided in Figure 1.[31]

Patients were considered to have acute respiratory failure if they required treatment in the intensive care unit, had a diagnosis of pneumonia or acute respiratory distress syndrome, and had an Acute Physiology and Chronic Health Evaluation (APACHE II) score ≥ 10. Patients were not included if they also met the criteria for severe congestive heart failure or severe chronic obstructive pulmonary disease. The results of that analysis are presented in Table 3.[31]

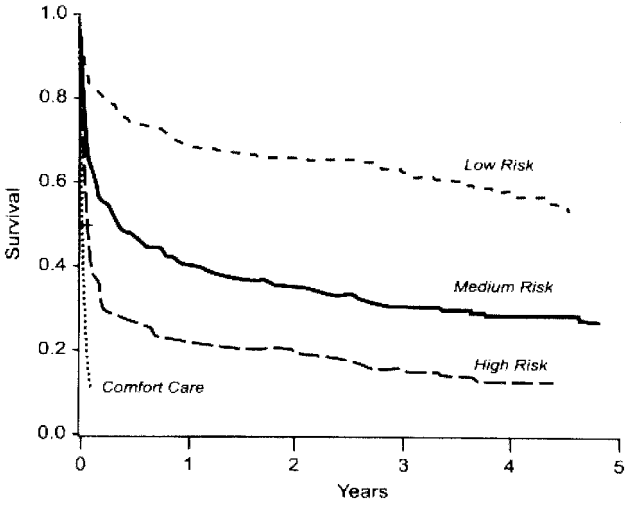

Fig. 1. Survival among low-risk patients (70% probability of surviving 2 months), medium-risk patients (51–70% probability of surviving 2 months), high-risk patients (< 50% probability of surviving 2 months), and patients with whom ventilator support was withheld in anticipation of death (comfort care). The numbers of patients at risk at time 0 were 292 for the low-risk group, 385 for the medium-risk group, 286 for the high-risk group, and 42 for the comfort-care group. At year 2 the numbers at risk were 136 in the low-risk group, 95 in the medium-risk group, and 36 in the high-risk group. At year 4 the numbers at risk were 47 in the low-risk group, 30 in the medium-risk group, and 11 in the low-risk group. (From Reference 31, with permission.)

For severely ill patients (1-year mortality ≥ 90%), the cost per QALY was $310,000. In 2-way sensitivity analyses that varied year-1 health-care costs, annual health-care costs after year 1, and annual mortality after year 1, values did not exceed $50,000 per QALY for low-risk patients.

These authors found that ventilator support and aggressive care are economically worthwhile for patients with relatively good short-term prognoses (expected 2-month survival > 50%). More than 70% of SUPPORT patients with acute respiratory failure met this criterion, and the incremental cost per QALY was between $29,000 and $44,000 for these patients. However, for patients with less than a 50% probability of surviving at least 2 months, aggressive intervention cost more than $100,000 per QALY, which does not compare favorably with other commonly used medical interventions.

For example, in 1998 dollars, coronary artery bypass surgery rather than medical therapy for patients with left main coronary artery disease cost about $9,500 per QALY,[33] medical therapy for severe hypertension cost about $28,000 per QALY,[34] and treatment with tissue plasminogen activator (t-PA) rather than streptokinase for myocardial infarction cost about $39,000 per year of life saved.[11]

Table 3. Cost Effectiveness Analysis Across Stratified Risk Groups With Pneumonia and Respiratory Failure Requiring Mechanical Ventilation

	Incremental Cost-Effectiveness (Dollars per QALY)		
	Low-Risk Patients	Medium-Risk Patients	High-Risk Patients
Baseline Assumptions	29,000	44,000	110,000
Annual Mortality After Year 1			
1/2 × baseline estimate	26,000	33,000	81,000
2 × baseline estimate	33,000	64,000	158,000
Year-1 Health-Care Costs			
1/2 × baseline estimate	24,000	29,000	67,000
2 × baseline estimate	39,000	76,000	200,000
Annual Health-Care Costs After Year 1			
1/2 × baseline estimate	19,000	38,000	99,000
2 × baseline estimate	48,000	56,000	130,000
Utility (quality-of-life weights)			
1.0	25,000	39,000	97,000
0.5	52,000	78,000	190,000
Discount Rate			
0%	28,000	39,000	100,000
10%	34,000	55,000	130,000

Adapted from Reference 31.
QALY = quality-adjusted life year

Summary

Based on these studies, the following recommendations can be made for the performance of cost efficacy studies in VAP.

For mortality-based studies, only data from prospective and blinded randomized trials is suitable for analysis. For cost minimization studies, observational studies may be useful but should use rigorous matching schemes similar to those described by Heyland et al.[23]

Estimates for the quality of life of patients surviving an episode of VAP should be based upon the disease that required mechanical ventilation or compared to data available for survivors of the respiratory distress syndrome, whichever diagnosis provides a lessened quality of life.

It is probable, in any case, that the greatest cost savings will come from altering treatment strategies. It must also be noted that cost-efficacy data in the ICU generally require a cohesive group with shared goals and agreed-upon diagnostic and treatment strategies. Several cost-effective measures may become ineffective if used in disparate ways by different team members. Considerable focus should be put on building a cohesive and unified approach to many issues seen in the ICU.

