EDITORIAL

Septic Shock — Evaluating Another Failed Treatment

Richard P. Wenzel, M.D., and Michael B. Edmond, M.D., M.P.H.

Sepsis, severe sepsis, and septic shock are progressively severe stages of the host's systemic inflammatory response to infection.[1] The latter stages carry increasing rates of end-organ failure and death. The spectrum of the sepsis syndrome remains a leading cause of death in the United States, and early intervention with appropriate antibiotics (matching the antibiogram susceptibilities to the drugs administered) saves lives. Specific to septic shock, a large retrospective cohort study involving 2731 adults in 14 critical care units showed an absolute decrease of 7.6 percentage points in the survival rate for each hour of delay in antimicrobial administration from the onset of hypotension.[2] Early recognition of severe sepsis or septic shock and the immediate initiation of effective antibiotic therapy are essential.

In the past decade, many clinicians have embraced additional strategies — with various levels of evidence to support their use — to improve the outcomes of severe sepsis and septic shock: the rapid infusion of intravenous fluids to reverse hypotension from reduced vascular resistance, the use of low-dose glucocorticoids (100 mg of hydrocortisone every 8 hours) in septic shock, low-tidal-volume ventilation (tidal volume, 6 ml per kilogram of ideal body weight) in patients with the acute respiratory distress syndrome, continual renal-replacement therapy in patients with kidney failure, and maintenance of blood glucose levels to less than 150 mg per deciliter (8.3 mmol per liter).

Since the inflammatory response to infection is complex, independent efforts have been made in the past two decades to block the activity of such likely biochemical triggers as endotoxin, tumor necrosis factor α, interleukin-1, and others. All clinical trials of agents that are designed to interfere with these pathways have not shown a benefit. However, in 2001, Bernard and colleagues[3] reported a modest improvement in all-cause mortality at 28 days associated with adjunctive therapy with recombinant human activated protein C, or drotrecogin alfa (activated) (DrotAA). The investigators found a death rate of 24.7% in treated patients versus 30.8% in controls, an absolute reduction of 6 percentage points and a relative reduction of 19%.[3] The efficacy of DrotAA was biologically plausible, because the drug has effects on anticoagulant activity that are thought to be important in reversing the adverse microvascular effects of sepsis. Nevertheless, the initial success could not be replicated in patients with a low risk of death or in children with severe sepsis.[4,5]

The outcomes of the trial were also clouded by a lack of consensus within the advisory panel of the Food and Drug Administration that evaluated evidence supporting the proposal to license DrotAA, as well as by the sponsor's use of a new master lot of cells to produce the drug after the trial had begun, uneasiness about serious bleeding in patients who received the drug, and ethical questions surrounding the sponsor's hiring of a public relations firm to assemble a task force (consisting of many members with conflicts of interest) to promote sepsis-treatment bundles that would include the drug — despite a single positive study and lingering controversies.[6-8]

Because a subgroup analysis of the first trial suggested a greater mortality benefit among patients who were more seriously ill, a new trial was proposed targeting patients at highest risk for death. Ranieri and colleagues[9] now report in the *Journal* the results of that trial, in which the use

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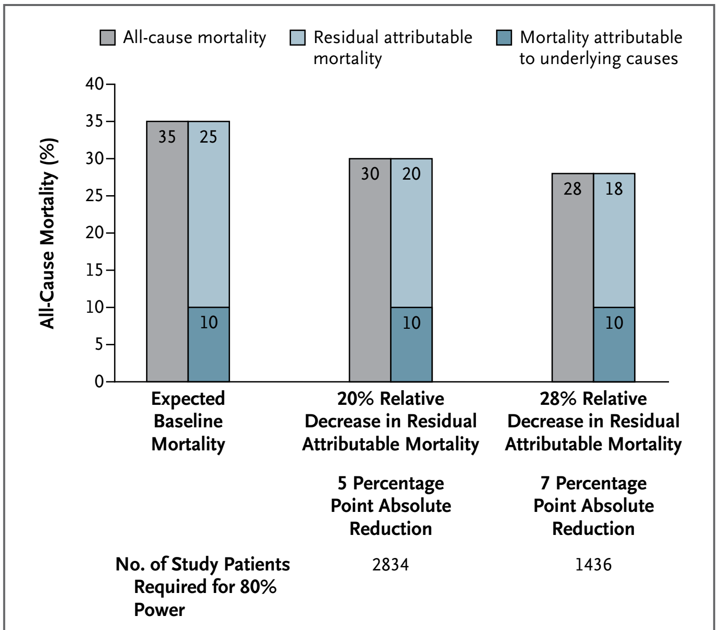

Figure 1. Theoretical Effect of a Drug for Septic Shock on All-Cause Mortality at 28 Days, According to Revised Estimates of Residual Attributable Mortality.

