Recovery trajectories following critical illness:
Can we really modify them?

Tim Walsh
Professor of Critical Care, Edinburgh University
Considerations

• What is the problem?
• What is the current evidence for rehabilitation interventions?
• Why might interventions designed to modify recovery trajectories be ineffective?
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• What is the current evidence for rehabilitation interventions?
• Why might interventions designed to modify recovery trajectories be ineffective?
The Post-Intensive Care Syndrome

• Decline in physical, psychological, or cognitive status following a critical illness

• Characterised by:
  – **Physical**: fatigue, muscle weakness, joint stiffness, pain, mobility issues
  – **Psychological**: anxiety, depression, PTSD
  – **Cognitive**: Acute cognitive decline

• Reduced HRQoL and ADLs
Functional outcomes and HRQoL following ARDS
Herridge et al NEJM 2011; 364: 1293–1304

Uncertain contribution of pre critical illness health

Steep trajectory of recovery during first 3-6 months
Impact of severe sepsis:
- 10.6% increase in prevalence of moderate-severe cognitive impairment
- Mean of 1.5 new limitations following sepsis
- Limitations across range of domains
- Declines persistent over 8 years follow-up
Quality of life in the five years after intensive care: a cohort study

Brian H Cuthbertson1*, Sian Roughton2, David Jenkinson3, Graeme MacLennan3, Luke Vale2,4
Considerations

• What is the problem?

• What is the current evidence for rehabilitation interventions?

• Why might interventions designed to modify recovery trajectories be ineffective?
What does the literature say?

Rehabilitation interventions for postintensive care syndrome: a systematic review.


18 trials; inpatient (n = 4 trials), outpatient (n = 9), and mixed (n = 5) healthcare settings

Total 2510 patients; low quality

Wide range of interventions and outcomes

Positive effects mostly reported for psychological outcomes (PTSD)
What does the literature say?

Exercise rehabilitation following intensive care unit discharge for recovery from critical illness


6 trials; (total 483 adult ICU participants).

Low quality; wide variability in intervention, design, and outcomes

3 trials reported effects on functional measures (relevance uncertain); 3 no effects

No reported effects on HRQoL
Major trials published since Systematic Reviews

**Increased Hospital-Based Physical Rehabilitation and Information Provision After Intensive Care Unit Discharge**

The RECOVER Randomized Clinical Trial

- US trial; 300 patients
- Ventilated “medical” ICU patients
- Physical therapy-based intervention
- ICU through remainder of hospital stay
- No effect on hospital stay
- No effect on most secondary outcomes
- Improvement in physical function subscales of HRQoL at 6 months

**A Randomized Trial of an Intensive Physical Therapy Program for Patients with Acute Respiratory Failure**

- US trial; 120 patients
- Ventilated >4 days; mainly “medical” ICU patients
- ICU through hospital stay (max 28 days)
- No effect on physical function or length of stay

**Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure**

A Randomized Clinical Trial

- US trial; 300 patients
- Ventilated “medical” ICU patients
- Physical therapy-based intervention
- ICU through remainder of hospital stay
- No effect on hospital stay
- No effect on most secondary outcomes
- Improvement in physical function subscales of HRQoL at 6 months
Increased Hospital-Based Physical Rehabilitation and Information Provision After Intensive Care Unit Discharge: The RECOVER Randomized Clinical Trial

Timothy S. Welsh, MD; Lisa G. Salisbury, PhD; Judith L. Memmelaer, PhD; Julia A. Boyd, PhD; David M. Griffith, MD; Guro-Huby, PhD; Susanne Kean, PhD; Simon J. Mackenzie, MBChB; Ashna Krishan, MSc; Stephanie C. Lewis, PhD; Gordon D. Murray, PhD; John F. Forbes, PhD; Joel Smith, PhD; Janice E. Rattray, PhD; Alastair M. Hull, MD; Pamela Ramsay, PhD; for the RECOVER Investigators

IMPORTANCE Critical illness results in disability and reduced health-related quality of life (HRQOL), but the optimum timing and components of rehabilitation are uncertain.

OBJECTIVE To evaluate the effect of increasing physical and nutritional rehabilitation plus information delivered during the post-intensive care unit (ICU) acute hospital stay by dedicated rehabilitation assistants on subsequent mobility, HRQOL, and prevalent disabilities.

