Predictive Technologies and Health Care Rationing

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B.A. (University of California at San Diego) 1988

THESIS

Submitted in partial satisfaction of the requirements for the degree of

Master of Science

in

Health and Medical Science

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA at BERKELEY

Approved:

Chair: Sheldon Margen 5/27/92

Date

5/29/92

Thomas E. Kuhlman 5-29-92

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INTRODUCTION

In the United States, at least six percent of all hospital beds are in the intensive care unit or coronary care unit[1]. The cost of treating a patient in an intensive care unit averages from $2,000 to $3,500 per day[2]. At least 10 to 40 percent of intensive care patients will not survive to hospital discharge[3,4]. Although intensive care is the standard practice for many patients with severe illnesses, no epidemiologic study has demonstrated conclusively that intensive care units are of benefit.

Virtually all acute care hospitals in the United States today have critical care units or intensive care units (ICUs). Having grown from special units designed to treat post-operative patients, they soon became important sites for treating and monitoring patients with cardiac disease. Today, every major category of disease may be found in the modern ICU, with common diagnoses being septicemia, post-surgical complications, cerebrovascular accidents, gastrointestinal bleeding, neoplasia, and respiratory failure. Intensive care units employ some of the most sophisticated medical technology, routinely monitoring the cardiopulmonary performance of patients and often providing assisted ventilation. ICU's are high-intensity in terms of their staffing, involving 24-hour physician supervision and nurse:patient ratios from 1:3 to 1:1.

In the last two decades, efforts to prospectively quantify the severity of illness of ICU patients have grown dramatically. In addition to the financial savings which could result from not admitting those patients who do not need intensive care and those patients for whom further intervention is futile, there are numerous other reasons for these efforts. A randomized study of patients into two treatment groups, one a traditional hospital setting and the other a critical care unit, is considered unethical because of the presumed

superiority of ICU care. Therefore, a means of comparing the severity of illness among distinct patient populations is needed. A predictive index calculated for each patient in the ICU accurately predicting the outcome of treatment could serve such a purpose. Likewise, such a predictive index would allow interhospital comparisons between ICU's or between different modes of treatment, controlling for severity of illness. Finally, such an instrument would aid intensivists in their decisions to admit or discharge patients to or from the ICU in times of triage.

With the enormous costs of health care spiraling out of control while millions are denied access to the health care system, there is ample reason to seek an improvement in the efficiency of intensive care. If physicians and nurses could identify which patients' illnesses were not severe enough to warrant an expensive stay in an ICU, which patients had much to gain, and which patients had no chance of recovery, a substantial amount of health care resources could theoretically be saved or diverted to those in greater need.

This thesis is divided into two Parts: the first is a review of the prognostic scoring systems for which results have been published. In this Part, I discuss all of the major systems designed to predict outcomes for general ICU patients, as well as many of the models which are only designed to predict outcome for patients with a particular diagnosis or treatment category. The second Part is a reporting of the experimental methods, results, and a discussion of implications of a clinical research project undertaken to identify the factors important in prospectively assessing the probability of short-term and long-term survival among ICU patients with septicemia.

PART I: REVIEW OF PROGNOSTIC SCORING INDICES

In attempting to predict the outcome for critical care patients, investigators have undertaken two methods. One method applies only to patients with a specific disease or organ failure, and the other type of predictive model is more generalizable, derived from and relevant for large heterogeneous ICU populations. The first method of prediction characterizes a subset of patients who suffer from the same presenting illness or condition and analyzes the factors which predispose them to survival. Analyses of this nature have been performed for many diseases and organ failures. Examples for some of the major organ systems follow.

Models Based on a Single Disease Category or Organ Failure

In 1971 Afifi et. al. described the Initial Descriminant Function (IDF) and the Accumulative Prognostic Index (API) after analyzing the physiologic variables associated with mortality among patients who became comatose after overdosing on one of three drugs[5]. In univariate analysis comparing the mean values of 25 variables between survivors and non-survivors (using a t-test), the author identified ten variables significantly different for non-survivors. Employing a stepwise discriminant analysis program, the author derived the following function based on the initial laboratory data obtained upon admission: IDF = .049 x systolic pressure - .2075 x mean central venous pressure + 6.749 x pH. An IDF greater than 53.16 resulted in that patient being classified as a survivor. Addition of the any or all of the remaining variables to the model resulted in no improvement in the predictive accuracy. Retrospectively tested, the IDF correctly classified 76 percent of patients as survivors or non-survivors. The API allows the

utilization of sequential measurements of physiologic variables and resulted in an overall predictive reliability of 83 percent.

For patients with acute pancreatitis McMahon and Playforth analyzed a number of methods of predicting outcome[6]. In a prospective study of 79 patients with acute pancreatitis, they tested the predictive power of the so-called Ranson criteria or Imrie criteria that are based upon laboratory measurements including the patient's white blood count (WBC), serum calcium, hematocrit, blood urea nitrogen (BUN) and other measures. They tested whether the presence of methemalbuminemia or hypocalcemia was an accurate predictor of outcome. Lastly, they analyzed the usefulness of peritoneal lavage in predicting outcome. The latter method, combined with a careful inspection of the lavage fluid, resulted in the fastest and most accurate prediction of disease outcome.

For patients admitted to the hospital because of acute burns, Feller and Tholen utilized an index based upon the age of the patient and the percent of the body burned to compare the outcome of burn treatment over a fifteen year period from 1965 to 1979[7]. By demonstrating with this index that patients in more recent years were as severely burned as patients in the 60's, the authors concluded that improved treatment methods were responsible for the improved outcomes of burn patients in more recent years.

In 1981, Champion, Sacco, et. al. described the Trauma Score, a predictive index based upon the respiratory rate, blood pressure, pulse, capillary refilling, and level of consciousness of trauma patients[8]. Together with age, the trauma scored proved a good predictor, showing a high degree of correlation to hospital mortality.

In cardiology, numerous studies have been undertaken to formulate of predictive indices[9-12]. In one such study, univariate analysis of selected hemodynamic and metabolic variables and discriminant function analysis were employed to identify arterial blood lactate levels, mean arterial pressure, diastolic pressure and partial pressure of carbon dioxide ($PaCO_2$) as reliable predictors of mortality in patients with acute myocardial infarction complicated by shock[9].

In addition, numerous other single organ based systems exist to predict mortality. For example, the Pulmonary Insufficiency Index was described by Bartlett in 1975 as a means to predict mortality among patients in respiratory failure[13]. For patients with liver failure and portal hypertension, Child described in 1964 a means of predicting outcome[14]. Each of these schemes allows physicians to assess the severity of a patient's illness early in the course of treatment. These systems are limited by the fact that the number of patients studied was usually small (except for the Burn Index), making them less statistically attractive. The conclusions drawn from their carefully selected patient study populations are not generalizable to the average critical care patient, who often has multi-organ disease. Nonetheless, these schemes find use by specialists and in clinical trials comparing specific therapies.

Generalizable Predictive Indices

OSF Model

William Knaus and his colleagues studied 5677 ICU admissions in 13 different hospitals to determine whether patient mortality was predictable on the basis of the number of organ systems in failure (OSF)[15]. This concept had shown promise in several previous studies: A study conducted by the National Heart, Lung and Blood Institute demonstrated that mortality is

associated with increasing numbers of organ systems in failure and that survival is unprecedented when five or more organ systems are in failure[16]. In other studies of organ failure, cancer patients had extremely poor prognosis with 1-2 organ systems in failure[17-19].

Knaus and his colleagues defined criteria for failure in cardiovascular, respiratory, renal, hematologic, and neurologic organ systems. Among patients with one or more organ system failures, advanced age (65 or greater) and number and duration of OSF's were identified as significant predictors of increasing mortality. Increased number and duration of OSF's was associated with increased length of stay in the ICU, increased treatment intensity, and increased mortality. Significantly, for the 99 patients with three or more OSF's persisting after three days, mortality was 98%. The only two survivors were both young, in excellent prior health, and had limited, although severe, primary disease. For patients with three or more OSF's persisting 5 or more days, survival was unprecedented (See Figure 1)

TISS

The Therapeutic Intervention Scoring System (TISS) was first described by Cullen and his associates in 1974 as a means to quantify the level of therapeutic intervention on behalf of ICU patients[20]. Points are assigned for every therapeutic intervention, and data is collected at the same time for every 24 hour period of treatment by a data collector who is familiar with the sophisticated therapeutic procedures and interventions of the modern ICU. Use of TISS in predicting outcome is based on the assumption that the level of therapeutic intervention is reflective of illness severity, and therefore, a good basis for predicting mortality.

In study of 226 consecutively admitted patients to an ICU, the TISS did not correlate with mortality as observed in the hospital, at one month,

and at 12 months after admission to the study[21]. However, in a retrospective analysis of these same patients, the authors identified variables which differed significantly among survivors and non-survivors[22]. A standard discriminate analysis identified age, sex, disease category, admission platelet count, admission creatinine, worst creatinine, and the need for dialysis as significant predictors of mortality. Patients were scored according to these variables by an unpublished formula which resulted in a score from -2.25 to +3.25, with increasing score favoring survival. Upon retrospective analysis of the 226 patients, none survived with a score of -1.25 or less.

In 1983, TISS was updated to reflect the changing practice of intensive care medicine[23] (See Figure 2). Based upon the authors' earlier studies they again measured physiologic variables and computed TISS scores in 199 patients with severe critical illness[24]. They found that patients with greater than 40% of their physiologic indicators were likely to die. However, the TISS scores were not predictive of mortality.

MPM

Lemeshow, Teres, et. al. initially derived the Mortality Prediction Model from data collected on 737 consecutive admissions to a medical/surgical ICU[25]. Excluded from consideration were coronary care, cardiac surgery, and burn patients. Data consisting of 137 condition, background, and treatment variables were collected at admission to the ICU and 24 hours later. Univariate tests of association, t-tests for continuous variables and chi-squared tests for categorical variables, found 12 admission variables and 26 variables collected at 24 hours which were significantly associated with hospital mortality. Subsequently, the authors performed a multivariate logistic analysis using a forward step-wise procedure. From the logistic coefficients, one can easily compute the odds

ratio (the likelihood that a patient with a given factor will die in the hospital relative to a patient without that same factor) or the overall probability of dying in the hospital for an individual patient. This multivariate analysis resulted in narrowing the number of variables significantly associated with hospital mortality to seven admission variables and seven 24 hour variables. Among those with the highest odds ratios were: level of consciousness, emergent admission, cancer, infection, number of organ system failures, age, and systolic blood pressure (See Figure 3).

Using the two multivariate models of admission and 24 hour data, the authors computed the individual patients' probabilities of hospital mortality. Using 50% as the cutpoint or decision criterion (that is, if the model results in a probability of 50% or greater then the patient is predicted to die; if less than 50% the patient is predicted to survive), the admission model correctly classified 87% of patients, and the 24 hour model correctly classified 85% of patients.

In order to verify prospectively the predictive power of MPM, the authors undertook another study of 1977 consecutive admissions to the same ICU[26]. For the admission model, the authors created an alternative model by removing the somewhat subjective OSF's as a variable and replacing it with whether the patient had CPR prior to ICU admission. Both of these admission models and the 24 hour model were utilized to predict hospital mortality. The original admission model with OSF's correctly classified 86% of patients as either survivors or non-survivors of their hospital stay. The sensitivity (correct classification of patients who died) was 50.25% and the specificity was 95%. The second admission model with CPR (Y/N) correctly predicted outcome for 85% of patients, with sensitivity 42.42% and specificity 95.25% However, the 24 hour model failed as a

predictor of hospital mortality. No results were given as the authors speculated that the original number of patients in the derivation of the 24 hour model was too small.

Shoemaker

In 1977, Shoemaker outlined a rationale for comparing physiologic data from non-survivors to survivors, instead of to normals[27]. Since physiologic derangements may represent compensatory changes having survival value, normals may not be the appropriate comparison group. Previously, Shoemaker observed a number of physiologic variables in survivors and non-survivors and computed the ranges for each of these two groups of variables[28] (See Figure 4). By noting when a variable for a particular patient fell outside the range of survivors, he predicted death. This method resulted in an average correct classification of 81% of patients studied retrospectively. When variables were observed at several different stages of disease and treatment and then analyzed cumulatively, retrospective predictive ability rose to 89%. The authors then verified the method prospectively[29]. Nevertheless, this method is vulnerable to a single spurious laboratory value.

In a study of 113 ICU shock patients admitted post-operatively after surgical procedures for life-threatening conditions, Shoemaker et. al. measured some 35 physiologic variables and described their ranges[27]. Each variable had some observations within the range of eventual survivors, some abnormal values of eventual non-survivors, and observations in an area of overlap between the ranges of those who would die and those who would survive. So, for a given variable (e.g. left ventricular stroke work), Shoemaker described a Range of Lethality, a Range of Survivability, and a Range of Overlap (See Fig. 3). If a value fell into the Range of Lethality, the

patient was predicted to die. In addition, the authors described "cutpoints" (CP) within the range of all values such that a value above CP_s was twice as likely to belong to a survivor and a value below CP_{ns} was twice as likely to belong to a non-survivor. In the early stage of post-operative care, 83% of patients were correctly identified on the basis of both the Range Criteria and the Cutpoint methods. In the middle stage after ICU admission, 72% were correctly classified by the Range Method and 81% by the Cutpoint method. In the late stage of critical care, the Range method was 90% correct, the Cutpoint method 96% correct.

