REHABILITATIVE INTERVENTIONEN FÜR PATIENTEN NACH KRITISCHER ERKRANKUNG. EIN SYSTEMATISCHER REVIEW.

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Abkürzungsverzeichnis

CINAHL	Cumulative Index to Nursing and Allied Health Literature (Datenbank)
Crisis	Traumafolgestörungen bei kritisch kranken Patienten nach schwerer Sepsis (klinische Studie)
CSCC	Center for Sepsis Control and Care
EMBASE	Excerpta Medica Database (Datenbank)
EPHPP	Effective Public Health Practice Project
EPOC	Effective Practice and Organization of Care Group
ITS	Intensivstation
Los-Cog-Train	Kognitive Langzeitfolgen und Funktionsverbesserungen bei Überlebenden einer schweren Sepsis nach computergestütztem Kognitionstraining (klinische Studie)
MEDLINE	Medical Literature Analysis and Retrieval System Online (Datenbank)
Neuro-SOS	Neurologische Folgen einer Sepsis (klinische Studien)
NeuroPAIN	Neurologische Konsequenzen und Veränderungen der Schmerzverarbeitung nach schwerer Sepsis und septischem Schock (klinische Studie)
NRSMG	Non-Randomized Studies Methods Group
PICS	Postintensive Care Syndrome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PsycInfo	Eigenname der elektronischen Datenbank der American Psychological Association
PTBS	Posttraumatische Belastungsstörung(en)
SMOOTH	Sepsis Survivors Monitoring and Coordination in Outpatient Health Care - Strukturierte Langzeitbegleitung für Patienten nach Sepsis (klinische Studie)

Inhaltsverzeichnis

Zusammenfassung

Wissenschaftlicher Rahmen und Hintergrund: *Das Postintensive Care Syndrome*
Durch die steigende Zahl der intensivmedizinischen Behandlungsfälle und bedingt durch medizinische Fortschritte gibt es zunehmend mehr Überlebende einer kritischen Erkrankung. Diese Patienten leiden häufig unter körperlichen, seelischen oder mentalen Folgeerscheinungen der kritischen Erkrankung und der Intensivbehandlung, dem sogenannten Postintensive Care Syndrome (PICS). Zur Prävention bzw. Behandlung des PICS scheint eine rehabilitative und langfristige Nachsorge notwendig. Eine systematische Effektivitätsbewertung von spezifischen Nachsorge- und Rehabilitationsmaßnahmen für Erwachsene nach Entlassung von der Intensivstation (ITS) ist bisher nicht verfügbar.

Fragestellung und Ziele: *Gibt es effektive Nachsorge- und Rehabilitations-interventionen?*
Haben spezifische Nachsorge- und/oder Rehabilitationsverfahren nach Entlassung von der Intensivstation positive Effekte auf die typischen Folgeerscheinungen einer kritischen Erkrankung (sogenanntes PICS) bei Erwachsenen? Ziel der Arbeit ist die erstmalige systematische und evidenzbasierte Zusammenstellung und Bewertung verfügbarer Interventionen.

Methodik: *Systematischer Review*
Erstellen eines systematischen Reviews nach PRISMA-Vorgaben mit extensiver Suche in den Datenbanken MEDLINE, EMBASE, Cochrane Central, PsycInfo und CINAHL, Handsuche und Screening von Quellenverzeichnissen relevanter Literatur. Einschluss aller zwischen September 1991 und Juni 2012 veröffentlichten vergleichenden Studien mit mindestens einem der folgenden Outcomes: gesundheitsbezogene Lebensqualität, Folgeerscheinungen kritischer Erkrankungen bzw. PICS-Symptome, funktionelle Besserung, Hilfsbedürftigkeit/Autonomie, Mortalität oder stationäre Wiedereinweisung. Eingebettet ist die Arbeit in das Forschungsfeld Langzeitfolgen der Sepsis des Center for Sepsis Control and Care (CSCC) Jena und des Instituts für Allgemeinmedizin des Universtitätsklinikums Jena.

Ergebnisse: *Vor allem Posttraumatische Belastungsstörungen sind beeinflussbar*
Insgesamt 18 Studien, die 2.510 Patienten umfassen und stationäre (n=4 Studien), ambulante (n=9) oder sektorübergreifende (n=5) Interventionen testeten, wurden eingeschlossen. Sie verwendeten 20 verschiedene Outcomes, die mit mehr als 45

Messinstrumenten erhoben wurden. Acht Studien wurden aufgrund guter bis moderater Studienqualität in die Effektivitätsbewertung einbezogen. Sie umfassen stationäre geriatrische Rehabilitation, ITS-Nachsorge-Sprechstunden, ambulante Rehabilitationsprogramme, Disease Management und ITS-Tagebücher. Fünf dieser Studien untersuchten den Einfluss auf Posttraumatische Belastungsstörungen (PTBS), wobei vier davon einen positiven Effekt zeigten: ITS-Tagebücher (n=2) reduzierten das Neuauftreten von PTBS nach drei Monaten und Symptome nach einem Jahr. In einer ITS-Nachsorge-Sprechstunde behandelte Frauen zeigten geringere Symptome und ein Selbsthilfemanual reduzierte Symptome nach acht Wochen, jedoch nicht nach sechs Monaten. Keines der anderen Outcomes konnte in mehreren Studien effektiv beeinflusst werden.

Diskussion: ***Begrenzte Anzahl methodisch guter Studien***
Ärzten, die mit der Nachsorge von Patienten nach einer überstandenen kritischen Erkrankung betraut sind, bietet diese Arbeit eine evidenzbasierte Übersicht. Es konnten acht mittel- bis hochqualitative Studien, die unterschiedliche Interventionen untersuchten, in die Effektivitätsbewertung einbezogen werden. Im Allgemeinen gab es keine umfassenden Effekte der Interventionen, jedoch teilweise einen Einfluss auf einzelne Outcomes, insbesondere auf PTBS. Ursächlich für die geringe allgemeine Effektivität der Interventionen in den berücksichtigten Studien könnte die Heterogenität der Studienpopulation kritisch Kranker sein sowie Einflüsse durch Selektionsbias und Attrition Bias. Die Durchführung einer Metaanalyse war aufgrund der begrenzten Daten nicht möglich. Die Suchstrategie war extensiv, jedoch wurden wegen der stark variierenden Begrifflichkeiten des Forschungsfeldes möglicherweise nicht alle relevanten Studien gefunden. Die Klassifizierung der Interventionen ist aufgrund ihrer Vielfältigkeit deskriptiv. Die Klassifikationsparameter dafür wurden aus der Zusammenschau der Interventionen eigenständig abgeleitet, da kein gültiger Klassifikationsstandard verfügbar und somit anwendbar ist.

Schlussfolgerungen: ***ITS-Tagebücher haben Potential für Verbesserung von PTBS***
Bisher gibt es kaum effektive Nachsorgeinterventionen für kritisch kranke Patienten. Auf der Grundlage dieser Arbeit können für PTBS-Symptome erste Empfehlungen für den Einsatz von ITS-Tagebüchern gegeben werden. Deren klinischer Einsatz ist effektiv und ihre Weiterverwendung sollte auch in der primärärztlichen Versorgung unterstützt werden.

Einleitung

Wissenschaftlicher Hintergrund

Bedingt durch eine alternde Bevölkerung und moderne intensivmedizinische Behandlungsmöglichkeiten steigt die Zahl der Patienten, die auf Intensivstationen behandelt werden (Vincent 2013). Im Jahr 2010 waren es deutschlandweit 2.055.087 Behandlungsfälle, wovon 359.710 (ca. 18%) eine künstliche Beatmung benötigten (Statistisches Bundesamt 2012).
Oftmals ist die Behandlung durch eine so genannte „kritische Erkrankung“ indiziert (Latronico und Bolton 2011). Für diesen in der internationalen Forschung und Literatur weiträumig genutzten Begriff gibt es bisher keine offizielle Definition. Allgemein ist eine kritische Erkrankung jedoch durch einen lebensbedrohlichen Zustand, der intensivpflichtig ist und mit Organdysfunktion(en) einhergeht, gekennzeichnet (Latronico und Bolton 2011, The Anaesthesia Review Group 2012, PubMedMeSH 1992).
Zunehmend mehr Patienten überleben eine kritische Erkrankung bedingt durch eine moderne und leistungsstarke Intensivmedizin (National Quality Measures Clearinghouse 2008). Nach der ITS-Entlassung leiden nicht wenige von ihnen unter körperlichen, seelischen und mentalen Folgeerscheinungen, was kürzlich im internationalen Konsens als „Postintensive Care Syndrome“ (PICS) definiert wurde (Needham et al. 2012).
Typische körperliche Langzeitkomplikationen sind Critical-illness Polyneuromyopathie (Latronico und Bolton 2011, Desai et al. 2011), Dysphagie (Macht et al. 2011), Kachexie (Reid et al. 2004, Pichard et al. 2009), anhaltende Organdysfunktionen (Opal 2011), chronische Schmerzen (Zimmer et al. 2006) und sexuelle Funktionsstörungen (Ulvik et al. 2008, Griffiths et al. 2006). Depression, Angststörungen und Posttraumatische Belastungsstörung (PTBS) zählen zu den häufigen seelischen Folgeerkrankungen (Davydow et al. 2008, Scragg et al. 2001, Myhren et al. 2010). Neurokognitive Defizite wie Delir oder neuaufgetretene bzw. durch die Erkrankung verstärkte Demenz zählen zu den mentalen Einschränkungen (Torgersen et al. 2011).
Dies reduziert die gesundheitsbezogene Lebensqualität (Oeyen et al. 2010), die allgemeine körperliche Belastbarkeit und Funktion (van der Schaaf et al. 2009) sowie die Selbstständigkeit in Aktivitäten des alltäglichen Lebens (Desai et al. 2011) der Betroffenen.

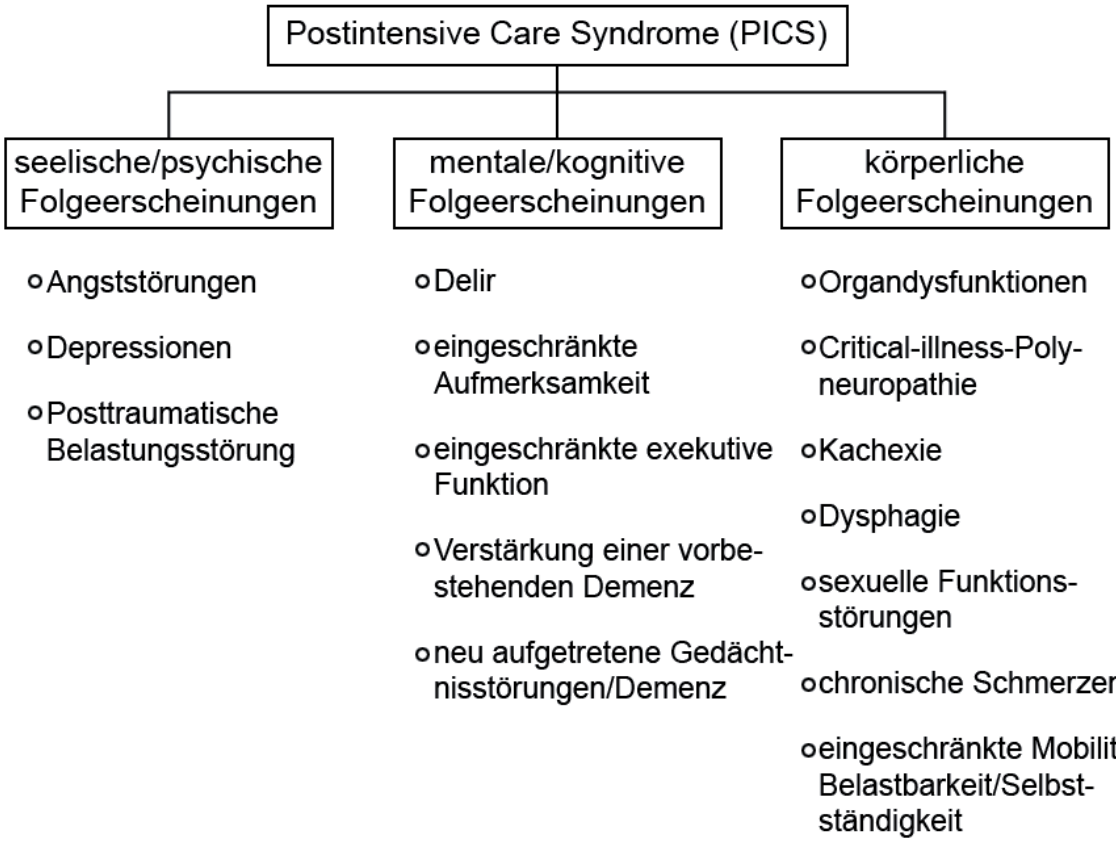

Abbildung 1: Konzept des Postintensive Care Syndromes mit seinen drei Teilaspekten und den zugehörigen Folgeerscheinungen einer kritischen Erkrankung

Die Langzeitfolgen kritischer Erkrankungen sind auch von volkswirtschaftlicher Bedeutung. Beispielsweise erkranken in Deutschland jährlich zwischen 44.000 und 95.000 Menschen an einer schweren Sepsis, nur einer von vielen kritischen Erkrankungen. Allein die Langzeitkomplikationen dieser Patienten führen zu geschätzten 5,6 Millionen € direkten und indirekten Kosten pro Jahr (Schmid et al. 2002).
Patienten nach einer kritischen Erkrankung benötigen daher eine Langzeitbegleitung nach der ITS und ggf. eine Prävention oder Behandlung eines möglichen PICS. Für mit der Nachsorge betraute Ärzte gibt es bisher keine systematische Übersichtsarbeit zur Zusammenfassung sowie Bewertung der Evidenz vorhandener Nachsorge- und Rehabilitationsstrategien. Lediglich die vom britischen Institute for Health and Clinical Excellence herausgegebene Leitlinie “Rehabilitation nach kritischer Erkrankung“ macht den Versuch, evidenzbasierte Informationen zusammenzutragen, greift dabei aber nur auf Daten bis 2009 zurück und enthält lediglich Empfehlungen bis zu drei Monaten poststationär (National Institute for Health and Clinical Excellence 2009). Diese Lücke soll durch den vorliegenden systematischen Review (Mehlhorn et al. 2014) geschlossen

werden. Untersucht wurden bis Juli 2012 veröffentlichte Studien, die zu einem Großteil eine Beobachtungsdauer über drei Monate hinaus aufweisen.

Rolle der Allgemeinmedizin und übergeordneter wissenschaftlicher Rahmen am Universitätsklinikum Jena

Da es sich beim PICS um ein heterogenes Syndrom mit einer Vielzahl verschiedener Störungen handelt, kann die Nachsorge der Patienten nicht durch eine ärztliche Spezialdisziplin allein bewerkstelligt werden. Insbesondere der Hausarzt ist gefordert, Zeichen eines PICS zu erkennen und eine entsprechende Versorgung einzuleiten und zu koordinieren (Schlette et al. 2009), vor allem da einige Aspekte des PICS wie psychische Folgeerscheinungen erst verzögert auftreten bzw. wahrgenommen werden (Desai et al. 2011). Da es die Erkenntnisse zu PICS und Versuche, dessen Symptome durch Interventionen zu beeinflussen, erst seit einigen Jahren gibt, steigt das Bewusstsein für die Wichtigkeit einer effektiven Nachsorge kritisch kranker Patienten an. Es muss jedoch davon ausgegangen werden, dass ärztlichen Primärversorgern die typischen Folgeerscheinungen und effektive Behandlungsmöglichkeiten nur eingeschränkt bekannt sind.
Laut dem Bellagio-Modell (Schlette et al. 2009), das die essentiellen Erfolgsfaktoren für eine moderne und leistungsfähige Primärversorgung zusammenstellt, gehören Forschung und Weiterentwicklung zu den Schlüsseldimensionen der Allgemeinmedizin. Daraus leitet sich für die forschende Allgemeinmedizin auch der Auftrag ab, vorhandene wissenschaftliche Evidenz zugänglich zu machen. Dies erfolgt insbesondere über die Durchführung von systematischen Reviews, wie in der hier vorliegenden Arbeit (Schlette et al. 2009).

Das Institut für Allgemeinmedizin des Universitätsklinikums Jena widmet sich der PICS-Forschung in Zusammenarbeit mit dem Center for Sepsis Control and Care (CSCC) Jena im Forschungsfeld Langzeitfolgen der Sepsis. Genauere Informationen zu dieser interdisziplinären Forschungseinrichtung sind unter www.cscc.uniklinikum-jena.de zu finden. Im Rahmen dieser Forschungen dient der hier vorliegende systematische Review, neben den bereits aufgeführten Zielen, der Zusammenstellung international vorhandener Daten, um laufende Interventionsstudien des CSCC im internationalen Kontext vergleichen und einordnen zu können. Außerdem bietet er eine Übersicht getesteter Interventionsverfahren und deren follow-up Zeiten, der genutzten Messinstrumenten mit Beurteilung von Validität und Reliabilität, eine Beschreibung der

jeweiligen Studienpopulationen sowie wichtiger Studienqualitätsaspekte. Diese Daten können bei bestimmten Forschungsprojekten des CSCC (z.B. Los-Cog-Train, NeuroPAIN, Neuro-SOS-Projekte und Crisis; siehe auch www.cscc.uniklinikum-jena.de/Forschung/Langzeitfolgen) in der Studiendurchführung berücksichtigt werden, für Vergleiche und Interpretationen dienen sowie für die Auswertung als auch für die Neuplanungen von Studien genutzt werden.
Nicht zuletzt dient die Zusammenstellung der Daten der Unterstützung von Hausärzten, um die langfristige Versorgung von Patienten nach einer kritischen Erkrankung zu optimieren und evidenzbasiert handeln zu können.

