Interest in longer-term outcomes after acute respiratory distress syndrome (ARDS) and the understanding of patterns of recovery have increased enormously over the past 10 years. Historically, the outcome of greatest interest after ARDS was pulmonary function and, ironically, the respiratory system may be one of the more resilient organ systems after an episode of severe lung injury. The evaluation of generic and disease-specific health-related quality of life (HRQOL) measures after ARDS has evolved to include a detailed evaluation of functional outcome, exercise capacity, neuropsychological morbidity, and in-person follow-up to catalog and describe the varied consequences of an episode of ARDS and its longer-term repercussions for patients and family.

Most patients who survive an episode of ARDS will sustain some degree of permanent disability1,2 and reduction in HRQOL as a consequence of intensive care unit (ICU)-acquired weakness, in addition to a spectrum of other physical disabilities.1–10 Patients may also develop significant new neurologic morbidity, including neurocognitive impairments, and psychiatric disorders.11–15 This legacy of muscle, nerve, and brain dysfunction comes at significant additional cost, with some reports stating that health care use after critical illness is similar to that of patients with chronic disease,2,10,16,17 which may represent an important public health concern.

This article highlights important advances in outcomes after ARDS and describes pulmonary outcomes, the most recent data on functional and neuropsychological
disability in patients, health care cost, family caregivers, and early models of rehabilitation and intervention.

LONG-TERM OUTCOME MEASURES AFTER ARDS

Survivors of acute lung injury or ARDS (ALI/ARDS) represent an important subset of complex critically ill and long-stay ICU patients. Most patients with ARDS spend weeks in the ICU and therefore constitute a subgroup of the chronically critically ill patient population, helping to highlight the enormous heterogeneity in outcomes within the chronically critically ill population. ALI/ARDS is estimated to affect 190,600 people per year in the United States and to be associated with 74,500 deaths and 3.6 million hospital days. More than 100,000 patients will survive ALI/ARDS each year, and this condition is now recognized as an important public health concern.

Pulmonary Function

After the initial description of ARDS by Ashbaugh and colleagues in 1967, a flurry of articles described pulmonary outcome in ARDS survivors over the first several months after ICU discharge. Overwhelmingly, these were case series or involved small cohorts, and reported good pulmonary recovery with a mild restrictive or obstructive pattern, or normal volumes and spirometry and a mild to moderate reduction in diffusion capacity. Given the subtlety of most reported derangements in pulmonary function after ARDS, the extent to which this influences functional and HRQOL outcomes, even though statistical associations were noted, may be difficult to determine. Furthermore, in most studies, the extent to which patients had preexisting pulmonary disease was unclear, and how underlying lung dysfunction might interact with severe lung injury, both during the acute critical illness and over the subsequent months to years while the lung is remodeling, remains uncertain.

McHugh and colleagues evaluated pulmonary function in 37 ARDS survivors at 3, 6, and 12 months after extubation and noted that pulmonary function improved substantially by 6 months, but little thereafter, and that greater severity of lung injury was associated with impaired return to normal lung volumes. They also noted that the Sickness Impact Profile (SIP) score paralleled the pulmonary function, but that most patients did not attribute their current health problems to breathing difficulties. Schelling and colleagues noted a relationship between the number of pulmonary function impairments and a reduction in HRQOL scores, and also found that these patients were less likely to return to work. Of all the pulmonary measures, the diffusing capacity of the lung for carbon monoxide (DLCO) was the only pulmonary function parameter that correlated with HRQOL. Heyland and colleagues noted a correlation between the physical function domain of the Medical Outcomes Study 36-item short-form health survey (SF-36) and FEV1, but this had reached the lower bound of normal by 6-month follow-up. Similar to the observation by McHugh and colleagues, their data suggested that pulmonary function was associated with the severity of lung injury in the ICU, although no data currently correlate ventilatory strategy with longer-term pulmonary outcome.

Neff and collaborators described a mix of restrictive and obstructive findings and a reduction in diffusing capacity in their report on 16 survivors of severe lung injury after trauma, and Orme and colleagues reported relatively preserved lung volumes and spirometry in their follow-up of 66 patients, and noted a persistent reduction in diffusing capacity. A more recent study by Masclans and colleagues again confirmed that some patients had mild restrictive disease 6 months after ARDS.
Pulmonary function data from the Toronto ARDS cohort study showed that most patients had recovery to normal or near normal spirometry within 6 to 12 months after ICU discharge, and that pulmonary function remained stable through to 5-year follow-up. Because approximately 40% of this cohort was seen in the home, data for lung volumes and DLCO were incomplete. Furthermore, this cohort was relatively young and had minimal reported preexisting pulmonary morbidity, although approximately half reported ever smoking.\(^1,10\)

Nobauer-Huhmann and colleagues\(^28\) were the first to perform imaging on patients with ARDS at 6 to 10 months after illness. In their sample of 15 patients, they noted that most had localized changes in the nondependent lung zones, and the investigators were able to document some association between severity of lung injury and duration of mechanical ventilation.\(^29\) Subsequently, Desai and colleagues\(^30\) reported CT findings in patients with ARDS 3 years after their illness and noted that reticular changes were most common but that areas of decreased attenuation and ground glass opacities were also observed, primarily in the anterior lung zones. Duration of mechanical ventilation was also associated with radiographic findings in this group, suggesting that this may reflect ventilator-induced lung injury.