Using these same 113 patients for further analysis, the authors retrospectively devised a new method of predicting outcome based upon the frequency distributions of the physiologic variables for survivors and non-survivors[30]. A point Q was chosen in the overlap region of each variable so that if Q were used as a cut point it would yield the highest percentage correct classification of outcome. A computer then generated the Severity Index from -1 to +1 (higher index favoring survival) based on the weighted average distance from Q for each variable. Over the stages of shock, this method resulted in the correct classification of 87-96% of the patients. With survival as the positive outcome, sensitivity ranged from 70-93% and specificity from 76-92%.

In a follow-up paper[31], Shoemaker ranked in order of predictive importance the variables measured in the previous studies. The commonly measured variables such as heart rate, temperature, and hemoglobin were the poorest predictors. More complex perfusion-related variables such as the efficiency of tissue O_2 extraction (ETOE), the red cell mass deficit (RCM), the O_2 transport/red cell mass ratio (OTR), peripheral vascular resistance (in

the early period only), left cardiac work (LCW), and blood volume (BV) were among the best predictors.

In prospective test of the Severity Index method, Shoemaker studied 156 post-operative shock patients using the methods of the previously published study[32]. The Index correctly predicted outcome in 147 of 156 patients for 94% accuracy. With survival as the positive outcome, the method demonstrated 95% sensitivity and 91% specificity.

In 1985 Shoemaker and Bland described a new method for predicting outcome by a computer-generated model based upon the probability of survival for 28 different physiologic variables[33]. While the authors do not fully explain the derivation of this model, it does compute an actual probability of mortality using the predictive ability of the 28 different variables. Using .50 as the decision criterion, the model correctly predicted 96% of patients in a group 220 patients, retrospectively. When the authors applied the model to 110 post-surgical shock patients prospectively, 94% were correctly classified by the model based on the last available values. The physiologic variables fell into four major categories: vital signs, systemic hemodynamics, pulmonary hemodynamics, and blood gas and oxygen metabolism.

CIS

The Condition Index Score (CIS) was described by Snyder et. al. in 1981 as a potential means of establishing objective criteria for admission to ICU's, comparing institutions or types of treatment, and establishing appropriate numbers of critical care beds in an area[34]. To begin, the authors defined 225 "conditions" representing diagnostic categories, clinical findings, physiologic derangements, and treatment interventions. For a study population of 498 consecutive admissions to a medical/surgical ICU,

each of the 225 conditions was recorded as present or absent, and the patients were followed during their hospital stay to determine outcome. The authors then employed a step-wise least squares regression to identify which of the conditions played a role in determining outcome. One Hundred and five conditions met the significance test of a partial F-test value greater than or equal to 1. The overall model accounted for 72% of the variability in outcome, according to the R^2 value of .72. Among the conditions with high regression coefficients and large F-values were encephalitis, nonreactive pupils, cerebrovascular accident with a change in consciousness, intracranial hypertension, cardiac arrest, pressor or antihypertensive infusion started, and the presence of an intra-aortic balloon pump.

To test the predictive accuracy of the model, the authors randomly selected 43 of the 498 study patients and plugged in their conditions into the regression model. Several of the patients who were clearly predicted to live died, and at least one patient clearly predicted to die (having the 6th worst score among the 43 patients), survived. No cut point or decision criterion was determined by the authors, but the model was at best 83.7% correct in classifying survivors and non-survivors. The CIS does, however, permit computing a probability score both at admission and over the course of ICU care with some level of accuracy.

APACHE

The APACHE system was first described by Knaus et. al. in 1981 after the authors completed a study of 805 patients in two hospital ICU's[35]. The only patients excluded from the study were patients with acute myocardial infarctions and those with burns. There were two parts to the data collected on behalf of each patient. The first consisted of 34 physiologic variables previously agreed upon by a committee of 7 physicians representing the

major specialties participating in critical care. Each of the variables was assigned a number of points from 0 to 4, based upon the degree to which it differed from normal reference values. For example, mean blood pressure in the normal range of 70-110 received no points, above normal pressure of 111-130 received 2 points, 131-159 earned 3 points, 160 or more earned 4 points. On the low side of normal, only two categories existed, 2 points for mean pressure from 51-69 and 4 points for a pressure of 50 or less. In this way, each variable was assigned ranges, awarding more points for values indicating the patient was more "sick". During the first 32 hours of ICU care, the most deranged value from normal was used in the calculation of the APACHE score. In the second part of the evaluation, a reviewer evaluated preadmission health status by an examination of the patient's past medical history. Each patient was assigned to preadmission health status.category A, B, C, or D (D being the worst)

The variables are nearly all commonly measured observations such as blood pressure, pH, ECG, blood urea nitrogen, temperature, etc. The investigators assumed that any variable not measured could be considered as normal, and therefor, would receive no additional points. A total physiology score (APS) was computed for each patient by adding the accumulated physiology points. The authors then compared the APS scores to the TISS points accumulated by individual patients. They found a high degree of agreement between the two scoring schemes. Next, the authors examined the relationship between APS and outcome, as defined by survival to hospital discharge, using multivariate logistic and probit regression techniques. Age, sex, operative status, organ system, and preadmission health category were other independent variables.

Based upon the regression formulas, patients were retrospectively evaluated for their probability of surviving. Using a .50 decision criterion, the APACHE model correctly classified 89% of the patients (correct classification = [true deaths + true survivors] / total patients). With survival as the positive outcome, the model was 97% sensitive and 49% specific.

In a multicenter verification of the APACHE system involving 1408 patients at 6 hospitals, the authors made two minor changes in the model[36]. First, they removed a variable, serum osmolality, finding that its removal caused no loss in the predictive power of the model. Second, they collected all the data within the first 24 hour of admission, not 32 hours. Then, using 613 patients at George Washington University Medical Center as the reference population, the authors performed a multivariate logistic regression analysis with APS score, age, sex, operative status, organ system, and preadmission health category as the independent variables. Within this regression model, the APS score was by far the most significant predictor of mortality. From this model, the authors predicted the outcome of the 795 patients at the other 5 hospitals within the 95% confidence intervals of each APS interval.

LeGall and his colleagues published a simpler version of Knaus' APACHE scheme in 1984[37]. Called the Simplified Acute Physiology Score (SAPS), the scheme depends only upon 14 physiologic variables and age. The authors studied 679 consecutive admissions to their ICU in France, measuring heart rate, blood pressure, temperature, respiratory rate, ventilation, 24 hr urine, BUN, hematocrit, serum glucose, white blood cell count, serum potassium, sodium, bicarbonate, and the Glasgow Coma Scale. With death as the positive outcome, the model was 56% sensitive and 82% specific. The receiver operator characteristic (ROC) curves for

SAPS and APS were extremely similar. The ROC curve is a method of demonstrating predictive accuracy without using a decision criterion such as .50. The ROC curve is a plot of sensitivity or true-positive rate against 1-specificity or false-positive rate (See Figure 6). The area under an ROC curve represents predictive accuracy, and one can compare these areas between two predictive models using a t-test. Those for SAPS and APS were not significantly different.

APACHE II resulted from a clinical appraisal and multivariate regression analysis of the 34 variables in APS by which the original investigators reduced the physiologic variables to 12 without losing explanatory power (as defined by R^2)[38]. The new model has slightly different weighting or point assignments from the original, and it now includes previous health status and other variables in this points scheme, assigning Chronic Health points, points for emergency surgery, and point for increasing age (See Figure 5). The 12 variables are similar to SAPS except that 24 hour urine, BUN, glucose and bicarbonate are omitted, creatinine and arterial pH are added, and the mean blood pressure is used instead of the systolic blood pressure. The new scheme had a high degree of inter-observer agreement (96%).

Knaus et. al. tested APACHE II on 5815 patients from 13 hospitals in the most extensive verification of a predictive model to date. Each 5 point increment of increasing APACHE II score carried a significant increase in hospital mortality. For example, APACHE II scores from 0-4 carried a 1.9% chance of mortality, but a score from 5-9 carried a 3.9% chance of mortality (X^2=5.28, p=.02). A multivariate logistic regression analysis found APS-12 (the new APS score), age, chronic health status, surgical status, and admitting diagnosis as significant determinants of outcome. The regression

model, using a decision criterion of .50, correctly predicted the outcome of 86% of patients in the study. The model was 47% sensitive and 94.9% specific with death as the positive outcome. Misclassification decreased as an individual's probability of death increased. Significantly, among 24 patients with septic shock and APACHE II scores greater than 40, there were no survivors.

In a demonstration of the types of studies that APACHE II may facilitate, Knaus et. al. published an interhospital comparison of outcome from intensive care[4]. Studying 5030 patients at 13 hospitals, the authors controlled for disease severity by comparing APACHE II scores. Noting that there were significant differences in mortality between some of the hospitals, they attributed these differences to factors external to the patients' illnesses, in this case the coordination and organization of the different critical care units.

In 1988, Kruse et. al. published their study comparing the APACHE II system to the clinical judgement of doctors and nurses in predicting outcome from intensive care[39]. The authors prospectively collected the data for calculation of APACHE II scores, and after admission evaluation they asked doctors and nurses involved in the care of each patient to assess the patient's probability of dying in the hospital. Using the regression model outlined in the APACHE II article, the authors calculated the patient's probability of mortality. Using .50 as the decision criterion, the APACHE II system correctly classified 79% of patients with sensitivity 67% and specificity 85% (with death as the positive outcome). The physicians and nurses varied by group (fellows, residents, interns and nurses) from 75 to 80% correct overall classification, 48-65% sensitivity, and 89-93% specificity. There was no significant difference in predictive power between

APACHE II or any of the provider groups. Likewise, the ROC curves were similar and the area under these curves was without significant difference as tested by the t-test.

Knaus and Wagner and colleagues have continued to improve the APACHE system, the most recent evidence of which is the new APACHE III model[40]. In addition to a number of technical changes in the model, APACHE III has been more reliable than clinical judgement in predicting hospital mortality among critical care patients[41].

In a study that goes to the heart of the resource allocation issue, Chang et. al. published a study in 1986 which demonstrated how APACHE II might be used to justify withholding of expensive treatment to patients who could not benefit from treatment[42]. First, the investigators studied 210 patients admitted to the ICU and calculated their expected probability of dying in the hospital based upon APACHE II. They noted that at a .50 decision cutpoint, the model was correct in 84.3 % of cases, with sensitivity 53.6% and specificity 95.5 % (with death as the positive outcome). However, at a decision point of .80, the specificity was 100%, indication that all predictions of death at that level of certainty were accurate. The authors then retrospectively evaluated 89 patients who had received the expensive therapy of total parenteral nutrition (TPN). They found that using a decision criterion of .60 resulted in 100% specificity. At this level, 7 of the patients were predicted to die, and they did. Finally, the authors prospectively tested this selection criteria on 26 ICU patients in need of TPN to see if that treatment could have been withheld. All 8 of the patients predicted to die according to the .60 APACHE II model did die. The authors concluded that such a criterion would have saved 28% of the cost of TPN for their 4-bed facility, a savings of some $15,000 annually, just for TPN. The cost savings

would have been much greater had the authors considered the withdrawal of other care, such as all ICU care in these patients.

Discussion of predictive models

Although Knaus' OSF data do not offer a formulaic means to calculate probability of survival, they do indicate that a physician might make individual treatment decisions in some cases based upon the number of OSF's and the patient's age. The system is widely generalizable and easily implemented. A problem exists in that definitions of organ system failure must be precise and identical in any multicenter trial, as a wide margin of error may exist with subjective determinations of OSF. The breakdown of mortality for each level of OSF could serve as a comparison for similar studies at other centers or for rough comparisons between ICU care and other forms of therapy. Perhaps its most promising use is as a complement to another scoring scheme and the clinician's assessment of prognosis in patient care decisions.

Because all intensive care patients are likely to receive massive support in terms of electronic monitoring, laboratory analysis, and nursing and physician visits, a predictive index based upon the level of therapeutic intervention is unlikely to be a very precise predictor of outcome. As Cullen demonstrated in the TISS studies, the derangement of physiologic variables hold far greater promise as indicators of future mortality among ICU patients. Nevertheless, TISS has proven valuable as a measure of the intensity of therapeutic intervention on behalf of critical care patients. It is now widely employed by investigators as a corroboration of statements that different patient groups received similar levels of medical care. It has further utility in assigning nurse:patient ratios and establishing future needs for ICU beds.

The Mortality Prediction Model has several important strengths beyond its ability to correctly predict outcome in a high percentage of cases. The method employs a logistic regression function which is better-suited than other models to describe a function with a binary dependent variable such as hospital death/survival[43,44]. It results in a regression function which one may use to compute the probability of the patient's dying in the hospital by simply plugging in the patient's data into the formula. The formula is objectively derived from analysis of actual patients and not formulated by a panel of experts as APACHE is. Additionally, the models are simple, consisting of only 7 variables in each, many of them overlapping into both models. These data are easily collected and recorded, and they are routine enough that data are unlikely to be missing for many patients. Finally, the admission model is not being influenced by treatment in progress which might otherwise correct grossly deranged physiologic variables (blood pressure, for example).

