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Original Research

CRITICAL CARE MEDICINE

Cost-effectiveness of Implementing Low-Tidal Volume Ventilation in Patients With Acute Lung Injury

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Background: **Despite widespread guidelines recommending the use of lung-protective ventilation (LPV) in patients with acute lung injury (ALI), many patients do not receive this lifesaving therapy. We sought to estimate the incremental clinical and economic outcomes associated with LPV and determined the maximum cost of a hypothetical intervention to improve adherence with LPV that remained cost-effective.**

Methods: **Adopting a societal perspective, we developed a theoretical decision model to determine the cost-effectiveness of LPV compared to non-LPV care. Model inputs were derived from the literature and a large population-based cohort of patients with ALI. Cost-effectiveness was determined as the cost per life saved and the cost per quality-adjusted life-years (QALYs) gained.**

Results: **Application of LPV resulted in an increase in QALYs gained by 15% (4.21 years for non-LPV vs 4.83 years for LPV), and an increase in lifetime costs of $7,233 per patient with ALI ($99,588 for non-LPV vs $106,821 for LPV). The incremental cost-effectiveness ratios for LPV were $22,566 per life saved at hospital discharge and $11,690 per QALY gained. The maximum, cost-effective, per patient investment in a hypothetical program to improve LPV adherence from 50 to 90% was $9,482. Results were robust to a wide range of economic and patient parameter assumptions.**

Conclusions: **Even a costly intervention to improve adherence with low-tidal volume ventilation in patients with ALI reduces death and is cost-effective by current societal standards.**

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Abbreviations: ALI = acute lung injury; ICER = incremental cost-effectiveness ratio; KCLIP = King County Lung Injury Project; LPV = lung-protective ventilation; PCEHM = Panel on Cost Effectiveness in Health and Medicine; QALY = quality-adjusted life-year

Acute lung injury (ALI) is responsible for up to 75,000 deaths in the United States each year.[1] To date, only one therapy has proven beneficial in reducing the mortality of ALI, namely, protocol-based delivery of pressure-limited, low-tidal volume ventilation (*ie*, lung-protective ventilation [LPV]).[2,3] Based on this evidence, many persons in the critical care community[4,5] have called for the use of LPV in all patients with ALI. Although ventilator practice has changed since the publication of the landmark randomized trial demonstrating the efficacy of LPV, a large proportion of patients with ALI still receive mechanical ventilation with tidal volumes above the goal of 6 mL/kg predicted body weight.[4,6–14] Barriers to the delivery of LPV include concern about adverse effects of low tidal volumes, inadequate knowledge of the LPV protocol, underrecognition of ALI, and an unwillingness of the bedside physician to relinquish control of the ventilator.[6,10,13]

Despite an increased awareness of the barriers to LPV delivery, ongoing investigation into improving adherence with this therapy is lacking.[15,16] Many of the barriers to LPV adherence could theoretically be overcome by implementing a multidisciplinary approach, including protocolized screening and care, bedside decision support, education of existing staff, and audit and feedback.[16] Yet, these approaches carry costs that must be weighed against the clinical benefits of LPV. The objective of this analysis was to determine the cost-effectiveness of LPV and to estimate the maximum cost at which a hypothetical intervention aimed at improving ICU-level LPV adherence remains cost-effective. Given the clinical benefits of LPV in patients with ALI, we hypothesized that even a costly intervention that increased LPV utilization would be cost-effective by current societal standards.

Materials and Methods

The study was approved by the Institutional Review Board of the University of Washington. Our goal was to determine the cost-effectiveness of LPV and the clinical and economic consequences of an intervention to improve adherence with LPV in ALI patients from the societal perspective. Currently, to our knowledge, there are no large multicenter studies evaluating the effectiveness of an intervention to improve adherence with LPV.[16] In the absence of evidence, we chose to model the cost-effectiveness of LPV by itself, recognizing that even an intervention with zero up-front costs has important downstream costs. We then estimated the maximum cost for a hypothetical ICU-level intervention aimed at improving LPV adherence, thus exploring the cost-effectiveness of LPV implementation under a worst-cost scenario.

