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<b>14. ABSTRACT</b> APICS-01 seeks to address clinical and operational knowledge gap for acute lung injury (ALI) survivors by defining patterns of unmet needs, resource utilization, readmissions, and long-term functional outcomes among ICU survivors. We will employ a prospective, multi-center, observational study of outcomes and healthcare utilization among 200 ALI survivors which are directly relevant to a military population. In the first year of award, APICS-01 secured all approvals, finalized all study materials, and initiated enrollment ahead of schedule. Enrollment is currently at 64 (ahead of a projected 50 at this point). Analysis of data will not occur until after enrollment is closed. Findings to date are of a highly effective multi-center collaborative performing a high-quality clinical study ahead of schedule. The screening activities are functioning well, the eligibility criteria are working well, and the enrollment curves are solid.					
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**1. INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

APICS-01 seeks to address the clinical and operational knowledge gap for acute lung injury (ALI) survivors by defining patterns of unmet needs, resource utilization, readmissions, and long-term functional outcomes among ICU survivors. We will employ a prospective, multi-center, observational study of outcomes and healthcare utilization among ALI survivors which are directly relevant to a military population. The study will enroll 200 patients at multiple civilian and Veterans Administration hospitals centers. We hypothesize that unmet needs in the first 1-4 weeks after hospital discharge will be associated with readmission or death after hospital discharge at 3 months, even after adjusting for the likelihood of having unmet needs.

**2. KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Acute Lung Injury, Long-term Outcomes, Intensive Care, Recovery from Illness/Injury

**3. ACCOMPLISHMENTS:**

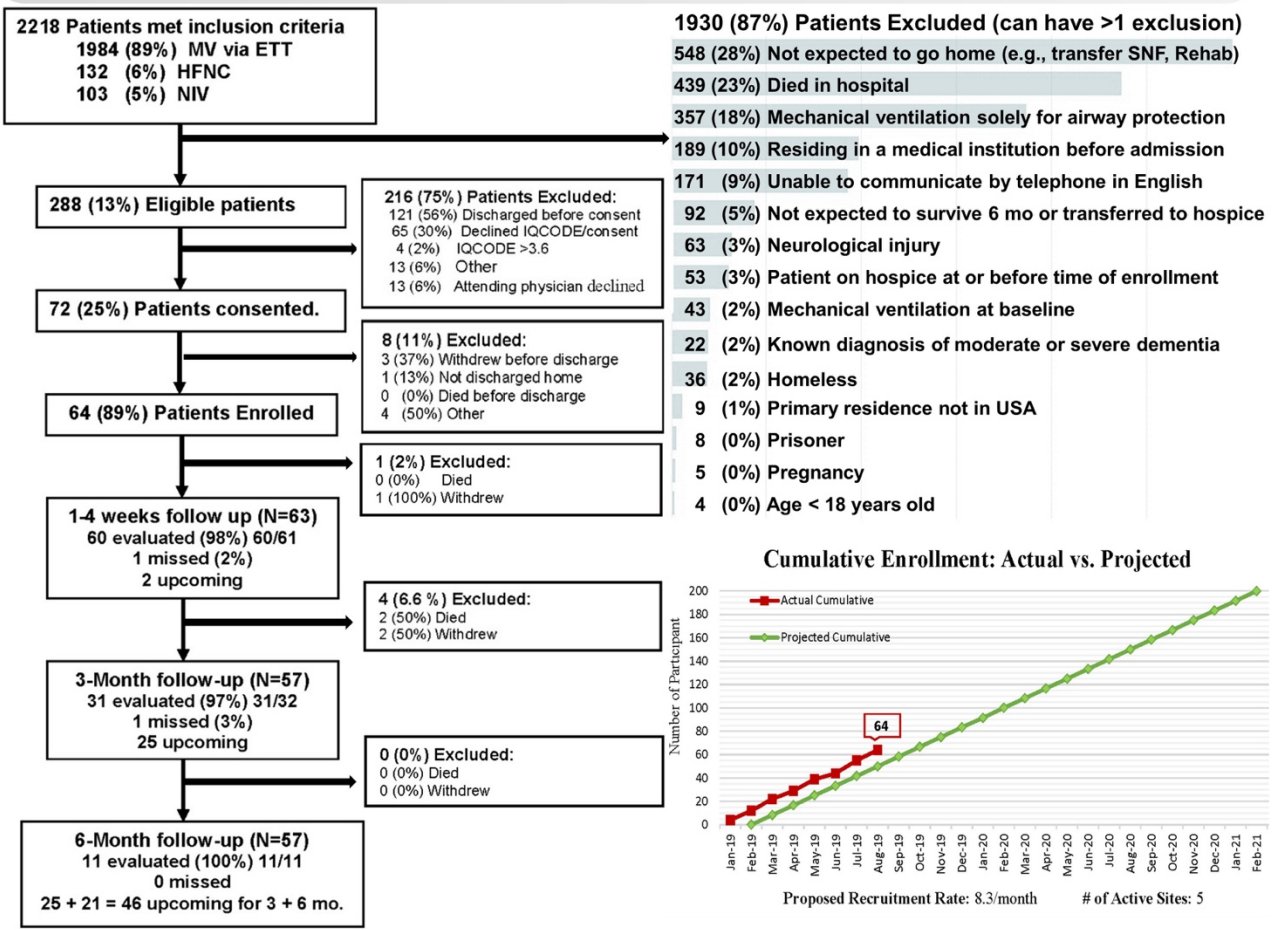
**What were the major goals of the project?**

**Major Task 1: Prepare Study for Data Collection and Execution.** We met all sub-tasks on or before schedule and achieved the major milestone of “Local IRB and HRPO Approval Obtained and Site Ready for Recruitment.” Central IRB approval (#181120) was received on 7/19/18 (ahead of schedule); HRPO approval (#E00320.1a and #E00320.1c) was received on 11/27/18 (ahead of schedule); Manual of Procedures July 2018 (ahead of schedule), Site Education and Training Packets November-December 2018 (ahead of schedule), REDCap Database November 2018 (ahead of schedule), Data Management Plan November 2018 (ahead of schedule), Clinicaltrials.gov registration 11/12/2018 (ahead of schedule).

**Major Task 2: Patient Enrollment and Data Collection.** As of August 31, 2019 (the first 11 months of the award) enrollment is at 64 patients, which comfortably exceeds our original milestone at the end of Year 1 of 50 patients enrolled. In terms of activities: Kick Off Meeting 1/15/19 (with first patient enrolled 1/20/19), all the investigator meetings are happening on-time and consistently

**What was accomplished under these goals?**

**Major Activities:** Primary activities in this study period were study preparation, study launch, and enrollment as described above. As indicated above, all goals were achieved ahead of schedule. Results were presented at the MHSRS 2019 meeting in Orlando as well as the Johns Hopkins ICU Rehabilitation conference. The following figure demonstrates the screening and enrollment activities within the study, using a CONSORT-style diagram and with a graphic to demonstrate greater-than-projected enrollment.



**Specific Objectives:** Assess the relationship between unmet needs after discharge and 3-month death or readmission, using inverse probability weighting to control for the propensity of having unmet needs.

**Significant Results or Key Outcomes:** All stated goals have been met.

**Other Achievements:** Nothing to Report

**What opportunities for training and professional development has the project provided?**

Nothing to Report

**How were the results disseminated to communities of interest?**

We published a framing paper in *Annals of the American Thoracic Society* (PMID 31162935; submitted to DoD at time of submission); we presented at Military Health System Research Symposium (MHSRS-19-00923); we had an abstract accepted at the Johns Hopkins Rehabilitation conference (abstract 8). After informing DoD, we issued a news release, which generated news

coverage, including newspaper and television, drawing attention to the needs of ALI survivors and the importance of this research to improving their plight.

**What do you plan to do during the next reporting period to accomplish the goals?**

*Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.*

For the next study period (Year 2) we will continue enrollment, cleaning of data, and preparation for the end of enrollment in Year 3. We will submit the APICS-01 protocol paper to a peer-reviewed journal for publication, with acknowledgment of federal support.

**4. IMPACT:**

**What was the impact on the development of the principal discipline(s) of the project?**

APICS-01 is the first study to our knowledge to carefully evaluate the first weeks after hospital discharge for ALI survivors. In that innovative setting, we are also studying the proportion of unmet needs as a marker of vulnerability and controlling—with innovative statistical techniques—for possible confounding. At this early stage of the work, the primary impact is mostly exemplary—highlighting the importance of this research topic. In addition, our published framing paper advanced understanding in the field of this important area.

**What was the impact on other disciplines?**

Nothing to Report

**What was the impact on technology transfer?**

Nothing to Report

**What was the impact on society beyond science and technology?**

The publication of the framing paper helped to advance conversations in public about the importance of care coordination and attention to early unmet needs among ALI survivors. This did help advance the societal conversation about our obligations to patients through the entire arc of illness through recovery.

**5. CHANGES/PROBLEMS:**

**Changes in approach and reasons for change**

Nothing to Report

### **Actual or anticipated problems or delays and actions or plans to resolve them**

We are enrolling ahead of schedule and are meeting or exceeding all benchmarks. We are mindful that recruitment/enrollment must be monitored consistently and have established contingency plans for improving enrollment should the rate of enrollment decrease.

