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Reasons for death in patients with sepsis and septic shock^{★,★★}

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Abstract

Purpose—sepsis has broad implications for both clinical care and interventional trial design. However, reasons for death in sepsis remain poorly understood. We sought to characterize reasons for in-hospital mortality in a population of patients with sepsis or septic shock.

Materials and methods—We performed a retrospective review of patients admitted to the intensive care unit with sepsis or septic shock who died during their index admission. Reasons for death were classified into 6 categories determined a priori by group consensus. Interrater reliability was calculated and Fleiss κ reported. The associations between selected patient characteristics (eg, serum lactate) and reason for death were also assessed.

Results—One hundred fifteen patients were included. Refractory shock (40%) and comorbid withdrawal of care (44%) were the most common reasons for death. Overall interrater agreement was substantial ($\kappa = 0.61$, $P < .01$). Lactate was higher in patients who died because of refractory shock as compared with those who died for other reasons (4.7 vs 2.8 mmol/L, $P < .01$).

Conclusion—In this retrospective cohort, refractory shock and comorbid withdrawal of care were the most common reasons for death. Following prospective validation, the classification methodology presented here may be useful in the design/interpretation of trials in sepsis.

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Keywords

Sepsis; Classification; Lactate

1. Introduction

Sepsis is a common and highly morbid clinical syndrome that affects more than 850 000 patients in the United States each year [1]. Although hospital survival rates have been improving over the past decade [2,3], mortality remains high, and sepsis continues to be the most common reason for death in noncardiac intensive care units (ICUs) [4].

To date, clinical and epidemiologic studies in septic populations have typically reported outcomes in terms of crude, all-cause mortality rates [5]. This practice, however, may obscure important heterogeneity in reasons for death among septic patients. Even when reasons for death are reported, there is no standard methodology, and results cannot be easily compared across trials [6]. Understanding the proximal cause of death in patients with sepsis not only is essential to directing the focus of clinical care but also is critical in the design and interpretation of interventional clinical trials. In a study geared toward improving hemodynamic function, for instance, patients who die of hypoxemia should perhaps be interpreted in a different light than those who die as a result of refractory shock. Furthermore, enriching trial cohorts with patients more likely to have a certain reason for death (eg, refractory shock) may limit the administration of a study drug to patients who are unlikely to benefit while allowing for a smaller overall sample size.

In the present study, we developed a methodology for classifying the reason for death in patients with sepsis and septic shock. We then applied this methodology to a retrospective cohort of patients with sepsis or septic shock who died during their hospitalization. Finally, we sought to identify patient characteristics associated with certain reason for death categories.

2. Materials and methods**2.1. Study population**

This was a retrospective, single-center observational cohort study of consecutive patients who were diagnosed with sepsis or septic shock and ultimately died in a tertiary care center between March 2013 and June 2014. Patients were included if they had evidence of systemic hypoperfusion (systolic blood pressure < 90, need for vasopressors, and/or lactate ≥ 4), infection was identified as the primary cause of hypoperfusion (determined via retrospective review of the clinical chart), and the patient died during their hospitalization. Patients were excluded if infection was not the primary cause of hypoperfusion, their age was less than 18 years, and/or there was concomitant pregnancy. The study was approved by the institutional review board at Beth Israel Deaconess Hospital, Boston, MA

2.2. Developing a tool for reporting reason for death

Six categories for cause of death were established and defined by the Center for Resuscitation Science at Beth Israel Deaconess Medical Center. The Center for Resuscitation Science is a multidisciplinary group of physicians from the fields of Emergency Medicine and Critical Care Medicine. The categories were (1) sudden cardiac arrest, (2) refractory shock, (3) respiratory failure, (4) neurologic withdrawal of care, (5) comorbid withdrawal of care, and (6) other. Detailed definitions for these categories can be found in Table 1. The categories and their definitions were arrived at by group consensus.

To distinguish between death related to progressive or sudden organ failure as opposed to withdrawal of care due to poor prognosis, reason for death was dichotomized for some analyses as sudden cardiac arrest, refractory shock, or refractory hypoxemia vs neurologic or comorbid withdrawal of care.

2.3. Retrospective review

Three physicians (YO, AM, SL) independently reviewed the clinical charts of all patients in the cohort. On the basis of these reviews, each patient was placed into 1 of the 6 cause-of-death categories described above.

In addition, the following information was abstracted from the electronic medical record: age, sex, medical comorbidities, initial laboratory values from the hospital admission, and suspected source of infection. Patients who underwent cardiopulmonary resuscitation prior to death were also identified.

