schools, now teaching ultrasound using a 4-yr curriculum (14). The Society of Ultrasound in Medical Education is championing this cause with the Association of American Medical Colleges and others (15). In the not-too-distant future, medical students graduating from medical school and entering residency will have the POC ultrasound skills required to perform an LE DVT US study, so will residents and fellows. One last morsel of food for thought has to be offered. It seems that if DVT development after major trauma is nearly unavoidable and one has but to look to find thousands around the country, the government may use its power more wisely by encouraging more people to wear seat belts, drive safely, not drive drunk, follow safety rules, and to the extent possible avoid being typically human and doing self-destructive things of all sorts. This will really decrease the number of patients developing DVTs on trauma services, regardless of whether one dares look with ultrasound or not (a task Critical Care Physicians are more than capable of doing).

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Resolving conflicting comparative effectiveness research in critical care*

Comparative effectiveness research has received keen interest from healthcare professionals, funding agencies, and researchers as a way to improve healthcare quality, efficiency, and costs. Broadly defined, comparative effectiveness research includes both observational studies and randomized controlled trials (RCTs). Of these, RCTs are widely considered near the top of the hierarchy of scientific evidence. In critical care, however, RCTs are clearly not feasible for every research question. They are expensive, time consuming, restricted to narrow patient populations, and usually conducted in an academic community setting. All of these issues limit their practicality and generalizability.

As a result, observational research is an important and increasing complement to RCTs as we develop best practice in the intensive care unit (1). In contrast to RCTs, observational research is often more efficient and generalizable (2). Administrative databases and clinical registries offer opportunities to study large, diverse patient populations with relative ease, and emerging statistical techniques such as propensity scores and instrumental variables purport to overcome the indication biases that traditionally plague observational studies of treatment effects (3). Yet even in these cases, the results of observational trials often conflict with RCTs, leading to erroneous conclusions and inappropriate treatment recommendations (4). In these cases, it is left to the consumers of research—patients, clinicians, and policy makers—to reconcile the results.

In this issue of *Critical Care Medicine*, Rimmer and colleagues (5) present us with that very challenge. They report a multinational, multicenter observational study of recombinant human activated protein C (rhAPC, drotrecogin alfa) among 7,392 subjects with septic shock enrolled from 1997 to 2007. They observed an overall low rate of rhAPC use among patients

*See also p. 2974.

Key Words: comparative effectiveness research; drotrecogin alfa; observational studies; propensity score; randomized trials

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with septic shock (4.7%) and a significant association between rhAPC and 30-day mortality in a propensity-matched analysis (hazard ratio 0.72, 95% confidence interval 0.52–1.00, p = .05). Such findings in favor of rhAPC use are consistent with an early randomized trial and multiple subsequent observational studies (6, 7). And yet, Eli Lilly and Company conducted a confirmatory, randomized trial (PROWESS-SHOCK) to refine target population and risk-benefit ratios for rhAPC. This trial found no significant benefit for rhAPC on 28-day mortality, and the drug was withdrawn worldwide (8).

So when studies conflict, what is the "right" answer? The first inclination is to rely on RCTs, and indeed there are many reasons why their conclusions are likely to be most reliable and valid. In contrast to other study designs, through the act of randomization RCTs protect against a common source of confounding termed "indication bias." This bias arises from the notion that patients who receive a treatment are fundamentally different than those who don't (9). For example, intensive care unit patients with severe sepsis who require vasopressors are more severely ill than those who don't. If we were to study the outcomes of patients who received vasopressors against controls in a large cohort study, our results may typically show that vasopressors are associated with harm. Yet these results would likely be due to the fact that treated patients were sicker in ways that cannot be measured through traditional approaches.

To attempt to overcome indication bias in their observational study of rhAPC, Rimmer and colleagues applied propensity score methods. They used all the variables they could measure to predict the probability a patient would receive rhAPC (the propensity score). Then they matched subjects receiving rhAPC to control subjects who did not on the propensity score. The propensity score matching helps balance baseline characteristics—a sort of pseudo-randomization. Yet in the end, propensity score methods are only as good as the variables measured in the dataset. They cannot account for unmeasured covariates, especially the subtle "unmeasurables" that govern the decision to prescribe a drug-like rhAPC. Thus they are far from a panacea as a method to remove bias (3). Only randomization can fully overcome these biases, supporting the role of RCTs as the best available clinical evidence (6).

Yet there are also valid reasons why observational studies can also be "right" and can indeed provide better data than even RCTs. Unlike RCTs, which typically are conducted in the academic setting under ideal conditions and with innumerable exclusion criteria, observational studies provide invaluable knowledge of practice patterns, treatment effects among "real" patients, and study phenotypes or subphenotypes not necessarily enrolled in preapproval randomized trials. They also may study patient-centered outcomes not mandated by drug approval agencies and could include more patients with greater power to detect small differences in treatment effects. Negative RCTs may be negative not because the drug doesn't work, but because the study was not conducted in the right setting, in the right patients, or with the power to detect clinically meaningful effect sizes in small subgroups. Ignoring this reality downplays the important role of observational studies in comparative effectiveness research, so long as that research is rigorously conducted. Recently, the Patient-Centered Outcomes Research Institute offered methodological standards for observational research that compliment standards for reporting (10, 11). These provide a roadmap for the future of comparative effectiveness research in critical care, without always relying on a randomized design.

The correct answer, then, is that neither RCTs nor observational research is always "right". Instead, we should approach each individual study with a critical eye weighing its strengths and limitations in the context of the previous literature and our prior beliefs. This is the idea of "Bayesian reasoning"—rather than providing irrefutable evidence, new clinical research should serve to inform and improve our decisions, not completely dictate our practice (12). Indeed, up to one third of the most cited clinical research trials are refuted or found to overestimate treatment effects, including many in critical care (13–15). Rather than expect perfection out of research, both clinicians and researchers must sharpen their interpretations and be wary of the strengths and weaknesses of randomized and nonrandomized study designs. We must move away from labeling studies "right" or "wrong." As long as they are well-conducted, conflicting studies provide complimentary findings that build a patchwork of evidence with which to guide our decisions.