Ziele der Arbeit

Ziel des systematischen Reviews

Der vorliegende systematische Review dient der Beantwortung der Frage:

Haben spezifische Nachsorge- und/oder Rehabilitationsverfahren nach Entlassung von der Intensivstation positive Effekte auf die typischen Folgeerscheinungen einer kritischen Erkrankung (sogenanntes PICS) bei Erwachsenen?

Sowie der Beantwortung der sich daraus ergebenden Teilfragen:

Welche spezifischen Interventionen, Therapien, Rehabilitationen, Disease Management Programme oder Nachsorgestrategien gibt es für Erwachsene nach kritischer Erkrankung im Allgemeinen bzw. für mehrere oder einzelne typische Folgeerscheinungen einer kritischen Erkrankung (Symptome von PICS)?

Sind die vorhandenen Interventionen effektiv, um typische Folgeerscheinungen einer kritischen Erkrankung bzw. PICS-Symptome zu verhindern oder zu verbessern?

Übergeordnete Ziele des Forschungsprojektes

Neben der Beantwortung der Reviewfragen diente die Erstellung des systematischen Reviews auch 1) der Darstellung der aktuellen Forschungslandschaft im Bereich der Interventionsstudien für PICS, 2) der Erstellung einer evidenzbasierten Übersicht über verfügbare rehabilitative Interventionen nach ITS-Aufenthalt für Ärzte, die mit der Nachsorge von Patienten nach einer kritischen Erkrankung betraut sind, 3) der Verbesserung der Versorgung von PICS-Patienten bzw. Patienten nach einer kritischen Erkrankung sowie 4) der Erhöhung des Bekanntheitsgrades von PICS und notwendiger Interventionen in der hausärztlichen Nachsorge durch Kommunikation und Verbreitung der Ergebnisse des systematischen Reviews.

Methodik

Wir erstellten den systematischen Review entsprechend der gültigen Empfehlungen der Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guideline (PRISMA-Leitlinie) (Moher et al. 2009, Liberati et al. 2009) und unter Berücksichtigung der methodischen und qualitativen Hinweise für die Erstellung von systematischen Reviews der Cochrane Collaboration (Higgins und Green 2011) und des Centre for Reviews and Dissimination, UK (Centre for Reviews and Dissemination 2009). Ein Protokoll für den systematischen Review wurde diesen Empfehlungen folgend im Vorfeld erarbeitet (siehe Anhang).

Wir führten eine systematische Literatursuche in den Datenbanken MEDLINE (via OvidSP), EMBASE, Cochrane CENTRAL, PsycInfo und CINAHL durch. Die in MEDLINE angewandte und für die weiteren Datenbanken adaptierte Suchstrategie sowie eine ausführliche Erklärung zum Aufbau der Suche sind im Anhang der Arbeit beigefügt. Die Suche wurde gemeinschaftlich mit einer erfahrenen Bibliothekarin (Frau Ute Troitzsch) erarbeitet und im Vorfeld von unabhängigen Experten geprüft. Zusätzlich erfolgte eine Handsuche in den von Januar bis Juli 2012 veröffentlichten Ausgaben von 18 ausgewählten Zeitschriften (siehe Anhang) sowie ein Screening der Literaturverzeichnisse eingeschlossener Publikationen. Bei der Suche gab es keine Einschränkungen bezüglich der Publikationssprache und alle Studien, die zwischen Januar 1991 und Juni 2012 in einer von Experten begutachteten Zeitschrift (peer-reviewed) erschienen sind, wurden eingeschlossen.

Der Studieneinschluss erfolgte unabhängig durch zwei Reviewer mittels stufenweisem Screening von Titel, Zusammenfassung und Volltext aller durch die Suche gefundenen Publikationen. Die statistische Übereinstimmung zum Studieneinschluss auf Volltextniveau bestimmten wir mittels Berechnung einer Kappa-Statistik.

Eingeschlossen wurden interventionelle Studien, die bei erwachsenen Patienten nach ITS-Aufenthalt mindestens eines der folgenden Outcomes erhoben: gesundheitsbezogene Lebensqualität, Häufigkeit oder Schwere von typischen PICS-Symptomen, körperlicher oder funktioneller Zustand, Notwendigkeit von Pflege bzw. Unterstützung, Aktivitäten des täglichen Lebens, Mortalität oder stationäre Wiedereinweisung. Ausgeschlossen wurden Studien, in denen die Intervention für den Patienten bereits auf der ITS begann (ausführliche Erklärung dazu siehe Anhang) sowie spezifische ITS-typische Prozeduren wie Entwöhnung von der Beatmung und bereits etablierte Rehabilitationsverfahren für definierte Erkrankungen wie Herzinfarkt,

Amputationen oder Schlaganfall. Die ausführliche Rationale für die gewählten Outcomes sowie die genauen Ein- und Ausschlusskriterien für die Studien können dem Protokoll des systematischen Reviews entnommen werden (siehe Anhang).
Die Datenextraktion erfolgte durch zwei Reviewer unabhängig voneinander in eigens dafür entworfenen und getesteten Tabellen. Die zu extrahierenden Daten wurden im Vorfeld im Protokoll festgelegt und können dort nachgelesen werden.
Für die Qualitätsbeurteilung der eingeschossenen Studien nutzten wir das Effective Public Health Practice Project (EPHPP) Quality assessment tool, das für interventionelle Studien verschiedener Designs entwickelt und validiert wurde (EPHPP tool siehe Anhang) (Thomas et al. 2004, National Collaborating Centre for Methods and Tools 2008, Effective Public Health Practice Project 1998). Für jede eingeschlossene Studie wurden durch zwei Reviewer die Komponenten Selektionsbias, Studiendesign, Confounder, Verblindung, Methodik sowie Dropouts und Studienabbrecher bewertet. Daraus ergab sich eine Gesamteinschätzung von schwacher, moderater oder hoher Studienqualität für jede eingeschlossene Studie. Je höher die Studienqualität eingeschätzt wurde, desto niedriger ist die Wahrscheinlichkeit, dass die Studienergebnisse durch eine Form von Bias verzerrt sind.
Das Studiendesign der eingeschlossenen Studien bestimmten wir entsprechend der Cochrane Non-Randomized Studies Methods Group (NRSMG) und der Cochrane Effective Practice and Organization of Care Group (EPOC) Leitlinien (Higgins und Green 2011, EPOC 2002). Die eingeschlossenen Interventionen klassifizierten wir nach stationär, ambulant sowie sektorübergreifend und teilten sie nach der Art ihrer Intervention in acht verschiedene Klassen ein (siehe dazu Tabelle 1 des Supplemental digital content des publizierten Papers). Da aufgrund der Heterogenität der eingeschlossenen Studien keine Metaanalyse möglich war, erstellten wir eine narrative Datensynthese.

Publizierte Originalarbeit

Rehabilitation Interventions for Postintensive Care Syndrome. A Systematic Review.

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Rehabilitation Interventions for Postintensive Care Syndrome: A Systematic Review*

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Objective: An increasing number of ICU patients survive and develop mental, cognitive, or physical impairments. Various interventions support recovery from this postintensive care syndrome. Physicians in charge of post-ICU patients need to know which interventions are effective.

Data Sources: Systematic literature search in databases (MEDLINE, EMBASE, Cochrane CENTRAL, PsycInfo, CINAHL; 1991–2012), reference lists, and hand search.

Study Selection: We included comparative studies of rehabilitation interventions in adult post-ICU patients if they considered health-related quality of life, frequency/severity of postintensive care syndrome symptoms, functional recovery, need for care, autonomy in activities of daily living, mortality, or hospital readmissions.

Data Extraction: Two reviewers extracted data and assessed risk of bias independently.

Data Synthesis: From 4,761 publications, 18 studies with 2,510 patients were included. Studies addressed 20 outcomes, using 45 measures, covering inpatient ($n = 4$ trials), outpatient ($n = 9$), and mixed ($n = 5$) healthcare settings. Eight controlled trials with moderate to high quality were considered for evaluation of effectiveness. They investigated inpatient geriatric rehabilitation, ICU follow-up clinic, outpatient rehabilitation, disease management, and ICU diaries. Five of these trials assessed posttraumatic stress disorder, with four trials showing positive effects: first, ICU diaries reduced new-onset posttraumatic stress disorder (5% vs 13%, $p = 0.02$) after 3 months and second showed a lower mean Impact of Event Scale-Revised score (21.0 vs 32.1, $p = 0.03$) after 12 months. Third, aftercare by ICU follow-up clinic reduced Impact of Event Scale for women (20 vs 31; $p < 0.01$). Fourth, a self-help manual led to fewer patients scoring high in the Impact of Event Scale after 8 weeks ($p = 0.026$) but not after 6 months. For none of the other outcomes did more than one study report positive impacts.

Conclusion: Interventions which have substantial effects in post-ICU patients are rare. Positive effects were seen for ICU-diary interventions for posttraumatic stress disorder. More interventions for the growing number of ICU survivors are needed. (*Crit Care Med* 2014; 42:1263–1271)

Key Words: aftercare; critical illness; intensive care; posttraumatic stress disorder; rehabilitation; review literature as topic

***See also p. 1320.**

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The aging population and expanding boundaries of medical treatment have led to an increasing number of patients treated in ICUs (1), mostly because of a life-threatening critical illness (2). Millions of patients require ICU treatment annually in the United States (3), and with recent advances in

critical care medicine, more patients survive ICU stays (4). But after ICU discharge, patients often experience persistent physical, mental, and cognitive symptoms (5, 6), which have recently been described as postintensive care syndrome (PICS) (7). Post-ICU patients may need long-term medical interventions to support recovery in inpatient and in outpatient settings. Data on effective intervention is scattered across scientific literature.

Post-ICU patients may suffer from physical problems like critical illness polyneuromyopathy (CIPNM; ICU-acquired weakness) (2, 5), dysphagia (8), cachexia or wasting syndrome (9, 10), organ dysfunction (11), chronic pain (12), sexual dysfunction (13, 14), etc., as well as mental health problems like depression, anxiety, or posttraumatic stress disorder (PTSD) (15–17) and neurocognitive impairments like new or worsening cognitive impairment or delirium (18). The impact of these problems is reduced quality of life (19–21), reduced functional status (6, 22), and reduced daily functioning (5, 6).

Post-ICU patients challenge healthcare systems, driving high costs through repeated hospital admissions (23). In Germany, productivity loss for sepsis patients alone is about 5.6 million € per year (24).

So far, research on interventions to support the recovery of post-ICU patients is scarce. The purpose of this systematic review is to assess, for the first time, the effectiveness of rehabilitation interventions in adult post-ICU patients.

METHODS

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (25, 26). According to these guidelines, we established a detailed study protocol in advance, which is available on request.

Data Sources and Searches

We systematically searched MEDLINE (via OvidSP), EMBASE, Cochrane CENTRAL, PsycInfo, and CINAHL. We used a combination of the following search blocks to perform a keyword search in title and abstract and a MeSH term search: critical illness (e.g., critical illness, sepsis, and respiratory distress syndrome), state after intensive care (e.g., after/postintensive care and discharge from intensive care), aftercare and rehabilitation (e.g., rehabilitation, follow-up, and aftercare), interventions in general (e.g., therapy, management, and intervention), and postacute setting (e.g., postacute, outpatient, and after hospital). A team of experienced clinicians designed the search strategy in collaboration with a professional librarian. The search strategy was independently peer reviewed before being carried out. Additionally, we performed hand searching in 18 journals (published in 2012 before July 13th). Searches imposed no language restriction and included all studies published in peer-reviewed journals from January 1991 to June 2012.

Study Selection and Inclusion Criteria

Citations were checked for eligibility by two reviewers independently at the title, abstract, and full-text levels (**Fig. 1**). Disagreements between reviewers were resolved by discussion with a third reviewer. Interrater agreement for the selection process was assessed by kappa statistic calculation on full-text level.

We considered comparative intervention studies (27–29) targeting adult post-ICU patients. We included studies if they reported on one or more of the outcomes: patients' health-related quality of life (HRQOL), frequency or severity of symptoms of PICS, physical or functional status, need for care, patients' autonomy in activities of daily living, mortality, or hospital readmissions. We excluded interventions beginning in ICU and specific ICU-related treatments, like prolonged acute care or weaning, as well as disease-specific rehabilitations for myocardial infarction, stroke, amputation, etc.

Data Extraction and Quality Assessment

We designed and piloted our data extraction forms following guidelines (28–30). Data items concerned study setting, population, intervention, study design, statistical analyses, confounders, test instruments used, outcome data, and study limitations. Items were extracted and checked by two reviewers.

Two reviewers independently assessed risk of bias and overall quality of individual studies using the validated Effective Public Health Practice Project Quality assessment tool (31, 32). For each study, reviewers rated six components (selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts) leading to an overall methodological quality rating for each study of strong, moderate, or weak, with strong quality indicating a low risk of bias. Reviewers resolved rating disagreements through discussion.

Data Synthesis and Analysis

We assessed study designs according to the Cochrane Non-Randomized Studies Methods Group and Effective Practice and Organization of Care Group guidelines (29, 30). The interventions were categorized by healthcare setting post hoc into inpatient, outpatient, and mixed (30) and into eight subcategories based on the nature of interventions (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A825). Due to heterogeneity of trials, no meta-analysis was possible, so we performed a narrative data synthesis.

RESULTS

Study Selection

We included 19 publications concerning 18 studies. We found 16 of the publications through databases and three by hand search (Fig. 1). Interrater agreement for inclusion after full-text review was excellent ($\kappa = 0.98$).

Study Characteristics, Risk of Bias, and Quality

Although nine studies claimed to be randomized controlled trials (RCT), after quality assessment only four trials (33–36) fulfilled randomization criteria for a valid RCT according to guidelines (37). The other five trials are regarded as controlled clinical trials (38–43). The nine remaining studies consisted of one non-RCT (44), one controlled before-and-after

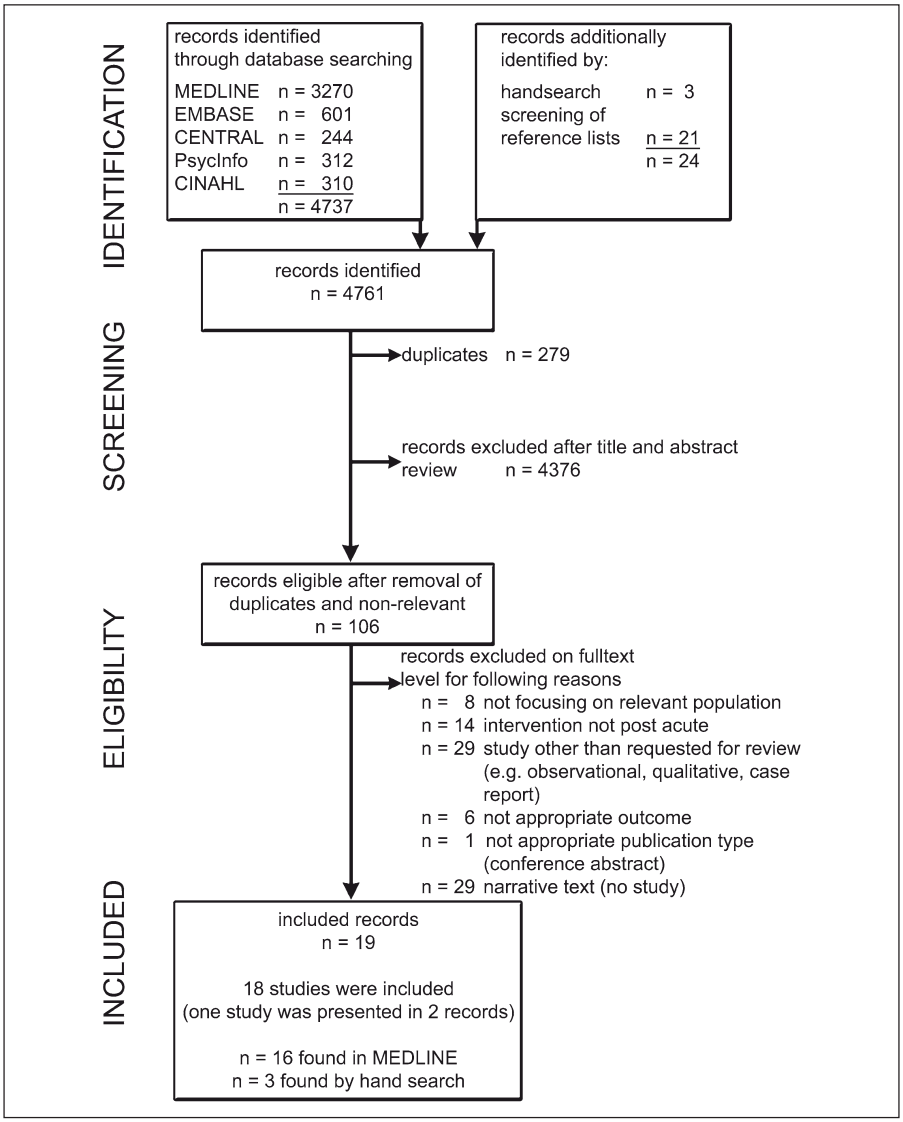

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of study inclusion.

study (45), two historically controlled trials (46, 47), and five before-and-after studies (48–52). Five of the publications were labeled as pilot or feasibility studies (33, 40, 44, 48, 50).

We rated the methodological quality of five publications as "strong" (34–36, 42, 46), four as "moderate" (38, 39, 43, 47), and 10 as "weak" (33, 40, 41, 44, 45, 48–52). The most common shortcomings we found are in blinding, selection bias, attrition bias, and lack of adequate control for relevant sociodemographic and clinical characteristics of participants (detailed information in **Supplemental Digital Content Text 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A825; and **Supplemental Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A825).