DESIGN, SETTING, AND PARTICIPANTS A parallel, group, randomized clinical trial with blinded outcome assessment at 2 hospitals in Edinburgh, Scotland, of 240 patients discharged from the ICU between December 1, 2010, and January 31, 2013, who required at least 48 hours of mechanical ventilation. Analysis for the primary outcome and other 3-month outcomes was performed between June and August 2013; for the 6- and 12-month outcomes and the health economic evaluation, between March and April 2014.

INTERVENTIONS During the post-ICU hospital stay, both groups received physiotherapy and dietetic, occupational, and speech/language therapy, but patients in the intervention group received rehabilitation that typically increased the frequency of mobility and exercise therapies 2- to 3-fold, increased dietetic assessment and treatment, used individualized goal setting, and provided greater illness-specific information. Intervention group therapy was coordinated and delivered by a dedicated rehabilitation practitioner.

MAIN OUTCOMES AND MEASURES The Rivermead Mobility Index (RMI) (range 0-15) at 3 months; higher scores indicate greater mobility. Secondary outcomes included HRQOL, psychological outcomes, self-reported symptoms, patient experience, and cost-effectiveness during a 12-month follow-up (completed in February 2014).

RESULTS Median RMI at randomization was 3 (interquartile range [IQR], 1-6) and at 3 months was 12 (IQR, 10-14) for the intervention and usual care groups (mean difference, −0.2 [95% CI, −1.3 to 0.9]; P = .71). The HRQOL scores were unchanged by the intervention (mean difference in the Physical Component Summary score, −0.1 [95% CI, −3.3 to 3.1]; P = .96); and in the Mental Component Summary score, 0.2 [95% CI, −3.4 to 3.8]; P = .91]). No differences were found for self-reported symptoms of fatigue, pain, appetite, joint stiffness, or breathlessness. Levels of anxiety, depression, and posttraumatic stress were similar, as were hand grip strength and the timed Up & Go test. No differences were found at the 6- or 12-month follow-up for any outcome measures. However, patients in the intervention group reported greater satisfaction with physiotherapy, nutritional support, coordination of care, and information provision.

CONCLUSIONS AND RELEVANCE Post-ICU hospital-based rehabilitation, including increased physical and nutritional therapy plus information provision, did not improve physical recovery or HRQOL, but improved patient satisfaction with many aspects of recovery.

TRIAL REGISTRATION isrctn.com Identifier: ISRCTN09412438

JAMA Internal Medicine 2015; 175: 901
The critical care patient pathway

**Pre-intensive care**
- Acute illness
- Co-morbidities
- Social problems

**Intensive care**
- Organ failures
- Infections
- Unconsciousness
- Weight loss
- Neuropathies
- Immobility

**Discharge to ward**
- Resolving organ failures
- Infections
- Poor appetite
- Fatigue
- Weakness
- Weight loss
- Joint stiffness
- Delirium
- Anxiety/depression
- Nightmares
- Sleep disturbance
- Emotional lability

**Discharge Home**
- Fatigue
- Slow weight gain
- Poor mobility
- Post-traumatic stress disorder
- Depression/anxiety
- Low health related quality of life

**Intervention period:**
3 months following ICU discharge (hospital plus early post-discharge period)
## RECOVER trial:
### Primary outcome (Rivermead Mobility Index)

<table>
<thead>
<tr>
<th>Time point</th>
<th>Usual care Median (quartiles)</th>
<th>Intervention Median (quartiles)</th>
<th>Adjusted mean difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3 (1, 7)</td>
<td>3 (1, 6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>8 (5, 10)</td>
<td>8 (6, 11)</td>
<td>-0.7 (-1.7 to 0.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>3 months</td>
<td>13 (10, 14)</td>
<td>13 (10, 14)</td>
<td>-0.2 (-1.3 to 0.9)</td>
<td>0.71</td>
</tr>
<tr>
<td>6 months</td>
<td>13 (7, 15)</td>
<td>14 (7, 15)</td>
<td>-0.4 (-1.9 to 1.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>12 months</td>
<td>13 (7, 15)</td>
<td>14 (9, 15)</td>
<td>-0.6 (-2.1 to 0.95)</td>
<td>0.47</td>
</tr>
</tbody>
</table>
# 3 month trial outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard Care</th>
<th>Intervention</th>
<th>Mean difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>10 (6, 23)</td>
<td>11 (6, 22)</td>
<td>0 (-2 to 2)</td>
<td>0.93</td>
</tr>
</tbody>
</table>
Current state of the evidence

• Physical rehabilitation interventions implemented after ICU discharge (general ward or post discharge)
  – Generally not effective in trials for clinical outcomes chosen

• Service redesign and/or follow-up interventions implemented after ICU discharge
  – Generally not effective in trials for clinical outcomes chosen
Considerations

• What is the problem?
• What is the current evidence for rehabilitation interventions?
• Why might interventions designed to modify recovery trajectories be ineffective?
Why might rehabilitation be “ineffective”?