Two ARDS cohorts have captured radiographic follow-up data after ARDS up to 5 years.\(^10,31\) The Toronto ARDS cohort study\(^10\) evaluated 25 patients through CT of the thorax at 5-year follow-up, with most scans showing radiologic abnormalities, the most common being nondependent minor pulmonary fibrosis consistent with ventilator-induced lung injury. Approximately one-third of these patients also had evidence of bronchiectasis or new pulmonary fibrosis associated with symptoms of dyspnea, sputum production, or minor obstructive or restrictive changes on pulmonary function. Linden and colleagues\(^31\) also documented a predominantly reticular pattern on CT imaging in 21 patients. This finding was consistent with fibrosis, but because these patients all received extracorporeal membrane oxygenation (ECMO), no ventral distribution was observed, and most had spirometry within the lower bound of normal. Greater duration of ECMO was associated with a reduction in the total lung capacity.

Pulmonary function outcomes may be heterogeneous after an episode of ARDS, but most young patients without documented preexisting lung disease regain normal or near-normal function with a persistent mild reduction in diffusion capacity. These patients seem to maintain stable pulmonary function up to 5 years after the initial episode of severe lung injury.\(^10\) The current spectrum of results suggests possible variability by smoking history, preexisting obstructive or restrictive pulmonary disease, physiologic restriction related to ICU-acquired weakness affecting respiratory muscles, presence of other pulmonary processes that fulfill the ARDS definition but have a different natural history (eg, cryptogenic organizing pneumonia), and loss to follow-up that continues to challenge validity and interpretation of follow-up data. Most outcome studies found that ARDS survivors are often unable to resume their prior physical function, but the degree of pulmonary dysfunction documented across studies does not solely explain this degree of functional limitation.

**Functional Disability**

Over the past several years, research has highlighted the concept of a continuum of weakness that begins within hours of mechanical ventilation,\(^32\) is evident through bedside evaluation within 1 week of ICU admission using the Medical Research Council scoring system,\(^33\) and may persist with incomplete recovery for years after ICU discharge (Fig. 1). A recent 5-year ARDS outcomes study illustrates that relatively young (median age, 45 years) previously working patients with few comorbidities may not regain their pre–critical illness functional status nor HRQOL by 5 years after ICU
discharge. The concept of ICU-acquired weakness has gained momentum over the past several years, but investigators have recently observed that it may cause irreversible functional disability. Furthermore, this persistent dysfunction may also be influenced by a spectrum of other physical and neuropsychological disabilities that continue to plague patients over the longer term.

Fig. 1. Survival, 6-minute walk distance and quality of life to 5 years after ICU discharge. Exact survival times were used for these analyses, whereas deaths indicated in the consort diagram were included between scheduled follow-up visits. Top panel: Kaplan-Meier curve to 5 years. Dashed lines represent the 95% CI. Middle panel: Distance walked in 6 minutes (meters and percent predicted); distance in meters is a solid line and percent predicted is a dashed line. Bottom panel: SF-36 subscale scores for physical component score and mental component score. (From Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 2011;364(14):1299; with permission.)
Neuromuscular Dysfunction

Muscle weakness and impaired function constitute an important morbidity of severe critical illness and have been described in most detail in ARDS survivors, but similar reports of functional disability in survivors of sepsis and chronic critical illness have been increasing, and clearly these conditions overlap. Reported disability and reduction in activities of daily living have been inferred to be a consequence of ICU-acquired muscle wasting and weakness syndrome.\textsuperscript{16,34}

Accurate characterization and potential intervention in neuromuscular disability after critical illness has many challenges. First, significant heterogeneity exists across different critically ill patient populations in terms of susceptibility and risk factors for neuromuscular dysfunction, and no validated measures currently help stratify patients according to risk and subsequent degree of acquired physical disability. Adding to the confusion, several different terminologies are used in the literature, including critical illness polyneuropathy, critical illness polyneuropathy and myopathy, ICU-acquired paresis, critical illness myopathy and/or neuropathy, ICU-acquired weakness, and critical illness neuropathy and myopathy (CINMA). Furthermore, muscle and nerve lesions often coexist, complicating the ability to understand discrete risk factors or natural history. Obstacles also exist in terms of testing methods, criteria for diagnosis, surveillance, and selection bias in evaluation and reporting. Sensory and motor evaluations are limited in heavily sedated patients, and clinical bedside testing and determination of the prevalence of these lesions may be unreliable. Despite these limitations, some excellent models for classifying these lesions were recently proposed.\textsuperscript{35}

A recent review of risk factors and prevention of ICU-acquired weakness\textsuperscript{28} highlights nonmodifiable factors, including multiple organ failure and severity of illness, and modifiable factors, such as muscle immobilization, hyperglycemia, and corticosteroid and neuromuscular blocker use. This long-term morbidity may be modified through changes in current ICU practice patterns but this awaits further study. The next section describes the muscle and nerve injuries relevant to survivors of ARDS that constitute the wasting and weakness syndrome observed after critical illness.

