Epidemiology and Outcomes of Acute Lung Injury*

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Acute lung injury (ALI) and its presentation with more severe hypoxemia, the ARDS, is a challenging entity for clinical investigation because, like many critical illness syndromes, it lacks an accepted diagnostic test and relies on a constellation of clinical findings for diagnosis. Despite these barriers, there have been important advances in the clinical and population epidemiology of ALI. This article will review recent studies of the incidence, diagnosis, etiologic and prognostic factors, relevant disease subsets, mortality, and long-term outcomes of ALI. A detailed understanding of the epidemiology and outcomes of ALI is essential for future research on mechanisms of both the acute presentation and long-term sequelae, for designing studies to identify genetic risk factors for developing ALI, and to develop strategies to treat or prevent the morbidity encountered by survivors.

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Key words: acute lung injury; diagnosis; epidemiology; incidence; mortality; prognosis; sequelae

Abbreviations: ALI = acute lung injury; CIM = critical illness myopathy; CIP = critical illness polyneuropathy; FiO2 = fraction of inspired oxygen; HRQL = health-related quality of life; NAECC = North American European Consensus Conference; PEEP = positive end-expiratory pressure; PTSD = posttraumatic stress disorder

A n understanding of the basic clinical epidemiology of a disease—its incidence, diagnosis, etiologic and prognostic factors, relevant disease subsets, mortality, and long-term outcomes—is essential to caring for patients with the disease and for designing studies to evaluate potential therapies. Epidemiologic studies describe the burden of disease in the population and allow investigators to track diseases over time and in different places. In the absence of randomization, epidemiologic studies use statistical and design methods to control for confounding in an effort to separate causal mechanisms from noncausal associations. In the past 5 years, the understanding of the epidemiology and outcomes of critical illness has benefited considerably from an increasing number of large multicenter cohort studies that have used increasingly more rigorous methodology.

Most introductions to reviews of the ARDS begin with a citation of the classic article by Ashbaugh and colleagues1 in the Lancet in 1967. This case series of 12 patients has been cited >1,200 times in the medical literature and contains insightful and relevant observations about the value of positive end-expiratory pressure (PEEP), the potential value of corticosteroids, the pathologic appearance of ARDS, and it proposes the idea that a single mechanism might account for the syndrome. This article will review recent and important advances in our understanding of the epidemiology and outcomes of acute lung injury (ALI). We will not address the therapeutic implications of recent clinical trials in patients with ALI.

Diagnosis And Definition

ARDS is a syndrome that is diagnosed by the presence of a constellation of clinical criteria consisting of acute hypoxemic respiratory failure with bilat-
eral radiographic opacities that may coexist with, but is not fully explained by, hydrostatic pulmonary edema. The terminology around ARDS became somewhat more confusing when the North American European Consensus Conference (NAECC) broadened the definition to include patients with milder hypoxemia. ALI includes patients with less severe hypoxemia (PaO₂/FIO₂ ratio < 300 mm Hg), and this categorization restricts the term ARDS to patients with a PaO₂/FIO₂ ratio < 200 mm Hg. Approximately 25% of patients with ALI present with a PaO₂/FIO₂ ratio from 200 to 300 mm Hg, and approximately 20 to 50% of these patients progress to ARDS within 7 days. Note that in the NAECC categorization, ALI refers to all patients with a PaO₂/FIO₂ ratio < 300 mm Hg and there is no specific term for patients with a PaO₂/FIO₂ ratio from 200 to 300 mm Hg whose oxygenation worsens have a higher mortality than those that improve; however, there are no predictors to identify patients who will progress to ARDS. There is no “gold standard” laboratory, imaging, or feasible pathologic test to diagnose ALI. Essentially, patients have ALI when they meet the criteria that a group of experts has decided constitutes the diagnosis. ALI is not the only syndrome studied in the ICU; in fact, many of the phenomena of interest in critically ill patients including multiple organ failure and sepsis are defined using consensus-based syndrome definitions. Syndromes pose unique problems to clinical investigators particularly when the operational characteristics (feasibility, reliability, and validity) of the definition have not been fully explored.