In the study by Ranieri et al.,[9] the sample-size calculation was based on an estimate of all-cause mortality of 35% in the placebo group. In one theoretical construct, it could be estimated that this rate of death consists of 10% from the patients' underlying disease and 25% from infection (residual attributable mortality), as shown in the graph at the left. Thus, a new adjunct sepsis drug would have an effect only on the component of residual attributable mortality, not on the component of underlying disease. The authors determined that the target study enrollment of 1500 patients would provide a power of 80% to detect an absolute reduction of 7 percentage points in all-cause mortality at 28 days in patients receiving the new sepsis drug, or a relative reduction of 20%. However, the middle graph shows that a relative reduction of 20% in the residual attributable mortality alone (from 25% to 20%) would reduce all-cause mortality by only 5 percentage points; thus, a statistical power of 80% for this analysis would require the enrollment of 2834 patients. The graph at the right shows that the targeted reduction of 7 percentage points in the residual attributable mortality (from 25% to 18%) would translate into an actual relative decrease of 28% in all-cause mortality, rather than the targeted 20%.

of DrotAA, as compared with placebo, had no significant effect on all-cause mortality among patients with septic shock.[9] The absolute between-group differences in all-cause mortality at 28 and 90 days were 2.2 and 1.4 percentage points, respectively — both trends slightly favoring placebo over DrotAA.

The strengths of the study include a focus on patients with the most advanced stage of sepsis — those with sustained shock and organ dysfunction. In addition, the definitions regarding the patients' conditions were precise; patients, investigators, treating clinicians, and representatives of the sponsor were all unaware of study-group assignments; and the study groups appeared to be similar after randomization.

A weakness of the study is that it did not achieve its stated statistical power of 80%, for the following reasons: The sample-size calculation was based on a rate of death of 35% in the placebo group. However, the end point of all-cause mortality was composed of the rate of death from patients' underlying disease plus the rate directly attributable to infection. Thus, if we assume that the 35% baseline rate of death included a 10% component from underlying disease and 25% from sepsis, any adjunctive therapy for sepsis would affect only the component of mortality from sepsis. Even with appropriate antibiotic treatment, there will be some residual deaths from sepsis (Fig. 1).[10] The stated goal of treatment with DrotAA was a relative reduction of 20% and an absolute reduction of 7% percentage points in all-cause mortality. Since DrotAA could have an effect only on the residual attributable mortality, a 20% relative reduction in the residual attributable mortality (from 25% to 20%) would result in a decrease in all-cause mortality from 35% to 30% — an absolute difference of 5 percentage points rather than the targeted 7 percentage points. Many more study patients would have been required to provide a power of 80% to detect a decrease of only 5 percentage points.[11] Stated another way, in order to achieve an absolute reduction of 7 percentage points in all-cause mortality, the residual attributable mortality would have needed to fall from 25% to 18% — a relative reduction of 28%, not 20%.

Despite its limitations, the large and well-conducted study by Ranieri et al. should end any further pursuit of a niche for DrotAA in the treatment of sepsis. The investigators' findings provide a sad chapter in the noble quest for a truly effective adjunct for the treatment of septic shock. This setback should inspire a redoubling of efforts to seek new approaches to treatment that are based on a more crystalline view of the biology of sepsis.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

Drotrecogin Alfa (Activated) in Adults with Septic Shock

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ABSTRACT

BACKGROUND
There have been conflicting reports on the efficacy of recombinant human activated protein C, or drotrecogin alfa (activated) (DrotAA), for the treatment of patients with septic shock.

METHODS
In this randomized, double-blind, placebo-controlled, multicenter trial, we assigned 1697 patients with infection, systemic inflammation, and shock who were receiving fluids and vasopressors above a threshold dose for 4 hours to receive either DrotAA (at a dose of 24 μg per kilogram of body weight per hour) or placebo for 96 hours. The primary outcome was death from any cause 28 days after randomization.

RESULTS
At 28 days, 223 of 846 patients (26.4%) in the DrotAA group and 202 of 834 (24.2%) in the placebo group had died (relative risk in the DrotAA group, 1.09; 95% confidence interval [CI], 0.92 to 1.28; P=0.31). At 90 days, 287 of 842 patients (34.1%) in the DrotAA group and 269 of 822 (32.7%) in the placebo group had died (relative risk, 1.04; 95% CI, 0.90 to 1.19; P=0.56). Among patients with severe protein C deficiency at baseline, 98 of 342 (28.7%) in the DrotAA group had died at 28 days, as compared with 102 of 331 (30.8%) in the placebo group (risk ratio, 0.93; 95% CI, 0.74 to 1.17; P=0.54). Similarly, rates of death at 28 and 90 days were not significantly different in other predefined subgroups, including patients at increased risk for death. Serious bleeding during the treatment period occurred in 10 patients in the DrotAA group and 8 in the placebo group (P=0.81).

