Published in final edited form as:

J Crit Care. 2010 December ; 25(4): 658.e7–658.e15. doi:10.1016/j.jcrc.2010.04.010.

Results from the National Sepsis Practice Survey: Use of drotrecogin alfa (activated) and other therapeutic decisions

James M. O'Brien Jr., MD, MSc,

Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Center for Critical Care, Department of Internal Medicine, The Ohio State University Medical Center, 201 Davis HLRI, 473 West 12th Avenue, Columbus, OH 43210

Scott K. Aberegg, MD, MPH,

Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Center for Critical Care, Department of Internal Medicine, The Ohio State University Medical Center, 201 Davis HLRI, 473 West 12th Avenue, Columbus, OH 43210

Naeem A. Ali, MD,

Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Center for Critical Care, Department of Internal Medicine, The Ohio State University Medical Center, 201 Davis HLRI, 473 West 12th Avenue, Columbus, OH 43210

Gregory B. Diette, MD, MHS, and

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Johns Hopkins School of Medicine, 1830 East Monument, 5th Floor, Baltimore, MD 21205

Stanley Lemeshow, PhD

College of Public Health, The Ohio State University, 320 West 10th Avenue, M-116 Starling-Loving Hall, Columbus, OH 43210

James M. O'Brien: James.O'Brien@osumc.edu; Scott K. Aberegg: scottaberegg@gmail.com; Naeem A. Ali: Naeem.Ali@osumc.edu; Gregory B. Diette: gdiette@jhmi.edu; Stanley Lemeshow: Lemeshow.1@osu.edu

Abstract

Purpose—We sought to evaluate factors associated with choices about provided care for patients with septic shock, including the use of drotrecogin alfa (activated) [DAA].

Materials and Methods—We administered a mail-based survey to a random sample of intensivists. Study vignettes presented patients with septic shock with identical severity of illness scores but different ages, body mass indices and co-morbidities. Respondents estimated outcomes and selected care beyond standardized initial care (e.g. antibiotics) for each hypothetical patient.

Results—For the majority of vignettes (99.1%), respondents added care, most commonly low tidal volume ventilation (87.6%) and enteral nutrition (73.3%). Choosing to administer DAA was not associated with predictions about mortality or bleeding. Vignettes with early-stage lung cancer were less likely to receive DAA. Time since medical school graduation was also associated with

Corresponding author: James M. O'Brien, Jr., MD, MSc, The Ohio State University Medical Center, Division of Pulmonary, Allergy, Critical Care and Sleep, Center for Critical Care, 201 Davis HLRI, 473 West 12th Avenue, Columbus, OH 43210, (614)247-7707, Fax (614)293-4799, James.O'Brien@osumc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

lower odds of selecting DAA. The majority of respondents (52.6%) chose identical care for all four completed vignettes.

Conclusions—There was wide variability in the therapeutic choices of respondents. The use of DAA was not associated with perceived risk of mortality or bleeding, as recommended by consensus guidelines. Physicians appear to base treatment decisions in septic shock on a consistent pattern of practice rather than estimates of patient outcome.

Keywords

Sepsis; septic shock; variation in care; drotrecogin alfa activated; acute lung injury

Introduction

Sepsis affects approximately 750,000 US patients annually and is a common cause of death [1,2]. The Surviving Sepsis Campaign has published guidelines for the management of severe sepsis and septic shock in an effort to provide direction about the appropriateness of various treatments [3,4]. Included in these guidelines are therapies thought to have value specifically in septic patients (e.g., drotrecogin alfa (activated) [DAA], corticosteroids) and those which have evidence for a broader range of critically ill patients (e.g., glucose control, nutrition).

Studies in various care settings [5–9], including in intensive care units [10–13], have shown variation in practice and outcomes, not explained by patient characteristics, such as severity of illness. We have previously shown that physicians with experience in treating septic shock predict a wide range of outcomes for hypothetical patients and that these predictions are associated with recommendations to limit care with curative intent [14].

In the current study, we sought to determine if there was variability in chosen care for standardized vignettes of septic shock or if a consensus emerged for particular therapeutic choices. We hypothesized that there would be a lack of a consensus as to the treatment of septic shock patients, beyond antibiotics, volume resuscitation, and supportive care. DAA is a recombinant form of activated protein C and is the only therapy specifically approved for severe sepsis. DAA is most effective in those at greatest risk of death [15,16] and it is suggested that predicted mortality risk be used in selecting appropriate candidates for treatment [3,4,17]. Since DAA also increases bleeding [18], physicians must also estimate the risk of bleeding to determine the risk-benefit profile for each patient [4,17]. Because of existing data and consensus recommendations, we hypothesized that the use of DAA would be associated with higher estimates of hospital mortality and lower estimates of bleeding by respondents choosing to use DAA.

