Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis*

Derek C. Angus, MB, ChB, MPH; Walter T. Linde-Zwirble; Gilles Clermont, MD, CM, MSc; Daniel E. Ball, BS, MBA; Bruce R. Basson, MS; E. Wesley Ely, MD, MPH; Pierre-Francois Laterre, MD; Jean-Louis Vincent, MD, PhD; Gordon Bernard, MD; Ben van Hout, PhD; for the PROWESS Investigators

Objective: **To assess the cost-effectiveness of drotrecogin alfa (activated) therapy, which was recently shown to reduce mortality in severe sepsis.**

Design: **Estimates of effectiveness and resource use were based on data collected prospectively as part of a multicenter international trial. Estimates of hospital costs were based on a subset of the patients treated in the United States (33% of all enrolled patients). Lifetime projections were modeled from published sources and tested in sensitivity analyses. Analyses were conducted from the United States societal perspective, limited to healthcare costs, and using a 3% annual discount rate.**

Setting: **A total of 164 medical institutions in 11 countries.**

Patients: **Adults ≥18 yrs of age with severe sepsis.**

Interventions: **Eligible patients were randomly assigned to receive a 96-hr intravenous infusion of drotrecogin alfa (activated) at 24 μg/kg/hr (n = 850) or placebo (n = 840).**

Measurements and Main Results: **Base Case: incremental short-term (days 1–28) healthcare costs per day-28 survivor; Panel on Cost-Effectiveness in Health and Medicine Reference Case: incremental lifetime healthcare costs per quality-adjusted life-year. Over the first 28 days (short-term Base Case), drotrecogin alfa (activated) increased the costs of care by $9,800 and survival by 0.061 lives saved per treated patient. Thus, drotrecogin alfa (activated) cost $160,000 per life saved (with 84.7% probability that ratio is <$250,000 per life saved). Projected to lifetime (lifetime Reference Case), drotrecogin alfa (activated) increased the costs of care by $16,000 and quality-adjusted survival by 0.33 quality-adjusted life-years per treated patient. Thus, drotrecogin alfa (activated) cost $48,800 per quality-adjusted life-year (with 82% probability that ratio is <$100,000 per quality-adjusted life-year). Estimates were generally robust to sensitivity analyses, although cost-effectiveness deteriorated to >$100,000 per quality-adjusted life-year if survivors lived <4.6 yrs on average. Drotrecogin alfa (activated) cost $27,400 per quality-adjusted life-year when limited to patients with an Acute Physiology and Chronic Health Evaluation II score ≥25 and was cost-ineffective when limited to patients with a score <25.**

Conclusions: **Drotrecogin alfa has a cost-effectiveness profile similar to that of many well-accepted healthcare strategies and below commonly quoted thresholds. (Crit Care Med 2003; 31:1–11)**

KEY WORDS: severe sepsis; intensive care unit; mortality; costs; cost-effectiveness; health economics; drotrecogin alfa (activated), protein C; recombinant human activated protein C

Severe sepsis is a syndrome characterized by systemic inflammation, coagulopathy, and acute organ dysfunction in response to infection (1). This syndrome affects 750,000 Americans each year, a third of whom die (2). Advances in our understanding of the pathophysiology of sepsis have led to several potential therapeutic agents, targeted mostly at the inflammatory cascade. However, these agents failed to improve patient outcomes in clinical trials and current standard of care consists of controlling the source of sepsis (e.g., draining an abscess or removing a central venous catheter), appropriately chosen antibiotics, and various forms of supportive therapies.

***See also pp. 306–311.**

From the Department of Critical Care Medicine, Clinical Research, Investigation and Systems Modeling of Acute Illness (CRISMA) Laboratory (DCA, GC), and the Center for Research on Health Care and Graduate School of Public Health (DCA), University of Pittsburgh, Pittsburgh, PA; Health Process Management, LLC, Doylestown, PA (WTL-Z); Eli Lilly and Company, Indianapolis, IN (DEB, BRB); Department of Medicine, Vanderbilt University, Nashville, TN (EWE, GB); Departments of Critical Care, Louvain University (P-FL), and Erasme University (J-LV), Brussels, Belgium; and the Julius Center for General Practice Medicine and Patient Oriented Research, University Medical Center of Utrecht, Utrecht, The Netherlands (BvH).

Funded by a research grant awarded to the University of Pittsburgh, a contract to Health Process Management, LLC, and internal support by Eli Lilly and Company.

Drs. Angus, Clermont, Ely, Laterre, Vincent, Bernard, and van Hout either currently provide or have provided consulting services to Eli Lilly and Company. Mr. Ball and Mr. Basson are employees and stockholders of Eli Lilly and Company and Mr. Linde-Zwirble is an employee of Health Process Management, LLC. The manuscript was prepared and submitted under the University of Pittsburgh Office of Research Publications Policy, as stipulated in the award to the University.

Dr. Angus, lead investigator for the economic analysis, was involved in all phases of the study and wrote the manuscript. Mr. Linde-Zwirble, senior statistician for the project, conducted all analyses, participated in all phases of the study, and read and critiqued all drafts of the manuscript. Dr. Clermont assisted in the analyses, conducted many of the simulations, and read and critiqued manuscript drafts. Mr. Ball was involved in all phases of the study, contributed to the writing of the manuscript, and read and critiqued all drafts. Mr. Basson aided in the statistical analyses, including merging the cost data with the clinical data, and read and critiqued all drafts. Drs. Ely, Laterre, and Vincent were involved in generating the clinical data, study design, subgroup analyses, and draft review and critique. Dr. Bernard, lead investigator for the clinical trial, was involved in study design and draft review and critique. Dr. Ben van Hout, senior health economist for the project, was involved in all phases of the study design, analysis, and manuscript preparation.

Address requests for reprints to: Derek C. Angus, MB, ChB, MPH, Room 604, Scaife Hall, Department of Critical Care Medicine, University of Pittsburgh, 200 Lothrop Street, Pittsburgh, PA 15213. E-mail: angusdc@ccm.upmc.edu

DOI: 10.1097/01.CCM.0000046067.70067.59

Bernard et al. (3) recently reported that drotrecogin alfa (activated) (Xigris, Eli Lilly, Indianapolis, IN) significantly reduced mortality from severe sepsis (19.4% adjusted relative risk reduction) in a large randomized trial (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis [PROWESS]). Drotrecogin alfa (activated) is a recombinant form of human activated protein C, an endogenous protein with antithrombotic, profibrinolytic and anti-inflammatory properties (4). Protein C, its endogenous precursor, is frequently deficient in sepsis (3, 5–8). Given the large observed reduction in mortality, clinicians presumably will be motivated to prescribe drotrecogin alfa (activated) in severe sepsis. Balanced against this clinical demand will be a consideration of the economic consequences of its use. To facilitate decision-making and healthcare policy, we conducted a cost-effectiveness analysis of drotrecogin alfa (activated) concurrently with the PROWESS trial.

MATERIALS AND METHODS

Clinical data collection in the trial was limited to 28 days after randomization. Our primary objective was to assess the incremental cost-effectiveness of drotrecogin alfa (activated) over the 28-day study period. This provided a "data-driven," short-term Base Case, following the recent recommendations of the American Thoracic Society (9). We also generated a long-term Reference Case based on lifetime estimates of costs and effects as per the guidelines of the U.S. Public Health Service Panel on Cost-Effectiveness in Health and Medicine (PCEHM) (10). We conducted our analysis from the U.S. societal perspective with inclusion of direct and indirect healthcare costs and exclusion of non-healthcare costs. To minimize potential bias toward drotrecogin alfa (activated) (9, 11), we specified all final analyses before viewing unblinded data, we attempted to make assumptions that were either neutral or biased against drotrecogin alfa (activated), and we filed a copy of our analysis plan with uninvolved investigators at the University of Virginia (Charlottesville, VA), McMaster University (Hamilton, Ontario, Canada), and Sheffield University (Sheffield, England).

Patients. PROWESS was a placebo-controlled, multicenter, randomized phase III trial in which 1,690 patients from 164 hospitals in 11 countries received study drug. Details of the clinical study were reported previously (3). Briefly, study drug was administered as a 96-hr intravenous infusion at 24 μg/kg/hr to adults (≥18 yrs of age) presenting with severe sepsis. Severe sepsis was defined as suspected or proven infection, evidence of systemic inflammation (three or more systemic inflammatory response syndrome criteria), and sepsis-induced dysfunction of one or more organ systems (1). Patients were included if they met all criteria within a 24-hr window, and drug infusion began within the subsequent 24 hrs. Because drotrecogin alfa (activated) has anticoagulant properties, patients at high risk of life-threatening bleeding (e.g., patients with severe thrombocytopenia or end-stage liver disease) were excluded. Patients were also excluded if they were pregnant or breast feeding, weighed >135 kg, were expected to die of a non-sepsis-related disease within a month, had severe human immunodeficiency virus disease (CD4 count ≤50 mm^3), were enrolled in another therapeutic trial, or had limitations on aggressiveness of care. Data collection included baseline clinical and demographic characteristics, information on hospital course, functional status [Katz Activities of Daily Living scale (12)] and destination at hospital discharge (if before 28 days), and survival and location at 28 days. The study began in July 1998 and enrollment stopped in June 2000 after the second interim analysis, based on a predefined stopping rule for drug effect.