Despite these strengths and the authors' conclusion that the MPM is an effective and simple method to predict outcome for ICU patients, it was derived from a single hospital. A few of the variables do involve subjective interpretation (e.g. suspected infection or number of OSF's), and there may be systematic inter-observor or interhospital variation in the collection of data.

Shoemaker's approach to predicting outcome by comparing data from survivors to data from non-survivors is not unique. However, his multi-faceted approach to analysis and comparison between the two groups is remarkable. Whether utilizing the Range, Cutpoint, Severity Index, or an automated index method, there is clearly predictive power in comparing survivors to non-survivors. Nevertheless, the small number of patients

studied at this single institution leads to speculation that the published ranges for physiologic variables need extensive further testing and verification before other ICUs will utilize the methods. In addition, Shoemaker's methods may be significantly less generalizable than other methods since the study population consisted exclusively of post-operative shock patients at a single center. Even though the patients underwent surgery for a wide variety of conditions, all developed common problems of tissue perfusion and oxygenation in the ICU. Furthermore, the authors often screened out patients with pre-existing conditions such as cardiac, liver, or nutritional disease which they felt might interfere with the physiologic data. Each of the Shoemaker methods involves an analysis of 28-35 variables, some obtained by invasive catheterization or monitoring. As Shoemaker found, more easily obtained and routinely recorded variables, such as blood pressure and pulse, were the least valuable in predicting outcome. It is likely that future efforts to employ these methods would be hampered by incomplete data.

One of the many weaknesses in the CIS model is that many of the 105 conditions occurred too infrequently to be of statistical significance. Perhaps testing the concept on a much larger patient population would solve this problem, but there are additional theoretical weaknesses. For a dependent variable such as death/survival which is binary, OLS regression is probably an inappropriate tool[43]. Furthermore, regression analysis of outcome and over 200 independent variables raises the strong likelihood of multicollinearity and autocorrelation. A step-wise regression procedure has inherent deficiencies as it is often used in place of a theory to select variables likely to play a role in determining outcome, an unfavorable analytic viewpoint.

In APACHE there was substantial variation among individual patients despite the overall high accuracy in predicting outcome. The authors emphasized that this model was designed for comparison among groups of patients and should not be utilized for individual patient care decisions. A problem exists in the assumption that any variable not tested is considered normal, since unrecognized disease processes may account for unexpected mortality. Additionally, the number of variables, 34, is quite large and doubtless includes some redundancies. However, APACHE employs a regression technique appropriate to binary dependent variable studies in logistic and probit. The authors of APACHE have also dealt with the problem of treatment influencing the score by using only the most deranged value over the first 24 hour of care. Nevertheless, as in all of the models described, therapy may influence even these initial values as treatments are often initiated in the emergency room or ward from which the patient was transferred to the ICU (a problem common to any assessment scheme). Multivariate regression requires large sample sizes and wide variation about the mean values in order to produce statistically meaningful results. A problem arises in the APACHE model if a hospital measures a variable with greater frequency than a comparison institution. More frequent measurements increase the chances of a spurious abnormal result and lead to an overestimation of mortality. In SAPS and APACHE II, the authors appear to have addressed many of the problems with the previous models. By virtue of their simplicity, these models are easily implemented and verified. There is unlikely to be significant interobserver bias, and few variables are likely to be missing.

In 1990, Schafer et. al. published a comparison of the APACHE II, SAPS, and MPM models in a prospective study of 941 patients at a single

institution[45]. They found that the models varied little in their overall reliability, with APACHE II correct 75.8% of the time, SAPS correct 75.6%, and MPM correct 73.3%. The models did vary in that SAPS had a much lower sensitivity and much higher specificity in predicting mortality than the other two models. In each case, the models performed substantially worse than they had in the original papers describing them. This study indicates that while promising, the models have not yet fully addressed the problem of interobservor bias.

Conclusion

There is much reason to suspect that the degree of physiologic derangement experienced by a patient during the course of an illness will foretell the outcome. Many of the variables commonly measured are windows to the homeostatic workings of the human organism attempting to restore health. For example, a measure of the systemic vascular resistance early in the course of shock allows the physician to "see" the patient's capacity to restore a sufficient blood pressure. If the SVR does not increase, it is unlikely the patient will recover.

The evidence that indices of physiologic derangement successfully predict outcome in the ICU is consistent and strong. The multitude of studies conducted, testing a variety of computational schemes, demonstrates that such models will accurately predict outcome 70-100% of the time.

Prognostic scoring systems based upon physiologic information gathered during the early course of disease show great promise as measures of the severity of illness or the capacity to recover. While systems based upon single diseases or organ systems cannot be applied to the wider ICU patient population, these may have value in corroborating claims that severity of illness is controlled for in clinical studies. The more

generalizable schemes based on physiologic measures and multi-organ system disease have far greater implications. These evolving schemes will play a role in individual patient care decisions. Despite the findings of Kruse, these systems do bring something new to the patient care world. For the first time, clinicians may now point to hard evidence when they take a stand to withdraw or withhold care in futile cases. Schneiderman et. al. have said treatment is futile when in the last 100 cases, medical treatment has been useless[46]. Nearly all of the models lent themselves to highly accurate predictions of mortality among patients with the very poorest prognoses, and several defined parameters beyond which survival was unprecedented. The models provide a basis for declaring that treatment is futile and that resources should not be expended.

A major problem exists in the use of hospital death as the dependent variable in many of the systems. While hospital mortality may represent a reasonably good yardstick for general outcome for large numbers of patients, it tells us little about an individual patient's expected duration and quality-of-life. In the APACHE III data, length of hospital survival ranged from one day to hundreds. If these models are ever applied to individual patient care decisions, greater attention must be paid to quality-of-life and length of life, even while in the hospital.

In the future, investigators must seek to streamline their predictive schemes further. The best of the models, APACHE II, is still a fairly complicated and time-consuming exercise. Further study of possible variables and weighting schemes is needed to devise a simpler index. Beyond simplification, the goals of future investigation must be to devise practical and ethical guidelines for the use of such models in patient care decisions. The models will undoubtedly find use in interhospital

comparisons and large clinical trials, but doctors, patients, and society may find great rewards in their application to individual patient care decisions. Their potential use for resource allocation and more humane treatment is promising, but the identification of the boundaries of "futility", and acceptance of those boundaries, may be our greatest challenge.

PART II CLINICAL RESEARCH ON OUTCOME OF SEPTICEMIA

Review of Septicemia Literature

Septicemia has been defined as "systemic disease caused by the multiplication of microorganisms in the circulating blood"[47] and as a "systemic disease caused by the spread of microorganisms and their toxins via the circulating blood"[48]. For purposes of this study, septicemia signifies disease in the presence of viable bacteria or fungi in the circulating blood, as demonstrated by positive blood culture. Although one author[49] rejects this term as imprecise, another author[50] believes this term is proper, and I use it in accordance with this author's proposed definition.

Septicemia is a common and severe disease encountered in the intensive care unit. Patients with septicemia often have multiple medical problems, such as severe respiratory disease, and a weakened immune system, as in patients with AIDS or malignancy. These patients are among the sickest in the ICU, and often they have the poorest prognosis. Many physiologic changes take place when a patient becomes septic (i.e. heart rate increases, blood pressure may fall, etc.), and these changes are commonly recorded in an ICU. Prognostic scoring indices, like APACHE II, include many physiologic variables that become deranged during an episode of septicemia.

Septicemia Outcome

Numerous authors have conducted studies of patients with septicemia in an effort to identify clinical or physiologic markers predictive of outcome. What follows is a summary of the literature relating to septicemia outcome and variables associated with better or worse outcome among septic patients.

In 1987 Miller and Wenzel conducted a study to determine the factors which were important in predicting hospital death and morbidity in hospital patients with nosocomial bloodstream infections[51]. The authors reviewed the charts of 385 patients to record etiologic organism, demographic variables, and a range of physiologic parameters associated with shock and poor outcome. Bloodstream infection was defined by the Kardex method of surveillance[52,53]. Severity of underlying illness was estimated using an unpublished method based on age, race, sex, and primary diagnosis (as listed by ICD-9 code). An initial univariate analysis by chi-squared test demonstrated an association between death and infection due to Pseudomonas aeruginosa, Candida spp., or greater than one organism simultaneously (polymicrobial infection). Employing a step-wise discriminant analysis including all variables in the study, Pseudomonas, Candida, respiratory failure, oliguria, and metabolic acidosis were predictive of death ($p<0.002$). When the physiologic variables were omitted from consideration in the multivariate function, age, Pseudomonas and Candida were predictors of death. The authors also employed a multivariate discriminant analysis to determine which factors were associated with the morbidity of shock. Pseudomonas, Candida, Enterococcus, Enterobacter, Klebsiella, and Serratia were organisms associated with one or more of the individual clinical parameters associated with shock (oliguria, hypotension, acidosis, respiratory failure, or hypothermia).

The results of this study indicate that, in addition to physiologic derangements of respiratory failure, oliguria, and acidosis, etiologic organism in septicemia is important in predicting morbidity and mortality. Particularly strong association with poor outcome was demonstrated for Pseudomonas and Candida, a finding which has been previously

reported[54-56]. The authors utilized a model for severity of disease based not on the level of physiologic derangement (as in the APACHE system), but on demographic data and primary underlying diagnosis. This model was not predictive of mortality, and was only statistically significant in predicting hypothermia, a clinical parameter associated with shock.

In 1987, Iyer et. al. published the results of their study of prognostic indicators in septicemia from a hospital in the U.K.[57]. In 137 episodes of septicemia, all documented by positive blood cultures, the authors found female sex, underlying hematologic malignancy, and respiratory source of infection significant predictors of death in univariate chi-squared analysis. Etiologic organism and age were not significantly associated with outcome. In a step-wise logistic multivariate regression, male sex, absence of hematologic malignancy, genito-urinary source of infection, and physiologic parameters fever, normal BUN, normal hemoglobin, and normal pulse were significant predictors of survival ($p<0.05$). The logistic model that included these variables predicted 71% of the variation in survival as dependant variable.

The results of this study indicate that age and etiologic organism may not be an independent predictor of short-term outcome. A prior study by Setia at al.[58] supports these findings. However, numerous studies have shown age to be associated with poor outcome[59-61]. Numerous studies have also shown etiologic organism, usually recorded simply as Gram-positive vs. Gram-negative bacterium, to be important in determining outcome[62-65]. Interestingly, of the four physiologic variables found to be significant in predicting outcome in this study, namely BUN, hemoglobin, pulse and temperature, each of them is included among the twelve parameters of the APACHE II system.

Three studies have focused on physiologic variables, primarily cardiovascular variables, in predicting outcome from septicemia. D'Orio et. al. conducted a prospective study of physiologic indices associated with outcome in 26 ICU patients with septic shock[66]. Using a step-wise discriminant analysis, the authors identified LVSWI/WP (left ventricular stroke work index/wedge pressure), white blood cell count, pO_2, and hematocrit as significant in predicting which patients survived or succumbed during the shock episode. Comparing the mean values among survivors and non-survivors, CI (cardiac index) and PVR (peripheral vascular resistance) showed statistical significance, but did not predict outcome in the discriminant multivariate model.

Although the majority of variables monitored in this study required the placement of indwelling catheters, the results of the discriminant function analysis include only one variable requiring such monitoring (LVSWI/WP). The remaining three parameters which were significant predictors are more easily collected, via arterial and venous puncture. Each of these three is included in the APACHE II system.

Groenveld et. al. reported that physiologic variables mean arterial pressure, blood lactate, and SVR were significantly different ($p<0.0005$) between 21 survivors of septic shock and 21 non-survivors of septic shock[67].

Pilz and Werdan compared APACHE II[38], SAPS[37], MOF[69], "Hannover Intensiv Score"[70], and two septicemia severity grading schemes[71,72] for their ability to predict outcome among 47 ICU patients with septicemia[68]. The authors also monitored a wide range of hemodynamic and physiologic parameters to identify those which predict outcome. Of all the scoring systems employed, APACHE II was the best predictor of whether

or not a patient responded to therapy by correcting hemodynamic derangements (sensitivity 67%, specificity 88%). Among the physiologic parameters, only a prompt return of the systemic vascular resistance (SVR) within 24 hours of initiation of septicemia therapy discriminated between survivors and non-survivors.

In retrospective study of 71 patients with septic shock, Arregui et. al.[73] also compared several prognostic scoring systems, including APACHE II, Mortality Prediction Model[25], Multi-Organ System Failure Model[15], two additional systems based on the number of organs in failure[69,71], and a grading scheme for septicemia[74] not discussed earlier in chapter 1. The scoring schemes which did demonstrate significant discriminating power between ICU survivors and non-survivors were APACHE II, the MOSF model described by Knaus, and the MOF model by Fry. Age, sex, admission type, and site of infection were not significant in a logistic regression model.

Roberts et. al. report that the additional risk for mortality from bacteremia persists beyond the days immediately following identification of the infection[75]. In their study of 37,156 blood cultures, 1,972 of which were positive, the authors demonstrated that septicemia is associated with an added risk of death which continues for at least 20-30 days after the finding of positive blood cultures. Fungemia, predominantly Candida spp., Pseudomonas, Serratia, and polymicrobial infections were associated with higher mortality. Also increasing the risk of mortality were infections from a respiratory, gastrointestinal, or multiple site of origin.

