Therapeutic Value of a Lung Protective Ventilation Strategy in Acute Lung Injury

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Note to Our Readers—

You may have noticed that recent journals have been exceptionally large. This increase in the number of articles per issue is short term. We are temporarily increasing the size of the journal to decrease time from acceptance to publication, eliminate backlog, phasing out an old manuscript system, and preparing for changes beginning with the January 2006 issue.

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Therapeutic Value of a Lung Protective Ventilation Strategy in Acute Lung Injury

Both observational and epidemiologic studies have identified clinical variables associated with a higher risk of mortality in patients with acute lung injury. The most consistent clinical risk factors for higher mortality have been sepsis as the cause of lung injury, chronic liver disease, underlying malignancy, older age, and higher severity of illness assessed by elevated acute physiology and chronic health evaluation or simplified acute physiology scores.[1–5] However, there is little information regarding the impact of supportive care therapies on outcomes in patients with acute lung injury.

In this issue of *CHEST* (see page 3098), Sakr et al[6] reports the results of an observational study carried out in 198 European ICUs that participated in the Sepsis Occurrence in Acutely Ill Patients study. All 3,147 adult patients admitted to participating ICUs in Europe during a consecutive 2-week period in 2002 were included in the study population; of this group, 393 patients had either acute lung injury or ARDS. The investigators tested the hypothesis that sepsis and the use of tidal volumes higher than those applied in the National Heart, Lung, and Blood Institute (NHLBI) ARDS Network (ARDSnet) study,[7] (> 7.4 mL/kg of predicted body weight [PBW]), would be associated with mortality in patients with acute lung injury. A total of 207 patients (53% of the sample with acute lung injury) received mechanical ventilation at least once during their clinical course of acute lung injury with a tidal volume different from the ARDSnet strategy.[7] Higher tidal volumes (> 7.4 mL/kg of PBW) were more common in nonsurvivors than in survivors (44% vs 34%, $p = 0.019$), and a multivariate analysis confirmed that the use of higher tidal volumes was an independent predictor of ICU mortality, with an odds ratio for death of 2.3 (95% confidence interval, 1.2 to 4.4; $p = 0.01$). Other independent risk factors for ICU mortality included the presence of cancer, the degree of multiorgan dysfunction, and higher mean fluid balance. Sepsis was not an independent predictor of mortality; however, the authors hypothesize that multisystem organ failure is the true cause of increased mortality from sepsis rather than the infection itself.

These data appear to confirm the results of the NHLBI ARDSnet clinical trial,[7] which reported that ventilation of acute lung injury patients with a tidal volume of 6 mL/kg of PBW reduced hospital mortality to 31%, compared to a mortality of 40% in patients receiving mechanical ventilation with a traditional tidal volume of 12 mL/kg of PBW. A follow-up study[8] by the ARDSnet has provided additional evidence that mortality has declined further to 26% with the use of the lower tidal volume, even though higher levels of positive end-expiratory pressure did not reduce mortality.

Although the results of the current study are interesting, there are some shortcomings to the study design, as the authors acknowledge. First, this was not a randomized trial testing different ventilation

strategies for acute lung injury; therefore, those patients receiving higher tidal volumes may have been treated differently from those receiving lower tidal volumes in ways that were not measured in this study. For instance, as the authors point out, the use of many treatment strategies found in recent trials to decrease mortality in sepsis (such as activated protein C, tight control of glucose, and corticosteroids for relative adrenal insufficiency) was not recorded. Secondly, the duration of time that patients with lung injury were exposed to tidal volumes > 7.4 mL/kg of PBW was not available, nor was the plateau pressure reported in these patients. Thirdly, the data were recorded only once per day, introducing the possibility that some patients had significant fluctuations in their ventilatory strategy not measured by this analysis. Finally, mean tidal volume did not differ significantly between survivors and nonsurvivors. As the authors point out, this finding may be due to the fact that mean values by their nature do not describe the degree of variation around the mean but rather reflect a simple average of all the values in the sample, thus tending to obscure variation. While this explanation may be correct, the lack of significant difference between the mean tidal volume in survivors and nonsurvivors does raise some concern about the conclusions of the study. Despite these limitations, the inclusiveness and size of the study population and the strength of the multivariable analysis suggest that the findings of this study should be considered seriously.