We generated a decision model comparing the ventilatory care of the ALI patient with and without use of an LPV protocol (Fig 1). Our model included a decision node for a hypothetical intervention aimed at improving LPV adherence at the ICU level. We then performed the following two analyses: a base-case analysis (Fig 1, *box*), evaluating the cost-effectiveness of LPV as the sole intervention; and an intervention-case analysis evaluating the influence of an intervention aimed at improving the adherence with LPV. As recommended by the Panel on Cost Effectiveness in Health and Medicine (PCEHM), we applied a lifetime time horizon in the analysis.[17]

Effects

We measured incremental effect as the number of life-years gained and number of quality-adjusted life-years (QALYs) gained between the non-LPV and the LPV arms of the decision model.[17] We modeled QALYs as previously described in critically ill populations with and without ALI.[18,19] The age of each hospital survivor was estimated from the King County Lung Injury Project (KCLIP), a population-based study of the incidence and outcomes of ALI.[1] We calculated the number of life-years by determining the age-matched mean life expectancy for each hospital survivor by ALI risk factor in our population using the 2004 life tables from the National Center for Health Statistics.[20] This life expectancy was further discounted by the expected reduction in life expectancy experienced by survivors of sepsis (51% reduction in long-term survival) and for nonsepsis survivors of ALI (10% reduction in long-term survival).[21,22] To generate QALYs, we multiplied the mean adjusted life expectancy by the mean Quality of Well-Being scale for 1-year survivors of ALI (0.60),[23] as recommended by the PCEHM for the calculation of QALYs.[17]

Costs and Resource Use

For the base case, we determined the difference in costs between the LPV arm and the non-LPV arm of the decision model, obtaining estimates of the costs for each day spent in the hospital (*ie*, in the ICU, receiving ventilation, or on the ward) from the medical literature (Table 1).[24,25] Because LPV does not affect the need for additional supportive therapies, including vasopressors, IV fluids, or diuretics, or the need for sedation and neuromuscular blockade, no other costs due to LPV were included in this analysis.[26,27] Posthospitalization costs for the first 2 years after hospital discharge were estimated from the literature and updated to 2008 US dollars.[28] For survival beyond the first 2 years, costs were calculated using age-specific medical expenditure data from the Statistical Abstract of the United States and the Bureau of Labor Statistics for 2006.[29,30] We assigned each hospital survivor the average posthospital expenditures of someone in the general population with the same life expectancy rather than the same age. This approach, used by other cost-effectiveness analyses in critical illness, assigns greater medical expenditures to survivors of ALI than those incurred by an age-matched general population because it assigns health-care costs based on the reduced life expectancy associated with survival after ALI. These costs include subsequent hospitalizations, outpatient care, rehabilitation costs, and home care costs. Annual costs were updated monthly for each year of survival for each patient until death using a time-dependent Markov model (Fig 1, Markov tree).

For the intervention case, we used the decision model to determine the maximum cost for an ICU-wide intervention that would remain cost-effective at the $50,000 per QALY gained threshold. ICUs were assumed to care for an average of 40 cases of ALI per year, which was estimated from KCLIP.

Likelihood of Events

Table 2 lists the probabilities of clinical events used in the decision model. We assumed that the relative risk reduction for application of the LPV protocol would mimic the results of the landmark clinical trial as well as a metaanalysis.[2,3] For the intervention-case analysis, the proportion of patients who receive LPV in the usual-care arm were estimated from the medical literature.[4,6–13] We assumed that a hypothetical intervention would improve adherence with LPV from a baseline value of 50% up to 90%.

Statistical Analysis

We performed a series of one-way and multi-way sensitivity analyses to evaluate the uncertainty in the decision model, varying all model inputs according to their specified ranges.