The authors found that 14.6 clinically significant episodes of bacteremia occur per 1,000 admissions to the hospital, a frequency comparable to that reported by Weinstein in an earlier paper[59]. The finding

that polymicrobial episodes of bacteremia result in a higher mortality has been reported by several authors previously[76-78].

To determine the excess mortality attributable to nosocomial bloodstream infections, Smith et. al. analyzed data from 34 medical ICU patients with nosocomial septicemia and compared these to data from 34 matched controls from the same ICU population[79]. Utilizing the APACHE II scores of patients to select controls based on the same severity of illness, the authors demonstrated that septic patients had approximately 28% excess mortality than their non-septic counterparts. Using the regression equation offered by Knaus for the APACHE II system, Smith verified that the regression model correctly predicted mortality in 384 ICU patients including the 34 matched controls. However, the bacteremic patients' mortality exceeded the mortality predicted by their APACHE function, and it exceeded the mortality of the control patients. The overall mortality of bacteremic patients in the study was eighty-two percent.

Previous studies have indicated that a high percentage of nosocomial bacteremias occur in the ICU, which typically contains less than ten percent of the hospital beds[80]. The authors note that the high mortality rate reported in this study exceeds that of other studies in which mortality ranges from 25 to 49 percent[81-83]. The high mortality also exceeds the 60% reported by Forgacs in a larger study of ICU patients[84].

In a study of 239 cases of community-acquired bacteremia in South Africa, Rayner and Willcox report increased mortality with the following characteristics: infection with Klebsiella or Group A, B, or C Streptococci, respiratory source of infection, confusion alone as the presenting symptom, white blood count below 2500, low platelet count, lack of fever, inappropriate or late antibiotic therapy, and complications including acute renal failure,

respiratory failure, shock, and DIC (disseminated intravascular coagulation)[85].

Because the cases were community-acquired and not nosocomial, the organisms most frequently encountered were somewhat different than those of most studies which had a fairly high number of Pseudomonas and fungal infections. Nevertheless, the results agree with previous and later studies which identify E. coli as an organism associated with better outcome. The physiologic abnormalities resemble those identified in other studies and in the APACHE II system.

As discussed in a Jacobs and Bone article[86], Kreger and McCabe reported a number of factors which were associated with increased mortality among 612 patients with gram negative bacteremia[87]. Azotemia, congestive heart failure, diabetes mellitus, and nosocomial infection were predictive of increased mortality, but race, gender, and underlying neoplasm were not. This review also sites the study by Winslow to buttress the assertion that shock is the single best predictor of poor outcome among septic patients[88].

Cooper et. al. report that among 96 patients with polymicrobial bacteremia, respiratory failure, hemolysis, and severity of underlying illness were significant predictors of mortality in a logic multivariate model ($p<0.001$)[89]. Severity of disease was measured by clinical judgement and recorded by placement into one of three categories based upon expected length of survival(<1 year, 1-5 years, or >5 years). Age, etiologic organism, temperature and white blood cell count were not significant in predicting outcome.

In an study of septicemia in the elderly in Israel, Sonnenblick et. al. reported that nosocomial infection and low body temperature were

significantly associated with mortality in a logistic regression model ($p<0.05$), and soft tissue or genito-urinary source of infection was associated with survival ($p<0.05$)[90]. Numerous variables showed significance in a univariate chi-squared analysis, including physiologic derangements and Klebsiella or Proteus as the organism. The authors site two studies noting that polymicrobial infection increases mortality[91,92].

In summary, numerous studies have demonstrated that etiologic organism, source of infection, severity of underlying illness, complications of septicemia, and several individual physiologic markers are important in determining outcome. Pseudomonas and fungi (Candida) are clearly strong predictors of poor outcome, and Klebsiella, Serratia, and polymicrobial infections are probably predictive as well. E coli is predictive of better outcome. Respiratory source of infection, and probably gastrointestinal source of infection, are predictive of poor outcome. Severity of illness is clearly an important predictor. APACHE II has proven to be an effective means of assessing illness severity in septic patients, but some scoring methods are not effective. Specific underlying diagnoses contributing to illness severity may individually affect outcome. These include hematologic malignancy, congestive heart failure, and diabetes mellitus. Complications of sepsis, particularly evidence of septic shock, are important in predicting outcome. Demonstrated complications which contribute to mortality include respiratory failure, azotemia, hypotension, disseminated intravascular coagulation (DIC) and hemolysis. Several individual physiologic markers are predictive of outcome, including systemic vascular resistance (SVR), low body temperature, white blood cell count, hematocrit, pO_2, and LVSWI/WP.

Obviously, many of these variables are interrelated: for example, a nosocomial respiratory infection by Pseudomonas may lead quickly to

complications of respiratory failure and hypotension, detected physiologically by a drop in pO_2, SVR and LVSWI/WP. The value of an index such as APACHE is that it reflects derangements in many of these variables by including an array of physiologic parameters and chronic health points. An even more valuable index is APACHE III, which changes daily with the status of the patient, instead of relying upon data gathered entirely during the first 24 hours of ICU stay.

Long-Term Outcome After Intensive Care

A number of studies have examined long-term outcome among critical care patients. The majority of these studies have been conducted outside the U.S., though several have occurred in this country. Some disagreement has arisen regarding the appropriate length of time that critical care patients need to be followed to capture their overall risk of mortality above the general population. Therefore, the studies often differ in the amount of time the patients are studied after admission or discharge. What follows is a thorough though not exhaustive discussion of the literature on the topic of long term survival after intensive care.

In 1989 Zaren and Bergstrom reported their findings from a study of all 980 patients admitted to the intensive care unit in Sweden over a one year period[93]. The overall ICU mortality was 9.6% and the mortality after one year after intensive care was 26.4%. The authors compared the cumulative mortality of the critical care patients to that of the general population of Sweden as calculated from actuarial data. They found that the observed mortality exceeded that of the general population for approximately six months after intensive care, at which point the rates became indistinguishable (See Figure 7). Based upon this information, the

authors recommend that followup from critical care be continued for one year so as to observe this trend. Additionally the authors studied patient characteristics and demonstrated that mechanical ventilation and underlying cancer were significantly associated with mortality. Lastly, the authors attempted to assess quality-of-life and health status among the surviving patients. Among those patients still alive after one year, 77.7% said their health status was the same or better than prior to intensive care.

The finding that mortality stabilizes after six months contradicts the findings of Dragsted and colleagues who demonstrated a stabilization of mortality 18-24 months after discharge94. LeGall reported a six month follow up time as appropriate[95]. Two previous studies corroborate the finding that cancer is associated with increased risk of mortality[25,96].

Campion et. al. published a study involving 2,693 patients admitted to the ICU at Massachusetts General Hospital[97]. The mean followup period was 360 days. Age, congestive heart failure, and mechanical ventilation were each associated with increased long term mortality.

Parno and co-workers reported on 558 patients, 63.5% of whom were still alive two years after intensive care[98]. Infection, renal failure, shock, coma, CPR administration, fever, myocardial infarction and coagulopathy were significantly associated with long term mortality as assessed by a modified Mantel-Haenzel procedure.

Prior studies have reported survival rates at six months of 72%[99]; at one year ranging from 27% to 89%[100-102], at 15 months of 73%[103], at two years of 64%[104], and 30% at four years[105].

LeGall and co-workers prospectively studied 228 unselected patients from the ICU of a French hospital and followed their status for one year after intensive care[95]. 66% of patients were discharged from the ICU, but survival

fell to 50% at six months. During their ICU stay, patients' severity of illness was rated on the basis of the number of organ systems in failure (the presence of severe septicemia was also considered an organ system failure). One year after intensive care, survival was 49%, suggesting that the risk of mortality after intensive care returns to that of the general population after six months. Factors significant in predicting long-term survival were age less than 50, health status prior to admission, and severity of illness, the best predictor ($p<0.001$).

In a study of ICU patients undergoing mechanical ventilation, Davis et. al. reported 56% hospital mortality[106]. Long term follow-up revealed 63% mortality one year after intensive care, and 72% mortality two years after intensive care. Primary diagnostic categories of pulmonary disease and cardiac disease were associated with significant increased mortality each year, whereas other diagnoses were not. The authors noted that the mean hospital charges for the patients studied was $12,300 at a time when the average hospitalized patient at this same hospital accrued charged of $1,809.

Ridley and colleagues reported the results of a long-term outcome study of critical care patients in Britain in 1990[107]. Of the 497 patients studied, 24% died in the ICU, and 48% were dead after two years. Univariate chi-squared analysis indicated that age, severity of illness as assessed by the APACHE II system, and diagnosis were predictive of long-term survival ($p<0.001$). Multivariate analysis with a Cox Proportional Hazards model resulted in age and severity of illness being the only significant predictors. Survival curves demonstrated that critical illness continues to shorten life expectancy even beyond six months after discharge, especially among the elderly. Among patients over 65, only 38%

were alive at two years. The authors note that although the APACHE II system does contain up to six points for age, this parameter should be weighted more heavily when considering long-term outcome.

In studies of quality-of-life after critical illness, two studies demonstrated significant deterioration after admission to an intensive care unit. Searle found that in a study of ICU patients, only 17% of the survivors returned to their normal level of quality-of-life as they experienced it prior to intensive care[108]. Ridley and Wallace demonstrated that among patients with a high quality-of-life prior to intensive care, there was a significant decrease after critical illness (with quality-of-life measured using the Rosser disability categories)[109].

In a study of 126 critical care patients in Israel, Yinnon, Zimran and Hershko reported that 63% were alive at discharge, 41% survived six months, and 37% were alive at one year[110]. The authors found that quality-of-life prior to admission was a significant predictor of long-term survival. This was assessed by interview with the patient while in the ICU, and the authors employed a number of measures including the Karnofsky score, the linear analogue self-assessment, quality of sleep, sexual activity, employment, and housing status. Among these measures, Karnofsky score, LASA score, employment and quality of sleep were significant ($p<0.05$) in predicting long-term survival, using a Wilcoxon matched-pairs signed-ranks test. Additionally, the authors found that, among the survivors after six months, quality-of-life was unimpaired when compared to preadmission.

In a Dutch study of mortality and quality-of-life after critical care, Jacobs and colleagues followed 313 patients in the ICU[111]. 76% survived to discharge, 61% survived six months, and 58% survived to one year. Severity of illness was assessed in the ICU using the simplified acute

physiology score (SAPS). Quality-of-life information before and after intensive care was assessed by a questionnaire which included questions about housing, drug use, readmissions, and physical impairments. The authors concluded that the best predictor of quality-of-life after critical care was health status prior to admission. Age and SAPS were also significant in predicting quality-of-life ($p<0.001$), but neither influenced the long-term quality-of-life when prior health status was taken into consideration. Among survivors two years after discharge, 77% said their physical condition was the same as prior to their critical illness.

To summarize, authors differ with regards to the appropriate time interval one should use to capture the effects of critical illness on long-term survival. Because several studies indicate that the risk of mortality is greater for ICU patients than for the rest of the population well beyond six months, it is appropriate to follow patients a full year or more. The long-term mortality after intensive care varies greatly from hospital to hospital and country to country. One year after hospital discharge, studies report 27-89% of patients remain alive, with several authors reporting survival of 50-60%. Severity of illness, age and health status prior to admission probably play the most important roles determining long-term outcome. Cardiopulmonary disease, specific diagnoses including cancer, and complications of the acute illness also predict long-term outcome. Lastly, therapeutic interventions including mechanical ventilation and CPR are predictive of poor outcome. As with predicting short-term outcome, many of the explanatory variables are highly correlated. Authors disagree about whether quality-of-life is restored among long-term survivors of critical illness.

Patients and Methods

All patients admitted to California Pacific Medical Center's Medical Intensive Care Unit (MICU) between January 1, 1987 and March 31, 1991 were part of this study. Data were recorded by an intensive care nurse and included the APACHE II score, based upon physiologic values obtained during the first 24 hours in the ICU, underlying diagnostic categories, procedures and interventions undertaken during the ICU stay, and complications while in the ICU. 266 episodes of septicemia involving 253 patients were identified in the ICU, based upon either a microbiology laboratory report or clinical evidence of septicemia including fever, tachycardia, hypotension, local infection or evidence of shock and organ failure.

Late in 1991, the chart of each patient was reviewed to supplement the data base with demographic information including sex, date of birth, race, and insurance status, as well as information about the type of admission - whether a transfer patient from another hospital or skilled nursing facility, or an admission through the emergency room, etc. Nine charts were either missing or so incomplete that we chose to discard them. We examined laboratory reports to determine if cultures drawn around the time of intensive care later grew out organisms. Lastly, we recorded from the charts all discharge ICD-9 code information regarding underlying or concurrent diagnoses, and we noted any complications which occurred during the ICU stay. The number of admissions to this hospital in the previous twelve months was also noted.

Follow-up took place more than one year after the last patient was discharged from the ICU. Using death records from San Francisco city and county, the state of California, and finally from national Social Security and

Death Index sources, the dates of death for all deceased patients were recorded. Approximately forty patients were telephoned directly to verify their status as alive more than one year after intensive care.

In 57 of the cases blood cultures did not produce organisms after culture, and these cases were omitted from the study. For patients with more than one ICU admission involving septicemia, only the first episode was considered for analysis. These last considerations resulted in an sample size of 188 consecutively admitted critical care patients with documented bacteremia or fungemia.