Of course, in the case of rhAPC, this discussion is purely academic. Now off the market, the drug will not be given to patients in septic shock. Yet the conflicting evidence between early RCTs and postapproval observational studies is a warning for when we encounter the next rhAPC. The only "wrong" action is to be overly optimistic about a single RCT or to overly dismiss observational studies because patients are not randomized. Just like at the bedside in the intensive care unit, our interpretation of comparative effectiveness research should consider the entire body of evidence.

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Mirror mirror on the wall: Physician and nurse perceptions of their quality of care for deteriorating patients*

It is well established that early recognition of physiologic compromise in a hospitalized patient impacts outcomes, including the prevention of cardiac arrest. Research has substantiated the benefit of the use of rapid response teams and early warning systems to detect alterations that can have clinical significance for hospitalized patients (1). However, clinician's perceptions of prompt recognition of clinical deterioration may differ from their actual response, posing implications for clinical care and patient outcomes. In this issue of *Critical Care Medicine*, the study by Dr. Ludikhuize and colleagues (2) validates this in its findings that physicians and nurses self-assessment of quality of care differed from expert assessments who judged the care as suboptimal. They conducted a cross-sectional study of all cardiac arrests or unplanned intensive care unit admissions over a 4-month period involving 47 patients in one intensive care unit setting in The Netherlands. All care-providers who were responsible for the patient in the 12 hrs prior to the adverse event (n = 233) were contacted to participate in a study assessing their perceptions of the quality of care provided to the patient. One hundred seventeen care-providers participated in the study. A total of 639 measurements of vital signs were taken in the 48 hrs prior to the event. Based on vital sign and early warning sign assessments, 81% of patients could be identified as being at risk for deterioration at a median of 14 hrs prior to the adverse event. However, self-perceived quality of care indicated that care-providers were satisfied with the care they provided to the patients prior to the event in terms of communication, cooperation, and coordination of care. Additionally, 32% of the care-providers indicated they did not experience any concerns about the patient's clinical condition prior to the event. An independent panel of experts independently rated each case for the possible presence of a delay in the recognition of the deteriorating state of the patient and whether the event could have been avoided (2). The expert panel identified that a delay was present in 28 (60%) of the cases.

The results of the study highlight the discrepancy in perceptions of caregivers and the evaluations of experts regarding delay in recognizing clinical deterioration in hospitalized patients. The authors cite that the study results likely represent a lack of critical appraisal by care-providers of their professional performance. The results of the study have implications for practitioners regarding the need for improving critical self-assessment to improve outcomes for hospitalized patients who experience deterioration in clinical status. Reflecting on the quality of care provided to patients exhibiting changes in status may be beneficial to care-providers to identify areas for improvement. Looking in the mirror may help clinicians to improve their performance on the quality of care provided to patients at risk for clinical deterioration.

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Activated protein C and septic shock: A propensity-matched cohort study*

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Background: **Septic shock is a highly inflammatory and procoagulant state associated with significant mortality. In a single randomized controlled trial, recombinant human activated protein C (drotrecogin alfa) reduced mortality in patients with severe sepsis at high risk of death. Further clinical trials, including a recently completed trial in patients with septic shock, failed to reproduce these results.**

Objective: **To evaluate the effectiveness of recombinant human activated protein C on mortality in a cohort of patients with septic shock and to explore possible reasons for inconsistent results in previous studies.**

Design: **Retrospective, 2:1 propensity-matched, multicenter cohort study.**

Setting: **Twenty-nine academic and community intensive care units in three countries.**

Patients: **Seven thousand three hundred ninety-two adult patients diagnosed with septic shock, of which 349 received recombinant human activated protein C within 48 hrs of intensive care unit admission between 1997 and 2007.**

Measurements and Main Results: **Our primary outcomes were mortality over 30 days and mortality stratified by Acute Physiology and Chronic Health Evaluation II quartile. Using a propensity-matched Cox proportional hazard model, we observed a 6.1% absolute reduction in 30-day mortality associated with the use of recombinant human activated protein C (108/311 [34.7%] vs. 254/622 [40.8%], hazard ratio 0.72, 95% confidence interval 0.52–1.00, $p = .05$) and noted consistent reductions in mortality among Acute Physiology and Chronic Health Evaluation II quartiles. A time to event analysis showed that the time to appropriate antimicrobials after documented hypotension decreased for each year of study ($p = .003$), a finding that was congruent with a decrease in annual mortality over the study period (odds ratio 0.96 per year [95% confidence interval 0.93–0.99], $p = .003$).**

Conclusions: **In this retrospective, propensity-matched, multicenter cohort study of patients with septic shock, early use of recombinant human activated protein C was associated with reduced mortality. Improvements in general quality of care such as speed of antimicrobial delivery leading to decreasing mortality of patients with septic shock may have contributed to the null results of the recently completed trial of recombinant human activated protein C in patients with septic shock. (Crit Care Med 2012; 40:2974–2981)**

Key Words: activated protein C; anticoagulants; critical illness; sepsis; septic shock

The pathobiology of sepsis and septic shock involves proinflammatory and procoagulant responses to an underlying infection (1). Activated protein C (APC) is an endogenous anticoagulant that inhibits activated cofactors V and VIII, thereby reducing thrombin generation. By virtue of its ability to reduce thrombin, APC also functions as an anti-inflammatory agent. APC also has anti-inflammatory properties that are independent of its effect on thrombin generation (2).