Critical Illness Polyneuropathy

Background and incidence

In 1984, Bolton and his Canadian colleagues published a landmark article describing challenges in liberating 5 critically ill patients from mechanical ventilation.\textsuperscript{36} These patients had a primary axonopathy on electrophysiologic testing which presented as a mixed sensorimotor neuropathy. It is now clear that CIP is very common in patients with the systemic inflammatory response syndrome (SIRS) and sepsis which frequently co-exist with ARDS. There are reports of an occurrence of CIP in 70% to 100% of longer stay ICU patients. It remains challenging to capture the true incidence of CIP because of poor consensus on surveillance, unclear criteria for definition and diagnosis, as well as timing and nature of testing. Where patients were evaluated solely on the basis of weakness, studies have reported an incidence of 25% to 36%.\textsuperscript{32,37} A rigorous systematic review on over 1400 critically ill patients, reported an incidence of CINMA of close to 50% (95% confidence interval 43–49%).\textsuperscript{38} These authors defined patients as having CINMA if they were evaluated using diagnostic tests (nerve conduction velocities, needle electromyography, direct muscle stimulation, histopathology of muscle or nerve tissue) or a combination of these test findings and clinical findings of muscle weakness, decreased or absent deep tendon reflexes, and or failure to liberate from mechanical ventilation. It is often very challenging to
identify weakness in unresponsive or minimally interactive critically ill patients. However, electromyography (EMG) testing will demonstrate abnormalities showing an initial primary axonal degeneration of the motor neurons, followed by the sensory neural fibers and this coincides with acute and chronic changes of denervation noted on muscle biopsies in affected patients. The impetus to screen for this lesion implies that it is important to detect this early to facilitate intervention. However, the ability to intervene in this process, the nature of an intervention and the natural history of this lesion is not currently known.

**Critical Illness Myopathy**

**Background and incidence**
The term critical illness myopathy (CIM) currently includes critical illness myopathy, acute quadriplegic myopathy, thick filament myopathy and necrotizing myopathy. This rather heterogeneous grouping has a reported incidence varying from 48% and 96% in prospective studies, some of which have included muscle biopsy. The pathology of CIM is that of a diffuse, non-necrotizing myopathy associated with fatty degeneration of muscle fibers, fiber atrophy and fibrosis. This has been described in patients with sepsis/ARDS but also in those receiving treatment with neuromuscular blockers and/or corticosteroids. The diagnosis of CIM distinct from CIP can be difficult since the phenotype of paresis with difficulty in weaning may virtually overlap and this is further compounded by the fact that these lesions often co-exist. Muscle biopsy may allow differentiation between these. A small case series of biopsies from survivors of severe ARDS showed chronic myopathic changes up to 2 years after the episode of critical illness thereby raising the possibility of residual muscle injury as the sole correlate for chronic functional disability observed in these patients.

The thick filament myopathy is characterized by loss of myosin filaments in the context of significant corticosteroid or neuromuscular blocker exposure and immobility. There has been speculation that this may represent a precursor to acute necrotizing myopathy since this form of CIM may show progression to myonecrosis. Acute necrotizing myopathy is distinguished by extensive myonecrosis with vacuolization and phagocytosis of muscle fibers and has also been associated with corticosteroid and neuromuscular blocker exposure. It is important to emphasize that steroids and paralytics may not necessarily be causally linked to this process since they will frequently be employed in sicker patients with multiple failed organ systems.

**Additional Physical Morbidities**
Several other physical sequelae may also influence functional outcomes, physical HRQOL, need for subsequent hospitalization, and accrued costs over time. These conditions have been studied in the most detail in survivors of ARDS and cataloged in recent ARDS publications. These sequelae include tracheal stenosis with subsequent need for tracheal resection complicated by malacia and T-tube placement, heterotopic ossification, contractures, frozen shoulders, hoarseness and voice changes, tooth loss, sensorineural hearing loss, and tinnitus, and these contributed to emotional outcomes, social isolation, and sexual dysfunction.

**Entrapment neuropathy**
The Toronto ARDS cohort study observed a 6% prevalence of peroneal and ulnar nerve palsies at 1-year follow-up. Although this represents only a small proportion of patients, these nerve palsies complicated rehabilitation therapy and precluded return to original work in some cases. By 5 years, these had resolved, as had foot drop in all patients.
**Heterotopic ossification**
Heterotopic ossification is the deposition of para-articular ectopic bone and has been previously associated with polytrauma, burns, pancreatitis, and ARDS. Heterotopic ossification is associated with paralysis and prolonged immobilization. A 5% prevalence of heterotopic ossification was reported at 1 year in ARDS survivors, with all patients having large joint immobilization and subsequent functional limitation. Heterotopic ossification is remediable with appropriate surgical intervention, and screening for this condition may help improve long-term functional outcomes. However, patients may be reluctant to undergo any surgical procedure after a severe critical illness because of fear of complications, and this may represent an important barrier to rehabilitation and return to prior functional status.