CONCLUSIONS
DrotAA did not significantly reduce mortality at 28 or 90 days, as compared with placebo, in patients with septic shock. (Funded by Eli Lilly; PROWESS-SHOCK ClinicalTrials.gov number, NCT00604214.)

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Recombinant human activated protein C, or drotrecogin alfa (activated) (DrotAA), was approved for the treatment of severe sepsis in 2001 on the basis of the Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study,[1] a phase 3 international, randomized, controlled trial that was stopped early for efficacy after the enrollment of 1690 patients with severe sepsis. Absolute mortality in the intention-to-treat population was reduced by 6.1 percentage points, a relative risk reduction of 19.4%. Subsequent subgroup analysis suggested that the mortality benefit was limited to patients with increased illness severity (i.e., those with more than one sepsis-related dysfunctional organ or with an Acute Physiology and Chronic Health Evaluation [APACHE] II score[2] of more than 24 [on a scale of 0 to 71, with higher scores indicating an increased risk of death]). The Food and Drug Administration limited its approval of the drug for use in patients with "a high risk of death" and requested additional trials involving less severely ill adults and children. These trials were terminated early for futility by independent data and safety monitoring committees.[3,4] Moreover, subgroups of patients at increased risk for death within the adult trial did not appear to benefit from the use of DrotAA. The lack of confirmatory data from placebo-controlled trials[5] called into question the results of the PROWESS study and thus the efficacy of the drug.[6]

DrotAA received marketing authorization from the European Medicines Agency for the treatment of adults with severe sepsis and multiple organ failure, but the approval was subject to annual review.[7] In 2007, the agency concluded that sufficient doubt existed to warrant a new placebo-controlled trial.[8] We conducted the PROWESS-SHOCK study to test the hypothesis that DrotAA, as compared with placebo, would reduce mortality in patients with septic shock.[9]

METHODS

STUDY PATIENTS

The study protocol has been published previously (www.springerlink.com/content/t3353213r20835ul/fulltext.pdf).[9] The trial was approved by the institutional review board at each study center, and written informed consent was obtained from patients or their legally authorized surrogates in accordance with local requirements.

Adult patients were eligible for inclusion if they had sepsis (infection and two or more signs of systemic inflammation), shock, and clinical evidence of hypoperfusion. We defined hypoperfusion as metabolic acidosis (base deficit, ≥5.0 mmol per liter; venous bicarbonate, <18 mmol per liter; or lactate, >2.5 mmol per liter) or renal or hepatic dysfunction. (Case definitions are provided in the protocol.) We defined shock as the need for treatment with norepinephrine at a dose of at least 5 μg per minute or an equivalent dose of another vasopressor for 4 hours or more, provided that at least 30 ml per kilogram of body weight of crystalloid or an equivalent volume of colloid was administered during the 8-hour interval surrounding the start of vasopressor treatment. We required that patients remain refractory to reasonable attempts to wean vasopressors and begin study treatment within 24 hours after the first dose of a vasopressor. (Full details regarding inclusion and exclusion criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Patients with coexisting illnesses with a high risk of death (e.g., metastatic cancer) were excluded. The clinical coordinating center confirmed the eligibility of each patient before randomization.

STUDY TREATMENTS

A centralized system randomly assigned patients to receive an intravenous infusion of DrotAA (Xigris, Eli Lilly) at a dose of 24 μg per kilogram of body weight per hour for 96 hours or matching placebo dissolved in 0.9% saline solution. Study-group assignments were concealed from patients, investigators, treating clinicians, and the sponsor. Temporary interruptions of the study infusion were mandated for invasive procedures; in such cases, the infusion was extended through day 6 (the treatment period) so that the 96-hour infusion could be completed wherever possible. All other treatments were at the discretion of treating clinicians.

EVALUATION OF PATIENTS

We assessed baseline demographic characteristics, preexisting conditions, organ function, sites of infection, microbiology results, and hematologic and laboratory measurements within 24 hours before the administration of a study drug. Blood samples for the measurement of protein C levels were collected on days 1 through 7. Assays

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to assess protein C activity were performed on an STA Compact coagulation analyzer with the use of the STA-Staclot protein C kit (Diagnostica Stago). Patients were followed until either 90 days or death.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was death at 28 days. Secondary outcomes included 28-day mortality in patients with severe protein C deficiency (plasma concentration, ≤50% of the lower limit of the normal range), 90-day mortality, measures of organ dysfunction, and safety. We examined heterogeneity of the treatment effect on mortality at 28 and 90 days in prespecified subgroups, as defined by the following baseline characteristics: APACHE II score (<25 or ≥25), number of organs that had failed, presence or absence of the acute respiratory distress syndrome (ARDS), the quartile of time from the onset of shock to the initiation of study treatment, plasma protein C level, glucocorticoid treatment, prophylactic heparin administration, recent surgery, and platelet count.