In 2001, recombinant human APC (rhAPC, drotrecogin alfa) received Food and Drug Administration approval for its use in patients diagnosed with severe sepsis at high risk of death (3). This indication was based on the results of a single phase III randomized controlled trial (PROWESS) (4). In that study, rhAPC reduced 28-day mortality in severe sepsis by 6.1% (30.8% vs. 24.7%, $p = .005$) (4). Ninety-day follow-up data from the original trial were

***See also p. 3090.**

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unable to demonstrate a sustained mortality benefit in the overall study population (5), and a subsequent placebo controlled trial of rhAPC in sepsis with low mortality risk showed no significant difference in 28-day mortality (18.5% vs. 17%, p = .34) (6). A third randomized controlled trial designed to study the efficacy and safety of rhAPC in children was stopped early after a second interim analysis suggested there was little chance of reaching the efficacy endpoint (7). To maintain licensing approval, a further randomized placebo-controlled trial in patients with septic shock was undertaken to confirm the efficacy of rhAPC (PROWESS-Shock) (8). The mortality rates in this study were substantially lower than expected given the inclusion criteria of septic shock, 26.4% vs. 24.2% in the rhAPC and control groups respectively, and rhAPC failed to reduce 28-day mortality. The drug was voluntarily removed from the worldwide market on October 25, 2011 (9).

The purpose of this study is to determine the effectiveness of rhAPC in a large multinational septic shock database and to identify possible reasons for the divergent results of previous trials. We hypothesize that the early administration of rhAPC to patients with septic shock is associated with reduced mortality.

METHODS

Data Source and Study Population

Data collection for this study was approved by the Research Ethics Board at the University of Manitoba and at all participating centers under a waived consent protocol. We identified patients ≥18 yrs of age who were admitted to an intensive care unit (ICU) between 1997 and 2007 with a diagnosis of septic shock from the Cooperative Antimicrobial Therapy of Septic Shock Database. The Cooperative Antimicrobial Therapy of Septic Shock database includes patient record data of consecutive patients with septic shock from 29 centers in Canada, the United States, and Saudi Arabia (10). Trained data research nurses and medical students maintain this database using a standardized and piloted data extraction template. Detailed variable definitions and data collection methods have been described in previous publications (10, 11).

Each potential patient was screened to ensure specific criteria for septic shock were met, as defined by the 1991 Society for Critical Care Medicine/American College of Chest Physicians Consensus Statement on Septic Shock (12). All patients were required to exhibit vasopressor-dependent shock. The definition of septic shock was kept consistent throughout the study period. Data were collected on each patient up to time of death, hospital discharge, or to a maximum of 30 days.

We identified 8670 patients with septic shock (including patients admitted from the emergency department, in-patient hospital wards, and interhospital transfers). The cohort was limited to patients on or after March 19, 1997, which corresponded to the date of first rhAPC use in the database. To minimize potential survival bias, patients who died within the first 48 hrs of shock onset were excluded, and patients were required to have received rhAPC within 48 hrs of shock (11, 13, 14). This also had the effect of limiting cases to patients with early administration of rhAPC.

Study Variables

Variables collected included patient demographics, baseline comorbid conditions, Acute Physiology and Chronic Health Evaluation (APACHE II) score (15), laboratory variables, and administration of ventilator or hemodynamic support. The site of presumed infection, microbiological culture results, time to first appropriate antimicrobial therapy following documentation of hypotension, and use of combination antibiotic therapy were also recorded. Appropriate antimicrobial therapy was defined as administration of antimicrobials with *in vitro* activity for the isolated pathogen or appropriate for the clinical syndrome in patients where no pathogen was isolated (10). Combination antibiotic therapy was defined as concomitant use of two or more appropriate, intravenous, bactericidal antibiotics with different mechanisms of action for at least 24 hrs after the onset of hypotension (11).

Outcome Measures

The primary outcome was mortality over 30 days using a Cox proportional hazard model. Given the presumed differential therapeutic effects of rhAPC according to severity of illness, findings that constituted the basis of the original licensing indication (4, 16), we also examined mortality stratified by APACHE II quartile as an *a priori* outcome. Other predetermined secondary outcomes included ICU and hospital mortality, lengths of stay, ventilator-free days, mortality stratified by time to appropriate antimicrobials and the type of infection, and mortality stratified by the number of organ failures on day 1 of ICU admission. Ventilator-free days were defined as the number of days between successful weaning from mechanical ventilation and day 30 (17).

Statistical Analysis

Baseline characteristics of the patients who did or did not receive rhAPC were compared using the Student's t test or the Wilcoxon's rank sum test for continuous variables, or the chi-square test for categorical variables. A propensity-matched analysis was undertaken for several reasons: to account for the nonrandom assignment of rhAPC, to mitigate potential confounding factors and selection biases, and to increase statistical efficiency. The propensity matching procedures were developed according to published methods (18–20). A propensity score for rhAPC use was developed using multivariable logistic regression and represented the probability that a patient would receive rhAPC based on variables known or thought to be relevant to its use or the outcome (21). The variables included in the derivation of the propensity score are outlined in Table 1. These variables included age, gender, APACHE II score, number of new organ failures on day 1 of ICU admission, type of organ failure (renal, respiratory, metabolic, or hematologic), comorbid conditions (liver failure, chronic obstructive pulmonary disease, diabetes, New York Heart Association class IV heart failure, dialysis dependency, malignancy, human immunodeficiency virus infection or AIDS, immunosuppression), bacteremia, location of primary infection, primary organism, need for ventilator or hemodynamic support, a variety of laboratory variables on day 1 of ICU admission (white blood cell count, platelet count, creatinine, bilirubin, bicarbonate, international normalized ratio), time to first appropriate antimicrobial, and the provision of appropriate or combination antimicrobial agents. To account for temporal and geographic practice variability, the date of intensive care admission and hospital site (region and academic/nonacademic) were also included as matching variables. The characteristics of the participating ICU's are included in Table 2. Propensity scores were used to match a patient who received rhAPC to a similar control patient using a 5 → 1 digit greedy macro algorithm (22). Patients were initially matched to controls on five decimals of the propensity score. For those that did not match on five decimals, they were matched using four decimals, and so forth down to a one-decimal match. Patients who received rhAPC and who remained unmatched at one decimal of the propensity score were excluded from analysis. To increase the power of the analysis, propensity matching was done using a 2:1 matching procedure where each patient of rhAPC was matched to two controls (23, 24). In order to include all relevant patient data into the calculation of the propensity score, a missing indicator variable was developed for those variables with missing data.