**Cosmesis**
The physical devastation after ARDS and critical illness cannot be overstated, and the way in which patients are transformed and struggle with dramatically changed appearance has significant long-term implications. Many patients experience often-devastating emotional effects related to their altered appearance. Recent 5-year data show that patients describe ongoing concerns about cosmesis, including scars from laparotomy, chest tube, central line, arterial line and tracheostomy insertion, burns, striae from volume overload, and facial scars from prolonged noninvasive mask ventilation. Many of these patients underwent tracheostomy revision. Patients reported that cosmetic concerns contributed to social isolation and sexual dysfunction.

**ARDS and Brain Injury**

**Neurocognitive impairments**
In their groundbreaking paper from 1999, Hopkins and colleagues evaluated 55 survivors of ARDS at 1 year after ICU discharge. At hospital discharge, all patients experienced cognitive impairments, including problems with memory, attention, or concentration, and a global loss of cognitive function. By 1-year follow-up, most patients showed improvement in overall cognitive function, but 30% still showed deficits on the Wechsler Adult Intelligence Scale–Revised; 78% had impairment of at least one cognitive function, including memory, attention, or concentration; and 48% experienced a decreased speed of mental processing. In the 2-year follow-up of this cohort, these same investigators reported no additional improvement in neurocognitive sequelae beyond 1 year (Fig. 2). Since these landmark papers, the literature continues to document an important prevalence of neurocognitive dysfunction in ARDS survivors and other groups of critically ill patients, and the important impact this has on HRQOL. Hopkins and colleagues were the first to report the significant effect this had on reported HRQOL outcomes, and Rothenhausler and colleagues also noted that ARDS survivors with neurocognitive sequelae had worse quality of life than individuals without neuropsychological dysfunction.

Currently, close to 1000 patients in 15 different cohorts have undergone neurocognitive evaluation after critical illness. Similar to the landmark findings from the Hopkins studies, other reports have documented cognitive impairments in 100% of patients at hospital discharge and in large numbers of patients up to 6 years. In most cases, impairments seem to improve most rapidly in the first 6 to 12 months after hospital discharge. Additional outcomes data in patients without ARDS help highlight the observation that different neurocognitive domains may be impaired in different ICU survivors, depending on the nature of the injury acquired during the episode of critical illness and its treatment, the presence of
underlying neurocognitive abnormalities, and other patient-specific vulnerabilities, including older age.

The effect of acute care hospitalization and critical illness on the brain remains poorly understood. It is unclear whether critical illness itself or its associated treatment causes the decline in cognitive function or simply further compromises preexisting brain dysfunction. In a recent report by Ehlenbach and colleagues, older adults without neurocognitive impairments or dementia underwent neurocognitive assessment before and after an acute care or ICU hospitalization. Those who had acute care or critical illness hospitalization experienced a greater decline in neurocognitive function and new incident dementia compared with individuals who were not hospitalized. These data suggest that the acute or critical illness may cause a significant decrement in neurocognitive function. Iwashyna and colleagues evaluated cognitive impairment in a group of patients with sepsis derived from the Health and Retirement Study and confirmed the observations outlined earlier. This longitudinal cohort showed that patients with severe sepsis developed new, important, and persistent neurocognitive dysfunction. The data from these studies suggest that an episode of acute or critical illness may be causally linked to a new compromise in neurocognition in older patients.

There remains little general awareness about neurocognitive dysfunction after critical illness, and no formal educational programs to assist patients, caregivers, or physicians caring for these patients. As physical rehabilitation programs become part of the ICU continuum of care, the importance of referral for neurocognitive rehabilitation may also need to be considered.

Psychiatric Morbidity

Psychiatric conditions after critical illness and ICU treatment are common. The range of depression reported in survivors of ARDS is 17% to 58%, and reports have suggested that patients with ARDS may experience a greater degree of depression compared with populations of general critically ill patients. Prospective evaluation of risk factors associated with depression in patients with ARDS showed relationships with longer
duration of mechanical ventilation, ICU length of stay, and sedation. A recent study assessing risk factors for depression and anxiety in ARDS survivors found that at 1 year, alcohol dependence, female gender, and younger age were predictors of depression, and that ratio of arterial oxygen tension to inspired oxygen fraction and duration of mechanical ventilation were predictors of anxiety. Predictors of depression at 2 years were depression and neurocognitive sequelae at 1 year, whereas the predictor of anxiety at 2 years was anxiety at 1 year. A recent study found that hypoglycemia may be an important risk factor for depression in ARDS survivors, and this warrants further study. The rates of depression in critically ill patients are similar to the 22% to 33% observed in chronically ill medical inpatients and 25% to 28% in patients with cardiac and pulmonary disorders.

