Poor physical recovery after critical illness: incidence, features, risk factors, pathophysiology, and evidence-based therapies

Yente Florine Niké Boelens[a,b], Max Melchers[a,b], and Arthur Raymond Hubert van Zanten[a,b]

Purpose of review
To summarize the incidence, features, pathogenesis, risk factors, and evidence-based therapies of prolonged intensive care unit (ICU) acquired weakness (ICU-AW). We aim to provide an updated overview on aspects of poor physical recovery following critical illness.

Recent findings
New physical problems after ICU survival, such as muscle weakness, weakened condition, and reduced exercise capacity, are the most frequently encountered limitations of patients with postintensive care syndrome. Disabilities may persist for months to years and frequently do not fully recover. Hormonal and mitochondrial disturbances, impaired muscle regeneration due to injured satellite cells and epigenetic differences may be involved in sustained ICU-AW. Although demographics and ICU treatment factors appear essential determinants for physical recovery, pre-ICU health status is also crucial. Currently, no effective treatments are available. Early mobilization in the ICU may improve physical outcomes at ICU-discharge, but there is no evidence for benefit on long-term physical recovery.

Summary
Impaired physical recovery is observed frequently among ICU survivors. The pre-ICU health status, demographic, and ICU treatment factors appear to be important determinants for physical convalescence during the post-ICU phase. The pathophysiological mechanisms involved are poorly understood, thereby resulting in exiguous evidence-based treatment strategies to date.

Keywords
critical illness, intensive care unit acquired weakness, intensive care unit, muscle weakness, rehabilitation

INTRODUCTION

Significant developments in intensive care medicine have improved survival rates, resulting in more intensive care unit (ICU) survivors [1]. However, surviving critical illness may cause new disabilities as part of the 'postintensive care syndrome' (PICS), comprising physical, mental and cognitive health problems [2].

This review focuses on long-term physical outcomes following critical illness. Long-term muscle weakness after ICU admission, also known as sustained ICU-acquired weakness (ICU-AW), is frequently observed and encompasses critical illness myopathy (CIM), critical illness polyneuropathy (CIP) or a combination [3■,4■■]. Typically, a Medical Research Council (MRC)-sum score <48 is the clinical diagnosis for ICU-AW [5]. ICU patients can lose >15% of their muscle mass within the first week of ICU treatment [6]. Consequently, reduced muscle mass and function impair the ability to perform instrumental activities of daily living and limit the chance of returning to work [7]. Hospital discharge to rehabilitation facilities or nursing homes is necessary in severe cases. Furthermore, in severe ICU-AW (MRC-sum <36), increased mortality up to 1 year after ICU admission has been observed [8].

[a]Department of Intensive Care Medicine, Gelderse Vallei Hospital, Ede, The Netherlands and [b]Wageningen University & Research, Division of Human Nutrition and Health, Wageningen, The Netherlands

Correspondence to Professor Arthur Raymond Hubert van Zanten, MD, PhD, Chair Department of Intensive Care Medicine & Research, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP Ede, The Netherlands. e-mail: zantena@zgv.nl

KEY POINTS

- New physical problems, such as muscle weakness, weakened condition and reduced exercise capacity, are frequently encountered in postintensive care patients.

- Injured satellite cells, epigenetic differences and hormonal and mitochondrial disturbances may be involved in sustained ICU-AW.

- Besides demographics and ICU treatment factors, preexisting health condition is an essential determinant for physical recovery following ICU discharge.

- At present, there is no evidence for therapies to stimulate muscle recovery in those with prolonged critical illness-induced muscle weakness. However, several potential therapeutic targets have been identified recently.

This review provides an updated overview of aspects of poor physical recovery after critical illness, covering its incidence, features, risk factors, pathophysiology, and evidence-based therapies.

INCIDENCE OF POOR PHYSICAL RECOVERY AND ITS FEATURES

Poor physical outcome is frequently encountered in ICU survivors (Fig. 1) [9▪▪]. The prevalence of CIP and a combination with CIM is encountered more frequently following ICU discharge than CIM alone [3▪]. Patients with CIM only are more likely to recover than patients with CIM and CIP [3▪,10▪]. Herridge and coworkers showed that exercise capacity five years after ICU-discharge is still below predicted performance in most acute respiratory stress syndrome (ARDS) survivors [11]. In another study, 40% reported persistent ICU-AW symptoms during 6-months to 10-year follow-up [10▪]. Remarkably, only 38% recovered, and 62% had persistent symptoms among those patients with ICU-AW at ICU discharge. Additionally, only 11.6% of the cohort was diagnosed with ICU-AW at ICU discharge by physicians, whereas 75% self-reported to have experienced ICU-AW symptoms following ICU-discharge, which stresses the need for ICU-AW awareness among treating physicians and adequate diagnostic procedures during follow-up after discharge [10▪].

A recent systematic review found that the mean 6-min-walking-distance-test (6MWD) in survivors remained below population norms following ICU-discharge [12▪▪]. A significant increase in mean 6MWD at 12 months compared to 3 months was observed, yet no difference between 12 and 60 months, indicative of stagnation of physical recovery at one year after ICU-discharge.

Notably, previous studies did not consider the prevalence of preexisting impairments. These should be taken into account to prevent overestimating the effects of critical illness on physical function [13]. However, pre-ICU functional performance is not always evaluated. Few published studies investigate new-onset physical problems following ICU discharge.