Unfortunately, among these 188 patients, 33 were lost to follow up even after searching the California death records and attempting to contact the patients directly. At the time of this writing, a search is underway through national Social Security and Death Indices to account for these 33 patients.

Statistical Methods

All patient information, with the exception of any personal identifying information, was uploaded to the UNIX system of the University of California at Berkeley. Statistical analysis was performed using the SAS system and ordinary least squares (OLS) or logistic techniques. All variables were examined for the skewdness of their distribution, and in three cases the variables were converted to log format to insure that the theoretical requirements for using the logistic statistical model remained true. A correlation matrix was generated for 58 variables to look for evidence of descriptive power among the variables and to assess potential multicollinearity. Based upon a review of the literature, the correlation coefficients, and our theory of which variables might contribute to an explanatory model of outcome, we selected approximately twenty-five

variables to form a model equation in OLS and logistic multivariate regression analyses. A separate logistic analysis was performed for each of five binary dependent variables: Deceased at hospital discharge, Deceased at one month after hospital discharge, alive two months after hospital discharge, Deceased at six months, and Deceased at one year. Ordinary least squares regression was performed for days of survival after hospital discharge, and days of survival following ICU discharge as continuous dependent variables. For this last analysis, patients who were still alive after one year were given truncated survival days amounting to more than 365 days of survival.

The independent variables selected for inclusion in the regression models represent all the categories of explanatory variables that have previously been tested in the literature. All models included our primary variable of interest: APACHE II score as an assessment of illness severity and physiologic derangement.

Demographic variables of race, sex, age, and marital status were included to assess their importance in explaining outcome after septicemia. Because many of the patients were over 65 with severe illnesses, it was thought that age might have significant explanatory power in determining long-term outcome. The other demographic variables, while not expected to yield significant results, might influence outcome, especially long-term, through their relationships to socioeconomic status and social support network. Insurance status, whether medicare, mediCal, private, uninsured, or some combination of these, was included to assess whether or not availability of treatment or reimbursement incentives played a role in influencing duration of survival after septicemia.

A number of hospitalization variables were tested, including a binary variable describing whether or not the patient had previously been an inpatient at this same institution within the past twelve months. Route of admission, whether by ambulance through the emergency room or via transfer from another hospital or skilled nursing facility (SNF) were tested to gain insight into the importance of emergent admissions, tertiary referrals and SNF transfers in determining outcome. Previous, Hospital and SNF transfer might indicate a more severe illness, or chronic underlying disease complicated by acute critical illness. Three organisms, all studied previously in other studies, were tested for their importance in explaining outcome from septicemia: E. coli, Staph epidermidis, and Pseudomonas.

Season of admission was included because of the possibilities that changes in the house staff might affect quality of care delivered or that climate changes might influence outcome in individual patients.

Acute clinical events or complications of the patient's illness, including respiratory arrest, cardiac arrest, altered mental status, and hypotension, were tested to determine if these events might contribute additionally to poor outcome, beyond the physiologic derangement they would cause and that would be detected by APACHE II. Likewise, more longstanding diagnoses, including AIDS or HIV positivity, hypertension, diabetes mellitus, and chronic renal failure, were tested since these might detract from the body's physiologic reserve and diminish its ability to overcome an acute illness such as septicemia. These co-diagnoses might also decrease a patient's long-term survival.

Lastly, we tested a number of therapeutic interventions, including intubation, mechanical ventilation, bronchoscopy, and hemodialysis. Each of these might indicate that a patient's condition had deteriorated to the point

of requiring mechanical support. By incorporating these interventions in the models, we tested whether the need for such support was significant in explaining death among septic patients.

All of the above variables were included in a step-wise regression analysis after forcing the variable Apache into the model. Because of the great tendency to multicollinearity among numerous variables reflecting illness severity, and because of the tremendous explanatory power of Apache as an independent variable, a step-wise procedure was employed to select only those independent variables that contributed additional explanatory power to the model after taking Apache into consideration. In the step-wise procedures, a variable was admitted to the model if it obtained a p-value less than or equal to 0.15 in a two-tailed test of significance.

Results

Among the 155 patients for whom our data is complete, 82 were male, 73 were female, and the mean age upon admission was 57.96 years. The average length of stay in the hospital, including the ICU care, was 22.74 days. The mean APACHE II score was 23.83. 75 patients were mechanically ventilated in the ICU and 22 patients underwent hemodialysis. 33 patients were HIV positive or carried the diagnosis of AIDS. 67 patients died while in the ICU (43.2%). 30 (19.4%) additional patients died during their hospital stay, resulting in 58 patients (37.4%) surviving at time of discharge from the hospital.

One month after discharge, 52 patients (33.5%) were still living. Two months after hospital discharge, 51 patients (32.9%) were still living. Six months after discharge, 36 patients (23.2%) remained alive. One full year after discharge, 28 patients (18.0%) were still alive.

APACHE II score was highly correlated with both short-term and long-term mortality. (See Table 2). Of the eight patients with APACHE II scores of 41 or above, all eight died in the ICU. Age was not highly correlated with short or long-term mortality. Of the four patients aged 91 and older, two of the four survived more than one year after hospital discharge.

Step-wise logistic procedure for the binary dependent variable Deceased at discharge resulted in only four explanatory variables attaining statistical significance at the .05 level: Apache, Asian, E coli, and Polymicrobial bacteremia. (See Table 3 for full model). Of these four explanatory variables, only APACHE was predictive of poor outcome. Odds ratios were computed for each of the four significant parameters. The odds ratio for Apache is 1.12 per unit increase in Apache II score. The odds ratios for Asian, E coli, and Polymicrobial are 0.233, 0.144, 0.351, respectively.

Step-wise logistic procedure for the binary dependent variable Deceased at 1 month after discharge also resulted in only four explanatory variables attaining statistical significance at the .05 level: Apache, with higher APACHE score resulting in increased mortality, and Asian, Staph epidermidis, and E coli, all resulting in decreased mortality. (See Table 4 for full model.) The odds ratio for Apache is 1.099 per unit increase in Apache II score. The odds ratios for Asian, Staph epidermidis, and E coli are 0.231, 0.385, 0.122, respectively.

Step-wise logistic procedure for the binary dependent variable Deceased at 2 months after discharge resulted in five explanatory variables attaining statistical significance at the .05 level: Apache, Fall season of admission, Asian, Staph epidermidis, and E coli. (See Table 5 for full model.) APACHE and Fall were predictive of poor outcome; Staph epi and E. coli were predictive of good outcome (survival). The odds ratio for

Apache is 1.100 per unit increase in Apache II score. The odds ratios for Fall, Asian, Staph epidermidis, and E coli are 3.646, 0.227, 0.414, 0.112, respectively.

Step-wise logistic procedure for the binary dependent variable Deceased at 6 months after discharge resulted in only four explanatory variables attaining statistical significance at the .05 level: Apache and Previous admissions, each increasing mortality, and Staph epidermidis, and E coli, both reducing mortality (See Table 6 for full model). The odds ratio for Apache is 1.084 per unit increase in Apache II score. The odds ratios for Previous, Staph epidermidis, and E coli are 2.562, 0.355, 0.074, respectively.

Finally, Step-wise logistic procedure for the binary dependent variable Deceased at one year after discharge resulted in these same four explanatory variables attaining statistical significance at the .05 level: Apache, Previous admissions, Staph epidermidis, and E coli. (See Table 7 for full model.) The odds ratio for Apache is 1.100 per unit increase in Apache II score. The odds ratios for Previous, Staph epidermidis, and E coli are 3.194, 0.224, 0.099, respectively.

The ordinary least squares regression for the dependent variable LICUSURV (days of survival after discharge from the ICU, log form) resulted in a a model that explains slightly more than 50% of the variation in survival time (R^2=.504), among survivors of intensive care. The following variables were significant at the .05 level: Apache score, Summer admission (p=.0505), Transfer from another hospital, Length of hospital stay, White, Previous admissions within the past year, E coli and Pseudomonas as etiologic organisms (See Table 8). Length of stay and E. coli were

predictive of better outcome (longer survival), and the other factors were predictive of poorer outcome.

The ordinary least squares regression for the dependent variable LHOSPSURV (days of survival after discharge from the hospital, log form) resulted in a a model that explains slightly more than 52% of the variation in survival time (R^2=.525), among survivors of hospitalization. At the .05 level, seven explanatory variables attained statistical significance: Apache, AIDS, hospital transfer, transfer from a skilled nursing facility (SNF), length of stay, White, and Pseudomonas. (See Table 9 for full model). All of these variables,except length of stay, predicted poor outcome (short duration of survival after hospital discharge).

Discussion of statistical results

APACHE II, our prospective measure of illness severity based upon physiologic derangements, age, and chronic health, was the most consistent and significant explanatory variable of models describing both long and short-term survival. As discussed in Part I of this thesis, there is strong theoretical and experimental evidence supporting the use of indices such as APACHE II in predicting short-term outcome. Our results demonstrate that APACHE II is also an important predictor of long-term outcome and the duration of survival after hospitalization, among survivors.

According to these results, etiologic organism plays an important role in short-term mortality and duration of survival after critical illness. These results confirm the numerous studies that have demonstrated the association between Pseudomonas and hospital mortality. Pseudomonas also contributes to a poor prognosis after intensive care, and after hospital discharge. E. coli was the second most consistent explanatory variable,

contributing as a significant independent variable in all but one of the regression models employed. These findings add further evidence that E. coli is a favorable prognostic sign among patients with septicemia, and it demonstrates that this favorable prognosis continues well after hospital discharge. Staph epidermidis was also significant in predicting better survival, but only long-term survival. The reasons for the importance of these etiologic organisms are multifactorial and not well understood[51]. Pseudomonas, as a common and dangerous nosocomial pathogen, produces a number of toxins and enzymes, including elastases and exotoxin A, believed to mediate aspects of the disease process. Pseudomonas also interferes with the host's defenses, inactivating complement and cleaving antibodies to its surface antigens. Finally, Pseudomonas is often exposed to the entire armamentarium of chemotherapeutic agents in an ICU, and colonies of highly resistant Pseudomonas arise. E. coli is the organism most commonly involved in septicemia of a genitourinary source and has not exhibited the pathogenicity of bacteria such as Pseudomonas. Staph epidermidis is a common component of skin flora, and blood cultures may yield spuriously high levels of this organism because blood is drawn through a needle that penetrates the skin. In-dwelling catheters also tend to accumulate Staph epidermidis, and blood drawn through these catheters may produce colonies on culture when no actual seeding of the bloodstream has occurred. Polymicrobial bacteremia was a significant predictor of survival at discharge. This finding contradicts previous studies that demonstrated increased mortality when multiples organisms were involved. Although I cannot explain this result, it is important to note that a high percentage of the polymicrobial episodes involved E. coli, a less toxic pathogen.

Several hospitalization variables played a significant role in explaining outcome. Previous admissions to this same hospital within the past twelve months was predictive of poor prognosis after discharge from the ICU, and an indicator of higher long-term mortality. Transfer from another hospital or a skilled nursing facility predicted shorter survival after discharge. These variables undoubtedly capture the long-term mortality risk from severe chronic disease. Repeated admissions in the past year may indicate a disease process with regular exacerbations over the course of a slower down-hill slide in health status. Patients transferred from a skilled nursing facility are likely to have an acute exacerbation of a severe underlying disease. Although it is less clear why patients transferred from another hospital would do more poorly, it is likely that these cases represent very severe illnesses which community hospitals in northern California were not equipped to handle.

Interestingly, greater length of stay in the hospital was associated with improved long-term outcome among survivors. Length of stay has not been demonstrated as an important explanatory variable in critical care outcome in the past, but one might expect it to predict *poor* long-term outcome. I suspect that the explanation for this result is that a great many of the patients that died during the course of their critical illness did so fairly soon after admission. A number of patients required a long hospital stay to overcome their critical illnesses, but once they did so, they returned to their lives, surviving a long period of time.

AIDS was significant in predicting poor survival after discharge from the hospital. It was the only disease, diagnosis or complication that proved significant in determining outcome from intensive care. The tragic nature of this disease, rendering its victims susceptible to opportunistic infections,

neoplasm, wasting, and dementia explains the poor long-term prognosis of those patients with AIDS who survive a bout of septicemia.

Two variables were unexpectedly significant in various models: race and season of admission. White race predicted short duration of survival after ICU or hospital discharge. Asian race predicted increased survival at discharge and up to 2 months after discharge. Summer season of admission was significant in explaining short duration of survival after ICU discharge, and Fall was significant in predicting mortality at 2 months after discharge. These results are difficult to explain. With regard to season, it is possible that in summer and fall, the less experienced interns and residents responsible for patient management contributed to the poorer outcome. With the high degree of supervision and the constancy of the ICU attending physicians, this seems a remote possibility. It is also possible that climate, the presence of allergens, or another seasonal variable contributes to poor outcome in summer and fall. With regard to race, ninety-seven of the original patients were classified as white, 16 as Asian. The small number of Asians and other minorities tends to cast doubt upon the findings that race explains outcome, since a few anomalous variations from expected outcome among the minorities would lead to these findings.

Discussion of APACHE and prognostic scoring systems

Douglas Wagner proposes three possible applications for the APACHE system: a) Quality Assessment, b) Resource Management, and c) Patient Care*.

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* During Dr. Wagner's April 1992 talk at the International Bioethics Institute Conference in San Francisco in, I understood him to propose three possible applications for the APACHE system.

