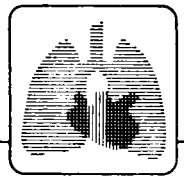

special report

Evaluation of Definitions for Sepsis

William A. Knaus, M.D.; Xiaolu Sun, M.D.; Per-Olof Nystrom, M.D.; and Douglas P. Wagner, Ph.D.*

Objective: **To evaluate the current definitions for sepsis and clarify and quantify the risk for intensive care unit (ICU) patients with sepsis.**

Design: **A prospective cohort analysis of 519 patients with a primary clinical diagnosis of sepsis treated in the ICUs of 40 US hospitals drawn from a nationally representative sample of 17,440 admissions.**

Measurements: **Patient's age, treatment location prior to ICU admission, comorbidities, origin of sepsis, daily physiologic measurements, therapeutic intensity, and subsequent hospital mortality rate.**

Intervention: **Patients were categorized into subgroups by important risk factors and into current clinical definitions of sepsis. Patients also were provided an individual risk of hospital mortality based on their individual predicted risk by using the first ICU day APACHE III score, treatment location prior to ICU admission, and etiology of sepsis.**

Results: **Patients with a designated urinary source of sepsis had a significantly lower baseline risk of death (30 percent) than patients with other causes (54 percent, $p<0.01$). Patients admitted to the ICU from the emergency department also had significantly lower mortality (37 percent) than patients admitted from hospital wards, other units within the hospital, or transferred from other hospitals (55 percent, $p<0.01$). Recognized definitions such as "sepsis syndrome" and "septic shock" identified groups of patients with significantly different mortality rates, 40 percent and 64 percent, respectively ($p<0.01$), but the range of individual patient risks within these groups were indistinguishable from the 211 patients (41 percent) that did not meet these definitions during the initial seven days of ICU treatment. Multivariate analysis using initial APACHE III score, etiology (urosepsis or other), and treatment location prior to ICU admission provided the greatest degree of discrimination (ROC = 0.82) of patients by risk of hospital death.**

Conclusions: **Sepsis is a complex clinical entity and could be viewed as a continuum with substantial variation in initial severity and risk of hospital death. One accurate description of sepsis is the continuous measure of hospital mortality risk estimated primarily from physiologic abnormalities.** ***(Chest 1992; 101:1656-62)***

APACHE III = acute physiology, age, chronic health evaluation; APS = acute physiology score; MOSF = multiple organ system failure; ROC = receiver operator characteristics; TISS = Therapeutic Intervention Scoring System

The clinical problem of sepsis remains an important and growing issue. Because of increasingly aggressive treatment of patients in advanced stages of illness, the incidence of and mortality from sepsis in hospital patients remains high. New efforts to improve survival[1-4] have also highlighted the current uncertainty of the specific diagnostic criteria used to define entry criteria and anticipated outcome for clinical trials.[5-10] Because of this confusion, new definitions have been developed. Unless these criteria produce unique homogenous groups or identify variables that substantially account for variation in patient risk factors, however, development of new definitions may not substantially increase understanding.

Moreover, with the changing nature of the patients developing sepsis, reliance on a few traditional risk factors may no longer be sufficient. For example, bacteremia, especially from Gram-negative enteric bacteria, has been a traditional diagnostic and prognostic factor.[5] But bacteremia is found in less than half of patients in clinical trials of sepsis[1-3] and is very uncommon in trauma and surgical patients with sepsis.[11-13] The exact role of bacteremia as an independent risk factor is also in doubt.[14,15] Indeed, some authorities now consider bacteremia a diagnosis rather than a risk factor.[8] Considering these and other complex challenges regarding the identification and treatment of sepsis, the recent call for comparable definitions may be premature. It presupposes insight regarding etiology and pathophysiology of this condition that may not currently exist.

In this article, we present evidence suggesting that, rather than the development of precise clinical definitions, patients identified as likely suffering from sepsis could be characterized by their risk of hospital mortality.

*From the ICU Research Unit, Department of Anesthesiology, the George Washington University Medical Center, Washington D.C. (Drs. Knaus, Sun, and Wagner), and the Department of Surgery, Linkoping University, Linkoping, Sweden (Dr. Nystrom).

