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MAJOR ARTICLE

Neither Blood Culture Positivity nor Time to Positivity Is Associated With Mortality Among Patients Presenting With Severe Manifestations of Sepsis: The FABLED Cohort Study

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Background. Sepsis is a leading cause of morbidity, mortality, and health care costs worldwide.

Methods. We conducted a multicenter, prospective cohort study evaluating the yield of blood cultures drawn before and after empiric antimicrobial administration among adults presenting to the emergency department with severe manifestations of sepsis. Enrolled patients who had the requisite blood cultures drawn were followed for 90 days. We explored the independent association between blood culture positivity and its time to positivity in relation to 90-day mortality.

Results. Three hundred twenty-five participants were enrolled; 90-day mortality among the 315 subjects followed up was 25.4% (80/315). Mortality was associated with age (mean age [standard deviation] in those who died was 72.5 [15.8] compared with 62.9 [17.7] years among survivors; $P < .0001$), greater Charlson Comorbidity Index (2 [interquartile range {IQR}, 1–3] vs 1 [IQR, 0–3]; $P = .008$), dementia (13/80 [16.2%] vs 18/235 [7.7%]; $P = .03$), cancer (27/80 [33.8%] vs 47/235 [20.0%]; $P = .015$), positive quick Sequential Organ Failure Assessment score (57/80 [71.2%] vs 129/235 [54.9%]; $P = .009$), and normal white blood cell count (25/80 [31.2%] vs 42/235 [17.9%]; $P = .02$). The presence of bacteremia, persistent bacteremia after antimicrobial infusion, and shorter time to blood culture positivity were not associated with mortality. Neither the source of infection nor pathogen affected mortality.

Conclusions. Although severe sepsis is an inflammatory condition triggered by infection, its 90-day survival is not influenced by blood culture positivity nor its time to positivity.

Clinical Trials Registration. NCT01867905.

Keywords. bacteremia; bloodstream infection; mortality; sepsis; survival.

Sepsis is a leading cause of hospitalizations, morbidity, mortality, and health care costs worldwide [1]. The annual incident cases of sepsis worldwide is estimated at 48.9 million, resulting in 11.0 million sepsis-related deaths [2]. Despite its significant global burden, the underlying pathophysiology of sepsis remains poorly understood.

Sepsis is recognized as a dysregulated host inflammatory response to systemic infection whose management rests upon timely diagnosis, early administration of antimicrobial therapy, aggressive resuscitation, and supportive care [1, 3, 4]. However, despite the institution of sepsis treatment bundles aiming for rapid recognition and early administration of empiric antimicrobial therapy, mortality rates for severe manifestations of sepsis continue to range between 20% and 30% [5, 6]. Reported risk factors for death include increasing age, immune dysfunction, delays in or receipt of noneffective antimicrobials, and associated organ injury [7–13]. The time

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interval between specimen collection and detection of bacterial growth by automated blood culture systems correlates with measures of bacterial inoculum [14] and is automatically captured in laboratory information systems. There is a relative paucity of data regarding the association between blood culture positivity as well as its time to positivity in relation to 90-day mortality rates among patients with severe manifestations of sepsis.

The initial results of the FABLED diagnostic study (Effect of Antimicrobial Administration on Blood Culture Positivity in Patients With Severe Manifestations of Sepsis in the Emergency Department) have been reported previously [15]. In this prespecified analysis, we present the FABLED cohort mortality data. We hypothesized that, among patients presenting to the emergency department with severe manifestations of sepsis, blood culture positivity, and a shorter time to blood culture positivity would be associated with an increased risk of death at 90 days.