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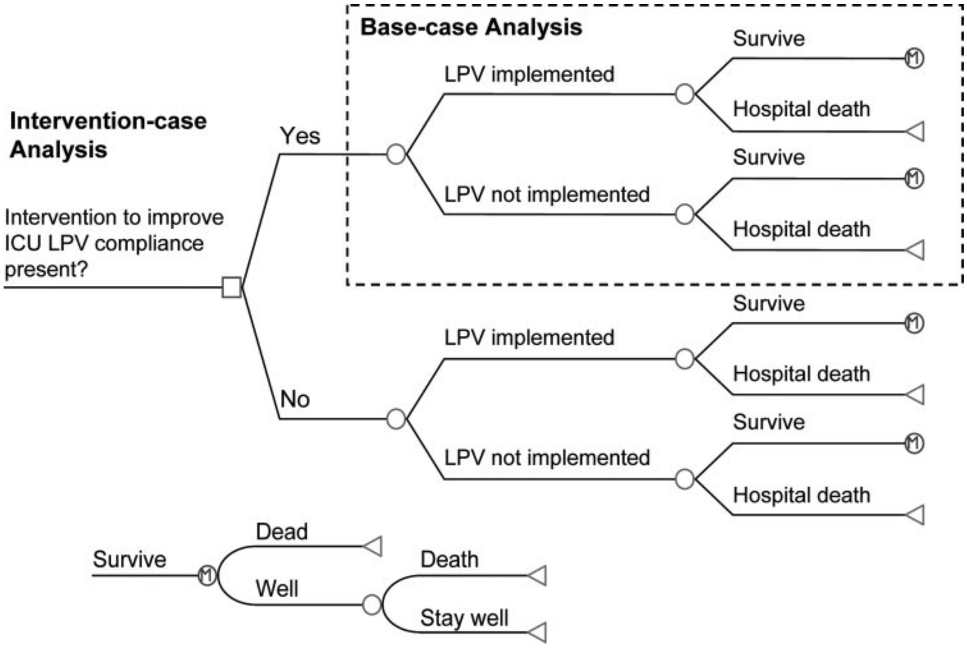

FIGURE 1. Simplified schema of the decision model. From left to right, the square node represents the decision to implement an intervention to improve LPV adherence. The hollow circular nodes are "chance nodes," representing the downstream consequences of the decision. The triangular nodes at the end of each pathway represent the cumulative costs and effects of each pathway. The circular nodes with a central "M" represent a patient surviving hospitalization and entering into a time-dependent Markov process (separate subtree). The subtree outlined by the dashed line was used for the base-case analysis. The actual tree used in the model incorporates risk factor (sepsis, trauma, other).

Parameters that had the greatest influence in the estimated incremental cost-effectiveness ratio (ICER) for the base-case model were plotted in a tornado diagram. To explore the relationships among the baseline rate of LPV adherence, intervention cost, and postintervention LPV adherence in the intervention-case analysis, we varied these three parameters in a three-way sensitivity analysis. The impact of the uncertainty in all of the parameters simultaneously was ascertained by performing a multivariate sensitivity analysis using Monte Carlo simulation. Each parameter in the model was assigned a distribution that closely fit the mean of the parameter and its uncertainty.[31] Ten thousand patients were simulated, and the ICER was calculated for each simulation. We identified the central region containing 95% of the estimates for the ICER.

Analyses were conducted using appropriate software (TreeAge Pro 2008; TreeAge Software; Williamstown, MA). All costs were converted to 2008 US dollars by using the gross domestic product deflator.[32] Both costs and effects were discounted at a 3% annual rate as recommended by the PCEHM.[17,33]

RESULTS

Base-Case Analysis

The lifetime cost of care for a patient with ALI receiving LPV was $106,821 compared to $99,588 for non-LPV ALI care, for a difference in cost of $7,233. The hospital mortality rate in the LPV arm was 31% compared to 40% in the non-LPV arm, resulting in a number of patients-needed-to-treat with LPV to save one life of 11. The discounted, age-adjusted average life expectancy for a hospital survivor with sepsis was 6.5 years, for a hospital survivor with trauma 13.4 years, and for patients without either trauma or sepsis 7.0 years. Patients receiving LPV had an average of 4.83 QALYs after hospital discharge; non-LPV care resulted in 4.21 QALYs. When short-term and long-term costs and utilities were combined, the incremental cost-effectiveness for the base case was $11,690 per QALY. This number reflects the cost of each QALY gained by delivering LPV to a patient with ALI. On combining costs and lives saved at hospital discharge, the incremental cost-effectiveness for LPV in the base case was $22,566 per life saved.

Intervention-Case Analysis

Assuming an ICU-wide intervention could improve LPV adherence from a baseline of 50 to 90% in an ICU caring for 40 patients with ALI per year, an intervention costing a maximum of $379,284 remained cost-effective. This value indicates that investing up to $9,482 in a single patient to ensure that the chances of that patient receiving LPV improve from 50 to 90% is a cost-effective strategy.

