



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Review article

Approach to critical illness myopathy and polyneuropathy in the older SARS-CoV-2 patients



Brendan McClafferty^{a,*}, Ibrahim Umer^a, Gary Fye^a, Douglas Kepko^a, Ricci Kalayanamitra^b, Zainab Shahid^a, Devyani Ramgobin^c, Alice Cai^b, Andrew Groff^b, Abani Bhandari^f, Chander Shekher Aggarwal^e, Ravi Patel^d, Dhirisha Bhatt^d, Hyma Polimera^d, Nitasa Sahu^d, Ramarao Vunnam^d, Reshma Golamari^d, Ashutosh Kumar^g, Rohit Jain^d

^a Lake Erie College of Osteopathic Medicine, United States

^b Penn State College of Medicine, United States

^c Touro College of Osteopathic Medicine, United States

^d Department of Internal Medicine, Penn State Milton S. Hershey Medical Center, United States

^e University College of Medical Sciences, Delhi, India

^f Department of Internal Medicine, KISTMC, Tribhuvan University, Nepal, India

^g Department of Pediatrics and Neurology, Penn State Milton S. Hershey Medical Center, United States

ARTICLE INFO

Article history:

Received 15 April 2020

Accepted 21 July 2020

Keywords:

SARS-CoV-2

COVID-19

Critical illness myopathy

Critical illness polyneuropathy

Intensive care unit-acquired weakness

Older adults

ABSTRACT

One of the major concerns of the health care community and the public surrounding the SARS-CoV-2 pandemic is the availability and use of ventilators. Unprecedented surges of patients presented to intensive care units across the country, with older adults making up a large proportion of the patient population. This paper illustrates contemporary approaches to critical illness myopathy (CIM), critical illness polyneuropathy (CIP), and critical illness polyneuromyopathy (CIPNM) in older patients, including incidence, risk factors, mechanisms for pathology, diagnosis, contemporary treatment approaches, and outcomes. We hope that the following analysis may help educate clinicians and ultimately decrease the duration of the mechanical ventilation required by these patients, resulting in improved clinical outcomes and an increase in ventilator availability for other patients in need.

© 2020 Elsevier Ltd. All rights reserved.

1. Introduction

In the setting of the SARS-CoV-2 pandemic, a high demand for mechanical ventilators creates an incentive to wean patients from ventilation promptly, so this life saving treatment is made available to other patients. Critical illness myopathy (CIM), critical illness polyneuropathy (CIP), or a combination of the two, critical illness polyneuromyopathy (CIPNM), particularly in older patients, can have immediate and lasting negative consequences if not detected and treated promptly. Weakness that develops while a patient is in the ICU complicates recovery and prolongs the

duration of both mechanical ventilation (up to 13 days for patients displaying CIPNM versus 3 days for those who do not) and the length of hospital stay [1,2]. These conditions often go undiagnosed or are only considered when patients fail to wean from ventilatory support, despite evidence that up to 62% of patients who experience failure to wean from ventilators have some underlying form of neuromuscular weakness [3]. Accurate early diagnosis and treatment of these conditions can help decrease the intensive care patient burden caused by the surge of SARS-CoV-2 patients requiring ventilation.

A 2011–2012 survey indicated that 68.8% of respondents underestimated the incidence of critical illness acquired weakness [4]. Among critically ill patients, muscle wasting occurs early and rapidly within the first ten days of illness [5]. Improving awareness of CIM, CIP, and CIPNM incidence and interventions can facilitate shorter hospitalizations, decreased mortality, and help fewer patients suffer from chronic disability as a result of critical illness, including pain, motor weakness, pulmonary insufficiency, and psychological stress [3,6]. These dysfunctions are contributors to post

Abbreviations: CIM, critical illness myopathy; CIP, critical illness polyneuropathy; CIPNM, critical illness polyneuromyopathy; PCIS, post intensive care syndrome; ANM, acute necrotizing myopathy; (IL-6), interleukin-6; SAA1, serum amyloid A1; ICUAW, ICU-acquired weakness; ARDS, acute respiratory distress syndrome.