Reliable syndrome definitions are important so that different clinicians and sites know that they are identifying similar patients using the same set of criteria. If effective treatments are developed, it is important for clinicians to be able to apply the definition to identify patients to treat. Unfortunately, the current criteria for ALI have poor reliability. The oxygenation component is sensitive to ventilator settings and FIO₂. Excluding cardiogenic or hydrostatic pulmonary edema on clinical grounds, even when a pulmonary artery catheter is present, is problematic. The use of markers of myocardial wall stretch, for example, brain natriuretic peptide, do not distinguish cardiogenic from noncardiogenic respiratory failure in relevant cases in the ICU. The chest radiographic definition, even when assessed by experienced investigators in the field, has poor reliability. There is no doubt that the current criteria identify an extremely heterogeneous patient popula-

tion. In one cohort of 70 trauma patients meeting ARDS criteria, 3 patients were extubated on the day they met diagnostic criteria and, at least post hoc, the patients fell into widely disparate groups with regard to duration of mechanical ventilation and severity of pulmonary dysfunction. There is limited evidence that this heterogeneity in outcome indicates variability in mechanism or response to therapy.

Face validity is generally established by input from experts in a consensus process. However, in the absence of an accepted “gold standard” for the diagnosis of ALI, establishing criterion validity of syndrome definitions is challenging. At least with regard to ARDS, varying definitions may identify similar patients. A study using autopsy data suggests that the NAECC criteria for ARDS only agree moderately with the pathologic diagnosis of diffuse alveolar damage.

Although the most commonly used, the NAECC categorization is not the only approach to classifying lung injury. The lung injury score, which includes the number of radiographic quadrants involved, hypoxemia, PEEP, and respiratory system compliance, has been proposed as an alternate method to grade the severity of lung injury. Because it provides a continuous score, this measure has been used to assess the effect of interventions on outcome; however, its superiority over a simple measure of oxygenation and its validity as a surrogate have not been established. Another attempt to clarify the diagnostic criteria for ALI using a more explicit Delphi consensus process identified slightly different criteria for diagnosis than those used by the NAECC. Specifically, this group proposed a more restrictive diagnosis by adding a PEEP requirement for oxygenation assessment, a static respiratory system compliance ≤ 50 mL/cm H₂O on standardized ventilator settings, a requirement for “airspace disease” in two or more quadrants on the chest radiograph, and the presence of a predisposing condition.

A direct comparison of the NAECC with the more restrictive Delphi definition using diffuse alveolar damage on autopsy specimens as a “gold standard” revealed that the Delphi definition and a lung injury score was more specific and there was a trend for the NAECC definition to be more sensitive. The limitations of this research are that it is not at all clear that diffuse alveolar damage is the only pathologic finding in ARDS, that this pathologic pattern identifies patients who are more or less likely to respond to therapies, that the desired sensitivity and specificity of a test depends on how it will be used, and that autopsy studies are obviously limited to patients who die. The predictive validity of distinguishing ALI and ARDS from other forms of acute respiratory failure are in doubt because these syndromes have very
similar 90-day mortalities. To the extent that one of the most important tests of the validity of a syndrome definition is its ability to identify patients who can benefit from a treatment, the NAECC definition has been validated by being the definition used in the ARDS Network clinical trials.

Until recently, clinical recognition of ALI was only important for research purposes. Now that effective interventions exist for ALI, diagnosis of ALI at the bedside is important for delivering quality care. Several studies show that clinical recognition, or at least documentation of the diagnosis, in practice is poor, ranging from 20 to 48%. Given these data, it is not surprising that administrative coding of ALI using International Classification of Diseases, Ninth Revision codes that relies on chart documentation is also poor.

**INCIDENCE**

Two factors make studies of the epidemiology of ALI difficult. First, problems with the reliability of the diagnosis and inaccuracy of administrative coding make population-based epidemiology expensive and difficult because careful quality control and prospective validation of cohorts is necessary. Second, since ALI is a critical illness and requires arterial blood gases and chest radiographs for diagnosis, and since patients are cared for in ICUs, the epidemiology of the syndrome is inextricably linked to health services research. Although this has not been explicitly studied, varying numbers of ventilators, intensive care beds, and even medical procedures that are risk factors for ALI will have an effect on the epidemiology of ALI.