Table 1—*Assumptions, Sources, and Values for Costs Used in Analysis*

Costs	Survivors	Nonsurvivors	All	Notes, Assumptions, and Sources
Duration of each type of hospital day, d				LOS data were derived from the KCLIP[1]; costs for each arm in the model were calculated by multiplying the cost for each different type of day by the LOS associated with that day; base-case values were varied by ± 2 SDs in two-way sensitivity analyses*
Ventilated ICU days (both arms)				
Sepsis	7.9 (10.7)	6.7 (8.5)		
Trauma	9.9 (7.5)	5.7 (6.6)		
Other	6.1 (10.4)	8.5 (12.6)		
Nonventilated ICU days (both arms)				
Sepsis	3.4 (5.1)	1.1 (3.1)		
Trauma	2.4 (3.6)	0.8 (1.9)		
Other	3.2 (4.2)	1.2 (4.4)		
Ward days (both arms)				
Sepsis	7.5 (9.5)	1.5 (5.8)		
Trauma	10.3 (11.2)	1.7 (5.6)		
Other	8.6 (14.9)	1.9 (5.4)		
Cost for each type of day, $US				Estimates reflect average daily costs of mechanically ventilated patients, nonventilated ICU patients, and a 50% reduction in cost associated with transfer to the floor[24,25]
Ventilated ICU day			5,232 (1,000–8,000)	
Nonventilated ICU day			3,563 (1,000–5,000)	
Ward day			1,782 (500–3,000)	
Posthospital medical costs				
First year			11,311 (5,000–22,000)	Incorporate all posthospitalization costs (subsequent hospitalizations, outpatient visits, rehabilitation, home care)[28]
Second year			8,448 (4,000–17,000)	
Beyond second year (age-specific)			(± 25%)†	Health-care expenditures based on the Statistical Abstract of the United States and the Bureau of Labor Statistics for 2006[29,30]
Death, $US			6,676 (5,007–8,346)	One-time cost at time of death; this cost approximates the societal cost for care associated with a fatal illness[45,46]

Values are given as mean (SD) or mean (range). LOS = length of stay.
*Assumes that LPV does not result in differences in length of stay other than that resulting from lower mortality.
†Adjusted age-specific health-care costs.

Sensitivity Analysis

Figure 2 shows the impact of the most influential individual parameters on the ICER for the base-case analysis. The ICER generated by the model was most sensitive to variability in the total number of ventilated days for patients with sepsis and the life expectancy of survivors with ALI due to sepsis. However, LPV remained cost-effective relative to non-LPV care over all ranges for each variable in the analysis.

Table 2—*Parameters Used in the Cost-effectiveness Model*

Parameter or Probability	Base-Case Value (Range)	Intervention-Case Value (Range)	Reference
Hospital volume of ALI patients/yr		40 (20–100)	1
Risk factor for ALI			1,47
Sepsis	72% (50–80)	72% (50–80)	
Trauma	7% (5–14)	7% (5–14)	
Other	21% (6–45)	21% (6–45)	
LPV protocol implementation			
Probability (LPV implemented/usual care)	0 (0–0)	0.50 (0.2–0.80)	6–14
Probability (LPV implemented/intervention)	1.0 (1.0–1.0)	0.90 (0.85–1.0)	
Mortality			
Relative risk of death (LPV)	0.78 (0.65–0.93)	0.78 (0.65–0.93)	2,3,48
Probability (death/no LPV)	0.4 (0.35–0.45)	0.4 (0.35–0.45)	2,3,48
Probability (death/LPV)*	0.31 (0.23–0.42)	0.31 (0.23–0.42)	2,3,48
Utility			
ALI survival	0.60 (0.4–1.0)	0.60 (0.4–1.0)	23
Death	0	0	

*Probability of death given by LPV, calculated by multiplying the relative risk of death for LPV by the probability of death for patients ventilated without LPV.

