Early Physiological Response to Intensive Care as a Clinically Relevant Approach to Predicting the Outcome in Severe Acute Pancreatitis

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Hypothesis: The physiological response to treatment is a better predictor of outcome in acute pancreatitis than are traditional static measures.

Design: Retrospective diagnostic test study. The criterion standard was Organ Failure Score (OFS) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score at the time of hospital admission.

Setting: Intensive care unit of a tertiary referral center, Auckland City Hospital, Auckland, New Zealand.

Patients: Consecutive sample of 92 patients (60 male, 32 female; median age, 61 years; range, 24-79 years) with severe acute pancreatitis. Twenty patients were not included because of incomplete data. The cause of pancreatitis was gallstones (42%), alcohol use (27%), or other (31%). At hospital admission, the mean±SD OFS was 8.1±6.1, and the mean±SD APACHE II score was 19.9±8.2.

Interventions: All cases were managed according to a standardized protocol. There was no randomization or testing of any individual interventions.

Main Outcome Measures: Survival and death.

Results: There were 32 deaths (pretest probability of dying was 35%). The physiological response to treatment was more accurate in predicting the outcome than was OFS or APACHE II score at hospital admission. For example, 17 patients had an initial OFS of 7-8 (posttest probability of dying was 58%); after 48 hours, 7 had responded to treatment (posttest probability of dying was 28%), and 10 did not respond (posttest probability of dying was 82%). The effect of the change in OFS and APACHE II score was graphically depicted by using a series of logistic regression equations. The resultant sigmoid curve suggests that there is a midrange of scores (the steep portion of the graph) within which the probability of death is most affected by the response to intensive care treatment.

Conclusion: Measuring the initial severity of pancreatitis combined with the physiological response to intensive care treatment is a practical and clinically relevant approach to predicting death in patients with severe acute pancreatitis.

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have all failed to show the accuracy or reliability needed for them to be adopted into general use.\(^{18}\)

Multiple factor scoring systems were first introduced to acute pancreatitis nearly 30 years ago.\(^{19}\) Newer systems such as the Organ Failure Score (OFS)\(^{20}\) and Acute Physiology and Chronic Health Evaluation II (APACHE II)\(^{21}\) score are used to evaluate the level of organ dysfunction at hospital admission and to determine disease severity. However, there is increasing recognition that organ dysfunction is a dynamic entity and that a single measurement of organ dysfunction does not indicate the true level of severity. A group of patients will respond to intensive care treatment, whereas those most at risk of dying will continue to deteriorate.\(^{22}\) The aim of this study was to examine the changes in organ dysfunction in response to the initial 48 hours of resuscitation and to characterize an approach to predicting the outcome in SAP that factors in the dynamic nature of the physiological response.

### METHODS

All patients with SAP who were admitted to the intensive care unit (ICU) of Auckland City Hospital, Auckland, New Zealand, from January 1, 1988, through December 31, 2001, were identified from a prospective computerized database. Data were extracted from this database and retrospective review of the medical records. A single surgeon (J.A.W.) managed all cases according to a standardized protocol.

The patient's age and sex were recorded. The cause of pancreatitis was classified as gallstones, demonstrated at ultrasoundography, endoscopic retrograde cholangiopancreatography, or laparotomy; alcohol use, when average daily intake exceeded 50 g in the absence of other causes; or other, when another or no cause was identified. The duration of symptoms before admission to the ICU and the length of ICU stay were recorded. The predicted severity was determined by using modified Glasgow criteria.\(^{23}\) Death from early multiple organ failure was defined as death occurring in the first 7 days of illness from multiple organ failure, and death from late infection was defined as death occurring after 48 hours of intensive care treatment.