Data from several population-based studies show a fairly consistent picture of the age, mortality, severity of illness, ratio of ARDS to ALI, and ratio of ALI to acute respiratory failure; however, there is almost a fourfold difference in incidence figures. This might be due to variations in study design or to differences in the availability and utilization of intensive care services in the regions studied. At least in the United States, where the most recent population-based data are available, the estimated 190,000 cases and 74,000 deaths from ALI each year represents an important source of mortality, morbidity, and health-care cost.

**RISK AND PROGNOSTIC FACTORS**

Review articles on ALI list dozens of potential risk factors for ALI including drugs, burns, inhalation injury, pancreatitis, amniotic fluid embolism, and transfusion. In most cohort studies and clinical trials, the majority of cases are caused by pneumonia followed by extrapulmonary sepsis, and finally trauma. Studies of risk factors for ALI are limited by varying degrees of rigor in establishing the definition for the risk factor. These studies are challenging because they require not only detailed data on the patients with ALI but on patients at risk for the syndrome who do not acquire it. Furthermore, the association between risk factor and ALI as well as the association between risk factor and death may be distorted by transfer and referral patterns in single-center studies.

Race, gender, body mass index, and age are common epidemiologic exposure variables. They are complex biological variables and likely are proxies for a variety of more proximal biological and social factors. African-American race and male gender are associated with increased death rates with ARDS as assessed by International Classification of Diseases, Ninth Revision codes on death certificates. This might occur because of genetic factors that predispose to ALI, because of differences in susceptibility to risk factors for ALI, or because of differences in access to or response to therapy. Thin patients with ALI are at increased risk of mortality and obese patients are at somewhat lower risk of mortality than patients with average weight. While there are many possible explanations for this association, one that must be considered is that the potential for misdiagnosis of ALI is greater in obese patients whose chest radiograph is poorly penetrated, who may meet oxygenation criteria due to basilar collapse when intubated, and whose respiratory system compliance is abnormally low. It is possible that obese patients with ALI have lower mortality because, in fact, they do not have ALI. The association between age and ALI onset is complex. Overall the incidence of ALI, as with many diseases, increases with age as people are more susceptible to the primary risk factor of sepsis. It is easier to define and study the at risk population in trauma and the relationship between age and ALI appears to be more complex. After adjusting for injury severity, the risk of ALI increases with age until age 60 to 69 years and then declines again. This may be due to a healthy aging effect or because the oldest trauma patients die before they can acquire ALI.

Diabetes and chronic alcohol consumption have emerged as interesting risk modifiers in the development of ALI. In a septic shock cohort, patients with diabetes were less likely to acquire ALI even after adjusting for confounding variables. This may be through a direct biological effect or because diabetic patients were more likely to have sepsis from genitourinary or soft-tissue sources and less likely to have pneumonia, which may make them less
likely to meet ARDS criteria. Chronic alcoholics may be at greater risk for ARDS than other patients, perhaps because their ability to quench free radicals is limited.

Numerous articles have explored variables that are associated with mortality in ALI or in ARDS (Table 1). Single-center studies and cohorts generated from single centers and clinical trials are problematic because of concerns over generalizability. Variables associated with mortality can be separated into modifiable treatment variables and nonmodifiable factors, for example, age or risk factor for ALI. Because of issues of indication bias, studies attempting to relate treatment variables to mortality in observational cohort studies are problematic and are best used to evaluate effectiveness or generate hypotheses. Independent risk factors for increased mortality identified in multicenter epidemiologic cohorts include the following: older age, worse physiologic severity of illness, shock on hospital admission, shorter stay in the ICU after ALI onset, longer hospital stay before ALI onset, increased radiographic opacity (in a study that included non-ALI acute respiratory failure), and immunosuppression. It is interesting to note that neither risk factor for ALI, which is likely confounded by age, nor degree of hypoxemia emerge as independent prognostic factors in ALI.

