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NARRATIVE REVIEW

ICU-acquired weakness

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Abstract

Critically ill patients often acquire neuropathy and/or myopathy labeled ICU-acquired weakness. The current insights into incidence, pathophysiology, diagnostic tools, risk factors, short- and long-term consequences and management of ICU-acquired weakness are narratively reviewed. PubMed was searched for combinations of "neuropathy", "myopathy", "neuromyopathy", or "weakness" with "critical illness", "critically ill", "ICU", "PICU", "sepsis" or "burn". ICU-acquired weakness affects limb and respiratory muscles with a widely varying prevalence depending on the study population. Pathophysiology remains incompletely understood but comprises complex structural/functional alterations within myofibers and neurons. Clinical and electrophysiological tools are used for diagnosis, each with advantages and limitations. Risk factors include age, weight, comorbidities, illness severity, organ failure, exposure to drugs negatively affecting myofibers and neurons, immobility and other intensive care-related factors. ICU-acquired weakness increases risk of in-ICU, in-hospital and long-term mortality, duration of mechanical ventilation and of hospitalization and augments healthcare-related costs, increases likelihood of prolonged care in rehabilitation centers and reduces physical function and quality of life in the long term. RCTs have shown preventive impact of avoiding hyperglycemia, of omitting early parenteral nutrition use and of minimizing sedation. Results of studies investigating the impact of early mobilization, neuromuscular electrical stimulation and of pharmacological interventions were inconsistent, with recent systematic reviews/meta-analyses revealing no or only low-quality evidence for benefit. ICU-acquired weakness predisposes to adverse short- and long-term outcomes. Only a few preventive, but no therapeutic, strategies exist. Further mechanistic research is needed to identify new targets for interventions to be tested in adequately powered RCTs.

Keywords: Critical illness, Muscle weakness, Diagnosis, Risk factors, Clinical outcome, Intervention

Introduction

Muscle weakness is a frequent problem in the intensive care unit (ICU). The weakness can be due to primary neuromuscular disorders that trigger the need for intensive care, such as Guillain–Barré Syndrome, myasthenia gravis, amyotrophic lateral sclerosis or multiple sclerosis, among others, but these conditions only account for < 0.5% of all ICU admissions [1]. More often, however, muscle weakness develops as a secondary disorder while patients are being treated for other life-threatening conditions. The latter has been labeled "ICU-acquired weakness" with the implication that this neuromuscular dysfunction has no plausible etiology other than the critical illness and its treatments [2]. ICU-acquired weakness is typically generalized, symmetrical, and affects limb (proximal more than distal) and respiratory muscles, whereas facial and ocular muscles are spared [3, 4]. Muscle tone is almost invariably reduced. Deep tendon reflexes can be reduced or normal. Weakness may originate from a neurogenic disturbance "critical illness polyneuropathy" (CIP), a myogenic disturbance "critical illness myopathy" (CIM), or a combination thereof labelled "critical illness neuromyopathy" [2, 5, 6]. Electrophysiological examination shows typical patterns of abnormalities. Also, the pronounced loss of muscle mass, that can exceed 10% over the 1st week in ICU, has been

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associated with functional impairment [7, 8]. Severe disuse muscle atrophy has been put forward as a separate entity of ICU-acquired weakness in the absence of electrophysiological abnormalities [4].

Prevalence of ICU-acquired weakness varies widely with the studied patient population and risk factors, the timing of assessment, the methods used for diagnosis, and inconsistent accounting for patients' pre-hospital muscle function or overall functional status (often overlooking age-related frailty) [4, 6, 9–12]. A systematic review reported a median prevalence of 43% (interquartile range 25–75%) over 31 studies [13]. Diaphragm dysfunction may develop more often than limb muscle weakness [14].

We here review the current insights into the pathophysiology, diagnostic tools, risk factors, short- and long-term consequences and management of ICU-acquired weakness.

Pathophysiology

The pathophysiology of ICU-acquired weakness remains incompletely understood, in part explained by practical and ethical issues complicating the study of underlying mechanisms in human patients. Indeed, mechanistic studies require harvesting of muscle or nerve biopsies, which is an invasive procedure. Also, the possibility to interfere with biological processes in human patients, e.g., by administering activators or inhibitors of assumed central players, is inherently limited in view of potential risks for the patients. However, studies in animal models have added valuable insights and, together with available patient study results, allowed to attribute ICU-acquired weakness to complex structural/functional alterations within the central nervous system, the peripheral nerves and the myofibers. In Fig. 1, the major pathways assumed to be involved, comprising loss of muscle mass and loss of muscle function, are briefly summarized in a conceptual framework [5, 15–17].

Muscle atrophy

The catabolic state of critical illness, with reduced anabolic effector hormones and increased catabolic hormones [18], and the mechanical unloading due to immobilization/denervation, explain the pronounced muscle wasting that contributes to weakness of myogenic origin in ICU patients [7]. Such loss of muscle mass is due to imbalanced protein turnover, with a reduced protein synthesis relative to accelerated breakdown by activated proteolytic systems, such as the ubiquitin–proteasome system [7, 8, 16].

Muscle dysfunction

Several factors contribute to loss of muscle function during critical illness.

Take-home messages

Critically ill patients frequently acquire muscle weakness while in the ICU, which adversely affects short- and long-term outcomes. No effective treatments are currently available whereas partial prevention of ICU-acquired weakness is possible by avoiding hyperglycemia, by postponing parenteral nutrition to beyond the first ICU week, and by minimizing sedation. Further mechanistic research is warranted in order to identify novel preventive and/or therapeutic strategies that can be tested in adequately powered RCTs.