### **Changes that had a significant impact on expenditures**

Nothing to Report

### **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

#### **Significant changes in use or care of human subjects**

Nothing to Report

#### **Significant changes in use or care of vertebrate animals**

Nothing to Report

#### **Significant changes in use of biohazards and/or select agents**

Nothing to Report

## **6. PRODUCTS:**

- **Publications, conference papers, and presentations**

#### **Journal publications.**

**Brown SM**, Bose S, Banner-Goodspeed V, Beesley SJ, Dinglas VD, Hopkins RO, Jackson JC, Mir-Kasimov M, Needham DM, Sevin CM, Addressing Post Intensive Care Syndrome 01 (APICS-01) study team. Approaches to Addressing Post-Intensive Care Syndrome among Intensive Care Unit Survivors. A Narrative Review. *Ann Am Thorac Soc*, 16(8), 2019, 947-956; published; federal support acknowledged.

#### **Books or other non-periodical, one-time publications.**

Nothing to Report

#### **Other publications, conference papers and presentations.**

James Jackson et al “Addressing Post-Intensive Care Syndrome (APICS-01),” 2019 Military Health Sciences Research Symposium, MHSRS-19-00923.

Narges Akhlagi, et al, “Addressing Post-Intensive Care Syndrome (APICS-01),” 8th Annual Johns Hopkins Critical Care Rehabilitation Conference, Baltimore, MD, abstract 8 (accepted; to be presented October 2019).

- **Website(s) or other Internet site(s)**

Nothing to Report

- **Technologies or techniques**

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Nothing to Report

- **Other Products**

The data are still being collected. Once the data are collected, they will represent a substantial contribution to our understanding of the outcomes of survivors of acute lung injury

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### What individuals have worked on the project?

**Name:** Samuel Brown

**Project Role:** Principal Investigator

**Researcher Identifier:** ORCID: 0000-0003-1206-6261

**Nearest Person Month Worked:** 3

**Contribution to Project:** Oversight of entire project.

**Funding Support:**

**Name:** Katie Brown

**Project Role:** Study Coordinator

**Researcher Identifier:**

**Nearest Person Month Worked:** 1

**Contribution to Project:** Study support, consenting patients, data entry into database

**Funding Support:**

**Name:** Dale Needham

**Project Role:** PI of the Data Coordinating Center

**Researcher Identifier:**

**Nearest Person Month Worked: 2**

**Contribution to Project:** Oversees all functions of the data coordinating center as well as local enrollments at the Johns Hopkins site.

**Funding Support:**

**Name:** Narges Akhlagi

**Project Role:** Senior research coordinator for Data Coordinating Center

**Researcher Identifier:**

**Nearest Person Month Worked: 2**

**Contribution to Project:** Reports to Dr. Needham. Works to maintain function of the data coordinating center including data processes oversight, communication with study team and related tasks.

**Funding Support:**

**Name:** Elise Caraker

**Project Role:** Study coordinator and telephone followup

**Researcher Identifier:**

**Nearest Person Month Worked: 2**

**Contribution to Project:** Study support, Telephone Followup, contacting study participants

**Funding Support:**

**Name:** Tejaswi Kalva

**Project Role:** Study Coordinator and telephone followup

**Researcher Identifier:**

**Nearest Person Month Worked: 2**

**Contribution to Project:** Study support, Telephone Followup, contacting study participants

**Funding Support:**

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

For Dr. Brown, the following grant support has completed: “Platelet Immune Responses in Aging and Influenza” (5% effort) and “Optimizing ICU Safety through Patient Engagement, System Science and Information Technology” (11% effort).

Dr. Brown became PI of the grant “Utah Clinical Ctr., NHLBI Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network” (now at 15% effort).

Dr. Brown received new funding for “Study of Treatment’s Echocardiographic Mechanisms – CLOVERS-STEM” (NIH, 20% effort) and “The Greater Plains Collaborative (GPC)/PCORnet 2.0 Clinical Research Network Infrastructure” (PCORnet, 5% effort), “Implementation of Computerized Clinical Support for Mechanical Ventilation of Patients with ARDS” (NIH, 3% effort).

For Dr. Mir-Kasimov, there is no change in other support.

For Dr. Needham, the following grant support has completed: “ICU-Acquired Neuromuscular Dysfunction and Outcomes in Acute Lung Injury” (NIH), “Discovery and Prediction of Novel Functional Outcome Phenotypes for ARDS” (NIH), “Patient Outcomes 6 and 12 Months after ARDS Network Trials” (NIH), “Patient Outcomes 6 and 12 Months after ARDS Network Trials (ALTOS Study)” (NIH), Improving Long-Term Physical & Mental Health After Acute Lung Injury (ICAP Study)” (NIH), “Comprehensive Unit-Based Safety Program (CUSP) for Ventilator-Associated Conditions and VAP Prevention” (AHRQ).

Dr. Needham received new funding for “Symptoms Assessment and Screening for laryngeal Injury Post-Extubation in ICU” (NIH, 15% Effort), “Novel Arm Restraint for Intubated Patients with Cognitive Impairment to Reduce Agitation, Sedation and Immobility” (NIH, 4% Effort), “Effect of Exercise on Inflammation-Induced Lung and Muscle Injury in Critical Illness (NEXIS-FLAME)” (NIH, 3% Effort), “Improving the Statistical Design and Analysis of Randomized Controlled Trials of Delirium Prevention and Treatment for Critically Ill Older Adults” (NIH, 13% Effort).

**What other organizations were involved as partners?**

Nothing to Report

**8. SPECIAL REPORTING REQUIREMENTS**

**COLLABORATIVE AWARDS: A collaborative award is present and an annual report for the collaborative report is being submitted.**

**9. APPENDICES: *There is one appendix, the published framing paper manuscript.***

# Approaches to Addressing Post-Intensive Care Syndrome among Intensive Care Unit Survivors

## A Narrative Review

Samuel M. Brown<sup>1,2\*</sup>, Somnath Bose<sup>3</sup>, Valerie Banner-Goodspeed<sup>3</sup>, Sarah J. Beesley<sup>1,2</sup>, Victor D. Dinglas<sup>4</sup>, Ramona O. Hopkins<sup>1,5</sup>, James C. Jackson<sup>6</sup>, Mustafa Mir-Kasimov<sup>7</sup>, Dale M. Needham<sup>4</sup>, and Carla M. Sevin<sup>6</sup>; for the Addressing Post Intensive Care Syndrome 01 (APICS-01) study team

<sup>1</sup>Center for Humanizing Critical Care and Pulmonary/Critical Care Medicine, Intermountain Medical Center, Murray, Utah; <sup>2</sup>Pulmonary and Critical Care Medicine, University of Utah, Salt Lake City, Utah; <sup>3</sup>Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts; <sup>4</sup>Outcomes After Critical Illness and Surgery (OACIS) group and Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland; <sup>5</sup>Psychology and Neuroscience, Brigham Young University, Provo, Utah; <sup>6</sup>Vanderbilt University Medical Center, Nashville, Tennessee; and <sup>7</sup>George E. Wallen Veterans Affairs Medical Center, Salt Lake City, Utah

ORCID IDs: 0000-0003-1206-6261 (S.M.B.); 0000-0002-5292-2010 (S.J.B.).

### Abstract

Critical illness can be lethal and devastating to survivors. Improvements in acute care have increased the number of intensive care unit (ICU) survivors. These survivors confront a range of new or worsened health states that collectively are commonly denominated post-intensive care syndrome (PICS). These problems include physical, cognitive, psychological, and existential aspects, among others. Burgeoning interest in improving long-term outcomes for ICU survivors has driven an array of potential interventions to improve outcomes associated with PICS. To date, the most promising interventions appear to relate to very early physical rehabilitation. Late interventions within aftercare and

recovery clinics have yielded mixed results, although experience in heart failure programs suggests the possibility that very early case management interventions may help improve intermediate-term outcomes, including mortality and hospital readmission. Predictive models have tended to underperform, complicating study design and clinical referral. The complexity of the health states associated with PICS suggests that careful and rigorous evaluation of multidisciplinary, multimodality interventions—tied to the specific conditions of interest—will be required to address these important problems.

**Keywords:** acute respiratory distress syndrome; post-intensive care syndrome; long-term outcomes; critical care outcomes

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\*S.M.B. is an Associate Editor of *AnnalsATS*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

A list of additional Addressing Post Intensive Care Syndrome 01 (APICS-01) study team members may be found before the beginning of the REFERENCES.

