Prognosis in Acute Organ-System Failure

WILLIAM A. KNAUS, M.D., F.A.C.P., ELIZABETH A. DRAPER, R.N., M.S., DOUGLAS P. WAGNER, PH.D.,
JACK E. ZIMMERMAN, M.D., F.A.C.P.

This prospective study describes the current prognosis of patients in acute Organ System Failure (OSF). Objective definitions were developed for five OSFs, and then 5677 ICU admissions from 13 hospitals were monitored. The number and duration of OSF were linked to outcome at hospital discharge for each of the 2719 ICU patients (48%) who developed OSF. For all medical and most surgical admissions, a single OSF lasting more than 1 day resulted in a mortality rate approaching 40%. Among both medical and surgical patients, two OSFs for more than 1 day increased death rates to 60%. Advanced chronologic age increased both the probability of developing OSF and the probability of death once OSF occurred. Mortality for 99 patients with three or more OSFs persisting after 3 days was 98%. The two patients who survived were both young, in prior excellent health, and had severe but limited primary diseases. These results emphasize the high death rates associated with acute OSF and the rapidity with which mortality increases over time. The prognostic estimates provide reference data for physicians treating similar patients.

From the Departments of Anesthesiology and Computer Medicine and the ICU Research Unit, The George Washington University Medical Center, Washington, D.C.

AT THE BEGINNING of this century, physicians were taught that patients did not die from their disease; they died from the physiologic consequences of the illness.[1] During the following decades, as the concept of homeostasis became better defined, acute physiologic abnormalities were still recognized as an important cause of death.[2] It was not until the development and widespread use of intensive monitoring and life supporting treatment that it became possible to detect and correct physiologic abnormalities selectively. When these new treatments were first used for patients with respiratory failure and acute arrhythmias, the results were dramatic and encouraging.[3,4] Enthusiasm for organ system support spread rapidly to other diseases.

In the mid-1970's, it was recognized that, for some patients, support of multiple organ system failure (OSF) did not result in improved long-term survival but merely delayed death.[5,6] At the same time, it was reported that patients with a variety of traumatic and nontraumatic conditions were dying in multiple OSFs.[7-9] The exact cause of this syndrome remains elusive, but as our experience with acute OSF grows, it is becoming clear that the major role of mechanical and pharmacologic support of OSF is to buy time—time during which the primary disease process can be identified and effectively treated. Used in this way, organ system support is life saving.

When the etiology of multiple OSFs is obscure or the underlying disease persists, however, the physician may ask if continued support is likely to result in cure or if it is only prolonging the dying process. One response to the uncertainty of this question is to supplement clinical judgment with objective estimates of prognosis.[10] This prospective study aims at providing such estimates by examining the outcome of a large number of patients with a variety of diseases who developed OSF during their acute illness.

Methods

Hospital and Patient Population

As part of a larger prospective effort aimed at investigating the role of acute physiologic abnormalities in outcome from severe disease, we studied 5677 consecutive intensive care unit (ICU) admissions to 19 ICUs within 13 hospitals. They include eight university and five large community medical centers (Table 1). Ten hospitals are teaching institutions, defined as having formal affiliations with medical schools and full-time, in-unit responsibilities for training residents in medicine, surgery, and anesthesiology. Ten of the 13 hospitals have full-time ICU directors who were involved to varying degrees in direct patient care.

The ICUs studied have similar technical and life supporting capabilities. Most are multidisciplinary units, although some limit themselves to either medical or surgical patients (Table 1). No coronary care units are included

---

Supported by Grant No. HS 04857 from the National Center for Health Services Research and Grant No. 8498 from The Robert Wood Johnson Foundation.

Address for correspondence: William A. Knaus, M.D., ICU Research, 2300 K Street, N.W., Washington, D.C. 20037. Telephone: (202) 676-2611.

Submitted for publication: May 20, 1985.

TABLE 1. *Description and Characteristics of 13 Hospitals and 19 Medical Surgical Intensive Care Units*

Hospital	Total Number Hospital Beds	Total Number Adult ICU Beds	Number Adult ICU Beds Studied	Type of ICU(s) Studied
Cooper Medical Center (NJ)	522	14	14	Mixed medical/surgical
George Washington University Medical Center (DC)	511	24	16	Mixed medical/surgical
Medical College of Georgia (GA)	706	21	6	Medical
Johns Hopkins University (MD)	1025	36	7	Medical
Maine Medical Center (ME)	533	32	20	Mixed medical/surgical
University of Maryland Hospital (MD)	729	31	10	Surgical
Massachusetts General Hospital (MA)	1092	90	20	Surgical (2 units)
Polyclinic Medical Center (PA)	556	14	6	Mixed medical/surgical
St. Francis Hospital (OK)	802	40	16	Mixed medical/surgical
South Shore Hospital (MA)	280	28	16	Surgical & mixed medical/surgical (2 units)
Stanford University Hospital (CA)	633	65	57	Surgical, medical, cardiac surgery (3 units)
University of Virginia Medical Center (VA)	683	44	16	Surgical
University of Wisconsin Hospital (WI)	548	36	32	Surgical, medical, mixed medical/surgical (3 units)

in this study. In this analysis, the four hospitals with multiple units are treated as a single entity since they have only minor variations in their operational characteristics. Further details on the hospitals and their ICUs are available elsewhere.[11]