2.4. Statistical analysis

Descriptive statistics were used to summarize the study population. Categorical variables are presented as counts and percentages. Fleiss κ was used to estimate agreement between reviewers.

The relationship between selected patient characteristics and dichotomized reason for death were determined by *t* test or Wilcoxon rank sum test as determined by the normality of the data. The assignments made by reviewer 2 were arbitrarily selected and used for these analyses. The same analyses were replicated using the assignments made by reviewer 1 and by reviewer 3, and the results are included in the supplement (Table S1 in the online version at <http://dx.doi.org/10.1016/j.jcrc.2016.11.036>). All statistics were performed using JMP 12 (SAS Institute Inc, Cary, NC).

3. Results

A total of 1568 patients with evidence of systemic hypoperfusion (as defined above) were identified. Of these, 251 (16%) patients died during their hospitalization. In retrospective review of the clinical chart, the primary etiology of hypoperfusion was determined to be infectious in 115 patients (45.8%). These 115 patients comprised the final study cohort. The mean age of the cohort was 70.3 (± 15.0) years, and 49.0% were female. Twenty-two (19.1%) patients had advanced malignancy at time of admission. The most common

suspected source of infection was pulmonary (50.0%). Summary statistics for the patient cohort are included in Table 2.

In the prespecified analysis, there was moderate agreement between the 3 reviewers ($\kappa = 0.55$, $P < .01$) with regard to reason for death. As only 1 reviewer (AM) used the “other” category, a κ statistic was also determined excluding those patients whose reason for death was initially listed as “other.” In addition, while still blinded to the selections of the other 2 reviewers, AM independently reassigned each patient initially listed as “other” into 1 of the other 5 categories that was felt to best fit the circumstances of death, and κ was again calculated. Those patients initially listed as “other” were generally those who had care withdrawn because of expected poor quality of life from sequelae of the acute presenting illness (eg, requirement for tracheostomy after pneumonia and severe acute respiratory distress syndrome).

Excluding patients initially listed as “other” ($n = 14$), there was substantial agreement among all raters with an overall κ of 0.64 ($P < .01$). After the patients initially labeled as “other” were reassigned to 1 of the other 5 categories, substantial agreement remained with a κ of 0.61 ($P < .01$, Fig. 1). The highest interrater agreements were seen in the categories of sudden cardiac arrest, refractory shock, and comorbid withdrawal of care, all of which had a κ of 0.65. The categories of refractory hypoxemia and neurologic withdrawal of care had few patients assigned and had the lowest κ values (Fig. 1). Overall, refractory shock and comorbid withdrawal of care were the most commonly selected causes of death in the cohort (Fig. 1). Only 10 (8.7%) patients ultimately received cardiopulmonary resuscitation prior to death.

The median initial lactate in the cohort was 3.4 mmol/L (interquartile range [IQR], 2.0-5.5). Patients whose reason for death was identified by reviewer 2 as sudden cardiac arrest, refractory shock, or refractory hypoxemia had higher median initial lactate levels than those whose reason for death was identified as neurologic or comorbid withdrawal of care (4.3 mmol/L [IQR, 2.3-6.0] vs 2.7 mmol/L [1.9-4.6], $P = .02$) and tended to be younger (67.7 ± 15.0 vs 73.3 ± 14.6 , $P = .05$). Patients whose reason for death was refractory shock had higher overall median lactate levels than patients with other reasons for death (4.7 mmol/L [IQR, 2.4-6.1] vs 2.8 mmol/L [IQR, 1.9-4.6], $P < .01$). Advanced malignancy was more common in patients who had comorbid withdrawal of care as compared with those who had other causes of death (27.5% vs 12.5%, $P = .04$).

Overall, 37% of patients died within the first 2 days of their ICU admission. The median time until death was longer for patients who underwent neurologic or comorbid withdrawal of care (6.0 [IQR, 2.8-12.3]) as compared with those whose death was attributed to sudden cardiac arrest, refractory shock, or refractory hypoxemia (3.0 [IQR, 1.0-8.0], $P = .01$).

Similar results were seen when using the classifications made by either reviewer 1 or reviewer 3 (Table S1 in the online version at <http://dx.doi.org/10.1016/j.jcrc.2016.11.036>).