Structural muscle alterations

Muscle biopsies show signs of inflammation or necrosis, pronounced infiltration of muscle with (or myofiber conversion to) adipose tissue and fibrosis in a remarkably high proportion of critically ill patients [8].

Microcirculatory disturbances

Microcirculatory changes include vasodilation and increased permeability, which allow leukocyte extravasation and tissue infiltration, local cytokine production and edema formation with increased intercapillary distance [5, 6, 15]. These changes can compromise perfusion and oxygen delivery. Involvement of edema-induced compression damage to muscles and nerves remains debated. Nevertheless, hypoperfusion may contribute to neuronal injury, axonal degeneration, and to a chronic membrane depolarization of terminal motor axons.

Bioenergetic failure

Insufficient oxygen supply to mitochondria may compromise mitochondrial energy production. However, the mitochondrial dysfunction in critical illness appears explained by impaired oxygen utilization, due to direct mitochondrial damage further aggravated by inflammation, hyperglycemia and free radicals, rather than by impaired oxygen delivery [15]. Dysfunctional mitochondria not only compromise energy provision but also amplify the production of free radical and reactive oxygen species, eliciting a vicious cycle of macromolecular and organelle damage.

Inadequate autophagy activation

Initially, increased autophagy was assigned a detrimental role as a contributor to muscle atrophy [15]. However, it has become clear that this important cellular quality control mechanism is actually insufficiently activated during critical illness, allowing accumulation of damage to mitochondria and other cellular components [19]. Impaired clearance of such damage results in degenerative changes which compromise muscle function, thus contributing to ICU-acquired weakness [8, 19, 20].

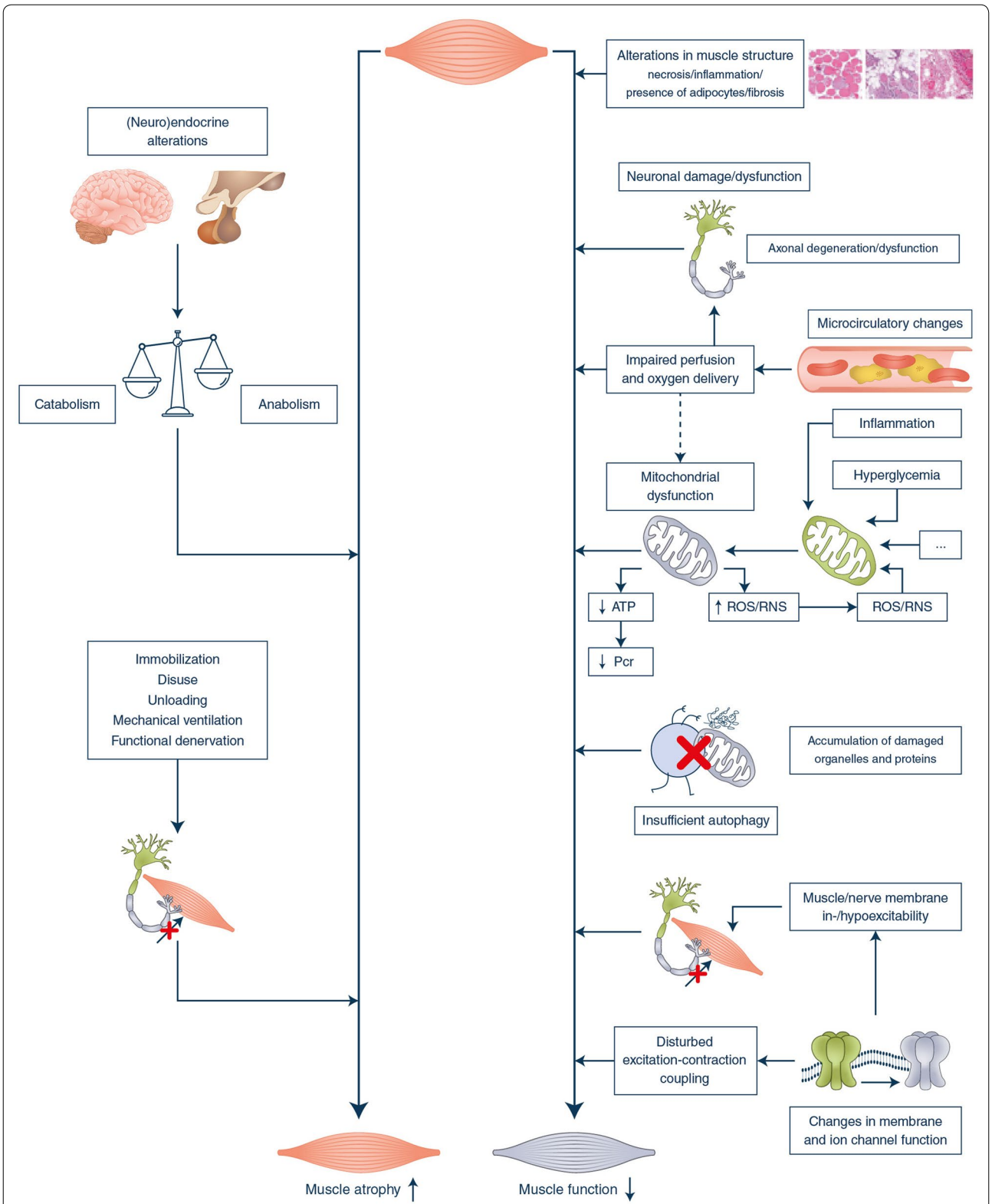


Fig. 1 Mechanisms implicated in the development of ICU-acquired weakness. A conceptual framework is shown of the major pathways that are assumed to be involved in the loss of muscle mass and loss of muscle function that contribute to the development of ICU-acquired weakness [5, 8, 15–17]. *ATP* adenosine triphosphate, *PCr* phosphocreatine, *ROS/RNS* reactive oxygen species/reactive nitrogen species. Mitochondria, proteins, neurons and ion channels indicated in green represent healthy organelles, molecules and cells, whereas grey symbols point to damaged/dysfunctional organelles, protein aggregates, cells and ion channels