Patient information was collected during 1982 with the exception of the George Washington University Medical Center (GWUMC), where data collection was from April 1979 through June 1981. The 12 collaborating hospitals collected data over a 2- to 10-month period until a minimum of 200 and a maximum of 500 unselected patients were studied. There were 1967 patients recorded from GWUMC. Patients eligible for the study included all admissions to the 19 participating ICUs. The only diagnoses systematically excluded were acute burns and uncomplicated myocardial infarctions. Patients with cardiogenic shock were included. Patients who were admitted to the ICU directly from the operating or recovery room were termed operative; all others were nonoperative.

Information Collected

For each patient, we recorded age, prior health status, diagnosis, indication for ICU admission, and operative status. During each ICU day, we recorded for each patient the extent of physiologic derangement and the type and amount of therapy received. We also noted the exact timing of all do-not-resuscitate (DNR) orders and followed all patients for outcome at both ICU and hospital discharge.

To measure the extent of each patient's physiologic derangement, we recorded the most abnormal value of 34 clinical and laboratory measurements commonly obtained in critically ill patients during each 24-hour period of intensive care.[11] "Most abnormal" was defined as the physiologic value most removed from the normal range, *e.g.*, the lowest blood pressure and serum pH for a patient in shock, the greatest creatinine value for a patient with acute renal failure, or the lowest platelet count for a patient with thrombocytopenia.

The type and amount of therapy received was measured using the Therapeutic Intervention Scoring System (TISS).[12] This system assigns a score of one to four to 80 possible interventions to provide a summary measure of the type and amount of ICU care. An increasing TISS score is associated with greater intensity of therapy.

Preadmission health status was determined by answers to a set of objective criteria for detecting pre-existing cardiovascular, respiratory, hepatic, and renal organ system dysfunction.[11] It was also noted if the patient met objective criteria for severe immunocompromise. All patients who met these definitions were considered in chronic failing health. All definitions for poor chronic health status were independent from the definitions for acute organ system failure.

Data collection at each of the hospitals was under the direct supervision of a coordinating center (GWUMC). Full-time research associates (usually ICU nurses) were instructed in data collection using strict definitions for physiologic measurements and standardized forms. Data were sent to the coordinating center for analysis and extensive error checking. This involved examining all physiologic values that were pertinent to our definitions of OSF, relating them to the patient's diagnosis and operative procedure, and contrasting the pattern recorded during the initial 24 hours with that on subsequent days. Correlations were also made with recorded therapy. For example, a patient entering the ICU in hematologic failure from a low hematocrit should have had a diagnosis compatible with the physiology, *i.e.,* hemorrhagic shock from a perforated ulcer. If the hematologic failure was resolved by the second ICU day, there should have been treatment, such as blood transfusions or emergency surgery, to account for the change. Questions were referred back to each hospital for clarification. No patients were excluded from this analysis because of inadequate data.

Definitions of Organ System Failure

Independent of the data collection, we developed objective physiologic criteria for the diagnosis of OSF. The criteria were obtained from a review of the clinical literature and later modified through an informal consensus of subspecialists. The definitions of OSF are in Table 2. Since our goal was to provide objective estimates of the probability of survival for patients receiving intensive therapy, we chose definitions that are clear, easily obtained, and relatively independent of therapeutic decisions.

Therefore, with one important exception, we systematically avoided including any therapeutic modalities in our definitions for OSF but based them on the presence of severe physiologic derangements. The one exception was the use of ventilator therapy as a criterion for respiratory failure if the patient was dependent on a ventilator after the initial 3 days (72 hours) in the ICU. The remaining definitions were applied irrespective of new or ongoing therapeutic interventions, such as volume expansion, infusion of blood components or vasoactive agents, dialysis, and so on.

Thus, our definitions of OSF specifically assume that each patient is receiving life supporting therapy directed at correcting abnormal physiology. They are designed to be *independently* applied to each 24-hour period.

For example, a patient would be in three OSFs on the fourth ICU day if he met the following criteria: dependent on a ventilator after 3 days (respiratory failure); a mean arterial pressure or pulse rate below 50 or a severe metabolic acidosis (pH <7.24, $PaCO_2 <49$) on at least one occasion during the 24 hours designated as Day 4 (cardiovascular failure); and a low urine output (<159 ml/8 h) or high serum creatinine ≥ 3.5 (renal failure) on that day. The same patient, however, could have had one, two, or three OSFs on his first day of OSF.

