

Special Article

AN ECONOMIC EVALUATION OF ACTIVATED PROTEIN C TREATMENT FOR SEVERE SEPSIS

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ABSTRACT

Background Recombinant human activated protein C was shown in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study to reduce mortality among patients with severe sepsis. A post hoc reanalysis by the Food and Drug Administration (FDA) of data from this study suggested that the reduction in mortality was restricted to patients with Acute Physiology and Chronic Health Evaluation (APACHE II) scores of 25 or more.

Methods We estimated the cost effectiveness of activated protein C as compared with conventional care for patients with severe sepsis. We performed an economic analysis involving all patients, as well as analyses of subgroups defined according to age and severity of illness. The probabilities of transition between clinical states and the estimates of resource use were derived from a population-based cohort of patients with severe sepsis. We used data on the effectiveness of activated protein C from the PROWESS study and analyses by the FDA.

Results The cost per life-year gained by treating all patients with activated protein C was \$27,936. It was more cost effective to treat patients with an APACHE II score of 25 or more (\$24,484 per life-year gained) than those with a lower APACHE II score (\$35,632 per life-year gained). The cost effectiveness of treating patients with an APACHE II score of 24 or less increased to \$575,054 per life-year gained when the FDA's estimates of effectiveness were considered. For patients with an APACHE II score of 25 or more, the cost per life-year gained increased with age (\$16,309 for patients less than 40 years of age; \$28,100 for those 80 years of age or older).

Conclusions Activated protein C is relatively cost effective when targeted to patients with severe sepsis, greater severity of illness (an APACHE II score of 25 or more), and a reasonable life expectancy if they survive the episode of sepsis. Further research is needed to determine the cost effectiveness of activated protein C for patients with sepsis and less severe illness. (N Engl J Med 2002;347:993-1000.)

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SEVERE sepsis is responsible for 6 to 15 percent of admissions to the intensive care unit (ICU)¹⁻³ and is associated with high mortality (30 to 50 percent).^{1,4} Its importance as a clinical problem is underscored by the extent of resources used to care for patients who have this condition.^{5,6}

Recombinant human activated protein C was recently approved by the Food and Drug Administration (FDA) for treatment of patients with severe sepsis; the approval was based on the 19.4 percent reduction in the relative risk of death (an absolute risk reduction of 6.1 percent) found in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study.⁴ In a post hoc analysis of data from that study that was performed by the FDA,⁷ the benefit of activated protein C appeared to be restricted to patients with more severe illness (i.e., those with an Acute Physiology and Chronic Health Evaluation [APACHE II] score of 25 or more; APACHE II scores range from 0 to 71, with higher scores predicting an increased likelihood of death⁸).

The FDA analysis has made the implications of differences in effectiveness according to APACHE II score a critical policy issue. Considering the estimated cost of recombinant human activated protein C (\$6,800 per therapeutic course), the potential frequency of use,¹ and the uncertainty regarding its effectiveness in patients with an APACHE II score of 24 or less, and acknowledging that resources may be taken from ICU budgets (or health care more broadly) to fund treatment with activated protein C, decision makers must determine its optimal use.

We collected clinical and cost information, including data from three-year follow-up in a cohort of pa-

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tients who had been admitted to an ICU with severe sepsis and had received conventional care. Using this complete data set and modeling the predicted improvement in short-term survival with activated protein C,⁴ we estimated the cost effectiveness of activated protein C for patients admitted to the ICU with severe sepsis.

METHODS

Study Design

Using an analytic horizon of a lifetime, we calculated the cost per life-year gained with recombinant human activated protein C (Xigris, Eli Lilly) as compared with conventional care for patients admitted to the ICU with severe sepsis. The calculation was performed for all patients and was repeated for subgroups stratified according to age and severity of illness. For the base-line analyses, we took the perspective of the purchaser of health care services; in the sensitivity analysis, we considered a broader societal perspective, incorporating the effect of indirect costs (in lost production) due to premature deaths.^{9,10} In base-line analyses, no adjustment was made for health-related quality of life in order to estimate quality-adjusted life-years, since no one has defined valid utility scores (representing overall health-related quality of life and ranging from 0, the worst imaginable health, to 1, perfect health) for survivors of sepsis. However, health-related quality of life is reduced among survivors of ICUs and sepsis,¹¹⁻¹⁴ and this reduction, too, is considered in the sensitivity analysis.¹⁴