### RESULTS

There were 112 patients admitted to the ICU with SAP during 14 years. Of these, 92 patients (60 male, 32 female) fulfilled the inclusion criteria and had a median age of 61 years (range, 24-79 years). The cause of pancreatitis was gallstones (42%), alcohol use (27%), or other (31%). Seventy-two (78%) patients had 3 or more modified Glasgow criteria 48 hours after hospital admission. Patients were admitted to the ICU at a median of 3 days after the onset of symptoms, and the median stay in the ICU was 5 days (range, 1-60 days). Thirty-two patients (35%) died during their hospital stay at a median of 10 days (range, 1-95 days) after the onset of symptoms, and a median of 5 days (range, 0-65 days) during 14 years. Of these, 92 patients (60 male, 32 female) fulfilled the inclusion criteria and had a median age of 61 years (range, 24-79 years). The cause of pancreatitis was gallstones (42%), alcohol use (27%), or other (31%). Seventy-two (78%) patients had 3 or more modified Glasgow criteria 48 hours after hospital admission. Patients were admitted to the ICU at a median of 3 days after the onset of symptoms, and the median stay in the ICU was 5 days (range, 1-60 days). Thirty-two patients (35%) died during their hospital stay at a median of 10 days (range, 1-95 days) after the onset of symptoms, and a median of 5 days (range, 0-65 days) during 14 years. Of these, 92 patients (60 male, 32 female) fulfilled the inclusion criteria and had a median age of 61 years (range, 24-79 years). The cause of pancreatitis was gallstones (42%), alcohol use (27%), or other (31%). Seventy-two (78%) patients had 3 or more modified Glasgow criteria 48 hours after hospital admission. Patients were admitted to the ICU at a median of 3 days after the onset of symptoms, and the median stay in the ICU was 5 days (range, 1-60 days). Thirty-two patients (35%) died during their hospital stay at a median of 10 days (range, 1-95 days) after the onset of symptoms, and a median of 5 days (range, 0-65 days).
after admission to the ICU. The OFS and APACHE II score were calculated for a median of 5 days (range, 2-39 days) after admission to the ICU.

There were 48 responders and 44 nonresponders (Table 1), with a greater mortality rate in the nonresponder group (48% vs 23%; Fisher exact test, \(P = .02\)). There was no significant difference in the rate of deaths from early multiple organ failure and late infection. There was a variation in the treatments between the 2 groups, with a higher percentage of nonresponders undergoing surgery (82% vs 40%; Fisher exact test, \(P < .001\)), parenteral nutrition (39% vs 13%; Fisher exact test, \(P = .007\)), and enteral nutrition (68% vs 31%; Fisher exact test, \(P < .001\)).

### SCORES AT HOSPITAL ADMISSION

The prediction of death by using the OFS and APACHE II score at admission to the ICU is shown in Table 2. The pretest probability of dying of SAP in this series was 35%. The posttest probability of dying of SAP was determined from the positive likelihood ratio for OFS and APACHE II score (Table 2). The posttest probabilities differed from the pretest probability in all of the groups. The group with the lowest scores (APACHE II score \(\leq 15\), OFS \(\leq 3\)) had positive likelihood ratios of approximately 0.1 that resulted in a substantial decrease in the posttest probability of dying (APACHE II score, 7%; OFS, 9%) from the pretest probability. In contrast, the group with the highest scores (APACHE II score \(\geq 26\), OFS \(\geq 9\)) had posttest probabilities of dying (APACHE II score, 76%; OFS, 86%) substantially higher than the pretest probability. The positive likelihood ratios (0.45 to 2.58) for the 2 intermediate groups resulted in posttest probabilities of dying in the range of 20% to 58%.

### SCORES ACROSS 48 HOURS

Table 3 shows that the physiological response to treatment was more accurate in predicting outcome than were the initial OFS and APACHE II scores alone. For example, 17 patients had an initial OFS of 7-8, and this equates to a posttest probability of dying of 58%, which is higher than the pretest probability of 35% (Table 3). Of these 17 patients, 7 were responders, and 10 were nonresponders. For those who responded to intensive care treatment, the posttest probability of dying was only 28%, which is less than the pretest probability (35%) and the posttest probability of the initial OFS alone (58%). In contrast, nonresponders had a posttest probability of dying of 82%, which is more than the pretest probability (35%) and posttest probability of the initial OFS alone (58%).
The effect of the delta OFS and APACHE II scores across 48 hours on the probability of death can be depicted by calculating a series of logistic regression equations. The sigmoid curve for the initial score was plotted, and then a separate curve was plotted for each delta score (for example, −4, −2, 0, +2, +4) (Figure). As an example, a patient with SAP who sought treatment at the ICU with an OFS of 6 had a predicted probability of dying of 38%. If organ dysfunction improved in the first 48 hours so that the OFS decreased to 4 (ie, a change of −2), the predicted probability of death halved to 19%. If, on the other hand, the physiological response during the first 48 hours was even greater such that the OFS was 2 (ie, a change of −4), the predicted probability of death decreased further to 7%.