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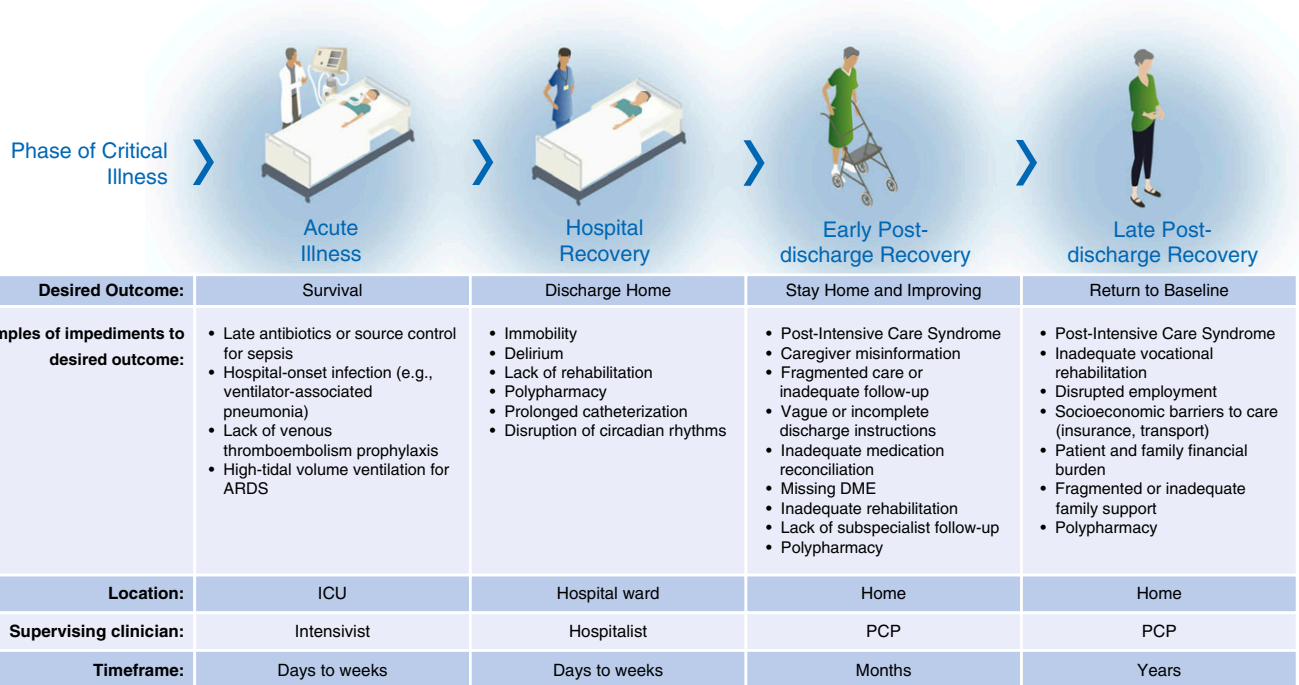
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The past two decades have seen significant improvements in mortality among patients admitted to intensive care units (ICUs), despite an increase in overall severity of illness (1). Promising improvements in quality of care have engendered a growing

population of ICU survivors who confront a wide range of difficulties that may persist for years after their discharge from hospitals. These difficulties that ICU survivors face have recently been termed—for heuristic and strategic rather than

biological or mechanistic reasons—the “post-intensive care syndrome” (PICS) (see Figure 1). The term “PICS” is intended to draw attention to new and/or worsening impairments in physical, cognitive, or mental health status arising after critical



**Figure 1.** The phases of critical illness. ARDS = acute respiratory distress syndrome; DME = durable medical equipment; ICU = intensive care unit; PCP = primary care provider.

illness and persisting beyond acute hospitalization (2, 3).

By way of example, acute respiratory distress syndrome (ARDS), a common cause of ICU admission (4), affects approximately 200,000 people and results in approximately 75,000 deaths, accounting for approximately 2.2 million ICU days annually in the United States alone (5). Over 100,000 ARDS survivors confront the long-term sequelae of critical illness every year in the United States. Similarly, every year, over 14 million patients survive sepsis hospitalizations worldwide; a majority of these patients experience sequelae of PICS (6).

The National Heart, Lung, and Blood Institute (7, 8), the National Institute on Aging (9), and critical care professional societies (2, 10, 11) have identified long-term functional outcomes after critical illness as a crucial target for research and clinical improvements (12). The societal burden of PICS among survivors is substantial, is anticipated to increase, and therefore represents a research priority for the critical care community. In this narrative review, we highlight existing evidence and experience with strategies aimed at preventing and treating the impairments

associated with PICS and additional areas of focus that could potentially ameliorate the burdens of critical illness survivors.

### The Plight of Critical Illness Survivors

Survivors of critical illness often confront residual disability after their critical illness, impairments from preexisting illness, and risks for the onset of new illnesses (especially sepsis). Added to these burdens are iatrogenic complications (especially from polypharmacy and care fragmentation) and mismatches between supports needed and supports provided during the vulnerable period after hospital discharge. Extensive studies have identified substantial, persistent impairments in physical, cognitive, and mental health outcomes; limitations in ability to perform activities of daily living; and impaired quality of life among ICU survivors (6, 13–28).

Each domain of post-ICU impairment may impact the other domains. Symptoms of depression adversely impact physical function (25), and ICU-acquired weakness is associated with reduced quality of life (29,

30). A number of studies have shown relationships between cognitive impairments and psychological outcomes. Depression, anxiety, and post-traumatic stress disorder are associated with worse cognitive function (31–34). Conversely, cognitive impairments are associated with development of worse depression and anxiety (35). Cognitive impairments are also associated with new or worsening dependencies in instrumental activities of daily living, such as shopping, food preparation, and management of medications and finances (36).

Relatedly, many survivors incur substantial healthcare costs, lose employment, and find their social networks reconfigured at high rates (37–42). Many ICU patients are readmitted to the hospital within the first 3–12 months, often for potentially preventable complications (43–45). The first two years after hospital discharge are especially costly for ICU survivors (14, 18, 46–49). A longitudinal cohort study of ARDS survivors in Maryland reported a 1-year readmission rate of 40% among survivors, with an associated median hospital cost of \$18,756 (interquartile range [IQR], \$7,852–\$46,174) (49). The costs to patients and families are

similarly high: ICU survivorship is associated with decreased return to work, and both patients and caregivers are plagued by loss of earnings (39, 50, 51). In addition, some survivors report an existential threat that comes from feeling abandoned in the face of great need (52, 53).

### Conceptual Framework for the Phases of Post-ICU Recovery

The different phases of critical illness and recovery can be empirically classified as acute illness, hospital recovery, and early and late postdischarge recovery. Each phase can be thought of as a distinct epoch with a mix of unique and similar problems. Figure 1 summarizes the various phases of critical illness and its aftermath, which may be amenable to interventions that attempt to prevent, ameliorate, or treat the underlying impairments of PICS. Identification of the issues associated with each phase encourages development of targeted strategies to mitigate the impediments to complete recovery. Interventions relevant to each of these phases have been studied, albeit with variable rigor and replicability.

Of all these phases, the early postdischarge period is perhaps the least well explored and represents a vulnerable period in the recovery from critical illness. Although some morbidity (e.g., cognitive dysfunction, lung injury) may be intrinsic to the disease processes underlying critical illness, other aspects of post-ICU morbidity may result from therapeutic exposures and decisions in the ICU. Still others will result from fragmented or inadequate care after discharge, leading to potentially modifiable risk of poor outcome. These varied etiologic mechanisms for the range of post-ICU morbidity and mortality likely have a substantial influence on the possible efficacy of preventive or therapeutic interventions to limit post-ICU disability. We structure the balance of this narrative review around these varied etiologies, and we attempt to address them and future directions for optimizing outcomes after ICU discharge.

### Acute Mechanistic Interventions

Little work has been done to explore acute mechanisms underpinning the

impairments observed in PICS. Most critical care randomized trials measure only short-term organ dysfunction outcomes, with survival or organ-free days as the primary outcome of interest. Generally, randomized trials of ICU-based interventions have only evaluated outcomes after hospital discharge as secondary or safety signals. This strategy is insensitive in determining the impact of interventions across the continuum of care for the critically ill population, which becomes a key issue as survivorship increases.

Some notable exceptions in which researchers have attempted to explore PICS-relevant outcomes after ICU-based interventions (e.g., early enteral nutrition [23, 24], rosuvastatin [54, 55], or haloperidol and ziprasidone for delirium [56]) have not suggested efficacy. Admitting the risk of  $\alpha$ -inflation when emphasizing possible efficacy signals on secondary outcomes, several pivotal ICU trials focused on sedation- and/or mobilization-related interventions have suggested improvement in key outcomes, including functional outcomes at hospital discharge or survival to 1 year (57–59). The ROSE (Reevaluation of Systemic Early Neuromuscular Blockade) trial of neuromuscular blockers in ARDS includes a carefully selected panel of postdischarge outcomes (60); results suggested no difference in outcomes to 12 months (61). More interventional trials that focus on the long-term outcomes of acute interventions are needed.

### Interventions to Mitigate PICS

A number of interventions have been attempted in heterogeneous groups of critical care survivors to ameliorate the different impairments associated with PICS. Table 1 summarizes the various interventions that have been studied to mitigate the effects of PICS. These interventions can be broadly classified into four domains—physical, mental and social health, cognitive, and care coordination. Various combinations of interventions across these domains have been studied through different time frames, such as during hospitalization and in early discharge and late discharge periods. Unfortunately, very few interventions have demonstrated efficacy. Much work remains to be done.

### Rehabilitation-based Interventions Have Yielded Mixed Results

Randomized controlled trials of physical rehabilitation interventions initiated several days after ICU admission have generally yielded no consistent evidence of benefit (2, 62–69). Clinical trials that focused on functional mobility, conducted by nurses, physical therapists, and/or occupational therapists and started within days of ICU admission, have demonstrated statistically significant benefits (59, 70–72). Beyond ICU discharge, studies have included in-hospital, outpatient, and home-based focused rehabilitation interventions—either formal or self-directed (using a rehabilitation manual)—without consistent evidence of significant efficacy (64, 73–76). Table 1 highlights exemplary interventions that have been studied. The most recent large meta-analyses suggest that exercise interventions may in fact be effective in terms of increased strength and decreased duration of mechanical ventilation (77, 78). The incremental benefits of adding nutritional therapy to rehabilitation interventions are a research priority (74, 79, 80); at least one controlled trial addressing this question is underway (NEXIS [Nutrition and Exercise in Critical Illness]; [www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier NCT03021902).