Membrane and ion channel dysfunction

Sodium channel inactivation is thought to contribute to the rapid, reversible hypo-excitability or in-excitability of nerve and muscle membranes in patients with ICU-acquired weakness [15]. Altered intracellular calcium homeostasis further contributes to impaired muscle contractility by affecting the excitation–contraction coupling.

Central nervous system involvement

Recent evidence suggests that central nervous system involvement with failure of coordinated repetitive firing within the motor neurons can be a very early event, preceding electrical failure in axons and nerve–muscle coupling [17].

Diagnosis

Several techniques are used to diagnose ICU-acquired weakness. These methods assess peripheral and/or respiratory muscles. Tables 1 and 2 give an overview of currently available techniques, with their advantages and disadvantages.

Assessment of peripheral muscle strength

To diagnose ICU-acquired weakness, ideally, a clinical quantification of muscle strength should be performed. This inherently implies a volitional technique, which has the drawback that the patients must be awake and cooperative and must comprehend the assessor's instructions. As patients are often unconscious or uncooperative, due to sedation or delirium, such clinical diagnosis is often not possible or is delayed. The most widely used volitional technique is the 6-grade Medical Research Council (MRC) sum score [2, 3, 21, 22]. This score yields a global estimation of motor function, pointing to clinically relevant muscle weakness when below 48 and severe muscle weakness when below 36 [11, 41]. However, differentiation in the higher range is difficult. A modified 4-grade score showed better inter-rater agreement for diagnosing ICU-acquired weakness than the classical 6-grade score [23], but requires further validation. The ordinal scale of the MRC sum score limits the sensitivity to detect more subtle changes in muscle function. In contrast, hand-held dynamometry for measuring handgrip and quadriceps strength provides a continuous quantitative measure, but representativeness for global muscle strength has been questioned [3, 21, 23, 24]. The "Scored Physical Function in Intensive Care Test", "Functional Status Score for the ICU" and "Chelsea Critical Care Physical Assessment Tool" provide information about the patients' functional abilities, but are less commonly used [25–27]. Finally, the 6-minute walking distance (6-MWD) assesses functional capacity, but is rather used to evaluate how patients perform at discharge and in post-ICU follow-up [27–29].

Electrophysiological assessments are also used to diagnose ICU-acquired weakness and can be applied to unconscious/uncooperative patients. Although CIP and CIM share many features on nerve conduction studies and electromyography, differentiation is possible in ideal circumstances, particularly when the patient is cooperative and voluntary muscle activation is possible (Table 3) [2, 5, 6, 22, 30, 42]. Single nerve conduction studies have shown promise as alternative for time-consuming full electrophysiological studies [22, 31, 32]. For differential diagnosis of CIP and CIM in uncooperative patients, direct muscle stimulation shows normal muscle excitability in CIP and reduced muscle excitability in CIM. However, expertise is not widely available and differential diagnosis is further complicated by the high co-occurrence of CIP and CIM.

A variety of imaging techniques have been evaluated to assess muscle mass, as a surrogate of muscle strength, some of which also can visualize muscle quality. Of these, ultrasonography is considered most promising [30, 33]. Although ultrasonography allows quick and repeated bedside evaluation of measures of muscle quantity and quality, it may underestimate muscle and protein loss [4, 30, 33, 34]. Furthermore, interpretation of the available studies is complicated by significant methodological defects, small sample sizes, and lack of standardization to control for operator dependency [30, 33]. The clinical relevance also remains to be determined [22, 35]. Computed tomography and magnetic resonance imaging can accurately and reliably detect infiltration of muscle by adipose tissue and quantify fat-free muscle mass, but are expensive, require specialized staff and software, and are logistically challenging [30, 33]. Furthermore, computed tomography exposes patients to a high level of radiation. Several of these limitations also apply to dual-energy X-ray absorptiometry and neutron activation analysis that assess body composition [33]. Bioelectrical impedance measurements also assess body composition, but results are affected by edema, skin temperature and positioning [33].

Finally, nerve and muscle biopsies can provide important information and have increased mechanistic understanding, but are invasive with potential for complications and require specialized expertise for obtaining the samples and interpreting findings [8, 15, 30, 36]. Biopsy analyses may allow differential diagnosis of CIP and CIM, but nerve biopsy is too invasive for routine clinical use and hence is no longer advised except in the context of scientific research (Table 3).