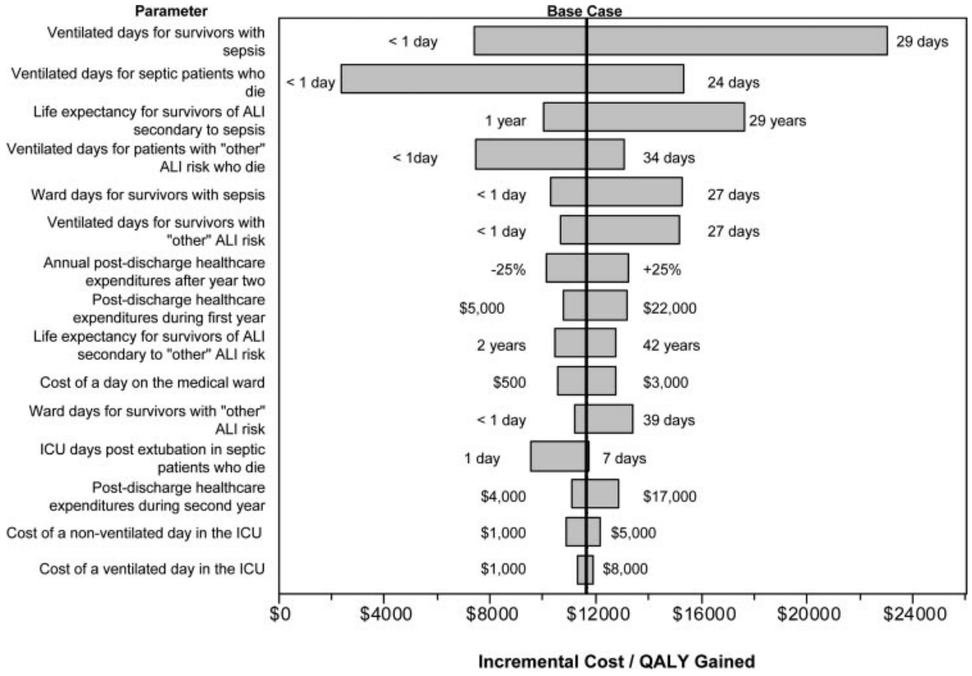

FIGURE 2. Tornado diagram. The effect of individual variables on the cost-effectiveness of LPV. Bars indicate how the cost-effectiveness of LPV vs no LPV changes when parameters are varied in one-way sensitivity analyses from the lowest to the highest extreme of their plausible range (extreme values are shown adjacent to bars). The base-case line represents the incremental cost-effectiveness calculated for the base case.

Probability-based sensitivity analyses for the base case indicated that most simulations were cost-effective according to standard thresholds (Fig 3). Of the 10,000 simulations, 84% had ICERs < $20,000 per QALY, 98.9% had ICERs < $50,000 per QALY, and 99.6% had ICERs < $100,000 per QALY.

Figure 4 shows a three-way sensitivity analysis for the intervention-case analysis. The maximal cost-effective per patient investment depended on the baseline rate of LPV adherence in an ICU and the projected rate of adherence postintervention. ICUs with lower rates of LPV delivery have much higher maximum intervention costs per patient, which remain cost-effective. However, a large per patient monetary investment aimed at improving the probability of LPV delivery remained cost-effective regardless of the baseline rates of LPV delivery. For example, ICUs interested in improving their LPV adherence from a baseline of 70 to 85% of patients could invest up to $3,556 per patient with ALI into an ICU-wide intervention to achieve this improved adherence. Interventions costing > $3,556 per patient in this particular ICU would cause the intervention to have an ICER of > $50,000 per QALY. Investing up to $7,112 per patient to achieve 100% adherence in the same ICU would remain cost-effective.

DISCUSSION

We utilized decision analysis techniques to model the clinical and economic outcomes associated with LPV and to determine the maximum cost of an intervention aimed at improving LPV delivery that remained cost-effective. The results of the analysis indicate that low-tidal volume ventilation is a highly cost-effective strategy. These findings were robust to an extensive sensitivity analysis. Based on current societal cost-effectiveness standards, we determined that the average ICU should be willing to spend up to $9,500 per patient with ALI to ensure that the patient receives LPV.

The United States spends more on health care than any other country, yet our health outcomes are consistently below average.[33] This discrepancy may in part result from misplaced priorities of health-care spending.[34] Each year, the National Institutes of Health allocates the majority of its research budget to basic science and the development of new treatments, yet < 1% of its budget is directed toward ensuring that patients receive such treatments.[34,35] As a result, many well-known cost-effective therapies are not delivered to the patients who could directly benefit. Instead, billions of dollars are spent on tests and treatments that lack evidence of effective-