TABLE 2. *Definitions of Organ-system Failure (OSF)*

If the patient had one or more of the following during a 24-hour period (regardless of other values), OSF existed on that day.

I. Cardiovascular failure (presence of *one or more* of the following):
   - A. Heart rate ≤ 54/min.
   - B. Mean arterial blood pressure ≤ 49 mmHg.
   - C. Occurrence of ventricular tachycardia and/or ventricular fibrillation.
   - D. Serum pH ≤ 7.24 with a P_aCO_2 of ≤ 49 mmHg.

II. Respiratory failure (presence of *one or more* of the following):
   - A. Respiratory rate ≤ 5/min or ≥ 49/min.
   - B. $P_aCO_2 \geq 50$ mmHg.
   - C. $A_aDO_2 \geq 350$ mmHg $A_aDO_2 = 713\ FIO_2 - P_aCO_2 - P_aO_2$.
   - D. Dependent on ventilator on the fourth day of OSF, *e.g., not* applicable for the initial 72 h of OSF.

III. Renal failure (presence of *one or more* of the following):*
   - A. Urine output ≤ 479 ml/24 h or ≤ 159 ml/8 h.
   - B. Serum BUN ≥ 100 mg/100 ml.
   - C. Serum creatinine ≥ 3.5 mg/100 ml.

IV. Hematologic failure (presence of *one or more* of the following):
   - A. WBC ≤ 1000 mm^3.
   - B. Platelets $\leq 20{,}000$ mm^3.
   - C. Hematocrit $\leq 20\%$.

V. Neurologic failure

Glasgow Coma Score ≤ 6 (in absence of sedation at any one point in day).

Glasgow Coma Score: Sum of best eye opening, best verbal, and best motor responses. Scoring of responses as follows: (points)
- Eye—Open: spontaneously (4), to verbal command (3), to pain (2); no response (1).
- Motor—Obeys verbal command (6); response to painful stimuli: localizes pain (5), flexion-withdrawal (4), decorticate rigidity (3), decerebrate rigidity (2); no response (1); movement without any control (4).
- Verbal—Oriented and converses (5), disoriented and converses (4), inappropriate words (3), incomprehensible sounds (2), no response (1). If intubated, use clinical judgment for verbal responses as follows: patient generally unresponsive (1), patient's ability to converse in question (3), patient appears able to converse (5).

* Excluding patients on chronic dialysis before hospital admission.

These definitions were applied to all OSF patients except those receiving chronic hemodialysis prior to hospital admission. Such patients could develop one or more of the four other OSFs but were *not* categorized as being in acute renal failure.

To designate neurologic failure, we used a Glasgow Coma Score of 6 or less.[13] A Glasgow Coma Score is obtained by summing the best responses during a simultaneous examination of ocular, motor, and verbal activity. The worst score (lowest) over a 24-hour period was recorded for each patient. When the patient was paralyzed

TABLE 3. *Intensive Care Unit Therapy and Mortality Rates According to Presence of Organ-System Failure (5677 ICU Admissions to 13 Hospitals)*

	No System Failure	One or More Organ-system Failures†
% Total admissions	52.0	48.0
% Total ICU days	28.0	72.0
% Total TISS points	23.0	77.0
% Cumulative mortality		
ICU*	0.5	19.0
Hospital*	5.0	31.0
Average ICU stay (days)*	2.1	5.6
Average total TISS points*	65.0	236.0

* $p < 0.01$.

† See Table 2 for definitions.

or sedated, neurologic scoring was not performed and the patient was not considered in neurologic failure. When a patient was intubated but not sedated, we used clinical judgment to estimate the best verbal response (Table 2).

Analysis

We initially compared the characteristics of ICU patients with and without physiologic evidence of OSF. We then related the number and duration of OSF with actual hospital mortality rates. To do this, we analyzed the hospital course for each OSF patient. The analysis began on the first day there was physiologic evidence of one or more OSFs. We then followed each patient until recovery from all OSF, death, or for 7 days. If a patient temporarily recovered from OSF but then relapsed, he re-entered the analysis on the day OSF reappeared counting from his original Day 1. This was very infrequent. A week was chosen as the maximal time to follow each patient since 85% died or were discharged from the ICU within that length of time.

Because the more frequently a physiologic value is measured, the more likely it is to be abnormal and the patient recorded to be in OSF, we examined the frequency of measurement of the physiologic values that define OSF among the 13 hospitals. To avoid the confounding effects of decisions to limit or withdraw therapy, we eliminated all such patients from the analysis the day after a DNR order was written. Although the multi-institutional nature of the study substantially reduced the probability that any one institution significantly influenced results, the larger proportion of OSF patients from GWUMC were contrasted with all others.

To examine further how interhospital variations in clinical philosophy or management might have influenced patient outcome, we contrasted the treatment provided to all OSF patients at the 13 hospitals by examining the type and amount of treatment provided at each hospital.