DISEASE SUBSETS

Arguments over whether ALI related to transfusion, direct lung injury, indirect lung injury, or the time course of presentation constitute fundamentally different diseases or not are longstanding. Various reports have suggested that direct (pneumonia, aspiration, contusion) and indirect (sepsis, trauma, drug overdose) causes of ALI result in characteristic radiographic and physiologic presentations. The findings are not consistent and fail to account for common scenarios with multiple risk factors (aspiration and drug overdose, pneumonia and sepsis, trauma, and pulmonary contusion). Recent data suggest that the amount of potentially recruitable lung and PEEP responsiveness is related less to the risk factor than the severity of lung injury. While it may be important to separate out these subsets for research purposes, their clinical implications have not been clarified. It is important to identify patients who meet criteria for ALI with underlying diagnoses that merit specific therapies, usually immunosuppressive treatment. These include idiopathic pneumonia syndrome after bone marrow transplantation, alveolar hemorrhage syndromes, bronchiolitis obliterans organizing pneumonia, acute eosinophilic pneumonia, or hypersensitivity pneumonia. In population cohorts and clinical trials of ALI, these diagnoses, at least when recognized, are rare.

Genetic Epidemiology

The field of genetic epidemiology of ALI is in its infancy. It is important to remember the advice of a review article on genetic epidemiology, “Use of standardized, reproducible [phenotype descriptions] with strict requirements for training, certification, and quality control is a fundamental principle of population-based research that needs to be translated to genetic epidemiologic studies.” Genetic, genomic, and proteomic evaluations of complex illnesses like ARDS rely on a mature clinical research arm to, at the least, reliably identify phenotypes for research. Whether or not this is possible given the limitations noted above is unclear. Phenotype heterogeneity must be considered along with other explanations of variability in exploratory studies of genetic associations in ALI.

Table 1—Incidence and Mortality of Patients With ALI and ARDS From Multicenter Cohort Studies

<table>
<thead>
<tr>
<th>Variables</th>
<th>United States, Rubenfeld et al4</th>
<th>Scandinavia, Luhr et al20</th>
<th>Australia, Bersten et al25</th>
<th>Europe, Brun-Buisson et al†</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALI (PaO₂/FIO₂ ≤ 300 mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases in cohort, No.</td>
<td>1,113</td>
<td>287</td>
<td>168</td>
<td>463</td>
</tr>
<tr>
<td>Incidence*</td>
<td>78.9</td>
<td>17.9</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Mean age, yr</td>
<td>60.6</td>
<td>59.8</td>
<td>62</td>
<td>54.6</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>38.5</td>
<td>41.4</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>ARDS (PaO₂/FIO₂ ≤ 200 mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence*</td>
<td>58.7</td>
<td>13.5</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Mortality, %</td>
<td>41.1</td>
<td>41.2</td>
<td>34</td>
<td>57.9</td>
</tr>
<tr>
<td>Ratio of ARDS cases to ALI cases, %</td>
<td>74</td>
<td>77</td>
<td>64</td>
<td>71</td>
</tr>
</tbody>
</table>

*Cases per 100,000 person-years.
†Not a population-based study and therefore incidence data not reported.
‡Mortality represents hospital mortality for United States and Europe, 90-day mortality for Scandinavia, and 28-day mortality for Australia.
Mortality

Several observations on the mortality of patients with ALI appear consistent. The mortality rates of patients who present with ALI (Pa\textsubscript{o}/F\textsubscript{i}O\textsubscript{2} ratio < 300 mm Hg) and those who present with ARDS (Pa\textsubscript{o}/F\textsubscript{i}O\textsubscript{2} ratio < 200 mm Hg) are similar and from 35 to 40%. Mortality after ALI is declining in recent years, although the explanation for this is not completely clear.\textsuperscript{41,42} Patients appear to die with ALI or from complications of their underlying risk factor as opposed to dying from unsupportable hypoxemic respiratory failure.\textsuperscript{43} The combination of declining short-term mortality and increasing incidence as the population ages suggests that caring for the long-term sequelae of survivors of ALI will be an increasingly important problem in the future.\textsuperscript{44}

Outcomes After ALI and ARDS

The literature on long-term outcomes after ALI and ARDS has evolved significantly over recent years. As more investigators have studied outcomes after lung injury, several robust observations have emerged. Most studies suggest that the major long-term consequences of lung injury are related to neuromuscular, cognitive, and psychological dysfunction rather than pulmonary dysfunction (Table 2). It is ironic that the organ systems that have the greatest impact on functional and quality of life outcomes are virtually ignored during the acute course of critical illness. A detailed characterization of the mechanism that causes these sequelae is lacking, as is an understanding of insights into preventive or therapeutic strategies.