### Approaches to Fragmented or Inadequate Postdischarge Care

In the current healthcare system, patients and families often experience unmet needs after hospital discharge. Such unmet needs include durable medical equipment (e.g., oxygen, noninvasive ventilation, mobility assistive devices), coordination with government assistance and community health programs, rehabilitation therapy, medication management, and psychotherapy/counseling. At one healthcare system, 68% of patients at an ICU aftercare and recovery clinic (A&R), a term we introduce to describe post-ICU clinics and similar activities, required targeted care not otherwise being provided—especially physical therapy, psychotherapy, and nutrition services (81). The range of common needs in the early discharge period are displayed in Figure 2. Especially important is

**Table 1.** Examples of interventions studied or proposed to ameliorate aspects of post-intensive care syndrome

Intervention	Time Frame		
	In the Hospital	Early after Discharge	Late after Discharge
Physical	Physical therapy and mobilization interventions (59, 68, 71, 73, 77, 119–121), nutrition assessment and treatment (79)	Outpatient physical therapy (63, 74, 75), nutritional supplementation (74), recovery manual (74), home-based rehabilitation (64, 67)	Rehabilitation manual (62), nurse-led clinic/care coordination (76), home-based rehabilitation (64)
Mental and social health	ICU diaries (122–132), early psychological intervention (133), nurse-led preventive psychological intervention (134), open visitation (135), animal-assisted intervention (136)	ICU diary debrief (137, 138), internet-based cognitive behavioral writing therapy for patients and partner (87), rehabilitation manual, occupational (62) rehabilitation (39)	Peer support for patients and families (139, 140)
Cognitive	Cognitive intervention (141)	Cognitive therapy (73), in-home cognitive therapy (67), computerized cognitive rehabilitation (142)	
Care coordination/ care plan	Transfer of elderly ICU patients to geriatric ward (143)	Hospitalist discharge clinic (88), multidisciplinary recovery clinic/center/program (85, 89, 144–146), medication management (84, 144), disease management support (147, 148)	Nurse-led mobile multidisciplinary care coordination (86)

Definition of abbreviation: ICU = intensive care unit.

addressing the risk of polypharmacy, especially overuse of (and failure to discontinue) proton pump inhibitors, antihistamines, corticosteroids, antibiotics, bronchodilators, anticholinergics, antidepressants, hypnotics, opioids, and antipsychotics (82–84).

Early experience with A&R services has suggested some of the limitations in current systems of health care. Experience at a prominent A&R clinic has identified medication reconciliation as a key unmet need and has suggested alternative approaches to integration of rehabilitation activities (85). In a small prospective cohort study of ICU survivors, all participants required at least one pharmacy intervention (e.g., dose adjustment, stopping or starting medications, administration of prophylactics, or monitoring for adverse drug reactions) with the median number of intervention per patient being 4 (IQR, 2–5) (84). Others have observed disorganized care among uncoordinated clinicians as a stumbling block for patients recovering from acute respiratory failure (86). Several innovative multidisciplinary interventions are currently being tested, including a mobile aftercare clinic (86) and early efforts at telehealth aimed at mitigating sequelae of critical illness (87).

Early experience at a Veterans Affairs hospital suggested that decreasing

fragmentation through a hospitalist-run clinic for patients recently discharged from the hospital was associated with decreases in death and hospital readmission; although this was not specific to the ICU, generalizability may be possible (88). Early suggestive evidence from a collaboration of acute care physicians and geriatricians further supports the potential utility of ICU A&R clinics (89). In Germany, a prospective randomized trial examined the impact of structured A&R services on postdischarge outcomes among sepsis survivors (90). A structured primary care intervention did not improve mental health–related quality of life at 6 months after hospital discharge (the prespecified primary endpoint); however, those in the intervention group may have had better physical function and fewer impairments in activities of daily living (91).

Three randomized controlled trials have explored the utility of outpatient ICU A&R clinics specifically. The PRACTICaL trial (A Pragmatic Randomised, Controlled Trial of Intensive Care postdischarge review clinics in improving Longer-term outcomes from critical illness) showed no increase in health-related quality of life with a nurse-led clinic in the United Kingdom (76). However, Jones and colleagues

demonstrated benefit to a rehabilitation manual-guided recovery program within the context of an A&R clinic in Liverpool (62). The RECOVER (Evaluation of a Rehabilitation Complex Intervention for patients following Intensive Care Discharge) trial showed that patients randomized to A&R support were more satisfied, but there was no difference across the various outcome measures evaluated (79). Notably, both intervention and control groups received a rehabilitation manual (62), which may have blunted the difference between control and intervention groups. A nurse-led intervention to improve psychological health through narrative construction (i.e., cocreating a meaningful story about the ICU admission) administered in conjunction with follow-up visits showed no benefit in its primary outcomes of health-related quality of life, sense of coherence, depression, or anxiety (92). Of note, these investigational A&R clinic models were generally associated with visits more than 3 months after hospital discharge, well after a relevant window of vulnerability.

A recent Cochrane review of five studies examining the impact of ICU A&R clinics suggested insufficient evidence to determine whether ICU A&R clinics were effective in identifying

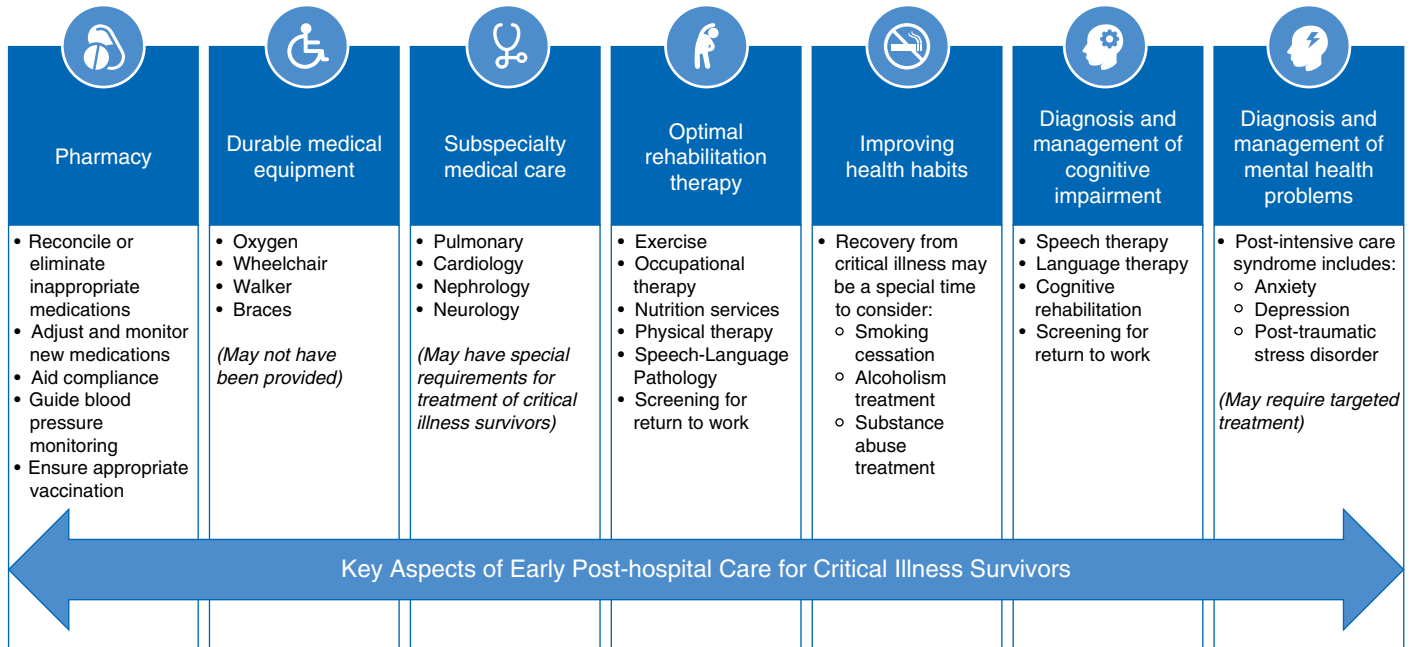


Figure 2. Key aspects of early post-hospital care for critical illness survivors.

and addressing new impairments across multiple domains of recovery (93). Whether support and coordination applied much earlier in the postdischarge course would be efficacious is not yet known. How best to staff such clinics is also unknown. Some advocate routine integration into primary care clinics (94), whereas others advocate for the presence of ICU clinicians in the design and staffing of clinics (95). Physical medicine and rehabilitation clinicians historically provide care for stroke survivors and others who have moved through inpatient rehabilitation. No comparative, quantitative data exist on the question, although patient and family identification with ICU clinicians, the analogy to surgical follow-up clinics, and some prospect of decreasing ICU clinician burnout favor, in our view, involving ICU clinicians (95). Whatever the conclusion, a multidisciplinary structure, with consultation as needed, seems prudent and is currently the most frequently encountered model for these clinics (personal communication, December 2018, Society of Critical Care Medicine THRIVE Post ICU Clinic Collaborative).

Despite the relative lack of firm efficacy data, the academic societies and many healthcare systems have supported

A&R clinics. The Society of Critical Care Medicine (SCCM) has prioritized innovation and development of A&R services, including clinics and peer support programs. After establishment of the THRIVE Task Force, dedicated to improving care for ICU survivors and their families, two learning collaboratives within THRIVE have exemplified the high interest in evaluating feasibility and effectiveness of ICU aftercare interventions. The two collaboratives are comprised of nearly 50 unique centers in the United States and abroad. Initial work includes surveying current models of peer support in use around the world and early infrastructure building to test innovative models of ICU aftercare in multidisciplinary outpatient clinics (96, 97). The Collaborative Assessment of ICU Recovery Needs study (NCT03513289), funded by SCCM, is the largest qualitative study of ICU survivors, carers, and clinicians to date, and it will serve as a signpost to the testing of promising ideas that patients and families suggest may work to optimize recovery after critical illness (98). The other academic societies have not undertaken similar activities; no current relevant society guidelines exist.