The outcomes of our analyses were life-years, costs, and the incremental cost per life-year gained. Costs and life-years were discounted at an annual rate of 5 percent.¹⁵ Costs were calculated on the basis of 2001 Canadian dollars and were converted to United States currency at the rate of 1 U.S. dollar to 1.47 Canadian dollars; amounts are given in U.S. dollars. Analyses were performed with the use of Data Pro software (TreeAge Software).

Conventional-Care Cohort

Annual mortality rates among survivors of sepsis are higher than those among control patients who are discharged from the hospital with diagnoses unrelated to infection,¹⁶ but the risk of death each year after discharge — overall and in subgroups defined according to age — has not been reported. Therefore, we undertook a cohort study to obtain accurate estimates of subsequent mortality and direct health care costs for surviving patients who have been hospitalized with severe sepsis. The local institutional review board approved the study.

The Calgary Health Region has three tertiary care hospitals, all with ICUs, that serve the local community (population, 0.9 million) and are regional referral centers for the rest of southern Alberta, Canada (population, 0.4 million). All the ICUs admit medical and surgical patients whose demographic and physiological data are abstracted prospectively each day and stored in a research data base. A total of 819 patients with suspected or known infection were admitted to one of these ICUs between April 1, 1996, and March 31, 1999; of these patients, 787 (96.1 percent) had a valid health care identification number in Alberta for the entire study period, permitting follow-up. To confirm that these patients had severe sepsis, a sample of 40 was selected randomly, and their charts were manually reviewed to determine whether the patients met the criteria for inclusion in the PROWESS study.⁴ Only one patient, with a perforated bowel, did not meet the criteria for severe sepsis. Of the remaining patients, 24 had refractory shock requiring vasopressor support, and 36 required mechanical ventilation. For the 787 patients who could be followed, we also determined whether there were preexisting conditions.¹⁷

Clinical Effects

To calculate the cost effectiveness of treatment with activated protein C, we used a Markov model. We considered weekly transitions between any two of four clinical states: alive in the ICU, alive on the hospital ward, alive at home, and dead. The starting point of the model was our cohort of patients with severe sepsis. The probabilities of death and of ICU or hospital discharge (i.e., the probability of transition from one of the above predefined states to another in the model) among patients who received conventional care were based on the observed hazard rates in our cohort of patients. For hospital survivors (patients who survived to discharge from the hospital), the subsequent rate of death was determined on the basis of data from the Alberta Vital Statistics data base for the first, second, and third years after hospital discharge (years 1, 2, and 3). Because we did not have data on vital statistics beyond July 1, 2001, the hazard rate for death in year 3 was censored for the 96 patients who were discharged home after July 1, 1998, and had not died before July 1, 2001. To account for increasing rates of age-related mortality after the three-year follow-up period, we adjusted the annual mortality rate noted in the third year of follow-up by the absolute age-specific increment in the mortality rate of the Canadian population.¹⁸ Hazard rates were also estimated for subgroups of patients stratified according to age (<40 years, 40 to 59 years, 60 to 79 years, or ≥80 years) and APACHE II score on admission (≤24 or ≥25). Separate models were created to analyze the cost effectiveness of treatment with activated protein C in the two subgroups defined according to APACHE II score; probabilities of transition between clinical states were based on the rates of transition observed in these two subgroups.