APACHE and similar predictive indices may find much use in **quality assessment** or quality control within health care institutions. Hospital staff could regularly compare the actual mortality data for patients with the expected mortality, as predicted by APACHE. One could calculate a crude mortality ratio from the observed and expected deaths, but a more useful analysis would come from examining the deaths in specific diagnostic categories, or from specific services in the hospital. For example, if there were an unexpectedly high number of patient deaths from a particular surgical service, these surgeons would have a responsibility to investigate their source, searching for systematic errors in procedure, post-operative care, or infection control. Regular comparisons of observed and expected deaths would provide foci of intervention for improving the survival of patients in the institution. Such comparisons, however, need not be limited to within institutions, and may be undertaken to compare the quality of care among different institutions or different forms of therapy. For example, as Knaus and colleagues demonstrated, investigators may compare the care provided by ICUs differing in their organizational pattern[36]. Such studies may now control for illness severity and utilize an easily quantifiable end point, i.e. hospital mortality, when assessing effectiveness of care. Even when the severity of illness differs between institutions, the observed mortality should not exceed the expected mortality of the individual institutions, as calculated by APACHE III.

Resource management, like quality assessment, may refer to resource allocation within an institution or among institutions. Within an institution, the APACHE system could serve the purpose of decision-aid when hospital staff must allocate the intensive care resources. When the intensive care unit is full, or when a large number of patients need intensive

care therapies or monitoring, the APACHE system may serve to quantify each potential admission's severity of illness. The likelihood of benefit for each candidate for admission to the intensive care unit can then be estimated, and resources allocated accordingly. In making triage decisions when the ICU is full and critically ill patients await admission to the Unit, the APACHE score could aid in identifying patients least likely to require intensive care, and those least able to benefit from it. With real-time APACHE scores illuminating computer screens in the ICU, a physician or triage nurse may be better-equipped to make discharge decisions in the Unit when an emergency case arises with a more pressing need of an ICU bed.

The question may be raised whether the ICU physician should discharge the patient with the lowest APACHE score, i.e. someone who may get along on the ward, or the highest APACHE score, someone whom they believe they have little chance of helping. Ethical arguments can be made to support either position on the basis of patient need. Neither the patient who can survive on the ward nor the patient whose condition is so severe that intensive care is of little benefit would have the strength of claim to an ICU bed as would the patient with an APACHE score in between.

Another question is whether a policy of utilizing APACHE as a gatekeeper tool for the ICU would lead to errors or abuse. An ICU admissions policy based upon a quantitative assessment of the severity of illness admittedly could be misused in cost-cutting efforts, but such a policy would be preferable to the system which currently exists in many hospitals. A policy centered upon the patient's quantified severity of illness might go a long way toward eliminating less ethical, non-medical rationales for provision of intensive care, such as political influence of the attending physician or squatter's rights (i.e. because a patient was in the ICU, that

patient should continue to be). As pointed out by Marshall and colleagues, both admission and discharge practices in an ICU can bend to numerous non-medical factors[112]. Among institutions, there is an important role for APACHE in resource allocation decisions as well. Community hospitals should routinely review the severity of illness and the observed mortality among critical care patients. When the ICU in one institution is consistently populated with more severely ill patients than in another, health care workers can make a strong argument for redistribution of critical care beds. If a community hospital routinely denies intensive care to patients who are more seriously ill than patients admitted to the ICU of a neighboring community hospital, a redistribution of ICU beds is in order, particularly when the mortality and morbidity levels are higher in the first institution. While this type of resource allocation would likely be most practical only among public institutions, it could be argued that these considerations should impact all institutions, as an extension of the certificate-of-need concept.

The last category of application for APACHE, outlined by Dr. Wagner, is that of **individual patient care**. Although overlapping significantly with resource management, patient care is the most difficult and controversial category. Nevertheless, it is reasonable and appropriate to make use of predictive powers such as APACHE's when considering the prognosis for individual patients. As the article in Science demonstrates, the APACHE system is more accurate than clinical judgement in assessing prognosis, as it considers an array of variables too large for the human mind to juggle at one time. For patients at very low risk of death, the APACHE system might serve to confirm clinical impressions of a good response to therapy, and this may translate into an early transfer to the hospital floor. Similarly, for

patients at very high risk of death, the APACHE system may serve a similar purpose: to confirm clinical impression of a poor response to therapy and to realistically compute the chances for survival. Physicians and nurses should rely upon the prognostic index in these situations to confirm clinical assessment of the patient's situation, and use them to support a frank discussion with the patient or his/her surrogate regarding treatment options. As David Thomasma points out*, the providers must listen to the patient's wishes and abide by them. A length and quality of life which is unthinkable to the physician may be quite acceptable to the patient, and quite worthy of further therapeutic efforts.

Yet, this obedience to patient's wishes ought not be unlimited. The level of medical intervention offered to a patient whose prognosis is so poor as to make him or her extraordinarily unlikely to benefit from that intervention must be negotiated between the physician and the patient or his/her surrogate, but the level of cure-oriented medicine provided in cases of futility must be negotiable only up to a point. It is unwise and socially irresponsible to offer, as standard default behavior, every form of treatment, no matter the expense or invasiveness of the procedure, to patients who cannot benefit from the therapy. APACHE and systems like it may help us face up to these situations more responsibly.

That "point" at which health care providers must change the default course of action and offer less than the complete range of full-scale curative interventions to patients considered unable to benefit should be agreed upon at a societal level, where futility, economic reality, and social

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* In Dr. Thomasma's comments to the audience following Dr. Wagner's talk at the International Bioethics Institute's conference, he discussed the responsibility of providers to respect patient autonomy.

responsibility can impact the debate. Medical practitioners are not in the business of "selling" services to anyone who can and will pay. Medicine is a profession which provides treatments to benefit the health of those who receive them. Just as it is professionally unethical and socially irresponsible to perform surgery on individuals who request but do not need it and cannot benefit, it is likewise irresponsible to continue to pursue high-cost, invasive interventions on patients after it becomes clear they can no longer benefit from such interventions. For such patients, a discussion of new therapeutic goals is necessary; these goals may include the relief of suffering, improvement of quality-of-life, and implementation of specific patient and family wishes, but they should not include reinstitution of cure-oriented therapy when no cure is achievable.

David Thomasma outlined a general framework by which physicians might ethically offer and negotiate treatment options*. Under his plan, patients would receive a menu of treatment options available to them, based upon their level of risk, their prognosis, or their ability to benefit. Most patients would receive the "full menu" of treatment options: intensive care, surgery, expensive and invasive cure-oriented therapies for the majority of patients in whom a "cure", or a significant return to an acceptable quality-of-life, is achievable. Those at the extreme of poor prognosis (i.e. nill ability to benefit) would have a limited menu of medical options, *based upon their ability to benefit*. Such a treatment scheme is compatible with Daniel Callahan's notion of "caring vs. curing" for those patients with the poorest of possible prognoses[113]. For patients at the end of life, faced with an insurmountable physiologic assault, health care providers must not offer "curing", from which the patient can no longer benefit, but "caring", which the patient needs most of all. In other words, in hopeless cases of nill prognosis,

the patient needs and should receive relief from suffering, compassion, and comfort, not hopelessly aggressive interventions serving only to delay the inevitable hour of death.

Unnecessarily providing medical therapies to patients who can no longer benefit from them does, in a very real sense, contribute to the multiple crises of lack of access to health care, unaffordability of insurance, and escalation of health care costs to financially strapped public and private institutions. As hospitals and ICUs serving the affluent pursue futile, cure-oriented treatments at any cost, the charges to third-party payers skyrocket. These same insurance companies and government institutions then restrict access to their policies, increase the limitations to their coverage, make collection more difficult for providers, and increase utilization review procedures, all steps the payers must take to maintain solvency while paying extraordinarily high costs for a relatively small number of critically ill patients. The effect of these steps is to increase the bureaucracy of medicine, interfere with physician-patient relationships, and most importantly, further diminish access to health care to the medically neediest and least wealthy members of society. The current high price of health care today benefits no one and exacerbates the distribution of of more and more treatments to fewer and fewer people.

"More" medical care is not "better" medical care. For patients at the end of life in a category of disease in which short-term survival is extremely unlikely and long-term survival is unprecedented, there is no benefit from "more" care; that is, high-tech, high-cost, cure-oriented medicine. There is obviously the potential for relief from suffering and for palliative interventions being of value, but this is not what ICUs are in the business of offering.

In addition to the recommended applications of APACHE outlined by Dr. Wagner, I would like to add a fourth and certain to be most controversial category - health care rationing. While public and professional outrage is expressed over proposals to ration medical care, millions of people are denied access to care because they are poor or unemployed or unlucky. To those who remain unconvinced that this society cannot afford to provide unlimited health care to all of its citizens all the time, the literature is growing to provide evidence for this sad, and often stark, reality[114-135]. Rationing is inevitable and already occurs. The only remaining question is whether it is better to continue rationing implicitly using criteria such as ability-to-pay, or whether it is better to ration explicitly using a criterion such as patient benefit.

The APACHE system is an example of the type of instrument medical practitioners could employ to begin to ration care on the more ethical basis of patient need, or ability-to-benefit. If large well-verified prognostic indices existed for the majority of medical therapies for severe illnesses, the health care system could provide coverage for all those patients with prognoses indicating they had a chance of benefitting from the treatment, and restrict the menu of available interventions for those patients who were unable to benefit. For predictive indices to be used in this fashion, they would have to attain an extremely high level of reliability in predicting outcome for individual patients.

By rationing I refer to macro-rationing, on the scale of populations. But in this rationing scheme, the decisions would be made not based upon some categorical criterion such as age or ability to pay, but upon an individual's medical needs. In Oregon, where the state has developed a different rationing scheme, prioritizing medical treatments based upon community understanding of the costs and benefits associated with each

treatment[136-38]. Based upon the overall public health care budget, a line is drawn below the list of those treatments the state can afford to reimburse and above the list of those treatments it will not pay for. In establishing this priority list rationing method, the Medicaid program will expand to provide health coverage for all of Oregon's poor.

While the Oregon plan goes a long way toward insuring that all its people receive appropriate care, it, and any other plan which focuses on limiting specific therapies, is flawed because it does not focus upon individual patients. Limiting the interventions to those most likely to benefit patients only approaches the achievable benefit and the cost-effectiveness of limiting coverage only to those patients who have the ability to benefit. Unfortunately for the few individuals under the Oregon plan with a medical condition requiring a treatment below the cut-off line, such as bone-marrow transplant for non-Hodgkins lymphoma, the rationing scheme fails. Many of these unfortunate patients have a high probability of benefitting very greatly from that intervention[139], but they are denied the treatment because, for the state as a whole, that intervention was not deemed cost-effective enough to be funded. If care were rationed according to ability-to-benefit, those non-Hodgkins lymphoma patients with favorable prognoses, as determined by clinical assessment and a prognostic scoring model, would receive their transplant. But the money for their treatment would have to come from the denial of care to some patients whose illnesses make them unable, or extremely unlikely, to benefit from treatment. An individual's strength of claim to health care resources depends entirely upon his or her probability of achieving improvement in health status as a result of receiving those resources.

A question that arises is whether a rigid rationing formula based upon a prospective assessment of the patient's ability to benefit would cause harm by coldly closing the door to medical care and ignoring patient autonomy. Any rationing scheme based upon an instrument such as APACHE ought not be dependent upon the computer tool as the sole criterion in making rigid and inflexible intensive care decisions. Rather, a principle of rationing on the basis of patient need should be upheld, with APACHE as an important piece in the clinical puzzle. When clinical data and APACHE score indicate a patient cannot benefit from cure-oriented treatment, the default presumption shifts to palliative, care-oriented treatment. In the absence of any contravening evidence or reasonable demand (such as a patient requesting a time-limited trial of intense therapy despite the quality-of-life trade-offs and discomfort), providers will not offer cure-oriented interventions and the menu of medical options will be shortened.

Granted, having the technical capacity to implement a rationing scheme based upon ability-to-benefit is not a reality. The non-Hodgkin's lymphoma patient is a good example why such a rationing scheme, while theoretically appealing, may be quite difficult to devise. Bone marrow transplant is not a primary treatment for non-Hodgkin's lymphoma, but is the most promising salvage therapy for patients whose disease relapses after chemotherapy[140]. It seems likely that for such a specific clinical situation, an accurate prediction of outcome would require a prognostic index specific for non-Hodgkin's lymphoma, not one based upon generalized physiologic derangement. This is not to say that an effective index might not be easily devised from tumor grade and stage and patient characteristics, but it indicates that all end-of-life predictions will not fit into one, or even a few, large prognostic models, such as APACHE. Furthermore, even with a good

model correctly applied to the patient group for which it was devised, as in APACHE III applied to ICU patients, the model will very rarely predict a patient has a 100% chance of dying. Nor does this prognostic index tell us anything about the quality-of-life that patient experiences before dying. However, a health care rationing model based upon an individual's ability to benefit from treatment is more ethical, not to say cost-effective, than any other. Even with a great many imperfections, incorrect predictions, and limitations, such a rationing scheme is preferable to the current one based upon socio-economic status, or one based upon patient wishes, or the theoretical cost-effectiveness of specific medical interventions, or categorical parameters such as age.