Differences between groups were analyzed using a Student's t-test with variations ≤ 0.05 considered significant.

Results

There were 5677 total ICU admissions at the 13 hospitals. Using the definitions in Table 2, 38% (2140) of the 5677 admissions entered the ICU in one or more OSFs. Among the remaining 3537 patients, only 16% (579) developed OSF later in their ICU stay resulting in a total of 2719 OSF patients.

Risk Factors for OSF

To identify patient characteristics associated with OSF, we compared the characteristics of the 2719 OSF patients to those without OSF. OSF was significantly more frequent among patients with nonoperative diagnoses ($p < 0.01$), age greater than or equal to 65 years ($p < 0.01$), and a pre-existing severe chronic disease ($p < 0.05$). Patients with septic shock or those admitted following a cardiac arrest were also more likely to develop multiple OSFs than patients with other diagnoses. The statistical probablity of developing OSF is thus substantially increased for ICU admissions who are elderly, in previously failing health, and have a nonoperative diagnosis, particularly sepsis.

Once OSF occurred, patients received consistently more treatment, stayed in the ICU longer, and had significantly higher death rates than patients without OSF (Table 3).

Outcome in Organ System Failure

Among patients with OSF, there were significant increases in hospital mortality rates associated with age ≥65 years ($p < 0.01$) and the number and duration of system failures ($p < 0.01$). Mortality rates were lower for patients with surgical diagnoses but only at low levels and short durations of OSF. The surgical patients admitted with one or two OSFs who resolved their OSF within 1 or 2 days had lower hospital mortality rates than nonoperative patients with the same number and duration of OSF. At all other levels and durations of OSF, differences between operative and nonoperative patients were smaller and insignificant for prognosis.

The most striking increases in mortality rates were associated with an increase in the number and duration of OSFs (Fig. 1). Day 1 is the first day each patient developed physiologic evidence of one or more OSFs. For 79% (2140) of the 2719 OSF patients, Day 1 was also their first day in the ICU. The 579 patients who developed OSF after the first ICU day usually did so early—within the second

Number of OSF		Day of Failure						
		1st	2nd	3rd	4th	5th	6th	7th
1	Percent Mortality*	22%	31%	34%	35%	40%	42%	41%
	No. Deaths	450	261	204	159	142	118	80
	No. Patients	2070	847	607	455	356	279	195
2	Percent Mortality*	52%	67%	66%	62%	56%	64%	68%
	No. Deaths	239	147	103	118	96	78	56
	No. Patients	458	219	156	191	171	122	82
≥3	Percent Mortality*	80%	95%	93%	96%	100%†	100%†	100%†
	No. Deaths	152	70	50	50	38	33	32
	No. Patients	191	74	54	52	38	33	32

FIG. 1. Hospital mortality according to number and duration of organ system failure (OSF) for 2719 OSF admissions to 13 hospitals. *To calculate confidence level: 95% confidence level (±2 standard deviation [std. dev.]). One std. dev. = $\sqrt{NPQ}$; N = total number; P = percent death rate; Q = 1 − P. For a patient with ≥3 OSFs on the fourth day of OSF, N = 52, P = 0.96, Q = 0.04; therefore, 1 std. dev. = 1.4 and 1.4/52 = 2.7%, so ±2 std. dev. = 96% ± 5.4%. Therefore, the next patient to have ≥3 OSFs on the fourth day of OSFs has a projected death rate from 90.6% to 100%. (Use of Poisson distribution yields equivalent results.) †Survival unprecedented with maximal statistical probability of survival of 10% (with 95% confidence).

or third ICU day. Only 71 patients (2.6%) temporarily recovered from OSF only to relapse later. As previously mentioned, these patients re-entered Figure 1 on the day OSF reoccurred counting from the original Day 1.

There were 99 patients who had three or more OSFs after 72 hours of intensive therapy; only 2 survived. Most (80%) of these patients were nonoperative admissions with diagnoses such as septic shock or cardiac arrest. Many (31%) were in severely failing health prior to hospitalization and a large proportion (49%) were 65 years of age or older. For example, there were nine patients age 65 or older with septic shock and three or more OSFs after the third day of failure. None survived despite an average of 7 days of intensive therapy.

The two patients who did survive three OSFs that persisted after 72 hours of therapy were a 17-year-old boy admitted for near drowning and a 35-year-old woman who had severe hypovolemic shock following perforation of a duodenal ulcer. Both had been in excellent health before hospitalization. These two patients emphasize the importance of considering previous health status, diagnosis, and age when estimating prognosis for patients with persistent multiple OSFs.