We assessed organ function using Sequential Organ Failure Assessment (SOFA) scores (on a scale of 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction). We used the SOFA score to measure the change from baseline to study day 7, using the mean arterial pressure and vasopressor dose to measure cardiovascular function, the ratio of the partial pressure of oxygen in arterial blood to the fraction of inspired oxygen to measure respiratory function, and the serum creatinine level to measure renal function.

STUDY OVERSIGHT

The steering committee designed the study in collaboration with the sponsor, Eli Lilly, as reported previously.[9] Coauthors from the Duke Clinical Research Institute performed the analysis. The steering committee wrote the first draft of the manuscript, and the two first coauthors made the decision to submit the manuscript for publication. All authors had full and independent access to all the data and vouch for the integrity, accuracy, and completeness of the analysis and its fidelity to the study protocol.[10]

STATISTICAL ANALYSIS

We determined that the planned enrollment of 1500 patients would provide a power of 80% at a significance level of 0.05 to detect an absolute difference of 7 percentage points (20% relative risk reduction) in the primary outcome of 28-day mortality from the placebo rate of 35%. An independent data and safety monitoring board conducted interim analyses, as described previously.[9] The protocol specified an increase in sample size if the 28-day mortality for 750 patients was less than 30%.

The final primary analysis used a P value of less than 0.05 with adjustment for interim analyses of the cumulative data. The 28-day primary efficacy analysis was conducted according to the intention-to-treat principle and documented in the statistical analysis plan, as described previously.[9-11] Patients with unknown survival status at 28 days or 90 days were excluded from the landmark analyses. In the time-to-event analyses, data for patients with unknown survival status were censored on the last day that patients were known to be alive.

We used a Cox proportional-hazards model to estimate the hazard ratio for death with the use of DrotAA versus placebo. We used a log-rank test to assess differences in survival curves between the two groups in the time-to-event analysis through 28 days and 90 days. Survival estimates were calculated with the use of the Kaplan–Meier method. We used the Wilcoxon rank-sum test to assess between-group differences in SOFA scores. Similarly, we used ranked analysis of variance to assess the change in protein C level from baseline to day 7 and to compare the two study groups. We used the Breslow–Day test for homogeneity of odds ratios to determine differences in the treatment effect across categories for each of the prespecified subgroups at 28 days. All safety analyses were conducted in the population of treated patients.

RESULTS

STUDY PATIENTS

Aggregate mortality after recruitment of 750 patients was 27.6%. Therefore, we increased the sample size to 1696 on May 12, 2010. Patients were enrolled from March 2008 through August 2011 at 208 sites in Europe, North and South America, Australia, New Zealand, and India (for details, see the Supplementary Appendix). From 27,816 potential patients, we recruited 1697, with 852 assigned to receive DrotAA and 845 assigned to receive placebo. We were able to evaluate the primary outcome in 1680 patients (99.0%) (Fig. 1).

