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The Acute Respiratory Distress Syndrome: Dialing in the evidence?

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The Acute Respiratory Distress Syndrome (ARDS) could be regarded as a prototypical disorder that benefited from a bench to bedside research approach. After its original description in 1967, the complex pathophysiology of ARDS has been slowly unraveled through extensive basic and translational research. Based upon this improved understanding of the mechanisms responsible for ARDS, a variety of groundbreaking clinical trials were subsequently designed and conducted. Several of these clinical trials identified relatively simple and biologically plausible interventions that improve the mortality of patients with ARDS. For example, the landmark ARDS network trial established that low tidal volume ventilation (6 cc/kg of predicted body weight) reduces mortality from 40 to 31%.¹ A meta-analysis of three other trials demonstrated that a strategy of high PEEP improves mortality for patients with moderate to severe ARDS.² Finally, early ventilation in the prone position resulted in a 16% absolute mortality risk reduction for patients with moderate to severe ARDS.³ In theory, these beneficial therapies should be relatively easy to implement; they are essentially free, involve turning the knobs on the ventilator or turning patients, and are relatively safe.

As the mechanistic and clinical understanding of ARDS advanced, concerns arose simultaneously about the diagnostic criteria used to define ARDS. A panel of experts was convened to evaluate the objective performance of various diagnostic criteria for ARDS using a consensus process. The result was the 2012 Berlin definition that made several changes to the diagnostic criteria for ARDS including: a graded severity based on degree of hypoxemia was created (mild, moderate, or severe ARDS), a minimal amount of PEEP was added as a specific diagnostic criterion, and the intubation requirement was removed for patients with mild ARDS.⁴

Until the LUNG SAFE study (published in the current edition of JAMA), little was known about how this Berlin definition of ARDS was being utilized and whether the results of landmark clinical trials were being implemented in clinical practice.⁵ Over four weeks during the winter of 2014, LUNG SAFE investigators conducted a large multinational

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prospective cohort study in almost 500 ICUs. This study has many strengths including: its large sample size, rigorous data collection, and provocative results. First, the LUNG SAFE study confirmed that ARDS is common, accounting for 10% of all ICU admissions and nearly a quarter of ventilated patients. Despite its relatively high incidence, the rate of clinician recognition of ARDS is surprisingly low. Only 60% of ARDS cases were identified at any point during their clinical course, and only 34% of cases were identified at the initial time that ARDS criteria were met. Therefore, the diagnosis of ARDS is frequently delayed and often not made at all. These low rates of ARDS recognition are particularly concerning given that clinicians likely knew their hospital was participating in an ARDS study. Thus, it is possible that there was a “Hawthorne effect” in the LUNG SAFE study, and that these rates of clinician recognition of ARDS actually overestimate the true identification of ARDS. Second, interventions with proven efficacy are not being utilized for patients with ARDS. Overall, 36% of ARDS patients were ventilated with potentially deleterious high tidal volumes of greater than 8 cc/kg of predicted body weight. ARDS patients also routinely received low levels of PEEP, well below the amount used in a high PEEP strategy. In addition, prone positioning was used uncommonly and at a similar frequency to other therapies that lack proven clinical efficacy (inhaled nitric oxide or systemic corticosteroids). Finally, the LUNG SAFE study confirmed that the in-hospital ARDS mortality remains too high at almost 40%.

What can be done to lower the unacceptably high mortality rate in ARDS? While there is certainly room to deepen our understanding of the pathophysiology of ARDS and to develop new targeted treatments, the LUNG SAFE study demonstrates that improved recognition of ARDS might be a good place to start. A recent report from the Institute of Medicine highlights that diagnostic errors harm an unacceptable number of patients, are more costly today than ever before, and are a substantial source of avoidable death.⁶ Why do well-intentioned, experienced, and intelligent providers fail to recognize ARDS? The Institute of Medicine report also underscores that diagnostic errors are “a consequence of the interplay between cognitive and system-related vulnerabilities.”⁷ From a cognitive standpoint, we all have a limited capacity of our short-term memory. Though controversial, short-term memory may only be able to hold 4 “chunks” of information at any one time.⁸ Though it is a coincidence that the Berlin definition has 4 major categories, it is easy to see how a clinician would have difficulty connecting and processing specific elements of patient data, especially when barraged with hundreds of pieces of clinical information during the initial phase of a critical illness.