### Possible Analogous Evidence from Oncology

In cancer care, survivorship clinics have become common. Survivor clinics have been suggested to provide incremental benefit over usual follow-up care, and attendance has been associated with decreased healthcare use (99, 100). Although the evidence base continues to evolve, the field is clinically well established and received (101, 102). Although cancer survivors are distinct from survivors of critical illness, they bear similar burdens of postacute morbidity across multiple domains (103). Whether the benefits seen with cancer survivor clinics could be realized among ICU survivors through a similarly multidisciplinary outpatient approach remains unclear.

### Early Postdischarge Interventions Work in Patients with Congestive Heart Failure

In congestive heart failure, coordinated A&R activities, such as structured telephone support, home visits, daily weights, educational materials, review of discharge plans, and related interventions, have improved readmission rates (104, 105). Because

heart failure is a reasonably coherent disease with protocol-driven treatments, these observations may not be fully generalizable to ICU survivors, who represent a heterogeneous group with largely syndromic presentations. Whether the specific techniques used in congestive heart failure will be relevant for ICU survivors is not known. To date, though, case management strategies appear to be among the most promising options, at least for improvement in healthcare use and readmission.

Parallels between patients with heart failure and sepsis survivors—suggested by inclusion of sepsis aftercare in the Centers for Medicare & Medicaid Services bundled payment care initiative—may exist. These concepts are part of the broader approach to postacute therapy that is tied to the specific needs and impairments of hospital survivors. It remains to be seen whether strategies motivated by the bundled payment care initiative and related programs are successful in improving patient-centered outcomes among sepsis survivors.

## Predictive Modeling and Personalization

One key void in the literature is a careful map of the needs of ICU survivors. Understanding the interface between individual patients and the healthcare system is a crucial next step. What services do patients require? Which specialists do they see? What needs remain unmet in the current healthcare environment? Do distinct groups of patients have distinct patterns of unmet needs and adverse outcomes after hospitalization? Despite the accumulation of data documenting extensive functional impairments after an ICU stay, the specific prevention and treatment needs of individuals with PICS spectrum conditions are not well defined.

As with much of critical illness, patient selection is almost certainly central to efficacy. Not only will some conditions (or some aspects of conditions) be unresponsive to treatment, but also patients will vary in their proportion of treatable conditions, and the etiology of each may

influence response to interventions. Although severity of acute illness and hospital-based physiology are strongly associated with hospital mortality (as exemplified by the myriad predictive models for ICU mortality), it is unclear which factors specifically drive postdischarge mortality and readmission among, for example, ARDS or sepsis survivors. One large predictive model identified preexisting chronic illness features as most predictive but had relatively poor discrimination for predicting 90-day unplanned readmission (106). In general, typical severity-of-illness scores and critical illness attributes are not strongly or consistently associated with functional outcomes in the months after hospital discharge (106, 107). Existing studies have identified possible associations between a few clinical predictors and individual outcomes (25, 33), including psychological outcomes (35, 108–113). Early work on phenotyping ARDS suggests a septic/inflammatory phenotype and a less inflammatory phenotype (114). Although that phenotype may affect response to ventilation with higher positive end-expiratory pressure and is associated with higher mortality, whether such phenotypes of acute inflammation map onto different postdischarge trajectories is not known (115). Distinct clusters with different clinical outcomes have similarly been identified among patients with severe sepsis or septic shock (116). Whether patients in such clusters have distinct postdischarge needs is unknown, nor is it known whether, for example, various causes of ARDS (e.g., trauma vs. pneumonia vs. pancreatitis) put patients at differential risk for PICS-related outcomes.

These realities emphasize the importance of methods to improve applications of interventions, including how best to select or enrich patient referrals to an A&R clinic. In the absence of reliable predictive models, many clinics have employed convenience definitions, including shock, respiratory failure requiring mechanical ventilation (especially if  $\geq 48$  h), and delirium (85, 117). Others use the presence of sepsis, prolonged ICU stay, receipt of extracorporeal membrane oxygenation, new organ failure, or the presence of tracheostomy or feeding tube at ICU

discharge to prompt ICU A&R referral (personal communication, December 2018, SCCM THRIVE Post-ICU Clinic Collaborative).

Finally, seamless care integration appears to be a key factor in ensuring optimal continuum of care for survivors of critical illness. With growing ICU survivorship and increasing burden of PICS, it is imperative to integrate post-acute care services targeting residual impairments into the discharge process. It is anticipated that this strategy may not only aid postdischarge recovery but also optimize resource use at a time when bundled episode-based care is becoming increasingly influential.

## Conclusions

Survivors of critical illness experience impairments across multiple domains that may persist long after their index episode of illness. The critical care community has labeled this phenomenon “PICS” to draw attention to a range of important problems confronting survivors and their families. Multiple interventions have been attempted to ameliorate PICS-related impairments. There is no “silver bullet” for a problem as complex and multifaceted as the spectrum of impairments frequently encountered within PICS. Observations regarding the lack of “steady, intimate” (118) care in contemporary medicine in general and congestive heart failure interventions in particular suggest that A&R activities may help address unmet discharge needs among ICU survivors. This aspect of post-ICU care remains poorly understood and therefore represents a research priority. A multicenter prospective cohort study (APICS-01 [Addressing Post-Intensive Care Syndrome]; [www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier NCT03738774) is currently underway to systematically examine the impact of care fragmentation on readmission and survival among survivors of acute respiratory failure, which is one of the major causes of PICS. ■

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## References

- Zimmerman JE, Kramer AA, Knaus WA. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. *Crit Care* 2013;17:R81.
- Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, *et al.* Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med* 2012;40:502–509.
- Elliott D, Davidson JE, Harvey MA, Bemis-Dougherty A, Hopkins RO, Iwashyna TJ, *et al.* Exploring the scope of post-intensive care syndrome therapy and care: engagement of non-critical care providers and survivors in a second stakeholders meeting. *Crit Care Med* 2014;42:2518–2526.
- ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–2533.
- Rubinfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, *et al.* Incidence and outcomes of acute lung injury. *N Engl J Med* 2005;353:1685–1693.
- Prescott HC. Preventing chronic critical illness and rehospitalization: a focus on sepsis. *Crit Care Clin* 2018;34:501–513.
- Lieu TA, Au D, Krishnan JA, Moss M, Selker H, Harabin A, *et al.*; Comparative Effectiveness Research in Lung Diseases Workshop Panel. Comparative effectiveness research in lung diseases and sleep disorders: recommendations from the National Heart, Lung, and Blood Institute workshop. *Am J Respir Crit Care Med* 2011;184:848–856.
- Spragg RG, Bernard GR, Checkley W, Curtis JR, Gajic O, Guyatt G, *et al.* Beyond mortality: future clinical research in acute lung injury. *Am J Respir Crit Care Med* 2010;181:1121–1127.
- Milbrandt EB, Eldadah B, Nayfield S, Hadley E, Angus DC. Toward an integrated research agenda for critical illness in aging. *Am J Respir Crit Care Med* 2010;182:995–1003.
- Deutschman CS, Ahrens T, Cairns CB, Sessler CN, Parsons PE; Critical Care Societies Collaborative USCLITG Task Force on Critical Care Research. Multisociety Task Force for Critical Care Research: key issues and recommendations. *Crit Care Med* 2012;40:254–260.
- Angus DC, Carlet J; 2002 Brussels Roundtable Participants. Surviving intensive care: a report from the 2002 Brussels Roundtable. *Intensive Care Med* 2003;29:368–377.
- Iwashyna TJ. Survivorship will be the defining challenge of critical care in the 21st century. *Ann Intern Med* 2010;153:204–205.
- Dowdy DW, Eid MP, Dennison CR, Mendez-Tellez PA, Herridge MS, Guallar E, *et al.* Quality of life after acute respiratory distress syndrome: a meta-analysis. *Intensive Care Med* 2006;32:1115–1124.
- Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, *et al.*; Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:683–693.
- Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-LOHR V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;160:50–56.
- Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2005;171:340–347.
- Heyland DK, Groll D, Caesar M. Survivors of acute respiratory distress syndrome: relationship between pulmonary dysfunction and long-term health-related quality of life. *Crit Care Med* 2005;33:1549–1556.
- Cheung AM, Tansey CM, Tomlinson G, Diaz-Granados N, Matté A, Barr A, *et al.* Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006;174:538–544.
- Hopkins RO, Weaver LK, Chan KJ, Orme JF Jr. Quality of life, emotional, and cognitive function following acute respiratory distress syndrome. *J Int Neuropsychol Soc* 2004;10:1005–1017.
- Hopkins RO, Herridge MS. Quality of life, emotional abnormalities, and cognitive dysfunction in survivors of acute lung injury/acute respiratory distress syndrome. *Clin Chest Med* 2006;27:679–689.
- Schelling G, Stoll C, Vogelmeier C, Hummel T, Behr J, Kapfhammer HP, *et al.* Pulmonary function and health-related quality of life in a sample of long-term survivors of the acute respiratory distress syndrome. *Intensive Care Med* 2000;26:1304–1311.
- Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, *et al.*; BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–1316.
- Needham DM, Dinglas VD, Bienvenu OJ, Colantuoni E, Wozniak AW, Rice TW, *et al.*; NIH NHLBI ARDS Network. One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. *BMJ* 2013;346:f1532.
- Needham DM, Dinglas VD, Morris PE, Jackson JC, Hough CL, Mendez-Tellez PA, *et al.*, NIH NHLBI ARDS Network. Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding: EDEN trial follow-up. *Am J Respir Crit Care Med* 2013;188:567–576.
- Bienvenu OJ, Colantuoni E, Mendez-Tellez PA, Dinglas VD, Shanholtz C, Husain N, *et al.* Depressive symptoms and impaired physical function after acute lung injury: a 2-year longitudinal study. *Am J Respir Crit Care Med* 2012;185:517–524.
- Bienvenu OJ, Gellar J, Althouse BM, Colantuoni E, Sricharoenchai T, Mendez-Tellez PA, *et al.* Post-traumatic stress disorder symptoms after acute lung injury: a 2-year prospective longitudinal study. *Psychol Med* 2013;43:2657–2671.
- Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010;304:1787–1794.
- Hughes CG, Patel MB, Jackson JC, Girard TD, Geervarghese SK, Norman BC, *et al.*; MIND-ICU, BRAIN-ICU investigators. Surgery and anesthesia exposure is not a risk factor for cognitive impairment after major noncardiac surgery and critical illness. *Ann Surg* 2017;265:1126–1133.
- Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, Shanholtz C, *et al.* Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med* 2014;42:849–859.
- Dinglas VD, Aronson Friedman L, Colantuoni E, Mendez-Tellez PA, Shanholtz CB, Ciesla ND, *et al.* Muscle weakness and 5-year survival in acute respiratory distress syndrome survivors. *Crit Care Med* 2017;45:446–453.
- Brück E, Schandl A, Bottai M, Sackey P. The impact of sepsis, delirium, and psychological distress on self-rated cognitive function in ICU survivors—a prospective cohort study. *J Intensive Care* 2018;6:2.
- Duggan MC, Wang L, Wilson JE, Dittus RS, Ely EW, Jackson JC. The relationship between executive dysfunction, depression, and mental health-related quality of life in survivors of critical illness: results from the BRAIN-ICU investigation. *J Crit Care* 2017;37:72–79.
- Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, *et al.* The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med* 2012;185:1307–1315.
- Mikkelsen ME, Shull WH, Biester RC, Taichman DB, Lynch S, Demissie E, *et al.* Cognitive, mood and quality of life impairments in a select population of ARDS survivors. *Respirology* 2009;14:76–82.
- Hopkins RO, Key CW, Suchyta MR, Weaver LK, Orme JF Jr. Risk factors for depression and anxiety in survivors of acute respiratory distress syndrome. *Gen Hosp Psychiatry* 2010;32:147–155.
- Hopkins RO, Suchyta MR, Kamdar BB, Darowski E, Jackson JC, Needham DM. Instrumental activities of daily living after critical illness: a systematic review. *Ann Am Thorac Soc* 2017;14:1332–1343.
- Marti J, Hall P, Hamilton P, Lamb S, McCabe C, Lall R, *et al.* One-year resource utilisation, costs and quality of life in patients with acute respiratory distress syndrome (ARDS): secondary analysis of a randomised controlled trial. *J Intensive Care* 2016;4:56.
- Ruhl AP, Huang M, Colantuoni E, Karmarkar T, Dinglas VD, Hopkins RO, *et al.*; with the National Institutes of Health, National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. Healthcare utilization and costs in ARDS survivors: a 1-year

