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EDITORIAL

Predictors of the Adult Respiratory Distress Syndrome

THE QUEST for therapeutic agents to prevent the adult respiratory distress syndrome (ARDS) has been hampered by the lack of accurate predictors of the syndrome. Without specific indicators, clinical studies to test the efficacy of preventative agents require large numbers of patients because only a minority of untreated patients will subsequently develop the syndrome. An accurate predictor is also necessary if a preventative intervention becomes available that is effective yet has adverse side effects. In this case the treatment may still be beneficial if its use can be restricted to those patients who have a very high likelihood of developing ARDS. At the same time the predictor must be sensitive enough to allow most patients who are destined to develop ARDS to receive the treatment. At first analysis, the approach for finding predictors would seem to be straightforward. However, after further consideration, the problem is found to be substantially more complex.

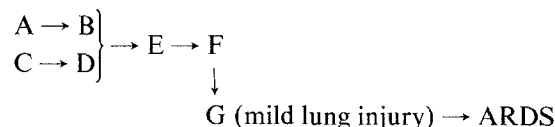
The first difficulty arises from the manner in which the syndrome is defined. Most studies of ARDS have used criteria that require the presence of a substantial amount of lung injury before the diagnosis of ARDS can be made. Milder lung injury that is qualitatively similar to that which occurs in ARDS certainly exists¹ and probably has similar pathogenic mechanisms. Therefore, any test for predicting ARDS that relies upon the presence of specific predisposing factors or putative mediators might then appear nonspecific because it is also positive in the milder cases.

Another reason for pessimism regarding the search for a universally applicable predictor is

that there are likely to be many distinct pathogenic mechanisms that cause ARDS. There is no a priori reason to assume that all cases of ARDS share a single pathway that leads to the increased capillary-alveolar permeability. It is possible, though, that common mechanisms do exist for large subgroups of patients, such as those having sepsis syndrome or gastric aspiration.

Predictive markers of ARDS may reflect events occurring anywhere along the pathway that leads to lung injury. At one extreme, a test might measure a genetic trait that increases the likelihood of a patient developing diffuse alveolar injury when a particular clinical situation arises. Examples of hypothetical genetic variants that might predispose to ARDS are those that allow excessive activation of inflammatory cascades, inadequate down-regulation of ongoing inflammatory processes, or insufficient inhibition of injurious products generated during inflammation. Although one can conceive of many possible genetic or acquired traits that would predispose to ARDS, at present no predictive factors of this type have been demonstrated.

Theoretically, the value of a particular predictive test also depends upon the type of therapeutic intervention that is being considered. For example, suppose the events leading to ARDS occur in the following temporal sequence:



If a predictive test detects $E \rightarrow F$ but the planned intervention blocks step $A \rightarrow B$, the test (even

though accurate) might be of little value. Waiting for the test to become "positive" might be too late to start treatment. This is particularly true if the pathway up to E is no longer required for ARDS to develop once F is activated. This concern is similarly applicable to those predictors of ARDS that are actually indicators of mild lung injury, ie, they detect G in the aforementioned hypothetical sequence. Unfortunately, many therapeutic agents that are beneficial in animal models of ARDS have been tested only when given to animals before the process of injury is initiated. Their effectiveness has generally not been tested when administered after lung injury has become manifested. Waiting until mild injury occurs might then be too late for those patients in whom the process of severe lung injury has already been set into motion. The most useful predictors would be those that monitor events close to the start of the pathogenic sequence, yet they must still be specific for ARDS. It is possible that a single predictor with these characteristics might not exist, and even if it does exist, it may be detectable for only a very limited period of time during the pathogenic process.

Despite these problems, tests that attempt to accurately predict ARDS have been developed along several different lines. Excellent epidemiology studies now exist that estimate the risk of developing ARDS in certain clinical situations.^{2,3} Although the majority of patients who develop ARDS usually fit into several diagnostic categories, the incidence of ARDS in even the highest of these risk groups is only 36%,² and each category represents only a small fraction of the total number of ARDS patients. In a study that restricted analysis to patients who were already intratracheally intubated because of the severity of their underlying illness, a subgroup (those with "sepsis syndrome") could be identified that had a 47% risk of developing ARDS.³ To further improve the utility of this type of an approach, multivariate analysis has been used. For example, data from a retrospective study of severely ill, intratracheally intubated patients were used to develop a predictive test relying on readily obtainable information.⁴ This test when applied in a subsequent prospective trial correctly categorized 10 of 19 (53%) patients who developed ARDS and 61 of 68 (81%) patients who did not.