The relationship between the scores (APACHE II score and OFS) at admission to the ICU and the probability of death is not linear. The sigmoid curve demonstrates that there is a midrange of scores (the steep portion) within which the probability of death is markedly affected by the response (or nonresponse) to intensive care treatment. For example, in the patient who sought treatment at the ICU with an OFS of 6 and failed to respond to intensive care treatment so that after 48 hours the OFS was 8 (a change of +2), the probability of dying increased from 38% to 62%. However, a patient who initially had an OFS of 2 that increased to 4 (a change of +2) after 48 hours had an increase in the probability of dying from 7% to only 19%. At the extremes of the sigmoid curve, the probabilities of death do not change to the same extent for the same delta OFS or APACHE II score. For example, a patient with an initial OFS of 12 that improved to 10 (a change of −2) after 48 hours of intensive care resulted in a decrease in the probability of dying from 97% to 89%. A much larger change in OFS (for example, 12 to 6, or a change of −6) would be required to reduce the probability of dying to less than 50%.

Results of this study show that the physiological response to the initial 48 hours of intensive care treatment can be used to predict death in patients with SAP. This approach appears to be superior to the prediction of death by using the initial score (OFS or APACHE II score) measured at the commencement of intensive care treatment. The Figure illustrates the way in which the direction and the extent of the physiological response to intensive care treatment is important in determining the final outcome. Measuring the initial severity of pancreatitis combined with the physiological response to intensive care treatment is a practical and clinically relevant approach to predicted death in patients with SAP.

Multiple organ failure is responsible for most deaths from SAP. Patients with early SAP develop fulminant multiple organ dysfunction syndrome within the first week and have a high mortality rate. Organ function continues to deteriorate in nonsurvivors within the first week of intensive care treatment. Some aspects of intensive care treatment may exacerbate pancreatitis. The restoration of normal hemodynamic functioning may mask inadequate resuscitation, and some inotropes may increase splanchnic vasoconstriction, which may lead to prolonged mesenteric ischemia and enhanced multiple organ dysfunction syndrome. Gastric intramuscosal pH (an indirect measure of mesenteric perfusion) can be used to predict outcome in severe pancreatitis.

Patients may also deteriorate further as a result of surgery, and current recommendations are to delay pancreatic necrosectomy as long as possible to allow the systemic inflammatory response and organ dysfunction to subside. This delay is not possible in all patients, some of whom warrant early intervention. In this current study, a significant majority of nonresponders underwent surgery; the decision was made because either infected pancreatic necrosis was identified or the patient had a persistent deteriorating course despite maximal intensive care treatment. Unfortunately, the adverse effect of surgery on organ dysfunction could not be evaluated from our data. Identifying who will benefit from early surgery is difficult. Measuring the physiological response to initial intensive care treatment may help in selecting which patients require early surgery and which can continue with nonsurgical treatment.

Although the level of organ dysfunction is an established determinant of outcome in critical illness, the...
usefulness of the response of organ function to treatment needs further evaluation. Predicting mortality from a change in the level of organ dysfunction has been proposed before. In a group of 31 patients predicted to have SAP (according to modified Glasgow criteria), the overall positive predictive value of mortality was 48%. This value increased to 81% in patients with decreasing organ function as measured by means of an increasing acute physiological component of the APACHE II score. A similar finding was reported by Buter et al in a study of 121 patients predicted to have SAP in which the group with worsening organ dysfunction had a higher risk of mortality. Larvin and McMahon also described a similar pattern between severe and mild "attacks" in their validation study of APACHE II scores in acute pancreatitis, which suggests that the hallmark of SAP is the initial deterioration in organ function. This concept is why the APACHE II score at 48 hours, the peak APACHE II score within 96 hours, and a deteriorating APACHE II score at 48 hours are more accurate in predicting outcome than admission score alone.