After propensity matching, we evaluated mortality over 30 days using a Cox proportional hazard model using a conditional, matched-pair analysis with a shared γ-frailty model. The shared frailty model incorporates the propensity-matched pairs into the Cox model. This matched-pair analysis was used for all outcomes involving the entire propensity-matched cohort. We used a standard Cox regression analysis for subgroup analyses. The hazard model incorporated data collected up to time of death, hospital discharge, or to a maximum of

Table 1. Baseline characteristics in the unmatched septic shock cohort

	Unmatched Cohort			Propensity-Matched Cohort		
	Recombinant Human Activated Protein C (n = 349)	Control (n = 7043)	*p*	Recombinant Human Activated Protein C (n = 311)	Control (n = 622)	*p*
General demographics						
Male [n, (%)]	197 (56.5%)	4040 (57.4%)	.74	175 (56.3%)	334 (53.7%)	.46
Age [yr, mean (SD)]	56.4 (16.5)	62.8 (16.1)	<.0001	57.9 (16.1)	57.4 (17.2)	.62
Mean shock date	April 24, 2004	April 25, 2003	<.0001	April 5, 2004	December 30, 2003	.09
Duration of hospitalization before shock (median, quartiles)	0 [0–2]	1 [0–8]	.002	0 [0–3]	0 [0–3]	.58
Acute Physiology and Chronic Health Evaluation II score[a] [mean (SD)]	26.0 (7.6)	25.2 (7.9)	.08	26.0 (7.7)	26.0 (8.0)	.97
Time to first antibiotic (hrs) [median, quartiles]	3.5 [1.3–8.8]	5.0 [1.9–12.0]	.0002	3.8 [1.5–9.0]	4.3 [1.5–10.3]	.66
Appropriate antibiotic	304 (87.1%)	5831 (82.8%)	.04	270 (86.8%)	535 (86.0%)	.74
Combination antibiotic therapy	126 (41.8%)	2192 (31.1%)	<.0001	123 (39.6%)	254 (40.8%)	.71
Geographic distribution						
Canada	311 (89.1%)	5611 (79.7%)	<.0001	278 (89.4%)	556 (89.4%)	.79
United States	36 (10.3%)	973 (13.8%)		31 (9.9%)	57 (9.2%)	
Outside North America	2 (0.6%)	459 (6.5%)		2 (0.6%)	9 (1.4%)	
Preexisting medical conditions, n (%)						
Liver failure	9 (2.6%)	534 (7.6%)	.0005	9 (2.9%)	23 (3.7%)	.52
Chronic obstructive pulmonary disease	39 (11.2%)	1114 (15.8%)	.02	38 (12.2%)	69 (11.1%)	.61
Diabetes mellitus	94 (26.9%)	1953 (27.7%)	.75	86 (27.7%)	177 (28.5%)	.80
Chronic kidney disease	31 (8.9%)	1109 (15.8%)	.0005	30 (9.7%)	64 (10.3%)	.76
Dialysis dependence	16 (4.6%)	559 (7.9%)	.02	15 (4.8%)	28 (4.5%)	.83
Malignancy	42 (12.0%)	1181 (16.8%)	.02	42 (13.5%)	85 (13.7%)	.95
Neutropenia	3 (0.9%)	292 (4.2%)	.002	3 (1.0%)	4 (0.6%)	.69
Immunosuppression	56 (16.1%)	1207 (17.1%)	.60	50 (16.1%)	98 (15.8%)	.90
New York Heart Association class IV	5 (1.4%)	207 (2.9%)	.10	5 (1.6%)	12 (1.9%)	.73
Recent surgical history, n (%)						
Elective surgery	51 (14.6%)	1037 (14.7%)	.95	48 (15.4%)	105 (16.9%)	.57
Emergency surgery	17 (4.9%)	566 (8.0%)	.03	17 (5.5%)	36 (5.8%)	.84
No surgical history	284 (81.4%)	5521 (78.4%)	.18	249 (80.1%)	490 (78.8%)	.65
Physiologic and laboratory variables at admission [median (quartiles)]						
Mean arterial pressure (mm Hg)	55.0 [49.0–61.0]	56 [49.0–62.0]	.88	56.0 [49.0–62.0]	58.0 [48.0–63.0]	.76
Admission white blood cell ($\times 10^6$ cells/L)	14.1 [4.6–24.3]	14.4 [7.4–21.6]	.92	14.1 [4.7–24.6]	15.8 [8.2–23.0]	.19
Platelet count ($\times 10^9$ cells/L)	157 [104–225]	174 [102–266]	.02	165 [109–237]	163 [98–245]	.78
Serum creatinine (μmol/L)	177 [114–272]	157 [96.0–263]	.05	172 [106–268]	168 [101–259]	.79
International normalized ratio	1.5 [1.3–1.8]	1.4 [1.2–1.8]	.36	1.5 [1.2–1.8]	1.4 [1.2–1.8]	.53
Bilirubin (μmol/L)	16.0 [8.0–26.0]	16.0 [9.0–34.0]	.02	16.0 [8.0–27.4]	15.0 [9.0–26.5]	.95
Serum bicarbonate (mEq/L)	18.0 [14.3–21.0]	19.8 [15.5–24.0]	<.0001	18.5 [15.0–21.9]	18.0 [14.0–22.0]	.23
Site of infection, n (%)						
Culture positive	257 (73.6%)	4825 (68.5%)	.04	226 (72.7%)	460 (74.0%)	.67
Blood culture positive	151 (43.3%)	2254 (32.0%)	<.0001	123 (39.6%)	248 (39.9%)	.92
Blood stream infection—primary	15 (4.3%)	430 (6.1%)	<.0001	14 (4.5%)	26 (4.2%)	.91
Blood stream infection—catheter	7 (2.0%)	261 (3.7%)		6 (1.9%)	10 (1.6%)	
Respiratory	158 (45.3%)	2811 (39.9%)		143 (46.0%)	271 (43.6%)	
Urinary tract	39 (11.2%)	746 (10.6%)		36 (11.6%)	68 (10.9%)	
Intra-abdominal	79 (22.6%)	1995 (28.3%)		73 (23.5%)	154 (24.8%)	
Central nervous system	12 (3.4%)	46 (0.7%)		3 (1.0%)	14 (2.3%)	
Skin and soft tissue	29 (8.3%)	546 (7.8%)		27 (8.7%)	52 (8.4%)	
Surgical site	4 (1.2%)	84 (1.2%)		3 (1.0%)	6 (1.0%)	
Cardiac/pericardial	1 (0.3%)	33 (0.5%)		1 (0.3%)	4 (0.6%)	
Other	5 (1.4%)	91 (1.3%)		5 (1.6%)	17 (2.7%)	
Type of infection, n (%)						
Group A Streptococcus	19 (5.4%)	156 (2.2%)	<.0001	15 (4.8%)	35 (5.6%)	.99
Non-group A Streptococcus	8 (2.3%)	83 (1.2%)		8 (2.6%)	20 (3.2%)	
Viridans streptococcus	2 (0.6%)	85 (1.2%)		2 (0.6%)	2 (0.3%)	
Streptococcus pneumoniae	43 (12.3%)	357 (5.1%)		33 (10.6%)	71 (11.4%)	
Staphylococcus aureus	37 (10.6%)	875 (12.4%)		37 (11.9%)	64 (10.3%)	
Enterococcus species	6 (1.7%)	219 (3.1%)		6 (1.9%)	9 (1.5%)	
Other Gram positives	1 (0.3%)	25 (0.4%)		1 (0.3%)	2 (0.3%)	
Escherichia coli	60 (17.2%)	982 (13.9%)		54 (17.4%)	101 (16.2%)	
Klebsiella	15 (4.3%)	372 (5.3%)		15 (4.8%)	33 (5.3%)	
Enterobacter	3 (0.9%)	165 (2.3%)		3 (1.0%)	6 (1.0%)	
Other enterobacteriaciae	10 (2.9%)	211 (3.0%)		9 (2.9%)	23 (3.7%)	
Pseudomonas	15 (4.3%)	336 (4.8%)		15 (4.8%)	25 (4.0%)	