A total of 71.7% of patients were recruited at

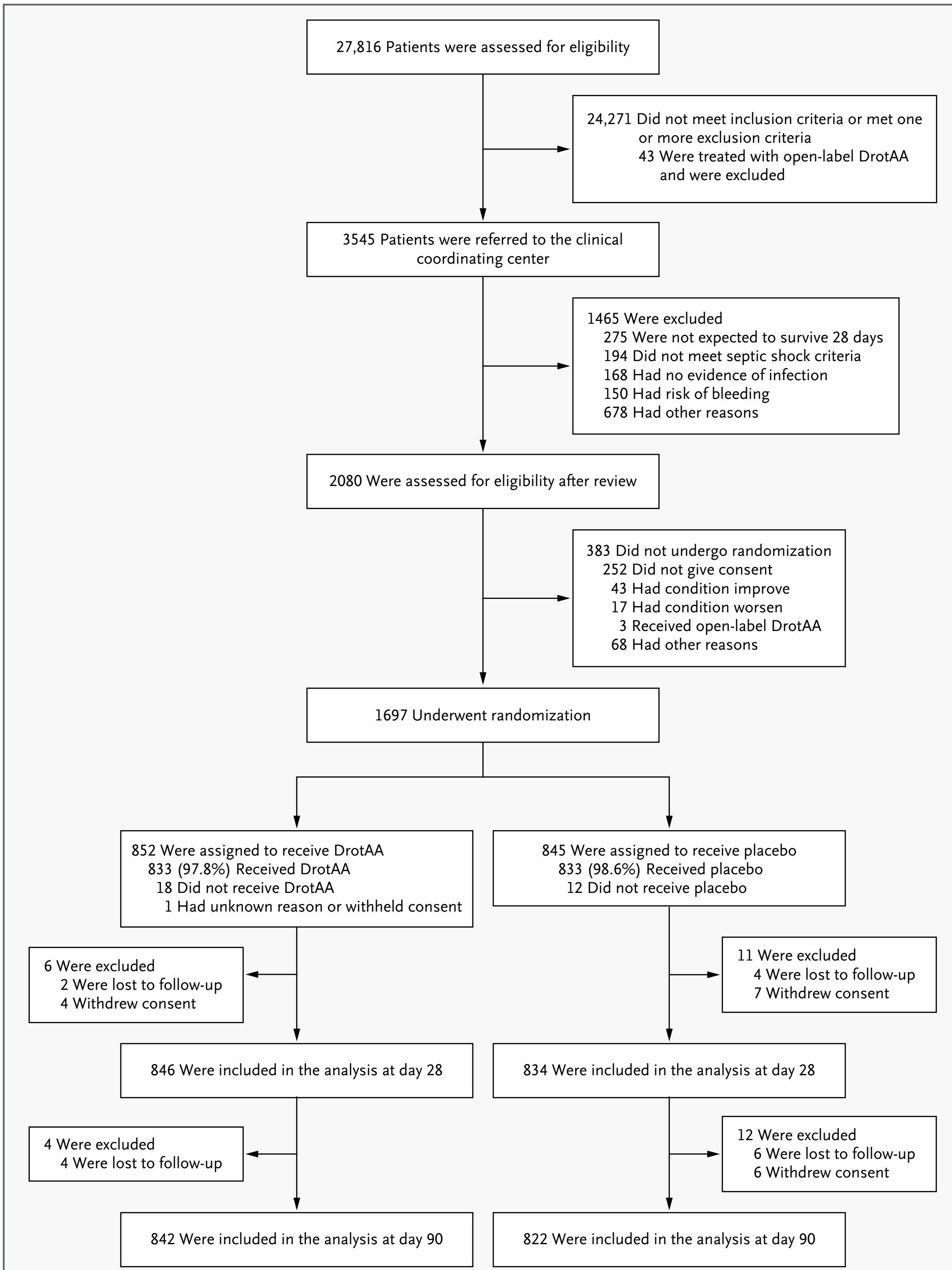

Figure 1. Screening, Randomization, and Follow-up of the Study Patients.

Screening procedures for all sites were not standardized, and not all sites returned screening logs. To screen for eligibility, sites were encouraged to identify all patients receiving vasopressors. If patients appeared to meet all inclusion and no exclusion criteria or if sites requested clarification, the clinical coordinating center was contacted. If the center confirmed eligibility, the site was authorized to randomly assign the patients. The reasons for exclusion are provided in Table S1 in the Supplementary Appendix. All patients who underwent randomization are included in the survival analysis for 28 and 90 days; data for patients with unknown survival status (i.e., those who were lost to follow-up or withdrew) were censored on the last day the patient was known to be alive. DrotAA denotes drotrecogin alfa (activated).

Table 1. Site and Cause of Infection.*

Variable	Drotrecogin Alfa (Activated)	Placebo
Primary site of infection — no./total no. (%)		
Lung	369/851 (43.4)	375/845 (44.4)
Abdomen	263/851 (30.9)	246/845 (29.1)
Urinary tract	97/851 (11.4)	112/845 (13.3)
Skin	48/851 (5.6)	45/845 (5.3)
Other site†	74/851 (8.7)	67/845 (7.9)
Positive blood culture — no./total no. (%)	270/851 (31.7)	239/845 (28.3)
Community-acquired infection — no./total no. (%)	654/850 (76.9)	654/845 (77.4)
Identification of infectious organism — no./total no. (%)	623/851 (73.2)	575/845 (68.0)‡
Sensitivity of infectious organism to administered antibiotics — no./total no. (%)§	514/611 (84.1)	481/571 (84.2)
Time from initiation of antibiotics to initiation of vasopressor — hr		
Median	2.5	2.5
Interquartile range	0–7.1	0–8.6
Source control of infection — no./total no. (%)¶	275/303 (90.8)	264/295 (89.5)

* There was no significant difference between the two study groups, except as indicated.
† Other sites included the central nervous system, blood, heart, pleura, reproductive tract, bone, and head.
‡ P=0.02
§ Drugs in this category are all antimicrobial agents that were administered before infusion of a study drug.
¶ Included in this category are patients who were treated for source control of infection (e.g., surgery, drainage, or removal of an infected central venous catheter) in the subgroup of patients for whom source control was deemed to be necessary. The type and frequency of organisms recovered from blood are provided in Table S3 in the Supplementary Appendix.