Another interesting finding of the study is the independent association of a higher fluid balance with mortality (odds ratio, 1.5; 95% confidence interval, 1.1 to 1.9; $p = 0.003$). This finding has been reported in other studies, including work from Mitchell et al.[9] Because fluid administration was not dictated by the study protocol nor distributed in a randomized manner, it is unclear if the higher mean fluid balance is a cause of higher mortality or is simply associated with patients who have increased pulmonary and systemic vascular permeability and thus require more fluids to maintain systemic perfusion. The results of the ongoing NHLBI Fluid and Catheter Treatment trial of 1,000 patients should be available later this year and will hopefully provide new information, based on a prospective randomization protocol, about the impact of a conservative vs fluid liberal strategy on mortality in patients with acute lung injury.

In summary, the results of this new observational study from Europe provide more evidence that a lung protective strategy with a lower tidal volume reduces mortality in patients with acute lung injury. There is also recent evidence that implementation of the ARDSnet protocol is not associated with any significant alterations in supportive care. For example, the use of sedation, neuromuscular blockade, IV fluids, or vasopressors was not altered by use of low tidal volume strategy.[10,11] Several studies[12–14] have now been published by the NHLBI ARDSnet that provide evidence that a lower tidal volume is associated with reduced markers of inflammation as well as reduced alveolar epithelial injury. The reduction in mortality in patients with acute lung injury is one of the most gratifying examples of experimental and clinical research that has improved patient care. In the mid- to late-1990s, mortality from acute lung injury in clinical trials was approximately 40%.[15] Based on the most recent evidence, mortality has now been reduced to 26%.[8] Physicians who care for patients with acute lung injury should use a lung protective ventilatory strategy, preferably the low tidal volume, plateau pressure-limited protocol that has been tested in two major clinical trials.[7,8]

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What's in a Day?

Each year in the United States, there are as many as 5.6 million cases of community-acquired pneumonia (CAP), accounting for 600,000 to 1.1 million hospitalizations and $23 billion in health-care expenditures.[1–4] Among hospitalized patients, CAP mortality rates average from 11 to 14%,[5] with each case costing between $5,000 and $7,500.[1,2] Initial treatment is empiric, directed against commonly encountered pathogens, and guided by local susceptibility patterns. Current guidelines for patients hospitalized with CAP recommend either monotherapy with a fluoroquinolone, or combination therapy with a macrolide plus either a β-lactam/β-lactamase inhibitor or third-generation cephalosporin.[2–4] While clinical outcomes appear to be equivalent for each strategy, concerns about emerging fluoroquinolone resistance have led the Centers for Disease Control and Prevention to recommend restricting the use of fluoroquinolones to specific CAP patient groups.[6] Nevertheless, the perceived increase in costs associated with a combination of drugs might lead some to choose fluororquinolone monotherapy instead.

In this issue of *CHEST* (see page 3246), Samsa and colleagues[7] present an article that essentially states that treating hospitalized CAP patients with combination therapy, although slightly more expensive from an antibiotic-related drug cost standpoint, is cost-saving overall as compared to fluoroquinolone monotherapy. As a clinician, you may ask yourself, why is this article about cost in *CHEST*, as opposed to a medical economics journal, and what are we meant to do about it? Ultimately, it is in *CHEST* because it offers an opportunity for clinicians to appraise not only the clinical benefits of a particular strategy, but the economic consequences as well. But why should clinicians learn about economic consequences of different antibiotic regimens when decisions about which antibiotics are available are typically made by hospital pharmacy and therapeutics committees? The reason is that the clinician, in the day-to-day care of patients, is the person who is best positioned to balance costs against clinical outcomes. If a study shows that a particular therapeutic regimen is less costly, yet produces equivalent or better outcomes without worrisome side effects,[8] then it is the clinician's responsibility to do something about it. In this instance, there is more than a day's savings associated with combination therapy, which clearly drives the difference in cost. This leaves you to answer the question, "What's in a day?" and, by extension, "Do I think I can get a day's savings by applying the results of this study to my patients?" If you believe that you can, then you should go out and get that day. Because studies like this will continue to be published in clinical journals, it is essential for clinicians to read and understand them, working out if the study is not only internally valid but also externally valid and generalizeable to their situation, and whether the authors have addressed all other areas of concern.

Given this background, let us review the study by Samsa and colleagues.[7] The authors compared estimated 30-day direct medical costs for a subgroup (n = 163) of patients in the CAP-IN trial, a randomized, open-label, industry-sponsored study that compared clinical outcomes for 212 hospitalized CAP patients treated with either IV levofloxacin followed by oral levofloxacin (the fluoroquinolone group) or IV azithromycin and ceftriaxone followed by oral azithromycin (the combination therapy group).[9] Costs in each group were estimated using details about the hospitalization and information collected at a 30-day follow-up interview, including dosage of various drugs, hospital days and location, number of work days lost, home care, and postdischarge health-care resource utilization. Unit prices were assigned to each item to obtain estimated costs by category, which were then summed to estimate overall costs

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