Table 1. *Continued*

	Unmatched Cohort			Propensity-Matched Cohort		
	Recombinant Human Activated Protein C (n = 349)	Control (n = 7043)	*p*	Recombinant Human Activated Protein C (n = 311)	Control (n = 622)	*p*
Haemophilus influenzae	2 (0.6%)	88 (1.3%)		2 (0.6%)	4 (0.6%)	
Other nonenterobacteriaciae	2 (0.6%)	108 (1.5%)		2 (0.6%)	3 (0.5%)	
Neisseriameningitides	9 (2.6%)	16 (0.2%)		0 (0.0%)	5 (0.8%)	
Moraxella catarrhalis	1 (0.3%)	16 (0.2%)		1 (0.3%)	2 (0.3%)	
Fungal	14 (4.0%)	269 (3.8%)		13 (4.2%)	29 (4.7%)	
Other	10 (2.9%)	451 (6.4%)		10 (3.2%)	26 (4.2%)	
Cointerventions, n (%)						
Ventilatory support	327 (93.7%)	5813 (82.5%)	<.0001	289 (92.9%)	575 (92.4%)	.79
Fluids within first hour (mean, SD)	1.73 (1.34)	1.49 (1.51)	.04	1.75 (1.36)	1.82 (2.17)	.66
Stress dose steroids	175 (50.1%)	2306 (32.7%)	<.0001	142 (45.7%)	294 (47.3%)	.64
Surgical source control	121 (34.7%)	2858 (40.6%)	.03	112 (36.0%)	225 (36.2%)	.96
New organ failures[b], n (%)						
Renal failure	247 (70.8%)	4032 (57.3%)	<.0001	213 (68.5%)	446 (71.7%)	.31
Hematologic failure	66 (18.9%)	1620 (23.0%)	.08	56 (18.0%)	115 (18.5%)	.86
Metabolic failure	227 (65.0%)	3262 (46.3%)	<.0001	194 (62.4%)	399 (64.2%)	.60
Respiratory failure	313 (89.7%)	5091 (72.3%)	<.0001	276 (88.9%)	539 (86.7%)	.37
Total number of day 1 organ failures (mean, SD)	4.3 (1.4)	3.7 (1.6)	<.0001	4.2 (1.4)	4.3 (1.5)	.62

Quartiles, p25, p75.

[a]The patients were assessed on the day of onset of shock. The range of scores for this test is 0–71; [b]definitions of organ failures: cardiovascular (systolic blood pressure <90 mm Hg or >40 mm Hg drop from normal or mean arterial pressure <65 mm Hg for at least 1 hr despite adequate fluid resuscitation [2 L saline or equivalent] or the use of vasopressors); renal (elevation of normal baseline creatinine to >1.5 × normal value); respiratory (ventilation required); hematologic (platelet count <80,000/mm^3); metabolic (lactate >3 mmol/L).

Table 2. Description of participating intensive care units

	n = 29
Setting, n (%)	
Academic	16 (55.2)
Community	13 (44.8)
ICU type, n (%)	
Medical	3 (10.3)
Medical and surgical	2 (6.9)
Mixed	24 (82.8)
ICU management style, n (%)	
Open	4 (13.8)
Closed	25 (86.2)
Location, n (%)	
Canada	22 (75.9)
United States	6 (20.7)
Other	1 (3.4)
Number of beds, mean (SD)	
Hospital	478 (206.7)
ICU	18 (8.5)

ICU, intensive care unit.