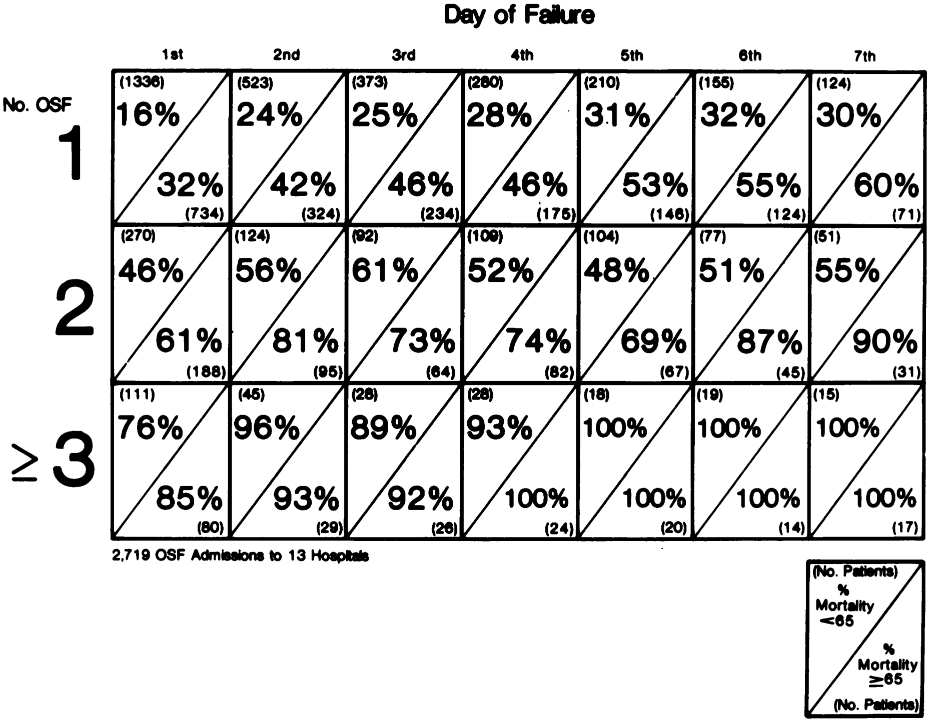
Advanced age (≥65 years) had an important impact on the probability of surviving OSF. Its influence was most prominent for patients with fewer than three OSFs. For patients ≥65 with one or two OSFs, mortality rates were frequently double those of younger patients. These results are presented in Figure 2, which contrasts results from OSF for patients ≥65 years of age with those for younger patients.

Analysis of Outcome Data

We examined whether institutional variations in monitoring therapeutic approach, or philosophy about aggressive treatment might have influenced these results. The frequency of measuring the physiologic values that determined OSF definitions showed little variation among the 13 hospitals. For example, in each hospital, vital signs, urine output, and neurologic status were universally determined every hour; serum creatinine was measured 2.4 times per OSF patient per day (range: 2.1–2.8). We contrasted GWUMC data (34% of the patients studied) with that from the other 12 hospitals. There was consistent and substantial agreement in hospital mortality rates for all categories of OSF.

We compared the treatment received by OSF patients at the 13 hospitals by relating the average type and amount of therapy provided for the level of physiologic derangement. One hospital provided 40% more therapy (TISS points) than all others. This resulted from extensive reliance on protocols emphasizing frequent laboratory testing and concentrated nursing care. When we examined the type of treatment provided, we found no substantial differences in the number of TISS points reflecting active life supporting treatment (*e.g.*, ventilator) or invasive monitoring (*e.g.*, pulmonary artery catheter). Most importantly, the increased amount of treatment at this one hospital had no influence on mortality rates for patients with three or more OSFs.

During their ICU course, 295 of the 2719 patients with OSF had DNR orders written. These 295 DNR patients



No. OSF	1st	2nd	3rd	4th	5th	6th	7th
1	(1336) 16% 32% (734)	(523) 24% 42% (324)	(373) 25% 46% (234)	(280) 28% 46% (175)	(210) 31% 53% (146)	(155) 32% 55% (124)	(124) 30% 60% (71)
2	(270) 46% 61% (188)	(124) 56% 81% (95)	(92) 61% 73% (64)	(109) 52% 74% (82)	(104) 48% 69% (67)	(77) 51% 87% (45)	(51) 55% 90% (31)
≥3	(111) 76% 85% (80)	(45) 96% 93% (29)	(28) 89% 92% (26)	(28) 93% 100% (24)	(18) 100% 100% (20)	(19) 100% 100% (14)	(15) 100% 100% (17)

FIG. 2. Variations in hospital mortality according to age and the number and duration of organ system failures.

had an average ICU length of stay of 8 days (range: 1–73) and the vast majority (94%) died within 3 days of the DNR order. Since the amount of life support available was limited, all patients with DNR orders were excluded from the analysis on the following day.

Discussion

The objective of this study was to provide estimates for the probability of survival from acute OSF. Our results indicate extraordinarily high mortality rates for patients with three or more OSFs that persist after 3 days of intensive therapy. There were 99 ICU patients in this study who had three or more OSFs 72 hours or more after OSF had first occurred. Two of these patients survived—both were young, in prior excellent health, and suffering from acute reversible diseases. For such patients and for those with other combinations and durations of OSFs, this analysis provided prognostic estimates with confidence limits small enough to supplement clinical decisions to limit or withdraw treatment (Fig. 1).