European sites and 14.1% at North American sites, with 14.2% recruited from other countries. Baseline characteristics were similar in the two groups (Table S2 in the Supplementary Appendix): 56.4% of the patients were men, and the mean (±SD) ages were 63.4±15.4 years in the DrotAA group versus 62.7±16.4 years in the placebo group. The mean APACHE II scores were 25.2±8.1 and 25.5±8.1 in the DrotAA and placebo groups, respectively; 84.1% of the patients had dysfunction of three or more organs.

The site of infection, cultured organisms, and antimicrobial treatments were similar in the two groups (Table 1, and Table S3 in the Supplementary Appendix). The most common sites of infection were the lung, abdomen, and urinary tract. A causative pathogen was identified before starting study treatment in 1198 of 1696 patients (70.6%); 509 of 1696 patients (30.0%) had positive blood cultures. The median time from the initiation of antibiotics to initial vasopressor therapy was 2.5 hours (interquartile range, 0 to 7.1) in the DrotAA group and 2.5 hours (interquartile range, 0 to 8.6) in the placebo group (P=0.98). The control of infection at the presumed source was accomplished in 275 of 303 patients (90.8%) in the DrotAA group and 264 of 295 (89.5%) in the placebo group (P=0.60).

STUDY TREATMENT AND COINTERVENTIONS

Study treatment was administered to 1666 of 1696 patients (98.2%) and was interrupted at least once in 593 of 1666 patients (35.6%). The mean total duration of study treatment was 83.3±26.7 hours in the DrotAA group and 85.1±25.1 hours in the placebo group. The major reason for interrupting a study treatment was an invasive procedure (in 215 of 306 patients with interruptions [70.3%] in the DrotAA group vs. 238 of 287 [82.9%] in the placebo group). Study treatment was stopped prematurely in 216 of 833 patients (25.9%) in the DrotAA group and 191 of 833 (22.9%) in the placebo group. In the two groups, the most common reason for premature discontinuation was the patient's death (Table S4 in the Supplementary Appendix). The proportions of patients receiving glucocorticoids and anticoagulants were also similar in the two groups, as were the number and site of surgical procedures performed during the treatment period (Table S4 in the Supplementary Appendix).

OUTCOMES

The status of patients at 28 days is provided in Table S5 in the Supplementary Appendix. At 28 days, 223 of 846 patients (26.4%) in the DrotAA group and 202 of 834 (24.2%) in the placebo group had died (relative risk in the DrotAA group, 1.09; 95% confidence interval [CI], 0.92 to 1.28; P=0.31). At 90 days, 287 of 842 patients (34.1%) in the DrotAA group and 269 of 822 (32.7%) in the placebo group had died (relative risk, 1.04; 95% CI, 0.90 to 1.19; P=0.56) (Table 2). In addition, the time-to-event analysis at 90 days showed similar results (hazard ratio, 1.07; 95% CI, 0.91 to 1.26; P=0.43 by the log-rank test) (Fig. 2A). There was no significant heterogeneity in the treatment effect on mortality at 28 days and 90 days in the prespecified subgroups (Fig. 2B, and Fig. S1 in the Supplementary Appendix). Changes in organ function during the 7-day study period

Figure 2 (facing page). Probability of Survival and Odds Ratios for Death, According to Subgroup.

Panel A shows Kaplan–Meier estimates for the probability of survival, which at 90 days did not differ significantly between patients receiving drotrecogin alfa (activated) (DrotAA) and those receiving placebo (hazard ratio, 1.07; 95% confidence interval, 0.91 to 1.26; P=0.43 by the log-rank test). Panel B shows the odds ratios and 95% confidence intervals for death from any cause among all patients in the predefined subgroups. The size of the symbols indicates the relative number of deaths. Although the odds ratio for death at 28 days was a specified outcome in the predefined statistical analysis plan (Fig. S1 in the Supplementary Appendix), odds ratios at 90 days are shown because the outcome at 90 days was deemed to be more relevant to clinicians and patients. The Acute Physiology and Chronic Health Evaluation (APACHE) II score ranges from 0 to 71 points, with higher scores indicating greater disease severity. Sequential Organ Failure Assessment (SOFA) scores range from 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction. Organ failure was defined as a SOFA score of 3 or 4 for any individual organ system. The protein C class indicates the percentage of normal protein C activity. ARDS denotes acute respiratory distress syndrome.