Materials and methods

Study sample and questionnaire

The study design and vignette design has been described in detail elsewhere [14]. Briefly, we randomly selected potential subjects from members of the Critical Care Assembly of the American Thoracic Society with a US mailing address. The study was reviewed by the Planning Committee of the Assembly and approved by the Ohio State University Biomedical Institutional Review Board. From 18 June to 24 September, 2007, we mailed self-administered surveys including a letter explaining the study purpose and a stamped return envelope. The initial mailing included \$10 cash incentive. Non-respondents received a duplicate survey 30 days after the initial mailing with no additional incentive. We mailed

762 surveys and received a response rate of 40.8%, representing 81.4% of the projected sample size for the primary outcome analysis.

Vignettes (see Additional Data File for “lowest risk” vignette) involved a male patient with community-acquired pneumonia who received initial care, including mechanical ventilation, volume resuscitation, and antibiotics. All had an acute physiology and chronic health evaluation (APACHE) II score of 25 with sepsis-associated shock, respiratory failure, and lactic acidosis. The patient was admitted to the ICU for further care. No patient preferences regarding goals of care were provided. Each patient had either a normal BMI (22 kg/m²) or an obese BMI (40 kg/m²), was either younger (50 years) or older (70 years), and had either no co-morbidities or recently diagnosed stage IIA non-small cell lung cancer. All respondents received the vignettes with the lowest (50 years old, no co-morbidities, normal BMI) and highest (70 years old, stage IIA non-small cell lung cancer, obese BMI) predicted mortality rates from pilot testing. Two additional vignettes were randomly selected for each survey with weighting designed to provide adequate sample sizes for comparisons of interest. The order of the vignettes within each survey was random.

For each vignette, respondents were asked if they would choose additional therapies, and, if so, which ones. Respondents were asked to predict outcomes, including the probability of hospital survival (referred to as ‘baseline mortality’) and a serious bleeding event (referred to as “baseline bleeding risk”) without additional interventions chosen after ICU admission. Respondents indicated their prediction by placing an ‘X’ on visual-analog scale, represented by a 10 cm horizontal line. All outcome predictions were determined by measuring the location of the X placed on the visual-analog scale in millimeters. We also collected demographic information about respondents.

Statistical plan

As reported previously, our primary hypothesis was that the studied patient factors would be associated with the predicted probability of hospital survival without additional interventions chosen after ICU admission (or baseline mortality) [14]. An *a priori* secondary hypothesis was that the use of drotrecogin alfa (activated) would be associated with respondent predictions about baseline mortality and baseline risk of serious bleeding. Exploratory analyses were also planned to determine vignette and respondent factors associated with other chosen care. We have previously published results of analyses related to limitation of care with curative intent [14].

The unit of analysis for all results was the individual study vignette. Each respondent completed multiple vignettes (up to four), so we used analyses which accounted for this non-independence (proc survey logistic). We considered responses to the same vignette by different respondents to be independent.

We defined our risk-adjusting methodology using an *a priori* plan. For the use of DAA, we included clinical factors from the vignettes (because they were a component of the experimental design) and predictions about baseline mortality and risk of serious bleeding (because these are recommended determinants of use), regardless of statistical significance. In a stepwise fashion, we then included additional respondent factors which were significantly associated with DAA use in the above model ($p < 0.05$) and/or altered the parameter estimate or odds ratio of any of the patient factors or predictions by at least 15%. For the risk-adjusting analyses for other chosen care, we again included clinical factors from the vignettes (regardless of statistical significance). In a stepwise fashion, predictions about baseline mortality, bleeding and problems with washing and dressing oneself in six month (assuming survival) and respondent factors were included if they were significantly

associated with the adjusted odds of each care practice ($p < 0.05$) and/or altered the parameter estimate or odds ratio of any of the patient factors by at least 15%.

We analyzed continuous variables with fractional polynomials to determine if transformation or categorization was appropriate and in no instance was this suggested. We used SAS (v9.1, SAS Institute, Inc., Cary, NC, USA) or Stata (SE10.0, StatCorp LP, College Station, TX, USA) for all analyses. These data were previously presented in abstract form at the 2008 American Thoracic Society International Conference [19].

Results

Additional chosen care

In the majority (99.1%) of vignettes, additional care was added, most commonly low tidal volume ventilation, enteral nutrition and strict regulation of glucose (Table 1). For only one practice were respondents consistent in their choice for greater than 90% of vignettes, namely the omission of "early" tracheostomy in 94.1% of vignettes. In 208 vignettes (18.5%), care other than those choices provided was suggested. Table 1 displays the alternate care practices chosen in at least 1% of vignettes.