A sub-study of the MONITOR-IC study concluded that new physical domain problems of PICS were the most symptoms reported one year after ICU discharge and are present in half of the patients [4▪▪]. Although possibly associated with other than the physical PICS domain, fatigue was the most reported new symptom. Weakened condition and muscle weakness were the subsequent most frequently encountered physical symptoms after one year [4▪▪]. Similar symptoms were reported in another sub-study with post-ICU patients treated for Coronavirus disease 2019 (COVID-19). Two-thirds reported one or more new physical problems one year after ICU treatment [14▪▪]. Hodgson and coworkers also evaluated ICU patients after severe COVID-19 [15▪]. In total, 71.3% reported persistent symptoms, of which 38.9% experienced new disabilities [15▪].

Coronavirus disease 2019 versus non-Coronavirus disease 2019 patients

COVID-19 ICU patients may be more vulnerable to ICU-AW than non-COVID-19 ICU patients due to a longer duration of mechanical ventilation and ICU stay [14▪▪]. Moonen *et al.* report that physical function at ICU discharge is more limited in COVID-19 ICU survivors than non-COVID-19 ICU survivors [16▪]. However, muscle function improved more promptly during hospital stay among COVID-19 versus non-COVID-19 ICU survivors, leading to similar functionality at hospital discharge [16▪]. When comparing new physical disabilities one year after ICU discharge in non-COVID-19 and COVID-19 patients, incidence rates are higher in the latter. Convalescence in the long term appears not necessary sooner [4▪▪,14▪▪]. Additionally, in COVID-19 ICU survivors, significant improvements in hand-grip strength (HGS) but not 6MWD were seen over time [17▪]. COVID-19 ICU survivors may experience impaired pulmonary diffusion capacity, resulting in decreased long-term exercise capacity rather than muscle dysfunction [15▪,18]. Although COVID-19's clinical features differ from classical ARDS, physical function recovery over time was worse in ARDS than
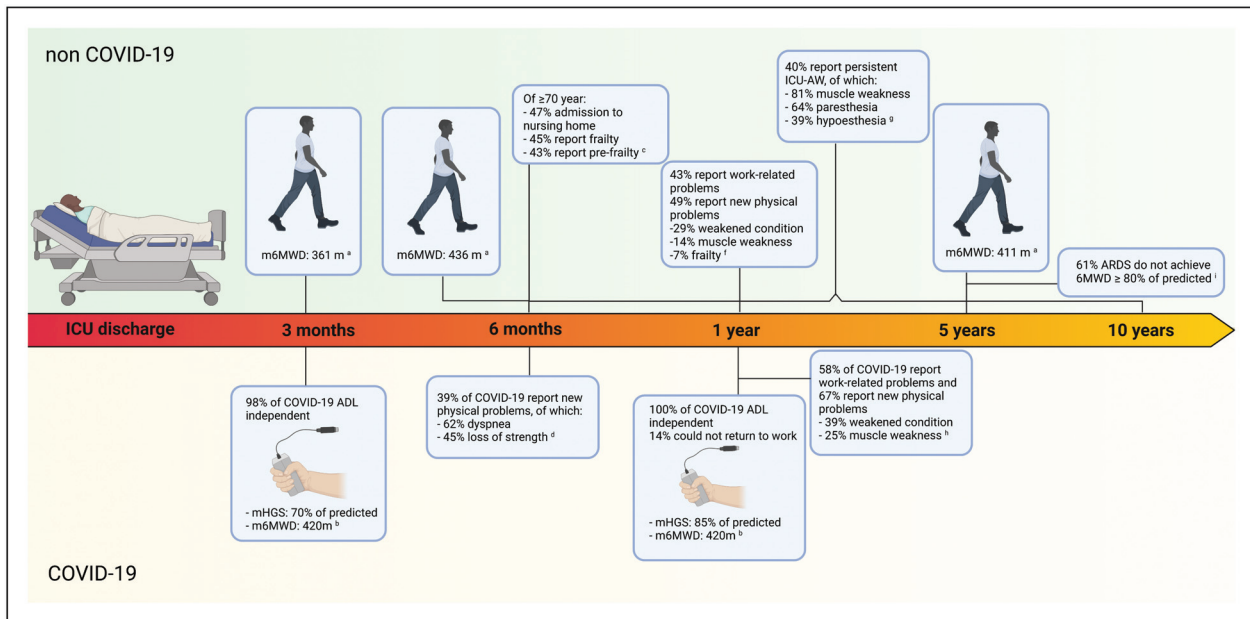
FIGURE 1. Visualized summary of study results regarding prevalence and incidence of impaired physical function following ICU-discharge in COVID-19 and non-COVID-19 patients. Legend: [a] Systematic review and meta-analysis including 16 studies and 1755 ICU survivors [12■■]; [b] Prospective single-center study including 114 COVID-19 ICU survivors, of which 98 analyzed at 3 months, and 51 analyzed at one year [17■]; [c] Prospective cohort study including 266 ≥ 70-year-old ICU-survivors [13]; [d] Prospective multicenter cohort study including 212 COVID-19 ICU-survivors [15■]; [e] Population-based cohort study including 546 ≥ 70-year-old ICU-survivors [33]; [f] Prospective multicenter cohort study including 2345 adult ICU-survivors [4■■]; [g] Prospective multicenter cohort study including 301 COVID-19 ICU survivors, of which 246 analyzed at one year [14■■]; [h] Single-center cohort study including 149 ICU-survivors [10■]; [i] Single-center cohort study including 109 ARDS ICU-survivors, of which 94 were analyzed at 5 years [11]. 6MWD, Six Minute Walking Distance; ADL, Activities of Daily Living; COVID-19, Coronavirus Disease 2019; ICU, intensive care unit; ICU-AW, ICU-acquired weakness; m6MWD, Mean Six Minute Walking Distance; mHGS, mean Hand Grip Strength. Created with BioRender.com.

in non-ARDS post-ICU patients [12■■]. Still, 86% of COVID-19 patients could return to work one year after ICU discharge, which is substantially higher than patients surviving classical ARDS (40%) [17■].