Clearly, many techniques have been developed to assess weakness. However, after exclusion of primary causes of

Table 1 Diagnosis of ICU-acquired weakness: assessment of peripheral muscles

Technique	Measures	Advantages	Disadvantages	References
Volitional functional testing		Functional measurement	Patients need to be awake and cooperative and comprehend how to perform the measurements Does not differentiate CIPNM from deconditioning	
MRC sum score—6 categories 0: no contraction 1: contraction without movement 2: movement, gravity eliminated 3: movement against gravity 4: movement against resistance 5: normal muscle force	Bilateral scoring of: Shoulder abduction Elbow flexion Wrist extension Hip flexion Knee extension Foot dorsiflexion Significant weakness: < 48/60 Severe weakness < 36/60	Gold standard Non-invasive, bedside testing Reliable and valid (at least for score 0–3) High inter-rater reliability (provided strict guidelines on adequacy and standardized test procedures and positions are followed) Overall estimation of motor function	May be affected by positioning of the patient and availability of limbs for assessment (e.g., limitations by pain, dressings, immobilizing devices) Ordinal scale, lower sensitivity to more subtle changes in muscle function, difficulty in differentiation between score 4 and 5 Weak correlation with physical functioning	[2, 3, 21, 22]
MRC sum score—4 categories 0: paralysis 1: > 50% loss of strength 2: < 50% loss of strength 3: normal strength	Same muscles as above weakness: < 24/36 to be validated	Non-invasive, bedside testing Excellent inter-rater reliability Excellent accuracy in diagnosing weakness Requires less discrimination between grades than 6-grade score	Concerns on potential subjectivity Further validation needed	[23]
Hand-held dynamometry	Handgrip strength weakness: < 11 kg for men, < 7 kg for women Quadriceps force	Gold standard, quantitative measure Non-invasive, quick and easy bedside testing High inter-rater reliability High sensitivity and specificity	Significant floor effect Uncertain whether representative of global muscle strength	[3, 21, 23, 24]
Scored Physical Function in Intensive Care Test (PFIT-s) Functional abilities scored 0–3	Shoulder flexion strength Knee extension strength Sit-to-stand assistance Step cadence	Feasible and safe Inexpensive Evaluates patients' functional abilities Validated, predictive of key outcomes	Floor effect at admission Ceiling effect at discharge	[25]
Functional Status Score for the ICU Functional abilities scored 0–7 0: not able to perform 7: complete independence	Rolling Transfer from spine to sit Sitting at the edge of bed Transfer from sit to stand Walking	Feasible and safe Evaluates patients' functional abilities	Has not undergone additional psychometric testing for validation and scale analysis	[26]
Chelsea Critical Care Physical Assessment Tool		Feasible and safe Evaluates patients' functional abilities	Has not undergone additional psychometric testing for validation and scale analysis	[27]
Six-minute walk test	Distance walked in 6 min	Assesses functional capacity	Only in late phase	[28, 29]
Electrophysiology				
Full nerve conduction studies (NCS) and needle electromyography (EMG)	CMAP amplitude and duration SNAP amplitude Nerve conduction velocity Fibrillation potentials Positive sharp waves Motor unit potentials	Can delineate CIPNM from deconditioning	Mildly invasive (EMG) Requires specialized training Partially requires patient cooperation (EMG) Anticoagulation therapy is a relative contra-indication	[22, 30]
Single NCS	Peroneal CMAP amplitude Sural SNAP amplitude	Shorter testing duration than full four-limb NCS/EMG (5–10 min vs 60–90 min) Less painful than full NCS/EMG Non-invasive No need for volitional patient movement Good to excellent sensitivity Good specificity (peroneal nerve)	Abnormal peroneal or sural NCS requires follow-up with full NCS/EMG (and ideally muscle strength testing) to confirm a CIPNM diagnosis	[31, 32]

Table 1 (continued)

Technique	Measures	Advantages	Disadvantages	References
Direct muscle stimulation	Muscle excitability	Can distinguish between CIP and CIM Patient does not need to be awake and cooperative	Requires specialized training Not widely available	
Imaging		Patient does not need to be awake and cooperative		
Ultrasonography	Evaluation quantity and quality Muscle area and thickness Central tendon thickness Muscle angiogenic activity/vascularization Fasciculations[a] Subcutaneous edema and intramuscular fluid Fat infiltration Intramuscular fibrous tissue Muscle necrosis and fasciitis (more advanced stages)	Bedside Easy and relatively quick Non-invasive, painless test Allows repeated measurements, valid and practical for daily routine use Equipment available in most ICUs Relatively inexpensive Free of ionizing radiation Close correlation with MRI and CT data Abnormal muscle echogenicity is a good screening test and predictor of prognosis	Does not measure muscle mass, muscle thickness underestimates muscle loss as compared with cross-sectional area Operator-dependent, precautions needed to obtain reproducible results Exactly same place for every evaluation Minimal amount of pressure Sufficient coverage of probe with gel Transducer perpendicular to imaged muscle Measure and control for SC tissue thickness Affected by obesity and edema Low accuracy to diagnose muscle weakness Does not discriminate between patients with or without weakness upon awakening	[3, 4, 22, 30, 33–35]
Computed tomography (CT)	Infiltration of muscle by adipose tissue Fat-free skeletal muscle	Highly accurate, highly reliable Valid in patients with severe fluid retention Allows evaluation of the deepest muscles	High cost, time-consuming Highly specialized staff and software needed Transport of patient outside ICU needed High level of radiation exposure (may be limited if only a single muscle group is assessed) Inappropriate for repeated monitoring	[30, 33]
Magnetic resonance imaging (MRI)	Infiltration of muscle by adipose tissue Fat-free skeletal muscle	Highly accurate, highly reliable Valid in patients with severe fluid retention	High cost, time-consuming Highly specialized staff and software needed Transport of patient outside ICU needed Inappropriate for repeated monitoring	[33]
Dual-energy X-ray absorptiometry	Body composition	Rapid Easily tolerated Allows whole-body scans	Radiation exposure (minimal) Expensive Transport of patient outside ICU needed Specialized personnel needed Inaccurate with abnormal hydration status Inappropriate for routine, repeated monitoring	[33]
Neutron activation analysis	Body composition	Very accurate Valid in patients with severe fluid retention Most often preferred reference for evaluating/calibrating alternative techniques	Time-consuming Radiation exposure Equipment available in only a few centers	[33]