Neal Cohen, ICU director at the University of California, San Francisco, expressed worry that third-party payers, including the federal government, might use a high APACHE score as a criterion for denying reimbursement*. Perhaps if the government did limit reimbursement for cure-oriented interventions in the "unprecedented" category, those patients who could not benefit from treatment, and increased access to medical care for the neediest of our population, this would represent a stride in the direction of more ethical, more equitable health care.

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* Dr. Cohen made those comments to the audience of the 1992 San Francisco International Bioethics Institute conference in his response to Dr. Wagner's talk.

Figure 1

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 / No. Patients	450/2070	261/847	204/607	159/455	142/356	118/279	80/195
2	Percent Mortality*	52%	67%	66%	62%	56%	64%	68%
	No. Deaths / No. Patients	239/458	147/219	103/156	118/191	96/171	78/122	56/82
≥3	Percent Mortality*	80%	95%	93%	96%	100%†	100%†	100%†
	No. Deaths / No. Patients	152/191	70/74	50/54	50/52	38/38	33/33	32/32

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).

Figure 2

TABLE I. Therapeutic Intervention Scoring System—1983

4 Points
- a. Cardiac arrest and/or countershock within past 48 h[a]
- b. Controlled ventilation with or without PEEP[a]
- c. Controlled ventulation with intermittent or continuous muscle relaxants[a]
- d. Balloon tamponade of varices[a]
- e. Continuous arterial infusion[a]
- f. Pulmonary artery catheter
- g. Atrial and/or ventricular pacing[a]
- h. Hemodialysis in unstable patient[a]
- i. Peritoneal dialysis
- j. Induced hypothermia[a]
- k. Pressure-activated blood infusion[a]
- l. G-suit
- m. Intracranial pressure monitoring
- n. Platelet transfusion
- o. IABA (intra-aortic balloon assist)
- p. Emergency operative procedures (within past 24 h)[a]
- q. Lavage of acute GI bleeding
- r. Emergency endoscopy or bronchoscopy
- s. Vasoactive drug infusion (> 1 drug)

3 Points
- a. Central iv hyperalimentation (includes renal, cardiac, hepatic failure fluid)
- b. Pacemaker on standby
- c. Chest tubes
- d. Intermittent mandatory ventilation (IMV) or assisted ventilation
- e. Continuous positive airway pressure (CPAP)
- f. Concentrated K+ infusion via central catheter
- g. Nasotracheal or orotracheal intubation[a]
- h. Blind intratracheal suctioning
- i. Complex metabolic balance (frequent intake and output)[a]
- j. Multiple ABG, bleeding, and/or STAT studies (> 4/shift)
- k. Frequent infusions of blood products (> 5 units/24 h)
- l. Bolus iv medication (nonscheduled)
- m. Vasoactive drug infusion (1 drug)
- n. Continuous antiarrhythmia infusions
- o. Cardioversion for arrhythmia (not defibrillation)
- p. Hypothermia blanket
- q. Arterial line
- r. Acute digitalization—within 48 h
- s. Measurement of cardiac output by any method
- t. Active diuresis for fluid overload or cerebral edema
- u. Active Rx for metabolic alkalosis
- v. Active Rx for metabolic acidosis
- w. Emergency thora-, para-, and pen-cardiocenteses
- x. Active anticoagulation (initial 48 h)[a]
- y. Phlebotomy for volume overload
- z. Coverage with more than 2 iv antibiotics
- aa. Rx of seizures or metabolic encephalopathy (within 48 h of onset)
- bb. Complicated orthopedic traction[a]

2 Points
- a. CVP (central venous pressure)
- b. 2 peripheral iv catheters
- c. Hemodialysis—stable patient
- d. Fresh tracheostomy (less than 48 h)
- e. Spontaneous respiration via endotracheal tube or tracheostomy (T-piece or trach mask)
- f. GI feedings
- g. Replacement of excess fluid loss[a]
- h. Parenteral chemotherapy
- i. Hourly neuro vital signs
- j. Multiple dressing changes
- k. Pitressin infusion[a]

1 Point
- a. ECG monitoring
- b. Hourly vital signs
- c. 1 peripheral iv catheter
- d. Chronic anticoagulation
- e. Standard intake and output (q 24 h)
- f. STAT blood tests
- g. Intermittent scheduled iv medications
- h. Routine dressing changes
- i. Standard orthopedic traction
- j. Tracheostomy care
- k. Decubitus ulcer[a]
- l. Urinary catheter
- m. Supplemental oxygen (nasal or mask)
- n. Antibiotics iv (2 or less)
- o. Chest physiotherapy
- p. Extensive irrigations, packings or debridement of wound, fistula or colostomy
- q. GI decompression
- r. Peripheral hyperalimentation/Intralipid therapy

Figure 3

TABLE 3. ICU admission multiple logistic regression model based on data from 737 patients

Variable[a]	$\hat{\beta}$	$\widehat{SE}(\hat{\beta})$	$\widehat{OR}$	95% CI
Constant	−3.000	1.500		
Level of consciousness	2.630	.464	13.87	5.59–34.45
Type of admission	1.630	.410	5.10	2.28–11.40
Cancer	1.490	.444	4.44	1.86–10.59
Infection	.677	.251	1.97	1.20–3.22
Number of organ system failures (one-system odds ratio)	.595	.121	1.81	1.43–2.30
Age (10-yr odds ratio)	.038	.007	1.46	1.26–1.69
Systolic blood pressure (SBP)[b]	−.048	.019		
$(SBP)^2$	.000131	.00007		

[a] Variables listed in decreasing order of significance based on $\widehat{OR}$.

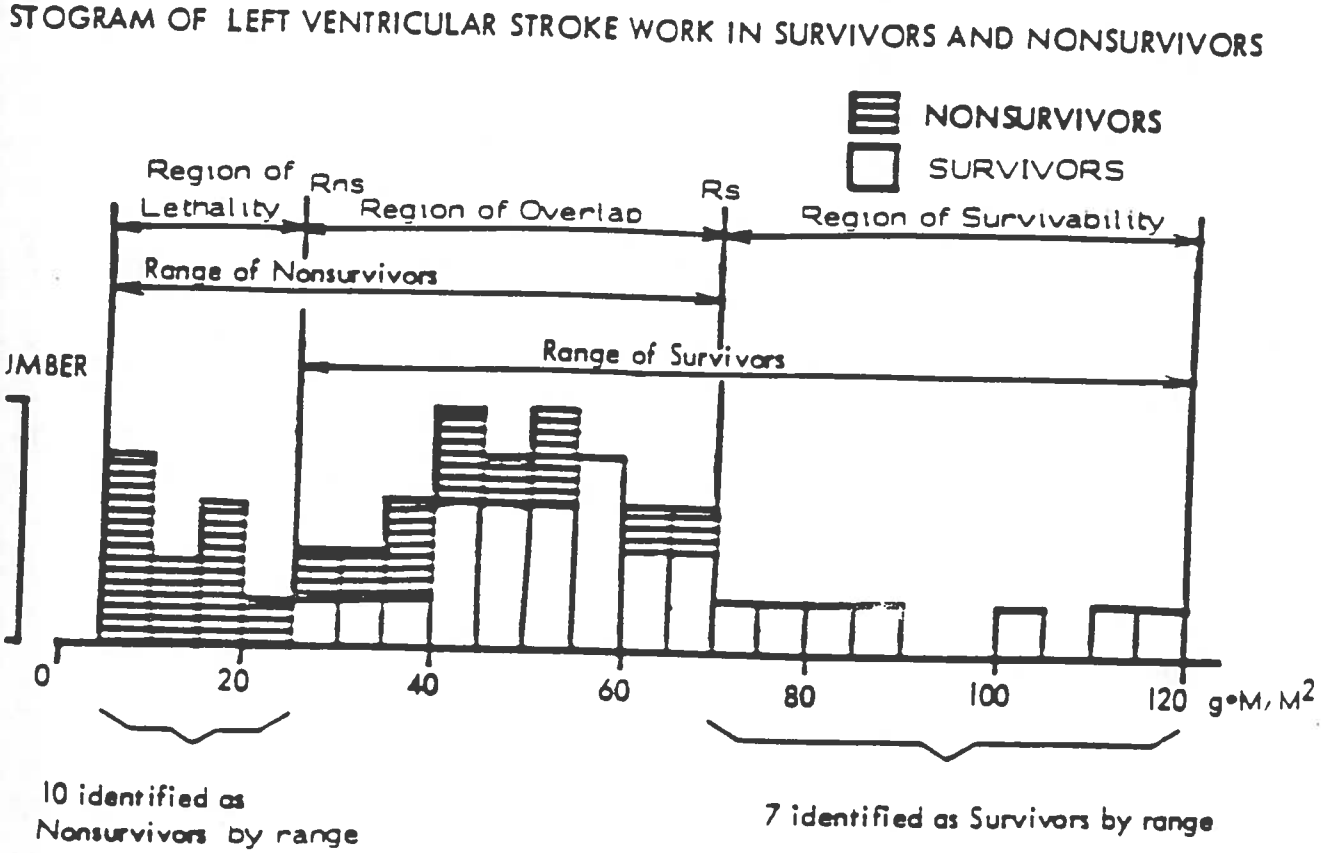
[b] Because both very low and very high levels of systolic blood pressure were associated with an increased risk of dying, both SBP and SBP^2 were included in the model.

TABLE 4. 24-h multiple logistic regression model based on data from 458 patients

Variable[a]	$\hat{\beta}$	$\widehat{SE}(\hat{\beta})$	$\widehat{OR}$	95% CI
Constant	−5.930	.779		
Level of consciousness	4.53	1.110	92.76	10.53–816.97
Infection	1.310	.297	3.71	2.07–6.63
Inspired oxygen fraction	1.170	.424	3.22	1.40–7.40
Shock	.998	.358	2.71	1.34–5.47
Type of admission	.928	.414	2.53	1.12–5.69
Age (10-yr odds ratio)	.038	.009	1.46	1.22–1.74
Number of organ system failures at admission (one-system odds ratio)	.336	.150	1.40	1.04–1.88

[a] Variables listed in decreasing order of significance based on $\widehat{OR}$.

Figure 4


STOGRAM OF LEFT VENTRICULAR STROKE WORK IN SURVIVORS AND NONSURVIVORS
NONSURVIVORS
SURVIVORS
Region of Lethality
Rns
Region of Overlap
Rs
Region of Survivability
Range of Nonsurvivors
Range of Survivors
JMBER
0
20
40
60
80
100
120
g•M/M2
10 identified as Nonsurvivors by range
7 identified as Survivors by range

0090-3493/85/1309-0818$02.00/0
Critical Care Medicine
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Vol 13, No 10
Printed in U.S.A.

Figure 5

APACHE II: A severity of disease classification system

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THE APACHE II SEVERITY OF DISEASE CLASSIFICATION SYSTEM

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	+4	+3	+2	+1	0	+1	+2	+3	+4
TEMPERATURE — rectal (°C)	≥ 41°	39°-40.9°		38.5°-38.9°	36°-38.4°	34°-35.9°	32°-33.9°	30°-31.9°	≤ 29.9°
MEAN ARTERIAL PRESSURE — mm Hg	≥ 160	130-159	110-129		70-109		50-69		≤ 49
HEART RATE (ventricular response)	≥ 180	140-179	110-139		70-109		55-69	40-54	≤ 39
RESPIRATORY RATE — (non-ventilated or ventilated)	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5
OXYGENATION A-aDO2 or PaO2 (mm Hg) a FIO2 ≥ 0.5 record A-aDO2 b FIO2 < 0.5 record only PaO2	≥ 500	350-499	200-349		a. 200 b. PaO2 > 70	a. 61-70		b. PaO2 55-60	a. 55 b. PaO2 < 55
ARTERIAL pH	≥ 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15
SERUM SODIUM (mMol/L)	≥ 180	160-179	155-159	150-154	130-149		120-129	111-119	≤ 110
SERUM POTASSIUM (mMol/L)	≥ 7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5
SERUM CREATININE (mg/100 ml) (Double point score for acute renal failure)	≥ 3.5	2-3.4	1.5-1.9		0.6-1.4		< 0.6		
HEMATOCRIT (%)	≥ 60		50-59.9	46-49.9	30-45.9		20-29.9		< 20
WHITE BLOOD COUNT (total/mm3) (in 1,000s)	≥ 40		20-39.9	15-19.9	3-14.9		1-2.9		< 1
GLASGOW COMA SCORE (GCS) Score = 15 minus actual GCS									
A Total ACUTE PHYSIOLOGY SCORE (APS) Sum of the 12 individual variable points									
Serum HCO3 (venous-mMol/L) (Not preferred, use if no ABGs)	≥ 52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	< 15

A AGE POINTS
Assign points to age as follows

AGE (yrs)	Points
≤ 44	0
45-54	2
55-64	3
65-74	5
≥ 75	6

C CHRONIC HEALTH POINTS
If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows
a for nonoperative or emergency postoperative patients — 5 points
or
b for elective postoperative patients — 2 points

DEFINITIONS
Organ insufficiency or immuno-compromised state must have been evident prior to this hospital admission and conform to the following criteria

LIVER Biopsy proven cirrhosis and documented portal hypertension episodes of past upper GI bleeding attributed to portal hypertension or prior episodes of hepatic failure/encephalopathy/coma

CARDIOVASCULAR New York Heart Association Class IV

RESPIRATORY Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction (e.g., unable to climb stairs or perform housework duties) or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (> 40 mmHg), or respirator dependency

RENAL Receiving chronic dialysis

IMMUNO-COMPROMISED The patient has received therapy that suppresses resistance to infection (e.g., immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids) or has a disease that is sufficiently advanced to suppress resistance to infection (e.g., leukemia, lymphoma, AIDS)

APACHE II SCORE
Sum of A + B + C
A APS points _____
B Age points _____ _____
C Chronic Health points _____
Total APACHE II _____

FIG. 1. The APACHE II severity of disease classification system.