Effects. For the Base Case, we measured incremental effect as the difference in the primary clinical end point of 28-day all-cause mortality. For the Reference Case, we estimated incremental effect as the number of life-years and quality-adjusted life-years (QALYs) gained, each discounted at a 3% annual rate as per PCEHM guidelines (10).

We calculated the number of life-years by generating an age- and gender-specific life expectancy for each 28-day survivor from U.S. Census 1998 life table data (13). We then adjusted that life expectancy using the relative risk of death for sepsis survivors (0.51) reported by Quartin et al (14). To illustrate, consider a 62-yr-old male survivor from PROWESS. The average life expectancy for a 62-yr-old American man is 18 yrs (13). However, multiplying 18 yrs by 0.51 (14), we predict the 62-yr-old sepsis survivor will only live 9.2 more years.

To generate QALYs requires multiplying each predicted remaining year of life by a numeric estimate (anchoring dead at 0 and perfect health at 1) of the quality of those years. Because there are no long-term quality-adjusted survival data for survivors of severe sepsis, we assigned to each 28-day survivor the average quality-adjusted survival of someone in the general population with the same life expectancy, rather than someone of the same age. We derived the general population quality-of-life estimates from the Beaver Dam Health Outcome Study, a longitudinal cohort study designed specifically to provide population data on health-related quality of life for mathematical modeling of QALYs for cost-effectiveness assessments (15).

Consider again the 62-yr-old male survivor. We predict he will live 9.2 yrs. The average age of an American man with a 9-yr life expectancy is 77 yrs (13). We therefore assign to our 62-yr-old sepsis survivor the sum of the average utilities across the 9-yr span from 77 to 85 yrs of age, which is 6.05 QALYs (15). In the Beaver Dam cohort, average quality-of-life scores decrease with advancing age. Therefore, our approach assigns lower quality-of-life scores to sepsis survivors than those of an age-matched general population. This is consistent with prior studies suggesting sepsis survivors have lower quality of life than population norms (16, 17).

Costs. For the Base Case, we measured incremental costs as the difference in healthcare costs (hospital, physician, study-drug, and postdischarge costs) between treatment and placebo during the first 28 days. We estimated hospital costs (including all pharmacy costs except those for study drug) from the detailed billing records of 552 of the 705 U.S. patients (cost cohort). This cohort represented all patients for whom we could obtain a readable detailed bill before locking and unblinding the dataset.

For each patient, we multiplied charges incurred during days 1–28 by the department- and institution-specific cost-to-charge ratios derived from the 1997 Centers for Medicare and Medicaid Services Hospital Cost Report (18). We adjusted these hospital cost estimates to year 2000 U.S.$ using the Consumer Price Index and multiplied them by 1.17 to reflect the addition of physician costs (19, 20). We estimated study-drug cost by multiplying the price of a vial of drotrecogin alfa (activated) by the minimum number of vials required based on the actual per-patient dosage in PROWESS. This approach allowed us to account for truncated dosing attributed to factors such as early death or bleeding. We assumed prices of $210 per 5-mg vial and $840 per 20-mg vial based on current pricing. To estimate postdischarge costs up to day 28, we assigned each postdischarge day a daily cost depending on patient location and summed over all days. Based on published sources, we assumed daily rates of $1,170 for subsequent acute hospital care [$1,000 per day (18) plus 17% for physician costs (19, 20)], $270 for care in a nursing home (21), and $200 for formal or informal supportive care at home (21).

For the Reference Case, we measured incremental costs as the difference in lifetime healthcare costs between treatment and placebo. We estimated lifetime costs as the day 1–28 costs (the Base Case costs) plus post-day 28 lifetime costs for survivors. We estimated post-day 28 lifetime costs using age-specific annual healthcare costs from the 1987 National Medical Expenditure Survey projected to year 2000 by the National Center for Health Statistics (http://www.meps.ahrq.gov/nmes/data/nmes95/nms00exb.dat). Because this survey excludes nursing home costs, we added estimates of age-specific annual nursing home costs from Spillman and Lubitz (22). As described above for quality of life, we assigned the age-specific costs based on each person's

predicted remaining years of life, rather than their actual age. Because average costs increase with age, this approach assigns higher costs to sepsis survivors than those incurred by an age-matched general population. As for long-term effects, we applied a 3% annual discount rate to costs.

Cost-Effectiveness Ratios. The Base Case cost-effectiveness ratio, CE_{base}, is the ratio of the incremental costs per incremental effects of drotrecogin alfa (activated) over placebo at 28 days. To correct for potential imbalances between the cost cohort and the overall trial, we derived an average cost adjusted to the proportions of survivors and nonsurvivors and, based on the blinded interim analysis, proportions of surgical and nonsurgical patients. Thus, the ratio is

$$CE_{base} = \frac{\sum_{i=1}^{4} p_{overall,\,i}^{treatment} \times C_{cost,\,i}^{treatment} - p_{overall,\,i}^{placebo} \times C_{cost,\,i}^{placebo}}{E_{overall}^{treatment} - E_{overall}^{placebo}} \quad [1]$$

where i takes four values (surgical survivors, surgical nonsurvivors, nonsurgical survivors, and nonsurgical nonsurvivors), $p_{overall,\,i}^{treatment}$ and $p_{overall,\,i}^{placebo}$ are the proportions from the overall trial, $C_{cost,\,i}^{treatment}$ and $C_{cost,\,i}^{placebo}$ are the average per-patient costs from the cost cohort for each value of i, and $E_{overall}^{treatment}$ and $E_{overall}^{placebo}$ are the 28-day survival rates from the overall trial. For the Reference Case cost-effectiveness ratio, $CE_{reference}$, we divided the difference in lifetime costs by the difference in life-years or QALYs between treatment and placebo, correcting for potential imbalances between the cost cohort and overall trial as described above for the Base Case.

Sensitivity Analyses. To test the sensitivity of the cost-effectiveness ratios to assumptions in our model, we varied our estimates of hospital costs, postdischarge to day 28 costs, drotrecogin alfa (activated) acquisition costs, lifetime costs, lifetime survival, and utilities by ±25%. We also ranged physician costs from half to double the original estimate (8.5% to 34% of hospital costs) and estimated $CE_{reference}$ without any long-term costs (10). We ranged all parameters in $CE_{reference}$ by ±25%, 50%, and 75% for presentation of sensitivity analysis in a tornado diagram. Because our estimates of survival and quality-adjusted survival were crucial for $CE_{reference}$, we conducted two-way sensitivity analyses in which we simultaneously varied the adjustment to life expectancy from 0.08 to 1 (equal to an average life expectancy of 1 to 25 yrs) and the average annual utility by ±25%. Because our analysis was conducted from the U.S. societal perspective, we recalculated CE_{base} and $CE_{reference}$ restricted to U.S. patients. We also generated $CE_{reference}$ using 0% and 5% discount rates for costs and effects and using a 3% discount rate on costs with no discount on effects (10). Finally, instead of applying the relative risk of death of 0.51 to the projected life expectancy of all day-28 survivors, we applied a worse penalty (0.39) to all those who survived septic shock and a slightly better penalty (0.53) to all those who survived without incurring shock. These estimates were also generated directly from the Quartin et al. (14) study, and represent the increased risk of death in the first year incurred by patients developing septic shock. After adjusting for the differences in proportions of these patient types in the Quartin et al. study, the overall risk is still 0.51. However, using two separate risks allows us to explore the consequences of the fact that survivors who had been "sicker" might have fewer years of life.