Most studies (n = 14) were conducted in Europe, three in the United States, and one in Australia. The majority of studies were single center (n = 13), with only five multicenter studies (34–36, 39, 50).

Participants

Studies included 2,510 patients, sample sizes ranging from 7 to 499, with an average of 139 participants. Fifteen studies tracked patients after critical illness in general, one after acute lung injury (50), and two studied patients with CIPNM (51, 52). One study exclusively recruited young men (44) and another only patients at least 75 years old (38).

Mechanical ventilation, ranging from 24 to 96 hours or with any length of time, was an inclusion criterion in seven studies (33, 34, 36, 39, 42, 43, 48, 50). Two studies additionally required a minimum length of stay in the ICU (34, 36). Length of stay in ICU, ranging from 24 (45) to 96 hours (46, 47, 49), alone was required in four studies. The remaining studies required neither a minimum stay in ICU nor mechanical ventilation.

Outcomes and Measures

Half of the studies did not differentiate between primary and secondary outcomes (33, 39, 42–45, 49–52). Eight studies assessed physical symptoms (33, 34, 39, 40, 48, 49, 51, 52) and 10 examined mental health symptoms, including symptoms of anxiety, depression, and PTSD (35, 36, 39, 41, 44, 46–50). Five studies reported on HRQOL (34, 35, 43, 45, 49), four on autonomy in daily activities (38, 40, 51, 52), and one on cognitive functioning (40). Few studies included need for care (38, 51), hospital readmission (42), mortality (42, 43), or nutrition (33).

Of all applied outcome test instruments, we found evidence of validation in (post)-ICU patients for the Short Form 36-item health survey (SF-36), Hospital Anxiety and Depression Scale (HADS), Post-Traumatic Stress Scale, Post-Traumatic Stress Syndrome 14-Questions Inventory, Impact of Event Scale-Revised (IES-R), Electromyography, Medical Research Council scale, and Manual muscle testing (53–63) (for detailed information, see **Supplemental Table 3**, Supplemental Digital Content 1, http://

links.lww.com/CCM/A825; and for abbreviations of test instruments, see footnote of **Supplemental Table 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/A825).

Interventions

Supplemental Table 4 (Supplemental Digital Content 1, http://links.lww.com/CCM/A825) provides a description of each intervention and study characteristics. Interventions varied widely in many aspects, including healthcare setting, healthcare providers, study design, and measures used.

Effectiveness of Interventions According to Setting

Our analysis of intervention effectiveness focused on the eight controlled trials with low or moderate risk of bias (34–36, 38, 39, 42, 43, 46, 47) (**Table 1**).

Inpatient Interventions

After ICU discharge, treatment in a specifically designed geriatric ward was not more effective than treatment in a general ward (38). Patients in the geriatric ward scored higher on the Barthel Index than the control group after discharge (75.6 ± 28.4 vs 64.6 ± 26.9) and 6 months later (81.5 ± 30.4 vs 70.5 ± 33.4), but this was not statistically significant. Many patients needed care in specialized wards and were not approached for the study, reducing the relevance of the study for the most vulnerable patients.

Outpatient Interventions

In a multicenter trial rated as strong methodological quality, consultations in an ICU follow-up service did not improve HRQOL or mental health more than standard care within a year of ICU discharge (35). Standard effect sizes (95% CI) of the SF-36 Physical health Component Score (PCS) and Mental health Component Score (MCS) to measure HRQOL were −0.8 (−3.6 to 2.0) and −0.6 (−3.9 to 2.8) after 6 months and 1.1 (−1.9 to 4.2) and 0.4 (−3.0 to 3.7) after 12 months. Another trial of moderate quality (46) suggested that women who spent 4 days or more in the ICU may have benefited from an ICU follow-up service regarding symptoms of depression and PTSD, regardless of previous psychological problems. Fourteen months after ICU discharge, a significant difference for PTSD (IES 31 vs 20 points, $p < 0.01$) was found. For depression, the 75th percentile of the HADS was significantly lower (–4.9 points, $p < 0.05$), but no relevant difference in median HADS depression points and no effects on anxiety were seen.

Two studies on outpatient rehabilitation programs (34, 39) were found: A self-help rehabilitation manual, supplemental to routine care (39), showed a trend of improved physical

TABLE 1. Overview of Outcomes in Trials Considered for Evaluation of Effectiveness, Significance of Findings, and Study Quality

Author	Study Type	Physical Function	Anxiety	Depression	Posttraumatic Stress Disorder
Inpatient interventions					
Ward-based rehabilitation in acute hospital care					
Somme et al (38)	CCT	–	–	–	–
Outpatient interventions					
Consultation in an ICU follow-up clinic					
Cuthbertson et al (35)	RCT	–	No	No	No
Schandl et al (46)	HCT	–	No	Partly[a]	Yes[a]
Rehabilitation programs/complex aftercare programs					
Jones et al (39)	CCT	Yes	No	No	Partly
Elliott et al (34)	RCT	No	–	–	–
Mixed interventions					
Disease management support service					
Daly et al (42) and Douglas et al (43)	CCT	–	–	–	–
ICU diary (given to patient after ICU discharge)					
Jones et al (36)	RCT	–	–	–	Yes
Garrouste-Orgeas et al (47)	HCT	–	No	No	Yes

CCT = clinical controlled trial, No = no significant difference in outcomes, RCT = randomized controlled trial, HCT = historical controlled trial, Yes = significant difference in outcome between intervention and control group, Partly = significant findings only in some outcomes.

[a]For women and not for men.

Dashes indicate no outcome in the study.

function. SF-36 Physical Function (SF-36 PF) score of experimental patients improved more over time than that of control patients ($p = 0.06$ for repeated analysis of variance incorporating SF-36 PF premorbid, at 8 wk and 6 mo). For PTSD, fewer experimental patients than control patients scored over the cutoff in the IES at the 8-week follow-up, indicating fewer symptoms ($p = 0.026$; percentage of patients and effect measure is not reported). This finding did not repeat at 6 months. No significant difference in the HADS depression or anxiety was seen.

A home-based physical rehabilitation program, tested in a strong quality, multicenter trial, did not show an effect on physical function or HRQOL 6 months after hospital discharge (34). Effect sizes ([Intervention mean change – Control mean change]/pooled SD of change) for SF-36 PCS and MCS were –0.14 and 0.13 at 8 weeks and 0.03 and 0.10 at the 26-week follow-up.

Mixed Healthcare Setting Interventions

A nurse-based cross-sectoral program for patients with chronic critical illness incorporating case management was assessed in one trial and presented in two publications (42, 43). Although called disease management, this intervention only fulfils the criteria of a disease management support service (64). The intervention was not associated with changes in any predefined outcome other than duration of readmission. Mean stay for interventional patients was 11.4 days (± 10.6 SD) versus 16.7 days (± 13.0 SD) ($p = 0.03$) (42). Only a partly positive result for HRQOL was found (43) as more interventional patients improved in SF-8 PCS within 2 months after hospital discharge (36.3% vs 29.2%, $p = 0.02$; post hoc analysis). The authors hypothesize that chronic critical illness may have a natural trajectory of continued morbidity, unaffected by additional postacute care coordination services.

Another cross-sectoral intervention used in different healthcare settings is the ICU dairy. It is a written record of the course of a patient's illness and treatment while in the ICU. The patient is given the diary as a tool to help address symptoms of PICS after ICU discharge. Of the interventions in this review, ICU diaries show the best evidence for a positive effect on mental health outcomes. One strong quality international multicenter trial found fewer new cases of PTSD at the 3-month follow-up (prevalence, 5% vs 13%; $p = 0.02$) (36). Another trial of moderate quality showed fewer symptoms of PTSD after 12 months, with a significantly lower mean IES-R (21.0 [± 12.2 SD] vs 32.1 [± 15.4 SD], $p = 0.03$) and fewer interventional patients scoring above the cutoff (50% vs 69%) (47). For anxiety and depression, evaluated at the 3-month follow-up, no significant difference was seen.

Cognition	Health-Related Quality of Life	Autonomy	Need for Care	Readmission	Mortality	Study Quality
–	–	No	No	–	–	Moderate
–	No	–	–	–	–	Strong
–	–	–	–	–	–	Strong
–	–	–	–	–	–	Moderate
–	No	–	–	–	–	Strong
–	Partly	–	–	Partly[c]	No	Strong/ moderate
–	–	–	–	–	–	Strong
–	–	–	–	–	–	Moderate

DISCUSSION

This review identified 18 comparative studies on the effectiveness of rehabilitation interventions in post-ICU patients. Only eight controlled trials had low or medium risk of bias and were therefore considered for evaluation of effectiveness. They studied inpatient geriatric ward-based rehabilitation, outpatient rehabilitation, ICU follow-up clinics, a disease management support service, and ICU-diary interventions. Four of five studies that used PTSD as outcomes showed positive impact on PTSD. For none of the other outcomes did more than one trial find a positive impact.

The ICU diary showed the best evidence for effectiveness in this systematic review. It is a potentially effective, low cost, and highly acceptable intervention (65, 66). Documenting symptoms and ICU events in a diary may facilitate communication about threatening intensive care memories and may help to prevent PTSD (65, 67). However, for ICU staff, writing the ICU diary means more work, and they tend to view it as part of good patient care (68). Evidence on rehabilitation for post-ICU patients is still limited, as stated by the British National Institute for Health and Clinical Excellence's guideline (69). As the ICU diary is an innovative intervention, it is not yet mentioned in the National Institute for Health and Care Excellence guidelines.

To explore the heterogeneity in these complex interventions, we examined the intensity of interventions as experienced by the patient. Intensity was operationalized in terms of duration of interventions, frequency of patient contact with healthcare professionals, and number of intervention elements (30, 70, 71). We found that the intensity of inpatient and outpatient rehabilitation interventions is high but mostly of short duration. Aftercare in ICU follow-up clinics was less intense but lasted up to 12 months. The ICU diary was the least intense intervention, with at most one contact to discuss the diary and no further intervention elements.

Still, the ICU diary showed good evidence for reducing symptoms of PTSD. Focusing on mental health only, it achieved an effect on the targeted symptom of PICS. Most interventions with high intensity, like ICU follow-up clinics or complex rehabilitation, tried to affect more than one aspect of PICS. This produced heterogeneous results, only showing effectiveness in single outcomes, mostly just for PTSD.

The lack of overall effectiveness of post-ICU interventions on physical and mental health might be attributed to a delayed beginning of rehabilitation efforts. Introducing interventions only when cognitive and physical decline has already set in and has become difficult to reverse seems insufficient. Physical rehabilitation beginning immediately on ICU admission resulted in a decreased time to achieve improvements in activity and better functional outcomes at ICU and hospital discharge in comparison to delayed rehabilitation (72).

Bias Across Studies and Methodologic Challenges

Both the targeted population of post-ICU patients and the interventions found are complex. The lack of overall effects may obscure positive effects of specific components of the rehabilitation interventions. In addition, the wide range of outcomes and measures made comparisons and meta-analysis impossible. Most studies did not report effect sizes, complicating interpretation of results.

Generalizability of the studies was reduced by selection bias because of exclusion of specific patients, particularly the most vulnerable patients. For most of the interventions, patients needed a certain degree of mobility and cognitive functioning. But in fact, immediately after ICU discharge, independent walking is impossible for nearly three quarters of patients, whereas about one third show cognitive impairments (73). Thus, the findings may apply mostly to less severe post-ICU patients. Furthermore, the fitter patients are before, or shortly after, a critical illness, the more likely they are to recover (74–76).

Attrition bias is caused by high mortality and morbidity after ICU, which lead to high death and dropout rates in study populations (5, 19). This may lead to an overrepresentation of healthier subjects in both the control and intervention groups.

Usual care provided in the control group patients is heterogeneous, with some control groups receiving extensive rehabilitation interventions. Hence, standard care in control groups might already be as good as additional interventions to support patients in recovery. Only some investigators described standard care well. Maybe patients generally receive some sort of rehabilitation treatment or dedicated follow-up, but this mostly was not examined.

Implications for Research

This review shows a need for more research on evidence-based, effective rehabilitation interventions for post-ICU patients. Rather than focusing only on main effects in post-ICU patients, we suggest examining the effects in subgroups of patients in more detail. Interventions could be tailored to individual patient characteristics and needs. Until now, post-ICU patients do not have a recognized rehabilitation pathway, such as patients with stroke, myocardial infarction, or lung injury (7). Comprehensive research on rehabilitation interventions should help to establish a multidisciplinary, specialized rehabilitation for ICU survivors. Future research would benefit from a scientific description of the specific population of post-ICU patients, as was recently started with the introduction of the PICS concept. A systematic classification of post-ICU patients, and specific interventions, as well as a set of outcome measures, would improve comparability of studies.

Implications for Clinical Practice

The PICS concept is new and preliminary. Research on PICS started recently and evidence is still heterogeneous. PICS may help clinicians to handle a complex situation of several individual syndromes with complex etiology and interrelationships in post-ICU patients. Post-ICU patients may benefit from interventions like trauma-focused cognitive-behavioral therapy, specialized rehabilitation, and psychiatrist treatment,

but often they do not have access to those interventions. Reasons for this are a lack of awareness of their needs in aftercare and not qualifying for the interventions without having a certain diagnosis (like stroke, myocardial infarction, lung injury, etc.) (7, 69). Raising awareness for the special needs of ICU survivors by applying the PICS concept and treating it as an established group of diagnoses may pave the way to special interventions for post-ICU patients.

In clinical practice, the rehabilitation and aftercare process for patients with critical illness is still fragmented. Considering the evidence for safety and effectiveness of early rehabilitation beginning in the ICU (72, 77–79), a continuum of care, starting with early rehabilitation and lasting beyond ICU and hospital discharge, is desirable to improve short- and long-term outcomes for ICU survivors.

This review also supports the importance of outpatient care for post-ICU patients. This may call for effective primary care delivery in this domain. Primary care physicians may support the recovery of post-ICU patients when being more involved in the delivery of rehabilitation interventions.

Limitations of the Review

Indexing of studies in the new field of post-ICU patient care is still insufficient, so we may have missed relevant studies. Given the heterogeneity of patients, interventions, and outcomes, it was challenging to categorize and aggregate the data, so we may have misclassified studies. As we accepted only studies published in peer-reviewed journals, some publication bias is possible. However, this might be negligible since most published trials did not find overall positive effects. Language bias was minimized by the unrestricted initial search. Research on this topic has only developed recently. More trials on physical exercise are ongoing (80).

CONCLUSION

There is still a long way to go in rehabilitation of post-ICU patients. More research of appropriate methodological quality is needed. This review suggests that symptoms of PTSD may be reduced by simple interventions like ICU diaries. To encourage patients to read and use an ICU diary if provided and to discuss it with them seems worthwhile in everyday practice to prevent symptoms of PTSD.

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Supplemental Digital Content

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Supplemental Digital Content Table 1: Categorization of interventions according to health care setting

Supplemental Digital Content Text 1: Details on Quality assessment of included trials

Supplemental Digital Content Table 2: Quality assessment of included studies – component rating and overall rating (using the EPHPP Quality assessment tool)

Supplemental Digital Content Table 3: Categories of Post Intensive Care Syndrome, corresponding outcomes and test-instruments used

Supplemental Digital Content Table 1: Categorization of interventions according to health care setting

Category	Subcategories	Studies
1. Inpatient interventions (n=4)		
	1.1. Ward-based rehabilitation in acute hospital care	Somme, 2010 (38); Salisbury, 2010 (33)
	1.2. Rehabilitation in rehabilitation center/ facility	Intiso, 2011 (51); Novak, 2011 (52)
2. Outpatient interventions (n=9)		
	2.1. Doctor's/ medical staff consultations	
	a) by GP	none
	b) by specialist/ in an ICU-follow-up clinic	*Cuthbertson, 200* (35); Schandl, 2011 (49); *Schandl, 2012* (46)
	2.2. Rehabilitation programs/ complex aftercare programs	*Jones, 2003* (39); McWilliams, 2009 (48); *Elliot, 2011* (34); Jackson, 2011 (40); Jones C., 2003 (44) ; Cox, 2012 (50)
3. Mixed interventions (n=5)		
	3.1. Disease management program	none
	3.2. Case management/ Disease management support service	*Daly, 2005* (42)*; Douglas, 2007* (43)
	3.3. ICU-diary	Knowles, 2009 (41); Backman, 2010 (45); *Jones, 2010* (36) *; Garrouste-Orgeas, 2012* (47)
	3.4. Other translational interventions	none

Italics: Trials included in the evaluation of effectiveness; n= number of studies in category

Supplemental Digital Content Text 1
Details on Quality assessment of included trials

The most common shortcomings we found in blinding, selection bias, attrition bias and lack of adequate control for relevant sociodemographic and clinical characteristics of participants. Only one study achieved blinding of participants and assessors (39). Half of the studies reported substantial participation denial, between 30% and 50% (34, 35, 40-43, 45, 46, 49), while four trials did not report agreement rates (39, 44, 48, 52). Only five studies had follow-up rates greater than 80% of patients in both the intervention and control groups (36, 41, 43, 50, 51).

40% of the studies adequately reported sociodemographic and clinical characteristics s while controlling for relevant confounders (34-36, 38, 42, 43, 46, 47). Most authors gave information on severity of illness using the APACHE II score. Reported patient details, like length of stay in ICU, mechanical ventilation, or sedation, occurrence of delirium, or delusional memories, varied widely. Only a third of studies provided data on morbidity or functional status of participants before ICU admission (36, 38, 39, 41, 46, 47), though these are well-known confounders for outcomes like HRQOL, physical function and psychological health (73-75). Five studies with potentially unbalanced baseline characteristics between the intervention and control groups did not adequately adjust for these differences (33, 34, 40, 41, 44) Five of eight studies providing a power calculation (34-36, 38, 39, 41-43, 46) (pilot/feasibility studies not considered) were underpowered (34, 38, 39, 41, 46).