Table 2. Study Outcomes and Adverse Events.*

Outcome	Drotrecogin Alfa (Activated)	Placebo	Relative Risk (95% CI)	P Value
Death — no./total no. (%)				
At 28 days	223/846 (26.4)	202/834 (24.2)	1.09 (0.92–1.28)	0.31
At 90 days	287/842 (34.1)	269/822 (32.7)	1.04 (0.90–1.19)	0.56
Change in SOFA score by day 7†				
Cardiovascular	−2.61±1.72	−2.69±1.70		0.44
Respiratory	−0.71±1.23	−0.70±1.19		0.84
Renal	−0.64±1.34	−0.64±1.34		0.99
Coagulation	−0.03±1.18	−0.04±1.15		0.92
Liver	−0.03±0.96	−0.03±0.91		0.63
At least one serious adverse event by day 28 — no./total no. (%)‡	119/833 (14.3)	96/833 (11.5)	1.23 (0.96–1.59)	0.11
At least one bleeding event during treatment period — no./total no. (%)				
Nonserious	72/833 (8.6)	40/833 (4.8)	1.80 (1.23–2.61)	0.002
Serious	10/833 (1.2)	8/833 (1.0)	1.25 (0.49–3.15)	0.81
Cerebral hematoma, cerebral or subarachnoid hemorrhage, or hemorrhagic stroke by day 28 — no./total no. (%)	3/833 (0.4)	3/833 (0.4)	1.00 (0.20–4.90)	1.00

* Plus–minus values are means ±SD.
† Sequential Organ Failure Assessment (SOFA) scores range from 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction. P values were calculated with the use of the Wilcoxon rank-sum test.
‡ A complete list of serious adverse events is provided in Table S6 in the Supplementary Appendix.

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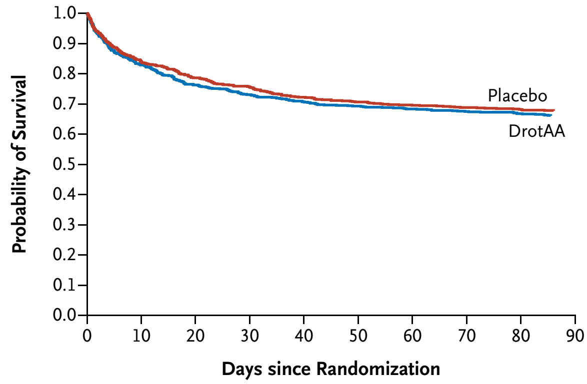
A Probability of Survival

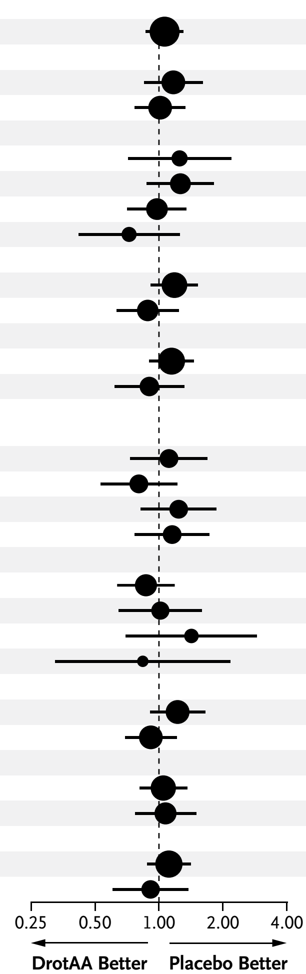


No. at Risk										
Placebo	845	703	656	622	593	579	569	563	557	553
DrotAA	851	701	645	616	596	584	576	567	561	555

B Odds Ratio for Death

Subgroup	No. of Patients	DrotAA	Placebo	P Value for Heterogeneity
		no. of deaths (%)		
All patients	1664	287 (34.1)	269 (32.7)	
APACHE II class				0.51
<25	827	108 (25.7)	93 (22.9)	
≥25	832	178 (42.6)	175 (42.3)	
No. of baseline organ failures				0.35
1 or 2	260	36 (27.5)	30 (23.3)	
3	560	88 (32.1)	78 (27.3)	
4	633	120 (37.0)	116 (37.5)	
5	211	43 (38.1)	45 (45.9)	
Recent surgery				0.18
No	1048	188 (35.5)	165 (31.8)	
Yes	616	99 (31.6)	104 (34.3)	
Baseline ARDS status				0.29
No	1209	205 (33.1)	178 (30.2)	
Yes	455	82 (36.8)	91 (39.2)	
Quartile of time from start of vasopressor to start of infusion				0.48
First	412	62 (31.8)	64 (29.5)	
Second	413	66 (29.3)	64 (34.0)	
Third	407	72 (36.4)	66 (31.6)	
Fourth	407	79 (38.0)	69 (34.7)	
Protein C class				0.63
≤40%	668	125 (36.5)	130 (39.9)	
41–60%	371	54 (28.7)	52 (28.4)	
61–80%	188	22 (23.7)	17 (17.9)	
>80%	92	10 (23.3)	13 (2.65)	
Baseline glucocorticoid exposure				0.17
No	836	127 (31.2)	116 (27.0)	
Yes	827	160 (36.9)	153 (38.9)	
Baseline prophylactic heparin exposure				0.91
No	1003	185 (35.7)	168 (34.6)	
Yes	661	102 (31.5)	101 (30.0)	
Baseline coagulation SOFA				0.41
0–1	1248	207 (33.2)	193 (30.9)	
2–4	389	76 (36.5)	70 (38.7)	

Odds Ratio (95% CI)



did not differ significantly in the two groups (Table 2). Protein C activity increased from baseline during the first 6 days in both groups; the mean increase was significantly greater in patients in the DrotAA group than in the placebo group on each of the first 4 study days ($P<0.001$) (Fig. S2 in the Supplementary Appendix).