Costs for the Conventional-Care Cohort

We estimated the weekly cost of conventional care for severe sepsis in the ICU and on the hospital ward, as well as the cost of subsequent health care for hospital survivors (see the Appendix). Estimating indirect costs for survivors was problematic, since no such estimates have been published and we did not have data on employment rates or the cost of patients' time (i.e., lost wages due to time spent obtaining care) after hospital discharge. However, in one study, only 16.9 percent of patients under 61 years of age who were discharged from a general ICU were subsequently employed.²² To estimate indirect costs, we multiplied this estimate of the employment rate (16.9 percent for patients younger than 60 years and 0 percent for patients 60 years of age or older) by the average gross annual salary of a full-time Canadian worker (33,384 Canadian dollars).²³

Clinical Effects of Activated Protein C

To estimate the increase in life expectancy attributable to treatment with activated protein C, we assumed a reduction in the risk of death from that in the conventional-care cohort during the first four weeks of the analysis based on the relative risk of death reported in the PROWESS study (0.80; 95 percent confidence interval, 0.69 to 0.94).⁴ We assumed no improvement in survival relative to the conventional-care group after 28 days and no difference in the length of stay between survivors treated with activated protein C and those receiving conventional care.²⁴

The original report on the PROWESS study stated that the effectiveness of activated protein C was consistent in all subgroups.⁴ However, as noted above, a post hoc analysis of the study data performed by the FDA reported a differential benefit according to APACHE II score: among patients with a score of 25 or more, the relative risk of death among patients treated with activated protein C, as compared with those given placebo, was 0.71 (95 percent confidence interval, 0.59 to 0.85), whereas among those with a score of 24 or less, the relative risk was 0.99 (95 percent confidence interval, 0.75 to 1.30).⁷ In our base-line and sensitivity analyses, we

considered both the estimates of effectiveness from the PROWESS study and those from the FDA analysis.

Cost of Care for Patients Treated with Activated Protein C

The acquisition cost of activated protein C is \$6,800 per therapeutic course. There was a small excess risk of serious bleeding (1.5 percent) in patients treated with activated protein C, as compared with those given placebo.⁴ The cost of managing clinically important gastrointestinal bleeding in the ICU has been reported to be \$8,306 per episode of bleeding²⁵; therefore, the additional cost to manage bleeding in a patient treated with activated protein C was estimated as \$122. Otherwise, the cost of caring for patients who were treated with activated protein C was assumed to be equal to that for patients who received conventional care.²⁴

Sensitivity Analysis

Various sensitivity analyses were performed. The cost-effectiveness analysis was repeated as a cost-utility analysis through the incorporation of a utility score into the outcome. As the base-line utility value, we used 0.6, which is the estimate of the overall health-related quality of life one year after hospital discharge in a group of patients admitted to the ICU with the acute respiratory distress syndrome.¹⁴ We used this estimate since the acute respiratory distress syndrome is similar to sepsis in terms of the associated mortality, the severity of illness,²⁶ and the scores on the Medical Outcomes Study 36-item Short-Form General Health Survey that have been reported in survivors.^{12,27}

We considered the effect of varying our estimate of the relative risk of death for patients treated with activated protein C within the 95 percent confidence interval reported in the original PROWESS trial.⁴ We varied the estimates of in-hospital and subsequent death rates by 25 percent to determine the effect on cost effectiveness. We also performed a sensitivity analysis in which we varied our estimate of the cost of hospital care and subsequent health care by 50 percent, since higher hospital costs would be expected in the United States.²⁸

To address limitations in classic univariate sensitivity analysis, Monte Carlo simulation was performed.^{29,30} Monte Carlo simulation makes possible the simultaneous sensitivity analysis of all variables for which the values were uncertain by replacing estimates of probabilities, utilities, and costs with specific probability distributions derived from the source data.³¹ Such simulation can also take into account the uncertainty with respect to the maximal cost per quality-adjusted life-year that decision makers would consider acceptable; it does so by means of a cost-effectiveness acceptability curve (for further details, see Supplementary Appendix 1, available with the full text of this article at <http://www.nejm.org>).

RESULTS

Conventional-Care Cohort

The base-line characteristics and the short-term clinical outcomes and associated costs of care for the cohort given conventional care are shown in Table 1.

