progress further to ARDS. Even in patients with ARDS, many have a very short duration of illness and have excellent outcomes, but our ability to clearly define this group of patients at the outset remains limited. If we cannot be sure in whom to intervene, any economic benefit from successful therapy quickly deteriorates due to massive overtreatment.

Finally we have to consider what downstream adverse effects there may be from intervening. Both glucocorticoids and anti-tumor necrosis factor therapies offered promise, but ultimately failed to show benefit both in bacterial and viral pneumonia in part due to excess side effects such as secondary infections (10). Although shutting down pulmonary inflammation may provide acute benefits, it may increase the risk of downstream complications. There is evidence that patients with ARDS are now older and have more comorbidities (11, 12). Another interesting issue is the possibility of genetic modification to secrete a specific protein that plays an important role in the control and pathogenesis of ALI/ARDS (13, 14). Will reducing the severity of ARDS, without affecting the underlying disease(s) responsible, produce real mortality and economic benefits, or will we be just keep some patients alive a little longer at great expense?

Overall Lee and colleagues are to be commended for their very detailed study and their new findings. KGF, given that it could be easily produced in large quantities and can be given systemically, avoiding the need to start mechanical ventilation preemptively, shows some promise. We should, however, recognize the severe limitations this and other experimental models of ARDS have and continue to try and produce data that answer the key questions: What is the window of opportunity to give the intervention? How long does the intervention continue to depress the immune response? What subgroup(s) of patients at risk for ARDS does this truly benefit? The increasing participation of large pharmaceutical companies in stem cell therapies and strong funding from research foundations and governmental agencies (15) is likely to expand new clinical trials in this field.

Author disclosures are available with the text of this article at www.atsjournals.org.

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The Berlin Definition of ARDS versus Pathological Evidence of Diffuse Alveolar Damage

A reliable definition of acute respiratory distress syndrome (ARDS) is essential for clinical trials, epidemiologic studies, and biological studies of pathogenesis. A reasonable working definition of ARDS is also needed for clinicians to make the diagnosis of ARDS and initiate treatments that will improve clinical outcomes, including lung protective ventilation. ARDS is a form of acute lung injury characterized by inflammation and increased endothelial and epithelial permeability to protein (1). The corresponding pathologic findings are lung edema, inflammation and hemorrhage, hyaline membranes, and alveolar epithelial cell injury (i.e., diffuse alveolar damage [DAD]); these findings on post mortem examination or lung biopsy have represented the gold standard. The 1994 American European Consensus Conference definition was the first definition to be widely adopted after
many prior definitions (2). However, a number of limitations prompted a reexamination that led to the recently published Berlin definition of ARDS (3). This definition identifies three mutually exclusive categories of increasingly severe ARDS based on the degree of arterial hypoxemia as measured by the PaO$_2$/FiO$_2$ ratio (P/F): mild—P/F 201 to 300 mm Hg; moderate—P/F 101 to 200 mm Hg; and severe—P/F ≤ 100 mm Hg. The segregation of ARDS patients by severity based on the P/F builds upon recent evidence indicating differential effects of interventions by ARDS severity (4, 5) and codifies recent trends to enroll the more severe end of the spectrum into clinical trials of higher-risk interventions (6).

The sensitivity and specificity of the Berlin definition overall, and for the three subsets of ARDS, was tested by Thille and colleagues (pp. 761–767) in this issue of the Journal using a remarkable 712-patient autopsy series gathered over the last two decades (7). Among all patients who met the Berlin definition of ARDS, only 45% had DAD. The finding of DAD increased to 58% in the most severe subset but fell to only 10 to 14% in the mild ARDS subset. However, if the pathological findings of pneumonia without DAD were added, then DAD or pneumonia, or both, was identified in 88% of the ARDS cases by the Berlin definition. Because pneumonia is the most common clinical cause of ARDS, the addition of criteria for pneumonia to the pathological correlates of ARDS seems sensible and important in future clinical–pathological studies of ARDS. DAD probably represents evidence of more severe lung injury, a conclusion supported by the investigators’ finding of a higher frequency of DAD in the patients with the worst hypoxemia and the highest lung weight (approximate measure of lung edema) in the post mortem examination.

