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Title: Optimizing post-intensive care unit rehabilitation

Short title: Post-intensive care rehabilitation

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Abstract

Intensive care unit (ICU) survivors face unique challenges after hospital discharge. In addition to an increased overall mortality and rates of hospital readmission, patients often experience difficulties in physical functioning, cognition, and mental health, collectively termed post-intensive care syndrome (PICS). To this date, there are no established strategies to address these deleterious outcomes. A number of studies have examined various unique methods to prevent and treat PICS symptoms, including early physical and occupational therapy, providing post-discharge education, or facilitating routine follow-up in post-ICU clinics. These trials have yet to demonstrate any substantial or meaningful effect in post-ICU patients, and collectively reinforce the need for further research to identify effective intervention for patients that survive critical illness.

Keywords: ICU acquired weakness, critical care, neuromuscular dysfunction, intensive care unit

Introduction

The intensive care unit (ICU) provides life-sustaining treatment to critically ill patients. In the United States alone, just over a quarter of hospital admissions (26.9%) involve ICU care [1]. Due to ever-advancing health care technology, a rising majority of ICU patients survive their hospitalization [2]. Survivors of ICU admission face unique long-term challenges. In addition to increased post-hospitalization mortality and rates of hospital readmission [3], survivors experience problems in multiple aspects of life, including physical functioning, cognition, and mental health. Collectively called post-intensive care syndrome (PICS), these long-term complications impact individual patient health care needs, and increase overall health services utilization [2,4,5]. Unfortunately, the best strategy to improve these negative outcomes has yet to be determined. There have been a number of studies

addressing the role of rehabilitation both in the ICU and after hospital discharge in an attempt to

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improve patient outcomes. This review article will review the fundamentals of PICS, and will summarize efforts at post-ICU rehabilitation, including post-ICU follow-up clinics.

Post-Intensive Care Syndrome

Up to two thirds of survivors of critical illness face long-term problems as a result of their acute illness, the associated therapies, and their pre-existing chronic conditions [6]. These problems include physical, cognitive, and mental impairments that have collectively been termed post-intensive care syndrome (PICS). PICS has widespread consequences after hospital discharge, including difficulty with self-care, decreased quality of life, and difficulty returning to work or social activities, all of which contribute to detrimental long-term health outcomes [7]. [Table 1]

Physically, PICS often manifests as ICU-acquired weakness (ICUAW) that ranges from generalized deconditioning to ICU polyneuromyopathy. Studies indicate that ICUAW is common, with an incidence of up to 25% among critically ill patients, and is associated with increased mortality, decreased ICU-free days, and a need for additional care after discharge [8,9]. As a result of this acquired weakness, ICU survivors may develop difficulties performing activities of daily living, and unfortunately these deficits may persist long after they return to home. A 2003 study (and later-published 5-year follow-up) evaluating the long-term outcomes of 109 survivors of acute respiratory distress syndrome (ARDS) found that patients had persistent exercise limitations and reduced physical quality of life (as measured by 6-minute walk distance and short form (SF)-36 questionnaire) up to 5 years post-ICU discharge [6,10,11]. The 6-minute walk distances were largely limited by weakness and muscle wasting, foot drop, dyspnea, and immobility of large joints [10,11]. Of note, physical deficits are not limited to

neuromuscular weakness; several studies have shown that ICU survivors, specifically those with acute

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lung injury, experience prolonged pulmonary dysfunction that contributes to poorer health-related quality of life. A 2007 study showed that ICU survivors of ARDS or severe acute respiratory syndrome had a reduced carbon monoxide diffusion capacity (DLCO) at 3 and 6 months post-discharge, but typically normalized by 1 year after hospital discharge [6,10,12]. A later 2013 study found that 25% of acute lung injury survivors had abnormal pulmonary function test (PFT) values (defined as <80% of predicted) at 180 days after initial diagnosis [13]. These abnormal values correlated with the presence of abnormalities on chest high resolution computed tomography (HRCT) scans as well as poorer quality of life, as measured by SF-36 and St. George Respiratory Questionnaire (SGRQ) questionnaires. Of note, these relationships were found to be independent of any neuromuscular dysfunction [13].