- Can’t comply
### Patient reported symptoms: hospital discharge and 3 months follow-up

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Hospital discharge</th>
<th>3 months follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (1&lt;sup&gt;st&lt;/sup&gt;; 3&lt;sup&gt;rd&lt;/sup&gt; quartile)</td>
<td>Median (1&lt;sup&gt;st&lt;/sup&gt;; 3&lt;sup&gt;rd&lt;/sup&gt; quartile)</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>2.5 (1.0, 5.0)</td>
<td>2.8 (1.1, 5.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.1 (2.7, 7.2)</td>
<td>4.9 (2.3, 7.3)</td>
</tr>
<tr>
<td>Pain</td>
<td>2.3 (0.8, 4.7)</td>
<td>3.3 (1.0, 5.2)</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>3.3 (1.1, 4.9)</td>
<td>3.6 (1.3, 7.2)</td>
</tr>
</tbody>
</table>

Visual Analogue Scale: Symptoms: 0 cm “no symptoms” to 10 cm “worst symptoms”
Progression of self-reported fatigue 3-12 months post ICU discharge: RECOVER trial data (unpublished)

Tertiles

Least

Mid

Most

3 months  FATIGUE  12 months
Why might rehabilitation be “ineffective”?  

- Can’t comply  
- Physiological “block” to recovery
Acute skeletal muscle wasting in critical illness.
Inflammatory fate of patients with low (<3 mg/L), medium (3–10 mg/L) and high (>10 mg/L) C-reactive protein (CRP) concentration.
Relationship between CRP, HNE, and functional recovery

Univariate analyses
- Higher HNE and CRP significantly associated with RMI 3 months after ICU discharge

Multivariable linear regression models
- Adjustment for age, gender, Functional Comorbidity Index, APACHE 2 score, days of mechanical ventilation
- HNE and CRP remained independently associated with RMI 3 months after ICU discharge

No relationship to CRP at ICU discharge

Why might rehabilitation be “ineffective”?  

• Can’t comply  
• Physiological “block” to recovery  
• Non-modifiable pre-existing factors
## Social deprivation and Co-morbidity: prevalence in the RECOVER trial population

<table>
<thead>
<tr>
<th></th>
<th>Usual Care (n=120)</th>
<th>Intervention (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male N (%)</td>
<td>70 (58)</td>
<td>67 (56)</td>
</tr>
<tr>
<td>Age (median (1\textsuperscript{st};3\textsuperscript{rd} quartiles))</td>
<td>62 (53, 69)</td>
<td>62 (51, 71)</td>
</tr>
<tr>
<td>Functional Comorbidity Index (median (1\textsuperscript{st};3\textsuperscript{rd} quartiles))</td>
<td>2 (1, 4)</td>
<td>2 (1, 4)</td>
</tr>
<tr>
<td>Patients classified as social class 4 or 5 (deprivation) N (%)</td>
<td>52 (43)</td>
<td>54 (45)</td>
</tr>
</tbody>
</table>
## Predictors of mortality in ICU survivor cohort

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio</th>
<th>LRT $\chi^2$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.45</td>
<td>285</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comorbidities (20 groups)</td>
<td>*</td>
<td>253</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU admission diagnosis (28 groups)</td>
<td>*</td>
<td>99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient admissions in previous year</td>
<td>1.18</td>
<td>53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAPS II score (per 10 pts)</td>
<td>1.09</td>
<td>12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.85</td>
<td>11</td>
<td>0.001</td>
</tr>
<tr>
<td>Social deprivation (most vs least)</td>
<td>1.21</td>
<td>4</td>
<td>0.04</td>
</tr>
<tr>
<td>Organ support during ICU admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>0.94</td>
<td>1</td>
<td>0.31</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>0.84</td>
<td>2</td>
<td>0.12</td>
</tr>
<tr>
<td>Vasoactive therapy</td>
<td>1.21</td>
<td>9</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Lone et al. AJRCCM 2016 PMID: 26815887
Patients surviving after >7 days of mechanical ventilation (Towards RECOVER programme)