30 days. A hazard ratio <1 indicates decreased mortality in the rhAPC group. Hospital and ICU length of stay and ventilator-free days were compared using the Wilcoxon's rank sum test. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

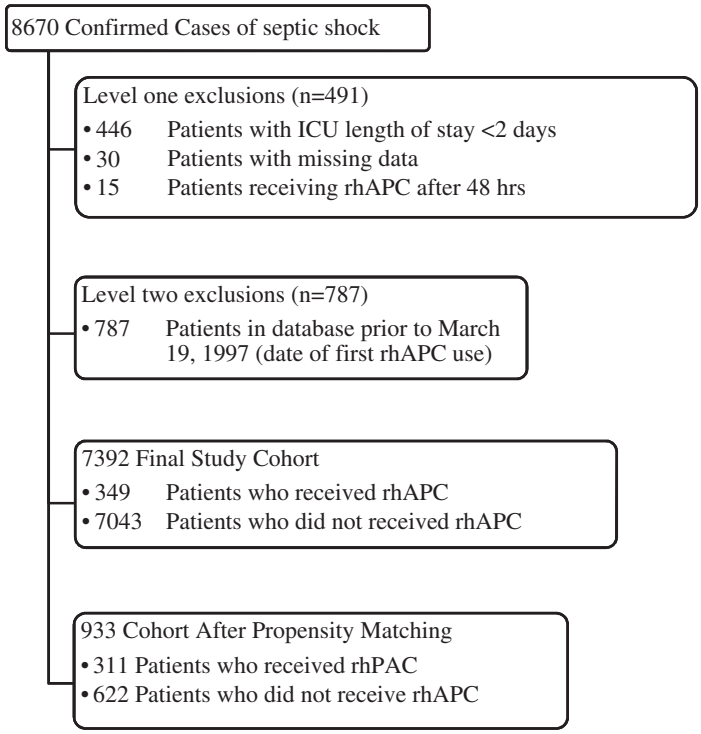

Figure 1. Patient flow through study. *ICU*, intensive care unit; *rhAPC*, recombinant human activated protein C.

RESULTS

Baseline Characteristics

Our final study cohort comprised of 7,392 patients, of whom 349 (4.7%) received rhAPC (Fig. 1). Baseline characteristics of the unmatched and propensity-matched cohorts are outlined in Table 1.

An appropriate propensity match was found for 311 (89.1%) of the 349 patients who received rhAPC. Propensity matching successfully eliminated all identified differences between the groups (Fig. 2, Table 1). The *c* statistic for the propensity derivation model

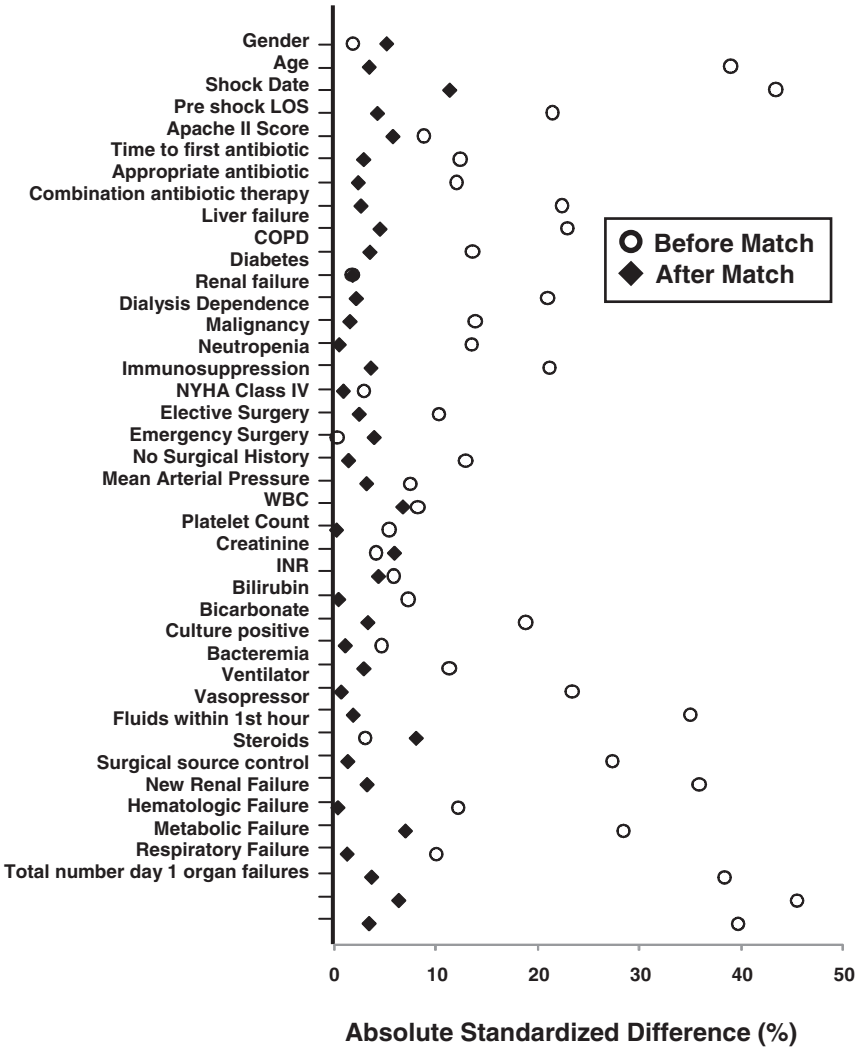

Figure 2. Absolute standardized differences in baseline characteristics of patients who received recombinant human activated protein C and controls before (*open circles*) and after (*diamonds*) propensity matching. *LOS*, length of stay; *COPD*, chronic obstructive pulmonary disease; *NYHA*, New York Heart Association; *WBC*, white blood cell; *INR*, international normalized ratio.

was 0.83. In the propensity-matched cohort, males comprised 56.3% and 53.7% of the rhAPC and control groups, respectively. The mean age of the rhAPC and control group was 57.9 yrs (SD 16.1) and 57.4 yrs (SD 17.2). The mean APACHE II score in the rhAPC and control group was 26.0 (SD 7.7) and 26.0 (SD 8.0), whereas the median time to first appropriate antimicrobial for those receiving appropriate antimicrobials only after documentation of hypotension was 3.8 (quartiles 1.5, 9.0) hrs in the rhAPC group and 4.3 (quartiles 1.5, 10.3) hrs in the control group. The mean number of organ failures in day 1 of ICU admission was 4.2 (SD 1.4) and 4.3 (SD 1.5) in the rhAPC and control groups, respectively.