Figure 6

Fig 4 --Receiver-operating characteristic curves for APACHE II (squares), fellows' (Xs), and nurses' (circles) predictions. Diagonal line represents predictive accuracy no better than chance.

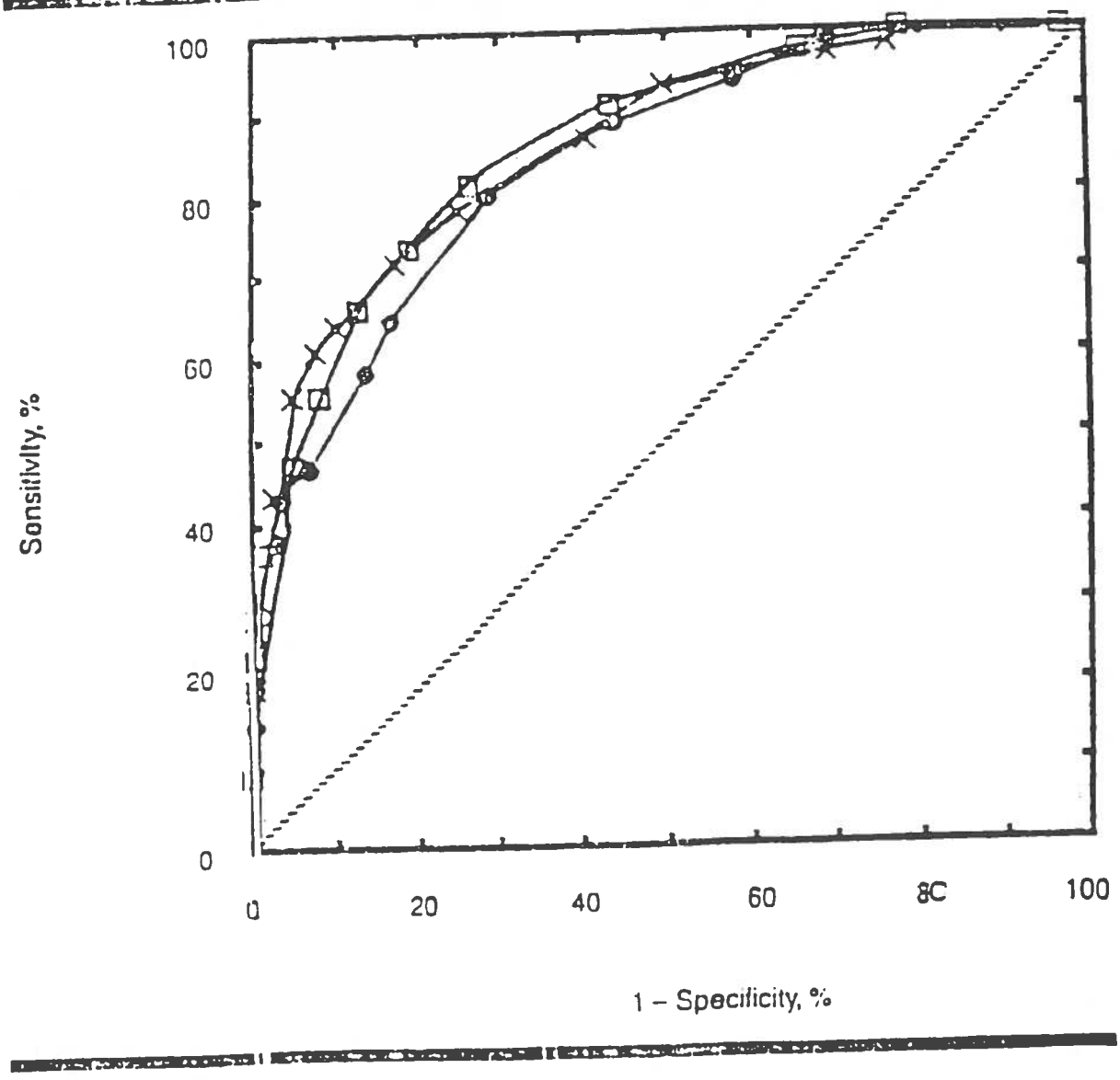

Figure 7

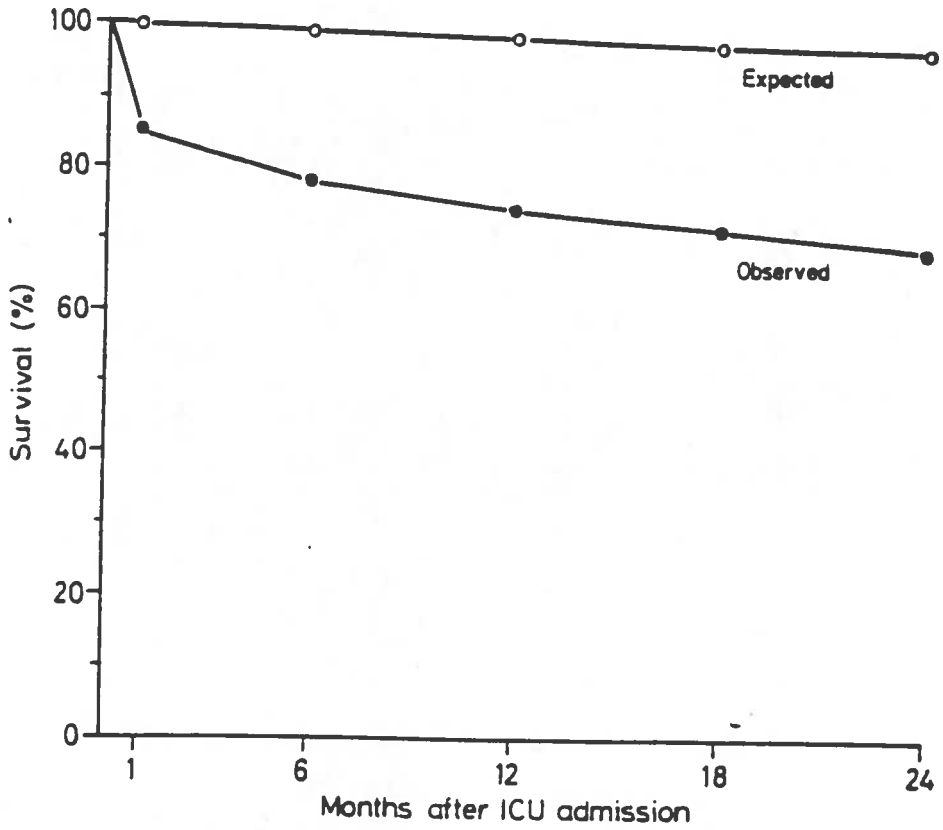

Fig. 1. The survival curves, observed and expected, for intensive care patients during 2 years of follow-up.

Table 1

Summary of Findings of Prognostic Scoring Systems

Model	Author	N	Accuracy	Important
OSF	Knaus	5677	good	OSF's,age.
TISS	Cullen	226	poor	therapeutic interventions.
TISS	Cullen	199	good	platelets, creatinine, age, phys vars, disease categ, dialysis.
MPM admission	Lemeshow	2714	86-87%	level of consc, cancer, infection, OSF's, emergent.
MPM 24hr	Lemeshow	458	85%, poor	age, systolic BP
Range	Shoemaker	113	81-89%	ETOE, RCM, OTR.
Cutpoint	Shoemaker	113	72-90%	PVR, LCW, BV.
Sever Index	Shoemaker	296	87-96%	
automated	Shoemaker	220	94%	
CIS	Snyder	498	83%	encephalitis, pupils,CVA,lev of cosc, intracranial P,card arrest, pressor infuse, intra-Aorta balloon pump.
APACHE (APS)	Knaus	2213	89%, good	34 physiol var's, age, disease cat.,chronic health.
SAPS	LeGall	679	good	14 physiol var's, age, disease cat.,chronic health.
APACHE II	Knaus	5815	86%	12 physiol var's, age, disease cat.,chronic health.

Table 2

Mortality	APACHE II score				
	0-10	11-20	21-30	31-40	41+
in ICU	0 (0%)	13 (27%)	32 (45%)	14 (70%)	8 (100%)
in hospital	1 (14%)	27 (55%)	44 (62%)	17 (85%)	8 (100%)
at 1 mo.	1 (14%)	32 (65%)	45 (63%)	17 (85%)	8 (100%)
at 2 mo.	1 (14%)	32 (65%)	46 (65%)	17 (85%)	8 (100%)
at 6 mo.	2 (29%)	38 (78%)	54 (76%)	17 (85%)	8 (100%)
at 1 year.	1 (14%)	40 (82%)	59 (83%)	18 (90%)	8 (100%)
Total patients	7	49	71	20	8

Table 3

Deceased at Hospital Discharge: Logistic Regression

Variable	Parameter Estimate	Standard Error	Odds Ratio
Intercept	-1.4870	.6697	
Spring	.0155	.5323	
Summer	.0542	.5200	
Fall	.6174	.5561	
APACHE	.1151*	.0278	1.12
AIDS	-.7156	.5069	
Asian	-1.4564*	.6387	.233
E. coli	-1.9365*	.6402	.144
Polymicrobial	-1.0477*	.4586	.351

*Significant at 95% confidence level, two-tailed test.

Table 4

Deceased at 1 Month: Logistic Regression

Variable	Parameter Estimate	Standard Error	Odds Ratio
Intercept	-.9175	.6721	
Spring	.1282	.5274	
Summer	.0641	.5145	
Fall	1.0577	.6051	
APACHE	.0940*	.0263	1.099
AIDS	-.0290	.5263	
Asian	-1.4644*	.6388	.231
Staph epiderm	-.9543*	.4164	.385
Polymicrobial	-2.1033*	.6298	.122

*Significant at 95% confidence level, two-tailed test.

Table 5

Deceased at 2 Months: Logistic Regression

Variable	Parameter Estimate	Standard Error	Odds Ratio
Intercept	-.9992	.6772	
Spring	.1472	.5277	
Summer	.0706	.5168	
Fall	1.2936*	.6336	3.646
APACHE	.0956*	.0266	1.100
AIDS	.1061	.5390	
Asian	-1.4836*	.6447	.227
Staph epiderm	-.8819*	.4208	.414
Polymicrobial	-2.1893*	.6407	.112

*Significant at 95% confidence level, two-tailed test.

Table 6

Deceased at 6 Months: Logistic Regression

Variable	Parameter Estimate	Standard Error	Odds Ratio
Intercept	-.5721	.7297	
Spring	-.0165	.5816	
Summer	.2284	.5833	
Fall	1.5604	.8080	
APACHE	.0811*	.0288	1.084
AIDS	.5549	.6800	
Previous Admits	.9408*	.4757	2.562
Staph epiderm	-1.0368*	.4878	.355
Polymicrobial	-2.6104*	.6986	.074

*Significant at 95% confidence level, two-tailed test.

Table 7

Deceased at 1 Year: Logistic Regression

Variable	Parameter Estimate	Standard Error	Odds Ratio
Intercept	-.2791	.7954	
Spring	-.3383	.6810	
Summer	.2031	.6441	
Fall	1.2941	.8647	
APACHE	.0956*	.0327	1.100
AIDS	.6556	.7591	
Previous Admits	1.1614*	.5449	3.194
Staph epiderm	-1.4982*	.5564	.224
Polymicrobial	-2.3161*	.7249	.099

*Significant at 95% confidence level, two-tailed test.

Table 8

(Log) ICU Survival: Ordinary Least Squares Regression

Variable	Parameter Estimate	Standard Error
Intercept	6.9085	.9032
Spring	.00232	.5380
Summer	-.9576#	.4812
Fall	-.9068	.5630
APACHE	-.09933*	.0230
Bronchoscopy	-1.3917	.8469
AIDS	.6587	.5476
Medicare	-1.5298	.9037
Hosp Transfer	-2.3402*	.8872
Log Days in Hospital	.5340*	.1761
Unmarried	-.7489	.4432
White	-1.1775*	.4097
Previous Admissions	-1.2922*	.3717
E. coli	1.4562*	.5329
Pseudomonas	-1.6201*	.6368

*Significant at the 95% confidence level.
#p=.0505

R-squared = .504434

Table 9

(Log) Hospital Survival: Ordinary Least Squares Regression

Variable	Parameter Estimate	Standard Error
Intercept	6.1248	.8021
Spring	.5453	.4743
Summer	-.3394	.4412
Fall	.1546	.5382
APACHE	-.0615*	.0206
AIDS	-.9031*	.4062
Hosp Transfer	-1.8953*	.7740
SNF Transfer	-2.0231*	.9432
Log Days in Hospital	.4495*	.1781
White	-.8098*	.3651
Previous Admissions	-.5592	.3376
Pseudomonas	-1.9311*	.6514

*Significant at the 95% confidence level.

R-squared = .52

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