PATHOGENESIS

Reduced muscle strength and weakness are mainly the results of an imbalance between synthesis and lysis of muscle proteins, leading to substantial muscle wasting and maintaining a catabolic state [6,19].

Acute phase

Several potential pathophysiologic mechanisms involved in muscle atrophy and dysfunction have been associated with developing ICU-AW (Fig. 2). Systemic inflammation and enhanced oxidative stress during critical illness results in upregulation of ubiquitin-proteolysis pathways and dysregulation of autophagy, which causes rapid and severe muscle proteolysis [19,20]. Inflammation and

hyperglycemia also induce loss of mitochondrial capacity and function, compromising energy production, resulting in muscle dysfunction and atrophy [19–21]. Furthermore, peripheral insulin resistance, disturbance of intracellular calcium homeostasis, lipid toxicity, muscle disuse, microcirculatory disturbances and cytokine release resulting in muscle denervation contribute to muscle weakness in the critically ill patient [19–21]. Recently, two less methylated epigenome regions, HIC1 and NADK2, were found in muscle tissue from ICU patients compared with controls [22■]. HIC1 regulates muscle regeneration and moderates the concentration of postsynaptic acetylcholine receptors, whereas NADK2 is involved in fatty lipid metabolism and mitochondrial stimulation [22■].

Post-intensive care unit phase

Although the pathophysiology of muscle atrophy and dysfunction during critical illness seems to be partially elucidated, the mechanisms involved in
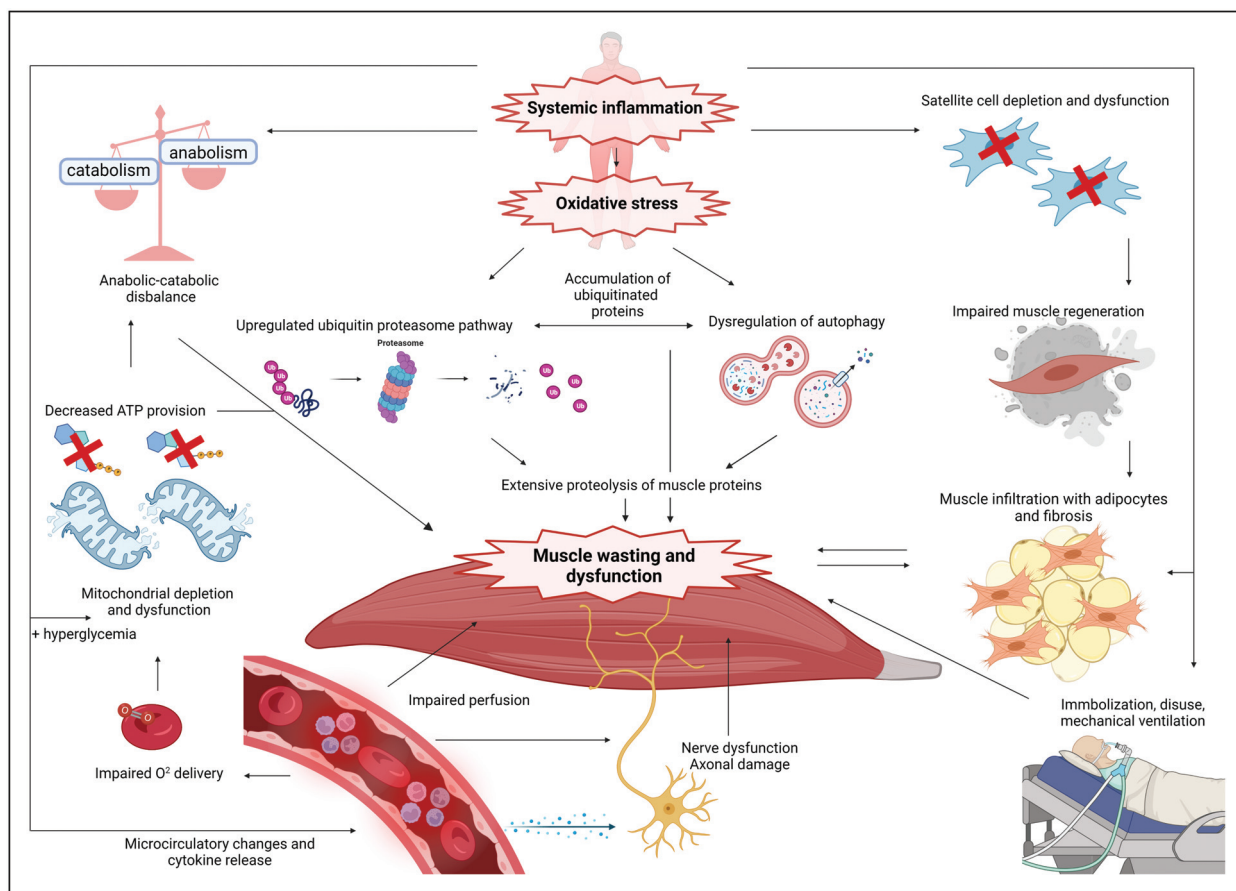
FIGURE 2. Heading: Pathophysiologic mechanisms possibly involved in developing acute muscle wasting and dysfunction during critical illness, resulting in ICU-acquired weakness. ATP, adenosine triphosphate; O^2, oxygen. Created with BioRender.com.