* Corresponding author at: Lake Erie College of Osteopathic Medicine, 1858 W Grandview Blvd, Erie, PA 16509, United States.

E-mail address: bmcclaffer15306@med.lecom.edu (B. McClafferty).

intensive care syndrome (PCIS), which has its own set of complications [7]. While over 50% of patients will recover completely from CIM, CIP, or CIPNM, those suffering muscular weakness may continue to experience symptoms from 4 weeks to two years after ICU discharge [7,8]. The CDC indicates that during March 1–30, 2020, 74.5% of patients hospitalized for SARS-CoV-2 were ≥ 50 years old, with the highest rate among adults aged ≥ 65 , so this is particularly an issue for older patients [9].

2. Incidence

Studies from 2015 and 2017 focused on determining the incidence of critical illness polyneuropathy, critical illness myopathy, and critical illness neuromyopathy as a group indicate that 40% of patients mechanically ventilated for seven or more days and 40.5% of patients who were ventilated for greater than 24 h developed ICU acquired weakness [10,11].

3. Risk factors

Pre-existing conditions in addition to underlying disease etiology increase the risk for developing CIM/CIP/CIPNM. Studies identified age, hyperglycemia greater than three days, delirium, and mechanical ventilation greater than five days to be independent predictors of intensive care unit-acquired weakness [11]. A 2005 study involving sixty-one critically ill patients also indicated CIP was associated with the presence and duration of systemic inflammatory response syndrome and the severity of cranial, respiratory, and cardiovascular organ failures [2].

A 2018 meta-analysis also indicated a statistically significant association between corticosteroid use and ICU-acquired weakness. The study suggests that where possible, corticosteroids should be limited, or the administration time shortened to reduce the risk of ICU-acquired weakness [12].

4. Proposed mechanisms

The pathophysiology of CIM and CIP is complex, multifactorial, and not completely understood. Both conditions are caused by some combination of critical insult to the body with cytokine overproduction leading to microvascular derangement, and metabolic and electrical (channel) alterations [13]. Although CIM and CIP can and do occur simultaneously in patients, their mechanisms are distinct and important to differentiate.

CIM is a combination of cachectic myopathy and acute necrotizing myopathy (ANM). Cachectic myopathy and ANM are characterized by loss of myosin [3,14]. Cachectic myopathy has been shown to trend with disuse and atrophy and is characterized specifically by loss of type 2 muscle fibers [15].

CIM differs from ANM as patients with CIM display normal creatinine kinase levels and CIM is due to loss of myosin along with further breakdown of the actin-myosin contractile bundle [15]. Decreased myosin heavy chain mRNA (as early as day five of ICU admission) and protein expression, along with increased expression of genes associated with atrophy in critically ill patients with myopathy have been demonstrated [16]. Studies have also found that high-dose corticosteroid exposure leads to selective thick filament loss [15,17–19]. Interestingly, animal models have shown both glucocorticoids and some sort of denervation (ex. non-depolarizing neuromuscular blockers) are necessary in the pathogenesis of CIM, further blurring the line between CIM and CIP [19]. This “two-hit” hypothesis is supported by a study which found dexamethasone only (no denervation) usage led to hypertrophy and increased levels of myosin heavy chain on newborn rat hearts [20]. Other stressors, both pharmaceutical and physiologi-

cal, have also been postulated to cause muscle wasting by driving an increased catabolic:anabolic ratio [6].

Interleukin-6 (IL-6) and serum amyloid A1 (SAA1) has been shown to be increased in patients with CIM, which fits with the apparent importance of acute phase response in pathogenesis of the disease. IL-6 is a proinflammatory cytokine that aids in the production of acute phase proteins and is also involved in host immunity. Langhans et al. noted statistically significant increased levels of IL-6 and SAA1 in the skeletal muscle of CIM patients as compared to non CIM patients. They also found SAA1 in CIM patients earlier in the hospital stay than in non-CIM patients [21]. This conclusion has been used to find novel treatment for the acute respiratory distress syndrome and long-term ventilator dependence seen in older patients with SARS-CoV-2 [22].