Supplemental Digital Content Table 2: Quality assessment of included studies – component rating and overall rating (using the EPHPP Quality assessment tool)

Study	Selection Bias	Study design (Allocation bias)	Confounders	Blinding (Detection and Performance bias)	Data collection methods	Withdrawals/ Drop-outs (Attrition bias)	Global quality rating
Backman, 2010 (45)	Weak	Moderate	Weak	not applicable	Strong	Weak	WEAK
Cuthbertson, 2009 (35)	Moderate	Strong	Strong	Moderate	Strong	Moderate	STRONG
Cox, 2012 (50)	Moderate	Moderate	Weak	Weak	Strong	Strong	WEAK
Daly, 2005 (42)	Moderate	Strong	Strong	not applicable	not applicable	Moderate	STRONG
Douglas, 2007 (43)	Moderate	Strong	Strong	Weak	Moderate	Strong	MODERATE
Elliott, 2011 (34)	Moderate	Strong	Strong	Moderate	Strong	Moderate	STRONG
Garrouste-Orgeas, 2012 (47)	Moderate	Moderate	Strong	Moderate	Strong	Weak	MODERATE
Intiso, 2011 (51);	Moderate	Moderate	Weak	Weak	Strong	Strong	WEAK
Jackson, 2011 (40)	Weak	Strong	Moderate	Moderate	Strong	Weak	WEAK
Jones, 2003 (39)	Weak	Strong	Moderate	Strong	Strong	Moderate	MODERATE
Jones, Colin, 2003 (44)	Weak	Moderate	Weak	Weak	Weak	Weak	WEAK
Jones, 2010 (36)	Strong	Strong	Strong	Moderate	Strong	Strong	STRONG
Knowles, 2009 (41)	Moderate	Strong	Weak	Weak	Strong	Strong	WEAK
McWillliams, 2009 (48)	Weak	Moderate	Weak	Weak	Strong	Weak	WEAK
Novak, 2011(52)	Weak	Moderate	Weak	Weak	Strong	Weak	WEAK
Salisbury, 2010 (33)	Moderate	Strong	Weak	Moderate	Strong	Weak	WEAK
Schandl, 2011 (49)	Moderate	Moderate	Weak	Weak	Strong	Weak	WEAK
Schandl, 2012 (46)	Moderate	Moderate	Strong	not applicable	Strong	not applicable	STRONG
Somme, 2010 (38)	Moderate	Strong	Strong	Moderate	Strong	Weak	MODERATE

Supplemental Digital Content Table 3: Categories of Post Intensive Care Syndrome, corresponding outcomes and test-instruments used

Category of PICS	Outcome	Test instrument/ measurement method (abbreviation; unit of measure)	Used in study
Physical impairments/ body function	Walking/ mobility	Time-Up and Go test (TUG; seconds)	(33, 40)
		Rivermead Mobility Index (RMI; score 0-15)	(33)
		10 metre Walk Test (10mWT; m/s)	(33, 52)
		Incremental Shuttle Walk Test (ISWT; meters)	(33, 48)
		Six Minute Walk Test (6MWT; meters)	(34, 48, 49, 52)
		Activities Balance and Confidence scale (ABC; score 0-100)	(40)
	Strength/ muscle functioning	Hand grip dynamometer (e.g. Jamar; kg)	(33, 49)
		Timed-Stands-Test (TST; seconds)	(49)
		Medical Research Council scale (MRC; grade 0-5 for muscle/muscle group)	(51)
		Manual Muscle Testing (MMT; ; grade 0-5 for muscle/muscle group)	(52)
		Electromyography (EMG; normal or abnormal muscle activity)	(51)
	Physical function in general	Short Form 36-item health survey Physical Function (SF-36 PF; scale 0-100)	(34, 39, 45, 49)
		Short Form 36-item health survey Physical health Component Score (SF-36 PCS; scale 0-100)	(34, 35, 45)
		Short Form 8-item health survey Physical Component Score (SF-8 PCS; scale 0-100)	(43)
	Exhaustibility	Breathlessness Visual Analog Scale (VAS; scale 0-100)	(33)
		Fatigue (VAS; scale 0-100)	(33)
	Body function	Joint stiffness (VAS; scale 0-100)	(33)
		Pain (VAS; scale 0-100)	(33)
	Nutrition	Calorie intake (% of required)	(33)
		Protein intake (% of required)	(33)
		Appetite (VAS; scale 0-100)	(33)
Mental health	Symptoms of depression	*Hospital Anxiety and Depression Scale depression subscale(HADS depression; score max. 21)*	(35, 39, 41, 46-50)
		Center for Epidemiologic Studies Depression Scale (CES-D; score 0-60)	(44)
	Symptoms of anxiety	*Hospital Anxiety and Depression Scale anxiety subscale (HADS anxiety; score max. 21)*	(35, 39, 41, 46-50)
	Symptoms of PTSD	Impact of Event Scale (IES; score 0-75)	(39, 46, 49)
		Impact of Event Scale-Revised (IES-R; score 0-88)	(47)
		Davidson Trauma Scale (DTS; 2 subscores 0-68; total 0-136)	(35)
		PTSD Diagnostic Scale (PDS; score 0-51)	(36)
		Post-Traumatic Stress Syndrome 14-Questions Inventory *(PTSS-14; score 14-98)*	(36)
		Post-Traumatic Stress Scale (PTSS; score 7-70)	(50)
	Mental health in general	*Short Form 36-item health survey Mental health Component Score (SF-36 MCS;* scale 0-100*)*	(34, 35, 45)
		Short Form 36-item health survey Mental health (SF-36 MH; scale 0-100)	(45, 49)
		Short Form 8-item health survey Mental health Component Score (SF-8 MCS; scale 0-100)	(43)
Cognitive impairments	Executive function	Tower test (achievement score of D-KEFS; score 0-20)	(40)
		Dysexecutive Questionnaire (DEX; score 0-80)	(40)

	General	Mini Mental State Examination (MMSE; score max. 30)	(40)
PICS in general/ further aspects	Health-related Quality of Life (HRQOL)	*Short Form 36-item health survey Physical and Mental health Component Score (SF-36 PCS and MCS; each scale 0-100)*	(34, 35, 45)
		Short Form 36-item health survey subscales (SF-36 all subscale; each scale 0-100)	(45, 49)
		Short form 8-item health survey Physical and Mental health component score (SF-8 PCS and MCS; each scale 0-100)	(43)
		EuroQoL 5D (EQ-5D; 245 health states transformed into index score; e.g. USA index score -0.11 – 1.0)	(35)
	Autonomy in activities of daily living (ADL)	Barthel Index (BI; score, max. 100)	(38, 51)
		Katz Index of independence in Activities of Daily Living (Katz ADL; score 0-6)	(40)
		modified Rankin Scale (mRS; scale 0-6)	(51)
		Functional Independence Measure (FIM; score 18-126/ motor FIM; score 13-91)	(52)
	Autonomy in instrumental activities of daily living (IADL)	Functional Activities Questionnaire (FAQ; score 0-30)	(40)
	Functioning, disability and health status in general	modified International Classification of Functioning, Disability and Health (modified ICF; code of absence or presence of problems used)	(52)
	Need for care	not specified	(38, 51)
	Return to home	not specified	(38, 51)
	Mortality	Mortality during readmission	(42)
		Mortality in general	(35, 43)
	Rehospitalization	Number of readmissions	(42)
		Days to first readmission	(42)
		Duration of readmission stay	(42)

Italics: Valid and reliable tests for (post-) ICU population

Supplemental Digital Content Table 4: Study characteristics of included studies (arranged according to health care setting category and subcategories)

Study and *Quality Assessment*	Description of intervention	Study design/ Single vs. Multi-centre/ Country of origin	Intervention group population: Age Sex Length of stay in ICU Mechanical ventilation Apache II	Selected baseline characteristics* of intervention group	Number enrolled / Number at final analysis	Times of assessment	Outcomes relevant for review
Inpatient interventions							
Ward-based rehabilitation in acute hospital care							
Somme, 2010 (38) *Moderate*	Rehabilitative treatment in a geriatric ward	CCT Single France	80.8 ± 3.9 38% ♂ NR NR 23 ± 8.1	BI: 34.6 ± 23.4 MMSE: 18.0 ± 6.7	45/23	**tb:** NR - after admission to geriatric ward **t1:** 7 days after hospital discharge **t2:** 6 months after ICU discharge	**pr:** change in autonomy (BI) tb to t1 **sec:** -"- to t2; need for care at t1; return to home at t1 + t2
Salisbury, 2010 (33) *Weak*	Additional physiotherapy and nutritional support on general ward	RCT Single UK	67 (44.5 - 77.8) 75% ♂ 23 (20.5 - 33.3) 21.5 (19 - 30.3) 31 (23.3 - 42)	NR	16/ 9 to 11	**tb:** NR -"on ICU" **t1:** 3 months after ICU discharge	PF at t1 (mobility: TUG, ISWT, RMI, 10mWT; body function: VAS for breathlessness/ joint stiffness/ pain/ appetite; strength: handgrip dynamometry; nutrition: calorie + protein intake)
Rehabilitation in rehabilitation center/ facility							
Intiso, 2011 (51); *Weak*	Inpatient neuro-rehabilitation (mean 76.2 ± 28.1 days)	BA Single Italy	58.4 ± 13.9 54,7% ♂ 37.8 ± 6.5 15.3 ± 8.2 42.5 ± 7.6	BI: 16.7 ± 8.6 MRC: 20.7 ± 15.8	42/ 37	**tb:** direct after hospital discharge **t1:** discharge from rehab (76.2 ± 28.1 d ~ 2-3 months after hospital discharge) **t2:** mean 31.7 ± 15.8 months after t1 (~3 yrs)	PF (muscular strength recovery: EMG, MRC), autonomy (BI, mRS) at t1 + t2
Novak, 2011 (52) *Weak*	Inpatient neuro-rehabilitation (mean 38 ± 19 days)	BA Single Slovenia	59.4 ± 15.9 40% ♂ NR NR NR	FIM: 78.7 ± 24.2 6MWT: 77.3 ± 115.5 10mWT: 1.5 ± 0.8	NR/ 27	**tb:** direct after hospital discharge **t1:** at discharge from rehab 38 ± 19 d; (~ 1 month after hospital discharge)	PF (muscle strength: MMT, mobility: 6MWT; 10mWT), autonomy (FIM, modified ICF)

Outpatient interventions							
Consultation in an ICU follow-up clinic							
Cuthbertson, 2009 (35) *Strong*	Nurse-led ICU follow-up, manual based physical rehabilitation; appointments 3 + 9 months	RCT Multi (3) UK	59 (46–49) 60% ♂ 2.9 (1.7–9.5) duration NR; 99% 19 (15–24)	SF-36 PCS: 33.4 ± 10.0 SF-36 MCS: 40.9 ± 15.2 EQ-5D: 0.52 (0.26–0.73) HADS anxiety: 7 (3–10) HADS depr.: 6 (3–9)	286/187	**tb:** median 9.5 days for IG vs 8.6 days for CG after ICU discharge) **t1:** 6 months later **t2:** 12 months	**pr:** HRQOL at t2 (SF-36); **sec:** HRQOL at t1 (SF-36; EQ-5D) and t2 (EQ-5D), PTSD at t1 and t2 (DTS), depression and anxiety at t1 + t2 (HADS), mortality at t2
Schandl, 2011 (49) *Weak*	Multidisciplinary ICU follow-up; appointments 6 + 12 months after ICU discharge	BA Single Sweden	52.6 ± 17.8 64% ♂ 7.2 (3.8-36.8) NR 21.4 ± 9.1	NR	61/30	**tb:** none **t1:** 3 months after ICU discharge **t2:** 6 months **t3:** 12 months	HRQOL (SF-36), PF (TST, Jamar, 6MWT), depression and anxiety (HADS), PTSD (IES) at t3
Schandl, 2012 (46) *Strong*	Multidisciplinary ICU follow-up; appointments at 3 + 6 + 12 months after ICU discharge	HCT Single Sweden	52 ± 18 0% ♂ 10 ± 7 duration NR; 81% 21 ± 8 [c]	NR	258/171	**tb:** none **t1:** 14 months after ICU discharge	**pr:** PTSD (IES), depression and anxiety (HADS) at t1
Rehabilitation programs/ complex aftercare programs							
Jones Colin, 2003 (44) *Weak*	Series of one life review interview per week over 6 weeks after hospital discharge	NRCT Single UK	41.2 (range 21-54) 100% ♂ 17.0 NR NR	NR	18/NR	**tb:** within 1 week after ICU discharge **t1:** NR - "6 months later"	depression (CES-D)
Jones, 2003 (39) *Moderate*	Routine ICU follow up AND 6-week self-help manual (education, self-directed exercise)	CCT Multi (3) UK	57 ± 17 54% ♂ 14 ± 20 duration NR; 100% 17 ± 5	HADS anxiety : 8 ± 5 HADS depr.: 6 ± 4	126/102	**tb:** NR - at general ward **t1:** 8 weeks after ICU discharge **t2:** 6 months after ICU discharge	depression and anxiety (HADS), PTSD (IES), PF recovery (SF-36 PF) at t1 and t2
McWilliams, 2009 (48) *Weak*	Exercise-based 6-weeks rehabilitation program (supervised exercise in group, education)	BA Single UK	56.8 ± 16.8 55% ♂ 11 (6–17) 11 (6–17) 15 (10.8–21.5)	6MWT: 278 (185-370) ISWT:180 (100–280) HADS anxiety: 8.2 (5–11) HADS depr.:7.2 (5.3–9)	43/22 to 38	**tb:** within 2 weeks after hospital discharge **t1:** 1 week after program (at least ~ 8 - 9 weeks after hospital discharge)	**pr:** change in PF (6MWT, ISWT); **sec:** changes in anxiety and depression (HADS)
Elliott, 2011 (34) *Strong*	8-weeks home-based physical rehabilitation program (exercise manual, supervised exercise)	RCT Multi (4) Australia	57.2 ± 17.0 61% ♂ 9.4 ± 8.7 5,9 ± 6.6 19,4 ± 12.6	SF-36 PCS: 31,7 ± 10.0 SF-36 MCS: 36,7 ± 15.1 6MWT: 291 ± 129	195/161	**tb:** within 1 week after hospital discharge **t1:** 8 weeks after hospital discharge **t2:** 26 weeks after hospital discharge	**pr:** PF (SF36-PF); sec: PF (6MWT), improvement of HRQOL (SF-36 PCS/MCS)

Jackson, 2011 (40) *Weak*	12 weeks in-home program for physical, functional, cognitive training (visits in person and televisits)	CCT Single USA	44 (41–63) 29% ♂ 2.1 (2.0–3.5) 1.4 (0.4–2.6) 21.0 (18.5–27.5)	Tower-Test: 8.0 (6.5-10.0) MMSE: 28.0 (25.0–29.0) TUG:18 (15–20)	22/15	**tb:** before hospital discharged **t1:** after completion of intervention (~ 3 months after hospital discharge)	**pr:** executive cognitive function (Tower test), PF (TUG); **sec:** cognition (MMSE, DEX), activity (ABC), autonomy (FAQ, Katz ADL) at t1
Cox, 2012 (50) *Weak*	12-weeks weekly sessions of telephone-based coping skills training	BA Multi (4) USA	50 (43-67) 43% ♂ 12 (9-20) 9 (7-19) 26 (24-38)	HADS anxiety: 12.2 HADS depr.: 11.2 PTSS: 33.5	7/7	**tb:** within 1 week before initiation of intervention (~ 1-5 weeks after hospital discharge) **t1:** 1 week after completion of intervention (~ 3-4 months after hospital discharge)	depression and anxiety (HADS), PTSD (PTSS)
Mixed interventions							
Disease management support service							
Daly, 2005 (42)/ Douglas, 2007 (43) *Strong*[a] *Moderate*[b]	8-weeks disease management support service delivered by advanced-practice nurse (case management activities)	CCT Single USA	60.7 ± 16.6 53,3% ♂ 17.3 ± 12.9 11.8 ± 10.6 APACHE III: 67.4 ± 26.9	SF-8 PCS: 30.6 ± 8.7 SF-8 MCS: 41.9 ± 12.8	334/247 to 198	**tb:** CG: within 2 weeks after hospital discharge IG: before hospital discharge **t1:** 8 weeks after hospital discharge	readmission patterns (rate, mortality, time to first readmission, duration), HRQOL (SF-8 PCS/MCS) , mortality at t1
ICU-diary (given to patient after ICU discharge)							
Knowles, 2009 (41) *Weak*	ICU-diary (given to patient ~ 1 month after ICU discharge; formal discussion with ICU staff)	CCT Single UK	NR 56% ♂ 10.0 (8-34) 7.0 (2-71) 17.0 (8-30)	HADS anxiety: 6.6 ± 3.9 HADS depr.: 6.7 ± 4.6	36/36	**tb:** 1 month after ICU discharge (median 30 d; range 21 d-8 months) **t1:** 3 weeks after handing over diary (~ 2 months after ICU discharge at an average)	**pr:** depression and anxiety (HADS) at t1
Backman, 2010 (45) *Weak*	ICU-diary (given to patient 2-8 weeks after ICU discharge; formal discussion with ICU staff)	CBA Single Sweden	50.7 ± 17.2 53% ♂ 11.4 (5.3 -20.8) 9 (2-15.5) 18.7 ± 7.3	NR	499/t1: 252, t4: 128	**tb:** none **t1:** 6 months after hospital discharge/after ICU discharge (both said in paper) **t2:** 12 months **t3:** 24 months **t4:** 36 months	HRQOL (SF-36 all 8 subscales, PCS/MCS) at t1 - 4
Jones, 2010 (36) *Strong*	ICU-diary according to guidelines; (given to patient 1 month after ICU discharge; formal discussion with ICU	RCT Multi (12) UK, Sweden, Italy, Portugal,	60 (18-81) 69% ♂ 13 (3-79) 8.8 (1-62.5) 20 (5-46)	PTSS-14: 22.5 (14-84)	352/322	**tb:** ICU memory tool 1 week after ICU discharge, PTSS-14 1 month after ICU discharge **t1:** 3 months after ICU discharge	**pr:** new cases of PTSD (PDS) at t1