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Reprint requests: Dr. Knaus, ICU Research, 2300 K Street NW, Washington, DC 20037

Material and Methods

The APACHE III database consists of 17,440 patient admissions to 42 intensive care units (ICUs) in 40 US hospitals; 26 hospitals were randomly chosen based on geographic location and size to represent US intensive care nationwide.[16] In this database, each patient was assigned a single diagnosis from a list of 212 mutually exclusive diagnostic entries. Each diagnosis described the immediate cause for admission to the ICU. Among the 212 choices were sepsis, and when available, the presumed origin of infection, *eg*, urinary, gastrointestinal, pulmonary. We emphasize that the patients chosen from this analysis lacked a clear etiologic diagnosis for their sepsis, such as bacterial pneumonia or intra-abdominal abscess. They represent a heterogenous and difficult to characterize group.

For each patient, we also collected a unique set of information describing the patient's vital signs and laboratory tests at the time of admission to the ICU. This information was then transformed into an APACHE III score consisting of an admission Acute Physiology Score (APS), which is composed of 17 physiologic measurements that result in a point score (range, 0 to 252) according to the number and severity of acute physiology changes. Existing preillness morbidity that affects the patient's immune status (AIDS, hematologic malignant neoplasm, metastatic cancer, immunosuppressive treatment, and cirrhosis or liver failure) is also part of the APACHE III score with an individual contribution of 0 to 23 risk points. Finally, risk points are awarded for age (0 to 24), completing a total APACHE III score of 0 to 299. The mean APACHE III score within the entire APACHE III database was 50, and the observed hospital mortality rate was 17 percent. There was a relationship between an increasing APACHE III Score and subsequent risk of hospital mortality.[16]

The APACHE III score can also be used to calculate a patient-specific mortality risk by using the APACHE III score, the specific disease etiology, and the patient's treatment location prior to the ICU admission in a multivariate equation.[16]

To complement this physiologic-based patient description, we also collected data on therapy on a daily basis using the Therapeutic Intervention Scoring System (TISS).[17]

To determine how specific definitions of sepsis grouped patients by risk, we reviewed definitions from the recent literature.[18-20] Fortunately, these definitions rely heavily on the same physiologic measurements employed in APACHE III data collection, *eg*, temperature, heart rate, respiratory rate, white blood cell count, oxygenation, and arterial blood pressure. Thus, we have been able to classify our patients according to the definitions of Bone et al,[1,7] *eg*, "sepsis syndrome" and "septic shock." Similarly, the presence of multiple organ system failure (MOSF) was defined by previously published criteria.[21]

To compare groups, we used the two-tailed t test for all continuous, normally distributed variables and a χ^2 test for all categoric variables. A least-square regression and logistic regression from Statistical Analysis System (SAS) was used to compute risk.

Results

Among the 519 sepsis patients, we found an equal sex distribution. Two-thirds of the patients were 65

Table 1—*Demographic and First-Day Clinical Characteristics of 519 ICU Admissions with Primary Diagnosis of Sepsis*

	Survivors (N = 272)	Nonsurvivors (N = 247)	Total (N = 519)
Mean age, yr	62.5 + 17.7	65.2 + 16.0	63.8 + 20
Age >65 yr, %	54	62*	58
Male:female	1:1	1.1:1	1:1
Severe comorbodity,† %	20	30*	25
Admitted from emergency department, %	47	30*	39
Transferred, %	53	70*	61
Readmitted, %	9	16*	13
Hyperthermia (T >38.3°C), %	46	45	46
Hypothermia (<35.5°C), %	5	17*	11
Intubated, %	24	64*	43
Spontaneous respiratory rate >20, %	63	32*	48
Hypoxemia (PaO_2 <75 mm Hg), %	33	50*	41
Hyperventilation (Pco_2 <32 mm Hg), %	39	44	41
Acidosis (HCO3 <20 mEq/L), %	40	54*	47
Tachycardia (>90 beat/min), %	86	88	87
Oliguria (urine output <30 ml/h), %	12	36*	23
Mental status change (GCS <15),‡ %	44	69*	56
Systolic pressure <90 mm Hg, %	50	71*	60
Vasopressors, %	47	78*	61
WBC >15,000/cu mm, %	50	49	49
WBC <4,000/cu mm, %	7	15*	11
Admission APACHE III score	70 + 26	103 + 31*	86 + 33
Admission TISS score	25 + 11	34 + 12*	29 + 12
First ICU Day APS change	21.4 + 21.2	13.2 + 25.9*	17.5 + 23.9
Mean ICU stay, day	9 + 26	8 + 10	9 + 20
Mean hospital stay, day	33 + 47	26 + 42	30 + 44
ICU mortality, %	0	66	31
Hospital mortality, %	0	100	48
Mean survival time, day§	. . .	15 + 28	. . .