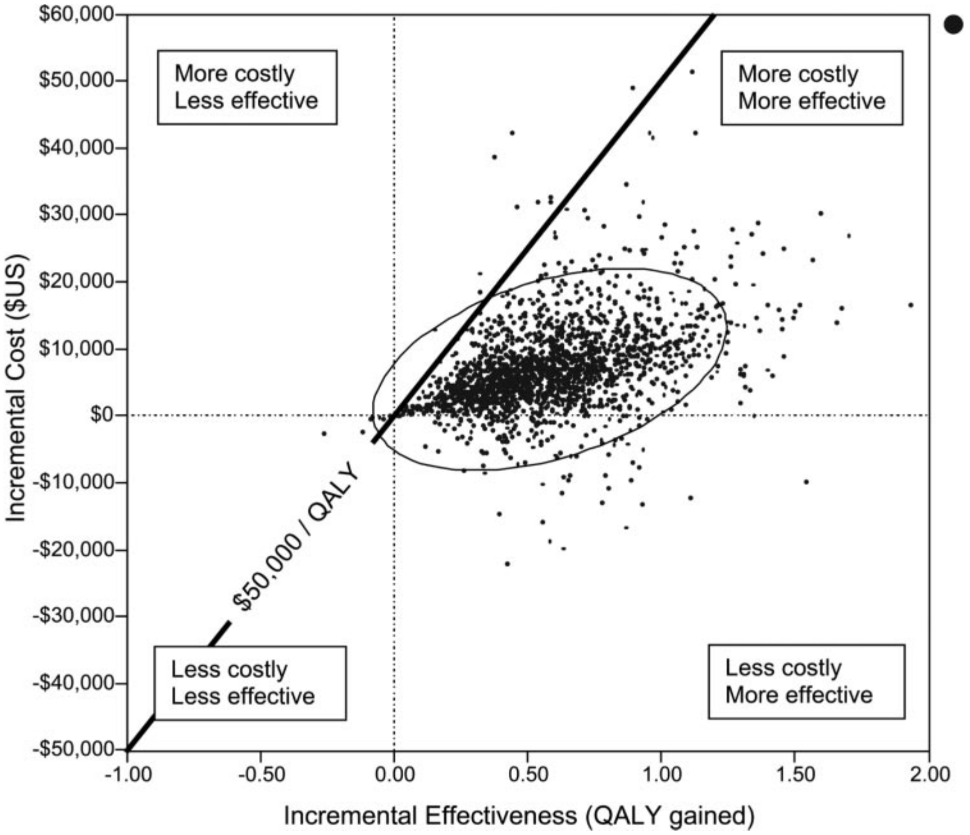

FIGURE 3. Probability-based sensitivity analysis. For each one of the 10,000 trials, values for the parameters in the model are selected from their respective distributions and an ICER is calculated. A 95% confidence ellipse is placed around 95% of the points and represents the uncertainty in the ICER estimate. Points falling above the dotted line have an ICER of > $50,000 per QALY; those falling below the line have ICERs of < $50,000 per QALY. A random 2,000 of 10,000 points are represented.

ness.[34,35] Critical care is not immune to these issues. In fact, a large proportion of these expenditures are attributable to care delivered in an ICU.[36]

In an effort to address these issues, policy experts have called for[34,35] a fundamental reordering of health priorities toward therapies known to be cost-effective. Although a necessary first step, prioritizing cost-effective therapies may not lead to improved health unless there is a concomitant effort to improve adherence to such therapies. To date, there has been minimal national effort to study and implement mechanisms to improve adherence to evidence-based practice in the ICU. More often, such investigation is initiated under local quality improvement efforts. Until we know exactly which therapies in the ICU are cost-effective and how to improve adherence to these therapies, the onus of providing care that is both evidence based and value based lies in the hands of the hospital, ICU, and individual providers.[37]

Our results have significant implications for ICUs and critical care providers who care for patients with ALI. Through implementing LPV, ICUs and critical care providers have the ability to decrease mortality and, as a result, increase the QALYs for their patients with ALI. Importantly, our model indicates that LPV can be provided at a lower cost than other commonly used ICU interventions (Table 3).