TABLE 1. BASE-LINE CHARACTERISTICS OF PATIENTS DURING THEIR INITIAL HOSPITAL STAY.*

VARIABLE	ALL PATIENTS (N=787)	AGE GROUP				APACHE II SCORE	
		<40 YR (N=89)	40-59 YR (N=203)	60-79 YR (N=386)	≥80 YR (N=109)	≤24 (N=519)	≥25 (N=268)
APACHE II score							
Mean	20.9	17.4	19.6	22.0	22.4	15.5	31.8
95% CI	20.3-21.6	15.2-19.5	18.3-21.0	21.1-22.9	20.8-24.0†	15.1-16.0	31.2-32.5
Male sex — %	55.8	50.6	54.7	59.1	50.5	57.2	52.0
Death — no. (%)							
By 28 days	242 (30.7)	11 (12.4)	54 (26.6)	130 (33.7)	47 (43.1)	96 (18.5)	146 (54.5)
Before hospital discharge	283 (36.0)	15 (16.9)	63 (31.0)	151 (39.1)	54 (49.5)	119 (22.9)	164 (61.2)
Length of stay — days							
In ICU							
Mean	6.4	8.0	6.2	6.6	5.0	5.8	7.8
95% CI	5.8-7.1	5.5-10.5	5.1-7.2	5.7-7.6	3.6-6.3	5.1-6.4	6.4-9.3‡
On ward							
Mean	29.1	32.6	29.2	30.1	22.5	30.7	24.9
95% CI	26.6-31.7	23.9-41.3	23.8-34.6	26.5-33.8	18.0-26.9	27.7-33.7	20.5-29.2§
Cost — \$¶							
In ICU							
Mean	20,528	24,520	21,142	20,937	13,892	18,176	25,182
95% CI	18,909-23,799	12,230-36,811	16,697-25,588	17,534-24,341	9,355-18,671	15,690-20,663	19,172-31,192‡
On ward							
Mean	12,422	13,472	13,284	12,278	10,239	13,295	9,922
95% CI	10,987-13,858	9,275-17,669	9,996-16,574	10,214-14,343	7,858-12,620	11,508-15,082	7,930-11,915

*The diagnosis on admission to the intensive care unit (ICU) was unspecified septic shock in 41.5 percent of patients, pneumonia in 33.8 percent, gastrointestinal perforation in 12.8 percent, ischemic bowel in 5.8 percent, intraabdominal infection without perforation in 4.2 percent, necrotizing fasciitis in 1.0 percent, and meningitis in 0.9 percent. Acute Physiology and Chronic Health Evaluation (APACHE II) scores range from 0 to 71, with higher scores predicting an increased likelihood of death. CI denotes confidence interval. Lengths of stay on ward and costs on ward are means for patients who were discharged alive from the ICU.

†P<0.001 by one-way analysis of variance for the comparison among the four age groups.

‡P=0.03 by a two-sided t-test for the comparison between the two APACHE II groups.

§P=0.02 by a two-sided t-test for the comparison between the two APACHE II groups.

¶Data include all hospital costs and physicians' charges.

||P<0.001 by a two-sided t-test for the comparison between the two APACHE II groups.

The mean age of patients was 61.1 years (95 percent confidence interval, 59.5 to 62.7). A total of 13.1 percent of the patients had a history of diabetes, 14.5 percent a history of cancer, 15.2 percent a history of myocardial infarction, 21.9 percent a history of congestive heart failure, and 20.2 percent a history of chronic obstructive pulmonary disease. A total of 504 patients (64.0 percent) survived to hospital discharge. Subsequent mortality and use of health care resources are shown in Table 2.

Cost-Effectiveness Analysis

The results of the overall base-line cost-effectiveness analysis, stratified according to age and severity of illness and incorporating the effect of the health-related quality of life, are shown in Table 3. The cost per life-year gained by treating patients with activated protein C is \$27,936. Given the relative risk of death after treatment with activated protein C that was reported in the FDA's reanalysis, it is significantly more cost effective to treat patients with an APACHE II score of 25 or more (\$19,723 per life-year gained) than to treat those with an APACHE II score of 24 or less (\$575,054 per life-year gained) (Table 3).