- longitudinal national US multicenter study. *Intensive Care Med* 2017; 43:980–991.
- 39 Kamdar BB, Sepulveda KA, Chong A, Lord RK, Dinglas VD, Mendez-Tellez PA, *et al.* Return to work and lost earnings after acute respiratory distress syndrome: a 5-year prospective, longitudinal study of long-term survivors. *Thorax* 2018;73:125–133.
  - 40 Robles AJ, Kornblith LZ, Hendrickson CM, Howard BM, Conroy AS, Moazed F, *et al.* Health care utilization and the cost of posttraumatic acute respiratory distress syndrome care. *J Trauma Acute Care Surg* 2018;85:148–154.
  - 41 Pfoh ER, Wozniak AW, Colantuoni E, Dinglas VD, Mendez-Tellez PA, Shanholtz C, *et al.* Physical declines occurring after hospital discharge in ARDS survivors: a 5-year longitudinal study. *Intensive Care Med* 2016;42:1557–1566.
  - 42 Lone NI, Gillies MA, Haddow C, Dobbie R, Rowan KM, Wild SH, *et al.* Five-year mortality and hospital costs associated with surviving intensive care. *Am J Respir Crit Care Med* 2016;194:198–208.
  - 43 Prescott HC, Langa KM, Liu V, Escobar GJ, Iwashyna TJ. Increased 1-year healthcare use in survivors of severe sepsis. *Am J Respir Crit Care Med* 2014;190:62–69.
  - 44 Prescott HC, Langa KM, Iwashyna TJ. Readmission diagnoses after hospitalization for severe sepsis and other acute medical conditions. *JAMA* 2015;313:1055–1057.
  - 45 Liu V, Lei X, Prescott HC, Kipnis P, Iwashyna TJ, Escobar GJ. Hospital readmission and healthcare utilization following sepsis in community settings. *J Hosp Med* 2014;9:502–507.
  - 46 Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, *et al.*; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364:1293–1304.
  - 47 Needham DM, Dowdy DW, Mendez-Tellez PA, Herridge MS, Pronovost PJ. Studying outcomes of intensive care unit survivors: measuring exposures and outcomes. *Intensive Care Med* 2005;31:1153–1160.
  - 48 Ruhl AP, Huang M, Colantuoni E, Lord RK, Dinglas VD, Chong A, *et al.* Healthcare resource use and costs in long-term survivors of acute respiratory distress syndrome: a 5-year longitudinal cohort study. *Crit Care Med* 2017;45:196–204.
  - 49 Ruhl AP, Lord RK, Panek JA, Colantuoni E, Sepulveda KA, Chong A, *et al.* Health care resource use and costs of two-year survivors of acute lung injury. An observational cohort study. *Ann Am Thorac Soc* 2015;12:392–401.
  - 50 Norman BC, Jackson JC, Graves JA, Girard TD, Pandharipande PP, Brummel NE, *et al.* employment outcomes after critical illness: an analysis of the Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors cohort. *Crit Care Med* 2016;44:2003–2009.
  - 51 Kamdar BB, Huang M, Dinglas VD, Colantuoni E, von Wachter TM, Hopkins RO, *et al.*; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. Joblessness and lost earnings after acute respiratory distress syndrome in a 1-year national multicenter study. *Am J Respir Crit Care Med* 2017;196:1012–1020.
  - 52 Walker W, Wright J, Danjoux G, Howell SJ, Martin D, Bonner S. Project Post Intensive Care eXercise (PIX): a qualitative exploration of intensive care unit survivors' perceptions of quality of life post-discharge and experience of exercise rehabilitation. *J Intensive Care Soc* 2015;16:37–44.
  - 53 Lee CM, Herridge MS, Matte A, Cameron JI. Education and support needs during recovery in acute respiratory distress syndrome survivors. *Crit Care* 2009;13:R153.
  - 54 Dinglas VD, Hopkins RO, Wozniak AW, Hough CL, Morris PE, Jackson JC, *et al.* One-year outcomes of rosuvastatin versus placebo in sepsis-associated acute respiratory distress syndrome: prospective follow-up of SAILS randomised trial. *Thorax* 2016;71:401–410.
  - 55 Needham DM, Colantuoni E, Dinglas VD, Hough CL, Wozniak AW, Jackson JC, *et al.* Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial. *Lancet Respir Med* 2016;4:203–212.
  - 56 Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, *et al.*; MIND-USA Investigators. Haloperidol and ziprasidone for treatment of delirium in critical illness. *N Engl J Med* 2018;379:2506–2516.
  - 57 Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, *et al.* Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;371:126–134.
  - 58 Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000;342:1471–1477.
  - 59 Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, *et al.* Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373:1874–1882.
  - 60 Sjoding MW, Schoenfeld DA, Brown SM, Hough CL, Yealy DM, Moss M, *et al.*; NHLBI Prevention and Early Treatment of Acute Lung Injury (PETAL) Network. Power calculations to select instruments for clinical trial secondary endpoints: a case study of instrument selection for post-traumatic stress symptoms in subjects with acute respiratory distress syndrome. *Ann Am Thorac Soc* 2017;14:110–117.
  - 61 Moss M, Huang DT, Brower RG, Ferguson ND, Ginde AA, Gong MN, *et al.* Early neuromuscular blockade in the acute respiratory distress syndrome. *N Engl J Med* 2019;380:1997–2008.
  - 62 Jones C, Skirrow P, Griffiths RD, Humphris GH, Ingleby S, Eddleston J, *et al.* Rehabilitation after critical illness: a randomized, controlled trial. *Crit Care Med* 2003;31:2456–2461.
  - 63 Denehy L, Skinner EH, Edbrooke L, Haines K, Warrillow S, Hawthorne G, *et al.* Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. *Crit Care* 2013;17:R156.
  - 64 Elliott D, McKinley S, Alison J, Aitken LM, King M, Leslie GD, *et al.* Health-related quality of life and physical recovery after a critical illness: a multi-centre randomised controlled trial of a home-based physical rehabilitation program. *Crit Care* 2011;15:R142.
  - 65 Herridge MS. The challenge of designing a post-critical illness rehabilitation intervention. *Crit Care* 2011;15:1002.
  - 66 Brummel NE, Jackson JC, Girard TD, Pandharipande PP, Schiro E, Work B, *et al.* A combined early cognitive and physical rehabilitation program for people who are critically ill: the Activity and Cognitive Therapy in the Intensive Care Unit (ACT-ICU) trial. *Phys Ther* 2012; 92:1580–1592.
  - 67 Jackson JC, Ely EW, Morey MC, Anderson VM, Denne LB, Clune J, *et al.* Cognitive and physical rehabilitation of intensive care unit survivors: results of the RETURN randomized controlled pilot investigation. *Crit Care Med* 2012;40:1088–1097.
  - 68 Morris PE, Berry MJ, Files DC, Thompson JC, Hauser J, Flores L, *et al.* Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: a randomized clinical trial. *JAMA* 2016;315:2694–2702.
  - 69 Moss M, Nordon-Craft A, Malone D, Van Pelt D, Frankel SK, Warner ML, *et al.* A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. *Am J Respir Crit Care Med* 2016;193:1101–1110.
  - 70 Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, *et al.* Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008;36:2238–2243.
  - 71 Hodgson CL, Bailey M, Bellomo R, Berney S, Buhr H, Denehy L, *et al.*; Trial of Early Activity and Mobilization Study Investigators. A binational multicenter pilot feasibility randomized controlled trial of early goal-directed mobilization in the ICU. *Crit Care Med* 2016;44:1145–1152.
  - 72 Schaller SJ, Anstey M, Blobner M, Edrich T, Grabitz SD, Gradwohl-Matis I, *et al.*; International Early SOMS-guided Mobilization Research Initiative. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. *Lancet* 2016;388:1377–1388.
  - 73 Brummel NE, Girard TD, Ely EW, Pandharipande PP, Morandi A, Hughes CG, *et al.* Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the