Table 1 (continued)

Technique	Measures	Advantages	Disadvantages	References
Bioelectrical impedance measurements	Body composition	Non-invasive, highly acceptable to patients Rapid and inexpensive Portable, easily performed at the bedside No radiation exposure Possibility of repeated monitoring	Distorted by hydration status/edema Affected by skin temperature Affected by body position Special device needed	[33]
Biopsy analyses				
Nerve and muscle biopsies	Degeneration and myelination status of nerve fibers Muscle fiber atrophy, necrosis, inflammation, fatty infiltration, fibrosis, vacuolation	Have increased mechanistic understanding	Invasive (nerve biopsy too invasive for routine clinical use) with risk of complications (bleeding, wound infection, pain) Specialized expertise needed for obtaining and interpreting samples Prognostic value poorly explored	[8, 15, 30, 36]

CMAP compound muscle action potential, *CT* computed tomography, *CIPNP* critical illness polyneuromyopathy, *EMG* electromyography, *ICU* intensive care unit, *MRC* Medical Research Council, *MRI* magnetic resonance imaging, *NCS* nerve conduction studies, *SC* subcutaneous, *SNAP* sensory nerve action potential

[a] Sign of spontaneous activity in the muscle and increased excitability of impaired motor nerves

Table 2 Diagnosis of ICU-acquired weakness: assessment of respiratory muscles

Technique	Measures	Advantages	Disadvantages	References
Volitional functional testing				
		Functional measurements	Patients need to be awake and cooperative and comprehend how to perform the measurements	
Maximal inspiratory and expiratory pressure	Inspiratory muscle strength Expiratory muscle strength	Measures global respiratory muscle strength High values exclude respiratory weakness Predictive of duration mechanical ventilation and mortality	Low values may also represent poor technique	[24, 37, 38]
Transdiaphragmatic pressure	Diaphragm strength weakness: Pdi_{max} < 60 cm H_2O	Specific measure of diaphragm strength High values exclude respiratory weakness	Invasive, requires esophageal + gastric balloons Difficult to obtain Low values may also represent poor technique	[38–40]
Non-volitional functional testing				
Transdiaphragmatic pressure in response to bilateral twitch phrenic nerve stimulation	Diaphragm strength weakness: Pdi,tw < 10 cm H_2O Phrenic nerve conduction time	Most objective Predictive of duration mechanical ventilation and mortality (better than maximum inspiratory pressure)	Invasive Requires magnetic stimulation Technically difficult to perform	[37–40]
Endotracheal tube pressure in response to bilateral phrenic nerve stimulation during airway occlusion	Weakness: Pet,tw < 11 cm H_2O		Invasive Requires magnetic stimulation Technically difficult to perform	[4, 39]
Imaging				
Chest X-rays	Diaphragm position	Readily available, bedside test	Low sensitivity and specificity	[38, 40]
Ultrasonography	Diaphragmatic excursion weakness: < 11 mm Diaphragmatic thickening fraction weakness: < 20%	Easy, bedside, non-invasive test Equipment available in most ICUs Relatively inexpensive Relatively good diagnostic performance to predict weaning outcome	Limited value during assisted breathing	[4, 38–40]

Pdi_{max} maximal transdiaphragmatic pressure, *Pdi,tw* transdiaphragmatic pressure upon twitch phrenic nerve stimulation, *Pet,tw* endotracheal tube pressure upon phrenic nerve stimulation, *SNAP* sensory nerve action potential

Table 3 Features of critical illness polyneuropathy and critical illness myopathy in electrophysiological and biopsy studies

	Critical illness polyneuropathy	Critical illness myopathy
CMAP amplitude	Decreased	Decreased
CMAP duration	Normal	Increased
SNAP amplitude	Decreased	Normal
Nerve conduction velocity	Normal or near normal	Normal or near normal
EMG at rest	Fibrillation potentials/positive sharp waves	Fibrillation potentials/positive sharp waves
MUP voluntary muscle activation	Long duration, high amplitude, polyphasic[a]	Short duration, low amplitude[a]
Repetitive nerve stimulation	Absence of decremental response	Absence of decremental response
Direct muscle stimulation	Normal muscle excitability	Reduced muscle excitability
Nerve biopsy[b]	Primary distal axonal degeneration of sensory nerve fibers, no demyelination	Normal
Muscle biopsy	Denervation atrophy of type 1 and 2 muscle fibers	Spectrum of abnormalities: myofiber atrophy, angulated fibers, necrosis, fatty degeneration, focal or diffuse loss of thick filaments

Information obtained from [2, 5, 6, 15, 22, 30, 36]. Aggregate diagnostic criteria for CIP and CIM are reported in [5]

CMAP compound muscle action potential, *EMG* electromyography, *MUP* motor unit potential, *SNAP* sensory nerve action potential

[a] MUPs of long duration, high amplitude and polyphasic appearance can be detected in CIP as a sign of collateral reinnervation of denervated muscle fibers, whereas MUPs of short duration and low amplitude are observed in CIM as a sign of reduced functional muscle fibers within each motor unit

[b] Sensory (sural) nerve and motor nerve (to gracilis muscle) biopsy are no longer advised except as a research procedure

neuromuscular diseases [1], diagnosis of ICU-acquired weakness from a practical point of view is currently limited to the use of clinical testing and electrophysiological studies.