Membrane dysfunction has also been implicated [23–25]. Allen et al. demonstrated normal nerve conduction velocities in critically ill CIM patients, but slowed conduction within individual muscle fibers. This was reproduced in another study on CIM patients which used muscle electron microscopy to show a loss of thick filaments with normal nerve histology. Rich et al. showed, in animal models, that steroid denervated muscles failed to generate action potentials in response to physiological stimulation, bolstering the idea that excessive steroid usage in critically ill patients is a risk factor for CIM. Rich also found that steroid-denervated muscles had reduced and dysfunctional voltage-gated sodium channels, and the decreased concentration of these channels aligned with progressively decreased excitability [24].

The exact mechanism of injury in CIP is also unknown. One theory is that systemic inflammation and overproduction of cytokines, nitric oxide, and oxygen radicals causes hypoxic and anaerobic conditions leading to decreased circulation of local axonal survival factors and subsequent Wallerian degeneration [26].

Another theory is that the chronic inflammation in CIP patients increases vascular permeability and leads to vasogenic edema [27]. Fenzi et al. biopsied the superficial peroneal nerve of critically ill patients with CIP and found decreased myelin density and axonal degeneration. They also found increased levels of E-selectin in the walls of endoneurial blood vessels, suggesting edema has an important part in the pathogenesis of CIP [28].

One last theory suggests CIP is related to dysfunction of voltage gated sodium channels [29]. This shared mechanism with CIM may underlie why both conditions often occur together.

5. Diagnosis methods

Difficulties in diagnosing CIM and CIP include, but not limited to intubation, sedation, delirium and cooperation. If sensation can be accurately assessed, CIM is distinguished by failure to wean off mechanical ventilation, flaccid limb weakness more common in proximal than distal extremities, rare extraocular muscle weakness, and facial muscle weakness more common than found in CIP. A reliable neurological examination for CIP will demonstrate atrophy and limb muscle weakness, decreased pinprick sensation peripherally, relative cranial nerve preservation, and absent or reduced tendon reflexes [30]. Shared symptoms of CIM and CIP include ventilatory muscle weakness, limb weakness with relative sparing of the extraocular and facial muscles, and reduced tendon reflexes. CIM begins within days, whereas CIP presents after two or more weeks [31].

It can be challenging to distinguish CIM from CIP. One way is by testing for muscle stretch reflexes: they will typically be present in CIM but will be absent in CIP. Also, sensation usually remains intact in CIM. This can be tested in the ICU by response to pinprick sensation if a patient is awake and alert [32]. As mentioned, creatine kinase and myoglobin levels may or may not be normal in

CIM. It is also important to note that elevated lab values may be due to other systemic illnesses.

Due to the high potential for altered sensorium in the older population most susceptible to CIM/CIP, it is not always feasible to conduct tests that involve patient cooperation or awareness. As such, skeletal muscle index measurement using CT imaging-based calculations can be used. At the time of admission to the ICU, these scores have been shown to be a valid predictor for ICU acquired weakness in septic patients [33]. A retrospective study showed that CT within four days of ICU admission showing low skeletal muscle area was a risk factor for death in critically ill mechanically ventilated patients [34]. Since aging is known to be characterized by sarcopenia and loss of skeletal muscle, the poorer outcomes seen in older patients could be attributed in part to CIM/CIP complications.

Nerve conduction studies and electromyography are also helpful diagnostic tools. CIM nerve conduction studies show reduced amplitude compound motor action potentials with preserved sensory response. Electromyography may show polyphasic motor unit potentials with or without fibrillations. CIP nerve conduction studies will show decreased amplitude (or absence) of sensory nerve action potentials. Electromyography would show axonal loss without demyelinating features [35].

When nerve conduction studies cannot be obtained or relied on due to patient cooperation, significant edema or lack of resources, other methods for diagnosis exist. For example, Rich et al. described a technique utilizing the fact that muscle is inexcitable in CIM and remains excitable in CIP. Comparison of direct muscle stimulation and nerve stimulation with measured amplitudes of muscle action potentials allow for differentiation [36]. In addition, the landmark Italian multicenter CRIMYNE-2 study published in 2014 concluded that the peroneal nerve test (PENT) to measure compound muscle action potential amplitude showed 100% sensitivity and 85% specificity in diagnosing CIP and CIM in critically ill patients. This technique has gained favor because it is speedy, easily reproducible and it does not require patient cooperation. Note, however, that the CRIMYNE-2 study excluded diabetic patients [37].