Subgroups. Although potentially limited by low statistical power, we wished to explore the cost-effectiveness distributions across several *a priori* defined clinically important subgroups. These included: age (>60 and ≤60 yrs); location before hospitalization (home or other); comorbidity [Acute Physiology and Chronic Health Evaluation (APACHE) II (23) chronic disease points]; severity of illness (APACHE II quartiles and presence or absence of shock); endogenous protein C level; microbiological etiology; and site

Table 1. Baseline characteristics of the overall and cost cohorts of PROWESS

	Overall Cohort (n = 1690)		Cost Cohort (n = 552)	
	Placebo (n = 840)	Treatment (n = 850)	Placebo (n = 276)	Treatment (n = 276)
Demographics				
Age				
Mean (SD)	60.6 (16.5)	60.5 (17.2)	61.0 (16.4)	60.2 (17.3)
% ≤60 yrs	43.6	44.1	44.6	46.4
% >60 yrs	56.4	55.9	55.4	53.6
Male, %[a]	58.0	56.1	55.8	50.4
Caucasian, %[a]	82.0	81.8	77.2	74.6
Weight (kg), mean (SD)	75.0 (18.5)	74.8 (17.9)	76.0 (20.6)	74.5 (19.7)
Prior location[a]				
Home	78.9	81.1	74.6	82.6
Skilled nursing facility	8.5	5.6	15.2	9.1
Another acute care hospital	9.3	9.3	6.2	5.4
Other	3.3	4.0	4.0	2.9
Functional dependencies, mean (SD)[a]	1.20 (2.12)	1.06 (2.02)	1.44 (2.32)	1.19 (2.15)
Comorbid conditions, %				
Hypertension[a]	35.0	38.2	44.9	47.8
COPD[a]	26.1	22.2	30.1	29.4
Diabetes	22.4	20.7	25.0	23.6
Malignancy	18.8	17.1	21.0	15.6
Prior myocardial infarction[a]	14.4	12.1	16.3	14.9
Congestive cardiomyopathy[a]	9.0	6.4	11.6	9.8
Reason for ICU admission, %[a,b]				
Medical	72.6	73.5	79.7	83.3
Surgical	27.4	26.5	20.3	16.7
Disease severity				
APACHE II[a]	25.0 (7.8)	24.6 (7.6)	25.8 (7.7)	25.1 (7.8)
Organ system failure, mean (SD)[a]	2.40 (1.10)	2.39 (1.12)	2.29 (1.02)	2.12 (0.98)
% in shock at enrollment	71.7	70.4	75.4	67.8
Median protein C activity, % of normal	50	47	50	48
Infection type, %[a]				
Gram-positive organism only	25.1	25.8	26.8	30.1
Gram-negative organism only	23.3	21.8	22.8	15.9
Mixed organisms	13.9	15.6	15.9	16.3
Culture negative or not obtained	32.3	33.5	27.2	32.6
Unconfirmed	5.4	3.3	7.3	5.1
Infection site, %[a]				
Lung	53.6	53.6	54.0	63.0
Intra-abdominal	19.9	20.0	13.8	12.3
Urinary tract	10.2	10.0	13.4	12.7
Other	16.3	16.4	18.8	12.0

Treatment, drotrecogin alfa (activated); SD, standard deviation; Functional dependencies measured by Activities of Daily Living Scale (12); Comorbid conditions and Reason for admission classified as per Acute Physiology Age and Chronic Health Evaluation (APACHE) II score (23); COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; Organ system failure and shock classified per Bernard et al (3).

[a]Significant difference ($p < .05$) between cost cohort (combined treatment arms) and remaining patients (n = 1138); [b]imbalances in the distribution of medical and surgical patients are corrected in the cost-effectiveness estimates because of the equation weight for surgical status.

of infection. Subjects were categorized as having septic shock if they met the criteria for cardiovascular dysfunction at any time within 6 hrs of study-drug infusion (3).

Statistical Analyses. We used the Wilcoxon's rank-sum test for comparisons of continuous data and the chi-square test for comparisons of categorical data as appropriate. To estimate the distributions around CE_{base} and $CE_{reference}$ for the entire cohort and for each subgroup, we generated sets of 1,000 simulated cohorts using bootstrapping with replacement (24, 25). We described these distributions using 95% confidence ellipses applying Fieller's method (26) on the bootstraps, and the estimated probability that the CE ratios fell below illustrative thresholds. We conducted statistical analyses and simulations in Datadesk (Data Description, Ithaca, NY) and SAS (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics. Baseline characteristics for the overall cohort and the cost cohort are provided in Table 1. The cost cohort differed from the remaining patients in several characteristics. Notably, a greater proportion of the cost cohort was admitted to the intensive care unit (ICU) for medical, rather than surgical, reasons, had more underlying disease, and were more frequently admitted from skilled nursing facilities. The distribution of baseline characteristics between treatment arms was similar for the overall and cost cohorts.

Patient Outcomes, Hospital Course, and Costs. At the primary clinical end point of 28 days, the observed mortality rates were 30.8% for placebo and 24.7% for drotrecogin alfa (activated) ($p = .005$). Although there were more survivors in the treatment arm, there were no significant differences in per-patient costs or resource use (excluding cost of study drug) over the first 28 days (Table 2). Surgical patients had significantly higher total ($43,695 vs. $30,228, $p < .001$) and mean daily ($2,606 vs. $2,234, $p < .001$) costs than medical patients. The average infusion time for drotrecogin alfa (activated) was 86 hrs and the average estimated drug acquisition cost was $6,595 ($7,055 for survivors and $5,193 for nonsurvivors).

Among survivors (n = 1221), there were no differences between treatment arms in location ($p = .88$) or functional status (Activities Of Daily Living score: 2.50 vs. 2.44, $p = .59$ for treatment vs. placebo) at day 28 (Fig. 1). Only 15% of surviving patients were still in the ICU at day 28 and 43.6% had been discharged to home. In the 15% of patients still in the ICU, there was no significant difference in day-28 organ dysfunction (Sequential Organ Failure Assessment score: 4.07 vs. 4.44, $p = .18$ for treatment vs. placebo) or intensity of care [Simplified Therapeutic Intervention Scoring System (TISS-28) (27) points: 27.2 vs. 27.1, $p = .94$ for treatment vs. placebo]. Among survivors still hospitalized on day 28 and in the cost cohort (n = 55 and 52 in the treatment and placebo arms), there were no significant differences in post-day 28 hospital resource streams between treatment arms (ICU length of stay: 7.1 vs. 5.9 days,

Table 2. Per-patient costs, resource use, and lifetime projections

	All			Survivors			Nonsurvivors		
Variable	Placebo	Treatment	*p*	Placebo	Treatment	*p*	Placebo	Treatment	*p*
Days 1–28									
ICU									
LOS, days	11.1	11.6	.51	12.7	12.9	.98	7.7	7.6	.85
TISS-28 (27), points									
Total	356.6	365.0	.71	391.1	392.4	.91	279.2	281.6	.93
Mean daily	32.1	31.6	.24	29.5	29.3	.49	38.1	39.0	.27
Cost, US$[a]	26,629	28,570	.48	28,950	30,548	.48	21,753	22,965	.86
Post-ICU									
LOS, days	6.0	6.1	.80	8.2	7.8	.12	0.8	0.7	.46
Cost, US$[a]	5,437	4,796	.30	7,107	5,706	.03	1,928	2,219	.98
Overall hospital									
LOS, days	17.1	17.6	.22	20.9	20.7	.82	8.5	8.3	.67
Cost, US$[a]	32,066	33,366	.72	36,057	36,254	.98	23,681	25,184	.89
Cost, US$ (with physician costs)[a]	37,517	39,038	—	42,187	42,417	—	27,707	29,465	—
Postdischarge to day 28, US$[b]	1,117	1,394	.55	1,586	1,833	.73	66	58	.92
Total day 1–28 costs[a,c]	39,034	40,677	.71	44,336	44,608	.99	27,895	29,538	.86
Total day 1–28 costs with study drug acquisition costs[a]	39,034	47,286	<.01	44,336	51,691	<.01	27,895	34,803	.21
Postday 28[d]									
Survival, yrs	8.6	9.2	.10	12.4	12.2	.37	NA	NA	NA
Quality-adjusted survival	5.9	6.3	.11	8.6	8.4	.34	NA	NA	NA
Costs, US$	101,428	109,015	.07	146,643	144,786	.50	NA	NA	NA
Total costs[a,c]	137,300	149,700	.09	189,366	192,110	.49	27,895	29,538	.86
Total costs with study drug acquisition costs[a]	137,300	156,309	.01	189,366	199,193	.05	27,895	34,803	.21

Treatment, drotrecogin alfa (activated); ICU, intensive care unit; LOS, length of stay; TISS, Therapeutic Intervention Scoring System; NA, not applicable. Survivor status was based on survival on study day 28. All figures were calculated from day of enrollment forward (i.e., prestudy hospital costs are excluded).

[a]Cost cohort ($n = 552$) only. Hospital costs were calculated by multiplying detailed hospital billing data, aggregated at the department level, by the department-specific cost-to-charge ratio (derived from the Centers for Medicare and Medicaid Services hospital cost report). All costs were projected to year 2000 estimates using the Consumer Price Index; [b]postdischarge to day 28 cost estimates were generated by multiplying daily unit costs for each specific location; [c]excluding drug acquisition costs for drotrecogin alfa (activated); [d]postday 28 costs were generated by summing annual age-specific healthcare costs from published Federal sources (see MATERIALS AND METHODS for more detail).