- Activity and Cognitive Therapy in ICU (ACT-ICU) trial. *Intensive Care Med* 2014;40:370–379.
- 74 Jones C, Eddleston J, McCairn A, Dowling S, McWilliams D, Coughlan E, *et al.* Improving rehabilitation after critical illness through outpatient physiotherapy classes and essential amino acid supplement: a randomized controlled trial. *J Crit Care* 2015;30: 901–907.
  - 75 McWilliams DJ, Atkinson D, Carter A, Foëx BA, Benington S, Conway DH. Feasibility and impact of a structured, exercise-based rehabilitation programme for intensive care survivors. *Physiother Theory Pract* 2009;25:566–571.
  - 76 Cuthbertson BH, Rattray J, Campbell MK, Gager M, Roughton S, Smith A, *et al.*; PRaCTiCaL study group. The PRaCTiCaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. *BMJ* 2009;339:b3723.
  - 77 Tipping CJ, Harrold M, Holland A, Romero L, Nisbet T, Hodgson CL. The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review. *Intensive Care Med* 2017;43:171–183.
  - 78 Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, *et al.* Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018;46:e825–e873.
  - 79 Walsh TS, Salisbury LG, Merriweather JL, Boyd JA, Griffith DM, Huby G, *et al.*; RECOVER Investigators. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: the RECOVER randomized clinical trial. *JAMA Intern Med* 2015;175:901–910.
  - 80 Arabi YM, Casaer MP, Chapman M, Heyland DK, Ichai C, Marik PE, *et al.* The intensive care medicine research agenda in nutrition and metabolism. *Intensive Care Med* 2017;43:1239–1256.
  - 81 Dettling-Ihnenfeldt DS, De Graaff AE, Nollet F, Van Der Schaaf M. Feasibility of post-intensive care unit clinics: an observational cohort study of two different approaches. *Minerva Anesthesiol* 2015;81: 865–875.
  - 82 Morandi A, Vasilevskis E, Pandharipande PP, Girard TD, Solberg LM, Neal EB, *et al.* Inappropriate medication prescriptions in elderly adults surviving an intensive care unit hospitalization. *J Am Geriatr Soc* 2013;61:1128–1134.
  - 83 Johnson KG, Fashoyin A, Madden-Fuentes R, Muzyk AJ, Gagliardi JP, Yanamadala M. Discharge plans for geriatric inpatients with delirium: a plan to stop antipsychotics? *J Am Geriatr Soc* 2017;65:2278–2281.
  - 84 Stollings JL, Bloom SL, Wang L, Ely EW, Jackson JC, Sevin CM. Critical care pharmacists and medication management in an ICU recovery center. *Ann Pharmacother* 2018;52:713–723.
  - 85 Sevin CM, Bloom SL, Jackson JC, Wang L, Ely EW, Stollings JL. Comprehensive care of ICU survivors: development and implementation of an ICU recovery center. *J Crit Care* 2018;46: 141–148.
  - 86 Khan S, Biju A, Wang S, Gao S, Irfan O, Harrawood A, *et al.* Mobile critical care recovery program (m-CCRP) for acute respiratory failure survivors: study protocol for a randomized controlled trial. *Trials* 2018;19:94.
  - 87 Gawlytta R, Niemeyer H, Böttche M, Scherag A, Knaevelsrud C, Rosendahl J. Internet-based cognitive-behavioural writing therapy for reducing post-traumatic stress after intensive care for sepsis in patients and their spouses (REPAIR): study protocol for a randomised-controlled trial. *BMJ Open* 2017;7: e014363.
  - 88 Burke RE, Whitfield E, Prochazka AV. Effect of a hospitalist-run postdischarge clinic on outcomes. *J Hosp Med* 2014;9:7–12.
  - 89 Khan BA, Lasiter S, Boustani MA. CE: critical care recovery center: an innovative collaborative care model for ICU survivors. *Am J Nurs* 2015;115:24–31; quiz 34, 46.
  - 90 Schmidt K, Thiel P, Mueller F, Schmuecker K, Worrack S, Mehlhorn J, *et al.*; Smooth Study Group. Sepsis Survivors Monitoring and Coordination in Outpatient Health Care (SMOOTH): study protocol for a randomized controlled trial. *Trials* 2014;15:283.
  - 91 Schmidt K, Worrack S, Von Korff M, Davydow D, Brunkhorst F, Ehlert U, *et al.*; SMOOTH Study Group. Effect of a primary care management intervention on mental health-related quality of life among survivors of sepsis: a randomized clinical trial. *JAMA* 2016; 315:2703–2711.
  - 92 Jensen JF, Egerod I, Bestle MH, Christensen DF, Elklit A, Hansen RL, *et al.* A recovery program to improve quality of life, sense of coherence and psychological health in ICU survivors: a multicenter randomized controlled trial, the RAPIT study. *Intensive Care Med* 2016;42:1733–1743.
  - 93 Schofield-Robinson OJ, Lewis SR, Smith AF, McPeake J, Alderson P. Follow-up services for improving long-term outcomes in intensive care unit (ICU) survivors. *Cochrane Database Syst Rev* 2018;11: CD012701.
  - 94 Vijayaraghavan BKT, Willaert X, Cuthbertson BH. Should ICU clinicians follow patients after ICU discharge? No. *Intensive Care Med* 2018; 44:1542–1544.
  - 95 Sevin CM, Jackson JC. Post-ICU clinics should be staffed by ICU clinicians. *Crit Care Med* 2019;47:268–272.
  - 96 McPeake J, Hirschberg EL, Christie LM, Drumright K, Haines K, Hough CL, *et al.* Models of peer support to remediate post-intensive care syndrome: a report developed by the Society of Critical Care Medicine Thrive International Peer Support Collaborative. *Crit Care Med* 2019;47:e21–e27.
  - 97 Kuehn BM. Clinicians aim to improve post-ICU recovery. *JAMA* 2019;321: 1036–1038.
  - 98 Haines K, McPeake J, Hibbert E, Boehm L, Iwashyna TJ, Sevin CM. Barriers and facilitators to implementing ICU follow-up clinics and peer support groups [abstract]. *Crit Care Med* 2019;47(1 Suppl):399.
  - 99 Staba Hogan MJ, Ma X, Kadan-Lottick NS. New health conditions identified at a regional childhood cancer survivor clinic visit. *Pediatr Blood Cancer* 2013;60:682–687.
  - 100 Sutradhar R, Agha M, Pole JD, Greenberg M, Guttman A, Hodgson D, *et al.* Specialized survivor clinic attendance is associated with decreased rates of emergency department visits in adult survivors of childhood cancer. *Cancer* 2015;121:4389–4397.
  - 101 McCabe MS, Bhatia S, Oeffinger KC, Reaman GH, Tyne C, Wollins DS, *et al.* American Society of Clinical Oncology statement: achieving high-quality cancer survivorship care. *J Clin Oncol* 2013;31: 631–640.
  - 102 Halpern MT, Viswanathan M, Evans TS, Birken SA, Basch E, Mayer DK. Models of cancer survivorship care: overview and summary of current evidence. *J Oncol Pract* 2015;11:e19–e27.
  - 103 Kline RM, Arora NK, Bradley CJ, Brauer ER, Graves DL, Lunsford NB, *et al.* Long-term survivorship care after cancer treatment – summary of a 2017 National Cancer Policy Forum Workshop. *J Natl Cancer Inst* 2018;110:1300–1310.
  - 104 Krumholz HM, Amatruda J, Smith GL, Mattera JA, Roumanis SA, Radford MJ, *et al.* Randomized trial of an education and support intervention to prevent readmission of patients with heart failure. *J Am Coll Cardiol* 2002;39:83–89.
  - 105 Feltner C, Jones CD, Cené CW, Zheng ZJ, Sueta CA, Coker-Schwimmer EJJ, *et al.* Transitional care interventions to prevent readmissions for people with heart failure [Internet]. Rockville, MD: Agency for Healthcare Research and Quality; 2014. Comparative Effectiveness Reviews, No. 133.
  - 106 Lone NI, Lee R, Salisbury L, Donaghy E, Ramsay P, Rattray J, *et al.* Predicting risk of unplanned hospital readmission in survivors of critical illness: a population-level cohort study. *Thorax* [online ahead of print] 5 Apr 2018; DOI: 10.1136/thoraxjnl-2017-210822.
  - 107 Brown SM, Wilson E, Presson AP, Zhang C, Dinglas VD, Greene T, *et al.*; with the National Institutes of Health NHLBI ARDS Network. Predictors of 6-month health utility outcomes in survivors of acute respiratory distress syndrome. *Thorax* 2017;72:311–317.
  - 108 Adhikari NKJ, Tansey CM, McAndrews MP, Matté A, Pinto R, Cheung AM, *et al.* Self-reported depressive symptoms and memory complaints in survivors five years after ARDS. *Chest* 2011;140: 1484–1493.
  - 109 Stevenson JE, Colantuoni E, Bienvenu OJ, Sricharoenchai T, Wozniak A, Shanholtz C, *et al.* General anxiety symptoms after acute lung