Table 2—Long-term Outcomes in ARDS Survivors and Caregivers

<table>
<thead>
<tr>
<th>Major morbidity in ARDS survivor</th>
<th>Minor morbidity in ARDS survivor</th>
<th>Caregiver and financial burdens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuromuscular dysfunction</td>
<td>Pulmonary dysfunction</td>
<td>Depression and PTSD during and after ICU stay</td>
</tr>
<tr>
<td>Critical illness polyneuropathy, critical illness myopathy</td>
<td>Entrapment neuropathy</td>
<td>Cost and time of providing care</td>
</tr>
<tr>
<td>Neuropsychological dysfunction</td>
<td>Heterotopic ossification</td>
<td></td>
</tr>
<tr>
<td>Depression, anxiety, PTSD</td>
<td>Tracheostomy site complications</td>
<td></td>
</tr>
<tr>
<td>Neuronal cognitive dysfunction</td>
<td>Striae</td>
<td></td>
</tr>
<tr>
<td>Abnormalities in memory, attention, concentration and executive function</td>
<td>Frozen joints</td>
<td></td>
</tr>
<tr>
<td>Neuropsychological dysfunction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In addition to the evolving literature on brain, nerve, and muscle dysfunction, there is a growing body of work describing pattern and cost of healthcare utilization after lung injury and the impact of critical illness on the family caregiver. As we continue to develop and test different interventions for survivors of critical illness, these economic and family burden issues will need to be incorporated into rehabilitation programs targeted at neuropsychological and neuromuscular dysfunction.

One of the methodologic challenges of studying the sequelae of critical illness is teasing apart the four factors that can influence long-term outcomes after ALI: premorbid health status, risk factor for ALI, ALI itself, and treatments for ALI. There are few studies comparing long-term outcomes of patients with ALI to critically ill control subjects without ALI.\textsuperscript{45} Even in these studies, it is difficult to separate ALI from variables that are inextricably linked to ALI, for example, duration of mechanical ventilation.

Health-Related Quality of Life

There are currently 13 studies (n = 557) that have evaluated health-related quality of life (HRQL) in survivors of ALI, and the findings of these studies have been recently summarized in a metaanalysis by Dowdy et al,\textsuperscript{46} who stratified their analysis by whether authors reported Short Form-36 as the HRQL outcome measure. Five of these studies (n = 330) used the Short Form-36; these results were pooled and showed that all eight domains were below the age- and sex-matched population normal. The mean HRQL decrements compared to control populations were similar across all five studies, and pooled estimates ranged from 15 to 26 points for all domains except for mental health (11 points) and role physical (39 points). Larger decrements were noted in the four physical domains (physical functioning, role physical, bodily pain, and general health perceptions) than in the four mental domains (vitality, social functioning, role emotional, and mental health).

The metaanalysis results help to highlight several issues. First, HRQL in different ALI populations is similar and therefore may be more amenable to the development of an intervention to address ALI-specific morbidity. Second, recovery in these patients appears to be both time specific and domain specific; and this, again, may be relevant in terms of understanding how to meet patient needs at different time points across the care continuum, from ICU through to ambulatory follow-up. Third, ALI survivors have significant and persistent reductions in
HRQL compared to the general population, but these reductions are not materially different from those of other, more general, populations of ICU survivors. Finally, these authors emphasized the paucity of data on very long-term HRQL outcomes (> 2 years) in larger populations of ALI survivors.

