TITLE: ACUTE RESPIRATORY DISTRESS SYNDROME AS A PRECURSOR TO POST-INTENSIVE CARE SYNDROME

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Introduction

      More than 6 million patients are cared for in an Intensive Care

Unit (ICU) annually in the United States (1-2), and millions more internationally. Acute

respiratory failure (ARF) is a common indication for ICU admission, one that afflicts

more than half of critically ill patients (3). Acute respiratory distress syndrome (ARDS) is

a severe, life-threatening form of ARF.

      With advances in care over the last 50 years, the majority of ARF and ARDS

patients survive. The survivorship literature is largely one that describes functional

impairments after critical illness. In this review article, we put forth the concept that ARF,

and ARDS more specifically, is a precursor to Post-Intensive Care Syndrome (PICS),

defined as new or worsening impairments in cognition, mental health, and/or physical

health after critical illness. This "precursor" paradigm, with a focus on potentially

modifiable risk factors in the ARDS patient, is suggested as a means to a better end for

patients with ARDS, by detailing care provisions and strategies to optimize short- and

long-term outcomes for a vulnerable subgroup of patients with an extended ICU length

of stay (Figure).

Acute Respiratory Distress Syndrome

      First described in 1967, ARDS is characterized as an acute, diffuse, inflammatory

lung injury (4-5). ARDS was initially known as "Adult" Respiratory Distress Syndrome. In

the seminal 1967 report, Ashbaugh and colleagues described 12 patients with acute

onset of respiratory failure, manifested by refractory hypoxemia, reduced lung

compliance, and diffuse alveolar infiltrates on chest radiograph following infection or

trauma (4). Pathologic findings in 6 of 7 deceased patients included hyaline

membranes, similar to those described in the pathophysiology of newborns with

respiratory distress syndrome (hence the later change from "Adult" to "Acute").

While the definition of ARDS has evolved over the past 50 years, most recently in

the Berlin Definition of 2012 (Table 1) (5), the cardinal feature of ARDS remains that the

acute lung injury leads to acute hypoxemic respiratory failure, often requiring initiation of

mechanical ventilation. Most cases of ARDS occur within 72 hours of an acute insult (4-

6). The three most common insults are pneumonia, sepsis, and aspiration of gastric

contents, which account for more than 85% of ARDS cases. Precipitants of ARDS can

be classified as direct or indirect. Direct insults include: pneumonia, aspiration,

pulmonary contusion, and inhalational injury. Indirect insults include: non-pulmonary

sepsis, shock, pancreatitis, burns, drug overdose, and cardiac arrest.

ARDS is an international public health threat, given its associated morbidity and

mortality. In LUNG-SAFE, an international study conducted across 459 ICUs in 50

countries, ARDS accounted for 10.4% of all ICU admissions, and 23% of patients

requiring mechanical ventilation (7). In the United States, it is estimated that ARDS

affects 190,600 patients annually, leading to 74,500 deaths and more than 100,000 new

ARDS survivors each year (8). These numbers are projected to increase as the

population ages.

Decades of clinical research have identified several evidence-based strategies to

reduce ARDS-related mortality. These strategies, incorporated into clinical practice

guidelines, include: lung protective ventilation (LPV), the early use of neuromuscular

blockade, and prone position ventilation in moderate to severe ARDS (9-12). Now, with

increased use of venovenous extracorporeal membrane oxygenation (ECMO) (13), survival is possible even for the most severe cases of ARDS.

Acute Respiratory Distress Syndrome Survivorship

Mortality

The birth of ARDS survivorship can be traced to the history of ARDS-related mortality. In 1979, twelve years after its initial description, less than 10% of patients with acute, severe respiratory failure enrolled in the original ECMO trial survived (14). Over the next two decades (1980s -1990s), through advances in critical care, ARDS-related mortality declined from 60% or greater to less than 50% (15).

In 2000, the Acute Respiratory Distress Syndrome Network published trial results that confirmed that mortality could be reduced in ARDS, through implementation of a LPV strategy wherein tidal volumes and plateau pressures were limited to 6 cc per kilogram of predicted body weight and 30 centimeters of water, respectively (10). Recent ARDS trials, layering additional interventions onto the use of LPV have demonstrated 28-day mortality ranging from 16% to 24% (10-11).

Unfortunately, outside of the clinical trial setting, mortality remains high. For example, in the LUNG-SAFE study, conducted in 2014, in-hospital mortality was 40% (7). As timely recognition of ARDS remains a challenge, and LPV remains underutilized, the opportunity exists to further improve ARDS outcomes over the next decade by more effectively translating evidence into practice. As an example of the evidence gap that we need to bridge, more than a third of ARDS patients in the LUNG-SAFE study received a tidal volume in excess of 8 mL/kg of predicted body weight (7).