In a recent systematic summary, Davydow and colleagues reported that 28% of ICU survivors had clinically significant depression, but sex, age, or severity of illness at ICU admission were not consistent risk factors for this. Early post-ICU depressive symptoms were a strong risk factor for subsequent depressive symptoms, and post-ICU depressive symptoms were associated with substantially lower HRQOL. In addition, episodes of depression may occur years after the critical illness. In the Toronto ARDS cohort study, more than 50% of patients had a physician-diagnosed episode of depression or anxiety between 2 and 5 years after ICU discharge.

The depression and anxiety observed after ICU treatment are likely multifactorial. Additional study is needed to better understand patient vulnerability, illness, and ICU treatment-specific determinants of mood and psychiatric disorders, and appropriate tools for diagnosis, treatment, and ongoing management.

Posttraumatic stress disorder is defined as a set of characteristic symptoms occurring after a traumatic event(s) where triggers include intense helplessness, fear or personal threat a serious personal threat. Diagnostic criteria include a history of traumatic event(s) associated with symptoms from each of three symptom clusters: hyperarousal symptoms, intrusive recollections and avoidant/numbing symptoms. A number of studies have examined the association between severe critical illness, its treatment and PTSD development. Schelling and colleagues pioneered this work and were the first to highlight the importance of PTSD to the critical care community. In a cohort of 80 ARDS survivors 4 years following discharge from the ICU, these investigators documented that almost one third of the ARDS survivors reported compromised memory, disturbing dreams, anxiety, and sleeping difficulties after ICU discharge, and 28% prevalence of PTSD. In this study, PTSD was associated with the number of adverse ICU-related memories recalled by patients.

In a different study sample, Kapfhammer and colleagues showed that 44% of critically ill patients fulfilled criteria for PTSD at hospital discharge and in 24% of patients, these persisted up to 8 years or longer. Davydow and colleagues reported that the median point prevalence of questionnaire-ascertained “clinically significant” PTSD symptoms was 22%, and the median point prevalence of clinician-diagnosed PTSD was 19% in populations of general critically ill patients. Predictors of post-ICU PTSD included history of psychopathology, greater ICU benzodiazepine exposure and post-ICU memories of in-ICU disturbing and/or psychotic experiences.

These authors also noted that female sex and younger age were less consistent predictors, and severity of critical illness was not a predictor. Post-ICU PTSD was associated with substantially lower HRQOL. The occurrence of PTSD in patients with ARDS may be higher, with Psychiatrist-diagnosed PTSD prevalence ranging from 44% at hospital discharge to 24% at 8 year follow-up. Memory for nightmares or delusions while in ICU as well as a complete absence of any ICU memories have also been noted as risks for PTSD. PTSD is currently considered another significant
sequela of critical illness/ARDS with an important contribution to job loss and long-term disability.13,57,66

Psychiatric disorders after critical illness may be a consequence of brain injury sustained from critical illness or its treatments, a psychological reaction to the emotional and physiologic stress of critical illness, or caused by other unknown factors. Additional candidate contributors may include medications, physiologic changes, pain, altered sensory inputs, sleep derangement, and an unfamiliar environment.67–69 A recent review article found an association between recall of delusional memories after ICU discharge and PTSD-related symptoms, depression, and anxiety.70 Although some suggestion has been made that factual memories could protect surviving patients from developing symptoms of PTSD, a recent study suggests otherwise. Myhren and colleagues71 evaluated 194 patients and found that 27% had symptoms of PTSD, and that the predictors in this study sample were higher education level, optimism, factual recall, and memory of pain.

How longstanding and debilitating psychiatric disorders may be after critical illness and the important deleterious impact they have on HRQOL, functional, and family caregiver outcomes are just starting to be appreciated. In response to these reports of significant mental health challenges, literature is now emerging evaluating potential interventions to prevent or reduce these psychiatric sequelae. A recent review article suggests that corticosteroid administration may protect patients against post-ICU PTSD.72 A novel and important study that used ICU diaries, which contained information and photographs from the ICU stay, suggested that these may reduce the incidence of PTSD.73 Of the patients who received the diary, only 5% had clinically significant PTSD symptoms compared with 13% of controls. This intervention seemed to be most effective for those with important early PTSD symptoms.73

HRQOL

HRQOL is defined as a set of causally linked dimensions of health, including biologic/physiologic, mental, physical, social, and neurocognitive functions, and health perception.4 Measures of HRQOL assess how disease and its treatment are related to physical, social, emotional, and neurocognitive functioning and have emerged as an important patient-centered metric of recovery from critical illness. Emerging evidence suggests that the degree of disability acquired during critical illness and the resultant decrement in HRQOL may be variable across patient populations and relate to differences in premorbid functional status, burden of comorbid illness, and nature and duration of critical illness and its treatment. This heterogeneity is important to consider when attempting to risk stratify patients for within-ICU and post-ICU rehabilitation interventions.