METHODS

Study Design

We conducted a multicenter, diagnostic study evaluating the yield of blood cultures drawn prior to and after administration of empiric antimicrobials among adults presenting with severe manifestations of sepsis. Patients were recruited in 1 of 7 emergency departments across Canada and the United States between November 2013 and September 2018. Details regarding the design, inclusion, exclusion criteria, and diagnostic procedures of the FABLED study have been described elsewhere [15]. In short, adults ≥18 years of age presenting to the emergency department with evidence of a systemic inflammatory response syndrome [16] and a presumed or confirmed source of infection were considered for inclusion. Patients required a marker of severity, including either a systolic blood pressure <90 mm Hg or a serum lactate level ≥4 mmol/L, for enrollment. Enrolled patients who had blood cultures drawn before and after the start of empiric antimicrobial therapy were followed to establish a prospective cohort. The study was approved by the research ethics board at each recruiting center.

Outcomes

The primary outcome of this study was 90-day mortality measured from the time of presentation to the emergency department. Survival was ascertained using proof of being alive at least 90 days after study recruitment as documented by a hospital or clinic visit in electronic medical records. For those in whom this proof was not available, date of death was confirmed using death certificates obtained from patient medical charts. Subjects for whom we could not unequivocally determine whether they were alive or dead were deemed lost to follow-up.

Covariates of interest included the presence of positive blood cultures before or after initiation of empiric antimicrobial therapy, the time to blood culture positivity, the source of infection, and the causative organism. Blood cultures growing contaminant organisms, defined as low-virulence skin flora within a single set of blood cultures [17] and confirmed as such by infectious diseases and medical microbiology specialists (M. P. C., C. P. Y.), were considered negative. Blood cultures were considered concordant when the growth of the same organism(s) was documented in blood cultures obtained both prior to and after receipt of empiric antimicrobials. In the setting of a polymicrobial infection, all noncontaminant organisms detected in the preantimicrobial cultures must have been present in the postantimicrobial blood cultures to have been considered concordant. Time to positivity of blood cultures was defined as the interval, in hours, between the time of blood culture draw to the time of microbial detection in the automated blood culture system. The blood culture platforms used in the participating institutions and their characteristics have been described elsewhere [15]. For the purposes of these analyses, the pathogens recovered were categorized as gram-positive, gram-negative, polymicrobial, or fungal species.

Sample Size

Sample size calculations for the FABLED diagnostic study yielded a target of 328 subjects. Assuming a 10% loss to follow-up with a conservative 35% bacteremia rate per sepsis literature and sepsis epidemiology [18, 19], we estimated that 103 bacteremic and 190 culture-negative subjects would have 90-day outcome data. Opting for a conservative predicted mortality among patients with severe sepsis, we postulated that 20% of bacteremic study subjects would die within the follow-up period [5, 6]. Since a 5%–10% difference in mortality had been reported between persons with culture-positive vs culture-negative sepsis [1, 20, 21], we based our estimates on a 5% between-group mortality difference with a 10% standard deviation (SD). Thus, assuming a sample size of 103 subjects per group (ie, ≥103 culture-positive subjects), 20% mortality with a 5% between-group difference and 10% SD, and a 2-sided α error rate of 5%, our follow-up cohort would provide 95% power to detect a difference in mortality between culture-positive and culture-negative subjects.

Statistical Analyses

All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, North Carolina). A 2-tailed P value < .05 was considered significant for all analyses. Patients in whom 90-day mortality data could not be unequivocally determined were deemed lost to follow-up and excluded from the analyses (3% of cohort). All remaining subjects had complete exposure and outcome data ascertainment.

Participants were classified per 90-day mortality status. Categorical variables were analyzed as proportions, normally distributed continuous variables using mean and SD, and other continuous data with median and corresponding interquartile range (IQR). Between-group comparisons were made using Fisher exact test for categorical data, *t* tests for normally distributed continuous data, and Wilcoxon tests for nonnormal data.

Univariate analyses were performed to evaluate for significant differences in microbiologic data between those who did and did not survive to 90 days. Results were presented as odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) and *P* values. Of note, the relationship between time to positivity and mortality was adjusted for incubation system in the otherwise univariate analyses, per data suggesting a significant difference in the speed of microbial detection per platform [22]. These adjustments were done using a simple logistic regression model with *P* values generated by the Wald χ^2 test.