	staff)	Denmark, Norway					
Garrouste-Orgeas, 2012 (47) *Moderate*	ICU-diary given to patient on general ward in envelope	HCT Single France	65.4 ± 16.8 67%♂ 18.2 ± 22.9 duration NR;77.6% NR	NR	143/ 56	**tb:** none **t1:** 3 months after ICU discharge **t2:** 12 months after ICU discharge	**pr:** anxiety and depression (HADS) at t1 + t2, PTSD (IES-R) at t2

age in years; in mean ± standard deviation or median (with interquartile range)
length of stay in ICU in days in mean ± standard deviation or median (with interquartile range)
mechanical ventilation: length in days in mean ± standard deviation or median (with interquartile range) or percentage of patients
Apache II: Acute Physiology And Chronic Health Evaluation Score (points in mean ± standard deviation or median (with interquartile range)); at admission to ICU
*: quantitative reported testing of function or used outcome tests at study inclusion/ shortly after ICU or hospital discharge; mostly at tb; for abbreviations of test-instruments see table 2
CCT: controlled clinical trial
RCT: randomized controlled clinical trial
BA: before-after study
CBA: controlled before-after study
NRCT: non-randomized controlled clinical trial
HCT: historically controlled trial
M: moderate
W: weak
S: strong
tb: time of baseline assessment
t1: time of first follow-up assessment
t2: time of second follow-up assessment, etc.
single: single-center
mulit: multi-center (number of centers)
NR: not reported
PF: physical functioning
pr: primary outcome
sec: secondary outcome; some studies did not differentiate between primary and secondary outcomes
IG: intervention group
CG: control group
[a]:for readmission, mortality
[b]: for HRQOL
[c]: data reported for female intervention group ; for data of male intervention group see original paper
Abbreviations and measures of test instruments:
10mWT: 10 metre Walk Test (m/s)
6MWT: Six Minute Walk Test (meters)
ABC: Activities Balance and Confidence scale (score 0-100)
BI: Barthel Index (score; max. 100)
CES-D: Center for Epidemiologic Studies Depression Scale (score 0-60)
DEX: Dysexecutive Questionnaire (score 0-80)
DTS: Davidson Trauma Scale (2 subscores 0-68; total 0-136)
EMG: Electromyography (normal or abnormal muscle activity)
EQ-5D: EuroQoL 5D (245 health states transformed into index score; e.g. USA index score -0.11 – 1.0)

FAQ: Functional Activities Questionnaire (score 0-30)
FIM: Functional Independence Measure (score 18-126)
HADS anxiety: Hospital Anxiety and Depression Scale anxiety subscale (score; max. 21)
HADS depr: Hospital Anxiety and Depression Scale depression subscale (score; max. 21)
IES: Impact of Event Scale (score 0-75)
IES-R: Impact of Event Scale-Revised (score 0-88)
ISWT: Incremental Shuttle Walk Test (meters)
Jamar: Hand grip dynamometer (kg)
Katz ADL: Katz index of independence in Activities of Daily Living (score 0-6)
MMSE: Mini Mental State Examination (score; max. 30)
MMT: Manual Muscle Testing (grade 0-5 for muscle/per muscle group)
modified ICF: modified International Classification of Functioning, Disability and Health (code of absence or presence of problems used)
MRC: Medical Research Council scale (grade 0-5 for muscle/per muscle group)
mRS: modified Rankin Scale (scale 0-6)
PDS: PTSD Diagnostic Scale (score 0-51)
PTSS: Post-Traumatic Stress Scale (score 7-70)
PTSS-14: Post-Traumatic Stress Syndrome 14-Questions Inventory (score 14-98)
RMI: Rivermead Mobility Index (score 0-15)
SF-36 MCS: Short Form 36-item health survey Mental health Component Score (scale 0-100)
SF-36 PCS: Short Form 36-item health survey Physical health Component Score (scale 0-100)
SF-36 PF: Short Form 36-item health survey Physical Function (scale 0-100)
SF-36: Short Form 36-item health survey
SF-8 MCS: Short Form 8-item health survey Mental health Component Score (scale 0-100)
SF-8 PCS: Short Form 8-item health survey Physical Component Score (scale 0-100)
SF-8: Short form 8-item health survey
Tower test: achievement score of D-KEFS (score 0-20)
TST: Timed-Stands-Test (seconds)
TUG: Time-Up and Go test (seconds)
VAS: Visual Analog Scale (scale 0-100)

Diskussion

Zusammenfassung der Ergebnisse des Reviews und Beantwortung der Reviewfragen

Mithilfe des systematischen Reviews konnten 18 vergleichende Studien, die 2.510 Patienten nach kritischer Erkrankung eingeschlossen hatten, identifiziert werden. Sie testeten stationäre (n=4 Studien), ambulante (n=9) oder sektorübergreifende (n=5) spezifische Nachsorge- und Rehabilitationsverfahren nach Entlassung von der ITS. Insgesamt 20 verschiedene Outcomes, erhoben mit mehr als 45 Messinstrumenten, wurden in den Studien verwendet. Acht Studien wurden aufgrund guter bis moderater Studienqualität in die Effektivitätsbewertung einbezogen. Sie umfassen stationäre geriatrische Rehabilitation, ITS-Nachsorge-Sprechstunden, ambulante Rehabilitationsprogramme, Disease Management und ITS-Tagebücher. Fünf dieser Studien untersuchten den Einfluss auf PTBS, vier davon mit einem positiven Effekt: ITS-Tagebücher (n=2) reduzierten das Neuauftreten von PTBS nach drei Monaten und PTBS-Symptome nach einem Jahr. In einer ITS-Nachsorge-Sprechstunde behandelte Frauen zeigten geringere Symptome und ein Selbsthilfemanual reduzierte Symptome nach acht Wochen, jedoch nicht nach sechs Monaten. Keines der anderen Outcomes konnte in mehreren Studien effektiv beeinflusst werden.

Zusammenfassend lässt sich die Hauptreviewfrage damit folgendermaßen beantworten: Bisher gibt es kaum effektive Nachsorge- und Rehabilitationsinterventionen für kritisch kranke Patienten. Auf der Grundlage dieser Arbeit können für PTBS-Symptome erste Empfehlungen für den Einsatz von ITS-Tagebüchern gegeben werden, deren klinischer Einsatz effektiv zu sein scheint.

Für den Einsatz von ITS-Tagebüchern, welche nach dem intensivmedizinischen Aufenthalt an die Patienten übergeben wurden, wurde in diesem systematischen Review die beste Evidenz für eine positive Beeinflussung seelischer Symptome des PICS gefunden. Dabei handelt es sich um schriftliche Aufzeichnungen, manchmal zusätzlich auch Fotos, die vom ITS-Personal, teilweise auch von Angehörigen des kritisch Kranken während des ITS-Aufenthalts (und teilweise über den gesamten stationären Aufenthalt) angefertigt werden. Das Tagebuch enthält Eintragungen zum individuellen Krankheitsverlauf des Patienten, zu notwendigen operativen Eingriffen, Vorgängen auf der ITS, Verhalten und Reaktionen des Patienten etc. ITS-Tagebücher sollen somit dem Patienten nach dem Krankenhausaufenthalt helfen, das Erlebte zu verstehen, Erinnerungslücken zu füllen und den ITS-Aufenthalt nachzuvollziehen (Knowles und

Tarrier 2009, Jones et al. 2010, Egerod et al. 2011). Sie sind kostengünstig und werden von den Patienten gut angenommen (Storli und Lind 2009, Egerod et al. 2007). Wahrscheinlich erleichtern die individuellen Eintragungen die Kommunikation über die ITS-Zeit und die damit verbundenen Erlebnisse der Patienten. Auch helfen sie, die Eindrücke und Ereignisse zu verarbeiten und beugen somit möglicherweise einer PTBS vor (Storli und Lind 2009, Egerod et al. 2011).
Die Intervention durch ITS-Tagebücher ist dabei fokussiert auf seelische Folgeerscheinungen und konnte auf diesem Gebiet positive Effekte erzielen.
Die meisten der anderen Interventionen, d.h. stationäre geriatrische Rehabilitation, ITS-Nachsorge-Sprechstunden, ambulante Rehabilitationsprogramme und Disease Management Support Service, die teilweise sehr intensiv versuchten verschiedene PICS-Symptome zu beeinflussen, hatten lediglich in einzelnen Outcomes Effekte. Meist auch hier im Bereich PTBS.

Mögliche Bias und methodische Qualität der eingeschlossenen Studien

Ursächlich für die fehlende generelle Effektivität komplexer Interventionen und Nachsorgeprogramme könnten die Heterogenität der Studienpopulation kritisch Kranker sowie Qualitätsaspekte wie Selektionsbias und Attrition Bias sein. Bias beschreibt eine Verzerrung der Studienergebnisse, d.h. jeden einflussnehmenden Prozess innerhalb der Studiendurchführung und -auswertung, der zu einer systematischen Abweichung der gemessenen Studienergebnisse von den eigentlich richtigen Ergebnissen führt (Juni et al. 2001). Ein Selektionsbias entsteht bei der Auswahl der Studienteilnehmer, ein Attrition Bias durch Abweichungen vom eigentlichen Studienprotokoll sowie durch den Verlust von Studienteilnehmern für die finale Auswertung der Ergebnisse (Drop outs/ loss to follow-up) (Juni et al. 2001).
Ein Selektionsbias entsteht in den meisten der im systematischen Review eingeschlossenen Studien dadurch, dass Patienten an den Interventionen nur teilnehmen konnten, wenn sie einen gewissen Grad an Mobilität und kognitiver Leistungen vorweisen konnten. Da aber direkt nach ITS-Entlassung fast drei Viertel aller Patienten deutliche körperliche Einschränkungen zeigen und ein Drittel aller Patienten kognitive Defizite aufweisen (van der Schaaf et al. 2008), muss davon ausgegangen werden, dass durch diese Selektion mit den Studienpopulationen eher fittere Patienten abgebildet wurden. Daher können die Studienergebnisse nicht für die Gesamtheit aller Patienten mit kritischer Erkrankung generalisiert werden. Außerdem sind die Population der Patienten nach kritischer Erkrankung sowie die Arten der Interventionen sehr

komplex und heterogen, was eine Verallgemeinerung der Studienergebnisse schwierig macht. Attrition Bias entsteht durch die natürlich bedingte hohe Mortalität und Morbidität nach einer kritischen Erkrankung (Desai et al. 2011, Winters et al. 2010). Sie führen zu hohen Drop-out Raten in den Studien, wodurch wiederum eher gesündere Patienten schlussendlich in die Auswertungen einbezogen werden. All diese Aspekte verschleiern möglicherweise positive Effekte der Interventionen bzw. von spezifischen Komponenten der Nachsorgeprogramme in den Studienauswertungen.
Die ausbleibende generelle Verbesserung für körperliche und mentale Einschränkungen durch komplexe Interventionen wie ITS-Nachsorge-Sprechstunde oder ambulante Rehabilitationsprogramme könnte zusätzlich durch einen verzögerten Beginn der Maßnahmen bedingt sein. So konnte nachgewiesen werden, dass ein sofortiger Beginn von physiotherapeutischer Beübung auf der ITS im Vergleich zu einer verzögert beginnenden Rehabilitation zu einer schnelleren Besserung körperlicher Einschränkungen und besseren funktionellen Outcomes führt (Thomas 2011).

Bedeutung der Ergebnisse für die klinische Praxis

Ärzten, die mit der Nachsorge von Patienten mit überstandener kritischer Erkrankung betraut sind, bietet die Publikation erstmals eine evidenzbasierte Übersicht von in vergleichenden klinischen Studien getesteten Interventionen für PICS. PICS ist ein neu definiertes Konstrukt, das die Folgeerscheinungen kritischer Erkrankungen als Syndrom zusammenfasst. Dadurch bietet das PICS behandelnden Ärzten die Möglichkeit, diesen heterogenen und aus verschiedenen Symptomen bestehenden Folgezustand zu beschreiben und dementsprechend auch zu erkennen und gezielten Behandlungen zuzuführen. Aus der klinischen Erfahrung heraus ist anzunehmen, dass Patienten, die in Folge eines ITS-Aufenthalts beispielsweise eine Depression, Angststörung oder PTBS entwickeln, von einer etablierten psychologischen Therapie, wie z.B. Verhaltenstherapie, profitieren könnten. Gleiches gilt für eine gezielte Rehabilitation wie es bei bestimmten Erkrankungen (Schlaganfall, Herzinfarkt etc.) bereits Standard ist. Doch oftmals fehlt Patienten nach einer kritischen Erkrankung eine derartig klare Diagnose, die den Zugang zu spezifischen Therapien ermöglichen würde. Mit einer Akzeptanz von PICS als eigenständige Diagnose, die bestimmte therapeutische Maßnahmen verlangt, könnte der Weg zu diesen Therapien für Betroffene geebnet werden. Ebenso könnte durch eine Verbreitung des PICS-Konzepts die Aufmerksamkeit für die Folgeerscheinungen einer kritischen Erkrankung erhöht werden und so bei den Patienten Probleme eher

identifiziert und entsprechend behandelt werden. Der vorliegende systematische Review trägt zu dieser „Öffentlichkeitsarbeit“ bei.
Außerdem unterstützen die Ergebnisse des systematischen Reviews den Einsatz von ITS-Tagebüchern als relativ einfache und kostengünstige Intervention. Ihre Erstellung auch auf deutschen Intensivstationen sollte erwogen werden. In der Intensivmedizin der Universitätsklinik Jena ist eine Einführung von ITS-Tagebüchern auf Grundlage der vorhandenen Interventionsstudien geplant. Sofern ein ITS-Tagebuch vorhanden ist, sollten Ärzte, die Patienten nach einer kritischen Erkrankung betreuen, ihre Patienten ermutigen, es zu lesen und Gespräche zu den Inhalten anbieten.
Insgesamt ist zu erkennen, dass sich die Rehabilitation und Nachsorge von kritisch Kranken über verschiedene Fachdisziplinen und Sektoren erstreckt (ITS, Normalstation, stationäre und ambulante Rehabilitation, ambulante hausärztliche und fachärztliche Betreuung, etc.). Dies führt zu einer Fragmentierung des Prozesses. Eine kontinuierliche Durchführung rehabilitativer Maßnahmen, beginnend in der ITS (Dowds 2007, França et al. 2010, Connolly et al. 2012) ist für eine Verbesserung der Patientenversorgung wünschenswert.

Bedeutung der Ergebnisse für die Allgemeinmedizin

Die Wichtigkeit der ambulanten Betreuung wird durch den systematischen Review ebenfalls aufgezeigt. Vor allem Hausärzte könnten durch die umfassende und langfristige ambulante Betreuung von Patienten (Schlette et al. 2009) eine effektive Prävention bzw. Behandlung des PICS unterstützen. Als Begleiter für Patienten mit chronischen Erkrankungen verbessern sie die Qualität und Effizienz der medizinischen Versorgung eines Gesundheitssystems (Lindenauer et al. 2007, Macinko et al. 2003, Starfield et al. 2005) und reduzieren unzweckmäßige, uneffektive oder übermäßige Facharztkontakte (Starfield et al. 2005).
Um dies auch bei PICS bewirken zu können, müssen Hausärzte in den interdisziplinären Nachsorgeprozess von PICS-Patienten mit einbezogen werden und sollten ambulant rehabilitative und therapeutische Maßnahmen einleiten können.
Bei der systematischen Literaturrecherche zum vorliegenden Review konnte jedoch keine Studie gefunden werden, die eine primärärztliche Nachsorge untersuchte oder den Hausarzt direkt mit einbezog. Ein ähnliches Konzept wie hausärztliche Konsultationen verfolgt die ITS-Nachsorge-Sprechstunde, die durch intensivmedizinisch spezialisiertes Personal als ambulante Sprechstunde an einer Klinik angeboten wird. Sie wurde in drei berücksichtigten Studien (Schandl et al. 2011, Schandl et al. 2012,

Cuthbertson et al. 2009) getestet und mit zwei der Studien in die Effektivitätsbewertung einbezogen (Schandl et al. 2012, Cuthbertson et al. 2009). Es wurde dabei lediglich in einer Studie (Schandl et al. 2012) eine leichte positive Beeinflussung von PTBS und Depressionen gefunden. Die zweite Studie (Cuthbertson et al. 2009) ergab eine negative Kostenbilanz bei fehlender Effektivität bezüglich gesundheitsbezogener Lebensqualität und psychischen Folgeerscheinungen gegenüber der üblichen hausärztlichen Nachsorge für PICS-Patienten. Dabei resultierte die negative Kostenbilanz aus der Bereitstellung von hochspezialisiertem Personal und zusätzlicher Einrichtung einer Spezialsprechstunde am Krankenhaus anstelle einer Integration der Sprechstunde in schon vorhandene Versorgungsstrukturen.