Herein lies one of the strengths of including pneumonia and other findings, such as alveolar hemorrhage and edema, with DAD when linking pulmonary pathological changes to the clinical syndrome of ARDS. For example, transient hydrostatic edema coexists with increased permeability to protein in approximately 30% of patients with a clinical diagnosis of ARDS (8). Further, mortality was reduced with low tidal volume ventilation in all of the different clinical disorders associated with lung injury in the ARDS Network lung protective ventilation trial (9), which included patients with the P/F ratios encompassed in the Berlin definition and likely included patients who did not have DAD as supported by the results of the current study (7).

Normal lung was found in approximately one in every eight patients who met the clinical definition of ARDS. Lungs are inflated at high pressure prior to fixation, and it is likely that these patients had atelectasis. It is also possible, given known difficulties with interpretation of portable chest radiographs in the intensive care unit, that pleural effusions or overlying soft tissue from obesity led to a false-positive radiograph (10). Standardized ventilator settings with higher positive end-expiratory pressure may eliminate patients with atelectasis masquerading as ARDS and thus modestly increase specificity (11). The Berlin definition allows for opacities on computed tomography (CT) scan that are not fully explained by pleural effusions or atelectasis to qualify for ARDS. In addition to atelectasis, interstitial cancer, emphysema, interstitial fibrosis, and lung abscess accounted for 40% percent of the false positives and may have been identified by CT. However, CT imaging to improve specificity is not a practical approach for most studies and clinical trials.

One of the most important findings from Thille and coworkers’ study was the observation that a lower proportion of DAD was found in patients with risk factors over the past decade (2001–2010). Patients in this more contemporary cohort were ventilated with lower tidal volumes in comparison to the 1991–2000 cohort managed prior to the publication of the ARDS Network’s lower tidal volume trial (12). Furthermore, at-risk patients ventilated for more than 72 hours also had a higher likelihood of having DAD. Taken together, these findings suggest for the first time in humans that lower tidal volume may reduce the development of DAD and thus more severe lung injury, and are in keeping with a substantial body of experimental work and recent observational studies showing possible prevention of ARDS with lower tidal volume ventilation in at-risk individuals (13).

Investigators have increasingly examined the effects of various interventions in subgroups of differing ARDS severity, again largely based on the P/F ratio. An individual patient metaanalysis of three large randomized clinical trials of higher positive end-expiratory pressure suggested harm in patients with mild ARDS, a group we now know was unlikely to have had DAD (4). A post hoc analysis of the ARDS Network trial demonstrated benefit of lower tidal volume ventilation and conservative fluid therapy in all the P/F subsets (14). Conversely, another metaanalysis suggests benefit from prone ventilation only for the most severe ARDS subset, perhaps because such patients have higher lung weights and more recruitable lung tissue regardless of the presence or absence of DAD (5). The lack of specificity for the Berlin definition presents a substantial challenge for drug discovery efforts seeking to cure more severe lung injury as reflected by the presence of pathological findings of DAD. However, this disconnect between the pathologic findings of severe lung injury and the clinical definition emphasizes the need for a more complete biological profile of ARDS patients, with an emphasis on the potential value of molecular phenotyping with protein biomarkers, gene expression, and specific genetic risk factors. Future progress in therapy to reduce ARDS mortality may require enhanced ability to characterize the ARDS patients by both clinical and biological criteria.