Ultrasound has not been demonstrated as a reliable diagnostic tool, and therefore may continue to serve best in the setting of research centers [38,39].

Finally, although rarely used due to their invasiveness and variable findings, muscle and nerve biopsy are the only definitive ways to diagnose CIM and CIP. CIM would show the characteristic atrophy of type 2 fibers with loss of myosin thick filaments, whereas CIP would show axonal degeneration greater in distal as compared to proximal segments [13].

5.1. Interventions

Modern interventions for CIM and CIP can be divided into prevention and treatment of ICU-acquired weakness (ICUAW) with the mainstay of prevention via reduction of the immobilized state. These treatments are subdivided into pulmonary rehabilitation and musculoskeletal mobilization.

5.2. Pulmonary preservation

Pulmonary rehabilitation is a multifactorial process focused on: removing retained airway secretions, exercising both primary and secondary respiratory muscles after being mechanically ventilated, and increasing measurable pulmonary values.

The most conservative, familiar option is incentive spirometry [40]. Another option is positioning the patient to increase ventilation, ventilation/perfusion ratio, and oxygenation. Mobilization and positioning the patient can increase respiratory volume, expiratory

flow rate, and residual functional capacity. On mechanically ventilated patients, the ideal position for patients is seated at approximately 30 degrees. This position typically results in efficient minute ventilation, increased respiratory rate and inspiratory flow rate due to the increased displacement of the ribs and allowing gravity to facilitate increased expansion [40,41]. In patients with SARS-CoV-2 on ventilation who have failed standard low tidal volume ventilation, prone ventilation is used because it decreases ventral alveolar distention and dorsal alveolar collapse [42]. Prone positioning, especially in early stages, have shown mortality benefits in patients with severe acute respiratory distress syndrome (ARDS). Prone positioning has not been proven to prevent organ system dysfunction, reduce length of stay in the ICU, or shorten the length of need for mechanical ventilation [43].

5.3. Early mobilization

One of the most successful measures to reduce the incidence of ICUAW is to begin mobilizing the patient as early as possible. A 2019 study showed starting mobilization as early as 5 days into an ICU stay can lead to patients standing sooner, walking sooner, having more ventilation free days, reducing the incidence of ICUAW, and increasing the discharge to home rate significantly [40,44]. Another study found even passive mechanical loading in deeply sedated and mechanically ventilated patients decreases the effects of CIM [45].

In bed cycle ergometry for ICU patients can be utilized in those who are awake and cooperative as well as those who are uncooperative or unconscious (active vs passive settings). This activity increases overall exercise capacity post discharge [40].

For patients who are unwilling or unable to begin early mobilization, basic positioning changes can be performed to significantly reduce nerve compression and increase blood flow to skin and superficial musculature thus reducing the rate of deconditioning. Patients who are immobile may also benefit from passive range of motion exercises and stretching. The muscle fiber architecture can be better preserved in this manner than without exercise [40].

5.4. Mechanical ventilation

Mechanically ventilated patients with ARDS secondary to SARS-CoV-2 are failing to wean from ventilators and as such, relying on them for long periods of time. One proposed mechanism causing long term dependence on mechanical ventilators is elevated IL-6 causing cytokine release syndrome and CIM/CIP [46]. This is based on data from patients with severe SARS-CoV-2 as well as SARS and MERS which showed increased IL-6 [46–49]. IL-6 inhibitors such as Tocilizumab are in phase three trials in the United States as potential adjunct therapy for mechanically ventilated COVID-19 patients, and while anecdotal support exists for its efficacy, further research is needed to ultimately determine its role in therapy.