Use of drotrecogin alfa (activated)

Drotrecogin alfa (activated) (DAA) was chosen in 55.9% of vignettes. Neither predicted baseline mortality nor risk of serious bleeding was associated with DAA administration (Table 2). The baseline risk of serious bleeding ranged from 1% to 94% with a median predicted risk of serious bleeding of 24%. As reported previously, there was a wide range of predictions regarding baseline mortality [14]. Increasing age of the physician respondent and increasing decades since medical school graduation were associated with lower odds of choosing DAA. Since these variables were co-linear, only decades since medical school graduation were included in the multivariable model. In the final multivariable model, early-stage lung cancer was associated with 24% lower odds of choosing DAA and every decade since medical school graduation was associated with 26% lower odds of DAA use. Inclusion of respondent recommendations to limit care with curative intent was not significantly associated with the choice of DAA and did not appreciably change the factors associated with DAA use (data not shown).

Among respondents completing all four assigned vignettes, the majority either gave DAA to all of their hypothetical patients ($n=124$, 45.8%) or to none ($n=93$, 34.3%). The remainder ($n=54$, 19.9%) were discretionary in their administration of DAA. Among the respondents who were discretionary in DAA use, older patient age and early-stage lung cancer were associated with 62% and 74% lower odds of DAA administration, respectively (Table 2). Neither baseline estimates of mortality or serious bleeding complications was associated with the odds of DAA administration in the final multivariable analysis. Time since the respondent completed medical school was no longer included in the model, based on our variable selection strategy. Respondent recommendations to limit care with curative intent in the multivariable models was not independently associated with the choice of DAA and did not change the observations about DAA choice among discerning respondents (data not shown).

Selection of other care

Table 3 shows the results of the multivariable analyses regarding factors associated with the choice of additional care. The only vignette factor independently associated with the choice of a particular practice was an 85% increased adjusted odds of "early" tracheostomy if the patient had an obese BMI rather than a normal BMI. Higher baseline predicted mortality

was associated with increased adjusted odds of choosing to administer additional antibiotics and to use low tidal volume ventilation. Higher predicted problems with washing and dressing oneself in six months (assuming survival and prior to the addition of any additional care) was associated with significantly higher adjusted odds of early tracheostomy. The number of decades since medical school graduation was associated with higher adjusted odds of choosing to use low-dose corticosteroids. The adjusted odds of choosing low tidal volume ventilation were lower among respondents employed in private practice and higher among those with critical care specialization. Private practice employment was also associated with higher independent odds of attempts to maintain normoglycemia.

Consistency of chosen care

Among individual respondents, there was consistency in additional care chosen. Table 4 shows that among respondents completing all four assigned vignettes, the majority of respondents either consistently chose or omitted each practice for all vignettes each respondent completed. Respondents showed the greatest degree of discrimination in the administration of DAA (given to some, but not all vignettes by 19.9% of respondents). Over half of respondents (52.6%) chose identical care for all six offered care practices for all four vignettes ($p < 0.0001$ compared to probability based on chance alone). Despite the consistent patterns of chosen care by individual respondents, there was considerable equipoise between respondents in the use or omission of offered care. Only "early" tracheostomy (omitted in all vignettes by 87.1% of respondents) and low tidal volume ventilation (selected in all vignettes by 84.1% of respondents) were chosen in a consistent manner by more than 70% of respondents.

Discussion

In this mail-based survey of physicians with experience caring for septic patients, the selection of DAA was not influenced by the physician's estimate of the risk of death or serious bleeding. Vignettes with early-stage lung cancer were less likely to have DAA selected and increasing time since medical school graduation was associated with lower odds of choosing DAA. Among the remaining choices for additional care, respondent predictions and vignette and respondent characteristics and were inconsistently associated with such choices. Across all respondents, there was no clear consensus for appropriate care. However, the majority of respondents chose the same combination of care for all of their individually completed vignettes.

The observed rate of DAA administration in this study (56%) greatly exceeds that in a recent observational study (6.5%) [20]. Because the current study used case-based vignettes, it is likely more accurate at measuring the intent to provide care, rather than the actual care provided. In at least one study, there is discordance between the perception of provided care and that which is actually provided to patients [21]. However, some of this may be due to differences between the perceptions of ICU directors, who were the subjects of that study, and the actual care which is decided by individual practitioners. While not specifically studied in sepsis, vignette-based studies have been found to be a valid measure of actual care [22,23]. Besides a difference between the intent to provide care and actual delivery, it is possible that characteristics of the vignette (e.g., enumerating organ failures and APACHE II score) caused respondents to over-report their actual use of DAA. However, we suspect that any possible over-reporting of DAA use is less likely to confound the observed lack of association between predicted mortality risk and selection of DAA, which was the primary focus of the study.