*p<0.01 between survivor and nonsurvivor groups. Numbers following + sign are SD.

†Severe comorbidity included AIDS, hepatic failure, hematologic malignant neoplasm, metastatic cancer, immunosuppression, cirrhosis.

‡GCS = Glasgow Coma Scale.

§Survival time account from ICU admission until hospital discharge.

Table 2—*Mortality Rates by the Sources of Infection*

Source Of Sepsis	No. of Patients (%)	Mortality (%)
GI tract	101 (20)	55 (55)
Pulmonary	98 (19)	53 (54)
Urinary tract	104 (20)	31 (30)*
Unknown	216 (42)	108 (50)
Total	519 (100)	274 (48)

*$p<0.01$ between urinary tract infection and other groups.

years or older (range, 17 to 102). One-quarter (25 percent) of them had one or more of the APACHE III comorbidities (AIDS, hepatic failure, hematologic malignant neoplasm, metastatic cancer, immune suppression, or cirrhosis) (Table 1). The patients were further classified, by presumed etiology, into pulmonary (98 patients), gastrointestinal (101), urinary tract (104), or sepsis of unknown origin (216) (Table 2).

The overall hospital mortality for the sepsis patients was 48 percent with a mean survival time, after ICU admission, of 15 days. There was a significant difference in the mean initial APACHE III score between the survivors and nonsurvivors (Table 1).

Approximately half (46 percent) of the patients had fever and 49 percent had leukocytosis at the time of ICU admission (Table 1). Tachycardia and mental status changes, hypotension, and requirement of vasopressors were common features in this study population. The therapeutic information (TISS points) revealed a concentration of points for treatment of respiratory, hemodynamic, and hematologic organ systems.

The majority (61 percent) of the patients were transferred to the ICU from hospital wards, other therapeutic units, or other hospitals. The remaining patients (202 or 39 percent) were admitted directly to the ICU from the emergency departments. Their hospital mortality rates were 55 percent and 37 percent, respectively ($p<0.01$).

The APACHE III scores were near normally distributed. There was a significant relationship between the

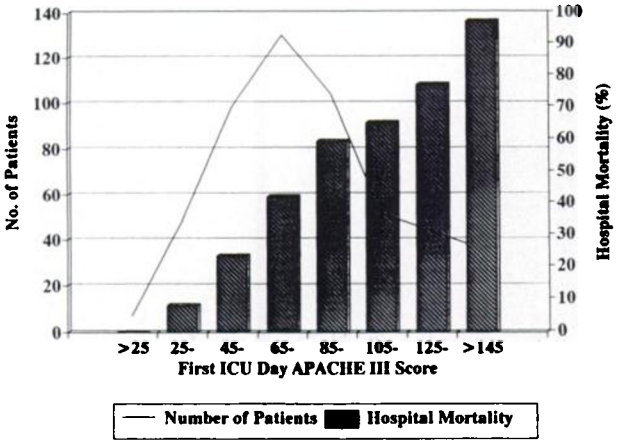

FIGURE 1. Distribution of first ICU day APACHE III score and subsequent outcome for 519 septic patients.

