Journal of Critical Care 33 (2016) 192–199

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Persistent inflammation and recovery after intensive care: A systematic review

David M. Griffith, MD [a,*], Matthew E. Vale, MBBS [a], Christine Campbell, PhD [b], Steff Lewis, PhD [b], Timothy S. Walsh, MD [a]

[a] Department of Anaesthesia, Critical Care and Pain Medicine, Edinburgh Medical School, University of Edinburgh, UK
[b] Centre for Population Health Sciences, Edinburgh Medical School, University of Edinburgh, UK

ARTICLE INFO

Keywords:
Intensive care
Critical illness
Rehabilitation
Inflammation
Recovery
Quality of life

ABSTRACT

Purpose: Physical weakness is common after critical illness; however, it is not clear how best to treat it. Inflammation characterizes critical illness, is associated with loss of muscle mass during critical illness, and potentially modifies post–intensive care unit (ICU) recovery. We sought to identify published reports on the prevalence of systemic inflammation after critical illness and its association with physical recovery.
Methods: This is a systematic review of the literature from MEDLINE, EMBASE, CINAHL, CPCI-SSH, and CPCI-S from January 1982 to December 2011.
Results: From 7433 references, 207 full-text articles were reviewed, 57 were eligible, and 22 were included. Inflammation was present in most patients at ICU discharge according to C-reactive protein concentration (range, 70%-100%), procalcitonin (range, 89%-100%), tumor necrosis factor α (100%), and systemic inflammatory response syndrome criteria (range, 92%-95%). Fewer patients had elevated myeloperoxidase concentrations (range, 0%-56%). At hospital discharge, 9 (90%) of 10 chronic obstructive pulmonary disease patients had elevated C-reactive protein. No studies tested the association between inflammation and physical recovery.
Conclusions: Inflammation is present in most patients at ICU discharge, but little is known or has been investigated about persistent inflammation after this time point. No studies have explored the relationship between persistent inflammation and physical recovery. Further research is proposed.

1. Introduction

Annually, around 10 000 patients are admitted to Scottish intensive care units (ICUs) with a critical illness; numbers are increasing, and the aging general population means that numbers of elderly patients are predicted to increase substantially over the next 20 years. Improvements in ICU treatment mean that approximately 75% of patients survive to hospital discharge [1], but many have persisting physical disability that reduces quality of life and places high care burden on families and health services. Although persistent ICU-acquired disability is now recognized, it is not clear how best to prevent or treat it [2].

The most prevalent symptoms for the ICU survivor are fatigue and muscle weakness [3,4]. Muscle biopsy studies reveal skeletal muscle abnormalities in virtually all patients recovering from critical illness [5]. These include axonal neuropathy, denervation, fiber atrophy, nonspecific neuropathy, and necrotizing myopathy. Recovery of muscle function after critical illness is often incomplete [2].

Critical illness is characterized by global activation of the immune system causing a coordinated sequence of events known as the systemic inflammatory response syndrome (SIRS). Inflammatory cytokines have an established role in regulating muscle mass. Tumor necrosis factor α, interleukin (IL) 1, IL-6, and endotoxin infusions result in muscle wasting syndromes [6,7] due to increased protein catabolism [8-12], inhibition of protein synthesis [13], inhibition of muscle cell differentiation [14], and reduced amino acid uptake [15]. Chronic diseases such as cancer, chronic obstructive pulmonary disease (COPD), heart failure, and end-stage renal disease as well as normal aging are associated with loss of muscle mass and function. Numerous studies have observed associations between markers of inflammation and muscle function in these groups [16-25].

Inflammation in critical illness has been extensively studied in the acute phase of the illness, but it is unclear how many patients have evidence of ongoing inflammation in the recovery phase. In addition, it is unclear how inflammation and muscle dysfunction are interrelated in the rehabilitation stage of critical illness. The aim of this systematic review is to collate the available data describing the prevalence of persistent and systemic inflammation after critical illness and to

* Corresponding author at: Department of Anaesthesia, Critical Care and Pain Medicine, Edinburgh Medical School, University of Edinburgh, Room S8210, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4SA, UK. Tel.: +44 131 242 6661; fax: +44 141 242 6578.
E-mail address: david.m.griffith@ed.ac.uk (D.M. Griffith).

http://dx.doi.org/10.1016/j.jcrc.2016.01.011
0883-9441/

establish whether inflammation is linked to markers of physical dysfunction in these patients. We aimed to seek data on persistent inflammation at 3 time points: at the point of ICU discharge, between ICU discharge and hospital discharge, and at any time point after hospital discharge.

2. Methods

This systematic review has been reported according to the relevant sections of the MOOSE guidelines for Meta-Analyses and Systematic Reviews of Observational Studies [26].