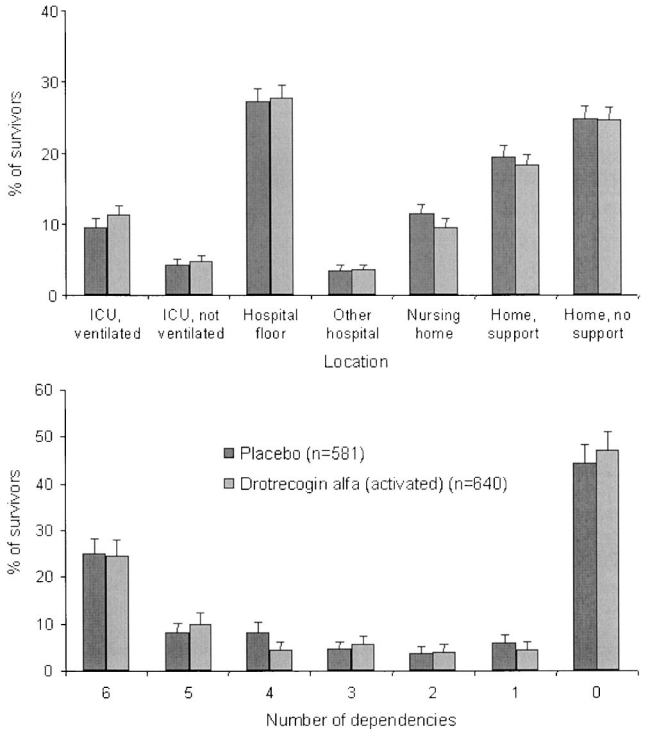

Figure 1. Location and functional status of survivors at day 28. The *upper panel* shows the distribution of survivors by location whereas the *lower panel* shows the distribution of survivors by functional status. Functional status was assessed by the Activities of Daily Living scale (12), which assesses functional dependence in six domains—bathing, dressing, toileting, transferring, feeding, and continence. The score ranges from 6 dependencies (fully dependent) to 0 dependencies (fully independent). *Dark bars* are placebo; *light bars* are treatment. There were no significant differences in either location (p = .88) or functional status (p = .59) by treatment arm. *ICU,* intensive care unit.

p = .67; hospital length of stay: 20.1 vs. 16.5 days, p = .6; and hospital costs: \$30,032 vs. \$25,259, p = .67 for treatment vs. placebo).

The average 28-day survivor was 58.1 yrs old and projected to live an additional 12.3 yrs at an average utility of 0.68, yielding 8.5 QALYs.

Cost-Effectiveness Estimates. Under the short-term CE_{base}, drotrecogin alfa (activated) increased costs by \$9,800 ± \$2,900 (67.3% of which was attributed to drug acquisition costs) and survival by 0.061 ± 0.022 lives saved per treated patient. Thus, drotrecogin alfa (activated) cost \$160,000 per life saved, with 84.7% and 97.9% probabilities that the ratio was <\$250,000 and <\$500,000 per life saved (Fig. 2).

Under the lifetime $CE_{reference}$, drotrecogin alfa (activated) increased costs by \$16,000 ± \$4,200 per treated patient, 39% of which (\$6,200) was attributed to long-term (post-day 28 until death) costs. The incremental life-years gained were 0.48 ± 0.29, and the incremental QALYs gained were 0.33 ± 0.21 per treated patient. Thus, without adjustment for quality of survival, drotrecogin alfa (activated) cost \$33,300 per life-year gained, with 89.1% probability that the ratio was <\$100,000 per life-year gained. Adjusting for quality of survival, drotrecogin alfa (activated) cost \$48,800 per QALY, with 82% probability that the ratio was <\$100,000 per QALY (Fig. 2).

Sensitivity Analyses. CE_{base} and $CE_{reference}$ were generally robust to our assumptions and estimates of costs and effects (Table 3). $CE_{reference}$ was most sensitive to changes in effects, and least sensitive to physician and postdischarge costs within the first 28 days (Fig. 3). In particular, although $CE_{reference}$ assumed 28-day survivors live 12.3 yrs, the cost-effectiveness of drotrecogin alfa (activated) remained <\$100,000 per QALY even if average survival decreased to 4.6 yrs (Fig. 4). Under the assumption that the average annual utility was 0.51 (a 25% reduction), the cost-effectiveness remained <\$100,000 per QALY until the average years of survival for day-28 survivors decreased to 6.6 yrs (Fig. 4). The cost per QALY reached \$100,000 when the average annual utility was cut to 0.33 and other factors were held constant. The cost per QALY did not exceed \$100,000 unless costs were several times higher than estimated (a 2.6-fold increase in study-drug acquisition costs, a 2.7-fold increase in long-term costs, a 5.8-fold increase in hospital costs, or a 62-fold increase in postdischarge costs up to day 28). Restricting analysis to U.S. patients, the incremental effect was larger (0.084 lives saved per treated patient), leading to better cost-effectiveness point estimates but with ranges that overlapped the primary estimates (CE_{base} = \$104,800/life saved, with 93.2% probability that the ratio was <\$250,000/life saved and $CE_{reference}$ = \$33,800/QALY, with 88.6% probability that the ratio was <\$100,000 per QALY). $CE_{reference}$ increased to \$53,600 per QALY at 5% annual discount and decreased to \$41,600 per QALY at no discount and \$38,300 per QALY at 3% discount on costs and 0% on effects. Applying different risks of death to those who survived with or without shock, $CE_{reference}$ increased to \$60,500 per QALY.

Subgroup Analyses. In general, the reduced sample sizes of the subgroups produced wide cost-effectiveness ranges with considerable overlap. Figure 5 shows the 95% confidence ellipses for the age, prior location, shock, and APACHE II analyses. All subgroup ellipses overlapped each other and the overall cohort ellipses (shown in gray). We found the same pattern of overlapping 95% confidence ellipses in the other subgroup analyses and, for most subgroups, the majority of the simulations fell below the \$500,000 per life saved and \$100,000 per QALY thresholds (Appendix). There was, however, some variation. For example, older patients had a worse $CE_{reference}$ because they were projected to live fewer years. Also, drotrecogin alfa (activated) seemed to be more cost-effective for patients who were more acutely ill, as evidenced by higher APACHE II scores (\$27,400/QALY for upper two APACHE II quartiles) or presence of shock (\$33,700/QALY). However, drotrecogin alfa (activated) seemed cost-ineffective for those in the lower two APACHE II quartiles and those without shock. Other subgroups that appeared different were generally of small sample size, limiting the strength of any inferences.

DISCUSSION

Drotrecogin alfa (activated) therapy for severe sepsis was shown to save lives (3). Excluding drug acquisition costs, we found this therapy did not significantly increase short-term costs or resource use. Survivors

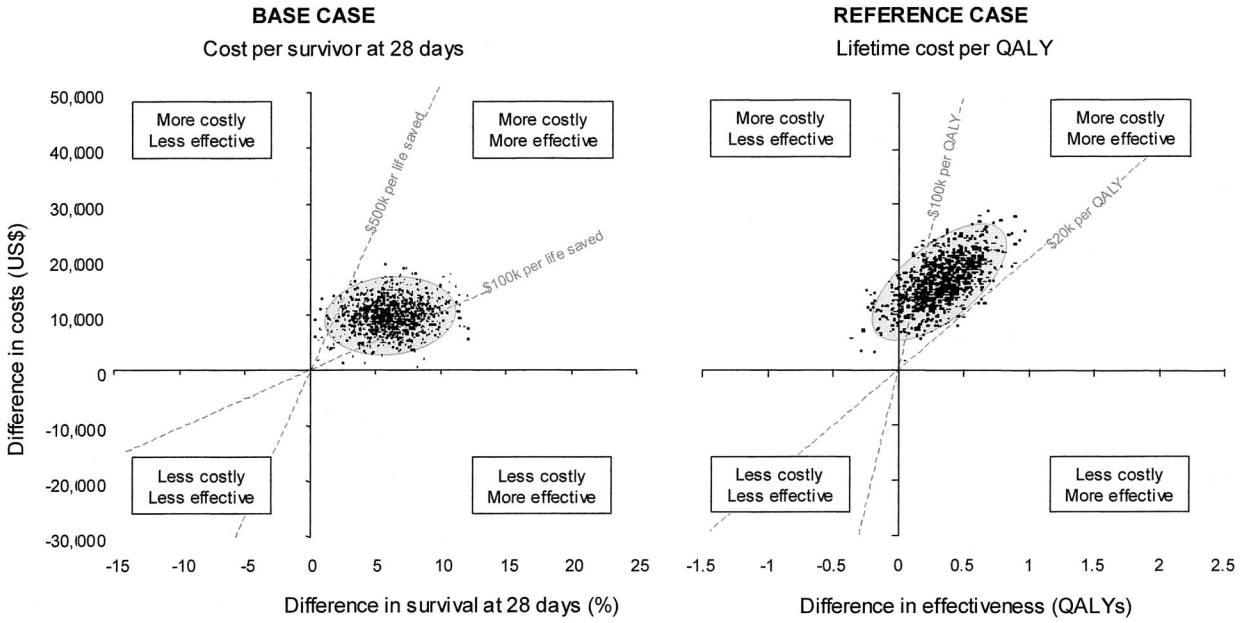

Figure 2. Cost-effectiveness of drotrecogin alfa (activated) in severe sepsis. The figure shows the Base Case cost-effectiveness ratio (*left panel*) and Reference Case cost-effectiveness ratio (*right panel*) distributions of the 1,000 simulations with the corresponding 95% confidence ellipses generated by Fieller's method (26). Incremental effects are shown on the *x-axes* and incremental costs are shown on the *y-axis*. Quadrants to the right of the y-axes represent regions where treatment with drotrecogin alfa (activated) is associated with a net gain in effects. Quadrants above the x-axes represent regions where treatment is associated with a net increase in costs. The *dashed lines* are illustrative thresholds. Regions below and to the right of the thresholds are more cost-effective than regions above and to the left of the thresholds. The *ellipses* are the smallest areas containing, with 95% confidence, the average incremental costs and effects. Both distributions are predominantly in the "more effective, more costly" upper right quadrant, with the majority of simulations falling below the $500,000 per life saved and, $100,000 per quality-adjusted life-year (41) thresholds. Although the Reference Case cost-effectiveness ratio ellipse crosses into the upper left quadrant (i.e., more costly and less effective), this area represents only 5.7% of the simulations.