How can hospitals, ICU directors, and critical care providers use the results of our analysis? We chose to evaluate the maximum cost of a hypothetical ICU-based intervention to improve LPV adherence that would remain cost-effective, allowing us to determine intervention cost under a hypothetical "most expensive" scenario. Despite evidence that many patients do not currently receive LPV,[4,6–12] some ICUs may implement this protocol in a higher proportion of patients, yet even these ICUs can improve their adherence to 100% in a cost-effective way. Using data from Figure 4, even an excellent ICU with baseline LPV adherence of 80% could spend as much as $4,750 per patient to achieve 100% adherence and, if our analysis is correct, still be within the standard criteria of cost-effectiveness. Therefore, in a typical 15-bed medical-surgical ICU that cares for 30 to 60 ALI patients per year,[38] a

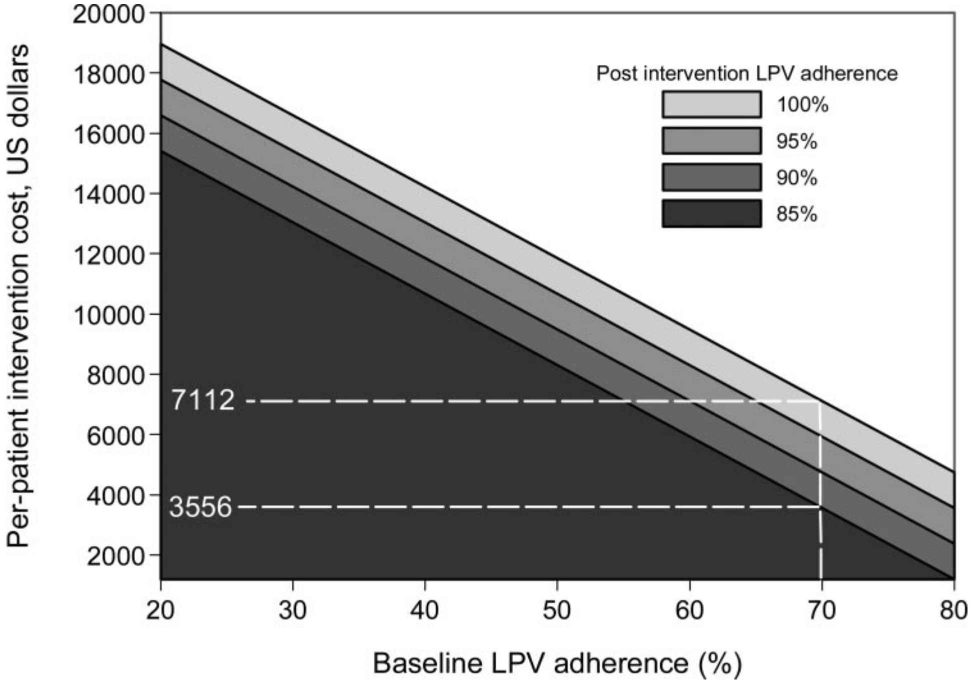

FIGURE 4. Three-way sensitivity analysis. The diagonal black lines represent the maximum per-patient intervention cost remaining cost-effective over the range of baseline LPV adherence rates for each postintervention adherence rate. For a given postintervention LPV adherence, all shaded areas falling below its diagonal line are cost-effective (ICER < $50,000 per QALY). All areas falling above the diagonal line are not cost-effective (ICER > $50,000 per QALY). The dotted lines provide examples of the cost required to improve LPV adherence from 70 to 85% or to 100%.

program to implement LPV in patients with ALI costing $140,000 to $280,000 per year would be cost-effective. These data can be used to justify quality improvement programs in critical care and will allow hospitals, ICU directors, and critical care providers to assess their need for interventions to improve adherence to LPV based on their local practice.

It is important to note that our cost-effectiveness estimates and the estimated maximum interventional cost that remains cost-effective are likely conservative. First, most hospital costs incurred by LPV result from the prolonged hospital stay for patients who survive ALI. We utilized estimates for the cost of hospital days that were based on average daily costs from the literature. Increasing length of stay, however, only incurs marginal costs, or the cost of each additional ICU day, rather than average costs.[39] Average costs are much higher because they include the first few days of ICU care, which typically are much costlier than subsequent days. The incorporation of marginal costs into our model would have