DAA appears to have the greatest benefit to risk ratio for patients at the highest risk of death from severe sepsis and the lowest risk of bleeding [16,24]. This is reflected in DAA labels

endorsed by the U.S. Food and Drug Administration [25] and the European Medicine Agency [26]. The study vignettes portray a patient with multi-organ system failure for whom the median baseline mortality predicted by respondents was 47% [14]. Compared to patients assigned to placebo in the pivotal study of DAA, this predicted mortality is higher than that seen among patients with three sepsis-related organ failures (34%) and among those with an APACHE II score of 25–30 (39%) [27]. Respondents also predicted a rate of serious bleeding which greatly exceeded that observed in clinical trials of DAA in subjects assigned to placebo [16,24].

In our experience, some clinicians use an APACHE II score greater than or equal to 25 as a threshold for treatment with DAA. If such a threshold were sufficient indication for treatment, we would expect DAA to have been chosen universally in the study. If, instead, the APACHE II score is a necessary (but not sufficient) indicator for treatment, we would expect decisions about DAA use to be driven by individual assessments of risks of dying and bleeding. However, there was no association between the predictions study respondents made about the risk of mortality or serious bleeding and the use of DAA. Even among respondents who discriminated amongst the vignettes regarding DAA administration, risk of death and bleeding were not associated with choosing DAA. While one might argue that the assessments of mortality and bleeding risk in this study are subjective and prone to variation, we suspect the process by which respondents made predictions about such events is similar to what occurs when these same respondents are caring for septic patients.

It is possible that the observed rate of DAA use is influenced by factors other than the perceived mortality and bleeding risks for each patient. The lack of benefit of DAA in subsequent studies of severe sepsis [24,28], concerns about changes in study design and DAA production in the study showing benefit [29,30] and perceived conflicts of interest in severe sepsis treatment guidelines [31] may affect clinicians' belief in the effectiveness of the drug. As a result of these remaining questions, DAA was only *suggested* for use in adult patients with severe sepsis with a clinical assessment of high risk of death [4]. However, current recommendations are that "each patient being considered for therapy...should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy" [25]. We suspect that remaining questions about the safety and effectiveness of DAA would lead some clinicians to avoid its use altogether. Among those who use DAA in any instance, an assessment of severity of illness and risk of bleeding would be evidence-based approach to patient selection for therapy. Our data suggest that, among those who chose DAA for any patient, neither the respondent's assessment of risk of death or serious bleeding was associated with the use of DAA. These findings suggest that, among those clinicians using DAA, its use is due to factors other than these risk assessments

Unlike risk of sepsis-related mortality and serious bleeding, the presence of early-stage lung cancer was associated with lower odds of the use of DAA. While such restriction may be appropriate if care with curative intent is otherwise limited, inclusion of respondent recommendations to limit aggressive supportive care did not affect this observation, arguing against such an explanation. For every decade since a respondent graduated from medical school, the odds of him or her choosing DAA dropped by 26%. This is a finding consistent with conclusions of a systematic review which found that older physicians and those who have been in practice longer are less likely to provide evidence-based therapies [32].

Only one offered process of care was "chosen" in more than 90% of vignettes – not performing tracheostomy during the first week of mechanical ventilation. This suggests a general lack of consensus between clinicians experienced in caring for septic patients and the most appropriate care. There appeared to be greater agreement on the use of certain practices (e.g. low tidal volume ventilation, not performing early tracheostomy) than others

(e.g. use of DAA, low-dose corticosteroids). It is possible that aspects of care for which greater consensus might exist were provided as default in the vignette as an intended design of the survey instrument. A survey of critical care nurses across U.S hospitals suggests that there was greater consensus in the use of the practices provided consistently across the study vignettes (e.g. vasopressors, thromboembolism prophylaxis) than those at the discretion of the study respondents (e.g. DAA, corticosteroids) [33]. Therefore, our selection of the therapeutic practices available to respondents could under-estimate the actual consensus regarding sepsis care.

While respondents varied substantially from one another in the therapies they chose for hypothetical patients, there was a striking consistency in the therapeutic approaches of each respondent to different hypothetical patients. A majority (52.6%) of individual respondents chose identical care for all completed vignettes, a result that is highly unlikely to occur by chance alone (0.00005% for seven practices across four vignettes). In contrast, individual respondents' predictions of baseline patient mortality varied based on vignettes factors, with an average difference between the highest and lowest of the four vignettes of 24.9% [14]. These findings suggest that the therapies a hypothetical patient received depended on the practice patterns of the physician respondent, rather than on the characteristics of the patient or on the respondent's estimates of the patient's outcomes. For treatments for which there are not high levels of evidence, it is reasonable that a clinician might choose different treatment plan than his colleague and apply this consistently to all patients. However, an association between patient outcomes and care practices now produces a lack of independence of observed outcomes between different clinicians' patients. In analyzing patient outcomes in observational studies, these effects due to the clinician should be considered to reduce bias. While less likely to be prone to such bias, randomized clinical trials may not be immune. Differences in care practices among clinical teams could affect the observed results by providing overly influential results to the study cohort (e.g., all subjects from a clinician who practices in a manner which affects outcome are assigned to a single treatment arm by chance).