6. Outcomes

Long term studies indicate CIM/CIP/CIPNM has worse outcomes for older patients. A 5-year longitudinal study (average participant was 61 years old at recruitment) of patients who were in the ICU for at least 5 days demonstrated a 44% mortality. This study attributed the particularly high mortality rate to the increased baseline age of its participants compared to other studies [50], further strengthening evidence of increased risk for older populations with CIM/CIP/CIPNM secondary to SARS-CoV-2. Another challenge to long term outcome that disproportionately impacts older patients is diaphragm dysfunction. A study of diaphragm dysfunction as an

independent variable revealed the 2-year survival was 64% in those with diaphragm dysfunction (average age 65) and 71% in those without diaphragm dysfunction (average age 47). Those who had ICU-acquired weakness in addition to diaphragm dysfunction had a survival rate of 36% compared to the survival of those with just ICU-acquired weakness which was 79% [51]. A separate prospective study showed diaphragm dysfunction had a negative effect on extubation success: there was 50% failure rate of weaning process and of those that failed, 50% had passed away [52].

7. Discussion

This review shows how and why CIM/CIP/CIPNM resulting from the SARS-CoV-2 pandemic can particularly impact older patients. We wish to emphasize the importance of early consideration of the potential impact of CIM/CIP/CIPNM, and the need for robust efforts to detect these syndromes and implement interventions for both improved individual patient outcomes and efficient utilization of mechanical ventilators in the current pandemic context.

There are several potential limitations on the interventions discussed here, including the psychological consequences of critical illness, baseline cognitive function, sedation, and requirements of positioning needed to adequately treat SARS-CoV-2 patients. For example, elderly patients with decreased baseline cognitive function, ranging from mild impairment to frank dementia may have additional difficulty regaining consciousness in an unfamiliar setting. The deleterious psychological consequences inherent to critical illness may be exacerbated in the SARS-CoV-2 patient who recovers surrounded by unfamiliar providers dressed in personal protective equipment obscuring their faces and eyes, interfering with human connections that could aid recovery. Moreover, providers may be redeployed physicians or nurses with little familiarity working in critical care and their inexperience may contribute to difficulty in recognizing the need for, and initiating, proper treatments and rehabilitation in this challenging context. Due to the respiratory pathology of SARS-CoV-2, fully controlled mechanical ventilation and prone positioning necessitating heavy sedation may become necessary. Delirium resulting from sedation would delay further interventions to reduce the incidence of CIM/CIP/CIPNM. These and other complications may erode patient abilities, motivation, and cooperation essential for engaging with pulmonary preservation and early mobilization rehabilitation.

8. Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this manuscript is consistent with those guidelines.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Koch S, Spuler S, Deja M, et al. Critical illness myopathy is frequent: accompanying neuropathy protracts ICU discharge. *J Neurol Neurosurg Psychiatry* 2011.
- [2] Bednarik J, Vondracek P, Dusek L, Moravcova E, Cundrle I. Risk factors for critical illness polyneuropathy. *J Neurol* 2005;252(3):343–51. <https://www.ncbi.nlm.nih.gov/pubmed?term=15791390>.
- [3] Shepherd S, Batra A, Lerner DP. Review of Critical Illness Myopathy and Neuropathy. *Neurohospitalist* 2017. <https://www.ncbi.nlm.nih.gov/pubmed/28042370/>.
- [4] Koo KKY, Choong K, Cook DJ, et al. Early mobilization of critically ill adults: a survey of knowledge, perceptions and practices of Canadian physicians and physiotherapists. *CMAJ Open* 2016.
- [5] Lodeserto F, Yende S. Understanding skeletal muscle wasting in critically ill patients. *Critical care (London, England)* 2014;18(6). <https://www.ncbi.nlm.nih.gov/pubmed/25673028>.
- [6] Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. *The Lancet Neurology* 2011;10(10):931–41. <https://www.ncbi.nlm.nih.gov/pubmed?term=21939902>.
- [7] Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. *Critical care (London, England)* 2015. <https://www.ncbi.nlm.nih.gov/pubmed/26242743>.
- [8] Apostolakis E, Papakonstantinou NA, Baikoussis NG, Papadopoulos G. Intensive care unit-related generalized neuromuscular weakness due to critical illness polyneuropathy/myopathy in critically ill patients. *J Anesthesia* 2015.
- [9] Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1–30, 2020. Centers for Disease Control and Prevention. https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e3.htm?s_cid=mm6915e3_w. 2020.
- [10] Appleton RTD, Kinsella J, Quasim T. The incidence of intensive care unit-acquired weakness syndromes: A systematic review. *J Intens Care Soc* 2015;16(2):126–36. <https://www.ncbi.nlm.nih.gov/pubmed/28979394>.
- [11] Diaz Ballve LP, Dargains N, Urrutia Inchaustegui JG, et al. Weakness acquired in the intensive care unit. Incidence, risk factors and their association with inspiratory weakness. Observational cohort study. *Revista Brasileira de terapia intensiva* 2017. <https://www.ncbi.nlm.nih.gov/pubmed/29236843>.
- [12] Yang T, Li Z, Jiang L, Xi X. Corticosteroid use and intensive care unit-acquired weakness: a systematic review and meta-analysis. *Critical Care (London, England)* 2018. <https://www.ncbi.nlm.nih.gov/pubmed/30075789>.
- [13] Zhou C, Wu L, Ni F, Ji W, Wu J, Zhang H. Critical illness polyneuropathy and myopathy: a systematic review. *Neural Regener Res* 2014.
- [14] Waclawik AJ, Sufit RL, Beinlich BR, Schutta HS. Acute myopathy with selective degeneration of myosin filaments following status asthmaticus treated with methylprednisolone and vecuronium. *Neuromuscular Disord: NMD* 1992.
- [15] Larsson L, Li X, Edström L, et al. Acute quadriplegia and loss of muscle myosin in patients treated with nondepolarizing neuromuscular blocking agents and corticosteroids: Mechanisms at the cellular and molecular levels. *Crit Care Med* 2000;28(1):34–45. <https://www.ncbi.nlm.nih.gov/pubmed/10667496>.
- [16] Wollersheim T, Woehlecke J, Krebs M, et al. Dynamics of myosin degradation in intensive care unit-acquired weakness during severe critical illness. *Intensive Care Med* 2014;40(4):528–38. <https://www.ncbi.nlm.nih.gov/pubmed/24531339>.
- [17] Hund E. Neurological complications of sepsis: critical illness polyneuropathy and myopathy. *J Neurol* 2001;248(11):929–34. <https://doi.org/10.1007/s004150170043>.
- [18] Singleton JR, Baker BL, Thorburn A. Dexamethasone inhibits insulin-like growth factor signaling and potentiates myoblast apoptosis. *Endocrinology* 2000. <https://www.ncbi.nlm.nih.gov/pubmed/10919283>.
- [19] Mozaffar T, Haddad F, Zeng M, Zhang LY, Adams GR, Baldwin KM. Molecular and cellular defects of skeletal muscle in an animal model of acute quadriplegic myopathy. *Muscle & Nerve* 2007. <https://www.ncbi.nlm.nih.gov/pubmed?term=16967495>.
- [20] Muangmingsuk S, Ingram P, Gupta MP, Arcilla RA, Gupta M. Dexamethasone induced cardiac hypertrophy in newborn rats is accompanied by changes in myosin heavy chain phenotype and gene transcription. Molecular and cellular biochemistry. <https://www.ncbi.nlm.nih.gov/pubmed/10942214>. 2000.
- [21] Langhans C, Weber-Carstens S, Schmidt F, et al. Inflammation-induced acute phase response in skeletal muscle and critical illness myopathy. *PLoS one*. <https://www.ncbi.nlm.nih.gov/pubmed?term=24651840>. 2014.
- [22] Zheng Y, Wang QY. Bioinformatics analysis on molecular mechanism of ribavirin and interferon- α in treating MERS-CoV. *Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi*. <https://www.ncbi.nlm.nih.gov/pubmed/26917533>. 2016.
- [23] Sander HW, Golden M, Danon MJ. Quadriplegic areflexic ICU illness: Selective thick filament loss and normal nerve histology. *Muscle Nerve* 2002;26(4):499–505. <https://www.ncbi.nlm.nih.gov/pubmed?term=12362415>.
- [24] Rich MM, Pinter MJ, Kraner SD, Barchi RL. Loss of electrical excitability in an animal model of acute quadriplegic myopathy. *Ann Neurol*. 1998;43(2):171–9. <https://www.ncbi.nlm.nih.gov/pubmed?term=9485058>.
- [25] Wang JT, Medress ZA, Barres BA. Axon degeneration: molecular mechanisms of a self-destruction pathway. *The Journal of cell biology*. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3255986/>. 2012.
- [26] Bannerman, Berek, Bevilacqua, et al. Enhanced expression of E-selectin on the vascular endothelium of peripheral nerve in critically ill patients with neuromuscular disorders. *Acta Neuropathologica*. <https://link.springer.com/article/10.1007/s00401-003-0704-3>. 1999.
- [27] Koch S, Bierbrauer J, Haas K, et al. Critical illness polyneuropathy in ICU patients is related to reduced motor nerve excitability caused by reduced sodium permeability. *ICMx* 2016;4(1). <https://www.ncbi.nlm.nih.gov/pubmed?term=27207148>.

