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Genetic Epidemiology of Acute Respiratory Distress Syndrome: Implications for Future Prevention and Treatment

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Acute lung injury and acute respiratory distress syndrome (ALI/ARDS) is a devastating form of respiratory failure characterized by intense inflammation and increased permeability in the lungs that usually develops in response to a major insult such as sepsis, trauma, pneumonia, burns, or multiple transfusions [1]. Despite the common occurrence of these risk factors, only a minority of patients who have these injuries develops ALI [2,3]. ALI/ARDS is now recognized as being more prevalent than initially thought, with an age-adjusted incidence of 86.2/100,000 person-years, with a mortality of 38.5%, and with significant morbidity among the survivors [4,5].

Because ALI has such high mortality and morbidity, any intervention that could prevent or treat ALI would have a significant impact on critical care medicine and on public health. Epidemiologic studies can contribute to prevention and treatment by determining the risk factors associated with variable susceptibility and outcomes that could be modified to decrease the risk of developing the disease or of having a poor outcome. The current understanding of why some patients develop and die from ALI and others do not is incomplete. Recently, discoveries about the genetic control and regulation of innate immunity and inflammatory response have raised the question of whether the multiple polymorphic alleles of genes that encode for cytokines and other mediators of inflammation may result in phenotypic differences in host inflammatory response. These differences may account for some of the heterogeneity in individual susceptibility to and prognosis in ARDS.

Since the initial description of ALI, there has been much research on the role of complement, endotoxin, and pro- and anti-inflammatory cytokine response in the pathogenesis and course of ALI/ARDS [6]. Protein biomarkers, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor-1, surfactant protein B (SFTPB), and von Willebrand's factor antigen, may be useful in predicting either development of or outcomes in ALI [7–11]. Although research on protein biomarkers in ALI/ARDS has contributed greatly to the understanding of the pathogenesis of ALI, it has not yet led to novel interventions.

Genetic epidemiology is a relatively new discipline that seeks to determine the role of genetic factors and their interactions with the environment in the occurrence of the disease or its outcome within a population [12]. Genetic epidemiology has been applied to the study of ALI. only recently. Genes hold several advantages over protein markers of lung injury, especially for possible prevention. Unlike cytokines, which can vary with the precipitant factor for ALI and with the time course of critical illness, a person's genotype is constant throughout the individual's life, regardless of health status. Thus, there is inherently less variability to the determination of genotypes than protein markers. The

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variation of many of the protein markers before and during critical illness means that the window of opportunity for assessment must be consistent and is likely to be narrow. Such a window for assessment may be especially impractical in the prevention of ALI/ARDS, because lung injury tends to develop rapidly, within hours to days of the predisposing injury. In addition, in ALI regional differences in the expression and concentrations of some cytokines, such as TNF-α, means that biomarkers may be best measured from alveolar fluid [13]. Measurements from the lungs are invasive, are vulnerable to technical variation, and are not always appropriate for severely hypoxic patients who have ARDS or for the nonintubated patients at risk. DNA for genotype assessment can be obtained easily from peripheral blood samples, and thus genotype assessment can be performed safely for any patient. Another advantage of genes is that any true genetic association with the disease is unlikely to be an epiphenomenon related to lung injury. Any variation in a protein marker may be a product rather than the cause of developing lung injury. The individual's genotype, however, precedes the lung injury and the precipitant to lung injury. Thus, any true genetic association supports the biologic causality of the gene or its product in the development of ALI/ARDS and the targeting of the gene in future preventions. Last, the invariant nature of the genome means that an individual's genetic predisposition to developing lung injury could be determined in advance and noted in the individual's medical records or, conceivably, on an encrypted microchip worn by the individual. This precaution would be especially useful in interventions to prevent ALI/ARDS, because the injury leading to ALI/ARDS is almost always unanticipated, and the window for intervention to prevent lung injury after the insult is narrow.

In the last few years, there has been a sudden explosion of studies of the genetic susceptibility of ALI/ARDS. The following sections review the recently published studies in the genetic epidemiology of ALI/ARDS and discuss the relative strengths and limitations of the current approach with a focus on the implications for future prevention and treatment. The possible applications and potential limitations to the translation of genomics and genetic epidemiology to future prevention and treatment of ALI/ARDS are discussed also.

Current approach and recent studies in the genetic epidemiology of acute lung injury/acute respiratory distress syndrome

Candidate-gene approach

Traditionally, the term "pharmacogenomics" referred to the application of whole-genome scanning for the discovery of new drug targets [14]. Genome-wide studies examining anonymous markers spaced throughout the entire genome are not yet practical in ALI/ARDS. Rather, all studies thus far have used the candidate-gene approach, which focuses on specific genes whose products have been well characterized as biologically important in the pathogenesis, progression, or manifestation of ALI/ARDS [15]. The candidate-gene approach is hypothesis driven and founded on current knowledge of the disease process. The validity of the candidate gene rests on the evidence supporting its selection as a candidate in ALI/ARDS. Table 1 details the candidate genes that have been studied in ALI/ARDS and the evidence supporting their selection.

The strongest candidates for investigation are the genes that have been linked to ALI in previous linkage studies, in association studies, or in animal models of the disease (Fig. 1) [51]. Investigations into the genetic determinants of ALI/ARDS have been undertaken only recently. The selections of many of the candidate genes in recently published studies were supported by previously published reports in other, similar conditions, such as neonatal respiratory distress syndrome for the *SFTPB* gene and sepsis for the *TNF-α*, *IL-10*, mannose binding lectin-2 (*MBL-2*), and *IL-6* genes. Conversely, several candidate genes found to be associated with ARDS (ie, the *+1580CT* polymorphisms in the *SFTPB* gene, the *T-1001G* and *C-1543T* polymorphisms in the pre–B-cell colony-enhancing factor [*PBEF*] gene, and the *codon 54* polymorphism in the *MBL-2* gene) were also found to be associated with increased risk for sepsis or septic shock in the same population [37,38,52]. Overall this finding suggests that genes and polymorphisms that have been implicated in sepsis would serve as strong candidate genes in ALI/ARDS.

In the absence of studies of ALI or related conditions, the biologic plausibility of the candidate gene in the pathogenesis of lung injury is important (see Fig. 1). There should be evidence supporting the importance of the gene product or function specifically in ALI.