That we are aware, this is the first study which demonstrates disparities in *provider* practice specifically for septic patients. Variation in care for severe sepsis patients has been demonstrated across U.S. academic medical centers but individual providers were not studied [34]. A study in Germany, where a country-wide approach to sepsis care has been established, found no statistically significant difference in sepsis care between intensive care units [21]. One single-center study demonstrated significant variation in daily discretionary costs (pharmacy, radiology, laboratory, blood bank and echocardiography) of care for ICU patients between individual providers but did not focus on sepsis [35]. The same investigators found variation in decisions to limit the use of life support between providers [36] and the decision to limit care with curative intent was associated with greater mortality, independent of severity of illness [37]. An association between differences in care with curative intent, as demonstrated in this study, and outcome remains unproven.

There are important limitations to these findings. Our response rate was below our projections, but it exceeded the reported rates of many mail-based survey studies involving physicians [38,39]. By incorporating randomization, a non-responder was as likely to receive a vignette as a responder, reducing the likelihood of biased results. This study was designed to examine respondent predictions about outcome and factors associated with choices about DAA, so the evaluation of other care practices should be conservatively considered post hoc analyses. We used multivariable techniques in an effort to adjust for possible confounding. However, we were limited in adjusting for factors collected in the survey and cannot exclude the possibility of residual confounding affecting the observed results. It is unknown if our findings can be generalized to physicians beyond those forming

the bulks of our study cohort, including non-U.S. physicians, those with less experience in caring for septic patients and non-medical intensivists. We are also uncertain as to the influence of the timing of the survey administration and existing evidence on the results. For example, the primary studies of DAA in adults were published in March 2001 [16] and September 2005 [24]. The initial Surviving Sepsis Campaign guidelines for the management of severe sepsis, including the use of DAA, were published in March 2004 [3] and updated in January 2008 [4]. This survey was administered between June and September 2007. While the results of the clinical trials were available to respondents, it is unclear how the revised guidelines (which were published several months after survey administration) might have influenced decisions about the use of DAA. While changes in the guidelines might have influenced the overall rate of use of DAA, we would still expect an association between predicted baseline mortality risk and bleeding risk and DAA use as this was included in both versions of the guidelines.

Conclusions

The majority of physicians with experience in treating sepsis select therapeutic interventions beyond antibiotics, volume resuscitation and support for organ failures. However, there is not a clear consensus for the appropriate treatment of septic shock patients. The choice of DAA therapy is not associated with assessments of mortality and bleeding risk, as recommended in consensus guidelines. The majority of individual physicians chose identical care for septic shock patients with variable clinical characteristics. It is possible that the disparities observed in this study of simulated septic shock patients exist in actual care and that these differences may also be associated with differences in outcomes. Appreciation of and adjustment for differences in provided care in observational studies and clinical trials may allow for more accurate assessment of factors associated with outcome in sepsis patients and improve care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of support: JMO is supported by the Davis/Bremer Medical Research Grant and NIH K23 HL075076

Reference List

1. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348:1546–1554. [PubMed: 12700374]
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303–1310. [PubMed: 11445675]
3. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32:858–873. [PubMed: 15090974]
4. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;36:296–327. [PubMed: 18158437]
5. Wennberg JE, Freeman JL, Shelton RM, Bubolz TA. Hospital use and mortality among Medicare beneficiaries in Boston and New Haven. *N Engl J Med* 1989;321:1168–1173. [PubMed: 2677726]