- injury: predictors and correlates. *J Psychosom Res* 2013;75:287–293.
- 110 Chelluri L, Im KA, Belle SH, Schulz R, Rotondi AJ, Donahoe MP, *et al*. Long-term mortality and quality of life after prolonged mechanical ventilation. *Crit Care Med* 2004;32:61–69.
- 111 Rattray JE, Johnston M, Wildsmith JA. Predictors of emotional outcomes of intensive care. *Anaesthesia* 2005;60:1085–1092.
- 112 Adhikari NKJ, McAndrews MP, Tansey CM, Matté A, Pinto R, Cheung AM, *et al*. Self-reported symptoms of depression and memory dysfunction in survivors of ARDS. *Chest* 2009;135:678–687.
- 113 Milton A, Schandl A, Soliman IW, Meijers K, van den Boogaard M, Larsson IM, *et al*. Development of an ICU discharge instrument predicting psychological morbidity: a multinational study. *Intensive Care Med* 2018;44:2038–2047.
- 114 Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA; NHLBI ARDS Network. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014;2:611–620.
- 115 Prescott HC, Calfee CS, Thompson BT, Angus DC, Liu VX. Toward smarter lumping and smarter splitting: rethinking strategies for sepsis and acute respiratory distress syndrome clinical trial design. *Am J Respir Crit Care Med* 2016;194:147–155.
- 116 Knox DB, Lanspa MJ, Kuttler KG, Brewer SC, Brown SM. Phenotypic clusters within sepsis-associated multiple organ dysfunction syndrome. *Intensive Care Med* 2015;41:814–822.
- 117 Wang S, Hammes J, Khan S, Gao S, Harrawood A, Martinez S, *et al*. Improving Recovery and Outcomes Every Day after the ICU (IMPROVE): study protocol for a randomized controlled trial. *Trials* 2018;19:196.
- 118 Gawande A. Tell me where it hurts. *The New Yorker* 2017 January 23; 36–45.
- 119 Kayambu G, Boots R, Paratz J. Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. *Intensive Care Med* 2015;41:865–874.
- 120 Chigira Y, Takai T, Igusa H, Dobashi K. Effects of early physiotherapy with respect to severity of pneumonia of elderly patients admitted to an intensive care unit: a single center study in Japan. *J Phys Ther Sci* 2015;27:2053–2056.
- 121 Berney S, Haines K, Skinner EH, Denehy L. Safety and feasibility of an exercise prescription approach to rehabilitation across the continuum of care for survivors of critical illness. *Phys Ther* 2012;92:1524–1535.
- 122 Jones C, Bäckman C, Griffiths RD. Intensive care diaries and relatives' symptoms of posttraumatic stress disorder after critical illness: a pilot study. *Am J Crit Care* 2012;21:172–176.
- 123 Egerod I, Christensen D, Schwartz-Nielsen KH, Agård AS. Constructing the illness narrative: a grounded theory exploring patients' and relatives' use of intensive care diaries. *Crit Care Med* 2011;39:1922–1928.
- 124 Jones C, Bäckman C, Capuzzo M, Egerod I, Flaatten H, Granja C, *et al*.; RACHEL group. Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial. *Crit Care* 2010;14:R168.
- 125 Egerod I, Christensen D. A comparative study of ICU patient diaries vs. hospital charts. *Qual Health Res* 2010;20:1446–1456.
- 126 Akerman E, Granberg-Axéll A, Ersson A, Fridlund B, Bergbom I. Use and practice of patient diaries in Swedish intensive care units: a national survey. *Nurs Crit Care* 2010;15:26–33.
- 127 Engström A, Grip K, Hamrén M. Experiences of intensive care unit diaries: 'touching a tender wound'. *Nurs Crit Care* 2009;14:61–67.
- 128 Egerod I, Christensen D. Analysis of patient diaries in Danish ICUs: a narrative approach. *Intensive Crit Care Nurs* 2009;25:268–277.
- 129 Garrouste-Orgeas M, Flahault C, Fasse L, Ruckly S, Amdjar-Badidi N, Argaud L, *et al*. The ICU-Diary study: prospective, multicenter comparative study of the impact of an ICU diary on the wellbeing of patients and families in French ICUs. *Trials* 2017;18:542.
- 130 Locke M, Eccleston S, Ryan CN, Byrnes TJ, Mount C, McCarthy MS. Developing a diary program to minimize patient and family post-intensive care syndrome. *AACN Adv Crit Care* 2016;27:212–220.
- 131 Levine SA, Reilly KM, Nedder MM, Avery KR. The patient's perspective of the intensive care unit diary in the cardiac intensive care unit. *Crit Care Nurse* 2018;38:28–36.
- 132 McIlroy PA, King RS, Garrouste-Orgeas M, Tabah A, Ramanan M. The effect of ICU diaries on psychological outcomes and quality of life of survivors of critical illness and their relatives: a systematic review and meta-analysis. *Crit Care Med* 2019;47:273–279.
- 133 Peris A, Bonizzoli M, Iozzelli D, Migliaccio ML, Zagli G, Bacchereti A, *et al*. Early intra-intensive care unit psychological intervention promotes recovery from post traumatic stress disorders, anxiety and depression symptoms in critically ill patients. *Crit Care* 2011;15:R41.
- 134 Richards-Belle A, Mouncey PR, Wade D, Brewin CR, Emerson LM, Grieve R, *et al*.; POPPI Trial Investigators. Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients (POPPI): protocol for a cluster-randomised clinical trial of a complex intervention. *BMJ Open* 2018;8:e020908.
- 135 Chapman DK, Collingridge DS, Mitchell LA, Wright ES, Hopkins RO, Butler JM, *et al*. Satisfaction with elimination of all visitation restrictions in a mixed-profile intensive care unit. *Am J Crit Care* 2016;25:46–50.
- 136 Hosey MM, Jaskulski J, Wegener ST, Chlan LL, Needham DM. Animal-assisted intervention in the ICU: a tool for humanization. *Crit Care* 2018;22:22.
- 137 Bäckman CG, Walther SM. Use of a personal diary written on the ICU during critical illness. *Intensive Care Med* 2001;27:426–429.
- 138 Combe D. The use of patient diaries in an intensive care unit. *Nurs Crit Care* 2005;10:31–34.
- 139 Mikkelsen ME, Jackson JC, Hopkins RO, Thompson C, Andrews A, Netzer G, *et al*. Peer support as a novel strategy to mitigate post-intensive care syndrome. *AACN Adv Crit Care* 2016;27:221–229.
- 140 Haines KJ, Beesley SJ, Hopkins RO, McPeake J, Quasim T, Ritchie K, *et al*. Peer support in critical care: a systematic review. *Crit Care Med* 2018;46:1522–1531.
- 141 Zhao J, Yao L, Wang C, Sun Y, Sun Z. The effects of cognitive intervention on cognitive impairments after intensive care unit admission. *Neuropsychol Rehabil* 2017;27:301–317.
- 142 Wilson JE, Collar EM, Kiehl AL, Lee H, Merzenich M, Ely EW, *et al*. Computerized cognitive rehabilitation in intensive care unit survivors: returning to everyday tasks using rehabilitation networks—computerized cognitive rehabilitation pilot investigation. *Ann Am Thorac Soc* 2018;15:887–891.
- 143 Somme D, Andrieux N, Guérot E, Lahjibi-Paulet H, Lazarovici C, Gisselbrecht M, *et al*. Loss of autonomy among elderly patients after a stay in a medical intensive care unit (ICU): a randomized study of the benefit of transfer to a geriatric ward. *Arch Gerontol Geriatr* 2010; 50:e36–e40.
- 144 Huggins EL, Bloom SL, Stollings JL, Camp M, Sevin CM, Jackson JC. A clinic model: post-intensive care syndrome and post-intensive care syndrome—family. *AACN Adv Crit Care* 2016;27:204–211.
- 145 Schandl A, Bottai M, Hellgren E, Sundin Ö, Sackey P. Gender differences in psychological morbidity and treatment in intensive care survivors – a cohort study. *Crit Care* 2012;16:R80.
- 146 McPeake J, Shaw M, Iwashyna TJ, Daniel M, Devine H, Jarvie L, *et al*. Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE): early evaluation of a complex intervention. *PLoS One* 2017;12:e0188028.
- 147 Daly BJ, Douglas SL, Kelley CG, O'Toole E, Montenegro H. Trial of a disease management program to reduce hospital readmissions of the chronically critically ill. *Chest* 2005;128:507–517.
- 148 Douglas SL, Daly BJ, Kelley CG, O'Toole E, Montenegro H. Chronically critically ill patients: health-related quality of life and resource use after a disease management intervention. *Am J Crit Care* 2007;16:447–457.