The Prognosis of the Adult Respiratory Distress Syndrome
Inappropriate Pessimism?

Since the adult respiratory distress syndrome (ARDS) was described in 1967, there have been numerous advances in supportive care in intensive care units but, allegedly, no improvement in survival.1 As we attempt to assess the value of supportive therapy in this syndrome, we rightfully turn to the clinical literature for objective data, and the results are discouraging. Reported survival in ARDS remains less than 50 percent in recently published studies,2,3 unchanged since the first description of supportive care,4 yet it seems to be the intuitive impression of many clinicians who care for critically ill patients that patients in groups with a known predisposition to ARDS, such as trauma, who develop respiratory failure are usually treated successfully and survive. Is it possible that the clinical literature is misleading us in its apparent pessimism?

The discrepancy between the perception of practitioners and the clinical literature suggests the possibility that criteria for inclusion for clinical investigations of ARDS in published studies may have inadvertently selected an atypical population of patients with a high incidence of severe underlying disease or multiple extrapulmonary organ system failure. The contribution of good supportive care to overall survival may have been seriously underestimated if patients who have acute pulmonary injury without multiple extrapulmonary organ system failure rarely meet stringent criteria for entry into ARDS studies anymore. If these “invisible” patients do well, they do not “count” in published studies.

Two criteria for inclusion, severe hypoxemia (alveolar/arterial ratio <0.3) and a simultaneous measurement of pulmonary arterial wedge pressure, may have increasingly introduced bias into published clinical studies, selecting a small subset of patients with an unusually poor prognosis; for example, because of increasing awareness of the uncertain risk-benefit ratio attending the use of pulmonary arterial catheters,5,6 there is a trend towards curtailment of their use except in settings where other organ system failure obscures assessment of intravascular volume and makes “trial-and-error” management hazardous. In straightforward cases that appear to be ARDS, often positive end-expiratory pressure (PEEP) may be used early to reduce the fractional concentration of oxygen in the inspired gas (FiO2) to a nontoxic level without invoking the hazards of pulmonary arterial catheters; however, early use of PEEP with improvement in gas exchange or an initial decision to forego insertion of a pulmonary arterial catheter makes patients ineligible for “publishable” studies of ARDS. If supportive therapy is effective, these patients remain ineligible. Experience at our institution would support two conclusions: first, that a majority of patients who appear to have “ARDS” clinically never meet publishable criteria for ARDS; secondly, that those who do meet publishable criteria have a high incidence of preexisting underlying disease which is likely a priori to be incurable. In a recent three-month period, we surveyed all mechanically ventilated patients and identified 27 patients, using broad clinical criteria for “ARDS.” These criteria included (1) a recognized predisposition to ARDS, (2) diffuse alveolar infiltrates on the chest x-ray film, (3) respiratory failure requiring mechanical ventilation with an FiO2 of greater than 0.4, and (4) the absence of a clinical history or roentgenologic findings of congestive heart failure; however, only seven of these patients satisfied the usual “publishable” criteria for ARDS. Five of those seven already had hepatic failure or a hematologic malignancy, both known predictors of a fatal outcome for ARDS.8,9 They died, yielding a mortality of 71 percent (5/7) in this “publishable” group. Consider the patients who didn’t meet publishable criteria for “ARDS” but constituted 74 percent (20/27) of the group; PEEP was usually used from the time of intubation, and 13 of 20 never achieved an alveolar/arterial ratio of less than 0.3 on PEEP. Furthermore, 15 of 20 patients never had a pulmonary arterial catheter placed. The latter group included all of the patients with trauma surveyed and all patients under the age of 30 years without severe preexisting underlying disease. Mortality in this group was only 30 percent (6/20). Thus, the requirement for a low alveolar/arterial ratio and a pulmonary arterial catheter skewed our “publishable” population of pa-

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patients with "ARDS" towards a small subgroup with a high incidence of a severe and predictably irreversible underlying disease and, not surprisingly, a high mortality.

The extent to which sampling bias may have arisen from criteria for inclusion is probably variable between institutions. Institutions with a large number of patients with cancer or underlying organ system failure, such as ours with a large transplantation program, may be particularly susceptible. Institutions which are liberal in the use of PEEP and conservative in the use of invasive monitoring will select a sicker subgroup using standard criteria for ARDS. It seems likely that diversity between institutions results in a covert non-uniformity in the patients included in published clinical studies of ARDS.

To better assess the real prognosis of noncardiogenic pulmonary edema, "criteria" for ARDS based on a low alveolar/arterial ratio and a pulmonary arterial catheter may need to be modified. Admittedly, it will be difficult for investigators working in the area to agree on new ones. Elimination of data from pulmonary arterial catheters will raise a risk of occasional inadvertent inclusion of patients with a component of unsuspected "cardiogenic" edema. Also, hemodynamic data, which are of interest in clinical studies, will be inaccessible in patients without pulmonary arterial catheters; however, it may be necessary to accept these limitations in order to more accurately assess prognosis and evaluate present methods of supportive care and new pharmacologic agents. The latter is particularly important; inclusion of a high percentage of predictably moribund patients with severe underlying organ failure or irreversible underlying diseases in clinical studies evaluating new therapy for "ARDS" will virtually preclude demonstration of a statistically significant benefit.

Three modifications in the design of future clinical studies might be helpful in reassessing the prognosis of respiratory failure associated with noncardiogenic pulmonary edema. First, future studies should provide clear descriptive data concerning the underlying diseases of patients with "ARDS." This will permit statistical exclusion of patients who already have severe underlying extrapulmonary disease which is likely to be irreversible per se at the time of onset of ARDS. Secondly, future studies should permit investigators to exclude congestive heart failure on clinical grounds without a requirement for Swan-Ganz catheters, recognizing that errors will occasionally occur. Thirdly, any attempt to quantify the severity of the oxygenation defect should be based on the initial arterial blood gas analysis after intubation before PEEP is added so that a rapid response to PEEP will not, by definition, exclude patients from studies of "ARDS."

Time-honored physiologic criteria have served an important purpose in the description and subsequent study of ARDS; however, changing clinical practice, including increasing skills in the provision of supportive care, and increasing selectivity in the use of invasive monitoring may have made them obsolete. Retaining criteria which exclude many patients who respond to therapy while inadvertently selecting a high proportion of hopelessly moribund patients will lead to inappropriate nihilism and will impede clinical evaluation of potentially beneficial types of therapy in the future.

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Markers of Sarcoidosis Activity

Recently, many simple and noninvasive tests have been developed to assist in making the diagnosis and measuring the activity of sarcoidosis. These biochemical markers may be present in serum or other biologic fluids. In general, these measurements are useful not for establishing the diagnosis of sarcoidosis,

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