The limitations of the Berlin definition largely reflect the limitations of the clinical phenotype for predicting specific acute pathologic events in the lung. However, grading patients with ARDS by severity of hypoxemia as proposed in the Berlin definition is one reasonable approach. Other criteria for diagnosis could include the presence of septic shock, since we know that the use of vasopressors at the time of diagnosis of ARDS is associated with a much higher mortality regardless of the P/F ratio (15). In addition, we need clinical and biologic criteria to identify patients with early lung injury who are not yet ventilated with positive pressure, and comprise a population of patients that may respond to therapeutic interventions that would not be so effective once patients develop ARDS and lung pathological findings of DAD.

Author disclosures are available with the text of this article at www.atsjournals.org.

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Idiopathic Pulmonary Fibrosis Pathogenesis and Novel Approaches to Immunomodulation
We Must Not Be Tyrannized by the PANTHER Data

Twenty years ago, in the absence of alternative candidate mediators and pathways, idiopathic pulmonary fibrosis (IPF) was widely viewed as “fibrosing alveolitis,” an immunologically mediated disorder in which inflammation was believed to precede and lead to fibrosis. Immune modulation was the only available treatment strategy around which a pathogenetic model could be built, and it is likely that this fact heavily influenced the thinking of that time. Furthermore, a significant minority of patients with IPF, diagnosed before the millennium, responded to corticosteroid therapy. It is now understood, aided by the reclassification of the idiopathic interstitial pneumonias in 2002 (1), that good treatment outcomes in patients previously diagnosed with IPF were associated with alternative diagnoses, including nonspecific interstitial pneumonia and desquamative interstitial pneumonia. However, the perception of a role for inflammatory pathways in IPF progression refused to die. In connective tissue disease, a histological pattern of usual interstitial pneumonia (the defining pattern in IPF) was found to be associated with bronchocentric inflammation and enlargement of lymphoid follicles, features predictive of a better treatment outcome (2). The emerging entity of “lung-dominant connective tissue disease” (3), although more generally applied to idiopathic nonspecific interstitial pneumonia, provided conceptual support for the hope that in some patients with IPF, suppression of autoimmune pathways might be beneficial. Furthermore, the reduction in IPF disease progression seen with “triple therapy” (prednisolone, azathioprine, and N-acetylcysteine) in the IFIGENIA study (4) could be interpreted as a beneficial synergistic effect.

The recently published placebo-controlled evaluation of “triple therapy” in IPF (5) might seem, at first sight, to lay finally to rest the notion that immunomodulatory therapies have an important future therapeutic role in IPF. However, the authors were careful to stop short of drawing this conclusion, and their caution in this regard is endorsed by the findings of Kahloon and colleagues in the current issue of the Journal (pp. 768–775) (6). The underpinning hypothesis of Kahloon and colleagues was that antigen-specific immune responses influence the rapidity of IPF progression. Heat shock protein 70 (HSP70) was identified as a candidate IPF autoantigen, based on discovery assays and the controlled observation of increased HSP expression in airway and alveolar epithelia, macrophages, and endothelium in six IPF transplantation explants. Anti-HSP70 autoantibodies, detected in 25% of a cohort of 122 IPF patients, were present in 70% of patients with acute exacerbations and were also associated with a much higher prevalence of early FVC decline and a strikingly higher mortality at 1 year. Importantly, these effects were independent of the baseline severity of disease and were not seen in patients with other interstitial diseases, despite a similar prevalence of anti-HSP antibodies.

The unequivocal linkage of anti-HSP antibodies to IPF-specific clinically important outcomes, independent of baseline severity, argues strongly against the possibility that anti-HSP antibodies are merely a nonspecific marker of tissue damage (representing a global increase in immunoglobulin production) and irrelevant to pathogenesis. Taken together, the lack of T-cell proliferation to the closely related HSP family member, GRP78, and the lack of association between anti-GRP antibodies and clinical outcomes, provides further support evidence of specific HSP autoantigenicity. The case advanced by Kahloon and colleagues would have been further strengthened by a search for antibodies to other heat shock proteins, with an exploration...