Table 3. Sensitivity analyses

		Cost-Effectiveness Ratio Range Base Case ($160,000/Life Saved)		Reference Case ($48,800/QALY)	
Parameter	Range (% of Original Value)	%Change	Range ($/Life Saved)	%Change	Range ($/QALY)
Hospital costs within first 28 days	±25	±7.5	147,900–171,700	±4.6	46,600–51,000
Physician costs within first 28 days	−50 to +100	−2.2 to +4.3	156,300–166,700	−1.3 to +2.7	48,100–50,100
Postdischarge costs up to 28 days	±25	±0.7	158,700–160,900	±0.4	48,600–49,000
Study drug costs	±25	±16.8	132,900–186,700	±10.3	43,800–53,800
Long-term costs	±25	NA	—	±9.7	44,000–53,500
	Remove long-term costs	NA	—	−38.9	29,800
Long-term survival	±25	NA	—	−11.4 to +25.8	43,200–61,400
Average utility (quality of life)	±25	NA	—	−20.0 to +33.3	39,000–65,000

QALY, quality-adjusted life-year.

seemed to be similarly ill in both treatment arms, as evidenced by similar organ function, functional status, and location at 28 days. This suggests the mortality benefit of drotrecogin alfa (activated) was not associated with any morbidity "penalty" (i.e., the penalty of avoiding death only to create worse morbidity). Balancing the short-term costs and effects, and including drug acquisition costs, drotrecogin alfa (activated) cost $160,000 per additional life saved at 28 days. Our PCEHM Reference Case estimate, based on projected long-term outcomes, is that drotrecogin alfa (activated) costs $48,800 per QALY. If limited to sicker patients, such as those with APACHE II scores ≥25, the cost per QALY further improved. These cost-effectiveness ratios are similar to, or better than, those for many healthcare strategies widely adopted in the United States (Fig. 6) (28–36).

Our estimate was generated from a large clinical trial. The magnitude of clinical effects is usually smaller in clinical practice (effectiveness) than in a carefully controlled clinical trial (efficacy) (37). Reasons include poor patient selection, failure to administer the therapy properly, and inappropriate provision of other elements of care. Our cost-effectiveness estimate is very sensitive to treatment effect and so failure to address these issues could worsen the cost-effectiveness ratio. However, the U.S. Food and Drug Administration approved the use of this therapy in patients at a high risk of death, such as those with multiple organ dysfunction or high APACHE II scores. Our subgroup analyses, although hampered by a lack of power, suggest that the cost-effectiveness would improve considerably if limited to such patients.

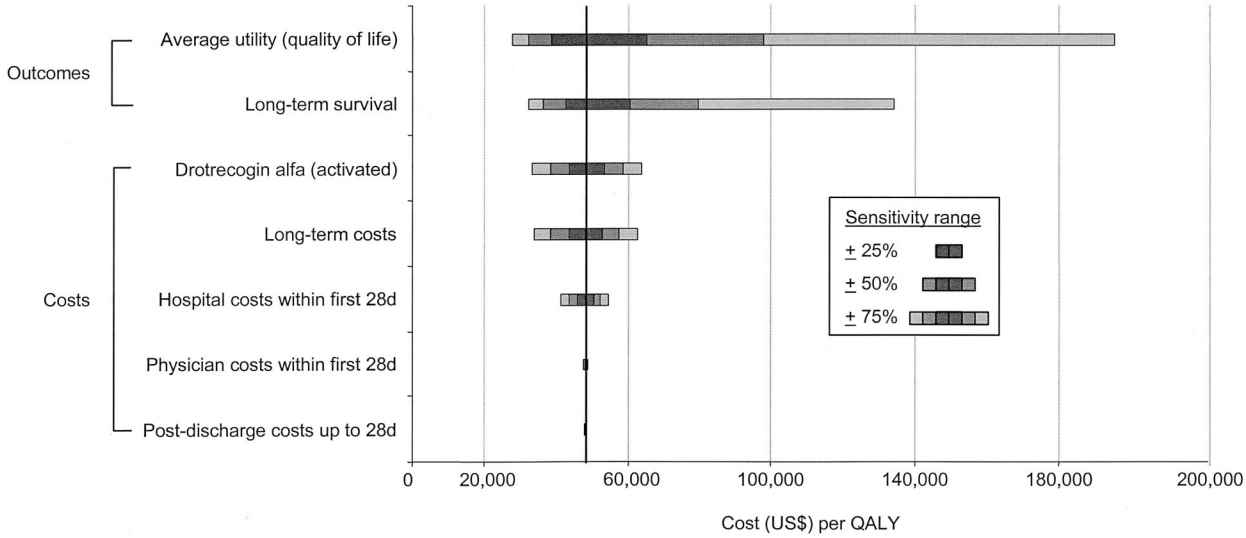

Figure 3. "Tornado Diagram" of Sensitivity of Reference Case to changes in average projected outcomes and costs. The *dark vertical line* indicates Reference Case cost-effectiveness ratio of $48,800 per quality-adjusted life-year (*QALY*). Our average projected outcomes and costs have been varied from 25% (the *darkest areas* on the horizontal bars) to 75% (the *light gray areas*). Even the most extreme variations of costs cause negligent-to-moderate changes in cost-effectiveness of drotrecogin alfa (activated) and keep it well inside the $20,000 to $100,000/QALY range. Only a 75% variation in survival or quality of life lifts the cost-effectiveness of drotrecogin alfa (activated) above $100,000/QALY. *28d*, 28 days.

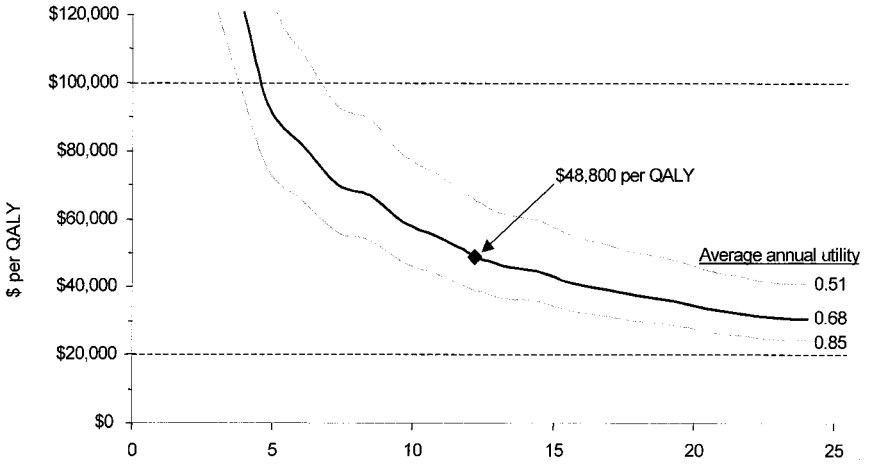

Figure 4. Sensitivity of Reference Case to the average projected survival and quality of life for day-28 survivors. Under the primary analysis, we assume the average duration of survival for day-28 survivors is 12.3 yrs, yielding a Reference Case cost-effectiveness ratio of $48,800 per quality-adjusted life-year (*QALY*) (*diamond*). If average survival is decreased, Reference Case cost-effectiveness ratio deteriorates but remains <$100,000 per QALY until projected survival is <4.6 yrs (*dark line*). The *gray lines* show the variation in cost-effectiveness by projected survival under different assumptions regarding average quality of life (*lower gray line* = 25% increase in average annual utility from 0.68 to 0.85 and *upper gray line* = 25% decrease from 0.68 to 0.51).

We conducted this analysis from the U.S. societal perspective. We have not generated cost-effectiveness ratios from the perspective of other countries primarily because of the logistic difficulties associated with concurrent estimation of costs outside the United States. However, this analysis provides an important reference point. We anticipate the major factors that will change our estimates as they are applied elsewhere will be differences in mortality reduction arising from the profiles of patients typically treated, use of co-interventions, drug acquisition costs, and years of life gained by sepsis survivors. Differences in the costs of other aspects of sepsis care are likely to have a smaller impact because there were no significant net differences in costs or resource use in the trial overall. Furthermore, in sensitivity analyses, we found several-fold increases in costs would be required before the $100,000/QALY threshold was exceeded—and most other countries have lower, rather than higher, healthcare costs. Of course, the extent to which a particular cost-effectiveness profile is deemed acceptable will vary by country and by competing pressures on healthcare budgets.