Considerable homogeneity in HRQOL outcomes exists across different cohorts of patients with ARDS,5 and the following is a brief, historical overview of the emergence of the literature on ARDS HRQOL outcomes, including recent data on 5-year outcomes.

In 1994, McHugh and colleagues6 prospectively evaluated pulmonary function and quality of life to assess recovery over time and evaluate the relationship between pulmonary function and functional disability. These investigators found that the SIP scores (Sickness Impact Profile-generic quality-of-life measure of the patient’s self-perceived physical and psychological condition) were low at extubation, rose significantly in the first 3 months, with only slight improvement to 1 year. When quality of life was assessed using a lung-related SIP score, only a modest proportion of the patients’ overall dysfunction was attributed to residual pulmonary problems. Weinert and colleagues4 administered the SF-36, which yields scores in eight domains,
including physical and social functioning, role limitations because of emotional or physical problems, mental health, vitality, bodily pain, and general health perceptions. Although they observed that all domains of the SF-36 were substantially reduced, the largest decrements occurred in role-physical and physical functioning. Some of the decrement in quality of life was attributed to pulmonary dysfunction, but most patients attributed reduced quality of life to generalized disability. Schelling and colleagues made similar observations about impaired physical functioning and inferred that disability was caused by pulmonary dysfunction; however, they did not assess this directly in their study. Davidson and colleagues assessed differences in HRQOL in ARDS survivors and comparably ill controls using the SF-36 and a pulmonary disease–specific measure (St. George’s Respiratory Questionnaire [SGRQ]) to determine the degree to which perceived physical disability in ARDS survivors was related to pulmonary dysfunction. Similar to previous reports, all domains of the SF-36 were reduced and the largest decrement was in the role-physical domain. ARDS survivors had significantly worse scores on the SGRQ compared with critically ill controls, which was postulated to suggest an ARDS-specific degree of physical disability. However, SGRQ was validated in patients with structural lung disease, and the three domains of the questionnaire—symptoms, activity, and impacts—may also be influenced by nonpulmonary factors, including ICU-acquired weakness and other physical disabilities documented in patients with ARDS. Therefore, the appropriateness and applicability of this measure in ARDS patients remains uncertain.

In a prospective cohort study of ARDS survivors, Angus and colleagues used the Quality of Well-Being (QWB) scale to measure quality-adjusted survival in the first year after hospital discharge. The mean QWB scores for the patients at 6 and 12 months were significantly lower than a control population of patients with cystic fibrosis. When QWB was disaggregated into its component subscores, the symptom component scores accounted for 70% of the decrement in perfect health at 6 and 12 months. Although respiratory symptoms were reported in almost half of the patients, the most common complaints were musculoskeletal and constitutional.

Orme and colleagues evaluated HRQOL and pulmonary function outcomes in a prospective cohort study of 78 ARDS survivors treated with higher tidal volume versus lower tidal volume ventilation strategies. Both groups (higher and lower tidal volumes) reported decreased HRQOL in physical functioning, physical ability to maintain their roles (role-physical), bodily pain, general health, and vitality (energy) on the SF-36. The pulmonary function abnormalities correlated with decreased HRQOL in domains reflecting physical function and were not related to ventilation strategy. An earlier paper by Cooper and investigators also failed to show any relationship between ventilation strategy and longer-term pulmonary, functional, or HRQOL outcomes.

A fairly recent meta-analysis of HRQOL studies in patients with ARDS found lower quality-of-life scores for ARDS survivors, consistent with previous reports. Of additional interest, the recovery of HRQOL in ARDS survivors may vary significantly across domains and over time, consistent with data from Hopkins and colleagues. Despite early improvement in the mental health domains, physical quality of life in ARDS survivors remains significantly lower compared with healthy populations years after ICU discharge.

Data on ARDS survivors are consistent with findings of studies involving more general populations of critically ill patients. A meta-analysis of quality-of-life studies in these patients consistently found lower quality-of-life scores compared to matched, normative controls at all time points (from hospital discharge to 66 months...
later) after ICU discharge.75 Furthermore, the investigators found larger decrements in the four physical domains (physical functioning, role-physical, bodily pain, and general health perceptions) than in the mental domains (vitality, social functioning, role-emotional, and mental health). The greatest gains occur in physical functioning, social functioning, and role-physical in the first 6 months, with only modest additional improvements thereafter.75 Recent ARDS outcomes data confirm these observations in a single cohort followed up for 5-years, with minimal loss to follow-up. This study shows little change in mental health domains over years, but an improvement in the physical component score of the SF-36 to approximately 2 years after ICU discharge, with a plateau below normal predicted values to 5 years. The most persistently affected domains at 5 years were those of general health and vitality (see Fig. 1).10