6. Wennberg JE, Freeman JL, Culp WJ. Are hospital services rationed in New Haven or over-utilised in Boston? *Lancet* 1987;1:1185–1189. [PubMed: 2883497]
7. Welch HG, Miller ME, Welch WP. Physician profiling. An analysis of inpatient practice patterns in Florida and Oregon. *N Engl J Med* 1994;330:607–612. [PubMed: 8302344]
8. Burns LR, Wholey DR. The effects of patient, hospital, and physician characteristics on length of stay and mortality. *Med Care* 1991;29:251–271. [PubMed: 1997754]
9. Greenfield S, Nelson EC, Zubkoff M, Manning W, Rogers W, Kravitz RL, Keller A, Tarlov AR, Ware JE Jr. Variations in resource utilization among medical specialties and systems of care. Results from the medical outcomes study. *JAMA* 1992;267:1624–1630. [PubMed: 1542172]
10. Angus DC, Linde-Zwirble WT, Sirio CA, Rotondi AJ, Chelluri L, Newbold RC III, Lave JR, Pinsky MR. The effect of managed care on ICU length of stay: implications for medicare. *JAMA* 1996;276:1075–1082. [PubMed: 8847771]
11. Rapoport J, Teres D, Steingrub J, Higgins T, McGee W, Lemeshow S. Patient characteristics and ICU organizational factors that influence frequency of pulmonary artery catheterization. *JAMA* 2000;283:2559–2567. [PubMed: 10815120]
12. Rapoport J, Teres D, Barnett R, Jacobs P, Shustack A, Lemeshow S, Norris C, Hamilton S. A comparison of intensive care unit utilization in Alberta and western Massachusetts. *Crit Care Med* 1995;23:1336–1346. [PubMed: 7634803]
13. Rapoport J, Gehlbach S, Lemeshow S, Teres D. Resource utilization among intensive care patients. Managed care vs traditional insurance. *Arch Intern Med* 1992;152:2207–2212. [PubMed: 1444680]
14. O'Brien JM Jr, Aberegg SK, Ali NA, Diette GB, Lemeshow S. Results from the national sepsis practice survey: predictions about mortality and morbidity and recommendations for limitation of care orders. *Crit Care* 2009;13:R96. [PubMed: 19549300]
15. Ely EW, Laterre PF, Angus DC, Helterbrand JD, Levy H, Dhainaut JF, Vincent JL, Macias WL, Bernard GR. Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. *Crit Care Med* 2003;31:12–19. [PubMed: 12544987]
16. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699–709. [PubMed: 11236773]
17. Xigris: Drotrecogin alfa (activated). U S Food and Drug Administration Center for Drug Evaluation and Research; 2008.
18. Bernard GR, Macias WL, Joyce DE, Williams MD, Bailey J, Vincent JL. Safety assessment of drotrecogin alfa (activated) in the treatment of adult patients with severe sepsis. *Crit Care* 2003;7:155–163. [PubMed: 12720562]
19. O'Brien J, Kearns M, Aberegg S, Ali N, Marsh C, Lemeshow S. Factors associated with predicted mortality of septic shock patients: Results from the National Sepsis Practice Survey. *Am J Resp Crit Care Med* 2008;177:A958.
20. Ferrer R, Artigas A, Suarez D, Palencia E, Levy MM, Arenzana A, Perez XL, Sirvent JM. Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. *Am J Respir Crit Care Med* 2009;180:861–866. [PubMed: 19696442]
21. Brunkhorst FM, Engel C, Ragaller M, Welte T, Rossaint R, Gerlach H, Mayer K, John S, Stuber F, Weiler N, Oppert M, Moerer O, Bogatsch H, Reinhart K, Loeffler M, Hartog C. Practice and perception--a nationwide survey of therapy habits in sepsis. *Crit Care Med* 2008;36:2719–2725. [PubMed: 18766100]
22. Walter SD, Cook DJ, Guyatt GH, Spanier A, Jaeschke R, Todd TR, Streiner DL. Confidence in life-support decisions in the intensive care unit: a survey of healthcare workers. Canadian Critical Care Trials Group *Crit Care Med* 1998;26:44–49.
23. Diette GB, Patino CM, Merriman B, Paulin L, Riekert K, Okelo S, Thompson K, Krishnan JA, Quartey R, Perez-Williams D, Rand C. Patient factors that physicians use to assign asthma treatment. *Arch Intern Med* 2007;167:1360–1366. [PubMed: 17620528]
24. Abraham E, Laterre PF, Garg R, Levy H, Talwar D, Trzaskoma BL, Francois B, Guy JS, Bruckmann M, Rea-Neto A, Rossaint R, Perrotin D, Sablotzki A, Arkins N, Utterback BG, Macias