Table 3—*Comparison With Other Widely Used Interventions in the ICU*

Interventions	Study/Year	Scenario	Cost-Effectiveness $/QALY*
Early goal-directed therapy in sepsis	Huang et al[19]/2007	Early goal-directed therapy in septic patients vs usual care	7,400
LPV		Low-tidal volume ventilation vs usual care in ALI patients	11,690
Drotrecogin alfa (activated)	Fowler et al[49]/2003	Severe sepsis with APACHE score > 24 vs standard therapy	15,100
	Angus et al[18]/2003	Severe sepsis with APACHE score > 24 vs standard therapy	31,300
ICD	Owens et al[50]/1997	ICD only (40% mortality reduction) vs amiodarone	46,000
Lung transplantation	Ramsey et al[51]/1995	ICD only vs standard care, assuming 10-yr survival	230,000
Cardiopulmonary resuscitation	Lee et al[52]/1996	In-hospital care vs none	280,000

The cost-effectiveness of LPV seems comparable to that of early goal-directed therapy for sepsis and is superior to the cost-effectiveness of therapy with activated protein C, ICDs, lung transplantation, and cardiopulmonary resuscitation. APACHE = acute physiology and chronic health evaluation; ICD = internal cardiac defibrillator.

*Cost inflated to 2008 US dollars.

resulted in a lower ICER for LPV and a higher maximum per patient investment to improve LPV adherence. Second, we considered an ICER of ≤ $50,000 per QALY as indicative that the intervention remained cost-effective. Many widely adopted critical care therapies, however, have ICERs that exceed this threshold (Table 3). Utilizing a QALY threshold that is more consistent with the societal value of health care ($200,000 per QALY)[40] would result in a much greater maximum, cost-effective cost for a hypothetical intervention to improve LPV adherence.

We were unable to populate our model with an actual intervention targeting LPV adherence because, to date and to our knowledge, no large-scale, community-based programs to improve the quality of care to mechanically ventilated patients exist.[16] There are, however, multiple theoretical interventions that a hospital could implement to improve LPV delivery. Higher intensity ICU staffing such as hiring 24-h intensivists may result in improved adherence to LPV.[41] Alternatively, hiring additional respiratory therapy staff dedicated to identifying ALI and implementing LPV may also result in greater adherence. Other interventions, such as the automated identification of ALI patients; auditing and feedback of LPV adherence data; using provider-specific adherence rates for pay-for-performance initiatives, computerized reminders, or decision support; and structured interactive education of staff all have the potential to improve adherence with LPV, yet none have been rigorously tested in this patient population.[42] Critical care investigators should test such interventions to determine whether they successfully improve LPV adherence rates and can be generalized to the broader community. Hospitals with smaller ICUs that do not have protocols for patients with ALI can invest money to develop ventilator protocols that implement low-tidal volume ventilation. Given the lack of evidence for ways to improve ventilatory practice, hospital and ICU policymakers can tailor their investment toward interventions that have the most local support.

We recognize a number of limitations to our analysis. First, estimates of the efficacy of LPV primarily derive from a single study conducted by the ARDS Network 2000.[2] Although estimates were corroborated with a metaanalysis,[4] pooled estimates of the relative risk reduction in mortality associated with LPV are largely driven by the ARDS Network study.[2] Moreover, mortality rates and the relative efficacy of LPV may have changed as ICU care has improved over time.[43] Second, we utilized the largest currently available, population-based sample of patients with ALI in the United States to derive estimates of length of stay for survivors and nonsurvivors. Accurate estimates of length of hospital stay for ALI patients were important because hospital expenses are primarily driven by the greater lengths of stay in patients surviving ALI. However, this cohort was collected in Washington State during 1999 to 2000 and may therefore not be able to be generalized to hospitals outside of the northwest United States or to contemporary patients with ALI. Nevertheless, our conclusions remain unchanged on varying these parameters in a sensitivity analysis.

Conclusion

Our results corroborate the findings of others that investing in methods to implement effective care can yield significant health benefits efficiently even when the implementation methods are expensive.[44] LPV is cost-effective by current societal standards. Average ICUs could invest thousands of dollars per ALI patient to ensure that LPV is delivered, and the combination of implementation and LPV would still cost < $50,000 per QALY. Given the persistent low rates of LPV delivery in the United States, scientists should now focus on investigating the effectiveness and eventually the cost-effectiveness of behavioral and system-level interventions that are aimed at improving adherence to LPV. Ventilator protocols, increased physician or nonphysician staffing, computerized ALI diagnosis and decision support, pay-for-performance measures, and benchmarking are all potential means to improve delivery of LPV that warrant further study.

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