Primary Outcome—Mortality Over 30 days and Mortality Stratified by APACHE II Score

In the shared γ-frailty Cox model using our propensity-matched cohort, use of rhAPC was associated with a significant reduction in mortality over 30 days (108/311 [34.7%] vs. 254/622 [40.8%], hazard ratio 0.72, 95% confidence interval [CI] 0.52–1.00, p = .05) (Fig. 3, Table 3). Consistent 30-day mortality results were obtained using a subset of patients who received rhAPC after drug licensing (81/222 [36.5%] vs. 188/444 [42.3%], hazard ratio 0.83, 95% CI 0.64–1.08). Subgroup analysis revealed nonsignificant reductions in mortality among all APACHE II quartiles (Table 3).

Secondary Outcomes

Mortality. The use of rhAPC was associated with significant reductions in both ICU mortality (hazard ratio 0.79, 95% CI 0.63–0.98, p = .03) and hospital mortality (hazard ratio 0.76, 95% CI 0.57–1.00, p = .05) (Table 4). In a subset of eight hospitals that contributed data from 1997 to 2007, the mortality of the untreated cohort decreased throughout the study period. The odds ratio of death associated with each study year was 0.96 (95% CI 0.93–0.99, p = .003). In this same population, a time to event analysis showed that the time to appropriate antimicrobials after documented hypotension decreased for each year of study (p = .003).

Other Clinical Outcomes. The use of rhAPC was associated with an increase in the median ICU length of stay (8 days [quartiles 4.6, 15] vs. 7 days [quartiles 4, 13], p = .03) and a trend toward increased hospital length of stay (18 days [quartiles 8, 36] vs. 16 days [quartiles 6, 32], p = .06). The use of rhAPC was not associated with a difference in ventilator-free days.

DISCUSSION

In this retrospective, 2:1 propensity-matched cohort of 933 patients with septic shock, use of rhAPC was associated with a significant reduction in mortality over 30 days. These findings are consistent with those of the initial phase III trial of rhAPC, with a similar absolute magnitude of survival benefit (6.1% in the PROWESS trial and 6.1% in the current study) (4). Also consistent with the results of our study are two other propensity-matched analyses, the first of which found rhAPC to be associated with reduced hospital mortality (40.7% vs. 46.6%, risk ratio 0.87, 95% CI 0.80–0.95, p = .001) (25). The second propensity-matched study of 216 patients (108 of whom received rhAPC) likewise showed a significant reduction in hospital mortality associated with the use of rhAPC (26). These positive findings are at odds with the recent PROWESS-Shock trial, which failed to demonstrate a survival advantage with rhAPC. We believe our data may provide insight about possible reasons for these discrepant findings.

On October 25, 2011, Eli-Lilly released preliminary results of the PROWESS-Shock study: a multinational phase III randomized controlled trial of rhAPC in

patients diagnosed with septic shock. That study recruited patients from 2008 to 2011. In the PROWESS-Shock study, rhAPC failed to meet the primary endpoint of a reduction in 28-day mortality (26.4% vs. 24.2% in the rhAPC and control groups, respectively) (8). The company withdrew drotrecogin alfa from the market in response to these data.

A possible explanation for these discrepant results is that the mortality of patients with septic shock has decreased since the initial PROWESS study (which recruited patients from 1998 to 2000) (27). In the press release from Eli-Lilly announcing the withdrawal of rhAPC, the mortality rate reported in PROWESS-Shock was substantially lower than anticipated given the entry criteria of septic shock (9). Although speculative, it is unlikely that rhAPC could have had the same absolute or even relative benefit in a population with lower baseline mortality since as baseline mortality risk falls, adverse effects of the experimental therapy may begin to outweigh any benefits. In our study, we observed that the mortality of patients with septic shock decreased over the study period. In a multivariable logistic regression model, the odds ratio of death decreased by 4% for each year from 1997 to 2007. Possible contributors to the decreasing mortality are improvements in the supportive care of patients with septic shock. In particular, there is heightened awareness regarding the importance of timely administration of appropriate antimicrobials and the clinical consequences of therapeutic delays (10), as well as strategies in place that target aggressive initial fluid resuscitation (28). Accordingly, our study demonstrates that the time to appropriate antimicrobial therapy after documented hypotension decreased for each year of study.

Another potential contributor to negative results in the recent trials is that rhAPC had already been licensed and was available outside of a clinical trial setting during their recruitment. It is therefore possible that patients who were felt to benefit most from rhAPC received the drug off trial. If clinical practice in the PROWESS-Shock study centers was similar to practice in centers that contribute data to the Cooperative Antimicrobial Therapy of Septic Shock database, however, off-study use of rhAPC would have been limited; in our data set, only 4.6% of patients with two or more organ failures or with APACHE II scores >25 received rhAPC.

The strength of our study is that all patients who received rhAPC during the study period were classified as cases. An additional strength of our study is our use of a large multinational clinical septic shock database that allowed for detailed modeling of relevant patient outcomes with adjustment for multiple demographic, laboratory, and physiologic variables. In contrast to our study, the previous propensity-matched studies used administrative data (25) and did not account for important factors associated with mortality in septic shock including time to appropriate antimicrobials, use of combination antibiotic therapy, and the date of ICU admission (26).

