Air Medical Journal 38 (2019) 7–9

Contents lists available at ScienceDirect

Air Medical Journal

journal homepage: http://www.airmedicaljournal.com/

Critical Care Update

ARDS: From Syndrome to Disease

Prevention and Genomics

David J. Dries, MSE, MD

Acute respiratory distress syndrome (ARDS) is a major clinical problem and the final pathway of lung injury from multiple etiologies. In light of relatively imprecise diagnostic criteria, there is often considerable uncertainty about whether or not a patient has ARDS. Diagnostic criteria for ARDS require the demonstration of bilateral infiltrates on chest x-ray and hypoxemia. Both of these findings can be manipulated by routine critical care interventions. Diagnostic uncertainty represents a potential source of bias in conducting ARDS clinical trials. ARDS can also be considered a consequence of other critical illnesses such as sepsis or pneumonia, making it an intermediate or surrogate outcome rather than a clinical end point itself. In fact, most patients with ARDS do not die from hypoxemia but from organ failure associated with the inciting disease process.

Here we review recent data designed to bring approaches to managing the syndrome of ARDS into better focus.

Introduction

Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. *JAMA*. 2018;319:698-710.

Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. *N Engl J Med*. 2017;377:562-572.

Sjoding MW, Cooke CR, Iwashyna TJ, Hofer TP. Acute respiratory distress syndrome measurement error: potential effect on clinical study results. *Ann Am Thorac Soc*. 2016;13:1123-1128.

Maiolo G, Collino F, Vasques F, et al. Reclassifying acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2018;197:1586-1595.

ARDS is a life-threatening form of respiratory failure. It affects 200,000 patients annually in the United States, resulting in nearly 75,000 deaths. Globally, ARDS accounts for 10% of intensive care unit (ICU) admissions, representing more than 3 million cases annually. Many statements regarding clinical criteria and pathogenesis for ARDS have been made. Unfortunately, we still struggle to classify and identify this syndrome. Relatively few treatment priorities have stood the test of multiple trials, and we are only beginning to appreciate the genetic signature of ARDS. For the first time, we have data suggesting that expression of the ARDS phenotype may alter the response to common clinical interventions.

Despite repeated definitions produced since the 1960s, we continue to work on reclassifying ARDS. The time-honored PaO_2/fraction of inspired oxygen threshold can clearly be affected by the application of mechanical ventilation and its settings, fluid and drug administration, and patient position. Perhaps most concerning is a significant potential for measurement error and its confounding effect on clinical study results. As an international group of authors note, measurement error in the characterization of ARDS "can seriously degrade statistical power and affect size estimates of clinical studies." Without consistent measurement strategy, data upon which guidelines and treatment protocols are determined continue to be flawed. ARDS continues to be a syndrome and the end point of multiple clinical pathways, and the best care that we can provide over 50 years after identifying the problem is supportive.

Prevention

Yadav H, Thompson BT, Gajic O. Fifty years of research in ARDS. Is acute respiratory distress syndrome a preventable disease? *Am J Respir Crit Care Med*. 2017;195:725-736.

Reilly JP, Christie JD. Is it possible to prevent ARDS? *JAMA*. 2016;315:2403-2405.

Abdulnour RE, Gunderson T, Barkas I, et al. Early intravascular events are associated with development of acute respiratory distress syndrome: a substudy of the LIPS-A clinical trial. *Am J Respir Crit Care Med*. 2018;197:1575-1585.

The view of ARDS as potentially preventable stems from early descriptions of its association with massive transfusion, excessive fluid resuscitation, and inappropriate use of mechanical ventilation. Since that time, lung-protective mechanical ventilation, fluid-restrictive resuscitation, prone positioning, and promotion of ventilation synchrony through the use of sedation and muscle relaxation have improved outcomes in ARDS by preventing further iatrogenic lung injury in an already injured lung.