Logistic regression models were designed to evaluate different positive blood culture characteristics, accounting for potential confounders, effect modifiers, and known predictors of mortality. Characteristics included the presence of a bloodstream infection prior to or after initiation of empiric antimicrobials, concordant blood cultures, and time to positivity among bacteremic patients. Time to positivity was chosen as the primary marker of interest because having a greater bacterial inoculum should result in a higher bacterial count in the blood collected, and thus a shorter time before a critical mass is detected and identified as "positive" by the automated blood culture platform.

The pathogen recovered was analyzed categorically without reference parameterization; categories were limited to gram-positive, gram-negative, and polymicrobial. The growth of *Candida* species in only 2 patients, both of whom survived, precluded the use of this microbial category in a logistic regression model. Source of infection was also analyzed categorically without reference parameterization; categories included gastrointestinal, genitourinary, respiratory, skin and soft tissue, other, and unknown source of infection. Evaluating the scatterplot depicting the relationship between time to positivity and mortality suggested that the optimal way to use this continuous variable was in a linear fashion. Because age, the presence of comorbidities, sex, and quick Sequential Organ Failure Assessment (qSOFA) score upon presentation have been associated with sepsis-related mortality in the literature, patient age, sex, Charlson Comorbidity Index, and positive qSOFA score (defined as a qSOFA score of ≥2 per clinical practice) were empirically included in the multivariate models. Since patient baseline characteristics revealed a significant between-group difference in abnormal white blood cell (WBC) count and malignancy, these 2 variables were also entered in the models. Finally, although the proportion of patients with dementia was different between groups, it was highly associated with both age and Charlson Comorbidity Index and thus not retained for the models. Multi-collinearity within the models was assessed. After computing the models, diagnostics were run to evaluate model fit and determine whether the residual data points were normally distributed. None of the models were overfitted. Results were presented as ORs with 95% CIs in the form of a forest plot for ease of visual interpretation.

Patient Consent Statement

Written informed consent to participate in the FABLED study was obtained from all patients, or their surrogate decision makers, as previously described [15].

RESULTS

The FABLED diagnostic study enrolled 330 participants, 5 of whom were excluded from the cohort study for lack of postantimicrobial blood cultures and 10 who were lost to follow-up. In total, 315 participants were retained in this cohort study (Figure 1). The overall 90-day mortality rate was 25.4%.

Baseline patient characteristics are presented in Table 1. The mean age of participants was 65.3 (SD, 17.7) years, 199 (63.4%) were male, and the median Charlson Comorbidity Index was 1 (IQR, 1–3). In the emergency department, 186 (59%) had a positive qSOFA score, 196 (62.2%) had a lactate level of ≥4.0 mmol/L, 178 (56.5%) had a systolic blood pressure <90 mm Hg, 40 (12.7%) had respiratory failure, and 49 (15.6%) required vasopressor support. Of the 102 patients with positive blood cultures prior to receiving antimicrobial therapy, 43 (42.1%) were infected with a gram-positive organism, 45 (44.1%) with a gram-negative organism, 12 (11.8%) had a polymicrobial infection, and 2 (2.0%) had a bloodstream infection with a *Candida* species.

When comparing subjects who died with those who survived to 90 days, patients who died were older (mean age, 72.5 [SD, 15.8] vs 62.9 [SD, 17.7] years; $P < .01$); had higher Charlson Comorbidity Index (2 [IQR, 1–3] vs 1 [IQR, 0–3]; $P < .01$); were more likely to have dementia (13/80 [16.2%] vs 18/235 [7.7%]; $P = .03$), malignancy (27/80 [33.8%] vs 47/235 [20.0%]; $P = .02$), and a positive qSOFA score (57/80 [71.2%] vs 129/235 [54.9%]; $P < .01$); and were less likely to have abnormal WBC count (55/80 [68.8%] vs 193/235 [82.1%]; $P = .02$). There was no significant difference in lactate, systolic blood pressure, respiratory failure, or vasopressor requirement in the emergency department between those who died and those who survived.