Morbidity of ARDS Survivors

While improving short-term outcomes in ARDS remains a priority, improving long-term outcomes has emerged as a complementary goal. The wake-up call, published nearly two decades ago, revealed the reality of life after ARDS. In the landmark study published in 1999, cognition was impaired in 73% of survivors at hospital discharge and 46% at 1 year (16).

Subsequent studies have confirmed that cognitive impairment affects between one-quarter and one-half of ARDS survivors (17-18), and survivors of critical illness more broadly (19-20). The cognitive abilities found to be most frequently compromised include: memory, executive function (including mental processing speed), and attention/concentration. These difficulties can impact life in innumerable ways, including difficulties with medication management, scheduling and maintaining appointments and, following a prescribed discharge plan. These life-altering, persistent changes can impact relationships and lead to caregiver stress (21).

Beyond cognitive impairment, mental and physical health are often also impaired after ARDS and critical illness, more generally (17-29). Mental health issues include depression, anxiety, and/or post-traumatic stress disorder. Functional impairment and physical decline are common after ARDS (22-25). Specifically, two of three ARDS survivors experience difficulty with activities of daily living such as: using the telephone, shopping, preparing meals, doing housework, laundering clothes, utilizing transportation, taking medications, and/or money management (26). Over a 5-year follow-up study interval, nearly 70% of ARDS survivors experienced physical decline (27). Additional physical impairments among ARDS survivors include reduced

pulmonary function and exercise tolerance, critical illness polyneuromyopathy, tracheal stenosis, joint contractures, hoarseness and/or voice changes (28-29).

Co-occurrence of new impairments, found to exist in one out of four survivors of general critical illness (21), appears to be more common amongst ARDS survivors (16-17). Moreover, impairment in one domain (e.g., depression), has been found to predict the development of impairment in a separate domain (e.g., physical function) (22), highlighting the inter-relatedness, and potentially causal relationship, of functional impairments.

PICS and PICS-Family (PICS-F)

In 2012, these constellations of impairments, common amongst ARDS survivors, was termed Post-Intensive Care Syndrome (PICS). PICS is defined as new or worsening impairment in the domains of cognition, mental health, or physical impairment after critical illness (30). Sepsis, the most common precipitant of ARDS, and mechanical ventilation, required in most ARDS cases, are established risk factors for PICS (19, 31-32). Additional, potentially modifiable PICS risk factors relevant to acute respiratory failure patients include: hypoxemia (16, 17), lower central venous pressures (17), shock (19), duration of delirium (33-34), glucose dysregulation (35), and prolonged bed rest (i.e., immobility). In addition, several non-modifiable risk factors associated with developing PICS after critical illness include: less years of education and frailty (23).

PICS-Family (PICS-F), defined as anxiety, post-traumatic stress disorder, depression, or complicated grief, recognizes the impact of critical illness on caregivers (30). To provide context to PICS-F, Cameron et al. found that 67% of caregivers for patients who survived prolonged mechanical ventilation had symptoms of depression,

symptoms that persisted in 43% of caregivers at 12 months (36). Risk factors for those afflicted included: younger age, those in whom the critical illness exerted a greater impact, those with less social support, and those who experienced a greater loss of control over their life (36).

Survivors who are able to return home often have substantial care needs. In three out of four cases, family members shoulder this responsibility (37). Financial hardship often ensues, as reduced employment or new unemployment affects half of family caregivers (24, 37).

PICS Prevention Strategies in the ICU

Given the identified risk factors for PICS development, concentrated amongst the mechanically ventilated, the ABCDE bundle, as originally described by Morandi and colleagues (38) has the potential to improve short- and long-term outcomes. Since its original description, the bundle has been extended to the ABCDEF bundle, to incorporate the importance of family-centered care (39-40).

As summarized in Table 2, the ABCDEF bundle prioritizes the coordinated efforts of sedation minimization and spontaneous breathing trials, the optimal assessment, prevention and management of pain, agitation, and delirium, selection and use of sedatives (when needed), early ambulation (beginning on day 1), and family engagement (38-41).

Individually, and collectively, the ABCDEF bundle has been shown to improve survival, reduce duration of mechanical ventilation and ICU length of stay, increase days alive and free of delirium and coma, and increase the likelihood of returning home functionally independent (38-46). As duration of delirium is associated with long-term

cognitive impairment, choice of sedation (i.e., avoid benzodiazepines) (47), prevention and management of delirium (44), and early ambulation (45), have the potential to improve short- and long-term outcomes through their ability to reduce duration of delirium.