- [28] Fenzi F, Latronico N, Refatti N, Rizzuto N. Enhanced expression of E-selectin on the vascular endothelium of peripheral nerve in critically ill patients with neuromuscular disorders. *Acta Neuropathol* 2003;106(1):75–82. <https://www.ncbi.nlm.nih.gov/pubmed/12698264>.
- [29] Piva S, Fagoni N, Latronico N. Intensive care unit-acquired weakness: unanswered questions and targets for future research. *F1000Research*. <https://www.ncbi.nlm.nih.gov/pubmed/31069055>. 2019.
- [30] Latronico N, Shehu I, Seghelin E. Neuromuscular sequelae of critical illness. Current opinion in critical care. <https://www.ncbi.nlm.nih.gov/pubmed/term=16015120>, 2005
- [31] Garnacho-Montero J, Amaya-Villar R, García-Garmendía JL, Madrazo-Osuna J, Ortiz-Leyba C. Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients. *Crit Care Med* 2005;33(2):349–54. <https://www.ncbi.nlm.nih.gov/pubmed?term=15699838>.
- [32] Mitobe Y, Morishita S, Ohashi K, Sakai S, Uchiyama M, Abeywickrama H, Yamada E, Kikuchi Y, Nitta M, Honda T, Endoh H, Kimura S, Sakano S, Koyama Yu. Skeletal muscle index at intensive care unit admission is a predictor of intensive care unit-acquired weakness in patients with sepsis. *J Clin Med Res* 2019;11(12):834–41. <https://doi.org/10.14740/jocmr4027>.
- [33] Weijs PJM, Looijaard WGP, Dekker IM, Stapel SN, Girbes AR, Straaten H, Beishuizen A. Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients. *Critical Care (London, England)* 2014;18(1):R12. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4028783/?report=reader>.
- [34] Khan J, Harrison TB, Rich MM, Moss M. Early development of critical illness myopathy and neuropathy in patients with severe sepsis. *Neurology*. <https://www.ncbi.nlm.nih.gov/pubmed/17060568>. 2006.
- [35] Rich MM, Bird SJ, Raps EC, McCluskey LF, Teener JW. Direct muscle stimulation in acute quadriplegic myopathy. *Muscle Nerve* 1997;20(6):665–73. <https://www.ncbi.nlm.nih.gov/pubmed/9149072>.
- [36] Latronico N, Nattino G, Guarneri B, et al. Validation of the peroneal nerve test to diagnose critical illness polyneuropathy and myopathy in the intensive care unit: the multicentre Italian CRIMYNE-2 diagnostic accuracy study. *F1000Research*. <https://www.ncbi.nlm.nih.gov/pubmed/25309729.3>. 2014.
- [37] Formenti P, Umbrello M, Coppola S, Froio S, Chiumello D. Clinical review: peripheral muscular ultrasound in the ICU. *Annals of intensive care*. <https://www.ncbi.nlm.nih.gov/pubmed/31101987>. 2019.
- [38] Witteveen E, Sommers J, Wieske L, Doorduyn J, van N, Alfen, Schultz MJ, van IN, Schaik, Horn J, Verhamme C. Diagnostic accuracy of quantitative neuromuscular ultrasound for the diagnosis of intensive care unit-acquired weakness: a cross-sectional observational study. *Ann. Intensive Care* 2017;7(1). <https://www.ncbi.nlm.nih.gov/pubmed/28382599>.
- [39] Zochodne DW, Bolton CF, Wells GA, et al. Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. *Brain* 1987. <https://www.ncbi.nlm.nih.gov/pubmed/3651796>.