persistent muscle dysfunction resulting in impaired physical recovery after ICU discharge remain poorly understood (Fig. 3) [20]. Dos Santos and coworkers report that mechanisms involved in acute critical illness-related muscle wasting, i.e., mitochondrial content, enhanced muscle proteolysis, and autophagy dysregulation, have normalized to baseline six months after ICU-admission [23]. Instead, sustained muscle weakness may be explained by persistently impaired muscle regeneration due to decreased numbers of muscle stem cells, better known as satellite cells [23,24]. During critical illness, these cells become depleted due to inflammation and appear to regenerate less in those patients with persistent muscle weakness despite resolved inflammation, indicating long-lasting injury to these cells [23]. Alterations of the epigenome of satellite cells are found in older individuals and those suffering from muscle pathology, reducing the capacity of these cells to regenerate [25]. Modification of these alterations may provide future therapeutic targets for sustained ICU-AW.

Remarkably, the muscle mass of critical illness survivors suffering from sustained muscle weakness

appears to normalize whereas contractility remains impaired months after ICU-discharge, suggesting an imbalance between muscle volume and strength [23,26]. Extensive inflammation during critical illness is responsible for alterations in the muscle structure, replacing muscle tissue with adipocytes or fibrosis [19,21]. This fatty infiltration persisted for months in a cohort of post-ICU patients with poor physical recovery [27]. In the same sample, muscle microRNA 490-3p and microRNA-744-p, both negative myogenesis regulators, were increased, potentially impacting the long-term muscle weakness of ICU survivors [28]. Even though these findings may represent some population variability, muscle microRNA regulation may serve as a potential treatment strategy to prevent dysregulated muscle regeneration.

The role of myostatin in musculoskeletal muscle wasting is recently gaining attention [6,29]. Myostatin is a negative regulator of myogenesis and is inversely correlated with inflammation in critically ill patients, possibly preventing excessive muscle wasting in the acute phase [29]. Controversially, complete myostatin inhibition prevents muscle
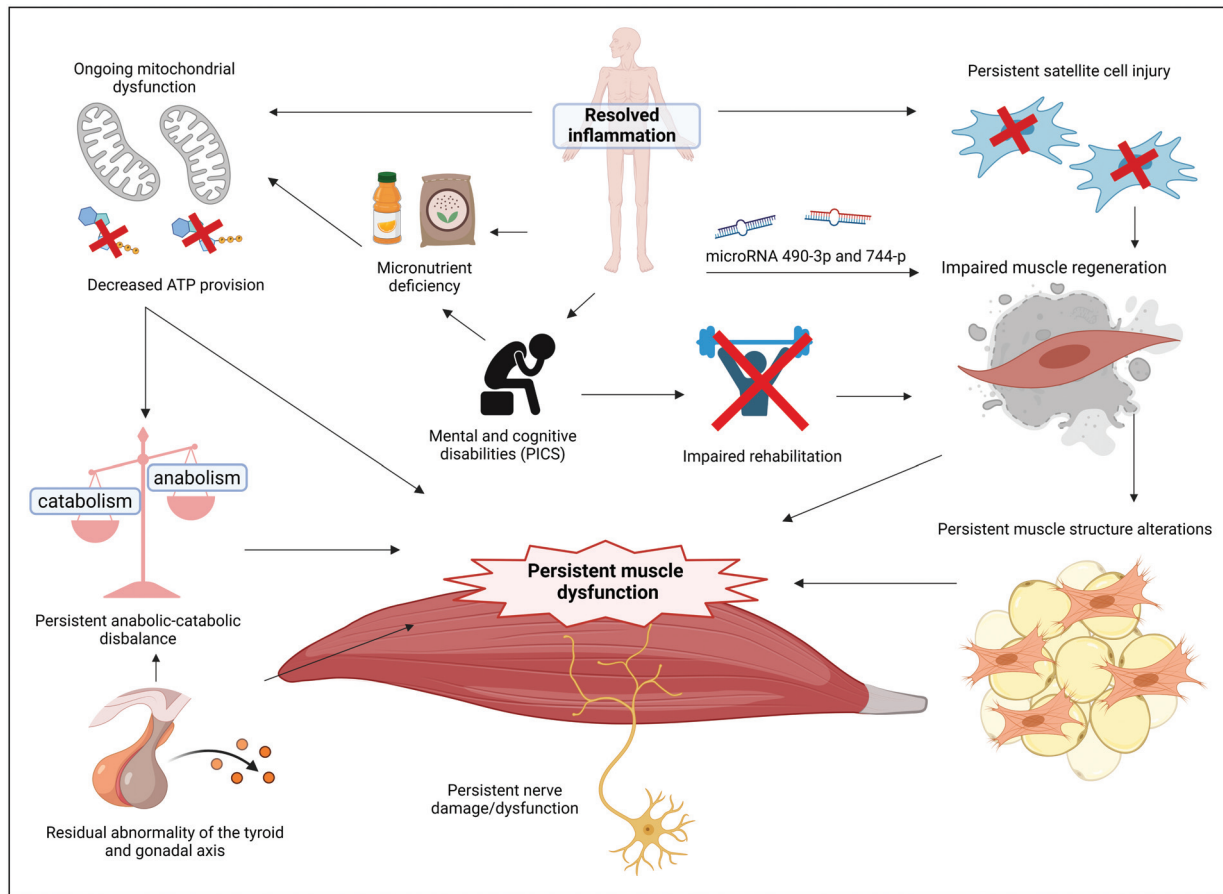
FIGURE 3. Heading: Pathophysiologic mechanisms possibly involved in prolonged muscle dysfunction following critical illness. ATP, adenosine triphosphate; HIC1, Hypermethylated in Cancer 1; NADK 2, Nicotinamide-adenine-dinucleotide Kinase 2; O2, oxygen; PICS, postintensive care syndrome. Created with BioRender.com.

wasting and improves survival in septic mouse models, providing a potential pharmacological target to attenuate critical illness-induced muscle atrophy [30■]. Myostatin was upregulated in patients 9–12 months after surviving major thermal trauma and inversely correlated with muscle strength [31]. However, these findings require confirmation in a general post-ICU population.