Folgende Aspekte sind bei der Interpretation dieser Studienergebnisse zusätzlich zu berücksichtigen:

- Die Patienten wurden innerhalb eines Jahres nur zweimal, d.h. nach drei und neun Monaten nach ITS-Entlassung zu Nachsorgeterminen in der Spezialsprechstunde gesehen, was angesichts der Vielfältigkeit und möglichen Schwere von PICS zu selten scheint.

- Insgesamt dauerte die aktive Nachsorge nur neun Monate. Jedoch treten insbesondere psychische Folgeerscheinungen auch mit Verzögerung auf (Desai et al. 2011) bzw. werden erst nach einer gewissen Zeit vom Patienten als belastend wahrgenommen. In der akuten Situation der kritischen Erkrankung steht der „Kampf ums Überleben“ im Vordergrund. Ist dieser überwunden, können Schmerzen, Polyneuropathien, Depressionen u.a. mehr in den Fokus des Patienten rücken. Daher scheint eine aktive Nachsorge von neun Monaten nicht langfristig genug zu sein.

- Die durch die Hausärzte durchgeführte Nachsorge könnte den Ergebnissen folgend genauso effektiv sein wie die der Spezialsprechstunde. Die Bestandteile dieser „üblichen“ Nachsorge wurden aber nicht dokumentiert.

Viele Aspekte der ITS-Nachsorge-Sprechstunde wie die Kontrolle der aktuellen Medikation, ggf. Überweisungen zum Facharzt, Gespräche über die akute Erkrankung etc. sind höchstwahrscheinlich auch Routinebestandteile der hausärztlichen Nachsorge. Lediglich das strukturierte Screening mittels ausgewählter Tests und Fragebögen

bezüglich typischer PICS-Symptome ist vermutlich kein standardmäßig durchgeführter Prozess. Somit könnte die Bereitstellung valider und reliabler Screeninginstrumente die hausärztliche Nachsorge zusätzlich unterstützen. Ein Großteil der Elemente der Spezialsprechstunde ist somit vermutlich bereits Bestandteil der primärärztlichen Nachsorge oder kann in sie integriert werden. Dies könnte ohne großen Zusatzaufwand zu einer effektiven und kostengünstigen Nachsorge für PICS-Patienten beitragen. Eine Übersicht vorhandener Testinstrumente unter Angaben zu Validiät und Reliabilität ist im Supplemental Digital Content der Publikation des systematischen Reviews (Mehlhorn et al. 2014) sowie bei Elliott et al. (Elliott et al. 2011) zu finden. Essentiell für eine effektive primärärztliche Behandlung ist somit vor allem das Wissen zu typischen PICS-Symptomen, eine strukturierte, valide Testung in Kombination mit der in der Primärmedizin typischen personenorientierten, kontinuierlichen und koordinierenden Versorgung (Lindenauer et al. 2007) sowie eine langfristige und bei Bedarf engmaschige Betreuung.

Dass dieses Konzept funktionieren kann, wurde an einem anderen Beispiel in einer Metaanalyse gezeigt. Speziell geschulte und gut organisierte Hausärzte, die die Möglichkeit für Rückfragen an Spezialisten hatten, sorgten bei Patienten mit Diabetes mellitus für eine mindestens gleich gute, teilweise auch bessere Blutzuckereinstellung, niedrigere Mortalität und für langfristigere, regelmäßigere Follow-ups als eine an die Klinik angegliederte Spezialsprechstunde (Griffin 1998).

Auch der Einbezug des Hausarztes für körperliche Rehabilitationsmaßnahmen ist nicht abwegig. Es war auffällig, dass keine der im Review eingeschlossenen Studien zur körperlichen Rehabilitation diesen Ansatz wählte. Die Übungsprogramme wurden in der Regel von ITS-Nachsorge-Schwestern bzw. durch eine ITS-Nachsorge-Sprechstunde koordiniert (Jones et al. 2003, McWilliams et al. 2009, Elliott et al. 2011, Jackson et al. 2012). Dass dieses Konzept möglich ist, zeigt die momentan laufende Studie HomeFit der Fakultät für Sportwissenschaften der Ruhr-Universität Bochum in Zusammenarbeit mit dem Institut für Allgemeinmedizin und Familienmedizin Witten/Herdecke (Hinrichs et al. 2011). Unter Koordination und Überwachung durch ihren Hausarzt erhalten geriatrische, chronisch kranke Patienten in der Häuslichkeit physiotherapeutisches, körperliches Training. Gezeigt werden soll, dass die Intervention zu einer gesteigerten Kraft und Mobilität der Probanden führt.

Bedeutung der Ergebnisse für die Forschung und für CSCC-Projekte

Insgesamt zeigt der Review den Forschungsbedarf im Bereich der Nachsorge von PICS auf, denn bisher besteht aufgrund fehlender effektiver Nachsorgeprogramme eine Versorgungslücke für Patienten nach einer kritischen Erkrankung. Ein erster Schritt zum Schließen dieser Lücke kann möglicherweise durch neue Interventionsstudien, wie beispielsweise vom CSCC Jena initiiert, gemacht werden. Die Daten des systematischen Reviews können dabei flankierende Hilfestellung für die Konzeption neuer Projekte bieten.
Auffällig ist ein Mangel an Interventionen, die den Hausarzt direkt in die Nachsorge der PICS-Patienten einbezieht. Die mangelnde Individualität der Interventionen scheint ebenfalls eine Schwachstelle zu sein. Lediglich in den Interventionen der ITS-Nachsorge-Sprechstunde (Cuthbertson et al. 2009, Schandl et al. 2011, Schandl et al. 2012) und dem identifizierten Disease Management Support Service (Daly et al. 2005, Douglas et al. 2007) werden die Interventionselemente und Empfehlungen für die Patienten direkt an ihre individuellen Test- und Monitoringergebnisse angelehnt und auf die relevantesten Störungen des Patienten bezogen. Beiden Interventionen fehlt jedoch die wahrscheinlich notwendige Langfristigkeit bzw. Engmaschigkeit. In den meisten der anderen Interventionen erhielt jeder Patient, unabhängig von seinen individuellen Einschränkungen, das gleiche Interventionsprogramm. Bezüglich der Involvierung des Hausarztes sowie einer langfristigen, individuellen Intervention kann zukünftig die derzeit laufende SMOOTH-Studie (Sepsis Survivors Monitoring and Coordination in Outpatient Health Care) (Schmidt et al. 2014) des CSCC und des Instituts für Allgemeinmedizin des Universitätsklinikums Jena nach ihrem Abschluss weitere Erkenntnisse liefern.

Der systematische Review zeigt auch, dass bestimmte PICS-Forschungsfelder bisher kaum bearbeitet sind. Beispielsweise untersucht jeweils nur eine Studie kognitives Training zur Verbesserung mentaler Folgeerscheinungen (Jackson et al. 2011) bzw. die Verbesserung von Schmerz bei PICS (Salisbury et al. 2010). Dies betont gleichzeitig die Wichtigkeit aktuell laufender CSCC-Interventionsstudien wie Los-Cog-Train bzw. NeuroPAIN für diese PICS-Symptome. Die Daten zu psychischen Folgeerscheinungen sowie zu Critical Illness Polyneuropathie aus den eingeschlossenen Studien können ebenfalls für Vergleiche mit neuen Interventionsstudien (bspw. Studien Crisis und Neuro-SOS des CSCC) genutzt werden.

Methodische Limitationen des systematischen Reviews

Ein systematischer Review nach PRISMA-Leitlinien ist gut geeignet, um vorhandene Evidenz zusammenzustellen, zu bewerten und Interessenten zugänglich zu machen (Centre for Reviews and Dissemination 2009, Higgins und Green 2011, Thomas et al. 2004). Aufgrund der Komplexität der relevanten Interventionen, war es erforderlich, neben randomisierten kontrollierten Studien weitere kontrollierte Studiendesigns einzuschließen, was entsprechend der Empfehlungen der Cochrane NRSMG und des Centre for Reviews and Dissemination erfolgte (Eccles et al. 2003, Higgins und Green 2011, Centre for Reviews and Dissemination 2009).
Das von uns für die Qualitätsbewertung der eingeschlossenen Studien ausgewählte EPHPP Quality Assessment Tool ist eines der wenigen validen und reliablen Instrumente für die gleichzeitige Qualitätsbewertung von randomisierten und nicht-randomisierten Studien (Deeks et al. 2003). Es wurde explizit für quantitative Interventionsstudien unterschiedlicher Designs und für systematische Reviews, die eine Effektivitätsbewertung von Interventionen verschiedenster Art durchführen, entwickelt (Thomas et al. 2004, National Collaborating Centre for Methods and Tools 2008). Seine Anwendung macht die Qualitätsbewertung der eingeschlossenen Studien transparent und reproduzierbar.
Die Suchstrategie für den systematischen Review war extensiv, aufgrund der stark variierenden Begrifflichkeiten des Forschungsfeldes wurden jedoch möglicherweise nicht alle relevante Studien gefunden. Die Anzahl der in der Effektivitätsbewertung einbezogenen Studien und der durch sie eingeschlossenen Patienten ist gering. Das Fehlen von Angaben zu statistischen Effektstärken in einem Großteil der Studien erschwerte die Effektivitätsbewertung. Die Klassifizierung der Interventionen ist bedingt durch ihre Vielfältigkeit lediglich deskriptiv. Die Klassifikationsparameter dafür wurden aus der Zusammenschau der Interventionen eigenständig abgeleitet, da kein gültiger Klassifikationsstandard verfügbar und somit anwendbar ist. Insgesamt war es aufgrund der Heterogenität der Studienpopulationen, der Interventionen und der Outcomes anspruchsvoll, die Daten zu klassifizieren und zusammenzufassen. Eine Metaanalyse war aus den genannten Gründen und der insgesamt begrenzten Daten nicht möglich.
Da wir nur Studien berücksichtigten, die in durch Experten begutachteten (peer-reviewed) Zeitschriften veröffentlicht wurden, ist ein Publikationsbias nicht auszuschließen. Dies scheint jedoch nicht relevant, da die meisten veröffentlichten Studien keine generelle Effektivität zeigten, in der Regel mit hohem Aufwand verbunden

sind und keine offensichtlichen wirtschaftlichen Interessen hinter den Interventionen stehen. Sprachbias wurde durch die Suche ohne Einschränkung der Publikationssprache minimiert.

Das Forschungsfeld der Interventionen für PICS hat sich erst in den letzten Jahren entwickelt und wird aktuell intensiv beforscht, wodurch die Erkenntnisse des vorliegenden Reviews durch aktuell laufende klinische Studien (Connolly et al. 2012) voraussichtlich in den folgenden Jahren erweitert werden.

Schlussfolgerungen

Mithilfe des systematischen Reviews konnten stationäre, ambulante und sektorübergreifende Nachsorgeinterventionen für kritisch kranke Patienten identifiziert werden. Dabei zeigte sich vor allem, dass PTBS-Symptome, insbesondere durch den Einsatz von ITS-Tagebüchern beeinflussbar sind. Der klinische Einsatz von ITS-Tagebüchern zur Vermeidung neuer PTBS und Reduktion von PTBS-Symptomen ist entsprechend der verfügbaren Daten effektiv und ihre Weiterverwendung sollte auch in der primärärztlichen Versorgung unterstützt werden, um PTBS-Symptomen vorzubeugen oder sie zu lindern. Die Einführung von ITS-Tagebüchern für kritisch kranke Patienten auf der Intensivstation erscheint sinnvoll. Sofern ein ITS-Tagebuch vorhanden ist, sollten Patienten ermutigt werden, es zu lesen und Gespräche zu den Inhalten angeboten werden.

Insgesamt gibt es bisher nur wenige postakute Interventionsstudien für PICS bei Erwachsenen mit mittlerer bis hoher methodischer Qualität, so dass nur begrenzt Daten vorhanden sind. Unter ihnen ist aktuell keine generell effektive Nachsorgeintervention für kritisch kranke Patienten. Für eine Reihe von PICS-Symptomen wie z.B. kognitive Defizite, chronische Schmerzzustände oder Störungen der Sinnesorgane gibt es keine oder allenfalls in Pilotstudien getestete Interventionen. Durch den systematischen Review konnte somit gezeigt werden, dass aufgrund fehlender effektiver Nachsorgeprogramme eine Versorgungslücke für Patienten nach einer kritischen Erkrankung besteht. Entsprechend der durch den systematischen Review identifizierten Daten können klinische Studien, wie beispielsweise die vom Institut für Allgemeinmedizin Jena koordinierte Studie SMOOTH und weitere Projekte des Forschungsfeldes Langzeitfolgen des CSCC Jena zur Verkleinerung dieser Lücke beitragen. Bei ihrer Auswertung wie auch bei der Konzeption von Folgeprojekten können mit dem vorliegenden systematischen Review identifizierte Daten genutzt werden.

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Anhang

Erklärung zum Aufbau der Suchstrategie

Ziel der Suche ist es, Interventionen zur Prävention, Nachsorge, Rehabilitation oder Behandlung des PICS im Allgemeinen oder für einzelne Komponenten des PICS nach Entlassung von der ITS zu identifizieren. Dazu ist eine komplexe Suchstrategie notwendig: einerseits da der Begriff Postintensive Care Syndrome erst seit dem Jahr 2012 definiert ist und die gewünschte Population von Patienten nach überstandener kritischer Erkrankung davor nicht ausschließlich durch einen Suchbegriff zu erfassen ist; andererseits um zu vermeiden, dass große Mengen an Literatur gefunden werden, die sich ausschließlich auf die akute kritische Erkrankung beziehen. Daher erstellten wir fünf Suchstrings, die wir in mehreren Schritten miteinander verknüpften.

Die ersten beiden Suchstrings beschreiben die Population. Suchstring 1 (Zeile 1 bis 11 der hier im Anhang veröffentlichten Suchstrategie in MEDLINE) fasst akute kritische Erkrankungen bzw. akute Begleiterscheinungen zusammen. Suchstring 2 (Zeile 12 bis 19) umfasst überstandene kritische Erkrankungen bzw. ITS-Behandlungen, also postakute Patienten. Im 3. Suchstring (Zeile 20 bis 33) sind Begriffe für Nachsorge, Rehabilitation und postakute Behandlungen zusammengefasst. Suchstring 4 (Zeile 34 bis 48) vereint Begriffe für Behandlungen bzw. Therapien im Allgemeinen. Um diese von der Akutbehandlung kritisch Kranker zu unterscheiden, gibt es den 5. Suchstring (Zeile 49 bis 59), der Begriffe für ein postakutes bzw. ambulantes Setting im Allgemeinen vereint.

Anschließend kombinierten wir die Suchstrings, wobei in jeder Kombination das postakute Setting eingeschlossen wird, entweder durch die genutzte Population, Behandlungsoptionen im postakuten Setting oder durch Hinzufügen von Begriffen, die das postakute Setting im Allgemeinen beschreiben (siehe auch Tabelle Anhang 1).

A: Die gesamte Population (Suchstring 1 und 2) wird kombiniert mit postakuten Behandlungen (Suchstring 3; Zeile 60 bis 61).

B: Begriffe der akuten Erkrankung (Suchstring 1) werden mit Therapieoptionen im Allgemeinen (Suchstring 4) und dem postakuten Setting (Suchstring 5) verknüpft (Zeile 62).

C: Postakute Patienten (Suchstring 2) werden mit Therapieoptionen im Allgemeinen (Suchstring 4) kombiniert (Zeile 63).

Durch eine Verknüpfung von A, B und C mit ODER (Zeile 64) werden Duplikate von Suchergebnissen der einzelnen Kombinationen ausgeschlossen. Ergänzt werden weitere Einschränkungen der Suchergebnisse (Zeilen 65 bis 68) durch Ausschluss bestimmter Begriffe entsprechend der Ausschlusskriterien des Reviews sowie bestimmter Publikationsformen und durch eine zeitliche Begrenzung für die Veröffentlichung der Literatur (Zeile 69).