The development of objective prognostic estimates designed for use in clinical decision making for individual patients is a new undertaking. A landmark in the field was the definition of criteria for brain death developed at Harvard Medical School in 1968.[14] This effort was required because advances in cardiorespiratory support made it possible to maintain physiologic balance in individuals with a permanently nonfunctioning central nervous system. Recent studies have carried this effort forward by providing outcome predictions for patients ~~with~~ cardiac arrest and other forms of nontraumatic coma who are not brain dead but have very low probabilities of meaningful recovery.[15-18] We recently reported that physicians in intensive care units appear to be using these predictions to supplement clinical judgment when writing DNR orders.[19]

Similar to the studies noted above, the results reported in Figure 1 permit the clinician to use clinical information obtained during the course of treatment to obtain objective estimates of the probability of recovery. These estimates can then be integrated into management decisions regarding how to proceed with treatment. Since the estimates are based on definitions prepared independently of data collection, clinicians can apply the results prospectively.

The results obtained from this study are in general agreement with studies that have examined specific diseases and reported an increasing mortality rate with an increasing number of OSFs. The recent analysis by Pine et al. of 106 patients with intra-abdominal abscess and OSF also found 100% mortality for 15 patients with three or more OSFs.[20] The National Heart, Lung and Blood Institute's data collection on outcome from acute respiratory failure found that survival became unprecedented only after five OSFs occurred.[21] Differences in definitions of OSF are why mortality rates are higher in our study. On the other hand, studies that have examined the outcome of cancer patients with advanced disease and respiratory failure have suggested an extremely unfavorable prognosis with only one or two OSFs.[22-24] Any application or extrapolation from our data, therefore, must take into strict account the nature and exact format of the underlying disease and the definitions used.

Considering the importance of the patient's major diagnosis in determining prognosis, it would have been useful to provide disease-specific estimates of prognosis. Even with the large number of patients studied, however, separation into individual diagnostic categories would have reduced the confidence limits of the predictions beyond the point of clinical usefulness.

Advanced chronologic age also has a marked and independent influence on the probability of dying from OSF. The results in Figure 2 indicate substantial increases in mortality rates for elderly patients with one or two OSFs. Thus, physicians using these estimates may wish to take into account the impact of the patient's age when determining the efficacy of continued treatment.

Usefulness and Limits of Predictions

Before using these prognostic estimates in clinical decisions, the clinician should examine their statistical and clinical foundations as well as their limitations. For all observed mortality rates in this study, there is a statistically derived confidence level associated with each prognostic estimate.[25] This confidence level varies with the number of patients studied and the number who died (see calculation in Figure 1). For combinations and durations of OSF for which estimated mortality is 100%, statistical analysis cannot conclusively state that an individual patient will or will not survive. All that can be said is that, considering past experience, no individual with these characteristics has survived, *i.e.*, survival is unprecedented.[25]

From both clinical and statistical viewpoints, our findings must also be examined for the influence or confounding variables. To evaluate the impact of including ventilator treatment as evidence of OSF, we compared the prognostic estimates obtained with and without this additional definition. Using ventilator therapy after 3 days increased the number of patients in the unprecedented survival group from 77 to 99 but did not increase the number of survivors. This suggests that inclusion of prolonged ventilator therapy as a definition for respiratory failure did not lead to an increase in the important false-positive rate, *i.e.*, patients predicted to die but survived. We found that this is not true, however, for other forms of life support such as vasoactive drugs increasing an otherwise low blood pressure. This illustrates the need to be cautious in using definitions based on existing therapy to make future therapeutic decisions.

Additional factors that might have affected our results were institutional variations in the intensity of monitoring, in decisions to limit or stop treatment, or in the efficacy of treatment. We found little variation among hospitals in their intensity of monitoring and no correlation between the number of tests performed and the outcome from OSF. Our decision to eliminate all DNR patients from the analysis the day after a DNR order reduced their impact on the final results.

Finally, we found that the type and amount of treatment had no influence on outcome for patients with three or more OSFs. The efficacy of treatment for *all* acutely ill patients is a more complex issue. There is evidence being reported elsewhere that, within this sample, one of the institutions performed better and one worse than others when treating their ICU patients.[26] Analyzing outcome for each of the cells in Figure 1 by each of the individual 13 medical centers, however, results in too few patients to permit meaningful comparison. Therefore, the results in Figure 1 may be subject to some minor individual institutional variation. This should be kept in mind when using these prognostic estimates.