Additionally, neuroendocrine alterations in patients with sustained muscle weakness are associated with decreased physical recovery. A higher reverse T3, and lower T3-reverse T3 ratio was found to be associated with lower HGS and shorter 6MWD five years after critical illness [32■]. Persisting abnormalities within the thyroid axis may increase the risk of long-term physical impairment. Nevertheless, the mechanisms involved remain unclear.

RISK FACTORS BEFORE, DURING AND AFTER INTENSIVE CARE UNIT ADMISSION

Females and the elderly are more prone to poor functional recovery after critical illness [4■■,10■,33].

A reduced ability to stimulate muscle protein synthesis during aging, known as anabolic resistance, develops [34]. Although younger patients may recover faster than the elderly, they do not always recover completely to their pre-ICU health status [11]. Differences between sexes remain unclear but may be associated with smaller preexistent muscle mass in women [5]. However, these patients generally also have a poorer pre-ICU health status [35]. Patients experiencing cognitive, mental or physical health issues before ICU admission are at risk for poor functional outcomes after ICU [4■■,15■,34]. Lastly, patients with middle education are less likely to become frail than patients with low education one year after ICU admission [4■■].

Several risk factors associated with developing ICU-AW are multiple organ failure, immobilization, hyperglycemia and systemic inflammation [9■■]. Additionally, the severity of illness and duration of mechanical ventilation are essential predictors of physical outcomes after critical illness [15■,21]. Emergency surgery ICU patients and, to a lesser extent, medical ICU patients report

significant deteriorations in physical function and quality of life one year after admission, whereas elective surgical patients may experience an improvement [4▪▪]. Elective surgical patients typically require short-term ICU admission, whereas other patients are more exposed to systemic inflammation and prolonged organ support [4▪▪]. Furthermore, corticosteroid treatment has been associated with ICU-AW development, particularly in mechanically ventilated patients [36]. Although corticosteroids attenuate systemic inflammation and improve hypoxemia, they induce catabolic effects on skeletal muscles [9▪▪,12▪▪]. Additionally, neuromuscular blocking treatment (NMBA) may be associated with muscle weakness as it causes complete muscle disuse, potentially attributing to ICU-AW. However, current guidelines do not recommend against prolonged therapy with NMBA as its effect on muscle wasting has not been confirmed [12▪▪,37].

Muscle strength at ICU discharge, measured by MRC-sum score, is a predictor for HGS, 6MWD and self-reported physical functioning at five years follow-up [38]. ICU length of stay (LOS) is a significant determinant for one-year physical outcomes; hospital LOS may also contribute to new-onset frailty [4▪▪,33].

EVIDENCE-BASED THERAPIES

Currently, no effective treatments are available, and physicians mainly focus on preventing ICU-AW by early mobilization and avoiding hyperglycemia [21,39].

Early mobilization

Several systematic reviews have been published addressing the effect of early mobilization during ICU admission on outcomes [40–43]. Results are inconsistent comparing these meta-analyses, possibly due to different definitions of early mobilization and inclusion of heterogeneous trials. The most recent and comprehensive meta-analysis, including sixty trials, found that early mobilization during ICU admission improved physical function at hospital discharge [44]. However, beneficial effects on physical function six months after discharge were not found in patients rehabilitated during ICU stay [42,44]. Additionally, evidence of rehabilitation initiated after ICU discharge is insufficient to prove its effect on functional recovery [45]. These findings suggest ongoing mechanisms, such as a persistently disturbing catabolism/anabolism balance, causing the inability to regain muscle function after discharge [23].

Hormonal therapies

Randomised controlled trials (RCT) studying growth hormone in ICU-patients failed to improve outcomes and even increased mortality [19]. However, the timing of treatment may be crucial as hormonal supplementation may act pro-inflammatory during critical illness. A different approach to influencing the gonadal axis would be through testosterone, as low testosterone levels may persist after discharge [46▪]. Treatment with the testosterone analog oxandrolone is beneficial in patients with severe burns to increase lean body mass during recovery [47]. Two small trials with oxandrolone in nonburn ICU-patients could not find an association with improved outcomes but did not focus on the long-term [48,49]. Both groups received a low nutritional intake implicating inadequate substrate administration for muscle regeneration. Moreover, oxandrolone was discontinued during ward stay, which would be the crucial therapeutic phase to regain muscle function for patients with sustained ICU-AW. Therefore, an RCT with testosterone analog in post-ICU patients is warranted to determine the effect on physical rehabilitation [46▪].