A criticism of current approaches to predicting outcome is that they are not particularly useful to the individual patient and perform better in the identification of patient groups. This propensity is best demonstrated by their modest likelihood ratios, which means that the pretest and posttest probabilities of death do not change to a clinically meaningful extent. A large prospective outcome study will need to be performed to determine whether the approach used in the present study offers advantages in the prediction of outcome in the individual patient.

Some limitations of the studies in which prognostic scoring systems in SAP are evaluated include differing end points, small numbers, and the lack of practical value. The present study goes some way to addressing these problems because a relatively large number of patients with established SAP rather than a prediction of SAP are investigated and because a straightforward method to account for the dynamic nature of organ failure is identified. However, this study is retrospective and includes a disproportionately high number of patients with SAP (mean ± SD APACHE II score at hospital admission, 19.9 ± 8.2). A prospective study that includes all patients with SAP (those treated in the ward and those requiring intensive care treatment) is needed to confirm the findings presented here.

Taking into account the degree of intensive care support required to maintain a particular level of organ function or the extent to which this support decreased across time might further enhance the approach offered in this study. A decreasing inotrope dose to maintain the blood pressure, for example, is a sign of improvement, yet it is not included in any physiological scoring method. Further improvement might be achieved by modifying the physiological scoring methods that contain some bias. For instance, the APACHE II score favors the elderly (eg, blood pressure factors), and the OFS favors pancreatitis due to gallstones by using serum bilirubin level as a marker of hepatic dysfunction. A variety of other scoring systems, such as the Therapeutic Intervention Scoring System, may overcome these biases but are yet to be validated for acute pancreatitis.

In the present study, the largest changes in predicted mortality rate occurred in patients whose initial score lay on the steep part of the curve and between the extremes of severity (Figure). These patients stand to gain the most from aggressive intensive care therapy. The current guidelines for the United Kingdom state that all patients with SAP require treatment in an ICU or high-dependency unit, yet only one third actually received such treatment according to a recent regional audit. The poor use of objective severity stratification (19%) and computed tomography (33%) suggests a failure to identify SAP and, by implication, the probable failure to initiate early intensive care therapy.

All patients predicted to have SAP, especially those with coexistent comorbidity, should receive early and optimal resuscitation and intensive care support. The Figure graphically demonstrates that all patients do not respond to the same degree. Because intensive care treatment is costly and resource constraint characterizes most health care systems, it is going to be necessary to triage patients. This triage should not be performed on the basis of the initial OFS or APACHE II score. Results of the present study suggest that an approach that incorporates the physiological response to intensive care treatment (the delta OFS or APACHE II score) is likely to be a better approach. For instance, a patient who seeks treatment and has an initial APACHE II score of 17 that increases to 21 is unlikely to benefit from any further intervention, whereas an initial score of 12 that decreases to 7 would encourage continuation. However, each component of the composite score has an error, and around each score is a confidence interval. The magnitude of the confidence interval will limit the application of this approach in the individual patient. At this stage, the Figure should not be used to make decisions about individual patients.

In conclusion, this study has highlighted the importance of the physiological response to intensive care treatment in predicting the outcome of SAP. The proposed approach takes into account the dynamic nature of early organ dysfunction. This dysfunction can be graphed (Figure) and shows the sigmoid response, which could provide a practical tool to track patient physiological response. Whether this approach can be used to help select individual patients for early surgical intervention or the withdrawal of intensive care treatment requires further investigation. What is clear is that patients should receive optimal intensive care treatment for at least 48 hours. The physiological response to this treatment is a useful predictor of outcome and better than a static score at hospital admission.

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