Blood culture results were assessed several ways, including the presence of bacteremia, persistent bacteremia, and time to positivity among bacteremic patients. None of these markers were associated with mortality on univariate analysis (Table 2). Likewise, the source of infection and the causative organism were not associated with mortality (Table 2). When entering each of the individual blood culture characteristics in

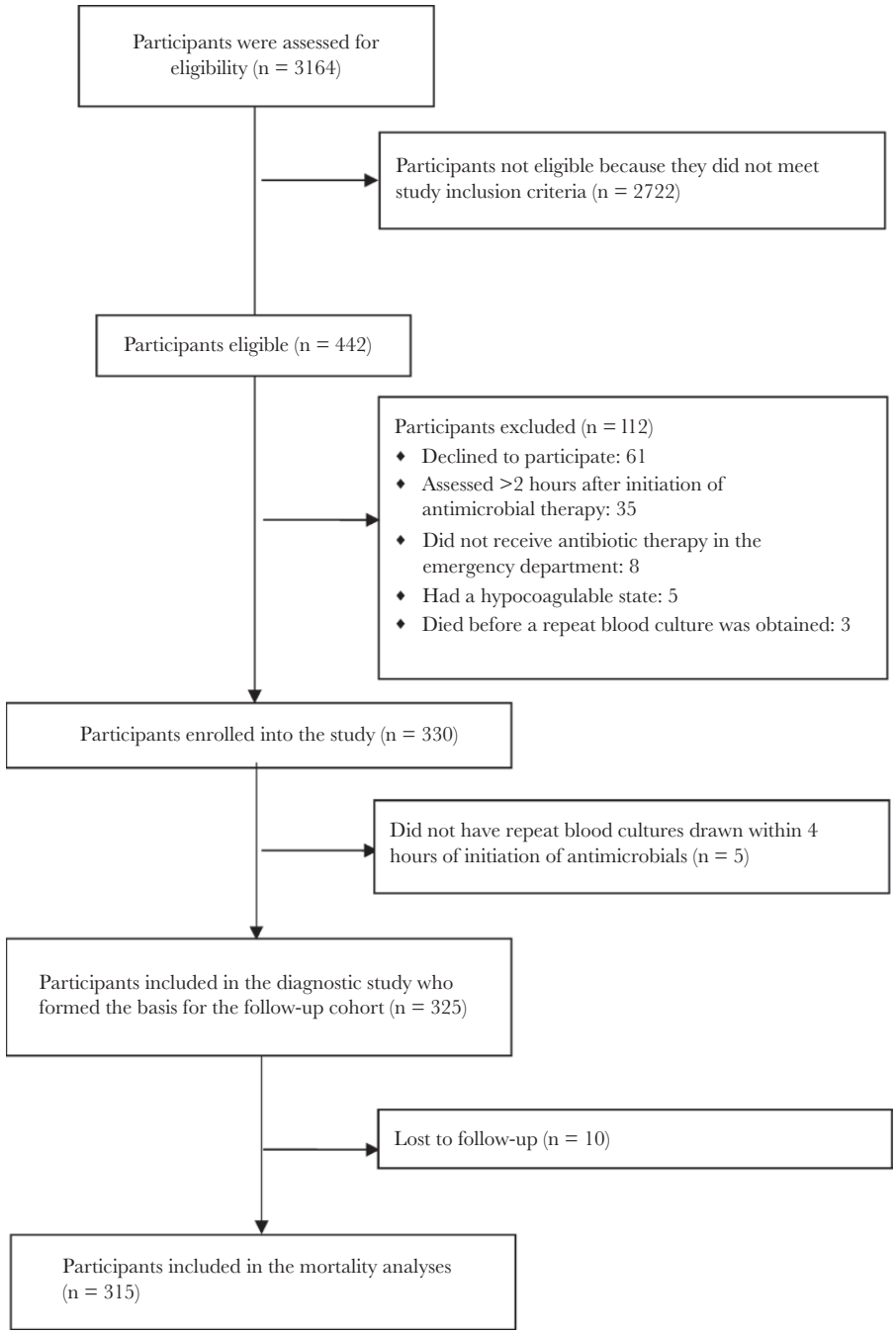

Figure 1. Study flow diagram.