Nr. des Such-strings	**Inhalt des Suchstrings**	**Kombination A**	**Kombination B**	**Kombination C**
1	akute kritische Erkrankung oder akute Begleiterscheinung	**X**	**X**	
2	postakute Patienten (nach überstandener kritischer Erkrankung oder ITS-Behandlung)	**X**		**X**
3	Nachsorge, Rehabilitation, Therapien, die postakut stattfinden	**X**		
4	Therapieoptionen im Allgemeinen		**X**	**X**
5	postakutes Setting		**X**	
		(1 or 2) and 3	**1 and 4 and 5**	**2 and 5**
A or B or C				

Tabelle Anhang 1: Inhaltliche Kombination der Suchstrings der durchgeführten Suche

Suchstrategie in MEDLINE

Datenbank: Ovid MEDLINE(R) Daily Update <June 12, 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

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1 (critical adj2 illness$2).ti,ab. (4051)

2 critical illness.sh. (13950)

3 (critical$2 adj2 ill).ti,ab. (23151)

4 sepsis.ti,ab,sh. (78268)

5 septic$.ti,ab. (49099)

6 ARDS.ti,ab. (6544)

7 respiratory distress syndrome.ti,ab. (16221)

8 respiratory distress syndrome, adult.sh. (13694)

9 (icu acquired adj (weakness or paralysis or paresis)).ti,ab. (37)

10 (intensive care adj2 acquired adj (weakness or paralysis or paresis)).ti,ab. (24)

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (154493)

12 ((intensive care or critical care or ICU or critical illness or ARDS or respiratory distress syndrome or sepsis) adj3 survivor$1).ti,ab. (684)

13 ((after or following or post) adj (intensive care or ICU or critical illness or ARDS or acute respiratory distress syndrome or sepsis)).ti,ab. (1642)

14 ((after or following or post) adj ((intensive care or ICU) adj admission)).ti,ab. (341)

15 13 not 14 (1301)

16 postintensive care.ti,ab. (17)

17 (chronic$4 adj (critical illness$2 or critical$2 ill)).ti,ab. (125)

18 (discharge adj2 (intensive care or critical care or ICU)).ti,ab. (802)

19 12 or 15 or 16 or 17 or 18 (2512)

20 rehabilitat$.ti,ab. (93535)

21 exp rehabilitation/ (133860)

22 (follow up adj3 (intensive care or ICU)).ti,ab. (167)

23 follow up care.ti,ab. (2221)

24 ICU clinic$1.ti,ab. (5)

25 aftercare$1.ti,ab,sh. (7427)

26 ((postacute or post acute or postdischarge or post discharge or after) adj care$1).ti,ab. (1921)

27 ambulatory care.ti,ab,sh. (36599)

28 aftertreatment.ti,ab. (119)

29 disease management.ti,ab. (6627)

30 exp disease management/ (22629)

31 patient care planning.ti,ab. (83)

32 exp patient care planning/ (48375)

33 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (313915)

34 therap$.ti,ab. (1583741)

35 treat$4.ti,ab. (3219066)

36 manage.ti,ab. (34750)
37 management.ti,ab. (593302)
38 interven$.ti,ab. (473482)
39 program$2.ti,ab. (422127)
40 physiotherap$.ti,ab. (13004)
41 train$3.ti,ab. (278485)
42 exercise.ti,ab. (154469)
43 exp Physical Therapy Modalities/ (111733)
44 psychotherap$.ti,ab. (29022)
45 exp psychotherapy/ (138969)
46 patient education.ti,ab. (10011)
47 patient education as topic/ (64887)
48 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 46 or 47 (5199139)
49 outpatient$1.ti,ab,sh. (98262)
50 ambulatory.ti,ab. (53914)
51 ((after or post or following) adj2 discharge$).ti,ab. (20338)
52 ((after or post or following) adj hospital).ti,ab. (4102)
53 (postacute or post acute).ti,ab. (1884)
54 ((general or family) adj practi$).ti,ab. (64235)
55 GP.ti,ab. (24350)
56 exp General Practice/ (61109)
57 primary health care.ti,ab,sh. (54068)
58 (primary adj (healthcare or care)).ti,ab. (61360)
59 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 (345684)
60 11 or 19 (155421)
61 60 and 33 (1991)
62 11 and 48 and 59 (1820)
63 19 and 48 (1436)
64 61 or 62 or 63 (4717)
65 (comment or editorial or news or newspaper article or letter or historical article or in vitro or introductory journal article or directory or interview).pt. (2013352)
66 (stroke or cancer or neoplasm or carcinoma or palliative or child$ or pediatr$ or infant$ or neonat$ or baby or babies or newborn$ or pregnan$ or obstetric$ or prenatal or (myocard$ adj infarction) or coronary syndrome or cardiac surgery or spinal cord or rat or rats or mice or mouse or murine or case report).ti. (3088637)
67 64 not 65 (4578)
68 67 not 66 (3683)
69 limit 68 to yr="1991 -Current" (3270)

Journals, in denen die Handsuche durchgeführt wurde

Die Handsuche wurde für die im Jahr 2012 herausgegebenen Ausgaben (bis einschließlich 13.07.2012) von Journals durchgeführt,

- die in den systematischen Review eingeschlossene Studien veröffentlichten,
- die eine Vielzahl relevanter Artikel zum Thema PICS beispielsweise in Form von narrativen Reviews oder qualitativen Studien veröffentlichten)
- die sich speziell mit Rehabilitation und Nachsorge beschäftigen

1. Journals mit Schwerpunkt Intensivmedizin
    a. Critical Care : Vol. 16/1 -16/4:
    b. Critical Care Medicine: Vol. 40/1 - 40/7; published ahead of print
    c. Intensive Care Medicine: Vol. 38/21 - 38/7; online first
    d. Critical Care Clinics: Vol. 28/1 - 28/3
    e. American Journal of Critical Care: Vol. 21/4
    f. American Journal of Respiratory & Critical Care Medicine: Vol. 185/1 – 186/1; articles in press
    g. Chest: Vol. 141/1-142/1
    h. JAMA: Vol. 307/1 - 308/2; online first

2. Journals mit Schwerpunkt Intensivmedizinische Pflege
    a. Nursing in Critical Care (Nurs Crit Care): Vol. 17/1 - 17/4; early view
    b. Intensive and Critical Care Nursing: Vol. 28/1 – 28/4; virtual issues
    c. Critical Care Nurse: Vol. 32/1 - 32/3
    d. Critical Care Nursing Clinics of North America: Vol 24/1 – 24/2
    e. Nursing research: Vol. 61/1 – 61/4; published ahead of print

3. Journals mit Schwerpunkt Rehabilitation
    a. Disability & Rehabilitation: Vol. 34/1 – 34/17; early online
    b. Archives of Physical Medicine & Rehabilitation: Vol. 93/1 – 93/7
    c. Clinical Rehabilitation: Vol. 26/1 – 26/7; online first
    d. Journal of Rehabilitation Medicine: Vol. 44/1 – 44/8; preview of unpublished papers
    e. Am J Phys Med Rehabil: Vol. 91/1 – 91/7; published ahead of print

Rationale für die Fokusierung auf Interventionen, die der Patient nach der ITS-Behandlung erhält

Heutzutage werden Strategien der frühen Rehabilitation als ein wichtiger Baustein der intensivmedizinischen Behandlung in industrialisierten Ländern angesehen (Denehy und Berney 2006). Wir gehen davon aus, dass die frühzeitige Rehabilitationsbehandlung ein routinemäßiger Bestandteil der Standardtherapie auf der ITS ist. Frühzeitige Rehabilitationsbemühungen fokussieren sich in der Regel auf die Entwöhnung von der Beatmung und die Prävention von Muskelschwund und körperlicher Schwäche. Diese Maßnahmen wurden in den letzten Jahren intensiv mit klinischen Studien untersucht und in mehreren systematischen Reviews zusammengefasst (Denehy und Berney 2006, Dowds 2007, Choi et al. 2008, O'Connor und Walsham 2009, Chlan 2009, França et al. 2010, Blackwood et al. 2011, Thomas 2011, White et al. 2011). Die Ergebnisse sind heterogen aber im Allgemeinen erwiesenen sich Maßnahmen der frühzeitigen Rehabilitation als sicher und zumindest teilweise effektiv, vor allem bei der Entwöhnung von der Beatmung, Zunahme der muskulären Kraft, Verbesserung der körperlichen Funktion und der Aktivitäten des alltäglichen Lebens.
Anhand dieser Publikationen lässt sich ableiten, dass eine Kombination aus frühzeitiger Rehabilitationsbehandlung und Rehabilitationsverfahren nach der ITS-Behandlung zu einem verbesserten Outcome für die Patienten führen kann, verglichen zu alleiniger Rehabilitation poststationär. Diese Aussage lässt sich treffen, ohne die Ansätze der frühzeitigen Rehabilitation in unserem systematischen Review erneut zu beurteilen.
Ziel unserer Arbeit war es vor allem, Kollegen, die mit der post-ITS Behandlung der Patienten konfrontiert sind, eine Übersicht über vorhandenen Nachsorge- und Rehabilitationsstrategien und deren Effektivität zur Verfügung zu stellen. Dieser Teil der Betreuung für Patienten mit (möglichem) PICS ist bisher nicht derart etabliert, wenig untersucht und noch kein standardmäßiger Bestandteil der Behandlung im Gegensatz zur frühen Rehabilitation auf der ITS. Um diesen Aspekt Rechnung zu tragen, haben wir im Paper in der Discussion den folgenden Absatz eingefügt:

“In clinical practice the rehabilitation and aftercare process for patients with critical illness is still fragmented. Considering the evidence for safety and effectiveness of early rehabilitation beginning in the ICU (15, 16, 20, 23) a continuum of care starting with early rehabilitation and lasting beyond ICU and hospital discharge is desirable to improve short- and long-term outcomes for ICU-survivors.”

QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES

COMPONENT RATINGS

A) SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

1 Very likely
2 Somewhat likely
3 Not likely
4 Can't tell

(Q2) What percentage of selected individuals agreed to participate?

1 80 - 100% agreement
2 60 – 79% agreement
3 less than 60% agreement
4 Not applicable
5 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

B) STUDY DESIGN

Indicate the study design

1 Randomized controlled trial
2 Controlled clinical trial
3 Cohort analytic (two group pre + post)
4 Case-control
5 Cohort (one group pre + post (before and after))
6 Interrupted time series
7 Other specify _____
8 Can't tell

Was the study described as randomized? If NO, go to Component C.

No Yes

If Yes, was the method of randomization described? (See dictionary)

No Yes

If Yes, was the method appropriate? (See dictionary)

No Yes

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

C) CONFOUNDERS

(Q1) Were there important differences between groups prior to the intervention?

1 Yes
2 No
3 Can't tell

The following are examples of confounders:

1 Race
2 Sex
3 Marital status/family
4 Age
5 SES (income or class)
6 Education
7 Health status
8 Pre-intervention score on outcome measure

(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?

1 80 – 100% (most)
2 60 – 79% (some)
3 Less than 60% (few or none)
4 Can't Tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

D) BLINDING

(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?

1 Yes
2 No
3 Can't tell

(Q2) Were the study participants aware of the research question?

1 Yes
2 No
3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

E) DATA COLLECTION METHODS

(Q1) Were data collection tools shown to be valid?

1 Yes
2 No
3 Can't tell

(Q2) Were data collection tools shown to be reliable?

1 Yes
2 No
3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

F) WITHDRAWALS AND DROP-OUTS

(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?

1 Yes
2 No
3 Can't tell
4 Not Applicable (i.e. one time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).

1 80 -100%
2 60 - 79%
3 less than 60%
4 Can't tell
5 Not Applicable (i.e. Retrospective case-control)

RATE THIS SECTION	STRONG	MODERATE	WEAK	
See dictionary	1	2	3	Not Applicable

G) INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?

1 80 -100%
2 60 - 79%
3 less than 60%
4 Can't tell

(Q2) Was the consistency of the intervention measured?

1 Yes
2 No
3 Can't tell

(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?

4 Yes
5 No
6 Can't tell

H) ANALYSES

(Q1) Indicate the unit of allocation (circle one)

community organization/institution practice/office individual

(Q2) Indicate the unit of analysis (circle one)

community organization/institution practice/office individual

(Q3) Are the statistical methods appropriate for the study design?

1 Yes
2 No
3 Can't tell

(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?

1 Yes
2 No
3 Can't tell

GLOBAL RATING

COMPONENT RATINGS

Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

A	**SELECTION BIAS**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
B	**STUDY DESIGN**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
C	**CONFOUNDERS**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
D	**BLINDING**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
E	**DATA COLLECTION METHOD**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
F	**WITHDRAWALS AND DROPOUTS**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	Not Applicable

GLOBAL RATING FOR THIS PAPER (circle one):

1	STRONG	(no WEAK ratings)
2	MODERATE	(one WEAK rating)
3	WEAK	(two or more WEAK ratings)

With both reviewers discussing the ratings:

Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?

No Yes

If yes, indicate the reason for the discrepancy

1	Oversight
2	Differences in interpretation of criteria
3	Differences in interpretation of study

Final decision of both reviewers (circle one):

1	**STRONG**
2	**MODERATE**
3	**WEAK**

PRISMA Checkliste für den publizierten Review

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1263
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1263
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1263-64
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	1264
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1264
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	1264
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	1264
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	1264; full search on request
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	1264
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	1264
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	1264
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	1264
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	1264

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	1264-65; 1268
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	1265; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	supplemental content Table 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	1265; supplemental content Text 1 and Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	a: 1266-67 b: not applicable
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	1268
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	1268
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	1268; 1269
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	1269
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1263

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Befürwortende Stellungnahme des Statistikers PD Dr. Oliver Kuss zum systematischen Review ohne Metaanalyse

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Statistical Review for

Rehabilitation interventions for Post Intensive Care Syndrome. A systematic review.

Mehlhorn J et al.

In their paper, Mehlhorn et al. conducted a systematic review on rehabilitation interventions in adult post-ICU patients.

There is only limited statistical analysis in the paper, instead and due to the heterogeneity of the retrieved studies, the authors constrained their analysis to a narrative review, and performed no meta-analyses. I have no objections concerning this point, indeed it is a widespread misbelief in clinical researchers that every systematic review must contain a meta-analysis.

In terms of other methodological issues, I feel that study design, conduct, and analysis were performed carefully and in compliance with the PRISMA guideline, which is the most recent guideline for performing systematic reviews.

From a statistical viewpoint, I recommend publication of the paper in your journal.

Yours,

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Editorial zum publizierten systematischen Review von Joseph Bienvenu

Effective Post-ICU Rehabilitation of Critical Illness Survivors: What Do We Know?*

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In this issue of *Critical Care Medicine*, Mehlhorn et al (1) provide a timely systematic review of postintensive care interventions to prevent or ameliorate complications of critical illness and intensive care, such as posttraumatic stress, depression, cognitive impairment, and physical weakness. These phenomena are so common in critical illness and ICU survivors (2–5) that a recent Society of Critical Care Medicine task force coined a term to encompass all of them, postintensive care syndrome (PICS), in order to raise awareness (6). It is encouraging that our clinical research colleagues across the globe have embraced this new term so quickly.

Before delving into what the authors found, it is important to note that Mehlhorn et al (1) did not address interventions that patients receive in intensive care. For example, the authors did not review studies of in-ICU interventions such as reducing sedation and providing early physical and cognitive therapy to improve physical strength and cognition, though such studies have shown promising results (7). Similarly, the authors did not review in-ICU psychological interventions that may help reduce post-ICU distress (8) or in-ICU medication interventions (e.g., stress-dose corticosteroids) that may prevent posttraumatic stress symptoms (9). Rather, the authors focused on the post-ICU rehabilitation stage.

At this early stage of research, the use of ICU diaries to prevent or ameliorate posttraumatic stress disorder (PTSD) symptoms appears to be the most promising of the post-ICU interventions studied on a large scale (10, 11). ICU diaries provide patients with invaluable information regarding what they actually went through, in contrast to what they remember going through—clouded by a state of acute brain dysfunction (e.g., many patients remember being imprisoned, tortured, sexually assaulted, and blood coming out of the walls). Note that the work of composing an ICU diary begins while a patient is critically ill and in ICU; however, from the patient's perspective, the intervention (i.e., the patient's reading and viewing the diary) begins during the recovery period. The use of ICU diaries is becoming common in Europe, where critical care clinicians often meet with patients at least once in follow-up; in fact, provision of diaries and outpatient meetings is considered part of good care in many countries. Although clinicians in North America are showing increasing interest in ICU diaries, to my knowledge they are not yet used routinely on this continent, and post-ICU follow-up clinics are just beginning in a few academic centers. Thus, we have much work to do before ICU diary use becomes commonplace on our shores. As noted by Mehlhorn et al (1), other tested interventions were less consistently effective in preventing or reducing PTSD symptoms in critical illness survivors (1). Importantly, the most common early interventions for PTSD symptoms, trauma-focused cognitive-behavioral therapy and "antidepressant" medications (12), have not been studied yet in this population.

Unfortunately, the current research landscape for other PICS phenomena is not as rosy as of yet. At least five studies have assessed the impact of post-ICU interventions (e.g., ICU follow-up clinics and rehabilitation programs) on depression symptoms, and the results are mostly negative—four of these studies are referenced in the systematic review of Mehlhorn et al (1), and an additional one assessed depression as a secondary outcome (13). Strikingly, none of the reviewed studies had high enough quality or numbers of enrolled patients to address interventions to improve cognition—a relatively new area of inquiry (4). Finally, a methodologically strong multisite home-based physical rehabilitation study showed no difference in physical function between groups randomized to the intervention and control groups, perhaps owing to the adequacy of "usual care" in this area (14). It seems likely that physical incapacity attracts substantially more attention in usual care settings than psychological distress (PTSD and depressive phenomena) or cognitive problems (e.g., executive dysfunction and memory problems).

Mehlhorn et al (1) have provided the field a methodologically rigorous systematic review on rehabilitation for postintensive care health problems. The authors highlight the current state of the science, which is promising for ICU diaries and PTSD symptoms, but less so thus far for other aspects of the PICS. Thus, it is clear we have much work to do to determine how we can best help those patients who make it through an acute critical illness, but who develop these common chronic sequelae. We need to be more aware of psychological distress and cognitive impairment in our patients and not just focus on physical rehabilitation. Indeed, it may be that we will be most successful in our rehabilitation efforts when we take a more holistic perspective, attending to psychological, cognitive, and physical problems together, as needed (15). This will be a substantial challenge for our healthcare systems, but this is a worthy endeavor.

*See also p. 1263.

Key Words: cognition; depression; intensive care unit; muscle weakness; posttraumatic stress disorder

The author has disclosed that he does not have any potential conflicts of interest.

DOI: 10.1097/CCM.0000000000000186

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Protokoll des systematischen Reviews

Protocol

(Rehabilitation) Interventions for Postintensive Care Syndrome:

A systematic review.

10.05.2012

1. Review objective

The objective of this review is to find out, if a specific medical post-acute care, rehabilitation or aftercare of typical critical illness-induced sequelae leads to a prevention or an improvement of these impairments. A special focus will be on sepsis as one important critical illness.

2. Background

In Germany there are approximately 79,000 newly diagnosed cases of sepsis and 75,000 of severe sepsis per year. That is an incidence about 116 and 110 per 100,000[1]. Although the hospital mortality of severe sepsis is reported to be around 55% in Germany [1] and the one-year mortality of sepsis varies between 21.5% and 71.9% [2] in general, there is still a considerable number of long term survivors. These patients often suffer from significant and persistent physical and non-physical impairments [3] after discharge from critical care eventually resulting in a reduced quality of life [2, 4].