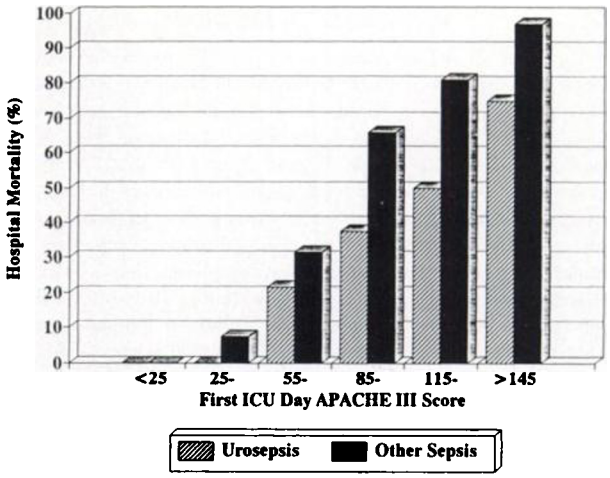

FIGURE 2. Relationship between first ICU day APACHE III score and mortality rates in urosepsis and sepsis from other sources.

first ICU day APACHE III score and the subsequent outcome across severity strata (Fig 1; $r=0.988$, $p<0.01$). Two-thirds of the deaths occurred in the ICU, those with higher APACHE III scores being more likely to die within the ICU. Patients with a urinary source of sepsis had substantially lower baseline risk of death than patients with other sources of sepsis (30 percent and 54 percent, $p<0.01$) (Table 2). When viewed from the perspective of APACHE III score, patients with urosepsis had a lower observed death rate at all levels of severity (Fig 2).

On admission to the ICU, a total of 252 or 49 percent of the patients met the definitions for sepsis syndrome or sepsis syndrome plus shock. The remaining 267 (52 percent) met neither definition (Table 3). During the subsequent seven days, an additional 56 patients (11 percent) met the definitions for a total of 308 patients or 59 percent.

The patients with sepsis syndrome and sepsis syn-

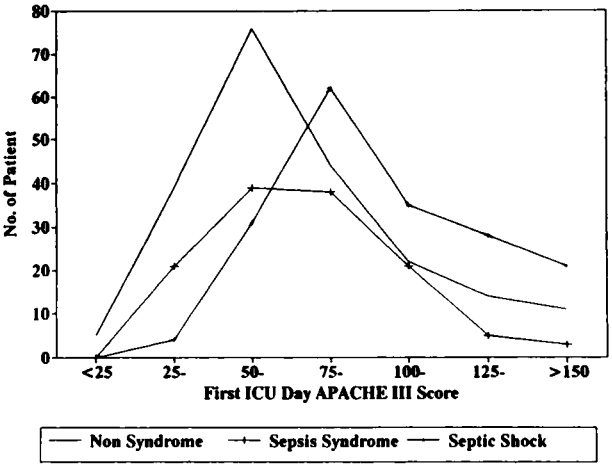

FIGURE 3. Distribution of first ICU day APACHE III score in 519 septic patients with sepsis syndrome (N = 127); with sepsis syndrome plus septic shock (N = 181); and those meeting neither definition (N = 211) during the initial seven ICU days.

Table 3—*Categorization of 519 ICU Admissions with Primary Diagnosis of Sepsis* by Definitions of Sepsis Syndrome and Septic Shock†*

	On ICU Admission No. (%)	During Initial 7 ICU Days No. (%)	Hospital Mortality,‡ %
Sepsis syndrome	106 } 252 (48)	127 } 308 (59)	40
Septic shock	146 }	181 }	64§
Nonsepsis syndrome	267 (52)	211 (41)	38

*Patients selected from APACHE III database.
†Bone RC et al.[7]
‡Hospital mortality of patients categorized during initial 7 ICU days.
§$p<0.01$ between sepsis syndrome and septic shock groups.

drome plus shock had significantly different hospital mortality rates (40 percent and 64 percent, $p<0.01$) (Table 3), explained in part by different APACHE III scores, but with considerable overlap in the distribution of individual first-day score. Their scores also overlapped with the remaining patients with sepsis who did not meet either definition (Fig 3).