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Discussion

Niederman: Joe, I agree with some of your concerns about the literature, but there have been some studies—although not methodologically perfect—that looked at the timing of appropriate therapy and concluded that there is a time point when appropriate therapy matters and a time point when it doesn't. That would imply that it may make a difference whether you do it, and when you do it.

The other thing that is inherently problematic in this whole question is that I think it's virtually impossible to study attributable mortality. I don't think that any of the designs can address it appropriately, because what you're comparing is the mortality of patients with pneumonia to those without pneumonia, but you're comparing the mortality with pneumonia in patients given therapy. If you truly wanted to know the attributable mortality of pneumonia, it would be unethical to ask the question, but the question you really want to know is whether a patient with pneumonia who got no therapy had a higher mortality than a patient without pneumonia. That would tell you the natural history of the disease.

So what we're really looking at is the excess mortality with therapy, and ultimately if you came up with the ideal therapy, there should be no attributable mortality. This doesn't mean it's not an important disease, and it doesn't mean it's not cost-effective and so forth to treat it. I think that there are inherently, by design and by necessity, limitations on how we are ever going to address this issue.

Solomkin: I share your concerns that defining attributable mortality with commonly used statistical devices is not possible. The larger issue, which covers VAP and other infections, is to understand the broader framework of assessing efficacy in the ICU. I also tried to define an intermediate ground between not treating patients and the position of very aggressive broad-spectrum therapy, a therapeutic approach Dave Park outlined.

One approach would be to do a study where patients with relatively low APACHE II score, of less than 10 or less than 15, would not be started on antimicrobial therapy until cultures are available. For such a study, some outcome other than mortality would be needed, since there would be no attributable mortality. One could use time-to-recovery of some physiologic variable. The question this study would answer is not, does therapy help, but rather, how quickly you need to give it. The real driver of resistance in the ICU, as has been mentioned many times here, is that many people start broad-spectrum therapy and then don't stop it. If it is demonstrated that the best strategy is to not start therapy until you know specifically what you're treating—

Niederman: I still have concerns about defining attributable mortality in the context in which it's been defined. I guess with the study design you've talked about it would be really tough to get anybody to agree to participate through informed consent. If you ask somebody, "Would you mind if we don't treat you, if we think you have an infection, until we're sure you have an infection?" I don't think people would agree to that.

Solomkin: That's a separate issue that has to do with rapport with the patient and your own belief in the importance to that patient of not exposing them to the serious problems of unnecessary antimicrobial therapy.

Kollef: There actually have been some trials where that has occurred. They've not been published. One was the daptomycin versus ceftriaxone trial for community-acquired pneumonia. One could argue that there were issues in that whole study overall, but that they showed a mortality difference favoring the comparators, as opposed to the intervention drug, which was daptomycin. That study was never published, but it would have been interesting to try to do something like a cost-effectiveness or attributable mortality analysis based on it.

Solomkin: In what way did they do this? They withheld therapy?

Kollef: It was daptomycin versus ceftriaxone; it was a multi-national study. They reported it to the FDA [Food and Drug Administration], but it's one of those trials that has led to registering studies through the *New England Journal of Medicine* and other journals, because there is an opportunity to learn from them and we don't get that opportunity.

There was also a study done that was looking at low-dose linezolid versus high-dose linezolid, 200 versus 600 mg twice a day, which was done at the FDA's request for VRE [vancomycin-resistant enterococci] infections, which had a strong trend toward a mortality difference, but that data was never published. One could look at meta-analyses of some of the randomized trials of therapies where patients actually got inadequate treatment in one arm versus the other, but I guess sometimes that data is just not available when these studies are done. It's hidden somewhere.

Solomkin: That's an important point, but I am not advocating that a study be done where inadequate therapy be given for the duration of the illness. There was a very nice review by Rex et al,[1] where they tried to come up with a numerical benefit of effective therapy. They argued that effective therapy gave a 70–80% cure rate, while ineffective therapy gave a 50–60% cure rate. So there are a lot of factors, and you get to a certain level—particularly, if you're looking at something like day-1 therapy versus day-2 or day-3 therapy—where you simply may not be able to see a difference.

REFERENCE

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Rello: I agree with you that severity of illness is the most important prognostic factor identified in epidemiological studies. But VAP usually is developing several days after intubation, particularly in episodes of late-onset pneumonia developed after one week of ICU admission. My question is, should we control for severity of illness at ICU admission or severity of illness at pneumonia onset?

Solomkin: I think you need to do both, because I think they predict separate events. One is the acute injury itself, where the acute septic injury or dramatic injury that brought them to the ICU, and then the later APACHE score, basically tell you the immediate physiologic consequences of the infection that you're acutely treating. There are 2 prices that the host has been asked to pay, which are separately measured. So, ideally, what you'd want to compare would be the APACHE II admission score to the unit and then the same APACHE II score when they're entered into a trial.

Chastre: But in doing that it is also possible to over-control for confounding factors. For example, using the severity of the disease at time of infection, you can increase the severity of the disease, and maybe the best solution would be to use the severity of the disease 2 or 3 days before the onset of infection. Do you agree?

Solomkin: The subject that this discussion addresses is how to match patients in case-controlled trials. Yes, and I think you can get to such a type match. We did a matched study [unpublished data] using surgical ICU patients suspected of having VAP at identical APACHE II scores, and the only difference was whether their protected-catheter lavage was positive or negative. There was absolutely no difference in outcomes.