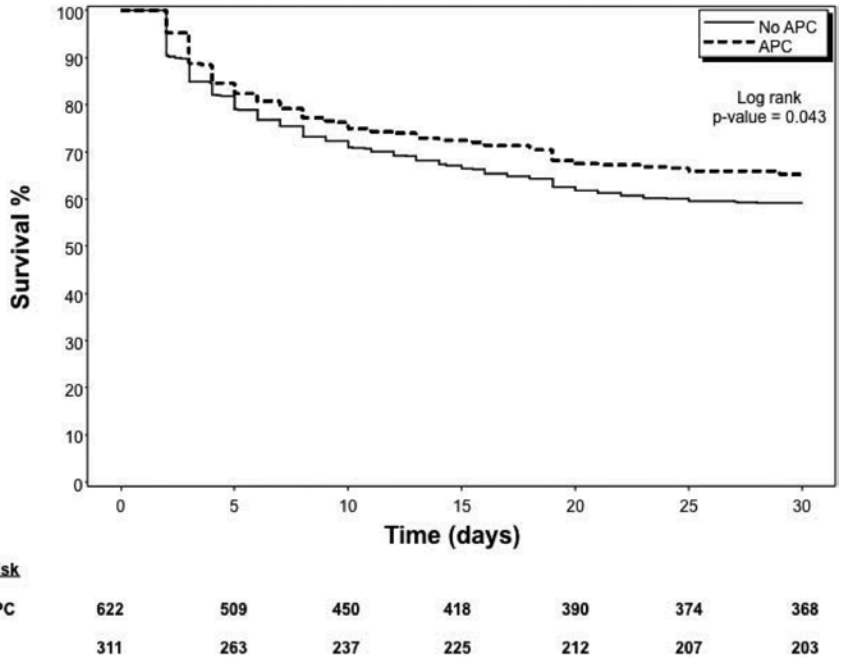

Figure 3. Adjusted Cox proportional hazard of mortality associated with recombinant human activated protein C (*APC*) in septic shock in the propensity-matched cohort.

Table 3. Mortality over 30 days

Septic Shock Cohort	Sample Size n	Mortality Rate by Recombinant Human Activated Protein C Status No. of Deaths/Total No. of Patients (%) Recombinant Human Activated Protein C	Control	Hazard Ratio (95% Confidence Interval)	*p*
Unadjusted[a]	7392	118/349 (33.8%)	3017/7043 (42.8%)	0.75 (0.62, 0.90)	.002
Adjusted for propensity score[b]	933	108/311 (34.7%)	254/622 (40.8%)	0.72 (0.52, 1.00)	.05
Stratified 30-day mortality analysis in matched cohort (Acute Physiology and Chronic Health Evaluation II quartile)					
5–19	204	6/63 (9.5%)	31/141 (22.0%)	0.40 (0.17, 0.95)	.04
20–25	238	17/80 (21.3%)	49/158 (31.0%)	0.64 (0.37, 1.12)	.12
26–30	205	27/72 (37.5%)	53/133 (39.9%)	0.92 (0.58, 1.46)	.72
31–53	239	47/75 (64.0%)	111/164 (66.7%)	0.87 (0.62, 1.22)	.40

[a]Cox proportional hazard model on the unmatched cohort; [b]Cox proportional hazard model using a conditional, matched-pair analysis with a shared γ-frailty model.

Table 4. Secondary mortality outcomes

Propensity-Matched Septic Shock Cohort	Sample Size n	Mortality Rate by Recombinant Human Activated Protein C Status No. of Deaths/Total No. of Patients (%) Recombinant Human Activated Protein C	Control	Hazard Ratio (95% Confidence Interval)	p
Hospital mortality					
Adjusted for propensity score[a]	933	129/311 (41.5%)	294/622 (47.3%)	0.76 (0.57, 1.00)	.05
Intensive care unit mortality					
Adjusted for propensity score[a]	933	98/311 (31.5%)	232/622 (37.3%)	0.79 (0.63, 0.98)	.03
30-day mortality stratified by the delay (hours) between documented hypotension and first appropriate antibiotic					
0.00–1.99	217	18/70 (25.7%)	26/147 (17.7%)	1.53 (0.84, 2.78)	.17
2–5.99	211	22/82 (26.8%)	42/129 (32.6%)	0.76 (0.46, 1.28)	.30
6+	283	42/86 (48.8%)	124/197 (62.9%)	0.68 (0.48, 0.96)	.03
30-day mortality stratified by infection type					
Gram positive	305	35/101 (34.7%)	73/204 (35.8%)	0.93 (0.62, 1.39)	.71
Gram negative	303	33/101 (32.7%)	75/202 (37.1%)	0.86 (0.57, 1.30)	.48
Fungal	46	7/14 (50.0%)	22/32 (68.8%)	0.65 (0.28, 1.51)	.31
Culture negative	247	30/85 (35.3%)	73/162 (45.1%)	0.74 (0.48, 1.13)	.16

[a]Cox proportional hazard model using a conditional, matched-pair analysis with a shared γ-frailty model

Although we analyzed data from a large, multicenter, multinational, septic shock database, the actual number of patients treated with rhAPC was relatively modest (n = 349), and reflects a potential limitation of our study. The Cooperative Antimicrobial Therapy of Septic Shock database is the largest clinical septic shock database known to us; low numbers of patients reflect low usage of rhAPC in clinical practice. Limited rhAPC use might reflect the presence of clinical contraindications, but more likely demonstrates suboptimal physician adoption of this controversial therapy consistent with previously published studies (29, 30). Another limitation has to do with the retrospective nature of this study. In such a retrospective analysis of a condition with a very high early risk of mortality, such as septic shock, there is the potential for survival bias. In addition, patients who survived long enough to receive rhAPC may also be more likely to live to a given endpoint than those who did not live long enough to receive such a therapy. In order to reduce these potential biases, death within 48 hrs was identified *a priori* as an exclusion criterion, and rhAPC had to be administered within that time frame for patients (11, 13, 14). In retrospective studies, unmeasured confounding variables may be present and cannot be accounted for in a multivariable logistic regression model or propensity-matched analysis. This represents an important limitation of this type of study. The lack of safety data available, including the need for allogeneic transfusion and bleeding complications, is another limitation of this study. These data are not captured in the Cooperative Antimicrobial Therapy of Septic Shock database; however, the mortality endpoints presented reflect and incorporate excess mortality due to bleeding, or transfusion.

CONCLUSIONS

In this retrospective, 2:1 propensity-matched, multicenter cohort study, the use of rhAPC in patients with septic shock was associated with a significant reduction in 30-day mortality. Decreasing baseline mortality over time and reduced delays in the administration of appropriate antimicrobial therapy may have contributed to the null results of the recently completed trial of rhAPC in patients with septic shock.

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