Our analysis was not sensitive to plausible variations in the estimates of the cost of the initial hospital stay, the cost of subsequent health care, or the discount

rate considered for costs and effects (Table 4). It was also not sensitive to the inclusion of indirect costs. It was sensitive to the estimate of the relative risk of death associated with treatment with activated protein C; as the relative risk approached the upper 95 percent confidence limit (0.94), the cost per life-year gained increased to \$74,612. When patients were stratified according to the severity of illness and the relative risk of death associated with activated protein C treatment reported in the PROWESS study (that is, when we assumed that there was no difference in effectiveness according to the severity of illness), the cost per life-year gained by treating patients with an APACHE II score of 24 or less was more favorable (\$35,632 per life-year gained).

Given the results shown in Table 3, treatment of patients under 40 years of age appears to be less cost effective than treatment of patients between 40 and 79 years of age. However, this finding was attributable to the lesser severity of illness in the younger patients in our cohort (Table 1). When the analysis was restricted to patients with an APACHE II score of 25 or more, the cost per life-year gained increased with increasing age, because the expected survival for older hospital survivors was lower (Table 4).

Figure 1 shows the results of our Monte Carlo simulation. There is an 86 percent probability that the use

TABLE 2. SUBSEQUENT RISK OF DEATH AND USE OF HEALTH CARE RESOURCES AMONG PATIENTS WHO SURVIVED TO HOSPITAL DISCHARGE.

VARIABLE	ALL PATIENTS (N=504)	AGE GROUP				APACHE II SCORE	
		<40 YR (N=74)	40-59 YR (N=140)	60-79 YR (N=235)	≥80 YR (N=55)	≤24 (N=400)	≥25 (N=104)
Risk of death after hospital discharge (%)							
Year 1	12.2	8.1	10.8	12.8	18.2	11.2	17.0
Year 2	5.2	4.4	4.0	7.4	6.7	3.4	11.5
Year 3	4.2	2.0	4.6	4.8	11.1	4.1	6.2
Time spent in the hospital after initial discharge (days)							
Year 1							
Mean	20.7	17.8	23.6	20.5	18.1	19.7	25.2
Median	4	0	3	7	8	4	8
Interquartile range	0-23	0-16	0-22	0-26	0-19	0-22	0-25
Year 2							
Mean	4.8	1.9	5.5	5.5	4.6	5.2	3.5
Median	0	0	0	0	0	0	0
Interquartile range	0-0	0-0	0-2	0-1	0-0	0-0	0-0
Year 3							
Mean	4.6	2.0	3.4	6.3	4.5	4.6	4.4
Median	0	0	0	0	0	0	0
Interquartile range	0-0	0-0	0-0	0-0	0-0	0-0	0-0
Mean health care costs after hospital discharge (\$)							
Year 1	14,181	13,900	14,081	15,357	9,880	12,671	20,528
Year 2	4,698	4,690	5,073	4,774	3,270	4,724	5,720
Year 3	4,579	4,125	4,111	5,241	3,666	4,618	4,200

*Data include direct health care costs for all hospitalizations, day surgeries, and visits to the emergency room in the Calgary Health Region, all hospitalizations occurring outside of the Calgary Health Region (but within Alberta), and all physicians' charges.

TABLE 3. COST EFFECTIVENESS OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR PATIENTS WITH SEVERE SEPSIS.*

GROUP OF PATIENTS	INCREMENTAL GAIN IN LIFE-YEARS PER PATIENT	INCREMENTAL COST PER LIFE-YEAR GAINED	INCREMENTAL COST PER QUALITY-ADJUSTED LIFE-YEAR GAINED
		dollars	
All patients	0.38	27,936	46,560
APACHE II score	0.01	575,054	958,423
≤24	0.76	19,723	32,872
≥25			
Age			
<40 Yr	0.30	31,158	51,930
40–59 Yr	0.40	25,991	43,319
60–79 Yr	0.40	27,392	45,652
≥80 Yr	0.32	32,393	53,989

*Data for all patients and for patients stratified according to age are based on the relative risks of death reported in the PROWESS study⁴ for patients treated with activated protein C as compared with those given placebo; data for patients stratified according to Acute Physiology and Chronic Health Evaluation (APACHE II) score are based on the relative risks reported in the reanalysis by the FDA.⁷

of activated protein C for all patients with severe sepsis would be cost effective if one were willing to pay \$50,000 per quality-adjusted life-year gained.