a multivariate model adjusting for age, male sex, Charlson Comorbidity Index, underlying malignancy, positive qSOFA score, and abnormal WBC count, the lack of association persisted (Table 3). When studied alone or adjusting for any of the blood culture results, the impact of a positive qSOFA score on the risk of mortality remained significant and unchanged (OR, 2.03 [95% CI, 1.17–3.51]), as did increasing age (per year increase in OR 1.03 [95% CI, 1.02–1.05]) and the presence of an abnormal WBC count (OR, 0.50 [95% CI, .27–.92]).

DISCUSSION

Our results demonstrate that several patient characteristics are associated with an increased risk of 90-day mortality among patients with severe manifestations of sepsis, including a positive qSOFA score. This finding is concordant with the published literature [23] and supports the use of the qSOFA score in the emergency department to classify individuals at higher risk of mortality. However, we were unable to demonstrate an association between blood culture positivity or its time to positivity

Table 1. Patient Characteristics per 90-Day Mortality

Characteristic	Survived (n = 235)	Died (n = 80)	All (N = 315)
Age, y, mean (SD)[a]	62.9 (17.7)	72.5 (15.8)	65.3 (17.7)
Male sex	154 (65.8)	45 (56.2)	199 (63.4)
Comorbidities			
Chronic kidney disease	19 (8.1)	5 (6.2)	24 (7.6)
Chronic pulmonary disease	47 (20.0)	18 (22.5)	65 (20.6)
Cirrhosis	4 (1.7)	2 (2.5)	6 (1.9)
Congestive heart failure	26 (11.1)	10 (12.5)	36 (11.4)
Dementia[a]	18 (7.7)	13 (16.2)	31 (9.8)
Diabetes	60 (25.5)	25 (31.2)	85 (27.0)
HIV or AIDS	15 (6.4)	1 (1.2)	16 (5.1)
Malignancy[a]	47 (20.0)	27 (33.8)	74 (23.5)
Charlson Comorbidity Index, median (IQR) [a]	1 (0–3)	2 (1–3)	1 (1–3)
qSOFA score[a]			
0	20 (8.5)	10 (12.5)	30 (9.5)
1	86 (36.6)	13 (16.2)	99 (31.4)
2	90 (38.3)	40 (50)	140 (41.3)
3	39 (16.6)	17 (21.2)	56 (17.8)
qSOFA positive[a]	129 (54.9)	57 (71.2)	186 (59.0)
Initial characteristics in the ED			
Heart rate >90 beats/min	196 (83.4)	63 (78.8)	259 (82.2)
Respiratory rate >20 breaths/min	144 (61.3)	46 (57.5)	190 (60.3)
Temperature >38°C or <36°C	123 (52.3)	39 (48.8)	162 (51.4)
WBC count >12 or <4 × 1000/mL[a]	193 (82.1)	55 (68.8)	248 (78.7)
Lactate ≥4.0 mmol/L	145 (61.7)	51 (63.8)	196 (62.2)
Systolic BP <90 mm Hg	132 (56.2)	46 (57.5)	178 (56.5)
Respiratory failure	30 (12.8)	10 (12.5)	40 (12.7)
Vasopressor requirement	35 (14.9)	14 (17.5)	49 (15.6)
Source of infection			
Gastrointestinal	40 (17.0)	13 (16.2)	53 (16.8)
Genitourinary	44 (18.7)	12 (15.0)	56 (17.8)
Respiratory	71 (31.2)	33 (41.2)	104 (33.0)
Skin and soft tissue	31 (13.2)	8 (10.0)	39 (12.4)
Other	11 (4.7)	4 (5.0)	15 (4.8)
Unknown	38 (16.2)	10 (12.5)	48 (15.2)
Pathogen recovered (n = 102)			
Gram-positive	38 (47.5)	5 (22.7)	43 (42.1)
Gram-negative	31 (38.8)	14 (63.4)	45 (44.1)
Polymicrobial	9 (11.2)	3 (13.6)	12 (11.8)
Candida species	2 (2.5)	0 (0)	2 (2.0)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BP, blood pressure; ED, emergency department; HIV, human immunodeficiency virus: IQR, interquartile range; qSOFA, quick Sequential Organ Failure Assessment; SD, standard deviation; WBC, white blood cell.