Iwashyna and colleagues34 recently noted similar outcomes, They found a persistent reduction in functional status after sepsis and critical illness. In their older patient study sample (median age, 77 years), they observed a high rate of new functional limitations in those who had no limits before their episode of sepsis (mean, 1.57 new limitations; 95% CI, 0.99–2.15). In those with reductions in activities of daily living before sepsis, the investigators noted an important further decrement in function. They observed that neurocognitive and physical decline persisted for at least 8 years after the episode of sepsis and that the episode of critical illness represented an important decline in the patients’ ability to live independently.34

The theme of acquired and persistent morbidity after an episode of critical illness is echoed further in a recent report on outcomes in chronically critically ill patients. Unroe and colleagues16 evaluated the trajectories of care and resource use for 126 patients with a median age of 55 years. These patients had an average of two comorbid conditions, and most were not employed at the time of ICU admission or were retired or disabled and receiving prolonged mechanical ventilation. At 1 year, only 11 patients (9% of the cohort) were alive and without functional dependency. Patients with poor outcomes were older, had more comorbid conditions, and were more frequently discharged to a post–acute care facility. The mean cost per patient was $306,135 (standard deviation [SD], $285,467), and the total cohort cost was $38.1 million, for an estimated $3.5 million per independently functioning survivor at 1 year.

These data indicate that HRQOL in ARDS survivors is adversely influenced by physical and neuropsychological morbidities and that an episode of severe lung injury changes the trajectory of functional outcome and may necessitate a change in employment and disposition in the case of poor premorbid function or organ reserve. The HRQOL data have helped raise awareness among the critical care community regarding long-term morbidity, and more recent in-person natural history cohort data have helped to “fill in the blanks” in terms of the specific determinants of these important decrements in function that persist for years after critical illness and that may represent permanent disability in many cases. Data from other ARDS cohorts with different study samples will help elucidate how robust these HRQOL and other outcomes are.76

Health Care Use and Cost

Limited data are available on the health care costs in patients with ARDS, with most data derived from the index hospitalization, and much less information on rehospitalization and accrued outpatient costs years after the critical illness. Angus and colleagues17 evaluated health care costs and long-term outcome after ARDS as part of their phase III study on nitric oxide. In their relatively young cohort (mean age, 50 years) with very few comorbidities at ICU admission and excellent premorbid functional status, the investigators observed hospital costs of approximately $50,000
exclusive of physician costs, and almost half of patients were discharged to another health care facility or to home with professional help. Of these patients, 24% were readmitted within 6 months and QWB scores were low, with most patients sustaining important decrements in function compared with baseline.

Costs were also reported by Cheung and colleagues\textsuperscript{2} in their 2-year ARDS outcomes study. Similar to the study by Angus and colleagues,\textsuperscript{3} this cohort was also relatively young and had few baseline comorbidities and, on average, spent several weeks in the ICU. Two-year mean costs, including those from the ICU stay, ward, and post-hospital discharge to 2 years were $97,810, $31,640, and $28,350, respectively. In the ICU, patients with more organ dysfunction acquired during their ICU stay, slower resolution of lung injury, burns, and an informal caregiver present had higher costs. Postdischarge costs were influenced most by the need for subsequent hospitalizations and inpatient rehabilitation. These hospitalizations were related to the risk factor for ARDS. These costs were similar to those previously reported by Valta and colleagues\textsuperscript{77} in a 1999 study on 59 Finnish patients with ARDS ($127,900 in Canadian 2002 dollars) and Hamel and colleagues\textsuperscript{78} in 2000 for 963 patients with ARDS or acute respiratory failure in the SUPPORT study ($94,500–$112,100 in Canadian 2002 dollars).

In the 5-year follow-up of the Toronto ARDS cohort study, outpatient costs continued to decrease to approximately $6000 to year 3 after ICU discharge but did not decrease beyond this in years 4 and 5. Medication costs and rehospitalization costs seemed to contribute most to these costs and were approximately three- to fourfold more than what one would expect for an age- and sex-matched patient population. This health care use was more consistent with the lower bound of that reported for chronic disease.\textsuperscript{10} Patients with a greater burden of comorbid illness had a greater rate of increase in cumulative cost over time (Fig. 3).

\textbf{Caregiver and Family Burden in Critical Illness}

The caregiver in critical illness experiences a twofold insult. Initially, they perform a bedside vigil for their loved one during the ICU stay and then are asked to assume complete responsibility for their family member who is often discharged home with complex medical needs, perhaps unresolved delirium, and compromised mobility. That many of these folks are unable to cope, and feel isolated and overwhelmed is hardly surprising.