In addition to physical morbidity, ICU survivors also develop increased rates of psychological disorders, including symptoms of depression, anxiety, and post-traumatic stress disorder (PTSD) [14]. Critical illness exposes patients to immense stressors including respiratory failure, delirium, and pain, all of which can lead to psychological distress [15], and up to 30% and 70% of ICU survivors report symptoms of depression and anxiety, respectively [16]. A 2004 study from Scotland found a 14% rate of PTSD amongst critically ill patients [6,15,17], and a study of patients following in a post-ICU clinic in the United Kingdom (UK) showed that 43.6% of ICU survivors reported sexual dysfunction that was associated with PTSD [6,18].

Finally, patients may develop long-term cognitive deficits after critical illness. These deficits can include problems with executive function, attention, and memory, all of which can affect patient quality of life and ability to return to work [19]. A study of 275 medical ICU survivors found the prevalence of

neurocognitive dysfunction to be 33% at 6 months post-discharge [20], and a more recent prospective

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study of 2929 elderly patients without dementia found that critical illness hospitalization was associated with greater cognitive decline when compared to those that were not hospitalized [19]. Notably, cognitive dysfunction is often not assessed during hospital follow-up. Because mild cognitive dysfunction can be difficult to detect, it is possible that neurocognitive deficits in post-ICU patients are frequently unrecognized and the prevalence is, in fact, higher than reported [6]. These unrecognized deficits, in addition to the above-mentioned psychological and physical deficits, can lead to increased patient morbidity, including economic hardship on patients and their family members [16].

Rehabilitation interventions for PICS: a review of literature

A number of studies have examined both in-hospital and post-discharge interventions to combat PICS morbidity, specifically involving physical therapy (PT). Interestingly, these follow-up studies have yielded conflicting results, potentially as a result of marked variations and inconsistencies in both the interventions utilized and the outcomes measured. [Table 2]

One of the early, and notably positive studies was conducted in 2009 by Schweickert et al [21]. This group assessed whether mechanically ventilated patients who received early physical and occupational therapies while in the ICU experienced increased rates of functional independence at time of hospital discharge. 104 patients from two medical ICUs at University of Chicago and University of Iowa hospitals were randomized to receive early therapy versus standard of care. The patients who received early interventions began therapy on day 1.5 versus 7.4 of their hospitalization, and were found to have better functional outcomes at hospital discharge, decreased duration of delirium, and more ventilator-free days compared with standard care [21]. There was no significant difference in hospital length of stay or hospital mortality.

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The remaining studies have had largely insignificant findings. A 2013 single-center trial in Melbourne, Australia by Denehy et al examined the effectiveness of providing PT as a continuum, providing patients with daily therapy starting at day 5 of ICU admission and progressing to twice-daily outpatient therapy for 8-weeks post-discharge [22]. Amongst 150 patients studied, there was no statistical difference between the intervention and usual care groups in 6-minute walk test (6MWT) or quality of life assessments, as measured by the Health Related Quality of Life (HRQoL) at 12 months post-discharge. Notably, the standard of care in this study involved daily PT with early mobilization practices, such that the control arm received more therapies than typically reported in many other studies. It is possible that there was no difference between the two study arms due to a higher level of baseline therapies provided to the control group.