Implications of These Estimates

There is a growing recognition that combined mechanical and pharmacological support of multiple OSFs may be restricted in its absolute efficacy.[27-31] Previous reports have not only documented a persistent high mortality rate with multiple OSFs, they have described a cascade of events after an injury or disease that appears to be associated with the development of the syndrome. The sequence is thought to begin with infection, whose persistence can then lead to immune system dysfunction, more invasive infection, altered peripheral metabolism, and hemodynamic instability.[32-34] At some point in this sequence, physiologic balance can be temporarily maintained with vasoactive drugs, artificial ventilation, and hemodialysis, but death cannot be avoided.

We acknowledge that future improvements in the design and application of life support therapy may make it possible for more OSF patients to survive and that these prognoses may change over time.[31] We believe, however, that the incremental value of such improvements will be small. Of greater benefit will be expanded basic understanding of the origins and pathophysiology of multiple OSFs.[32-34]

The need for prompt recognition and treatment of clinical problems that could lead to OSF was highlighted in this study. Only 71 of the 1611 patients who developed

OSF and responded to therapy with full recovery went on to relapse later. In contrast, mortality increased rapidly when OSF persisted. After only 24 hours, mortality for patients with three or more OSFs was over 90%. For patients 65 or older, recovery was very unlikely if only two OSFs persisted for 24 hours. This emphasizes the need to concentrate both clinical care and research on the early phases of organ system dysfunction. If such efforts can help us avoid or promptly treat OSF more often, the prospects for improved survival are great.

Regardless of future research progress, however, there will always be patients for whom the power of our science is limited and for whom further treatment cannot alter outcome. For such patients, decisions to limit therapy are appropriate, but they will remain complex. This is because they involve questions concerning the wishes and competence of the patient, fears of legal liability, as well as the accuracy of the medical prognosis.[35] The statistical estimates provided by this study address only the aspect of prognosis. And, while we believe they are an important part of the analysis, they are not intended to be prescriptive.

In treating an individual patient, the clinician in combination with the patient or the patient's family must decide what role, if any, such estimates should have. If, after such discussion, the decision is to reduce treatment, it will be consistent with acknowledged ethical practice of not prolonging death unnecessarily (death with dignity) and of distributing medical resources equitably so that scarce resources will more likely be available to those that can benefit. If, on the other hand, one decides to continue aggressive therapy, it will be a more informed knowledge of the probability of success. Thus, prognostic information, when properly used, could improve both the quality and compassion of our care.

Acknowledgments

This study would not have been possible without the substantial and invaluable contribution of time and talent from the following people who provided the high quality data essential for meaningful results: Carolyn Bekes, M.D., W. Eric Scott, M.D., George Kuhn, R.N., Cooper Medical Center, Camden, New Jersey; Peter E. Dans, M.D., Jeanne Keruly, R.N., Warren R. Summer, M.D., Johns Hopkins Hospital, Baltimore, Maryland; Paul Cox, M.D., Phyllis Ogrodnik, R.N., Susan Brown, R.N., Maine Medical Center, Portland, Maine; David J. Cullen, M.D., Roberta Keene, R.N., Massachusetts General Hospital, Boston, Massachusetts; David Mize, M.D., Robert Bevis, M.D., Medical College of Georgia, Augusta, Georgia; Robert C. Gilroy, M.D., Carey Goodrich, R.R.T., Polyclinic Medical Center, Harrisburg, Pennsylvania; Gerald E. Gustafson, M.D., Helen Epstein, R.R.A., Barbara Reynolds, R.N., St. Francis Hospital, Tulsa, Oklahoma; Jean Henderson, R.N., M.S., Kenneth W. Travis, M.D., James M. Klick, M.D., South Shore Hospital, South Weymouth, Massachusetts; James F. Silverman, M.D., Judith Moran, R.N., Ph.D., Michael Rosenthal, M.D., Stanford University Hospital, Stanford, California; Baekhyo Shin, M.D., Mary McKinley, R.N., University of Maryland Hospital, Baltimore, Maryland; John W. Hoyt, M.D., Mike Flannagan, University of Virginia Medical Center, Charlottesville, Virginia; Mary Kay Kohles, B.S.N., M.S.W., Dennis G. Maki, M.D., Jean Grube, R.N., University of Wisconsin Hospital and Clinics, Madison, Wisconsin.

We are also indebted to the following individuals for their invaluable research assistance and careful editing that were so essential for the completion of this analysis: Diane Lawrence Reba, Gladys Campbell, Agnes Courtney-Jenkins, Jean Wolff, Tom Wineland, Lauri Yablick, David Abrams, Jerry Tietelbaum, Netta Fedor, Terry Kuznicki, Maxine Smith.

The authors are solely responsible for the content and conclusions of this study. No endorsement from sponsoring or collaborating institutions is intended or should be implied.