Implications for Local Resources

The pharmacy budget for our three local–regional ICUs (with a total of 42 beds and 2040 admissions per year) was \$1.6 million in 2001. In 2001, 285 patients were admitted to these ICUs with severe sepsis; of these patients, 101 had an APACHE II score of 25 or more. If we assume that 30 percent of patients have contraindications to the use of activated protein C (that is, that 200 patients would have been treated), the estimated cost for activated protein C in our health care region in 2001 would have been \$1.36 million. If use were limited to those with an APACHE II score of 25 or more, then the estimated cost for activated protein C would have been \$482,800.

DISCUSSION

We estimated the cost per life-year gained with the use of activated protein C treatment in all patients with severe sepsis and the cost per life-year gained with its use in subgroups defined according to age and severity of illness. When only direct costs were considered, the cost per life-year gained varied from \$25,991 to \$32,393 among the age groups. The cost per quality-adjusted life-year gained was higher (\$43,319 to \$53,989) because of the reduction in ongoing health-related quality of life for survivors of sepsis.

TABLE 4. SENSITIVITY ANALYSIS OF THE COST PER LIFE-YEAR GAINED BY TREATING PATIENTS WITH SEVERE SEPSIS WITH RECOMBINANT HUMAN ACTIVATED PROTEIN C.*

VARIABLE USED IN ANALYSIS	INCREMENTAL COST PER LIFE-YEAR GAINED
	dollars
All patients (base-line analysis)	27,936
Relative risk of death with activated protein C†	
0.69	20,821
0.94	74,612
Base-line risk of in-hospital death	
Risk reduced by 25%	32,466
Risk increased by 25%	25,286
Subsequent risk of death among hospital survivors	
Risk reduced by 25%	25,132
Risk increased by 25%	30,803
Cost of activated protein C	
Reduced to 50% of list price	18,318
Reduced to 75% of list price	23,127
Cost of ICU, hospital, and subsequent health care	
Reduced by 25%	26,191
Increased by 25%	29,682
Increased by 50%	31,428
Inclusion of both direct and indirect costs	26,933
Discount rates for costs and effects	
No discounting	19,840
Costs, 3% discount; effects, 3% discount	24,711
Costs, 6% discount; effects, 3% discount	23,816
Utility scores for hospital survivors‡	
0.5	55,873
0.6	46,560
0.7	39,909
0.8	34,921
Subgroups stratified according to APACHE II scores	
With the relative risk of death reported in the FDA reanalysis ⁷	
APACHE II score ≤24	575,054
APACHE II score ≥25	19,723
With the relative risk of death reported in the PROWESS study ⁴	
APACHE II score ≤24	35,632
APACHE II score ≥25	24,484
Subgroups of patients with an APACHE II score ≥25, stratified according to age§	
<40 Yr	16,309
40–59 Yr	18,923
60–79 Yr	22,021
≥80 Yr	28,100

*Data exclude indirect costs. Since these values are predominantly reported in cost per life-year gained, they cannot be compared directly to economic evaluations of other health care interventions in which cost per quality-adjusted life-years are reported. Reductions and increases are as compared with values in the base-line analysis.

†The relative risk of death was varied within the 95 percent confidence interval reported in the PROWESS study.⁴

‡Data are costs per quality-adjusted life-year gained. The utility score represents overall health-related quality of life and ranges from 0, the worst imaginable health, to 1, perfect health.

§The relative risk of death reported in the PROWESS study was used for this analysis.