According to general consensus acute sepsis should be treated on ICU. In Germany this shall be the case [5]. Many of the reported health implications could be due to the ICU-treatment setting. Considering this, it is reasonable and shown that patients with sepsis as well as critical illness treated on ICU develop similar long-term impairments [6].

We are not aware of data on the nationwide number of cases of critical illness. But if we regard the data reported by the Federal Statistical Office Germany on 2,055,087 ICU-cases nationwide in 2010 of which 359,710 cases (18%) needed ventilation, we can conclude that a significant share of these patients suffer from critical illness and that the related long-term impairments are likely to represent a major public health problem [7].

From an economic point of view severe sepsis leads to indirect costs due to productivity loss between 2,622 and 5,660 million Euro per year in Germany. Most of these costs result from premature death [8]. Further data show that most of the money and resources required to treat survivors of severe sepsis is needed during the first year after hospital discharge and 90% of these costs are due to repeated hospital admissions [9]. Therefore aftercare should aim at reducing the need of inpatient treatment, especially during the first year, to mobilise major savings.

Unfortunately it is to be assumed that the typical problems arising from sepsis and critical illness are often not recognised or not appropriately assessed or managed in aftercare. In Germany there is no specific Disease Management Program for sepsis or ICU-survivors. The information given in the S2k guidelines for Prevention and follow-up care of sepsis of the German Sepsis Society and the German Interdisciplinary Association of Intensive Care and Emergency Medicine [10] is shortcut reflecting the missing evidence for general recommendations. In the UK the NICE Clinical Guideline 83 “Rehabilitation after critical illness” was established in 2009 but the authors state evidence is often missing and it contains recommendations only for up to three months after hospital discharge [11]. There is no practicable, evidence-based information available for the general practitioner how

to treat sepsis- or critical illness-specific morbidity after discharge from hospital in the short- and long-run.

That is why a systematic review on the effectiveness of aftercare therapy of sequelae of sepsis and critical illness should be conducted.

As shown in the NICE Guideline [11] only little evidence for a special aftercare program for critical illness or sepsis could be found until 2009. Hence the relevant impairments will be identified and literature will also be searched for evidence in rehabilitation and aftercare for each sequela and not only for structured aftercare programs in general. These efforts aim at identifying available evidence to derive general recommendations. Implementing the findings in all-day practice may thereby improve aftercare for survivors of critical illness and sepsis.

3. Definition of sepsis and critical illness

According to the S2k guidelines for Prevention and follow-up care of sepsis of the German Sepsis Society and the German Interdisciplinary Association of Intensive Care and Emergency Medicine [10] sepsis is a complex and systemic inflammatory reaction of the body to an infection and it is recommended to use the given diagnostic criteria according to the ACCP/SCCM Consensus Conference Committee.

For critical illness there is no official definition even though this term is widely used. In general it describes a potential life-threatening condition, that is treated on ICU and which comes along with organ dysfunction and failure [12]. According to the OvidSP MeSH heading critical illness is “A disease or state in which death is possible or imminent.” and The Anaesthesia Review Group belonging to the Cochrane Collaboration defines critical as follows: “Relating to, indicating, or being the stage of a disease at which an abrupt change for better or worse may be anticipated with reasonable certainty; being or relating to an illness or condition involving danger of death” [13].

Recently an international stakeholders’ conference defined the term “Postintensive Care syndrome” to “describe new or worsening problems in physical, cognitive, or mental health status arising after a critical illness and persisting beyond acute care hospitalization” [14].

4. Aims of the review and resulting review questions

To answer the review object the following aims were defined:

1. Identifying specific interventions for each sequela useable in aftercare and evaluation of their influence on outcome
2. Identifying aftercare programs for each sequela and evaluation of their influence on outcome
3. Identifying aftercare programs or chronic disease management programs for critical illness and/or sepsis in general and evaluation of their influence on outcome
4. Identifying rehabilitation programs or strategies for each sequela and evaluation of their influence on outcome

5. Identifying specific rehabilitation programs or strategies after critical care and/or sepsis and evaluation of their influence on outcome

As specific intervention is understood a defined treatment, e.g. a medication or operation aiming to reduce a certain morbidity. An aftercare program consists of periodical, structured patient consultations and screening for impairments with interventions if necessary (similar to a chronic disease management program or an ICU-follow up clinic program like in the UK). According to the OvidSP MeSH heading rehabilitation means the “restoration of human functions to the maximum degree possible in a person or persons suffering from disease or injury”. So in this context a rehabilitation program is seen as a physical or psychological training or a combination of both aiming to reduce a certain sequela or to improve the whole medical situation after critical illness or sepsis. This program should be possible in an inpatient or outpatient setting or if thought as an inpatient treatment, there should be the possibility to initiate it after discharge from the acute care hospital.

The listed aims of the review were refined into clinical issues and into corresponding review questions.

No.	Structured clinical question	Review question
1	Identification and evaluation of specific interventions for each of the identified long-term sequela applicable to post-acute care for adult patients	What are possible interventions/ therapeutic strategies for each long-term sequela in the aftercare setting for adult patients who have developed these impairments after a period of critical illness or sepsis? What is the effect of these interventions on outcome?
2	Identification and evaluation of aftercare programs or chronic disease management programs for each sequela of sepsis or critical illness for adult patients after critical care	Are there any aftercare programs or chronic disease management program geared to a listed sequela of critical illness or sepsis for adult patients after critical care? Do they have any effects?
3	Identification and evaluation of aftercare programs or chronic disease management programs after sepsis or critical illness in adult patients	Are there any aftercare programs or chronic disease management programs addressing adult patients who suffered from sepsis or critical illness and do they have any effects?
4	Identification and evaluation of rehabilitation programs or rehabilitation strategies for each listed long-term sequela in adult patients after critical care who have developed this sequela	Are there any specific rehabilitation programs or rehabilitation strategies for each listed long-term sequela in adult patients after critical care who have developed this sequela and do they have any effects?
5	Identification and evaluation of rehabilitation programs or rehabilitation strategies in general after sepsis or critical illness for adult patients who have developed physical or non-physical morbidity after critical care	Are there any specific rehabilitation programs or rehabilitation strategies for adult patients after critical care who have developed physical or non-physical morbidity and do they have any effects?

5. Sepsis or critical illness induced sequelae

Physical morbidity	Choice of relevant data and relevant literature
CIP/CIM/ICU-AW (critical illness polyneuropathy/ Myopathy/ ICU-aquired weakness)	observed in nearly 50% of ICU patients with sepsis, multi organ failure or prolonged mechanical ventilation [12, 15-17]
dysphagia	dysphagia is present in 84% of patients who needed mechanical ventilation and it is persistent as well as independently associated with poor patient outcomes [18]
cachexia/ waisting syndrome	critical illness is associated with an increase in metabolism, greater energy requirements and loss of body mass [19, 20]
organ dysfunction	especially acute renal failure and impairment of the lung function, e.g. ARDS, due to mechanical ventilation are associated to critical illness and sepsis (according to the definition given); it is stated that "most of the septic patients residing in ICUs at present have survived their initial septic insult, yet remain critically ill for prolonged periods with sepsis-induced multiorgan dysfunction"[10, 12, 21]
chronic pain	six month after discharge caregivers of chronically ill patients were most distressed by patient's pain or discomfort [22, 23]
sexual dysfunction	three years after discharge from trauma icu one third of patients reports an impaired sexual function [24, 25]
impairments in ADLs and IADLs	one year after critical illness >50% of the patients still have ADL impairments correlated with difficulty in walking and grip strength; >70% have IADL impairments [3, 15, 26]

Non-physical morbidity	Choice of relevant data and relevant literature
neurocognitive dysfunction (delirium, progressive dementia)	incidence of cognitive impairments in critical ill patients after ICU discharge is about 64%; severe sepsis is associated with substantial and persisting new cognitive impairment [3, 27]
depression	The median point prevalence of clinically significant depressive symptoms in survivors of general care was 28% [15, 26, 28]
anxiety	The reported prevalence of anxiety ranges from 12% to 43% [15, 29-31]
post-traumatic stress disorders (PSTD)/ symptoms	the median point prevalence of clinician-diagnosed PTSD was 19% in general intensive care unit survivors [26, 28, 32]

6. Review team and authors contributions

Function	Suggested Person	Contribution
Reviewer 1	Juliane Mehlhorn	main investigator: coordinating the project, doing literature search, exclusion by title/abstract/fulltext, data extraction, quality assessment, writing the full manuscript for the

		dissertation thesis and the manuscript for publication in an international peer-reviewed journal
Reviewer 2	Dr. Antje Freytag	co-investigator: check of search strategy; exclusion by title/abstract/fulltext; check of study inclusion; second data extraction; second quality assessment; check of data synthesis, results, discussion, conclusion; revision of manuscript
Reviewer 3 (where needed)	Dr. Konrad Schmidt	help to find consensus if necessary; input and revision of manuscript
Librarian	Fr. Ute Troitzsch (ThULB)	Support for development and implication of electronic search and data management
Statistician (where needed)	ZKS/IMSID	advise and check for statistics if needed
Advisory Board	Prof. Dr. Jochen Gensichen (PI); Prof. Dr. Frank M. Brunkhorst; Prof. Dr. Jürgen Graf; Prof. Michel Wensing	check of exposé and protocol, data synthesis, results, discussion, conclusion; hints for literature search; input and revision of manuscript, co-authors for paper, Prof. Gensichen thesis supervisor for dissertation

7. PICOS and inclusion/exclusion criteria

	Included	**Excluded**
Participants	- adult survivors of sepsis or critical illness in post-acute care/ aftercare or in rehabilitation after the ICU-treatment was finished, who could or who have developed typical sequelea of sepsis or critical illness	- patients in acute treatment (on ICU) or if prolonged acute care outweighs concers of aftercare or rehab - patients under 18 years - palliative care - subgroups of patients with special rehabilitation needs that are already scientifically assessed and delivered as part of their care pathway and who did not develop an unanticipated, ongoing critical illness, e.g. stroke, CNS injury or bleeding, myocardial infarction/ cardiac surgery, cancer and amputations - interventions with proofed effect and numerous publications/ guidelines or reviews prior to this review like: pulmonary rehab, parenteral nutrition, artificial

		nutrition, weaning procedures
Interventions	- medical therapy of sequelae - structured aftercare programs or chronic disease management program for sepsis/critical illness - structured aftercare programs or chronic disease management program for one sequela - rehabilitation of one sequela - rehabilitation after sepsis or critical illness - physiotherapy in aftercare - psychotherapy in aftercare - patient education/giving Information - interventions administered to the patient after ICU-discharge	- (early) rehabilitation on ICU - weaning procedures/ rehabilitation aiming mainly at weaning - ICU outreach teams to oversee/ support ward management of the patients after ICU discharge
Comparisons	- outcomes with vs. outcomes without intervention - outcomes of one intervention vs. outcomes of another intervention - severity or frequency of illness or sequelae before and after intervention	- only recording course of sequelae without any intervention
Outcomes	- health related quality of life - mortality - nursing home admission - need for care - repeated hospital admissions - ADL – activities of daily living - IADL – instrumental activities of daily living - frequency of sequelae - severity of sequelae - physical functioning/ recovery	
Studies	- randomized controlled trials - controlled clinical trials - cohort analytic (two group pre and post) - case control studies - cohort studies (one group pre and post)	- case reports - unpublished trials - conference abstracts

As unpublished trials are excluded a certain kind of publication bias is possible.

8. Literature search and selection

All studies meeting the review questions between September 1991 until the day when the literature search is conducted will be identified. Literature search will be conducted in MEDLINE via OvidSP, EMBASE and The Cochrane Library. Hand

search of relevant magazines will be added. A keyword search for title and abstract and a MeSH-term search will be done. Among others the search terms will include “sepsis”, “septic”, “critical ill*”, “after ICU”, “rehabilitation”, “after care”, “post-acute care”, “disease management”, “follow-up”, “treatment”. A skilled librarian will support the development and implementation of the electronic search.

The complete search strategy with dates of the search will be recorded.

One reviewer will exclude irrelevant articles evident from the titles and abstracts. Any double publication of one study will be recorded and thereafter removed. Afterwards full-text of identified papers will be obtained and checked for eligibility according to the inclusion and exclusion criteria by two reviewers independently. Studies without available specific data will be excluded as well. Reference of identified studies will be checked for further relevant papers for inclusion. If any relevant systematic review or meta-analysis is found the included studies will be checked for eligibility in this review.

It’s anticipated that the number of controlled randomized trials will be low and heterogeneous as well as in general only a moderate amount of relevant data will be found. That is why the search criteria will be quite broadly defined and different study types have to be included.

The references will be managed with the help of excel and EndNote.

9. Data extraction

Data extraction for the key data points will be performed by one reviewer and will be critically reviewed and checked by a second researcher. Reviewers will not be blinded to the report authors, journals, date of publication, sources of financial support or results. All relevant data will be extracted and added to an excel table prepared for this review. It will be tested in advance and, if necessary, modified before the start of the review. If a modification has to be done during the review, a record of corrections or amendments to the data extraction form will be kept.

General data items are:

- *general:* Reviewer (performing data extraction); Date of data extraction; study ID; author; title; citation; type of publication; year; country of origin; language; conflict of interests; funding; study design; single/ multi centre; is it an intervention/rehabilitation/after care program?; is it for sepsis/ critical illness/certain sequela(e)
- *recruitment:* population (in general); inclusion criteria; exclusion criteria; recruitment procedures (randomization,…), blinding; unit of allocation
- *intervention*: kind of intervention; setting in which the intervention is delivered; care provider (GP, physician in clinic, nurse,…); treatment in control group; duration of intervention; point in time of intervention; length of follow up; point in time for baseline assessment; point in time of follow-up measurements
- *analyses*: total number enrolled; number enrolled in intervention group; number enrolled in control group; number of drop-outs, lost to follow up, … in intervention group; number of drop-outs, lost to follow up, … in control group; number

intervention group included in analysis; number control group included in analysis; theoretical number of patients needed for power; was the number for power achieved?; type of analysis (ITT, PP); percentage of patients receiving the allocated intervention; was the consistency of the intervention measured?; unintended intervention?
- *outcome data:* primary outcome; secondary outcome; used data collection tool for primary outcome (test instrument); is it valid and reliable?; unit of analysis*;* statistical methods; outcome data summary (in words)
- *miscellaneous:* author's conclusion(s); study limitations; confirm eligibility; exclusion criteria if not eligible; correspondence required?; relevant references?; reviewer's notes

The *outcomes* will be extracted in detail with two separate forms listing the outcomes, used test instruments and outcome results comparing intervention to control group as well as the development of the outcomes over time.

A special date extraction form for the *baseline characteristics of the study population* regarding sex, race, age, education, APACHE II-score, mechanical ventilation hours, renal support therapy, length of stay in ICU, length of stay in hospital, SF-36 general health score before ICU-stay, admission/ICU-diagnosis, especially sepsis, and intensive care unit type will be rendered.

Any disagreements between the reviewers in the data extraction will be noted and resolved by consensus among the researchers or if not possible by the third researcher prior to the quality assessment and data synthesis. If that doesn't lead to consent the discrepancy will be reported.

10. Quality assessment

The "EPHPP Quality Assessment Tool" will be used. The available printed form will be transformed into an SPSS-form. The quality assessment will be conducted by two independent reviewers and any disagreements will be noted and resolved by consensus among the researchers or if not possible by an additional independent researcher. The degree of agreement will be reported by kappa statistics.

11. Data synthesis

A narrative synthesis will be performed and combined with tables. In the end an overview of the results addressing the review-questions will be given and strength of evidence will be considered. If against the anticipation it becomes apparent after the searching and selection that a quantitative synthesis for one or more aspects (meta-analysis) is possible it will be added.

12. Peer review

After finishing the systematic review a peer review e.g. by members of the advisory board and/or further health experts is aspired before publication/dissemination.

13. Dissemination

The review will be rendered for a dissertation in medicine. Furthermore the publication in a relevant journal is aimed at. Moreover, for spreading relevant information the presentation on congresses is envisaged.

14. Competing interests/ Conflict of interests

Any conflict of interest will be reported.

15. Funding

So far there is no funding for the review.

16. Protocol amendment 2013

For methodological improvements a search in the databases CINAHL and PsycInfo is added. Not only one reviewer will excluded irrelevant articles evident from the titles and abstracts but two reviewers independently. A Kappa statistic for interrater agreement will be calculated for inclusion of studies on fulltext level.

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Ehrenwörtliche Erklärung

Hiermit erkläre ich, dass mir die Promotionsordnung der Medizinischen Fakultät der Friedrich-Schiller-Universität bekannt ist,

ich die Dissertation selbst angefertigt habe und alle von mir benutzten Hilfsmittel, persönlichen Mitteilungen und Quellen in meiner Arbeit angegeben sind,

mich folgende Personen bei der Auswahl und Auswertung des Materials sowie bei der Herstellung des Manuskripts unterstützt haben:

- Dr. Antje Freytag
- Professor Jochen Gensichen
- Nico Schneider,

die Hilfe eines Promotionsberaters nicht in Anspruch genommen wurde und dass Dritte weder unmittelbar noch mittelbar geldwerte Leistungen von mir für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen,

dass ich die Dissertation noch nicht als Prüfungsarbeit für eine staatliche oder andere wissenschaftliche Prüfung eingereicht habe und

dass ich die gleiche, eine in wesentlichen Teilen ähnliche oder eine andere Abhandlung nicht bei einer anderen Hochschule als Dissertation eingereicht habe.

Ort, Datum Juliane Mühlberg, geb. Mehlhorn