References

1. Bean RB. Sir William Osler: Aphorisms. New York: Henry Shuman, 1950.
2. Cannon WB. Organization for physiologic homeostasis. Physiol Rev 1929; 9:399–424.
3. Ibsen B. The anaesthetist's viewpoint on the treatment of respiratory complications in poliomyelitis during the epidemic in Copenhagen, 1952. Proceedings of the Royal Society of Medicine 1954; 47:6–8.
4. Horwitz RI, Feinstein AR. Improved observational method for studying therapeutic efficacy. JAMA 1981; 246:2455–2460.
5. Cullen DJ, Ferrara LC, Briggs BA, et al. Survival, hospitalization charges, and follow-up results in critically ill patients. N Engl J Med 1976; 294:982–987.
6. Civetta JM. The inverse relationship between cost and survival. J Surg Res 1973; 47:217–227.
7. Bave AE. Multiple, progressive, or sequential systems failure: a syndrome of the 1970's. Arch Surg 1980; 115:136–140.
8. Eiseman B, Beart R, Norton L. Multiple organ failure. Surg Gynecol Obstet 1977; 144:323–326.
9. Fry DE, Pearlstein L, Fulton RL, et al. Multiple system organ failure: the role of uncontrolled infection. Arch Surg 1980; 115:136–140.
10. Feinstein AR. An additional basic science for clinical medicine: I. the constraining fundamental paradigms. Ann Intern Med 1983; 99:393–397.
11. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II—a severity of disease classification system. Crit Care Med 1985 (in press).
12. Keene AR, Cullen DJ. Therapeutic Intervention Scoring System: update 1983. Crit Care Med 1983; 11:1–3.
13. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. Lancet 1974; ii:81–84.
14. Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. A definition of irreversible coma. JAMA 1968; 205:337–340.
15. Levy DE, Bates D, Cardonna JJ, Niall EF. Prognosis in non-traumatic coma. Ann Intern Med 1981; 94:293–301.
16. Longstreth WT, Diehr P, Inui TS. Prediction of awakening after out-of-hospital cardiac arrest. N Engl J Med 1983; 308:1378–1382.
17. Bedell SE, Delbasco TL, Cook EF, et al. Survival after cardiopulmonary resuscitation in the hospital. N Engl J Med 1983; 309:569–576.
18. Levy DE, Caronna JJ, Singer BH, et al. Predicting outcome from hypoxic-ischemic coma. JAMA 1985; 253:1420–1426.
19. Zimmerman JE, Knaus WA, Sharpe SM, et al. The use and implications of do not resuscitate orders in intensive care units. JAMA (in press).
20. Pine RW, Wertz MJ, Lennard ES, et al. Determinants of organ

malfunction or death in patients with intra-abdominal sepsis: a discriminant analysis. Arch Surg 1983; 118:242–249.

21. National Heart, Lung and Blood Institute, Division of Lung Diseases. Extracorporeal Support for Respiratory Insufficiency: A Collaborative Study. Bethesda, MD: National Institutes of Health, 1979.
22. Schuster DP, Marion JM. Precedents for meaningful recovery during treatment in a medical intensive care unit: outcome in patients with hematologic malignancy. Am J Med 1983; 75:402–408.
23. Carlon GC. Acute respiratory failure in cancer patients. Curr Probl Cancer 1978; 4:47–57.
24. Snow RM, Miller WC, Rice DC, Khalil AM. Respiratory failure in cancer patients. JAMA 1979; 241:2039–2042.
25. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? JAMA 1984; 249:1743–1746.
26. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Evaluation of outcome from intensive care in major medical centers. Ann Intern Med (submitted).
27. Galletti PM. Replacement of the heart with a mechanical device: the case of Dr. Barney Clark. N Engl J Med 1984; 310:312–313.
28. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure: a randomized prospective study. JAMA 1979; 242:2193–2196.
29. Hook EW, Horton CA, Schaber DR. Failure of intensive care unit support to influence mortality from pneumococcal bacteremia. JAMA 1983; 249:1055–1057.
30. Knaus WA. Changing the cause of death (editorial). JAMA 1983; 249:1059–1060.
31. Downing TP, Sadeghi AM, Baumgartner WA, et al. Acute physiologic changes following heart-lung allotransplantation in dogs. Ann Thorac Surg 1984; 37:479–483.
32. Cerra FB, Border JR, McMenamy RH, Siegel JH. Multiple systems organ failure. *In* Cowley RA, Trump BF, eds. Pathophysiology of Shock, Anoxia and Ischemia. Baltimore: Williams and Wilkins Press, 1982.
33. Zapol WM, Trestad RL, Snider MT, et al. Pathophysiologic pathways of the adult respiratory distress syndrome. *In* Tinker J, Rapin M, eds. Care of the Critically Ill Patient. Heidelburg: Springer-Verlag, 1983.
34. Bell RC, Coalson JJ, Smith JD, Johanson WG. Multiple organ system failure and infection in adult respiratory distress syndrome. Ann Intern Med 1983; 99:293–298.
35. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Deciding to Forego Life-sustaining Treatment: Ethical, Medical, and Legal Issues in Treatment Decisions. Washington, DC: Government Printing Office, 1983.