A logistic regression equation was developed with hospital mortality as the dependent variable, and first ICU day APACHE III score, etiology (urosepsis or other sources of sepsis), and location prior to ICU admission (ward or emergency department) as independent variables. All three independent variables were significantly related to the hospital mortality risk. The partial Wald χ^2 of logistic regression were 100.23, 16.27, 11.78, respectively, ($p<0.001$), which were stable in logistic regression analysis by using each individual variable independently. The receiver-operator-characteristics (ROC) curve = 0.82. This equation was then used to compute a risk of hospital mortality estimate for each patient on his or her initial day of ICU treatment. The distribution of risks for patients who met definitions for septic syndrome with or without septic shock were then compared with patients who never developed these criteria during the initial seven days of ICU treatment (Fig 4). The

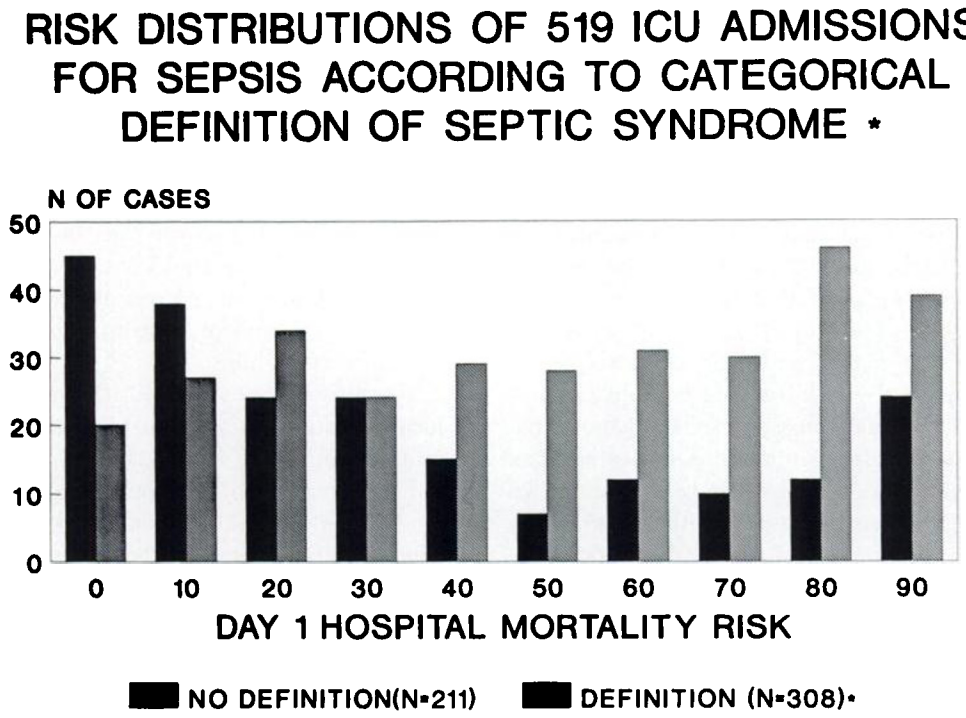

FIGURE 4. Distribution of first ICU day APACHE III calculated risk of hospital mortality for 519 septic patients with sepsis syndrome with or without septic shock (N = 308) and those meeting neither definition (N = 211) during the initial seven ICU days. Risk predictions are calculated from APACHE III first-day hospital mortality risk equation (reference 16).

results indicate a wide distribution of mortality risks for both groups of patients. The ICU admissions who met the definitions did have more cases with a higher risk than patients who met neither definition, but both groups had substantial numbers of cases at all risk levels.