[a]Significant differences were observed between groups with regard to age ($P < .01$), dementia ($P = .03$), malignancy ($P = .02$), Charlson Comorbidity Index ($P < .01$), qSOFA ordinal score ($P < .01$), qSOFA positivity defined as a score of qSOFA ≥2 ($P < .01$), and abnormal WBC count ($P = .02$).

in relation to 90-day mortality on univariate and multivariate analyses. While essential for antimicrobial selection and stewardship practices, our data suggest that blood culture results in isolation cannot be used to predict mortality in this patient population.

We assessed blood culture results in 3 orthogonal and complementary ways. First, we evaluated whether the presence of bacteremia, before administration of empiric antimicrobials, after initiation of antimicrobial therapy, or at any time, was associated with an increased risk of 90-day mortality. In univariate and multivariate analyses, controlling for confounders and effect modifiers that might mask its effect, bacteremia was not associated with an increased risk of mortality at 90 days. Second, we assessed whether the occurrence of bacteremia both prior to and following initiation of antimicrobial therapy might represent greater disease severity and thus have an impact on the observed 90-day mortality. Again, in both univariate and multivariate analyses, this was not the case. We then sought to establish whether a marker of the extent of infectious inoculum—that is, the rapidity of microbial growth in blood culture

Table 2. Microbial Data and Its Relationship to 90-Day Mortality per Univariate Analyses

Characteristic	Survived (n = 235)	Died (n = 80)	Odds Ratio (95% CI)	*P* Value
Any positive blood culture[a]	83 (35.3)	23 (28.8)	0.74 (.42–1.28)	.34
Concordant blood cultures[b]	44 (18.7)	15 (18.8)	1.00 (.52–1.91)	1.0
Pathogen recovered[c]	80 (34.0)	22 (27.8)	1.17 (.99–1.38)	.06
Source of infection[d]	235 (100)	80 (100)	0.97 (.82–1.14)	.69
Time to positivity of preantimicrobial blood culture, h, median (IQR)	14.0 (12–17)	12.0 (10–17)	1.01 (.93–1.09)	.86
Time to positivity of postantimicrobial blood culture, h, median (IQR)	17.5 (14–29)	15.5 (11–23)	0.97 (.92–1.01)	.16

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; IQR, interquartile range.

[a]Refers to a positive blood culture either pre- or postantimicrobial administration.

[b]Refers to a positive blood culture in which all microbial pathogens recovered from the preantimicrobial blood culture are recovered in the postantimicrobial blood culture.

[c]Refers to the pathogen recovered: gram-positive (n = 43), gram-negative (n = 45), polymicrobial (n = 12), or *Candida* species (n = 2).

[d]Refers to the source of infection: gastrointestinal (n = 53), genitourinary (n = 56), respiratory (n = 104), skin and soft tissue (n = 39), other (n = 15), or unknown (n = 48).

media—would modify the 90-day mortality risk. Measuring the effect of time to positivity, among blood cultures positive either before or even after administration of antimicrobials, had no effect on the risk of death.