Assessment of respiratory muscle strength

Volitional testing of global respiratory muscle strength via maximal inspiratory and expiratory pressure or of diaphragm strength via transdiaphragmatic pressure is again limited by the requirement of an awake and cooperative patient [24, 37–40]. Measurement of transdiaphragmatic or endotracheal tube pressure in response to phrenic nerve stimulation can circumvent this problem, but it is invasive, requires magnetic stimulation and is technically difficult [4, 37–40]. Also imaging techniques are being used. However, chest X-rays have low sensitivity and specificity and ultrasonography has limited value during assisted breathing [4, 38–40].

Risk factors

Several independent risk factors for developing ICU-acquired weakness have been identified, mostly from observational studies, although often not unequivocally (Fig. 2).

A first group of risk factors are not modifiable The severity of critical illness is an important determinant. Thus, a higher severity of illness score, sepsis and inflammation, multiple organ failure, as well as a longer duration of mechanical ventilation and ICU stay, were found to be predictive [11, 43–45]. In fact, ICU-acquired weakness is most frequent in patients with persistent critical illness [46]. The relationship with mechanical ventilation could be reciprocal given that prolonged ventilation increases the risk of ICU-acquired weakness and diaphragmatic dysfunction which, vice versa, increase the risk of prolonged ventilation and failed weaning [13]. Another illness-related risk factor is a high lactate level [45]. Further, a higher risk of weakness may apply to women than to men, and to older as compared with younger patients [11, 43, 45]. Also, premorbid disability and frailty may predispose to the severity of weakness. Intriguingly, premorbid obesity was found to be an independent protective factor against development of ICU-acquired weakness and against muscle atrophy [47].

Some risk factors are modifiable These include the degree of hyperglycemia that develops in response to the severe stress of critical illness and the administration of parenteral nutrition (vide infra) [20, 45, 48–51], but also several drugs that are used to treat critically ill patients. For example, dose and duration of vasoactive medications, mostly β-agonists, are associated with a higher risk of ICU-acquired weakness [44]. In meta-analyses, the use of corticosteroids has been associated with risk of ICU-acquired weakness in heterogeneous patient populations [52] and when focusing exclusively on patients with sepsis [53]. However, one study suggested a protective effect of corticosteroids when hyperglycemia as a side effect was avoided [49]. The reported adverse relationship between the use of neuromuscular blocking agents (NMBAs) and muscle weakness remains