Discussion

We describe a group of 519 patients whose single most important indication for admission to intensive care was the clinical impression of sepsis. Their overall hospital mortality of 48 percent and their acute physiologic disturbance (Table 1) suggest they match closely the patients chosen for recent clinical trials. Indeed, 252 or 48 percent met formal criteria for sepsis syndrome or sepsis syndrome plus shock (Table 3) on ICU admission, and 308 or 59 percent qualified during their initial seven days in the ICU. It is also very likely, however, that the remaining 41 percent suffered primarily from sepsis. The major alternative diagnoses that can have roughly similar physiologic profiles to sepsis, *ie*, posttraumatic or postoperative inflammation, pancreatitis, or vasculitis were all alternative diagnoses within the APACHE III data collection and were not selected for these patients. An independent reliability study has confirmed the reliability of this data collection.[22]

The overall impression gained from analysis of these 519 patients is that the clinical condition we now recognize as sepsis is complex. Much of this complexity resides in the observation made previously that sepsis is not a definitive diagnosis, but rather a collection of signs and symptoms that may or may not be associated with definitive evidence of infection.[9] Another major contribution to complexity, highlighted by this study, is the marked variation in the severity of the acute presentation that ranges from a mild febrile illness to severe shock (Fig 1). Further adding to its complexity is that sepsis is now frequently occurring in patients with varying combinations of other acute and chronic illnesses, especially those that disturb the body's natural immune defenses and can limit the inflammatory response. In this database, 25 percent of the patients had a substantial comorbidity affecting their immune status. Any attempt at classification and description of patients with sepsis must take all these observations into consideration.

We have attempted to do that by first detailing the acute physiologic disturbances that are an essential part of the sepsis condition, and then using them as the basis on which to investigate the role that other patient and treatment factors may have in diagnosis and prognosis. Our results suggest that the patients identified in the APACHE III study as being primarily admitted to the ICU for treatment of sepsis are very heterogeneous in terms of risk of death. Some have only minor variations in physiologic balance and are at very low risk of death. As the degree of initial physiologic imbalance increases, as measured by increasing APACHE III scores, so does the risk of death (Fig 1).

We also observed, however, that applying currently proposed definitions, such as sepsis syndrome or septic shock, to this heterogenous group of patients did not significantly improve our ability to identify subgroups at discrete and homogeneous levels of risks. The results in Figures 3 and 4 demonstrate that regardless of the definition chosen, there are still patients at varying degrees of physiologic disturbance and risk of death represented. These findings led us to our major conclusion that while categoric definitions of sepsis may be useful in selecting patients for entry into clinical trials, they may not be useful in characterizing individual, or perhaps even group, risks. What our results suggest rather is that the current clinical condition of sepsis, at least as it is applied to a subset of critically ill patients admitted to ICUs, is a continuous state with the prognosis determined, in large part, by the degree of physiologic imbalance at the time of admission.

In completing this analysis, we investigated how other initial patient-specific factors, such as the origin of sepsis, or treatment selection factors, such as the patient's location prior to ICU admission, influence outcome. We discovered that patients with a urinary source of sepsis had a significantly lower risk of death for the same degree of initial physiologic disturbance than patients with gastrointestinal, respiratory, or other sources of sepsis (Table 2 and Fig 2). This is in agreement with other observations and may be related to the speed of discovery of the infection and the ability to eradicate the focus.[23,24] It is important to point out, however, that recent clinical trials in sepsis have not reported on distribution of this important prognostic variable.[3]

We also discovered that the patient's treatment location immediately prior to ICU admission was an independent risk factor, adding to the degree of outcome explained by admission physiology and etiology. This observation is most likely related to lead time bias, and when in the course of an illness the episode of sepsis occurred. This phenomenon has been described previously.[25,26]

Limitations

The major limitations of these results are related to the limited number and heterogeneous character of patients chosen for this analysis. At ICU admission, 519 of these patients were given a primary clinical diagnosis of sepsis, but were not suffering from a more specific diagnosis such as pneumonia, trauma, or intra-abdominal abscess. It is possible that the application

of proposed definition for sepsis to more patients with a well-defined diagnosis, such as bacterial pneumonia, would result in a more homogeneous grouping by risk. Such analysis will be the subject of further investigation. This analysis also did not evaluate the applicability of the sepsis definitions over time to patients with more definitive diagnoses, such as pneumonia or trauma. Again, such analysis will be the focus of subsequent publications.

It is also possible that following patients beyond seven days of ICU treatment would result in a slight increase in the total number of patients meeting the definitions.[27] Since less than 15 percent of the total 17,440 consecutive ICU patient admissions from APACHE III database remained in the ICU for seven or more days,[16] any such increase is projected to be small.