Regarding choice of sedation, a provocative one remains the option to use "no sedation" (48). In a randomized trial conducted by Strom and colleagues, a strategy of no sedation led to reduced duration of mechanical ventilation and length of stay (48), benefits achieved without long-term psychological distress (49). Given the opioid epidemic, evidence that opioid use leads to hyperalgesia that may prompt opioid-seeking behavior (50), and the knowledge that nearly half of ICU survivors report chronic pain (22, 51), strategies to minimize opioid use are warranted for long-term health. A novel, complementary strategy to minimize sedation, which led to less anxiety, was the use of self-initiated, patient-directed music during mechanical ventilation (52). Whether music therapy in the ICU results in less long-term psychological distress remains unclear; regardless, this trial highlights the potential value of non-pharmacological interventions to improve psychological well-being in the ICU.

Additional care strategies to mitigate PICS, beyond reducing duration of delirium, include: avoiding hypoglycemia (i.e., glucose < 60 mg/dl) (17, 35, 53), avoiding lower central venous pressures (17), and avoiding hypoxemia (16-17). Regarding oxygenation, traditionally, trials targeted partial pressure of arterial oxygen (PaO2) between 55 and 80 (10-12). However, evidence to support targeting oxygenation in the 80-100 range exists, as the odds of cognitive impairment at 12 months was found to be 1.5 times greater among ARDS survivors from the Fluid and Catheter Treatment Trial

with lower oxygenation levels (mean PaO2 71 (interquartile range (IQR): 67,80) in the impaired group compared to 86 (IQR: 70, 98) in the non-impaired group) (17).

Patient Diaries

Recommended by the international family-centered care guidelines (39), ICU diaries are a complementary strategy to reduce psychological distress amongst patients and their loved ones. Patient diaries are written accounts of a patient's ICU journey. They are written in lay language by family members and staff in the ICU, and account what happened during critical illness on a daily basis. They are written for the patient and may include pictures. Patients often have little memory of their ICU stay, which can cause feelings of distress and anxiety, perpetuated by delusional memories. Patient diaries can potentially reconstruct the illness narrative for patients, which may help individuals understand what happened to them. It may also help patients understand why their recovery is more difficult than may have been anticipated. Research has demonstrated that patient diaries, alongside structured follow up, reduced signs and symptoms of PTSD in patients and family members at pre-specified time points during recovery (54-56).

Support for Patients and Families Post-Discharge

Family members of critical care survivors are known to have significant emotional and social challenges following a loved one's critical illness. These challenges may contribute to PICS-F. Family members provide much of the daily care that ICU survivors require in the months after discharge (24), a reality that may amplify PICS-F symptoms. Therefore, adequate support and recognition of this vulnerable group, in a manner not routinely done in modern day critical care, is urgently needed.

During the ICU stay, issues of survivorship are rarely addressed (57). To more effectively support patients and family members, education of what to expect after critical illness is necessary. These preparatory efforts, begun in the ICU through verbal and/or written forms of communication (39), should continue throughout the acute care hospitalization and into the post-discharge care environment. A proactive communication strategy, designed to inform, educate, and prepare survivors and their caregivers along the care continuum (58), may serve to combat the "relocation stress" that frequently occurs upon ICU discharge (59) and as patients transition from the stabilization to the preparation and post-discharge adjustment phases of recovery (59).

Future Directions for the Management of Post-Intensive Care Syndrome Post-ICU Discharge

At present there is limited evidence to manage or treat PICS following ICU discharge. Interventions which have been tested to date include: support by a rehabilitation specialist in the acute hospital setting following critical care, ICU recovery clinics (Nurse-Led), and primary care management interventions (60-62). Theories around this lack of effectiveness have been proposed and include a lack of engagement with family members and loved ones, a lack of focus on social issues which survivors face during recovery, and a failure to look beyond traditional healthcare services during the recovery phase. Issues around appropriate staff involvement and the outcome measures selected in these studies have also been discussed (63).

A paradigm shift therefore is required. A movement from a sole focus on the biomedical mechanisms of recovery, to an understanding of what makes individuals

healthy is crucial. During critical care recovery this will include an emphasis on how we can support the social problems which patients face as well as the known physical, emotional and cognitive problems.

Health and Social Integration

Related to the concepts of PICS and support for ARDS survivors, evolving literature now describes the social challenges which survivors of critical care face. In addition to the previously described problems of reduced employment, financial shock, and housing issues (64-65), social isolation may also occur in this group. Social isolation has been defined as "a state in which the individual lacks a sense of belonging socially, lacks engagement with others, has minimal number of social contacts and they are deficient in fulfilling and quality relationships" (66).

Social isolation is known to increase morbidity and mortality and may worsen cognitive problems in subsets of the population (67-68). To add to these challenging circumstances, individuals who come from the worst socio-economic backgrounds are often most affected by PICS (23), leading to an even more difficult recovery.