- WL. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005;353:1332–1341. [PubMed: 16192478]
25. Drotrecogin alfa (activated). United States Food and Drug Administration Center for Drug Evaluation and Research; 2008. p. 1-9.
 26. Xigris. European Medicines Agency; 2008.
 27. Drotrecogin alfa (activated) [recombinant human activated protein C (rhAPC)]. Food and Drug Administration Briefing Document; 2001.
 28. Nadel S, Goldstein B, Williams MD, Dalton H, Peters M, Macias WL, Abd-Allah SA, Levy H, Angle R, Wang D, Sundin DP, Giroir B. Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial. *Lancet* 2007;369:836–843. [PubMed: 17350452]
 29. Warren HS, Suffredini AF, Eichacker PQ, Munford RS. Risks and benefits of activated protein C treatment for severe sepsis. *N Engl J Med* 2002;347:1027–1030. [PubMed: 12324562]
 30. Eichacker PQ, Natanson C. Recombinant human activated protein C in sepsis: inconsistent trial results, an unclear mechanism of action, and safety concerns resulted in labeling restrictions and the need for phase IV trials. *Crit Care Med* 2003;31:S94–S96. [PubMed: 12544982]
 31. Eichacker PQ, Natanson C, Danner RL. Surviving sepsis—practice guidelines, marketing campaigns, and Eli Lilly. *N Engl J Med* 2006;355:1640–1642. [PubMed: 17050887]
 32. Choudhry NK, Fletcher RH, Soumerai SB. Systematic review: the relationship between clinical experience and quality of health care. *Ann Intern Med* 2005;142:260–273. [PubMed: 15710959]
 33. Durthaler JM, Ernst FR, Johnston JA. Managing severe sepsis: a national survey of current practices. *Am J Health Syst Pharm* 2009;66:45–53. [PubMed: 19106344]
 34. Yu DT, Black E, Sands KE, Schwartz JS, Hibberd PL, Graman PS, Lanken PN, Kahn KL, Snyderman DR, Parsonnet J, Moore R, Platt R, Bates DW. Severe sepsis: variation in resource and therapeutic modality use among academic centers. *Crit Care* 2003;7:R24–R34. [PubMed: 12793887]
 35. Garland A, Shaman Z, Baron J, Connors AF Jr. Physician-attributable differences in intensive care unit costs: a single-center study. *Am J Respir Crit Care Med* 2006;174:1206–1210. [PubMed: 16973977]
 36. Garland A, Connors AF. Physicians' influence over decisions to forego life support. *J Palliat Med* 2007;10:1298–1305. [PubMed: 18095808]
 37. Chen YY, Connors AF Jr, Garland A. Effect of decisions to withhold life support on prolonged survival. *Chest* 2008;133:1312–1318. [PubMed: 18198259]
 38. Asch DA, Jedrzejewski MK, Christakis NA. Response rates to mail surveys published in medical journals. *J Clin Epidemiol* 1997;50:1129–1136. [PubMed: 9368521]
 39. Cummings SM, Savitz LA, Konrad TR. Reported response rates to mailed physician questionnaires. *Health Serv Res* 2001;35:1347–1355. [PubMed: 11221823]

Table 1
Additional care chosen after ICU admission

All vignettes represented a male patient with septic shock and multiorgan failure due to community-acquired pneumonia. All vignettes received antibiotics, volume resuscitation and organ support for shock and respiratory failure. Respondents were asked to select additional care to provide upon ICU admission. Respondents could also select no additional care or provide additional care as free text.

Care chosen	Vignettes in which care was selected, N (%)
Use low tidal volume ventilation (e.g. 6ml/kg predicted body weight)	985 (87.6%)
Begin enteral nutrition	825 (73.3%)
Maintain strict normoglycemia with insulin infusion (e.g. 80–110 mg/dl)	745 (66.2%)
Add drotrecogin alfa (activated)	629 (55.9%)
Add low-dose (e.g. 200 mg/day hydrocortisone) corticosteroids	601 (53.4%)
Add additional antibiotics	425 (37.8%)
Perform early (e.g. first week of ventilation) tracheostomy	66 (5.9%)
No change in current care	10 (0.9%)
Other care (specified by respondent) *	208 (18.5%)
Assess adrenal function (e.g. ACTH stimulation test)	50 (4.4%)
Vasopressin	49 (4.4%)
Use ICU prophylaxis measures (e.g., semi-recumbent position)	34 (3.0%)
Less intense control of blood glucose	22 (2.0%)
Increase and/or add catecholamine vasopressor	21 (1.9%)
Discuss goals of care	14 (1.2%)
Continue resuscitation to specified hemodynamic goals	12 (1.1%)

* Only care chosen in at least 1% of vignettes is shown.

Table 2
Factors associated with selection of drotrecogin alfa (activated)

All vignettes represented a male patient with septic shock and multiorgan failure due to community-acquired pneumonia. All vignettes received antibiotics, volume resuscitation and organ support for shock and respiratory failure. Respondents were asked to select additional care to provide upon ICU admission. Respondents could also select no additional care or provide additional care as free text. Mortality and bleeding predictions were estimated prior to any additional chosen care, including drotrecogin alfa (activated). The adjusted odds ratios and confidence intervals represent the regression including all displayed variables (see **Methods** for variable selection strategy). Analyses including “all respondents” included all returned surveys. Analyses including “discriminating respondents” only included surveys in which respondents chose DAA for some, but not all vignettes.