Several potential strategies may exist to enhance the clinician’s ability to recognize ARDS. In hospitals with electronic health record systems, an electronic surveillance system may be able to screen the medical record and proactively prompt clinicians when ARDS is suspected. Electronic surveillance tools for ARDS have been developed, validated in single centers, and have shown promise as a highly sensitive tool that outperforms manual screening.^{9,10} Therefore, larger scale research studies are needed to determine whether these electronic tools accurately “sniff out” and help to identify patients with ARDS. To diagnose ARDS, a clinician must also be able to perform specific tests such as arterial blood gases and chest radiographs. In resource limited settings, these tests may not be routinely performed or available at the time of the clinician’s initial evaluation. There is increasing

evidence that the more readily available pulse oximetry may be used to determine a SpO₂/FiO₂ ratio and identify hypoxemia; instead of requiring an arterial blood gas to calculate a PaO₂/FiO₂ ratio. In a recent epidemiological study examining the incidence of ARDS in a Rwandan referral hospital, investigators used pre-specified SpO₂/FiO₂ ratios to fulfill the hypoxemia diagnostic criteria. Similarly, lung ultrasonography may be able to identify bilateral infiltrates in place of a chest x-ray.¹¹ As the evidence supporting the validity of SpO₂/FiO₂ ratios and lung ultrasonography accumulates, an addendum to the Berlin hypoxemia and chest radiographic criteria may be necessary to facilitate and expedite the diagnosis of ARDS.

Even if the clinical recognition of ARDS were dramatically improved, a large gap still exists between evidence and practice. One explanation for this gap might be that the critical care community has become somewhat cautious about adopting new therapies. The initial results of several groundbreaking critical care trials including intensive insulin therapy and activated protein c were not replicated in subsequent clinical trials.^{12,13} Unfortunately, changing clinical behavior to improve quality of care is difficult. Implementation science can help identify methods that effectively translate research findings into clinical practice. Traditional methods such as guidelines, presentations at conferences, and publications in journals clearly are not sufficient to change practice in ARDS. The failure to implement effective strategies for ARDS likely goes beyond a lack of knowledge and extends to the attitudes and beliefs of nurses, respiratory therapists, and critical care physicians.¹⁴ Therefore, more effective implementation strategies may require identifying local champions, building a network of healthcare professionals dedicated to patient quality, and engaging multiple members of the interprofessional team that care for ARDS patients. In support of these implementation approaches, a multifaceted knowledge transfer intervention was able to enhance adherence with six ICU process measures in 15 ICUs in Ontario, Canada.¹⁵

An additional barrier to the implementation of low tidal volume ventilation, higher PEEP, and prone ventilation may be that no manufacturer or proprietor has a direct financial incentive to increase uptake and utilization. However, there are other important stakeholders. Research funding agencies have invested a tremendous amount of money to advance our understanding of ARDS and test novel therapies in clinical trials. If the ultimate goal of this investment is to improve outcomes, it makes sense that research funding agencies would also develop an implementation research portfolio. For example, the National Heart Lung and Blood Institute recently created the Center for Translational Research and Implementation Science to focus on narrowing the gap between evidence and practice. Other important stakeholders could include payers. When evidence is not translated into practice, payers potentially bear the financial burden. A financial investment in implementation science by payers could lead to a sound return – with both improved patient outcomes and decreased costs.¹⁶

We should be proud of the advances that have been made in the care of ARDS. The problem is that high quality care has not routinely reached the bedside of every patient. Proven therapies such as low tidal volume ventilation are not being effectively utilized in many clinical settings around the world. As a medical and critical care community, we should

prioritize the proper implementation of beneficial therapies, engage the necessary stakeholders, and take the last steps to dial in the evidence for the treatment of ARDS.

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