Physical Disability: Long-term Pulmonary Sequelae

The findings from early case series to more recent prospective cohort studies are consistent and suggest that the majority of patients do not have significant long-term pulmonary dysfunction after lung injury. Most studies have noted a persistent reduction in diffusion capacity, which does not appear to be of important functional consequence. Neff and colleagues reviewed 30 studies that evaluated pulmonary function in ARDS survivors, and reported significant variability in the proportion of patients with obstructive (0 to 33%) and restrictive (0 to 50%) defects as well as compromised diffusion capacity (33 to 82%). The spectrum of pulmonary dysfunction that occurs in this minority of ALI survivors may relate to population heterogeneity arising from evolving definitions or severity of ARDS, ICU ventilatory strategy, history of lung disease or smoking, and the presence of other pulmonary processes that fulfill the ARDS definition but have a very different natural history (e.g., cryptogenic organizing pneumonia). Comprehensive studies evaluating gas exchange, cardiac function, and pulmonary pressures during exercise are still lacking, and it is difficult to state conclusively that these factors do not contribute to the exercise limitation observed in survivors of ARDS.

Physical Disability: Musculoskeletal Sequelae

Survivors of ALI have persistent functional limitation captured as a decreased distance walked in 6 min. At 1 year and 2 years after ICU discharge, ARDS survivors had evidence of muscle wasting and weakness and could achieve only 66% of their predicted exercise capacity. The precise determinant(s) of this long-term exercise limitation remains unclear, but possible contributors may include critical illness-related neuromuscular disease, entrapment neuropathies, and heterotopic ossification. Critical illness polyneuropathy (CIP) is characterized electrically and morphologically by a primary axonal degeneration of motor and sensory fibers, mainly affecting the lower limbs of critically ill patients. Critical illness myopathy (CIM) is an acute primary myopathy that requires more specialized investigation with electrophysiologic testing and muscle biopsy and is, as a result, more likely to go undiagnosed. The true prevalence of CIP and CIM is difficult to ascertain because they are dependent on patient case-mix, timing, and technique used for diagnostic testing. CIP and CIM have been associated with difficulties with weaning from mechanical ventilation, and CIP has been suggested as an independent predictor of hospital mortality. Muscle wasting and weakness in ARDS survivors most likely represents CIP and/or CIM, and retrospective data suggest that their prevalence may be as high as 60% in high-risk patients. It is still unclear whether these entities always coexist or can occur separately; and, as such, many authors, for simplicity, have referred to them as a single continuum of neuromyopathic complications. There are no comprehensive natural history data on the incidence, nature, or rate of recovery from CIP/CIM in survivors of critical illness. Because they cause both motor and sensory disturbances, CIP and CIM may inhibit patient recovery both in the acute ICU setting and in longer-term rehabilitation and may have a significant impact on long-term quality of life. In short, they may represent one of the most important complications of severe critical illness. A high proportion of ALI survivors have musculoskeletal complaints, but these are not always attributed to their critical illness.

Compression neuropathies may contribute to functional limitation after ARDS. One study noted a 6% prevalence of peroneal and ulnar nerve palsies. Although this represents only a small proportion of patients, these nerve palsies complicate rehabilitation therapy and may preclude return to original work. Heterotopic ossification is the deposition of para-articular ectopic bone and has been associated with polytrauma, burns, pancreatitis, and ARDS. Heterotopic ossification has been linked to paralysis and prolonged immobilization. There was a 5% prevalence of heterotopic ossification in the Toronto ARDS cohort study, with all patients having large-joint immobilization, leading to important functional limitation. Heterotopic ossification is remediable with appropriate surgical intervention and treatment may help to improve long-term functional outcomes.

Neuropsychological Disability: Emotional Function After ARDS

Psychiatric or emotional morbidity following ALI includes depression, anxiety, and posttraumatic
stress disorder (PTSD). It is still unclear whether emotional disorders constitute a psychological reaction to profound emotional and physiologic stress are a consequence of direct brain injury sustained from ALI and its treatment, or a combination of these. The prevalence and severity of these mood disorders are variable and may also change over time. Hopkins and colleagues evaluated depression in survivors of ARDS at 1 year and 2 years using the Beck Depression Inventory. They found that 16% of patients had symptoms of moderate-to-severe depression at 1 year, and this increased to 23% at 2 years. They found no correlation between depression and cognitive dysfunction and were unable to identify risk factors for the development of depression. Weinert and colleagues found that 43% of patients with ALI reported symptoms of depression, and Angus and coworkers reported a 50% prevalence of depression and anxiety at 1 year in ARDS patients. The observed depression and anxiety after ICU treatment are likely multifactorial, and further study will be needed to better understand patient predisposition and illness- and treatment-specific determinants of affective morbidity.