Strengths of our study include randomization, blinded assessments, a prospectively defined analysis plan that minimized potential investigator bias, and estimation of hospital costs directly from the trial. Because of a lack of follow-up beyond day 28, we had to make assumptions regarding life expectancy, long-term costs, quality of life, and duration of treatment effect. Our sensitivity analysis is encouraging because it suggests our Reference Case was reasonably robust to these assumptions. It also showed that we would require several years of follow-up to improve our estimates. We projected survival based on the age and sex of individual survivors and an average "penalty" for surviving sepsis. We would have preferred to project based on a richer set of individual characteristics but no such data exist in the sepsis literature. Indeed, the study by Quartin et al. (14), although the richest source of data thus far on survival after sepsis, focused on patients hospitalized at Veterans' Administration hospitals, and recruited patients in the 1980s. Thus, the representativeness of both patients and treatment patterns may be less than ideal. Nevertheless, we did as-

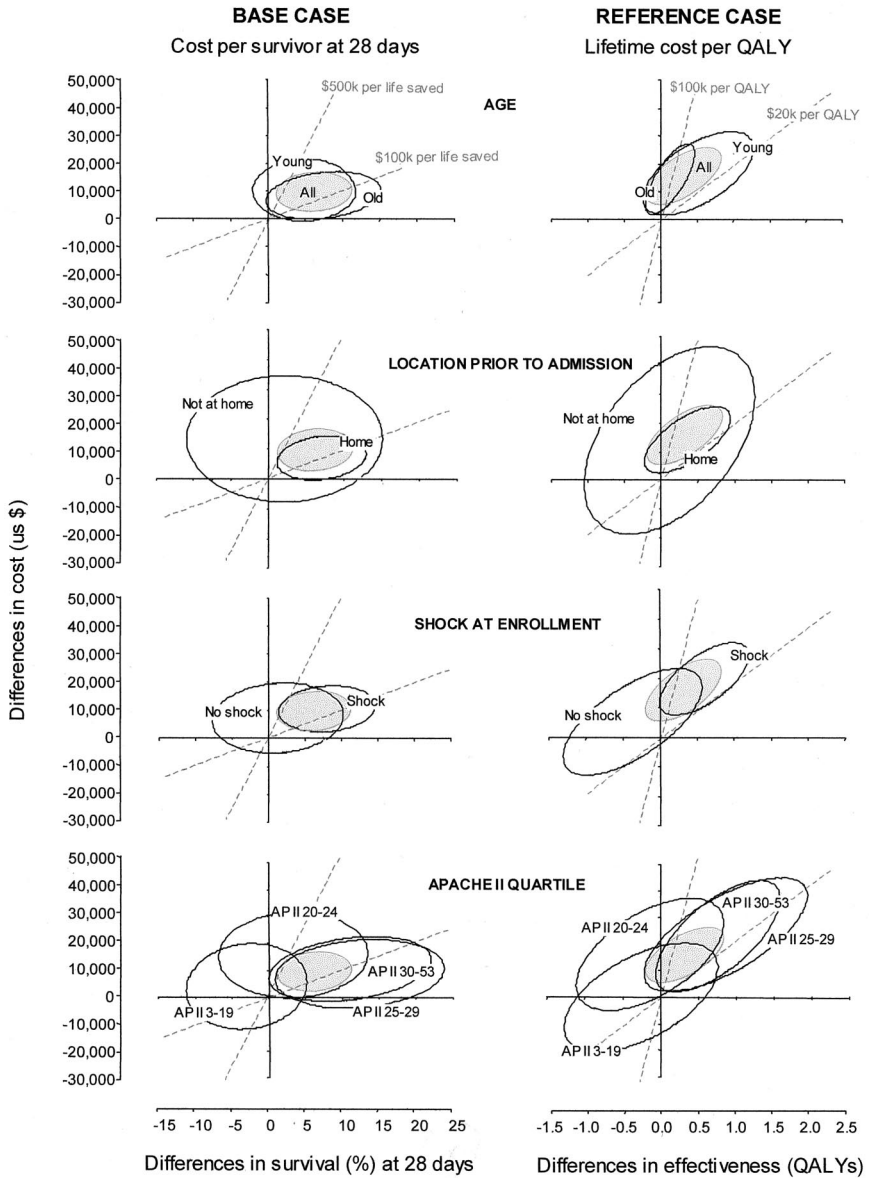

Figure 5. Subgroup cost-effectiveness analyses. The figure shows the 95% confidence ellipses generated by Fieller's method (26) for four sets of subgroup analyses (age >60 or ≤60 yrs; location before hospital admission; shock; and Acute Physiology and Chronic Health Evaluation [*AP*] II quartile). The graph *axes*, *scales*, and *threshold lines* are duplicates of Figure 2 (see Fig. 2 legend for explanation). The 95% confidence ellipses for the overall trial are shown in *gray* for reference. The subgroup *ellipses* are larger because of the smaller sample sizes. This is easily seen in the second row where the much larger ellipse (not at home before admission) represents 20% of the cohort whereas the smaller ellipse (home before admission) represents 80% of the cohort. In all instances, the subgroup ellipses overlap each other and the overall trial ellipses. *QALY*, quality-adjusted life years.

sign different risks of death to survivors based on different severity of disease in sensitivity analyses, with only small changes in our cost-effectiveness assessments. Furthermore, our estimate of quality of life was very similar to that reported in a recent study of sepsis patients (38).

In measuring costs, we adopted an approach that balanced the difficulties of comprehensive data collection against what was practical in a large, multicenter trial. Use of department-specific cost-to-charge ratios to estimate hospital costs from detailed billing data were shown to be accurate when compared with more rigorous cost accounting methodologies (39). The short-term costs that we estimated from published sources (physician and postdischarge costs) did not have a large influence on our results when tested in sensitivity analyses. Long-term costs were also based on published data

Our findings suggest that the use of drotrecogin alfa (activated) in patients with severe sepsis is associated with a favorable cost-effectiveness profile, especially if restricted to the Food and Drug Administration approved use.

and are dependent on the accuracy of our estimates of life expectancy. Ideally, we would have only included the portion of long-term costs that was consequent to the sepsis, but separating these costs is problematic. We therefore estimated all down-stream healthcare costs, which probably biases our estimate against drotrecogin alfa (activated), as shown in the sensitivity analysis.

Therapies for sepsis currently under investigation, such as low-dose steroids or other recombinant coagulation proteins, may augment or diminish the effectiveness, and cost-effectiveness, of drotrecogin alfa (activated). PROWESS had several important exclusion criteria. The cost-effectiveness of drotrecogin alfa (activated) for patients meeting exclusion criteria is unknown and probably quite variable. Although we observed some trends in the subgroup analyses, there was considerable overlap in the confidence ellipses, limiting statistical inference. We would therefore urge caution against overinterpretation of the subgroup analyses. We would also point out that the sensitivity analyses were designed to assess the robustness of the overall estimates to key assumptions. They were not designed to help physicians select particular patients for treatment. For example, although the cost-effectiveness deteriorated if average survival was <4.6 yrs, that does not mean we recommend only treating patients who are expected to live at least 4.6 yrs.

In general, applying the results from cost-effectiveness analyses can be difficult. For example, although this analysis suggests that drotrecogin alfa (activated)