In an effort to improve upon these types of tests and make them applicable to a broader range of patients, the predictive values of various laboratory measurements have been investigated. One of the earlier areas of study involved monitoring complement activation. The possibility that complement activation might be a useful predictor of ARDS arose from reports that neutrophils were sequestered within the lungs of patients with ARDS.^{5,6} The suggestion that active components of complement might be responsible came from later investigations demonstrating that complement was activated during hemodialysis and was associated with pulmonary neutrophil sequestration and hypoxemia.⁷ Furthermore, intravascular complement activation in laboratory animals caused diffuse lung injury.^{8,9}

In 1980 Hammerschmidt et al reported that patients with trauma, sepsis, or shock who subsequently developed ARDS often had signs of complement activation.¹⁰ Of 31 patients at risk for ARDS, 6 had active complement fragments (C5a-like activity) in their plasma and all 6 subsequently developed the syndrome. Of 26 patients without C5a in their plasma, none developed ARDS. Unfortunately, more recent studies of patients at risk for ARDS have not demonstrated that complement activation is a highly specific predictor of ARDS.¹¹⁻¹³ This is not entirely surprising considering that complement activation is known to occur in many clinical situations (eg, septic shock), while ARDS develops in only a minority of these cases. The occurrence of lung injury from complement activation alone was also called into question with the finding that the blood gas alterations seen in patients undergoing hemodialysis could be totally explained by the loss of carbon dioxide across the dialysis membrane and did not necessarily imply the presence of lung damage.¹⁴ Furthermore, active complement components were subsequently shown to be insufficient to cause lung injury in the rabbit even though neutrophils were still sequestered within the lungs.¹⁵ Although complement activation by itself is not a specific predictor of ARDS, it is quite possible that in many cases of ARDS, it is an important component in the pathogenic process. In these situations, additional factors that have yet to be fully elucidated are clearly necessary.

Alterations within the coagulation system have also been suspected of playing a role in the lung injury of ARDS.^{16,17} Tests that are used to diagnose diffuse intravascular coagulation are often positive in patients with ARDS and have been suggested to be of predictive value for the syndrome.¹⁸ However, prospective studies subsequently demonstrated that critically ill patients often have evidence of diffuse intravascular coagulation whether or not they go on to develop ARDS.¹⁹ Fibrinopeptide D, a cleavage product of fibrinogen and fibrin, might be more specific for ARDS.²⁰ Whether the plasma level of this fragment has predictive value in patients at risk remains to be determined.

A variety of other mediators have been suggested as being part of the pathogenic process of ARDS based on preliminary human studies and data from animal experiments. These mediators include the products of arachidonic acid metabolism,²¹ platelet activating factor,²² histamine,²³ and serotonin.²⁴ At present none of these agents have been adequately studied to evaluate their role as predictors of ARDS.

Blood neutrophils have been suspected of causing lung injury in many but not all cases of ARDS.²⁵ The proposed mechanism involves activation of circulating neutrophils leading to their aggregation and sequestration within the lung. The activated neutrophils then release agents that damage lung parenchyma. A study of patients at risk for ARDS revealed that the number of circulating leukocytes often decreased at the onset of ARDS.²⁶ In addition, neutrophils obtained from circulating blood of patients with ARDS have been shown to be altered in a manner suggesting *in vivo* activation.²⁷ Detection of neutrophil-derived products might therefore predict impending ARDS. Lactoferrin, a constituent of neutrophil granules, has been found to be elevated in critically ill patients. In a prospective study of 19 patients, the 8 who developed ARDS had higher circulating levels of lactoferrin than did those without severe lung injury.²⁸ Serum lysozyme and breath hydrogen peroxide, other products of neutrophils, have also been found to be elevated in patients with ARDS.²⁹ It remains to be determined from larger studies whether these measurements when performed on critically ill patients will separate those who progress to ARDS from those who do not.

Plasma concentrations of fibronectin, a glycoprotein with opsonic and cell adhesive activities, were found to be decreased in patients with various critical illnesses such as sepsis and diffuse intravascular coagulation.³⁰ Because fibronectin is believed to be important for maintaining vascular integrity, its usefulness as a predictor of ARDS has been evaluated. A prospective study of critically ill, intratracheally intubated patients confirmed that plasma fibronectin concentrations were low when compared to normal, healthy individuals.³¹ However, there was no difference in fibronectin levels between those critically ill patients who went on to develop ARDS and those who did not.

Various measurements that probably reflect mild or early vascular injury have been tested as predictors of ARDS. Angiotensin converting enzyme, a protease found in relatively high concentrations in pulmonary capillary endothelial cells, can be detected in plasma of normal individuals. In patients with ARDS, the serum activity of angiotensin converting enzyme has been found to be low.³² As a predictor of ARDS, the test probably lacks adequate sensitivity and specificity because levels are low in other lung conditions such as chronic obstructive pulmonary disease and are normal in a significant number of patients with ARDS.³³ Other pulmonary vascular activities, such as the clearance of various molecules from blood during transit through the lungs, might provide a means to detect early lung injury. For example, decreased extraction of serotonin^{34,35} and prostaglandin E₁³⁵ from circulating blood of patients with ARDS has been described. Whether these tests can reliably predict ARDS remains to be seen.

It is possible that materials obtained from other body fluids such as bronchoalveolar lavage might provide better predictors. However, the inability to easily obtain these specimens from nonintubated patients will limit broad scale application. For any test to achieve widespread use, it must be possible to perform the measurement quickly and reproducibly at an acceptable risk and cost.

In summary, no single predictor is currently available that can be used with high sensitivity and specificity to identify patients destined to develop ARDS. Multivariate analysis applied to the previously mentioned measurements may

increase the predictive accuracy of the information present in the currently available epidemiologic studies. More likely though, only a better understanding of the various pathogenic mechanisms of ARDS will lead to the development of

accurate, clinically applicable predictors of the syndrome.

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