The 2016 RECOVER trial focused on therapy provided during patients' post-ICU acute hospital stay, and demonstrated similarly insignificant results [23]. Specifically, 240 patients who were discharged to the floor from a single-ICU in Scotland were randomized to receive multimodal therapy (physical, occupation, speech and language, and nutrition) coordinated by a dedicated rehabilitation practitioner, versus usual care. The usual care group still received similar therapies, albeit at a decreased frequency (2-3 fold). The investigators found no difference between the intervention group and usual care groups with regards to mobility, as evaluated by the Rivermead Mobility Index, and no difference in HRQoL, anxiety, depression, or PTSD at 3-months post-discharge. There was a similar trajectory of recovery between the two groups. The only significant finding was an improved score on a patient satisfaction questionnaire. The authors postulated that the negative findings could be related to truncated

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treatment times -- many of the study patients had a relatively short post-ICU hospital stay or were discharged despite significant mobility impairments per current practice standard of care [23].

The 2016 Revive trial examined a multi-modal intervention initiated after hospital discharge [24]. Overall, 60 patients from 6 hospitals in Northern Ireland who had been ventilated for greater than 96 hours were randomized to receive a 6-week home therapy intervention versus standard of care (no additional home support) after discharge. The home intervention involved an individually-tailored therapy program involving two physical therapist-supervised and one unsupervised hour-long exercise session per week, of which most occurred in the hospital gym. At 6-week follow-up, there was no statistical difference in physical functioning, as measured by the SF-36 questionnaire, between the two groups. There was a significant difference in some of the secondary outcomes, including the SF-36 role physical, chronic disease self-efficacy scale, and readiness to change questionnaire.

The 2016 PRaCTICaL trial was a nurse-lead follow up program that assessed an intervention that spanned both in-hospital and post-discharge locations [25]. Overall, 286 patients from three UK hospitals were assigned to a manual based, self-directed rehabilitation program developed by physical therapists, or standard of care. The rehabilitation intervention was initiated in the hospital, and continued for three months after discharge, during which time the patients were formally monitored at nurse-led clinics. The clinic visits allowed for referral to a medical or mental health specialist, or formal physical therapy, when indicated. The study found no difference in health related quality of life, as measured by the SF-36 questionnaire, at 12 months. At 6 and 12 months after discharge, similar percentages of patients had returned to work, and there were not differences in satisfaction rates

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between groups. Of note, the intervention group was significantly more expensive and the follow-up program was not cost effective [25].

Finally, the 2016 Smooth trial evaluated a primary care intervention on mental health outcomes of ICU sepsis survivors from 9 German ICUs [26]. The study involved 291 patients who were randomized to receive post-discharge teaching by a case manager on sepsis sequelae, versus usual care. Following this training, the intervention group was monitoring via serial telephone calls for 12 months for the presence of ongoing symptoms and self-management behaviors (monthly telephone contact for 6 months, followed by every 3 months for 6 additional months). The intervention group's primary care providers also received training on evidence-based post-hospitalization sepsis care. The study found that there was no difference between the groups at 6 months post-discharge in mental health-related quality of life, as measured by the Mental Component Summary Score of the SF-36 survey. Additionally, there were no significant differences in physical HRQoL and other mental health outcomes. The only significant findings were increased measures of functional outcomes in the intervention group – the patients receiving the primary care intervention had better physical functioning and less physical disability as measured by the Extra Short Musculoskeletal Function Assessment XSFMA-F, as well as fewer impairments in their activities of daily living. In summary, rehabilitation and mental health interventions demonstrated rare benefits to post-ICU patients, regardless of the scope or timeframe of the intervention.

Post-ICU clinics

Dedicated post-ICU outpatient clinics are an alternative to the largely therapy-based interventions outlined above. These clinics can include a wide variety of interventions, including recognition and

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treatment of patient comorbidities, medication reconciliation, promotion of financial resources, and functional and psychological rehabilitation [27]. The clinics may also provide resources for family members and caregivers [27]. Of note, there is no standard format to these clinics, and they can include various types of practitioners and follow-up intervals.