ARDS prevention can be considered in the context of primary, secondary, and tertiary strategies. Primary prevention attempts to manage risk by altering behavior and exposure before disease onset. These strategies can be universal and given to all patients whether they have an increased risk of developing ARDS or not. Secondary prevention targets patients at high risk for developing disease, whereas tertiary prevention uses therapies instituted to treat established ARDS.

Primary Prevention

A number of common interventions fall under the heading of primary prevention for ARDS. For example, seasonal influenza and pneumococcal pneumonia are common reasons for hospital and ICU admission and

1067-991X/$36.00

https://doi.org/10.1016/j.amj.2018.11.018

are associated with considerable mortality. A substantial portion of individuals admitted to the ICU with influenza develop ARDS. The efficacy of the influenza vaccine offers an opportunity to reduce the impact of influenza on ARDS, whereas pneumococcal vaccines reduce invasive pneumococcal lung disease. Routine immunization consistent with current infection prevention guidelines can be expected to prevent a significant number of severe pneumonia cases. Because pneumonia is a common pathway for ARDS, reduction in its incidence will prevent end-stage lung injury.

Aspiration pneumonitis is another risk factor for ARDS. Improvements in perioperative medicine have resulted in a decline in aspiration in the perianesthetic period. These interventions include a reduction in gastric volume by preoperative fasting, rapid sequence intubation, and ensuring the return of airway reflexes before removal of the endotracheal tube. Promoting aspiration precautions is another example of primary prevention in hospitalized patients.

Secondary Prevention

Although some patients progress directly to ARDS, a substantial proportion of affected individuals may only develop full expression of this problem after being exposed to one or more potentially preventable risk factors. The opportunity to prevent ARDS begins at the time of the first health care contact and requires the reduction of "second hits." In a rapidly developing condition like ARDS, the window of opportunity for risk prediction, early detection, and prevention is small.

Secondary prevention opportunities that follow the initial health care contact include the avoidance of excessive fluid administration, optimal antibiotic coverage at the time of hospital admission, transfusion reduction, and administration of mechanical ventilation with a tidal volume < 8 mL/kg.

Because many critically ill patients may receive mechanical ventilation soon after health care contact, early administration of lung-protective mechanical ventilation is an attractive secondary ARDS prevention strategy. Lung-protective ventilation is safe in patients without ARDS as well. The most recent data support the role of individualizing ventilatory strategies based on patient physiology. One such approach focuses on trying to reduce driving pressure (calculated as plateau pressure – positive end-expiratory pressure in passively ventilated patients). This strategy is based on the concept that in ARDS only part of the lung may be participating in gas exchange with the remaining lung collapsed or flooded. Reducing the tidal volume to reflect functional lung size may be more biologically relevant than prescribing the tidal volume by predicted body weight. Driving pressure is a surrogate marker of tidal volume scaled to lung compliance and has been shown to be a ventilator variable that effectively stratified the risk of death in a retrospective review of the massive data set gathered by the ARDS Network (ARDSNet) Investigators. Further study of this approach is needed.

Successful secondary prevention strategies are dependent on the identification of patients at high risk for ARDS before the development of the full syndrome. ARDS prediction systems are now being published such as the lung injury prediction score, which is based on clinical data obtained within the first 6 hours after presentation in the emergency room. Other predictive scores have also been published. Another group of secondary prevention strategies is derived from the recognition that inflammation is important in ARDS pathophysiology. Thus, glucocorticoids may be a reasonable choice for ARDS prevention. Steroids reduce the production of proinflammatory cytokines, downregulate adhesion molecules, and reduce neutrophil migration. Glucocorticoids have already been shown to have a valuable adjunct role in the management of pneumonia, particularly in patients with an exaggerated inflammatory response. Additional data are needed to determine a role for steroids in a preventive strategy for ARDS. Steroids may be given intravenously or as inhaled therapy, which may be an attractive means to bring medication directly to the injured lung.