2.1. Search strategy

Electronic databases EMBASE, MEDLINE, and CINAHL were systematically searched using the OVID user interface. In addition, gray literature sources were searched for conference citations (CPCI-SSH and CPCI-S) using the Web of Science interface. An example search strategy for the MEDLINE database is given in Table 1. We searched for studies published between January 1982 and December 2011 of human ICU patients who had a clinical or biochemical marker of systemic inflammation measured.

2.2. Study characteristics

Inclusion and exclusion criteria are summarized in Table 2. Studies carried out in medical, surgical, or mixed ICUs were considered. Studies including children, neonates, neurosurgical, or postoperative cardiothoracic patients were not considered.

A study was deemed to include a measure of systemic inflammation if it recorded all of the SIRS criteria (ie, white cell count, respiratory rate, body temperature, and heart rate), C-reactive protein (CRP), or any established proinflammatory mediator (eg, IL-1, IL-6, or tumor necrosis factor α [TNF-α]).

For a study to be considered, the marker of systemic inflammation had to be measured at 1 of 3 prespecified time points: within 24 hours of ICU discharge, between ICU discharge and hospital discharge, and after hospital discharge.

If a study reported a measurement of systemic inflammation while the patient was in ICU, it was included if sampling continued until ICU discharge. If there was no reference to ICU discharge, the study was only considered if the last sample taken was at a time point greater than 14 days after ICU admission. This considers that there was reasonable probability that most patients being sampled at this time point would have been discharged from ICU. In such studies, the authors were contacted for further information.

No language restrictions were placed on the search. Where an English abstract was available, the study remained in the review provided that there was sufficient information in the abstract. Where no English abstract was available, foreign language publications were excluded.

Table 1
Search strategy for MEDLINE and EMBASE databases

1	interleukin*.ti,ab.
2	(CRP or TNF* or "C-reactive").ti,ab.
3	inflammation/
4	acute phase reaction/
5	systemic inflammatory response syndrome/
6	C-reactive protein/
7	interleukin-1 alpha/
8	interleukin-1 beta/
9	interleukin-6/
10	interleukin-8/
11	tumor necrosis factor/
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	(critical adj3 care).ti,ab.
14	(intensive adj3 care).ti,ab.
15	(intensive adj3 therapy).ti,ab.
16	(ICU or ITU).ti,ab.
17	(critical$ adj3 ill$).ti,ab.
18	Critical illness/
19	Critical care/
20	Intensive care/
21	intensive care units/
22	respiratory care units/
23	intensive care unit/
24	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25	humans/not animals/
26	12 and 24 and 225
27	limit 28 to yr = "1982 -Current"
28	remove duplicates from 29

Table 2
Review inclusion and exclusion criteria

Inclusion	Exclusion
Participants are human AND Adults >16 years old AND ICU patients or survivors AND Included measurements of the clinical or molecular manifestations of the systemic inflammation at ICU discharge or any time point after ICU discharge	Studies of patients in cardiothoracic ICUs, coronary care units, or neurosurgical ICUs. Studies including participants <16 years old.

2.3. Selection of studies

Deduplication was carried out automatically using the OVID user interface (Ovid Technologies, New York, NY), then manually using Endnote X4 software (Thompson Reuters, New York, NY). After this, the title list was searched to remove clearly irrelevant studies (eg, studies of pediatric, neonatal, cardiothoracic, or neurosurgical patients; review articles; editorials; case reports; and commentaries). The abstracts of the remaining studies were screened independently by 2 authors, and those not meeting the inclusion criteria were excluded. Disagreements about eligibility were resolved by discussion between the 2 screening authors. An inclusive approach was adopted. Where it was not clear from the abstract whether a study should be included, it remained in the review list.

Full-text versions of the remaining articles were obtained whenever possible using the resources of the National Health Service (NHS), University of Edinburgh, and the British Library. Where an article could not be retrieved in full text and there was insufficient information in the abstract to determine eligibility, it was excluded from the review (4 articles).

The full-text articles were reviewed independently by 2 authors against inclusion and exclusion criteria. This resulted in a final short list for further evaluation and data extraction.

2.4. Data extraction

Each short-listed article was reviewed by 1 author looking specifically for an estimate of prevalence of systemic inflammation. Where a prevalence estimate was not provided in the text, attempts were made to contact authors for raw data to allow calculation of prevalence estimates. Acknowledging that raw data may not be available in older studies, authors were asked if they could provide summary measures (central tendency and sample variability). Authors were contacted by e-mail and traditional mail on 2 occasions, 1 month apart, thus allowing 2 months in total to respond after the initial contact.