Post-ICU clinics have been most notably utilized in the UK. A UK care guideline (NICE CG83) was released in 2009 advocating routine post-ICU care, including a functional assessment 2-3 months after discharge and the addition of rehabilitation assessment for patients with slow recovery or new physical, cognitive, or mental health morbidity [28]. Interestingly, despite these national guidelines, clinic implementation in the UK has remained quite low – a 2013 postal survey found that post-ICU follow-up was offered in only 48 of 182 hospitals (albeit the survey had a response rate of only 76%) [29].

Barriers to post-ICU clinics

Given limited routine ICU clinic implementation despite proven morbidity associated with ICU survival, there must be obstacles that limit prioritization of post-ICU care. Most importantly, there is no proof of concept for ICU-specific follow-up clinics. Despite multiple interventional studies addressing PICS, there have been no findings that show a substantial benefit to post-ICU care. In addition to this, it is unclear what unique features of care ICU survivors need, in comparison to patients hospitalized and discharged from a general hospital ward. ICU survivors and acute care survivors are similar, as both of these patient groups may experience physical, cognitive, mental health, and quality of life impairment related to their hospitalization [3]. However, there are important differences between the two groups that may affect post-discharge needs. In comparison to patients admitted to the general hospital ward, ICU patients have increased severity of illness and often require life support in the form of mechanical ventilation,

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continuous renal replacement therapy, or intravenous medication. These factors likely increase post-discharge needs, although it is unclear what these specific needs may be.

Second, and largely as a result of their lack of concept, is a general lack of funding to support routine implementation of post-ICU clinics. There are no studies demonstrating a direct financial benefit to the clinics, and so there is minimal perceived value for stakeholders to invest in their use. Of note, ICU survivors have a higher rate of 90-day hospital readmissions [3,30]; post-ICU clinics could become cost beneficial if they could prevent readmissions. In patients receiving major surgery (specifically thoracic aortic aneurysm repair), those who had early primary care provider (PCP) follow-up had lower 30-day readmission rates (20.4% vs 25.0%), specifically in patients with complicated hospital courses [31]. Post-discharge care for ICU survivors may too, reduce readmissions, however further studies are needed to confirm this hypothesis and prove any financial benefits.

Another barrier to post-ICU clinics is a shortage of appropriate staff. With little guiding data, it is unclear whom the appropriate providers are to staff a follow-up clinic. There is a severe shortage of intensivists in the United States, and therefore utilizing intensivists in post-ICU clinics when they are arguably more-needed in the ICU can be difficult [6]. Further, while intensivists have first-hand experience in patient care within the ICU, they have not been specifically trained in outpatient continuity care and may not be the best staffing choice. Outpatient primary care providers are an alternative staffing option, however these providers have less experience and training with critically ill patients, and may not be adept at understanding or managing patients post-critical illness. We need additional research into the best-suited providers for ICU follow-up clinics in order to best utilize staffing resources.

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Next, it is unclear how to appropriately integrate post-ICU care with usual PCP visits or post-hospital care. Post-ICU impairments often began pre-ICU admission, and delaying regular primary care visits for a specific ICU follow-up visit may delay or complicate management of a patient's chronic, pre-ICU illness. Additionally, patients often need coordination of and follow-up with multiple specialists after their hospitalization, and a PCP who will follow the patient longitudinally may be better suited to organize this care. Many aspects of PICS including refractory mental illness or chronic pain may benefit from PCP management rather than visits with a specific-ICU provider did not care for the patient prior to their acute illness. Further research is needed to address the ideal method of integration of ICU follow-up clinics with primary longitudinal medicine.

Finally, with little positive supporting data, it is unclear if there is a true clinical need for ICU follow-up clinics. Clinics are often poorly attended. In a 2012 review of post-ICU clinics, Modrykamien reported that clinics often have too few patients and many no-shows [6]. Patient may miss their follow-up visit as a result of a wide-range of complications, including lack of transportation, severity of illness, ongoing institutionalization, feeling overwhelmed, or fear of return to an ICU-associated environment [6]. Telemedicine appointments may be a cost- and time-effective method for patients that have trouble getting to a hospital-based clinic, however this has yet to be studied in ICU survivors. In addition to poor follow-up rates, patients may be obtaining follow-up elsewhere, whether that is by a PCP or a specialist, and may not need dedicated ICU-specific follow-up. We need to investigate needs and barriers of patients who do not follow up.