Nutritional therapy

A different approach would be through nutritional therapy to restore the anabolic state and stimulate muscle regeneration [50]. Nevertheless, the beneficial effects of elevated protein intake have not yet been shown. In an RCT, personalized nutritional goals were estimated to cover 100% of the requirements in one group, whereas the other group received standard nutrition [51]. Although protein provision was higher in the first group, no difference in self-reported physical function was seen in patients six months after critical illness. Remarkably, early parenteral nutrition (PN) (<48 h) compared to late PN (≥ 8days) was found to increase muscle weakness, but not muscle wasting, during ICU stay [52]. The authors attributed this to more efficient autophagy control among patients who received late PN. Additionally, infusion of ketone bodies or ketogenesis in the acute phase of critical illness attenuated muscle weakness in a murine sepsis model [53]. Ketones can provide energy in conditions of mitochondrial dysfunction. However, this finding requires further exploration in human studies. After 4–7 days of ICU admission, adequate protein and energy intakes are needed to prevent loss of muscle mass and function [50,54].

These nutritional requirements are often not achieved in the post-ICU period, negatively affecting long-term outcomes [55,56]. Research focusing on optimal nutrition strategies during the post-ICU

phase is lacking. A recent RCT in non-ICU patients showed that protein supplementation in hospitalized elderly with sarcopenia improved physical performance, reducing rehabilitation time and hospital LOS [57▪]. Although these patients differ from ICU patients as the latter may suffer from inflammation and oxidative stress, protein supplementation may still provide an anabolic signal. It could be a potential treatment strategy in patients suffering from muscle wasting during the post-ICU phase, yet it requires further research.

In contrast to Dos Santos *et al.*, mitochondrial damage was found in animals surviving sepsis to persist in those with sustained muscle weakness despite resolved inflammation [23,26]. Moreover, Dos Santos and colleagues did not investigate the actual mitochondrial function, which may contribute to sustained ICU-AW [23]. Consequently, mitochondrial resuscitation with micronutrients after ICU discharge may be interesting, as many vitamins and trace elements are involved in the optimal functioning of mitochondria [58]. High dosages of single micronutrients failed to show benefits. Therefore, a strategic antioxidant cocktail may be more clinically efficient [59▪].

Mesenchymal cells

Considering persistent satellite cell injury as a pivotal driver of poor muscle regeneration, targeting these cells may be a valuable treatment target [23]. Their functionality may be restored by mesenchymal stem cells. In septic murine models, these cells improved muscle recovery, decreased necrosis and fibrosis, and decreased plasma levels of pro-inflammatory cytokines and procalcitonin [24]. No human studies have been published involving mesenchymal cell therapy to regain muscle function in post-ICU patients.

CONCLUSION

Poor physical recovery is among the most debilitating and reported aspects of PICS among ICU survivors. As most studies do not consider the preexisting health condition when addressing new physical symptoms, the actual incidence of new disabilities is not precisely known. The pre-ICU health status, demographic, and ICU treatment factors appear to be important determinants for physical convalescence post-ICU. The pathophysiological mechanisms involved are poorly understood, thereby resulting in exiguous evidence-based treatment strategies to date. More research into the pathophysiology and promising multimodal therapies involving nutritional, exercise rehabilitation, and

hormonal therapies in the post-ICU period are warranted.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
▪ of special interest
▪▪ of outstanding interest

1. Wischmeyer PE, San-Millan I. Winning the war against ICU-acquired weakness: new innovations in nutrition and exercise physiology. Crit Care 2015; 19 (Suppl 3):S6.
2. Needham DM, Davidson J, Cohen H, *et al.* Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med 2012; 40:502–509.
3. Intiso D, Centra AM, Bartolo M, *et al.* Recovery and long term functional
▪ outcome in people with critical illness polyneuropathy and myopathy: a scoping review. BMC Neurol 2022; 22:50.
Recently published systematic review and meta-analysis reporting the incidence of ICU-AW following ICU admission, differentiating between different ICU-AW manifestations such as CIM, CIP and the combination.
4. Geense WW, Zegers M, Peters MAA, *et al.* New physical, mental, and
▪▪ cognitive problems 1 year after ICU admission: a prospective multicenter study. Am J Respir Crit Care Med 2021; 203:1512–1521.
A large, Dutch multicenter study providing interesting insights into the incidence of PICS-related problems one year after ICU survival. This study adjusted for pre-ICU health status, providing a valid picture of the impact of critical illness on problems following ICU-admission.
5. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med 2014; 371:287–288.
6. Puthucheary ZA, Rawal J, McPhail M, *et al.* Acute skeletal muscle wasting in critical illness. JAMA 2013; 310:1591–1600.
7. Hopkins RO, Suchyta MR, Kamdar BB, *et al.* Instrumental activities of daily living after critical illness: a systematic review. Ann Am Thorac Soc 2017; 14:1332–1343.
8. Hermans G, Van Mechelen H, Clerckx B, *et al.* Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Respir Crit Care Med 2014; 190:410–420.
9. Wang W, Xu C, Ma X, *et al.* Intensive care unit-acquired weakness: a review of
▪▪ recent progress with a look toward the future. Front Med 2020; 7:559789.
A recent systematic review and meta-analysis investigating the efficacy of physical rehabilitation in the ICU, including the most recent studies available.
10. Meyer-Friessem CH, Malewicz NM, Rath S, *et al.* Incidence, time course and
▪ influence on quality of life of intensive care unit-acquired weakness symptoms in long-term intensive care survivors. J Intensive Care Med 2021; 36:1313–1322.
A cohort study investigating the incidence of ICUAW for a period up to 10 years after ICU discharge, including comparisons of CIM and CIP. This information provides insights for different disease outcomes.
11. Herridge MS, Tansey CM, Matte A, *et al.* Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 2011; 364:1293–1304.
12. Parry SM, Nalamalapu SR, Nunna K, *et al.* Six-minute walk distance after
▪▪ critical illness: a systematic review and meta-analysis. J Intensive Care Med 2021; 36:343–351.
A comprehensive systematic review and meta-analysis giving an overview of studies evaluating an objective performance-based physical function measurement (6MWD), providing longitudinal information on physical function recovery over the first 5 years after critical illness.