During the first 28 days, one or more serious adverse events were recorded in 119 of 833 patients (14.3%) in the DrotAA group versus 96 of 833 patients (11.5%) in the placebo group ($P=0.10$) (Table 2, and Table S4 in the Supplementary Appendix). During the treatment period, nonserious bleeding events were more common among patients receiving DrotAA than among those receiving placebo (in 72 of 833 patients [8.6%] vs. 40 of 833 [4.8%], $P=0.002$), as were serious bleeding events (in 10 of 833 patients [1.2%] vs. 8 of 833 [1.0%], $P=0.81$), although the latter difference was not significant.

DISCUSSION

In this large international study involving critically ill adults with septic shock, DrotAA did not reduce mortality at either 28 or 90 days, as compared with placebo. The lack of benefit was consistent across predefined subgroups.

The strengths of the trial lie in both its design and its execution. From the results of previous randomized trials, we identified a clinically relevant population of patients who were likely to benefit from treatment with DrotAA, and we predefined a limited number of relevant subgroups within this population.[1,3,12-18] The characteristics of the patients we recruited matched the population we targeted. The baseline characteristics indicated a high degree of disease severity: 97.5% had multiple organ dysfunction, 90.2% had metabolic acidosis, and more than half had an elevated lactate level that persisted after fluid resuscitation. The baseline protein C level was markedly reduced in many patients. All patients remained dependent on vasopressors at study entry; most were treated with norepinephrine, with a median dose of 21 to 24 μg per minute at the start of study treatment. The baseline APACHE II score (which was designed to estimate the risk of death among critically ill patients rather than to assess the eligibility of individual patients for particular treatments) was somewhat lower than expected. Similar APACHE II scores have been reported in a trial of treatments for septic shock,[19] and such scores may reflect improved early resuscitation, since they are sensitive to lead-time bias.[20,21]

We used an adaptive design[22] that allowed us to increase the sample size to maintain adequate statistical power, since some trials involving patients with severe sepsis showed lower-than-expected mortality.[19,23,24] To reduce the risk of assignment bias, we concealed study-group assignments before and after randomization, and to minimize crossovers, we used a standardized process to select hospitals and intensive care units that did not regularly treat patients with DrotAA. The success of these processes is evident in the excellent compliance with study treatment and the minimal crossover observed in the study. We achieved near complete follow-up and followed a predefined, published statistical analysis plan. We used mortality as an outcome that is less subject to biased ascertainment than other outcomes.[25] We focused on mortality at 90 days,[18] since 45% of the patients were still hospitalized at 28 days, a percentage similar to that reported in the PROWESS study.

Our trial also has some limitations. We did not collect comprehensive data to study the coagulation or inflammatory responses during infusion of the study drugs, although such data exist from previous trials.[1,3,12,13,17,26] The between-group difference in protein C activity in our trial was similar to that seen in the PROWESS study,[27,28] and this finding combined with the expected increase in nonserious bleeding events in the DrotAA group[5,13] indicates that the patients received the intended treatment; both are indirect markers of the biologic activity of DrotAA. Mortality in the placebo group was low, as compared with historical data,[1,29-31] but consistent with that observed in more recent observational studies[32,33] and trials.[34,35]

Our findings are consistent with results of the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) and the Resolution of Organ Failure in Pediatric Patients with Severe Sepsis (RESOLVE) trials, which showed that DrotAA did not reduce mortality in children or adults with severe sepsis who had a low risk of death.[3,4] Our results are consistent with the finding in the ADDRESS trial in that DrotAA was not effective in patients with an increased disease severity.[4] We cannot explain

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the inconsistency between our findings and the reduction in mortality at 28 days that was observed in the PROWESS study.[1] Our findings of similar mortality at 90 days are consistent with those of the PROWESS study at 3 months, at which time mortality was not significantly reduced by DrotAA.[36]

Our study showed that DrotAA was not beneficial when administered to a population of patients for which it was an approved treatment. The fact that we found no benefit in any of the prespecified subgroups should reassure clinicians who no longer have DrotAA available to treat patients with septic shock.[37]

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APPENDIX

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