FINDING A NEW PARADIGM: THE EXPONENTIAL MORTALITY OF SEVERE SEPSIS

A SYSTEMATIC REVIEW

MICHAEL P. DAILEY, M.S. (MICRO), M.D., FACP, DEAN KARAMPELAS, M.D., J.D.

ABSTRACT

Severe sepsis with evidence of greater than or equal to 3 organ failure on admission has 60% to 75% mortality in observational studies. [1,2] Kaplan-Meier survival curves of major randomized control studies (RCT) were analyzed to determine the combined 3-day, 7-day, and 28-day mortality. The mortality curve of severe sepsis with multiple organ failure is exponential. The highest rate of death is at the day of the admission to the trial (hospital).

The massive cytokine release that occurs on or around the day of admission to a hospital, with the resulting disseminated intravascular coagulation, is more analogous to an acute myocardial infarction than to a specific bacterial disease process. COVID-19 and other non-infectious severe illnesses are associated with a similar terminal physiologic process.

Implications for the interpretation of previous randomized control trials and the need to change our sepsis treatment paradigm are discussed. In order to achieve massive savings in health care expenditures, with treatment of Severe Sepsis before cytokine release, early treatment of disadvantaged groups, as well as all others, will be critical.

INTRODUCTION

The mortality rate for severe sepsis has not changed in decades. Given the continued 60-70% mortality as documented in several major severe sepsis observational studies, we decided to explore the combined rate of mortality after admission in these major trials in hopes of learning more about the mechanism of this disease process. Note that the Kaplan-Meier survival curves in multiple major studies are virtually superimposable on each other. This suggests that there may be a common pathophysiologic mechanism involved.

METHODS

Mortality data from 5 major trials of severe sepsis therapy were reviewed. [3, 4, 5, 6, 7] Cohorts with clearly defined protocols that did not use activated Protein C (APC) were analyzed as a group. The 28-day mortality of each of these cohorts was obtained from the studies. The 28-day mortality was chosen because the PROWESS trial only reported 28-day mortality. More than 80% of all deaths occurred in 28 days in these studies. Kaplan-Meier mortality curves in each trial were analyzed to calculate the area under the curve (AUC) for day 3 and day 7 of 28 days, in order to calculate mortality for those days. Table 1 summarizes this data. Graph 1 depicts the mortality curve from Table 1.

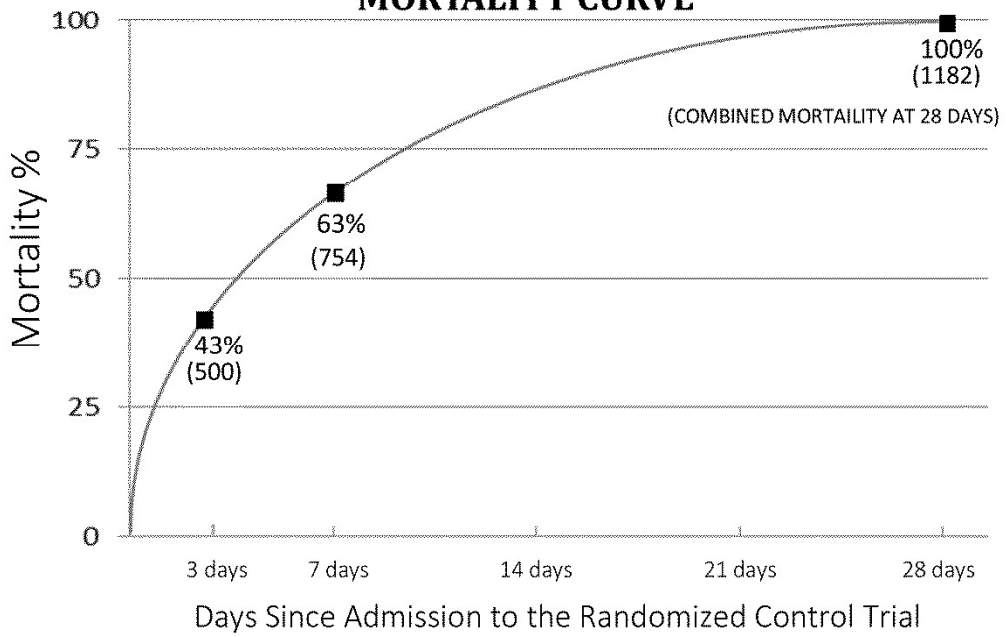
Table 1
Mortality in Severe Sepsis/MOF

Year	Trial	DAY 3	DAY 7	DAY 28
2001	PROWESS Placebo*	78	135	259
2002	PROWESS-SHOCK Placebo*	71	115	202
2014	ProCESS	71	98	165
2014	ARISE/ANZICS	113	178	244
2015	ProMISE	167	228	312
	TOTALS	**500** (42.3%)	**754** (63.8%)	**1182** **

***Only cohorts using a defined severe sepsis protocol were chosen**

****81% of total mortality occurred in 28 days in studies other than PROWESS**

Graph 1
MORTALITY CURVE



COMBINED 28-DAY MORTALITY (all cohorts)

RESULTS

The mortality curve of severe sepsis with multiple organ failure(MOF) (see Graph 1) is exponential. The highest rate of death is at the day of admission to the trial. Deaths that occurred in these studies prior to randomization are not included in the final reports.

CONCLUSIONS

Randomized control trials (RCTs) of severe sepsis with multiple organ failure have a much lower mortality than observational studies. The reasons for this were delineated in a recent journal article. [8] The exclusion criteria in RCTs eliminate many patients that are admitted but not expected to survive the entry process.

The finding that the highest rate of death is at admission to the trial (hospital) is similar to a 50-mph head-on collision. The injuries are so severe that the highest rate of death is at the event itself. While analogous to a myocardial infarction, in disseminated intravascular coagulation (DIC), the clotting occurs in the entire blood stream.

One possible explanation for this observation may relate to profound dehydration and toxicity at admission. This may result in the human body sensing that it is bleeding to death with activation of DIC. Similar to an acute myocardial infarction, the damage occurs very early but death may take weeks and at great expense.

This pathophysiology would explain several previous observations. The cytokine IL-6 is present at levels 12,000 times normal at admission and dissipates over 3 to 4 days in both survivors and in those who died. [9] The levels are higher in those who died than in survivors. The highest rate of mortality on admission correlates with the peak IL-6 levels.

The exponential death rate on the day of admission would explain variable results with activated Protein C (APC) depending on the average time of initiation of therapy. APC was initiated in approximately 24±12 hours in PROWESS and in an average of 60 hours in PROWESS-SHOCK. [3,4] At 60 hours after entry into the study, approximately one-third of RCT patients have expired (not counting the deaths in patients that did not quality for entry into the study).

Early accelerated mortality would also explain why disadvantaged individuals, who might delay care until the last moment, have higher mortality. [10]

Recent studies have demonstrated a similar IL-6 “explosion” on admission with COVID-19 as well as other non-infectious severe illnesses. IL-6 inhibitors like tocilizumab have shown significant promise in severe COVID. [11,12,13] COVID-19 and severe sepsis with multiple organ failure appear to have the same terminal vascular event.

The exponential mortality and pathophysiology of Severe Sepsis/ MOF on the day of admission suggests that tocilizumab or activated Protein C admitted within a few hours of admission would likely provide significant improvement in this lethal syndrome. The majority of patients are acutely ill on admission or very shortly thereafter. The timing of intervention is critical. This should also raise questions about the adequacy of outpatient care and follow-up for acute infections.

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