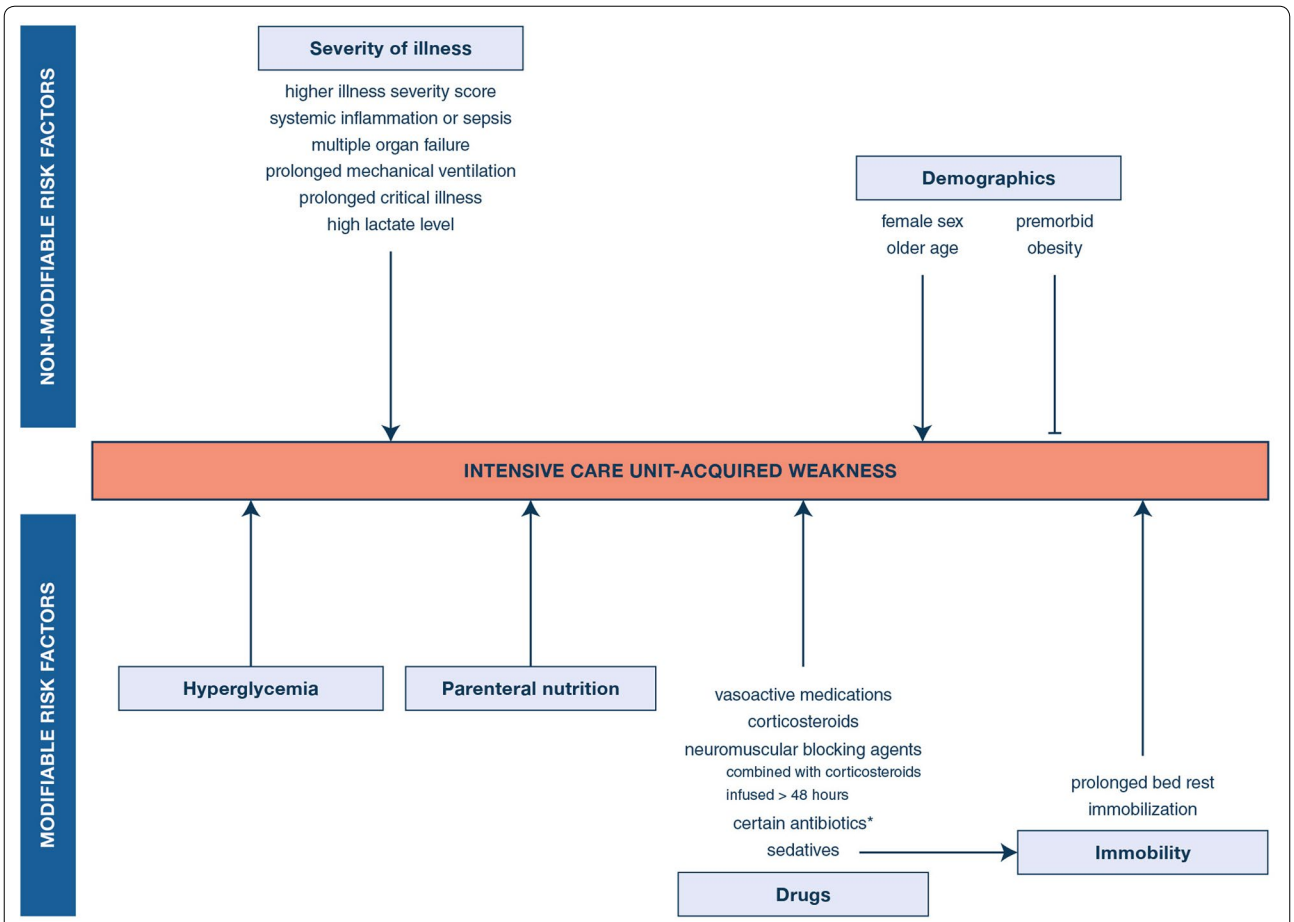


Fig. 2 Overview of risk factors of ICU-acquired weakness. Observational and randomized controlled trials have identified a wide range of non-modifiable and modifiable risk factors associated with the risk of developing weakness in the ICU [11, 43–58]. *certain antibiotics, such as aminoglycosides and vancomycin, have been independently associated with ICU-acquired weakness, although not unequivocally [45, 57, 59]. Other antibiotics, such as clindamycin, erythromycin, quinolones, polymyxin, tetracycline and vancomycin may affect the neuromuscular junction, but have so far not been independently associated with ICU-acquired weakness [45, 60, 61]

uncertain [45, 54, 55]. An RCT comparing 48-h infusion of cisatracurium with placebo, both under deep sedation, in ARDS patients did not observe a significant impact [56]. However, a 48-h infusion of cisatracurium with concomitant deep sedation tended to increase the risk of ICU-acquired weakness as compared with absence of routine neuromuscular blockade and lighter sedation targets, with significance reached for weakness present on day 28, but not for weakness present on day 7 or at any time through day 28 [57]. Also, when co-administered with corticosteroids or infused for > 48 h, NMBAs may promote weakness [54]. Certain antibiotics, including aminoglycosides and vancomycin, have also been independently associated with ICU-acquired weakness [45, 58]. The association between sedatives and weakness may be indirect, as separating effects of sedatives from those of sedation-induced immobility and bed rest is difficult [62]. Continued sedation is thought to have a more pronounced effect on muscle atrophy and weakness than when a patient is conscious but immobile in the absence of sedation [9].

Acute and long-term consequences

Developing ICU-acquired weakness elicits a range of acute and long-term adverse outcomes (Fig. 3).

Short-term consequences

The development and severity of ICU-acquired weakness, as assessed clinically at awakening, have been independently associated with higher risk of in-ICU and in-hospital death [63, 64]. This association has mostly been documented for limb muscle weakness [14]. It has also been observed for diaphragm dysfunction, but not unequivocally [14, 65]. Limb and respiratory muscle weakness have further been identified as independent predictors of prolonged need of mechanical ventilation

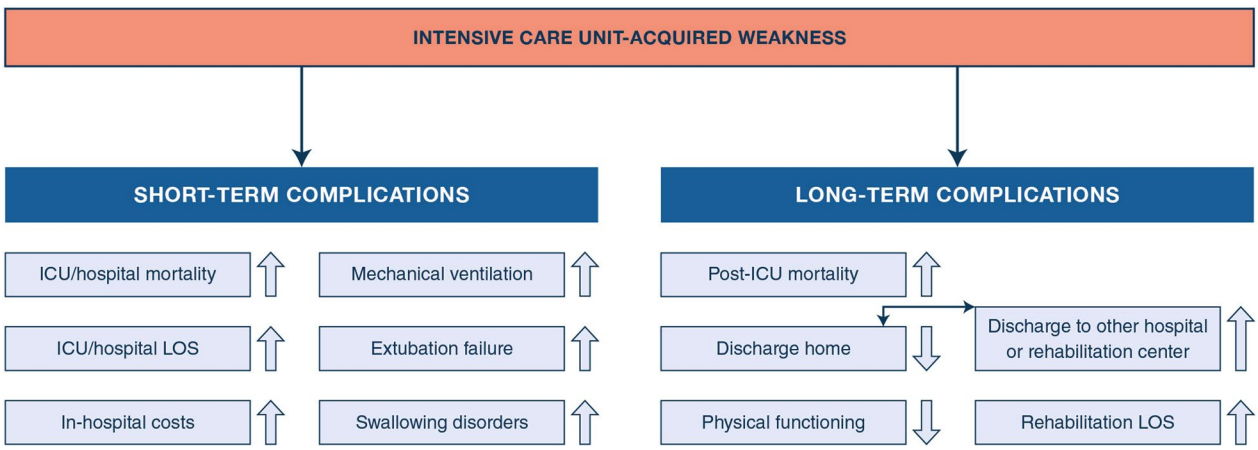


Fig. 3 Overview of short-term and long-term consequences of ICU-acquired weakness. The development of weakness in the ICU has been associated with a wide range of adverse consequences in the short term as well as the long term [14, 42, 63–76]. *LOS* length of stay

[66, 67]. Limb muscle weakness at extubation was independently associated with higher extubation failure rates in medical patients [68]. Among predominantly surgical patients with limb muscle weakness, 80% also showed diaphragmatic dysfunction [69]. Extubation failed in 50% of them, with need for reintubation within 72 h, among whom 50% died in ICU. Muscle weakness has also been associated with a longer duration of ICU and hospital stay and with increased in-hospital costs [14, 70, 71]. Neuromuscular weakness has further been suggested as a key mechanism contributing to ICU-acquired swallowing disorders, including post-extubation dysphagia [72]. Weakness of the abdominal muscles can impair effective cough [3].