Tertiary Prevention

Improvement in critical care and organ support has led to a growing population of ARDS survivors. These individuals frequently suffer from impaired cognition, mental health, and physical function, collectively known as post–intensive care syndrome. Strategies to prevent or reduce the impact of post–intensive care syndrome include the ABCDE bundle. The first part of the ABCDE bundle is awakening and breathing coordination with daily interruption of sedation, spontaneous breathing trials, and regular reassessment of readiness for ventilator removal. Monitoring and appropriate management of delirium including early physical therapy constitute the remainder of this bundle. For example, early mobilization has been shown to reduce the time on mechanical ventilation and improve functional mobility by the time of hospital discharge. Minimizing secondary infectious complications also reduces the time on mechanical ventilation, prevents prolonged ICU and hospital stay, and incrementally reduces the risk of late sequelae of ARDS.

Genomics

Famous KR, Delucchi K, Ware LB, et al. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *Am J Respir Crit Care Med*. 2017;195:331-338.

Shankar-Hari M, McAuley DF. Acute respiratory distress syndrome phenotypes and identifying treatable traits: the dawn of personalized medicine for ARDS. *Am J Respir Crit Care Med*. 2017;195:280-281.

Rogers AJ. Genome-wide association study in acute respiratory distress syndrome. Finding the needle in the haystack to advance our understanding of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2018;197:1373-1374.

Reilly JP, Christie JD, Meyer NJ. Fifty years of research in ARDS. Genomic contributions and opportunities. *Am J Respir Crit Care Med*. 2017;196:1113-1121.

Rezoagli E, Magliocca A, Catenacci SS. Identification of biological phenotypes in acute respiratory distress syndrome. From biomarkers to clinical outcome. *Am J Respir Crit Care Med*. 2018;197:1209-1211.

Despite progress associated with the identification of clinical risk factors and improving the ventilator approach for patients with ARDS, clinical risk factors alone poorly predict which patients will improve and survive ARDS. Several laboratories seek to determine if genetically determined ARDS risk may be a useful tool.

The genetic contribution to ARDS is not immediately apparent. Unlike other diseases, there is no perfect knockout animal model of ARDS to implicate one gene or pathway as the critical determinant of ARDS pathogenesis. Evolutionary pressures from traumatic injury to host pathogen interactions suggest significant human genetic diversity with the potential to impact ARDS risk. Tools of genetic research are now being applied to the study of ARDS.

Unique challenges associated with studying the ARDS genotype have limited genetic studies of the syndrome to date. ARDS is a complication of a significant environmental insult such as pneumonia, sepsis, or traumatic injury. The requirement for a large environmental insult prevents the use of genetic linkage studies of family pedigrees to identify genetic influences on ARDS risk or mortality. ARDS is also a heterogeneous disease with multiple different pathogenic processes contributing differently in different patients depending on clinical as well as genetic factors. This heterogeneity may weaken the effect estimate if genetic variance affects some forms of ARDS but not others, making it difficult to identify potential gene variance in traditional association studies. Finally, ARDS lacks a simple diagnostic test and is underrecognized by clinicians.

Driven by completion of the Human Genome Project, technological progress in detecting and cataloging human DNA variation has stimulated additional studies into ARDS. In 2012, ARDS geneticists produced carefully conducted studies of trauma-associated ARDS cases. However, even among a relatively homogeneous clinical population, cases of ARDS collected to date yield inadequate genome-wide diagnostic power.

Although one focus of ARDS genomic research has been to study larger populations in an effort to maximize statistical power, there is a growing recognition that some of the heterogeneity of ARDS risk and outcome may be explained by different underlying biology resulting in a similar clinical presentation. Genomic signals may be difficult to detect if all ARDS cases are analyzed together without consideration of biology because one genetic variant may not address all presentation possibilities for ARDS.