Other recent cohorts have sought to assess whether the presumed source site of infection or specific pathogen recovered might influence a septic patient's risk of mortality. A recent meta-analysis highlights that the source of infection is unlikely to be a significant determinant of mortality in this population [24]. The 10-year prospective administrative cohort by Zahar et al, which included >3500 patients with severe sepsis, reported that pathogen species and the site of infection did not influence mortality [25]. Our study corroborates these findings as neither the source of infection nor causative pathogen were associated with a difference in 90-day mortality. Once patients develop severe manifestations of sepsis, it is possible that microbial factors become relatively less important to determining clinical outcomes as a dysregulated host response becomes responsible for disease manifestations. The prognostic significance of microbial factors in earlier stages of sepsis may be different than in our study population.

Our study has several strengths. First, we recruited a critically ill group of patients (32.6% had a positive blood culture, 25% died within 90 days) and had excellent study retention (97% of the study population). Furthermore, we performed a pragmatic study reflecting standards of practice in emergency departments and microbiology laboratories across 7 centers in Canada and the United States, increasing the generalizability to the results.

A potential limitation of our study is that the quantity of blood drawn for culture varied between study sites due to heterogeneous laboratory practices and differences in study protocol per local research ethics board specifications. However, the total blood volume cultured from subjects at all participating centers before and after antimicrobial administration was ≥60 mL, which should suffice for pathogen recovery [26]. Furthermore, our sample size was insufficiently large to observe significant differences from certain bacterial species or different antimicrobial therapies on the risk of mortality. For example, it is possible that a larger cohort study would have found a statistically significant relationship between organism and 90-day risk

Table 3. Microbiologic Data and Its Relationship to 90-Day Mortality[a]

Characteristic	Survived (n = 235)	Died (n = 80)	Total (N = 315)	Odds Ratio (95% CI)	*P* Value
Positive blood culture prior to antimicrobials	80 (34.0)	22 (27.5)	102 (32.4)	0.66 (.37–1.20)	.18
Positive blood culture after antibiotics	47 (20.0)	16 (20.0)	63 (20.0)	0.79 (.40–1.57)	.51
Any positive blood culture	83 (35.3)	23 (28.8)	106 (33.6)	0.65 (.36–1.18)	.16
Concordant blood cultures	44 (18.7)	15 (18.8)	59 (18.7)	0.81 (.40–1.63)	.56
Pathogen recovered	80 (34.0)	22 (27.8)	102 (32.3)	1.07 (.89–1.29)	.51
Source of infection	235 (100)	80 (100)	315 (100)	0.99 (.83–1.17)	.88
Time to positivity of preantibiotic blood culture, h, median (IQR) (n = 100)	n = 79 14.0 (12–17)	n = 21 12.0 (10–17)	13.0 (11–17)	1.02 (.93–1.12)	.69
Time to positivity of postantibiotic blood culture, h, median (IQR) (n = 60)	n = 44 17.5 (14–29)	n = 16 15.5 (11–23)	17.0 (13–24)	0.96 (.91–1.02)	.18

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; IQR, interquartile range.

[a]Multivariate model adjusting for age, Charlson Comorbidity Index, the presence of malignancy, a positive quick Sequential Organ Failure Assessment score, an abnormal white blood cell count, and male sex.

of mortality, as patients with positive follow-up blood cultures with gram-negative organisms are known to be at increased risk of poor outcomes [27].

In conclusion, neither blood culture positivity nor its time to positivity was associated with 90-day mortality among adults presenting to the emergency department with severe manifestations of sepsis. These findings support the ongoing use and research into bundles of care aimed at treating both the infectious and inflammatory aspects of sepsis, since blood culture results alone do not appear to be a significant driver of mortality in this patient population.

Notes

Disclaimer. The findings and conclusions in this study are those of the authors and do not necessarily represent the official position of the National Institutes of Health (NIH). The funding bodies had no input as to the study design; collection, analysis, or collection of data; writing of this report; nor the decision to submit the paper for publication.