Categoric Descriptors vs Individual Risk

We realize that individual risk prediction is a new undertaking in clinical research. Much of clinical description has historically concentrated on categoric descriptions. Even the most recent large-scale clinical trial of monoclonal therapy in sepsis used severity scoring only to designate patients into high (>25 APACHE II points) or low (<25 APACHE II points) severity ranges.[3] The difficulty with such an approach is that even well-defined categories may contain a variety of individual risk. Examination of Figure 1 indicates that choosing a cut-off APACHE III score of 95 (the rough equivalent of the APACHE II 25 criteria) would yield one group of patients with hospital mortality risks varying from 0 to 65 percent; the other 50 to 97 percent. Relying on proposed definitions like septic syndrome will also result in patients with a wide distribution of hospital mortality risk (Fig 4). This risk distribution is also not very dissimilar to patients with sepsis who do not meet this definition.

Given the complex pathophysiologic response to sepsis, and the limited potential action of new therapy, it is very unlikely that a single novel therapeutic agent will influence outcome for patients at all levels of risk. Even the use of penicillin for treatment of pneumococcal sepsis left untouched the mortality rate of patients whose severity of infection or physiologic reserve resulted in death within a few days.[28] It has also been emphasized recently that the use of intensive care life support techniques have not influenced the mortality of these severely ill patients.[29]

We are now faced with the introduction of therapies (*eg*, monoclonal antibodies) with a much more limited therapeutic indication than prior advances such as penicillin. This makes it necessary to measure even more precisely the risk of individual patients across such a broad range of risk levels.[30] An analysis that does not take into consideration the combination of significant individual baseline patient and selection risk factors may not be able to reduce this patient variation sufficiently to detect important effects from new interventions. This is obviously true if the risk factor is not identified before randomization. It may still be true, even if randomization has been employed to distribute risk factors, because randomization alone may not distribute all risk factors that act conjointly to influence individual patient risk.[31]

For example, this analysis suggested the patients presenting to the emergency department with a diagnosis of urinary tract sepsis have the lowest overall risk of death at any level of physiologic severity than patients with other sources or pre-ICU treatment locations (Fig 2). Patients transferred from a hospital room or other ICU with a GI or other source of infection are at the highest baseline risk. Examination of the distribution of these individual risk factors across treatment and control groups by examination of mean values between groups may not disclose variations in individual risks and could confound or even invalidate an analysis of an effective but marginally influential new therapy.[31]

Reduced Variables and Sepsis-Specific Scoring

We did not, as has been suggested by others,[19] attempt to isolate a smaller number of physiologic variables than the 17 used by APACHE III, that could provide adequate risk stratification or prediction. While this might be possible, our current uncertain knowledge of the underlying pathophysiology involved in sepsis makes us hesitate to reduce the scope of variables, especially for a condition that can have an influence on such a variety of organ systems. The observation that fewer than half of the septic patients in this database had fever or leukocytosis (Table 1), both long considered as classic signs for sepsis, also urges caution in the context of reducing the number of variables.

Likewise, the suggestion[19] that distinct diseases, such as sepsis, should have a distinct scoring system with individual weighting of physiologic abnormalities based on a possible unique risk pattern for that disease encounters two substantial challenges. First, the number of cases needed within well-defined diagnostic categories that would be capable of demonstrating a consistent and unique weighting scheme disease by disease would require a database substantially larger than the 17,440 patients contained within the current APACHE III file. Second, the technical ability of defining homogeneous patient groups within which such an analysis could be accomplished has been challenged by these very results. For example, within the 519 patients with sepsis in this study, the 104 patients with a urinary source had a significantly different relationship between the admission level of

APACHE III score and hospital mortality (Fig 2). Any attempt to find a unique weighting system for sepsis will be confounded with this and other currently known and unknown risk factors that would subdivide patients into different conditions within a single disease category. Therefore, until our basic understanding of the pathophysiology of sepsis improves and substantially larger clinically accurate databases are collected, we believe a broad general approach to severity scoring, risk stratification, and outcome prediction is warranted.

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