4. Discussion

In the present study, we characterized the reasons for death in a cohort of patients admitted to the hospital with sepsis or septic shock. Overall, the most common reasons for death were refractory shock and comorbid withdrawal of care. Certain patient characteristics were associated with the ultimate reason for death. In particular, initial lactate was highest amongst patients who ultimately died because of refractory shock. Patients who died because of comorbid withdrawal of care were more likely to have known, advanced malignancy at the time of admission.

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [7], is a clinical syndrome that can include a very heterogeneous population of critically ill patients [8]. Although attempts have been made to better categorize patients with sepsis into more homogenous categories [9], treatment algorithms and clinical trials frequently include all patients who carry a “sepsis” diagnosis [8]. This may lead to a heterogeneity of treatment effect, in which some patients benefit from a specific intervention whereas others are harmed and the overall effect of that intervention appears ineffective [10]. Ideally, interventions would be targeted to the populations most likely to benefit from a given therapy.

Along these lines, the use of all-cause mortality as an end point in most sepsis clinical trials [5] may obscure potentially beneficial effects of new pharmacologic therapies or interventions, particularly in studies with smaller sample sizes. A novel agent developed to improve hemo-dynamics in sepsis, for instance, may appear ineffective with respect to overall mortality if a large number of patients in a clinical trial have care withdrawn because of advanced cancer and prespecified, conservative goals of care. When all-cause mortality is used as the end point in sepsis trials, the investigational therapy must either possess an exceptionally strong treatment effect or enroll a large enough sample size to overcome the weight of patients who do not stand to benefit from the therapy. The need to distinguish between “all-cause” mortality and “cause-specific” mortality is increasingly well recognized in the cardiology literature [11].

Despite the importance of considering reason for death when designing/interpreting clinical trials in sepsis, no standard reporting methodology exists. Causes of death recorded on death certificates are notoriously inaccurate and do not have a standard format [12,13]. In one large study by Mayr et al [14], the reason for death was determined in 3700 critically ill patients, a minority of whom had been admitted with sepsis. In that study, the most common reason for death was *acute, refractory multiorgan dysfunction* defined as at least 4 failing organs, mean arterial pressure less than 60, and a metabolic derangement (eg, lactate elevation). A total of 55% of patients in that study had potentially life-sustaining treatment withheld or withdrawn prior to death. In the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis trial, an independent committee adjudicated the reason for death in patients who died during the trial. Overall, they determined that 84.2% of deaths were sepsis related and that the most common reason for death was multiple organ failure [6]. In a retrospective review of death from septic shock at a single center in France, the most common cause of death in the first 72 hours after admission was multiple organ

failure due to the primary infection (82%). Deaths after 72 hours were more commonly attributed to end-of-life decisions (29%) and nosocomial infection (20.4%). [15] The 3 recently completed large trials of early goal-directed resuscitation for septic shock chose all-cause mortality as an end point and do not report on the specific reason for death in those who died [16-18].

In the present study, we developed an approach for the categorization of reasons for death among septic patients who die during their hospitalization. We believe that the strength of our classification scheme lies in its ease of use and the inclusion of specific categories for comorbid and neurologic withdrawal of care. In keeping with accepted interpretation criteria (κ 0.0 = poor agreement, 0.01-0.20 = slight, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = substantial, and 0.81-1.0 = almost perfect), the interrater agreement among 3 independent physicians in this study was substantial although not excellent [19,20]. The κ statistic here may underestimate the true level of agreement given the relatively large number of categories from which the physicians could choose [20,21]. Still, the lack of better agreement among the physician reviewers speaks to the difficulty in identifying the specific reason for death in this complex and heterogeneous population. In addition, the retrospective nature of the study limited the information available to the reviewers. We expect better agreement in future, prospective studies using this classification scheme.

Overall, the most common causes of death (regardless of reviewer) were refractory shock and comorbid withdrawal of care. Patients who died because of refractory shock were generally younger, were less likely to have an advanced malignancy, and had higher median initial lactate levels. The suspected source of sepsis did not predict the ultimate reason for death. Although these data should be considered exploratory, we believe that the identification of patient characteristics associated with specific causes of death may allow for future trials to focus on patients most likely to benefit from the studied intervention and potentially exclude those patients likely to have care withdrawn because of preexisting medical comorbidities.

In addition to the research applications of these results, we believe that understanding reasons for death in septic patients has important clinical applications with regard to patient-centered care, quality assurance monitoring, and end-of-life discussions. With respect to patient-centered care, knowing that a patient is at risk of death from cardiovascular collapse, for instance, may be important in tailoring clinical management. For quality assurance, having hospitals track reasons for death in sepsis might allow for intervention if there is an increase in one area or another. Finally, better understanding reasons for death may allow for more focused end-of-life discussions with patients and their families.