	All respondents (n=271)		Respondents who discriminated in choosing DAA (n=54)	
	Adjusted odds ratio (95% C.I.)	p value	Adjusted odds ratio (95% C.I.)	p value
70-years old (versus 50-years old)	0.81 (0.63 – 1.04)	0.10	0.39 (0.19 – 0.80)	0.01
Stage IIA NSCLC (versus no cancer)	0.76 (0.59 – 0.99)	0.04	0.24 (0.12 – 0.51)	<0.01
BMI 40 kg/m ² (versus 22 kg/m ²)	0.93 (0.74 – 1.17)	0.53	0.70 (0.34 – 1.44)	0.33
Baseline predicted hospital mortality (per 10% increase)	1.07 (0.96 – 1.19)	0.25	0.99 (0.84 – 1.16)	0.86
Baseline predicted probability of a serious bleeding event (per 10% increase)	0.98 (0.88 – 1.09)	0.72	1.00 (0.88 – 1.17)	0.86
Decades since respondent's medical school graduation	0.74 (0.59 – 0.93)	0.01	1.25 (0.92 – 1.69)	0.16

95% C.I. = 95% confidence interval; BMI = body mass index; NSCLC = non-small cell lung carcinoma.

Table 3

Factors associated with additional chosen care

All vignettes represented a male patient with septic shock and multiorgan failure due to community-acquired pneumonia. All vignettes received antibiotics, volume resuscitation and organ support for shock and respiratory failure. Respondents were asked to select additional care to provide upon ICU admission. Respondents could also select no additional care or provide additional care as free text. Baseline mortality was considered the predicted mortality if no additional care, other than the care instituted prior to admission to the intensive care unit (ICU), was added. Respondents were asked to provide estimates of problems washing and dressing himself at six months, assuming the patient survived. The top row indicates the outcome for each regression model with the column below displaying the adjusted odds ratios and confidence intervals of the variables included in that model (see **Methods** for variable selection strategy).

	Add antibiotics	Add low-dose corticosteroids	Use low tidal volume ventilation	Maintain strict normoglycemia	Perform early tracheostomy	Begin enteral nutrition
Vignette factors						
70-years old (versus 50-years old)	1.12 (0.87 – 1.45)	1.14 (0.91 – 1.41)	0.85 (0.58 – 1.24)	0.86 (0.67 – 1.09)	0.86 (0.53 – 1.42)	0.90 (0.64 – 1.16)
Stage IIA NSCLC (versus no cancer)	0.57 (0.82 – 1.42)	1.14 (0.89 – 1.45)	0.70 (0.47 – 1.04)	1.13 (0.89 – 1.44)	1.02 (0.61 – 1.69)	1.00 (0.76 – 1.32)
BMI 40 kg/m ² (versus 22 kg/m ²)	0.90 (0.72 – 1.12)	0.86 (0.70 – 1.06)	0.86 (0.60 – 1.24)	1.05 (0.84 – 1.31)	1.85 (1.09 – 3.14)	0.90 (0.70 – 1.14)
Respondent predictions (per 10% increase in predicted outcome)						
Baseline predicted hospital mortality	1.33 (1.18 – 1.50)		1.25 (1.06 – 1.47)			
Predicted problems washing and dressing self					1.15 (1.00 – 1.32)	0.04
Respondent factors						
Decades since medical school graduation		1.30 (1.03 – 1.63)				
Employed in private practice			0.34 (0.16 – 0.76)	2.32 (1.43 – 3.78)		

	Specialty in critical care medicine	Add antibiotics		Add low-dose corticosteroids		Use low tidal volume ventilation		Maintain strict normoglycemia		Perform early tracheostomy		Begin enteral nutrition	
						3.09 (1.17 – 8.14)	<0.01						

BMI = body mass index; NSCLC = non-small cell lung carcinoma.

Table 4
Consistency of care practices chosen by respondents

The table indicates the number of respondents choosing particular care for a patient with septic shock after ICU admission. Only respondents completing all four vignettes in his/her survey (n=271, 93.8% of respondents) are included.

	Selected for ALL vignettes	Selected for NONE of the vignettes	Respondent either selected vignettes for ALL vignettes or NONE of the vignettes
Use low tidal volume, n (%)	228 (89.8%)	26 (10.2%)	254 (93.7%)
Maintain strict normoglycemia, n (%)	169 (66.8%)	84 (33.2%)	253 (93.4%)
Begin enteral nutrition, n (%)	182 (74.3%)	63 (25.7%)	245 (90.4%)
Use low-dose corticosteroids, n (%)	132 (54.3%)	111 (45.7%)	243 (89.7%)
Perform "early" tracheostomy, n (%)	4 (1.7%)	236 (98.3%)	240 (88.6%)
Add additional antibiotics, n (%)	82 (36.6%)	142 (63.4%)	224 (82.7%)
Add drotrecogin alfa (activated), n (%)	124 (57.1%)	93 (42.9%)	217 (80.1%)
Selected same care across ALL processes and ALL vignettes			143 (52.6%)