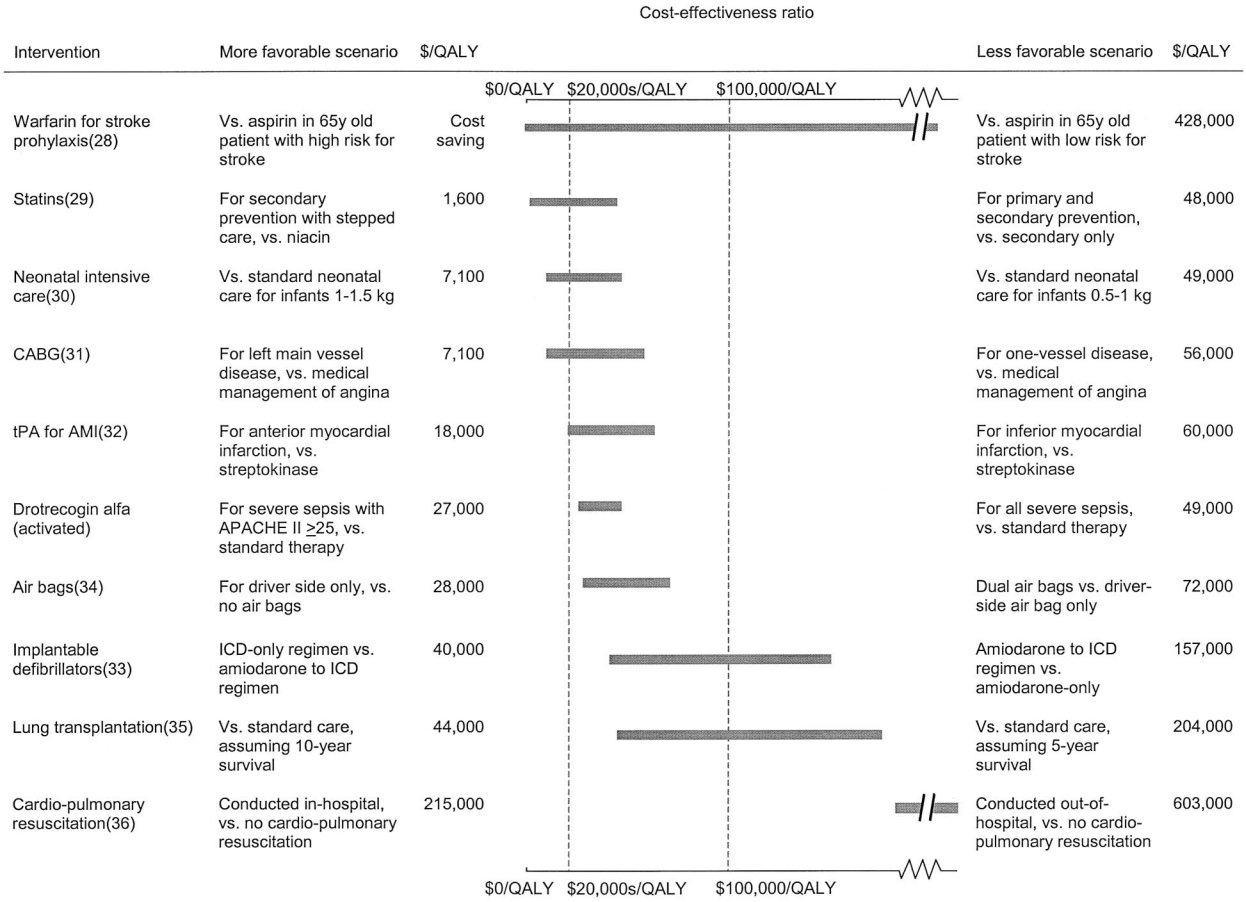

Figure 6. Comparison with other widely used interventions. The figure shows cost-effectiveness ratios under different scenarios for some widely adopted interventions in the United States. *Vertical dashed lines* indicate the reference points of $20,000/quality-adjusted life-year (*QALY*) and $100,000/QALY. Costs have been inflated to year 2000 U.S. dollars. The cost-effectiveness of drotrecogin alfa (activated) is comparable to most interventions and seems better than the cost-effectiveness of implantable defibrillators, lung transplantation, and cardiopulmonary resuscitation. *CABG*, coronary artery bypass graft; *tPA*, tissue plasminogen activator; *AMI*, acute myocardial infarction; *ICD*, implantable cardioverter defibrillator.

has a potentially favorable cost-effectiveness ratio from the societal perspective, it will require additional outlay of costs. Furthermore, these costs will largely be incurred by hospitals and hospital pharmacies. The pharmacy director may find a favorable societal cost-effectiveness ratio irrelevant when balancing the bottom line. The result could be the development of overly restrictive treatment guidelines focused on avoiding unwanted escalations in hospital costs despite the potential for improved survival and reasonable long-term cost-effectiveness projections. The simplest way to address this conflict is to compensate hospitals for additional expenses. The Medicare, Medicaid SCHIP Benefits Improvement and Protection Act of 2000 (Section 533[b], Public Law 106554) is designed to address this issue by providing additional payments to hospitals that provide new technologies or services that substantially improve patient outcome. The Centers for Medicare and Medicaid Services determined that drotrecogin alfa (activated) meets the required criteria (40) and, therefore, hospitals will receive additional compensation when using drotrecogin alfa (activated). Hopefully, this program will help minimize financial disincentives and promote appropriate use.

CONCLUSIONS

In summary, despite the high acquisition costs of approximately $7,000, drotrecogin alfa (activated) has a cost-effectiveness profile that compares very favorably with many widely accepted healthcare strategies. Our findings were generally robust to a wide-ranging sensitivity analysis but future studies of the long-term impact of drotrecogin alfa (activated) will also be helpful. Indeed, the economic analysis of anti-sepsis strategies in general would benefit from more natural history studies of sepsis and extended follow-up in interventional trials. Our findings suggest that the use of drotrecogin alfa (activated) in patients with severe sepsis is associated with a favorable cost-effectiveness profile, especially if restricted to the Food and Drug Administration approved use.

ACKNOWLEDGMENTS

We are indebted to the hard work of all staff who contributed to this study at the 164 institutions around the world. We also acknowledge the thoughtful comments of many colleagues who critiqued our study. We thank Drs. Alfred Connors (University of Virginia), Deborah Cook (McMaster University), and Christopher McCabe (Sheffield University) for agreeing to accept copies of our analytic plan filed before we viewed unblinded data. We are most grateful to Tony Dremsizov, MBA, for his tireless efforts in his preparation, copyediting, and critique of the manuscript.

REFERENCES

1. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20:864–874
2. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
3. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699–709
4. Esmon CT: The protein C anticoagulant pathway. *Arterioscler Thromb* 1992; 12: 135–145
5. Fourrier F, Chopin C, Goudemand J, et al: Septic shock, multiple organ failure, and disseminated intravascular coagulation: Compared patterns of antithrombin III, protein C, and protein S deficiencies. *Chest* 1992; 101: 816–823
6. Lorente JA, Garcia-Frade LJ, Landin L, et al: Time course of hemostatic abnormalities in sepsis and its relation to outcome. *Chest* 1993; 103:1536–1542
7. Boldt J, Papsdorf M, Rothe A, et al: Changes of the hemostatic network in critically ill patients: Is there a difference between sepsis, trauma, and neurosurgery patients? *Crit Care Med* 2000; 28:445–450
8. Powars D, Larsen R, Johnson J, et al: Epidemic meningococcemia and purpura fulminans with induced protein C deficiency. *Clin Infect Dis* 1993; 17:254–261
9. Angus DC, Rubenfeld GD, Roberts MS, et al: Understanding costs and cost-effectiveness in critical care: Report from the Second American Thoracic Society Workshop on Outcomes Research. *Am J Respir Crit Care Med* 2002; 165:540–550
10. Weinstein MC, Siegel JE, Gold MR, et al: Recommendations of the Panel on Cost-Effectiveness in Health and Medicine. *JAMA* 1996; 276:1253–1258
11. Kassirer JP, Angell M: The *Journal's* policy on cost-effectiveness analyses. *N Engl J Med* 1994; 331:669–670
12. Katz S, Ford AB, Moskowitz RW, et al: Studies of illness in the aged: The index of ADL—A standardized measure of biological and psychosocial function. *JAMA* 1963; 185: 914–919
13. Anderson RN: United States life tables, 1998. Washington, DC, Centers for Disease Control and Prevention (2001), National Vital Statistics Reports, Vol. 48, No. 18
14. Quartin AA, Schein RM, Kett DH, et al: Magnitude and duration of the effect of sepsis on survival. *JAMA* 1997; 277:1058–1063
15. Fryback DG, Dasbach EJ, Klein R, et al: The Beaver Dam Health Outcomes Study: Initial catalog of health-state quality factors. *Med Decis Making* 1993; 13:89–102
16. Perl TM, Dvorak L, Hwang T, et al: Long-term survival and function after suspected gram-negative sepsis. *JAMA* 1995; 274: 338–345
17. Davidson TA, Caldwell ES, Curtis JR, et al: Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. *JAMA* 1999; 281:354–360
18. Health Care Financing Administration: 1997 Hospital cost reports. Baltimore, MD, HCFA, 1999
19. Whittle J, Lin CJ, Lave JR, et al: Relationship of provider characteristics to outcomes, process, and costs of care for community-acquired pneumonia. *Med Care* 1998; 36: 977–987
20. Ellis SG, Miller DP, Brown KJ, et al: In-hospital cost of percutaneous coronary revascularization: Critical determinants and implications. *Circulation* 1995; 92:741–747
21. Antos J, Bilheimer L, Welch P: Medicare spending on post-acute care services: A preliminary analysis. Washington, DC, Congressional Budget Office, 1997
22. Spillman BC, Lubitz J: The effect of longevity on spending for acute and long-term care. *N Engl J Med* 2000; 342:1409–1415
23. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13: 818–829
24. Efron B: Bootstrap methods: Another look at the jackknife. *Ann Stat* 1979; 7:1–26
25. Cheng RCH: Bootstrap methods in computer simulation experiments. *In:* Lilegdon WR, Goldsman D, Goldsman C, et al (Eds). Proceedings of the 1995 Winter Conference on Simulation (WSC '95, Arlington, VA, Dec 3–6). New York, ACM Press, 1995
26. Fieller EC: Some problems in interval estimation. *J Royal Stat Soc B* 1954; 16:175–183
27. Miranda DR, de Rijk A, Schaufeli W: Simplified Therapeutic Intervention Scoring System: The TISS-28 items—Results from a multicenter study. *Crit Care Med* 1996; 24: 64–73
28. Gage BF, Cardinalli AB, Albers GW, et al: Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA* 1995; 274: 1839–1845
29. Stinnett AA, Mittleman MA, Weinstein MC: The cost-effectiveness of dietary and pharmacologic therapy for cholesterol reduction in adults. *In:* Gold MR, Siegel JE, Russell LB, et al (Eds). Cost-Effectiveness in Health and Medicine. New York, Oxford University Press, 1996, pp 349–391
30. Boyle MH, Torrance GW, Sinclair JC, et al: Economic evaluation of neonatal intensive care of very-low-birth-weight infants. *N Engl J Med* 1983; 308:1330–1337
31. Weinstein MC, Stason WB: Cost-effectiveness of coronary artery bypass surgery. *Circulation* 1982; 66:III56-III66
32. Kalish SC, Gurwitz J, Krumholz HM, et al: A cost-effectiveness model of thrombolytic therapy for acute myocardial infarction. *J Gen Intern Med* 1995; 10:321–330
33. Owens DK, Sanders GD, Harris RA, et al: Cost-effectiveness of implantable cardioverter defibrillators relative to amiodarone for prevention of sudden cardiac death. *Ann Intern Med* 1997; 126:1–12
34. Graham JD, Thompson KM, Goldie SJ, et al: The cost-effectiveness of air bags by seating position. *JAMA* 1997; 278:1418–1425
35. Ramsey SD, Patrick DL, Albert RK, et al: The cost-effectiveness of lung transplantation: A pilot study. *Chest* 1995; 108:1594–1601
36. Lee KH, Angus DC, Abramson NS: Cardiopulmonary resuscitation: What cost to cheat death? *Crit Care Med* 1996; 24:2046–2052
37. Linden PK, Angus DC, Chelluri L, et al: The influence of clinical study design on cost-effectiveness projections for the treatment of Gram-negative sepsis with human anti-endotoxin antibody. *J Crit Care* 1995; 10:154–164
38. Drabinski A, Williams G, Formica C: Observational evaluation of health state utilities among a cohort of sepsis patients. *Value Health* 2001; 4:130
39. Schwartz WB, Mendelson DN: Hospital cost containment in the 1980s: Hard lessons learned and prospects for the 1990s. *N Engl J Med* 1991; 324:1037–1042
40. Federal Register, Vol. 67, No. 148, August 1, 2002, pp 50009–50015
41. Laupacis A, Feeny D, Detsky AS, et al: How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Can Med Assoc J* 1992; 146:473–481