- [40] Jang MH, Shin M-J, Shin YB. Pulmonary and physical rehabilitation in critically ill patients. *Acute Crit Care* 2019;34(1):1–13. <https://www.ncbi.nlm.nih.gov/pubmed/31723900>.
- [41] Nydahl P, Sricharoenchai T, Chandra S, Kundt FS, Huang M, Fischill M, Needham DM. Safety of patient mobilization and rehabilitation in the intensive care unit. Systematic review with meta-analysis. *Annals ATS* 2017;14(5):766–77. <https://doi.org/10.1513/AnnalsATS.201611-843SR>.
- [42] Pan C, Chen L, Lu C, et al. Lung Recruitability in SARS-CoV-2 Associated Acute Respiratory Distress Syndrome: A Single-center, Observational Study. *American journal of respiratory and critical care medicine*. <https://www.ncbi.nlm.nih.gov/pubmed/32200645>, 2020.
- [43] Taccone P, Pesenti A, Latini R, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. <https://www.ncbi.nlm.nih.gov/pubmed/19903918>. 2009.
- [44] Zhang L, Hu W, Cai Z, et al. Early mobilization of critically ill patients in the intensive care unit: A systematic review and meta-analysis. *PLoS one*. <https://www.ncbi.nlm.nih.gov/pubmed/31581205>. 2019.
- [45] R.C. Kalamgi L. Larsson Mechanical Signaling in the Pathophysiology of Critical Illness Myopathy *Front. Physiol.* 7 10.3389/fphys.2016.00023 <http://journal.frontiersin.org/Article/10.3389/fphys.2016.00023/abstract>.
- [46] Castilletti C, Bordi L, Lalle E, et al. Coordinate induction of IFN- α and - γ by SARS-CoV also in the absence of virus replication. *Virology*. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7111739/>. 2005.
- [47] SHI S, PENG J, LI Y, QIN C, LIANG G, XU L, YANG Y, WANG J, SUN Q. The expression of membrane protein augments the specific responses induced by SARS-CoV nucleocapsid DNA immunization. *Mol Immunol* 2006;43(11):1791–8. <https://doi.org/10.1016/j.molimm.2005.11.005>.
- [48] Tseng K, Perrone LA, Zhu H, Makino S, Peters CJ. Severe Acute Respiratory Syndrome and the Innate Immune Responses: Modulation of Effector Cell Function without Productive Infection. *J Immunol*. <https://www.jimmunol.org/content/174/12/7977>. 2005.
- [49] Allen DC, Arunachalam R, Mills KR. Critical illness myopathy: Further evidence from muscle-fiber excitability studies of an acquired channelopathy. *Wiley Online Library*. <https://onlinelibrary.wiley.com/doi/full/10.1002/mus.20884>. 2007.
- [50] Haines KJ, Berney S, Warrillow S, Denehy L. Long-term recovery following critical illness in an Australian cohort. *J Intensive Care* 2018;6(1). <https://www.ncbi.nlm.nih.gov/pubmed/29445502>.
- [51] Saccheri C, Morawiec E, Delemazure J, Mayaux J, Dubé B-P, Similowski T, Demoule A, Dres M. ICU-acquired weakness, diaphragm dysfunction and long-term outcomes of critically ill patients. *Ann. Intensive Care* 2020;10(1). <https://www.ncbi.nlm.nih.gov/pubmed/31900667>.
- [52] Jung B, Moury PH, Mahul M, et al. Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. *Intensive Care Med* 2016.