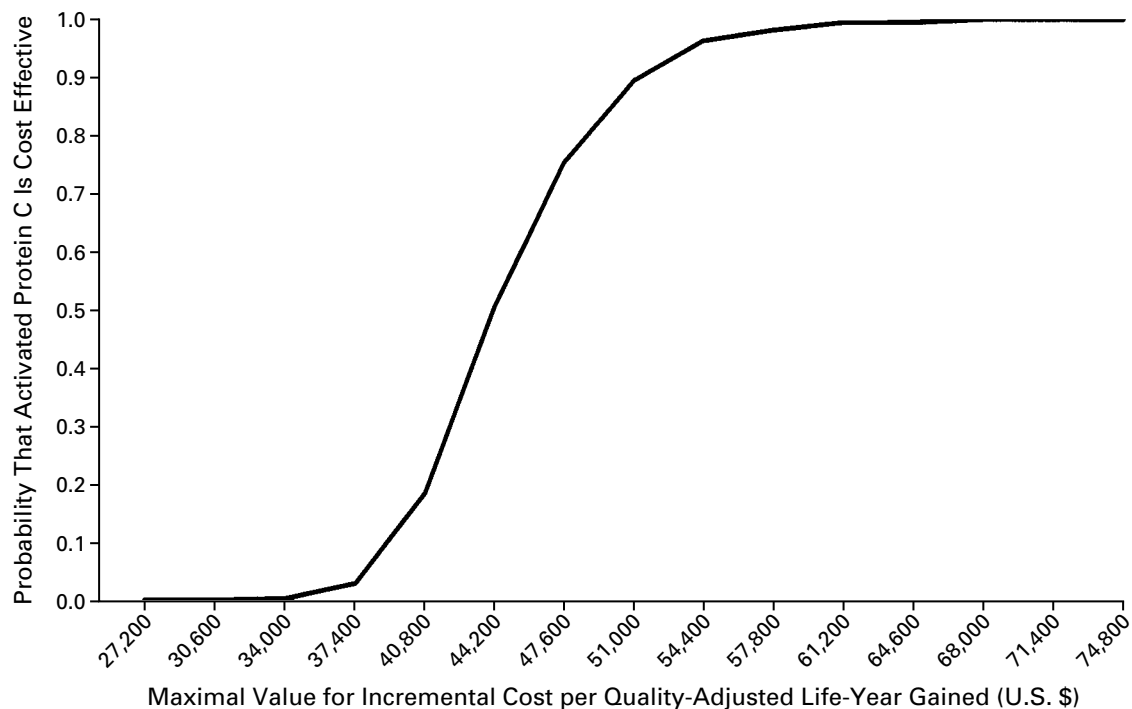


Figure 1. Cost-Effectiveness Acceptability Curve of Activated Protein C Treatment for All Patients with Severe Sepsis.

The graph summarizes the results of our Monte Carlo simulation, in which estimates for each variable in our analysis were replaced by probability distributions. The curve represents the probability that the use of activated protein C is associated with a cost per quality-adjusted life-year gained that is lower than the corresponding cost-effectiveness ratios displayed on the x axis. For example, there is an 86 percent probability that the use of activated protein C would be cost effective if one were willing to pay \$50,000 per quality-adjusted life-year gained.

Those unfamiliar with decision analysis may find the modeling and statistical techniques to be complex and nontransparent. A simple model can approximate the results of our Markov analysis. Treatment with activated protein C of 100 unselected patients with severe sepsis would be expected to yield an additional 6 survivors.⁴ Our model predicts that survivors of sepsis have an average life expectancy of 8.1 years (total life-years gained by treatment of 100 patients with activated protein C, 48.6 years). On the cost side, there is an immediate expense of \$680,000 ($\$6,800 \times 100$ patients), and the cost of caring for 6 survivors for 8.1 years is \$478,565 (according to data reported in Tables 1 and 2). According to this simple model, the cost per life-year gained is \$23,839 ($\$1,158,565 \div 48.6$ years), which is similar to that reported in Table 3.

Treatment with activated protein C was most cost effective in patients with an APACHE II score of 25 or more. This was true whether we used the relative risk of death for patients with an APACHE II score of 25 or more reported in the PROWESS study⁴ or

that reported in the FDA's reanalysis.⁷ However, the reanalysis suggested that treatment with activated protein C was not effective for patients with an APACHE II score of 24 or less; therefore, the cost-effectiveness ratio for treatment of this subgroup was extremely unattractive (\$575,054 per life-year gained). Clearly, the results in this subgroup are dependent on the validity of the post hoc reanalysis performed by the FDA. However, given the discrepancy between the published study results and the reanalysis, it would be reasonable to restrict the use of activated protein C to patients with an APACHE II score of 25 or more until convincing evidence of effectiveness and cost effectiveness in patients with less severe illness becomes available.