Conclusions

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Currently, ICU care success is based on patient survival to floor transfer and hospital discharge.

However, it is clear that ICU survivors experience far-reaching negative health consequences that can persist long after discharge. Improving these outcomes after critical illness is a mandate to the critical care community. Before we consider ICU follow-up clinics as recommended care, we need a better proof of concept. In prior trials, the interventions studied had widely varying scopes and timeframes, with a range of measured outcomes. These inter-study differences make it difficult to draw clear conclusions about appropriate post-ICU care. Additional research is key to establishing a better proof of concept, and with this, we expect financial and ideological support to emerge to drive further evaluation of post-ICU care structure and outcomes.

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Table 1. Features of post-ICU syndrome (PICS)

Post-ICU Syndrome		
Physical	Mental	Cognitive
<ul style="list-style-type: none"> • ICU acquired weakness <ul style="list-style-type: none"> • Deconditioning • ICU polyneuromyopathy • Pulmonary dysfunction 	<ul style="list-style-type: none"> • Depression • Anxiety • Post-traumatic stress syndrome 	<ul style="list-style-type: none"> • Difficulties with executive function, attention, and memory
Decreased quality of life Problems with self-care Difficulty returning to work or social activities Economic hardship on patients and families		

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Table 2. Summary of rehabilitation intervention trials

	Year	Subject	Intervention	Control	Primary outcome	Results
Schweickert et al	2009	104 ICU patients receiving MV < 72 hours	Early exercise and mobilization via PT and OT during daily interruption of sedation while in ICU	Standard care	Independent functional status (ability to perform 6 ADLs) at hospital discharge	59% of intervention group vs 35% of control group reached primary outcome (p=0.02; odds ratio 2.7)
Denahy et al	2013	150 ICU survivors (92% received MV)	Intensive daily exercise in the ICU and hospital ward, followed by biweekly exercise in the outpatient setting for 8 weeks	Standard care	6MWT at 12 months	No significant difference
RECOVER trial (Walsh et al)	2016	240 ICU survivors who received ≥48 hours MV	Rehabilitation (involving PT, OT, SLT, and nutrition care) delivered on the hospital ward at 2-3 fold frequency of usual care. Also involved individual goal setting and care coordination/delivery by a dedicated rehabilitation practitioner	Standard care	Rivermead Mobility Index at 3 months	No significant difference
REVIVE trial (McDowell et al)	2016	60 ICU survivors who received >96 hours MV	Personalized outpatient exercise program (consisting of 2 supervised and 1 unsupervised exercise session per week) for 6 weeks	Standard care	Health related quality of life (measured with the SF-36) at 6 months	No significant difference

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PRaCTICal trial (Cuthbertson et al)	2016	286 ICU survivors (98% received MV)	Nurse-led, ICU follow-up program that involved self-directed PT and clinic appointments. The program started in the hospital and continued for 3 months post-discharge	Standard care	Health related quality of life (measured with the SF-36) at 12 months	No significant difference
SMOOTH trial (Schmidt et al)	2016	291 ICU survivors (84% received MV)	Multimodal program involving post-ICU training for patients on sepsis sequelae, followed by outpatient patient monitoring by case managers via telephone for 12 months post-discharge. Consulting physicians with a background in primary and critical care also provided clinical decision support to PCPs	Standard care	Change in mental health related quality of life (measured with the SF-36) between ICU discharge and 6 month follow-up	No significant difference ¹

ICU, intensive care unit; MV, mechanical ventilation; PT, physical therapy; OT, occupational therapy; ADL, activity of daily living; 6MWT, 6 minute walk test; SLT, speech and language therapy; SF, short form; PCP, primary care provider.

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