13. Ferrante LE, Pisani MA, Murphy TE, et al. The association of frailty with post-ICU disability, nursing home admission, and mortality: a longitudinal study. Chest 2018; 153:1378–1386.

14. Heesakkers H, van der Hoeven JG, Corsten S, et al. Clinical outcomes among
■■ patients with 1-year survival following intensive care unit treatment for COVID-19. JAMA 2022; 327:559–565.
A comprehensive substudy of the MONITOR-ICU study in COVID-19 patients using the exact same study methods as Geense et al. (ref. 4), making it possible to compare incidence rates of new physical outcomes in COVID-19 and non-COVID-19 ICU survivors.

15. Hodgson CL, Higgins AM, Bailey MJ, et al. The impact of COVID-19 critical
■ illness on new disability, functional outcomes and return to work at 6 months: a prospective cohort study. Crit Care 2021; 25:382.
A large multicenter, prospective cohort study describing the incidence of self-reported new disabilities and functional impairment, following severe COVID-19 requiring ICU-admission.

16. Moonen H, Strookappe B, van Zanten ARH. Physical recovery of COVID-19
■ pneumosepsis intensive care survivors compared with non-COVID pneumo-sepsis intensive care survivors during postintensive care hospitalization: The RECOVID retrospective cohort study. J Parenter Enteral Nutr 2021; 46:798–804.
A restrospective cohort study comparing physical recovery during hospital stay in COVID-19 and non-COVID pneumosepsis ICU survivors. One of few reports comparing recovery among COVID-19 and non-COVID-19 ICU survivors.

17. Latronico N, Peli E, Calza S, et al. Physical, cognitive and mental health
■ outcomes in 1-year survivors of COVID-19-associated ARDS. Thorax 2022; 77:300–303.
This prospective longitudinal study evaluated physical outcomes in COVID-19 patients 3, 6 and 12 months after ICU discharge. Objective measures are used to measure physical function.

18. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021; 397:220–232.

19. Friedrich O, Reid MB, Van den Berghe G, et al. The sick and the weak: neuropathies/myopathies in the critically ill. Physiol Rev 2015; 95:1025–1109.

20. Batt J, Herridge MS, Dos Santos CC. From skeletal muscle weakness to functional outcomes following critical illness: a translational biology perspective. Thorax 2019; 74:1091–1098.

21. Vanhorebeek I, Latronico N, Van den Berghe G. ICU-acquired weakness. Intensive Care Med 2020; 46:637–653.

22. Van Dyck L, Guiza F, Derese I, et al. DNA methylation alterations in muscle of
■ critically ill patients. J Cachexia Sarcopenia Muscle 2022; 13:1731–1740.
A cohort study derived from the EPaNIC trial contributing to the unsolved puzzle of the pathophysiology behind ICU-AW by providing novel insights into the role of muscle DNA methylation alterations following critical illness.

23. Dos Santos C, Hussain SN, Mathur S, et al. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay. A pilot study. Am J Respir Crit Care Med 2016; 194:821–830.

24. Rocheteau P, Chatre L, Briand D, et al. Sepsis induces long-term metabolic and mitochondrial muscle stem cell dysfunction amenable by mesenchymal stem cell therapy. Nat Commun 2015; 6:10145.

25. Massenet J, Gardner E, Chazaud B, Dilworth FJ. Epigenetic regulation of satellite cell fate during skeletal muscle regeneration. Skelet Muscle 2021; 11:4.

26. Owen AM, Patel SP, Smith JD, et al. Chronic muscle weakness and mito-chondrial dysfunction in the absence of sustained atrophy in a preclinical sepsis model. Elife 2019; 8:e49920.

27. Walsh CJ, Batt J, Herridge MS, et al. Transcriptomic analysis reveals abnormal muscle repair and remodeling in survivors of critical illness with sustained weakness. Sci Rep 2016; 6:29334.

28. Walsh CJ, Escudero King C, Gupta M, et al. MicroRNA regulatory networks associated with abnormal muscle repair in survivors of critical illness. J Cachexia Sarcopenia Muscle 2022; 13:1262–1276.

29. Wirtz TH, Loosen SH, Buendgens L, et al. Low myostatin serum levels are associated with poor outcome in critically ill patients. Diagnostics 2020; 10:574.

30. Kobayashi M, Kasamatsu S, Shinozaki S, et al. Myostatin deficiency not only
■ prevents muscle wasting but also improves survival in septic mice. Am J Physiol Endocrinol Metab 2021; 320:E150–E159.
A well designed animal study providing novel and interesting insights into the role of myostatin in sepsis-induced muscle wasting.

31. Wallner C, Wagner JM, Dittfeld S, et al. Myostatin serum concentration as an indicator for deviated muscle metabolism in severe burn injuries. Scand J Surg 2019; 108:297–304.

32. Vanhorebeek I, Derese I, Gunst J, et al. Persisting neuroendocrine abnorm-
■ alities and their association with physical impairment 5 years after critical illness. Crit Care 2021; 25:430.
This study investigated long-term neuroendocrine abnormalities after ICU among patients with poor phsyical recovery. This papers suggests potential targets to improve long term outcomes after critical illness.