One characteristic that has shown some promise in ARDS research is platelet count and function. Platelets are critical in the pathogenesis of ARDS because they contribute to microvascular coagulation, immune activation, and endothelial damage. Genetics of differential platelet traffic in ARDS patients are a current source of active investigation.

It appears that any one genetic variant will typically explain only a small proportion of ARDS risk. Thus, at present, it remains unlikely that bedside genotyping for ARDS risk variance will play a significant role in the contemporary care for patients with ARDS. Genomic research will continue to identify plasma or imaging markers associated with ARDS development or associated mortality.

Although progress with genome investigation is proceeding slowly, phenotypic or clinical expression studies are beginning to produce intriguing results. Famous et al from the ARDS Study Network have identified two distinct ARDS subphenotypes using data obtained from two ARDSNet trials. Combining statistical assessment of preexisting clinical data and laboratory specimens, these investigators identified subphenotypes of patient response to ARDS based on clinical simulation. Data used to perform the initial analysis identifying clinical subphenotypes came from two of the ARDSNet trials: ARMA (the initial low tidal volume study published in 2000) and ALVEOLI (Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury). These separate trials identified two subphenotypes. One subphenotype was associated with increased levels of inflammatory biomarkers, acidosis, and shock. This inflammatory subphenotype was present in patients from the ARMA and ALVEOLI data sets. Patients could also be divided into groups based on the response to PEEP. In one subphenotype, higher PEEP was beneficial but harmful in the other subphenotype. The first subphenotype also did not present a proinflammatory response.

Famous et al repeated the subphenotype analysis using a third data set from the ARDSNet. Data from the FACTT trial (Fluid and Catheter Treatment Trial) were used with the hypothesis that the two subphenotypes would respond differently to randomly assigned fluid therapy. In the initial analysis by these investigators, one subphenotype was (again) characterized by higher levels of inflammatory cytokines and adhesion molecules. These investigators predicted that this subphenotype would have higher mortality and fewer ventilator-free days in response to liberal fluid administration. After analysis of the FACTT data, these authors confirmed two ARDS subphenotypes in the three separate clinical trials with similarity in characteristics and outcomes across all three data sets. A conservative fluid strategy was associated with improved mortality in the subphenotype having higher inflammatory markers but had the opposite effect if additional inflammatory markers were not present. Further analysis of laboratory specimens obtained in the three trials suggested that measurement of interleukin 6, soluble tumor necrosis factor receptor levels, and vasopressor use could identify the two subphenotypes. A more effective three-variable model under investigation uses serum interleukin 8 levels, serum bicarbonate, and tumor necrosis factor receptor one.

In the next column, I will further discuss ARDS therapies.

Summary Points

- A confounding factor in research into acute respiratory distress syndrome (ARDS) is uncertainty regarding pathogenic mechanisms and triggers for this phenomenon. Thus, lacking a clear biologic definition, ARDS is currently described as a syndrome without a consistent pathogenesis, which could allow focused exploration of treatment and prevention strategies.
- ARDS may be a preventable insult. Potentially valuable interventions include reducing infection risk, avoidance of damaging mechanical ventilation strategies, and selective anti-inflammatory medications.
- Optimal bedside care in the ARDS patient is beginning to focus on sedation control, frequent spontaneous breathing trials, and early mobilization.
- Phenotypic studies are identifying differential responses to ARDS therapy from large clinical data sets. One group has a hyperinflammatory response with increased sensitivity to therapies such as aggressiveness of fluid administration and positive end-expiratory pressure settings.

Acknowledgments

The authors gratefully acknowledge the assistance of Ms. Sherry Willett in preparation of this series for *Air Medical Journal*.

David J. Dries, MSE, MD, is the Surgery Department Chair at HealthPartners Medical Group and a professor of surgery and adjunct clinical professor of emergency medicine at the University of Minnesota in St Paul, MN, and can be reached at david.j.dries@healthpartners.com