As a result of these complex issues, it is crucial that providers look beyond the delivery of traditional healthcare strategies for this vulnerable group and instead focus on the delivery of health. One of these strategies may include partnering with social care agencies who can provide expertise in the social problems which individuals face. One such model has been piloted in the UK.

Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE) is a five week peer supported rehabilitation program for patients and their caregivers. InS:PIRE, which runs on a cohort basis, aims to provide individualized health

and social care resources, which patients and their caregivers need to make a safe and effective recovery. This program has been piloted in one site thus far and has demonstrated a signal of improved quality of life for the participants involved (69-70).

Peer Support

One of the key facets of the InS:PIRE program is the use of peer support. Peer support has been defined as the "process of providing empathy, offering advice, and sharing stories between Intensive Care Unit (ICU) survivors. It is founded on the principles that both taking and giving support can be healing, if done with mutual respect" (71). Peer support can build social relationships that may have a positive influence on health and well-being. In contrast, social isolation is known to exacerbate illness and predict mortality in many disease states. Peer support strategies, therefore, may produce psychological, social, and health benefits in this setting (72-73).

Although common as a method of support in other disease trajectories such as diabetes and cancer, peer support models, as yet, are not commonly found in the critical care population. However, since 2015 the Society of Critical Care Medicine, under the umbrella of their Thrive initiative, have developed a peer support collaborative across three continents, to support the development of peer support models of care for this vulnerable population. A number of potential models of peer support have been proposed internationally including: in person community support groups, models embedded in follow up clinics, and virtual and psychologist-led peer support groups (72-73). Many of these models are still evolving and are currently undergoing evaluation to help understand this potential mechanism for support. However, early evaluations are promising and could signal the improvement in quality of life which has previously eluded researchers.

PICS and PICS-Family Assessment

Post-hospital discharge, whether in a long-term acute care hospital, skilled care facility, acute rehabilitation setting, or an ICU recovery clinic or primary care provider's office, we recommend that providers be aware of PICS and standardize their practice to identify ICU survivors and assess for functional impairments. Adapted from the core outcome measurement set for clinical research in acute respiratory failure survivors (74-75), potential screening tests include the Hospital Anxiety and Depression scale (HADS) (76), Impact of Event Scale-Revised (IES-R) (77), and Montreal Cognitive Assessment (MoCA) (78) for anxiety, depression, post-traumatic stress disorder, and cognitive impairment, respectively. Additionally, the EuroQoL can be used as a screening test for physical function and pain (79). For an objective functional assessment, the 6-minute walk test is a valid, reliable, and reproducible measure that can be followed longitudinally (74-75). While recommended for research purposes, each of these measures are commonly used in clinical practice. For family members experiencing psychological distress, we recommend considering the HADS and IES-R as screening tools.

For those who screen positive for neuropsychological impairment, we recommend referral to experts for more formal evaluation and treatment, if the impairment identified in the screening test is outside of the scope of the providers' routine practice. For those who screen positive for either neuropsychological or functional impairment, we also recommend referral for occupational and/or physical therapy to facilitate recovery.

Conclusion

Millions of patients who experienced acute respiratory failure are discharged from Intensive Care Units annually. Long-term impairment is common, under recognized, and costly. The impact extends beyond survivors. While impairment and losses are presently the norm, survivors are resilient (22), and evidence exists to mitigate PICS development, beginning immediately upon ICU admission and continuing well beyond hospital discharge.

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Figure. Interventions to mitigate post-intensive care syndrome along the continuum of care.

Table 1. Berlin definition of ARDS, which includes the requirement of a minimal level of

positive end-expiratory pressure of 5 cm of water (adapted from references 5, 80).

Criteria	Definition
Acute	Onset within 7 days of a known precipitant (e.g., sepsis)
Bilateral	Bilateral infiltrates not explained by effusion, lobar/lung collapse, or nodules
Non-cardiac in origin	Respiratory failure not fully explained by hydrostatic edema, as judged clinically, or by objective assessment (e.g. echocardiography) if no risk factors for ARDS are present
Severe	Categorized, according to the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, as mild (201 to 300), moderate (101 to 200), or severe (less than or equal to 100 mm Hg), which were associated with mortality and duration of mechanical ventilation (mild: median 5 days, IQR: 2, 11; moderate: 7 days, IQR: 4, 14; severe: 9 days, IQR: 5, 17)

Table 2. ABCDEF bundle, adapted from references 38-40.

Bundle Element	Specifics	References
A	Assess, Prevent and Manage Pain	38-41, 50-51
B	Both spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT)	41
C	Choice of analgesia and sedation, with suggestion to limit use of benzodiazepines and opioids	38-51
D	Delirium: Assess, prevent, and manage	42-44
E	Early mobility and exercise	45
F	Family engagement and empowerment, including ICU diaries	39