APPENDIX

We generated 1,000 simulated cohorts for each subgroup. Each simulation randomly draws actual patients from the appropriate subgroups, sampling with replacement. The output of each simulation is a point estimate of the cost effectiveness of drotrecogin alfa (activated) (activated) for that particular subgroup. The distribution of the 1,000-point estimates reflects the combined variation associated with the numerator (differences in costs) and denominator (differences in effects) for that subgroup. Because the distribution is a ratio of two differences, each of which has its own distribution, it cannot easily be described by confidence intervals. Hence, we present the distributions as 95% confidence ellipses (seen in Fig. 4). All subgroup ellipses overlap each other and the ellipses of the overall cohort. We present four of the subgroup analyses in the main article because we believe the graphical representation, and the particular four subgroups chosen are informative to the reader. We present the remaining analyses here.

An additional measure of the subgroup distributions is the proportion of simulations falling below a particular threshold (Appendix Table). This provides a measure of the strength of evidence that the therapy is cost effective, at least as reflected by that threshold. The choice of thresholds is somewhat arbitrary. We chose $100,000/QALY because this is the upper limit of the grade C recommendation for clinical use as proposed by Lau pacis et al (41). The base case threshold of $500,000 per life saved corresponds to the reference case thresholds under the conservative assumption that each survivor only lives five QALYs.

Appendix Table

		Mortality			Short-Term (28-Day) Base Case			Lifetime Reference Case			
Subgroup	%Overall Cohort	Placebo	Treatment	Absolute Reduction	Incremental Cost	Cost Effectiveness	Probability <$500,000/ Life Saved	Incremental QALYs per Treated Patient	Incremental Cost	Cost Effectiveness	Probability <$100,000/ QALY
All patients	100.0	30.8	24.7	0.061	9,800	159,800	97.9	0.328	16,000	48,800	82.0
Age, yrs											
<60	43.8	20.5	15.7	0.048	10,500	221,700	82.9	0.517	16,600	32,200	89.3
>60	56.2	38.8	31.8	0.070	8,200	116,400	96.7	0.127	14,000	110,500	44.4
Prior location											
Home	80.0	29.3	22.4	0.069	7,200	104,200	99.0	0.356	14,200	40,000	86.1
Other	20.0	36.7	34.8	0.019	13,100	676,700	46.3	0.108	14,600	135,400	46.2
Co-morbid conditions											
None	79.6	26.5	23.9	0.026	7,900	307,100	70.4	0.053	9,800	184,900	44.2
Any	20.4	47.2	27.8	0.193	15,700	80,900	100.0	1.338	37,800	28,300	99.4
APACHE II[a]											
Quartiles											
3–19	25.6	12.1	15.1	−0.030	3,800	Dominated	14.6	−0.280	−500	Dominated	22.3
20–24	26.0	25.7	22.5	0.032	15,900	495,800	52.0	−0.144	16,100	Dominated	20.0
25–29	21.7	35.8	23.5	0.123	9,300	76,100	98.1	0.847	24,000	28,400	95.0
30–53	26.7	49.0	38.1	0.109	10,700	98,700	97.8	0.741	23,000	31,100	96.4
Shock status[b]											
No shock	29.0	22.3	21.0	0.012	7,000	565,200	47.1	−0.365	5,000	Dominated	10.4
Shock	71.0	34.2	26.3	0.080	10,700	133,800	98.6	0.592	20,000	33,700	97.0
Median protein C activity											
<40	36.4	27.6	41.8	0.142	16,600	117,300	99.9	0.669	31,000	46,200	89.5
41–60	27.6	27.1	24.7	−0.024	2,900	Dominated	28.3	0.101	1,300	12,600	63.2
61–80	17.6	18.7	25.3	0.066	9,600	144,600	86.3	0.139	15,400	110,700	53.0
>80	11.5	15.6	26.7	0.111	1,900	16,700	95.8	0.653	12,800	19,700	83.7
Unknown	6.9	27.5	24.6	−0.028	7,500	Dominated	35.8	0.016	6,000	365,600	54.8
Infection type											
Gram-positive only	25.4	22.8	32.7	0.099	7,500	76,200	99.3	0.583	17,900	30,700	91.0
Gram-negative only	22.5	24.3	28.6	0.042	7,200	170,200	80.4	0.063	9,100	143,400	51.8
Mixed organisms	14.8	21.8	26.5	0.047	8,500	180,700	77.2	−0.120	11,300	Dominated	35.0
None/not obtained	32.9	25.6	32.5	0.069	8,600	126,000	96.1	0.607	18,000	29,600	92.7
Unconfirmed	4.3	46.4	33.3	−0.131	18,600	Dominated	9.0	−1.174	−1,400	Dominated	9.2
Infection site											
Lung	53.6	25.0	33.6	0.086	7,700	89,500	99.2	0.677	17,900	26,400	97.6
Intra-abdominal	19.9	27.6	30.5	0.029	17,800	616,000	48.1	−0.275	18,000	Dominated	12.8
Urinary	10.1	21.2	20.9	−0.002	13,900	Dominated	34.0	−0.767	7,800	Dominated	6.0
Other	16.4	22.3	28.5	0.062	2,400	38,300	88.1	0.601	10,600	17,600	85.8

QALY, quality-adjusted life-year; functional dependencies measured by Katz Activities of Daily Living Scale (12); co-morbid conditions classified per Acute Physiology and Chronic Health Evaluation (APACHE) II score (23); shock defined per Bernard et al. (3); median protein C activity defined as percentage of normal; Dominated, point estimate was more costly and less effective.

[a]The lifetime reference case cost-effectiveness ratio for patients in the combined upper two quartiles (APACHE II score, ≥25) was $27,400/QALY. This increased to $33,800/QALY when, in sensitivity analysis, we assigned the relative risks of death of 0.39 and 0.53 to 28-day survivors with and without shock. Drotrecogin alfa (activated) was dominated in the combined lower two APACHE II quartiles (APACHE II score, <25) under both the primary and sensitivity analyses; [b]Repeating the shock/nonshock subgroup analyses when ascribing the relative risks of death of 0.39 and 0.53 to survivors with or without shock (rather than a common risk of death of 0.51 to all survivors), the lifetime reference case increased from $33,700/QALY to $40,300/QALY for shock patients, whereas it remained dominated for nonshock patients.