Our analysis also suggests that it may be appropriate to target activated protein C to patients who would have a longer life expectancy if they survived their episode of sepsis (that is, patients without coexisting conditions that substantially limit life expectancy). This point can be illustrated by returning to our simple model. If the life expectancy of a survivor of sepsis

is only two years (because of the presence of serious coexisting disease), then the cost per life-year gained rises to \$96,548 (or \$160,913 per quality-adjusted life-year gained).

Our study has several strengths. It conforms to existing guidelines for the performance of economic evaluations.^{15,32} Moreover, the transparency and generalizability of our results are enhanced by the modeling of the effect of the intervention on a population-based cohort of patients for whom follow-up with respect to mortality and resource use was essentially complete for three years.

There is some controversy as to whether the results of an economic analysis performed in one country can be generalized to other countries.³³ However, the results of our analysis were not sensitive to the estimates of immediate hospital costs or subsequent health care costs — the variables that are most likely to vary among countries. The analysis was sensitive to the estimate of the clinical effectiveness of activated protein C; however, patients from 11 countries were enrolled in the PROWESS study, and no difference in effectiveness according to country was reported.⁴ Cost effectiveness was dependent on the age of the patient and the severity of illness, but our cohort of patients had base-line characteristics and in-hospital mortality rates similar to those of patients with severe sepsis in ICUs in the United States.¹ Therefore, we believe that our results are applicable to centers in the United States.

Recombinant human activated protein C is the first approved biologic therapy for patients with severe sepsis. Given that its use will be associated with substantial immediate cost and that the potential population of eligible patients will be large, it is essential to consider its effectiveness and cost effectiveness in various populations of patients before its use becomes widespread. The use of activated protein C in patients with severe sepsis, greater severity of illness, and a reasonable life expectancy if they survive the episode of sepsis is associated with a cost-effectiveness ratio similar to those for other accepted medical therapies. Of course, activated protein C is associated with an incremental cost and will require resources from within current ICU budgets or health care budgets more broadly.

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APPENDIX. CALCULATION OF COSTS

The cost of care per week in the ICU and on the ward was calculated by determining the mean of the hospital costs and physicians' charges per patient per day, then extrapolating to a per-week figure. Other methods of calculating costs were considered within the sensitivity analysis. The cost of health care for hospital survivors for years 1, 2, and 3 after hospital discharge was calculated as the sum of the annual cost of hospitalizations, emer-

gency room visits, and day surgery occurring within the Calgary Health Region, the cost of hospitalization for patients admitted to hospitals within Alberta but outside of the Calgary Health Region, and all physicians' claims. We assumed that the direct cost of care remained constant after year 3; this assumption was tested in a sensitivity analysis.

For patients within the Calgary Health Region, the costs of all episodes of inpatient care, day surgery, and emergency room visits are captured. The cost of inpatient care was calculated by a method described in the provincial and national guidelines for management information systems.^{19,20} This method combines allocation and assignment of all direct and overhead costs associated with an inpatient encounter during the entire hospital stay. The costs we included represent the cost of treating the patient rather than charges or payments; the quality of the data on costs has been ranked highly.²¹ The cost of subsequent hospitalization for patients admitted to hospitals within Alberta but outside of the Calgary Health Region was determined through the use of the data bases of hospital discharges and physicians' charges at Alberta Health and Wellness. Physicians' claims for the initial stay in the ICU and on the ward, as well as for subsequent hospitalizations and all outpatient visits, were acquired from Alberta Health for all patients and for subgroups defined according to age and APACHE II score. Costs for the third year of follow-up were censored as of March 31, 2001; for the patients with censored data, costs for the third year were estimated by direct extrapolation from the data for the observation period. Again, we assumed that these costs remained constant after year 3; this assumption was tested in the sensitivity analysis.

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