<table>
<thead>
<tr>
<th>Table 4: Risk factors for mortality over 1 year after ICU discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>FIM at day 7 after ICU discharge (per 30 points)</td>
</tr>
<tr>
<td>Age by decade</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>ICU LOS by week</td>
</tr>
<tr>
<td>Charlson score per point</td>
</tr>
</tbody>
</table>

Herridge et al. AJRCCM Published online 14-March-2016 10.1164/rccm.201512-2343OC
HRQoL: importance of pre-ICU admission comorbidity

  - General mixed ICU population; high prevalence of comorbidity
  - Comorbidity and pre-existing illness explained most of HRQoL reduction at 6 months
  - Absolute burden of reduced HRQoL greatest in previously comorbid; incremental effect of ICU admission significant in previously healthy
HRQoL trajectories: data from RECOVER trial cohort complete case analysis (unpublished data)

In complete cohort analyses HRQoL plateaus (at reduced scores) after a few months in most patients

Comorbidity prior to ICU admission (FCI) strongest independent factor associated with patient reported outcomes 12 months post ICU discharge

Multivariable regression analyses: predictors of outcomes 12 months after ICU discharge

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposure</th>
<th>Beta</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS</td>
<td>Age</td>
<td>-0.046</td>
<td>0.642</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>1.312</td>
<td>0.523</td>
</tr>
<tr>
<td></td>
<td>SIMD Quintile</td>
<td>0.921</td>
<td>0.270</td>
</tr>
<tr>
<td></td>
<td>FCI</td>
<td>-1.614</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>APACHE 2</td>
<td>-0.032</td>
<td>0.729</td>
</tr>
<tr>
<td></td>
<td>Days of Mechanical Ventilation</td>
<td>0.062</td>
<td>0.687</td>
</tr>
<tr>
<td>MCS</td>
<td>Age</td>
<td>0.302</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>1.014</td>
<td>0.566</td>
</tr>
<tr>
<td></td>
<td>SIMD Quintile</td>
<td>0.359</td>
<td>0.583</td>
</tr>
<tr>
<td></td>
<td>FCI</td>
<td>-2.057</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>APACHE 2</td>
<td>0.113</td>
<td>0.375</td>
</tr>
<tr>
<td></td>
<td>Days of Mechanical Ventilation</td>
<td>0.024</td>
<td>0.803</td>
</tr>
</tbody>
</table>

Figure 1 – Change in physical component scale (PCS) (filled circles) and mental component scale (MCS) (filled triangles) between 3 months and 12 months
Why might rehabilitation be “ineffective”?

• Can’t comply
• Physiological “block” to recovery
• Non-modifiable pre-existing factors
• Outcomes lack validity, responsiveness, and/or discriminant value
  – Mortality
  – HRQoL
  – Physical function measures
  – Length of stay
Re-building life after ICU: A qualitative study of the patients’ perspective

Kate S. Deacon*
Do existing tools “capture” post-ICU HRQoL?
Lim et al J Crit Care 31 (2016) 183–193

EQ-5D and SF-36 “miss” substantial domains that matter to ICU survivors
Mixed methods analysis

• Satisfaction questionnaires completed at 3 month primary outcome assessment

• Focus groups with survivors and family members from usual care and intervention groups

Patient Reported Experience Measures (PREMs) of rehabilitation
Patient experience of relevant domains of rehabilitation

High value placed on:
- Information provision
- Eating/nutrition support
- Physical therapy
- Coordination

Strong concordance with qualitative analysis of focus groups
Definitions

Rehabilitation

reintegration; recovery; recuperation; treatment; therapy

Recovery

revival; recuperation; healing; renewal; reclamation
Definitions

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revival; recuperation; healing; renewal; reclamation
Can we modify recovery trajectories?

• Post critical illness survivorship is an emerging priority for health care systems

• Population heterogeneity, especially modifiable versus non-modifiable disability, needs greater understanding
  – Non-frail/comorbid versus frail/multimorbid

• Intervention development is complex, and may need a more “system” level approach
  – “Holistic” support versus “function/symptom based” therapies

• Greater understanding of appropriate trial design, population sub-division, and outcome measures are needed

• Quality of care from the patient perspective is not interchangeable (or perhaps measureable) with traditional outcome measures