PTSD is the development of characteristic symptoms that occur following a traumatic event(s) in which triggers include a serious personal threat experienced with helplessness and intense fear. The diagnostic criteria include a history of traumatic event(s) accompanied by symptoms from each of three symptom clusters: hyperarousal symptoms, intrusive recollections, and avoidant/numbing symptoms. Kapfhammer and colleagues were the first to introduce the concept of PTSD resulting from critical illness and ICU treatment; in a more recent publication, they demonstrated major impairments in quality of life related to PTSD, up to 8 years after the episode of ARDS. PTSD has been linked to the number of adverse ICU-related memories recalled by patients. Memory for nightmares or delusions while in the ICU as well as a complete absence of any ICU memories have also been perceived as traumatic events. We are just beginning to appreciate how longstanding and debilitating mood disorders are following critical illness and the important contribution they have to decreased HRQL. Although there are lessons from other fields on interventions to reduce PTSD symptoms after acute illness, no direct extrapolations can be made to ALI.

Neuropsychological Disability: Cognitive Impairment in ARDS Survivors

Hopkins and colleagues published the seminal long-term cognitive outcome study in ARDS survivors in 1999. In this natural history cohort, they found that 100% of ARDS survivors had cognitive impairments at the time of hospital discharge. At 1-year follow-up, 30% of the survivors had decreased intellectual function and 78% had impaired memory, attention, concentration, and/or mental processing speed. At 2-year follow-up of this same patient cohort, 47% had neurocognitive impairments with no interval improvement from 1 to 2 years. To date, eight additional cohort studies have independently corroborated the high incidence of neurocognitive dysfunction in survivors of lung injury. These findings are robust and have an important impact on ability to return to work and on HRQL. Very little is currently known about the pathophysiology of brain injury, its relation to acute ICU delirium, and treatment modalities that might prevent or decrease this morbidity.

Caregiver and Financial Burden After Critical Illness

As more patients are surviving critical illness and are discharged from hospital more quickly, the burden of caregiving has shifted to family members. In the United States, 31% of families report a loss of most or all of their savings. Challenges for the caregiver begin during the ICU stay where they may experience overwhelming stress and distress. Azoulay and colleagues reported that posttraumatic stress symptoms consistent with a moderate-to-major risk of PTSD were found in 33% of ICU family members. Challenges for the caregiver continue following hospital discharge, when new morbidities become apparent and may complicate care in the home. Chaboyer and colleagues have shown that the degree of caregiver burden is related to patient neuropsychological dysfunction as compared with severe physical disability. It is still unclear whether or how long caregiver burden persists and how this affects the care of the patient and the ability of the family to recover from this catastrophic event.

Health-care use and costs after ARDS are driven primarily by need for hospital readmission and inpatient rehabilitation. Hospital readmissions were related to the risk factor for ARDS, and need for inpatient rehabilitation was related to generalized muscle wasting and weakness and treatment for the consequences of polytrauma. This information allows us to gain insight into the specific nature of the longer-term physical impairments responsible for health-care costs after ALI/ARDS and may help to inform the development of interventions to decrease morbidity and health-care utilization following ICU discharge.
CONCLUSIONS

ALI is no longer a disease of specialty interest to the pulmonologist and intensivist at academic centers. Research suggests that it is common, lethal, underrecognized, treatable and, for survivors and their caregivers, a source of significant ongoing impairment. Ongoing research activities to improve the reliability and validity of diagnostic criteria for ALI, genetic risk factors, mechanisms of long-term impairment, and interventions to prevent or treat the sequelae of ALI will hopefully yield useful answers to the challenges of this patient population.

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