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References

1. Cohen J, Vincent JL, Adhikari NK, et al. Sepsis: a roadmap for future research. Lancet Infect Dis **2015**; 15:581–614.
2. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet **2020**; 395:200–11.
3. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med **2017**; 45:486–552.
4. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA **2016**; 315:801–10.
5. Fleischmann C, Scherag A, Adhikari NK, et al; International Forum of Acute Care Trialists. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med **2016**; 193:259–72.
6. Stevenson EK, Rubenstein AR, Radin GT, et al. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis. Crit Care Med **2014**; 42:625–31.
7. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med **2017**; 376:2235–44.
8. Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. Am J Respir Crit Care Med **2017**; 196:856–63.
9. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med **2006**; 34:1589–96.
10. Sterling SA, Miller WR, Pryor J, et al. The impact of timing of antibiotics on outcomes in severe sepsis and septic shock: a systematic review and meta-analysis. Crit Care Med **2015**; 43:1907–15.
11. Rhee C, Dantes R, Epstein L, et al; CDC Prevention Epicenter Program. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. JAMA **2017**; 318:1241–9.
12. Rannikko J, Syrjänen J, Seiskari T, et al. Sepsis-related mortality in 497 cases with blood culture-positive sepsis in an emergency department. Int J Infect Dis **2017**; 58:52–7.
13. McCormack D, Ruderman A, Menges W, et al. Usefulness of the Mortality in Severe Sepsis in the Emergency Department score in an urban tertiary care hospital. Am J Emerg Med **2016**; 34:1117–20.
14. Haimi-Cohen Y, Vellozzi EM, Rubin LG. Initial concentration of *Staphylococcus epidermidis* in simulated pediatric blood cultures correlates with time to positive results with the automated, continuously monitored BACTEC blood culture system. J Clin Microbiol **2002**; 40:898–901.
15. Cheng MP, Stenstrom R, Paquette K, et al; FABLED Investigators. Blood culture results before and after antimicrobial administration in patients with severe manifestations of sepsis: a diagnostic study. Ann Intern Med **2019**; 171:547–54.
16. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest **1992**; 101:1644–55.
17. Baron EJ, Weinstein MP, Dunne WM Jr, Yagupsky P, Welch DF, Wilson DM. Cumitech 1C, blood cultures IV. Baron EJ, coordinating ed. **2005**. Washington, DC: ASM Press.
18. Kumar A, Zarychanski R, Light B, et al; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. Crit Care Med **2010**; 38:1773–85.
19. Yealy DM, Kellum JA, Huang DT, et al; ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. N Engl J Med **2014**; 370:1683–93.
20. Gupta S, Sakhuja A, Kumar G, et al. Culture-negative severe sepsis: nationwide trends and outcomes. Chest **2016**; 150:1251–9.
21. Phua J, Ngerng W, See K, et al. Characteristics and outcomes of culture-negative versus culture-positive severe sepsis. Crit Care **2013**; 17:R202.
22. Butler-Laporte G, Yansouni CP, Paquette K, et al. Real-world time to positivity of 2 widely used commercial blood culture systems in patients with severe manifestations of sepsis: an analysis of the FABLED study. Open Forum Infect Dis **2020**; 7:ofaa371.
23. Jiang J, Yang J, Mei J, et al. Head-to-head comparison of qSOFA and SIRS criteria in predicting the mortality of infected patients in the emergency department: a meta-analysis. Scand J Trauma Resusc Emerg Med **2018**; 26:56.
24. Motzkus CA, Luckmann R. Does infection site matter? A systematic review of infection site mortality in sepsis. J Intensive Care Med **2017**; 32:473–9.
25. Zahar JR, Timsit JF, Garrouste-Orgeas M, et al. Outcomes in severe sepsis and patients with septic shock: pathogen species and infection sites are not associated with mortality. Crit Care Med **2011**; 39:1886–95.
26. Baron EJ, Scott JD, Tompkins LS. Prolonged incubation and extensive subculturing do not increase recovery of clinically significant microorganisms from standard automated blood cultures. Clin Infect Dis **2005**; 41:1677–80.
27. Maskarinec SA, Park LP, Ruffin F, et al. Positive follow-up blood cultures identify high mortality risk among patients with gram-negative bacteraemia. Clin Microbiol Infect **2020**; 26:904–10.