The present study had a number of limitations. Foremost, this was a small, single-center study, which limits its external validity. Future studies of this classification scheme should include more patients and additional study sites (including nonacademic, community hospitals). This is especially important as significant variability likely exists with regards to the initial, aggressive care of patients with major life-limiting comorbidities (e.g. advanced malignancy). In addition, the retrospective nature of the work may have contributed to the lower-than-expected interrater agreement.

5. Conclusion

In the present study, we classified reasons for death in a cohort of patients with severe sepsis or septic shock and found that the majority died because of either refractory shock or comorbid withdrawal of care. Furthermore, we identified potential predictors of specific reasons for death. We believe that the reasons-for-death classification system presented here may be useful in the design and interpretation of future clinical trials in sepsis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Reasons for death by reviewer.

Table 1

Reasons for Death Category Definitions.

Reason for death	Definition
Sudden cardiac arrest	Sudden cardiac arrest not preceded by any of the below. Most patients will receive cardiopulmonary resuscitation; however, some patients otherwise receiving full ICU care may have a do-not-resuscitate order. If the patient has a sudden cardiac arrest, is resuscitated, and then later dies as a consequence of the sudden cardiac arrest, the patient should be classified here.
Refractory shock	Death from progressive, refractory hemodynamic shock despite aggressive ICU care. Most patients will have received multiple vasopressors. If the decision to withdraw care is made based on progressive shock with initial aggressive care, the patient should be included here.
Refractory hypoxemia	Death from progressive, refractory respiratory failure/hypoxemia despite aggressive ICU care. Most patients will die on maximum ventilator settings. If the decision to withdraw care is made based on progressive respiratory failure/hypoxemia with initial aggressive care, the patient should be included here.
Neurologic withdrawal of care	Withdrawal of care decided by the clinical team or family due to an expected poor neurological recovery (includes patients meeting brain dead criteria and with massive intracranial pathology).
Comorbid withdrawal of care	Withdrawal of care by the clinical team/family/patient due to an underlying, either preexisting or newly discovered, terminal illness or expected poor quality of life .
Other	Any mode of death not fitting in the above categories.

Table 2

Cohort Characteristics Overall and Divided by Reason for Death.

Demographics	All patients (N = 115)	Death from sudden cardiac death, refractory shock, or refractory hypoxemia* (n = 54)	Death from neurologic or comorbid withdrawal of care* (n = 61)	P value*
Age (mean, SD)	70.3 (15.0)	67.7 (15.0)	73.3 (14.7)	.05
Sex (% female)	49.0	47.5	51.8	.65
Selected comorbidities (n, %)				
Advanced malignancy (ie, stage III or IV)	22 (19.1)	8 (13.1)	14 (25.9)	.09
Early stage or prior malignancy	30 (26.1)	12 (20.0)	18 (33.3)	.10
Congestive heart failure	34 (30.0)	24 (39.3)	10 (18.5)	.02
Renal disease (total)	28 (24.3)	15 (24.6)	13 (24.1)	.95
Renal disease on dialysis	11 (10.0)	7 (11.5)	9 (16.7)	.46
Cirrhosis	19 (16.5)	13 (21.3)	6 (11.1)	.15
Dementia	7 (6.1)	2 (3.0)	5 (9.2)	.20
Source of sepsis (n, %)				
Pulmonary	50 (43.5)	24 (39.3)	26 (48.2)	.34
Urine	6 (5.2)	3 (4.9)	3 (5.6)	.88
Intra-abdominal	13 (11.3)	8 (13.1)	5 (9.3)	.52
Bloodstream	0 (0.0)	2 (3.3)	2 (3.7)	.90
Skin/soft tissue	9 (7.8)	7 (11.5)	2 (3.7)	.12
Gastrointestinal	17 (14.9)	7 (11.5)	10 (18.5)	.29
Unknown	16 (13.9)	10 (16.4)	6 (11.1)	.41
Initial lactate, mmol/L (median, IQR)	3.4 (2.0-5.5)	4.3 (2.25-6.0)	2.7 (1.9-4.6)	.02
Days to death after ICU admission (Median, IQR)	4.0 (1.0-10.0)	3.0 (1.0-8.0)	6.0 (2.8-12.3)	.01
Underwent cardiopulmonary resuscitation (n, %)	10 (8.7)	10 (16.4)	0(0)	<.01

* Reason for death assignments as determined by reviewer 2.