33. Hajeb M, Singh TD, Sakusic A, et al. Functional outcome after critical illness in older patients: a population-based study. Neurol Res 2021; 43:103–109.

34. Paddon-Jones D, Rasmussen BB. Dietary protein recommendations and the prevention of sarcopenia. Curr Opin Clin Nutr Metab Care 2009; 12:86–90.

35. Geense WW, van den Boogaard M, Peters MAA, et al. Physical, mental, and cognitive health status of ICU survivors before ICU admission: a cohort study. Crit Care Med 2020; 48:1271–1279.

36. Yang T, Li Z, Jiang L, Xi X. Corticosteroid use and intensive care unit-acquired weakness: a systematic review and meta-analysis. Crit Care 2018; 22:187.

37. Murray MJ, DeBlock HF, Erstad BL, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient: 2016 update-executive summary. Am J Health Syst Pharm 2017; 74:76–78.

38. Van Aerde N, Meersseman P, Debaveye Y, et al. Five-year impact of ICU-acquired neuromuscular complications: a prospective, observational study. Intensive Care Med 2020; 46:1184–1193.

39. Anekwe DE, Biswas S, Bussieres A, Spahija J. Early rehabilitation reduces the likelihood of developing intensive care unit-acquired weakness: a systematic review and meta-analysis. Physiotherapy 2020; 107:1–10.

40. Menges D, Seiler B, Tomonaga Y, et al. Systematic early versus late mobiliza-tion or standard early mobilization in mechanically ventilated adult ICU patients: systematic review and meta-analysis. Crit Care 2021; 25:16.

41. Doiron KA, Hoffmann TC, Beller EM. Early intervention (mobilization or active exercise) for critically ill adults in the intensive care unit. Cochrane Database Syst Rev 2018; 3:CD010754.

42. Fuke R, Hifumi T, Kondo Y, et al. Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: a systematic review and meta-analysis. BMJ Open 2018; 8:e019998.

43. Zang K, Chen B, Wang M, et al. The effect of early mobilization in critically ill patients: a meta-analysis. Nurs Crit Care 2020; 25:360–367.

44. Wang YT, Lang JK, Haines KJ, et al. Physical rehabilitation in the ICU: a systematic review and meta-analysis. Crit Care Med 2022; 50:375–388.

45. Connolly B, Salisbury L, O'Neill B, et al. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness: executive summary of a Cochrane Collaboration systematic review. J Cachexia Sarco-penia Muscle 2016; 7:520–526.

46. Wischmeyer PE, Suman OE, Kozar R, et al. Role of anabolic testosterone
■ agents and structured exercise to promote recovery in ICU survivors. Curr Opin Crit Care 2020; 26:508–515.
Excellent and comprehensive review adressing the urgency for research into treatment strategies for post-ICU muscle weakness, advocating for trials investi-gating the efficacy of anabolic medications, exercise and nutrition to enhance the convalescence of critical illness survivors.

47. Li H, Guo Y, Yang Z, et al. The efficacy and safety of oxandrolone treatment for patients with severe burns: a systematic review and meta-analysis. Burns 2016; 42:717–727.

48. Bulger EM, Jurkovich GJ, Farver CL, et al. Oxandrolone does not improve outcome of ventilator dependent surgical patients. Ann Surg 2004; 240:472–478; discussion 8-80.

49. Gervasio JM, Dickerson RN, Swearingen J, et al. Oxandrolone in trauma patients. Pharmacotherapy 2000; 20:1328–1334.

50. van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convales-cence phases. Crit Care 2019; 23:368.

51. Allingstrup MJ, Kondrup J, Wiis J, et al. Early goal-directed nutrition in ICU patients (EAT-ICU): protocol for a randomised trial. Dan Med J 2016; 63:A5271.

52. Hermans G, Casaer MP, Clerckx B, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med 2013; 1:621–629.

53. Goossens C, Weckx R, Derde S, et al. Adipose tissue protects against sepsis-induced muscle weakness in mice: from lipolysis to ketones. Crit Care 2019; 23:236.

54. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019; 38:48–79.

55. Ridley EJ, Parke RL, Davies AR, et al. What happens to nutrition intake in the post-intensive care unit hospitalization period? An observational cohort study in critically ill adults. JPEN J Parenter Enteral Nutr 2019; 43:88–95.

56. Wittholz K, Fetterplace K, Clode M, et al. Measuring nutrition-related out-comes in a cohort of multitrauma patients following intensive care unit discharge. J Hum Nutr Diet 2020; 33:414–422.

57. Rondanelli M, Cereda E, Klersy C, et al. Improving rehabilitation in sarcopenia:
■ a randomized-controlled trial utilizing a muscle-targeted food for special medical purposes. J Cachexia Sarcopenia Muscle 2020; 11:1535–1547.
A randomized controlled trial investigating the effect of nutritional supplementation in sarcopenic elderly to restore physical function. This study shows beneficial effects in non-ICU patients and provides promising information for a realistic intervention in post-ICU patients.

58. Wesselink E, Koekkoek WAC, Grefte S, et al. Feeding mitochondria: potential role of nutritional components to improve critical illness convalescence. Clin Nutr 2019; 38:982–995.

59. Moonen H, Van Zanten ARH. Mitochondrial dysfunction in critical illness
■ during acute metabolic stress and convalescence: consequences for nutrition therapy. Curr Opin Crit Care 2020; 26:346–354.
A comprehensive review regarding the role of mitochondrial dysfunction during critical illness and convalescence, addressing the potential of nutritional therapies in order to restore mitochondrial functioning.