Researchers have begun to focus on the importance of caregiver outcomes and interactions with caregivers of ICU survivors to understand the effect of critical illness on the family unit. Recent work indicates that close to 60% of ICU survivors who received long-term mechanical ventilation still required the assistance of a family caregiver 1 year after the critical illness.\textsuperscript{79} Existing evidence suggests that providing this care may have a deleterious impact on caregivers, and may compromise HRQOL compared with age- and sex-matched persons.\textsuperscript{80} Furthermore, significant mental health issues have been reported among caregivers, including PTSD,\textsuperscript{81} emotional distress,\textsuperscript{80,82–84} caregiver burden,\textsuperscript{85} depression,\textsuperscript{86} and anxiety.\textsuperscript{87}

In a recent review, Johnson and colleagues\textsuperscript{88} concluded that caregivers experience burden from the patient’s physical and psychological dysfunction and the challenges of managing complex care in the home. Lifestyle disruption and provision of high levels of care\textsuperscript{80} also contribute to poor caregiver outcome.\textsuperscript{80,84} Much of the current research has been limited by the cross-sectional design and follow-up of 1 year after hospital discharge.\textsuperscript{89} Caregiver needs will likely change over time as patients move through different transitions in their recovery and attempt reintegration into their prior lifestyle or return to work; very little is currently known about these longer-term transitions and the support or educational needs of the caregiver.
Perhaps one of the most fundamental limitations in constructing appropriate rehabilitation programs after critical illness is the current inability to risk stratify patients. Risk stratification is a fundamental tenet on which many other disciplines devise robust algorithmic treatment approaches to clinical problems. The heterogeneity of critically ill populations is an important barrier that must be addressed to understand differences in functional outcome across different patient groups and the various factors that seem to drive a broad spectrum of outcome. For the sake of discussion and contrast, an enormous difference exists in functional outcome between relatively young survivors of ARDS\textsuperscript{1,75} and older chronically critically ill patients,\textsuperscript{16} despite the apparent similarities of severity of illness and a protracted ICU length of stay. The young, previously working group with lung injuries had few comorbid disorders,\textsuperscript{33} very low mortality after ICU discharge, and a significant, albeit less-than-predicted, improvement in functional status at 1 year, and virtually all returned to independent living. These outcomes are in stark contrast to an older group of chronically critically ill patients with a significant burden of comorbid disease, with a 44% mortality rate at 1 year after ICU discharge and only 11% experiencing a good (ie, alive with no functional dependency) outcome.

Current interventional work focuses on early mobility, which several studies have shown is safe and feasible and alters short-term outcome in those patients who were previously functional.\textsuperscript{89–94} It is practical and logical to trial physiotherapy and occupational therapy interventions in those who have a high likelihood of benefit.\textsuperscript{92} However, this approach, although important and laudable, will not determine how interventions

\textbf{Fig. 3.} Cumulative costs to 5 years after ICU discharge stratified by number of comorbid conditions at ICU admission. Lower line is $\leq 1$ comorbid condition and upper line is $\geq 2$ comorbid conditions. (\textit{From} Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 2011;364(14):1302; with permission.)
should be tailored to meet individual needs nor how they should be differentially applied, because almost no guidelines exist on specific patient subgroups. For example, offering these interventions to subpopulations of patients whose muscles and nerves have sustained injury so profound that they have lost any potential for rehabilitation will inappropriately raise expectation. Many models have been proposed for complex rehabilitation after critical illness, but none has focused on how to tailor the program to individual need nor has shown long-term efficacy.95–98 A recent, multicenter, randomized trial assessing HRQOL in 286 critically ill patients compared outcomes from a nurse-led intensive follow-up program versus standard care at 12 months. No difference was seen in HRQOL on the physical or mental health component scores; however, the nurse-led follow-up program cost significantly more than standard care.99 Alternatively, a self-help manual with instructions for physical therapy improved 6-month outcomes in physical function assessed using the SF-36 HRQOL instrument, and perhaps patients and families used this guide to tailor recommendations to individual need, although this was not studied explicitly in this trial.100

This article has also outlined important neuropsychological disability, and some early work has evaluated potential interventions to improve these outcomes. Jones and colleagues73 evaluated whether a prospectively collected diary of a patient’s ICU stay could reduce the development of new-onset PTSD during convalescence after critical illness. Patients with an ICU stay of more than 72 hours were recruited to the study. Intervention patients received their ICU diary at 1 month after ICU discharge, and assessment of the development of PTSD was made at 3 months. The investigators found an associated decrease of new-onset PTSD in the diary group. These early data are promising, but further understanding of the longer-term effect of the diary intervention is warranted.

SUMMARY

Current ARDS outcomes literature suggests that patients will sustain some degree of neuromuscular, functional, or neuropsychological morbidity as a result of their severe lung injury, and that may not be wholly reversible, even in younger patients who were previously working and highly functional. Pulmonary outcomes are likely to be very good in patients who are younger and have no premorbid pulmonary disease. Some studies suggest that ARDS will interact with underlying pulmonary pathology and that outcomes may be more compromised. Health care costs are high, but younger patients who receive support in transitioning back to work return at an overwhelming rate. Patients with more comorbid illness and premorbid functional disability will have poor longer-term outcomes. Family caregivers of patients with ARDS may acquire new mood disorders that impair their HRQOL and also may modify outcomes in patients surviving lung injury. ICU-acquired weakness represents a major morbidity, and studies on interventions such as early mobility and ICU multidisciplinary interventions are promising, but more work must be performed on risk stratification so that programs can be tailored to individual and family needs.

REFERENCES