Associations do not necessarily reflect causality. However, a propensity score-matched analysis of patients with and without ICU-acquired weakness suggested that weakness may not merely be a marker but could also be a mediator of poor outcome [70]. Weak patients had a lower likelihood for earlier live weaning from mechanical ventilation, earlier live ICU discharge and earlier live hospital discharge than patients without weakness (Fig. 4a). In addition, in the group of weak patients, 6-MWD at hospital discharge was shorter, in-hospital costs were higher and more patients were discharged to rehabilitation centers or other hospitals (Fig. 4b).

Clearly, ICU-acquired weakness has been associated with worse short-term outcome. However, weakness status or any minimal cutoff of the MRC score is not a sole determinant of whether a patient can be discharged from the ICU, as this decision is based on the patient no longer being dependent on vital organ support.

Long-term consequences

Survivors of critical illness face an increased risk of late death [70, 78], which is even higher when patients had experienced ICU-acquired weakness [70]. Indeed, in a propensity score-matched analysis, one-year mortality was higher in weak (MRC sum score < 48) than in not-weak patients (Fig. 4c) [70]. Strikingly, the likelihood of late death was further increased when weakness persisted until ICU discharge, and even more so for patients with a more severe degree of persistent weakness (MRC sum score < 36, Fig. 4c). An independent association with higher one-year mortality was also found for a reduced compound muscle action potential (CMAP) on ICU day 8, irrespective of clinical weakness diagnosed by the MRC sum score [42], and for respiratory muscle weakness evidenced by a low maximal inspiratory pressure [73]. Even a mild reduction in muscle strength not yet meeting the threshold of clinically relevant weakness (lower raw MRC sum score, but MRC sum score ≤ 55 being most predictive) and nerve/muscle dysfunction (abnormal CMAP) at ICU discharge have recently been independently associated with a worse five-year survival [77]. Being weak (MRC sum score < 48) at hospital discharge has also been associated with a worse five-year survival [74].

Following ICU discharge, ARDS patients showed a slow improvement in the severe wasting they suffered from in ICU and in 6-MWD [79–81]. However, even 5 years after ICU discharge, patients still experienced varying degrees of weakness and reduced walk and exercise ability [81]. New functional disabilities in activities of daily living also can persist for at least 8 years after sepsis [82]. A large heterogeneous cohort of critically ill patients showed lower handgrip force, shorter 6-MWD and reduced physical quality of life 5 years after ICU admission [78].

(See figure on next page.)

Fig. 4 Impact of ICU-acquired weakness on short-term outcome and one-year and five-year survival. **a** Kaplan–Meier plots show the cumulative proportion of well-matched long-stay patients (ICU stay > 7 days) with (MRC < 48 at first evaluation) and without ICU-acquired weakness (MRC ≥ 48 at first evaluation) over time who were alive and weaned from the ventilator, discharged alive from the ICU, and discharged alive from the hospital. Patients who died were censored after the last patient had been weaned alive, discharged alive from the ICU or discharged alive from the hospital, respectively. Plots were redrawn in JMP®Pro14.0.0 (SAS Institute, Cary, NC) from the data described in [70]. Hazard ratios and 95% confidence intervals below 1, for the effect of weakness versus no weakness, illustrate a lower chance of earlier live weaning, of earlier live ICU discharge and of earlier live hospital discharge for patients with as compared with patients without ICU-acquired weakness. **b** Medians, interquartile ranges and 10th and 90th percentiles of 6-min walking distance at hospital discharge and total billed costs, as well as the distribution of the discharge destination, are shown for well-matched long-stay patients (ICU stay > 7 days) with (MRC < 48 at first evaluation) and without ICU-acquired weakness (MRC ≥ 48 at first evaluation), illustrating worse acute morbidity and higher healthcare-related costs for weak patients, as reported in [70]. **c** One-year survival for matched long-stay patients (ICU stay > 7 days) with (MRC < 48 at first evaluation) and without ICU-acquired weakness (MRC ≥ 48 at first evaluation) are shown (left panel), together with Cox regression estimates for one-year survival for all long-stay patients with ICU-acquired weakness according to whether weakness persisted until final examination in the ICU or not (middle and right panel). The survival curves visually display the model predicted survival time for the "average" patient according to the Medical Research Council (MRC) sum score at final examination in the ICU as described in [70]. The middle panel compares patients who recovered from weakness (MRC ≥ 48 at last evaluation) with all patients who did not (MRC < 48 at last evaluation), whereas the right panel further distinguishes persistently weak patients into patients who remained moderately weak (MRC 36–47) or severely weak (MRC < 36). One-year survival was lower for weak patients as compared with not-weak patients. Survival was further lowered when weakness persisted and was more severe as compared with recovery of weakness at ICU discharge. **d** Five-year survival is shown for patients according to MRC sum score at final examination in the ICU > 55 versus ≤ 55 (left panel), according to normal or abnormal CMAP on day 8 ± 1 (middle panel), or according to the combined information of the MRC sum score at final examination in the ICU > 55 or ≤ 55 and normal or abnormal CMAP on day 8 ± 1 (right panel) (adapted from [77]). Five-year survival was lower for patients with an MRC sum score at final examination in the ICU ≤ 55 versus > 55 and for patients with an abnormal versus normal CMAP on day 8 ± 1. *CMAP* compound muscle action potential, *HR* hazard ratio, *MRC* Medical Research Council sum score

A small study observed reduced maximal voluntary contraction, rate of force development and endurance time 1 year after ICU discharge, but no signs of neural impairment [83]. Importantly, the acquisition of weakness in the ICU appeared to be a major independent determinant of long-term weakness, other morbidities and poor quality of life after ICU discharge [75, 76]. Weakness at ICU discharge, even if mild and not yet considered as clinically relevant, has recently been independently associated with lower handgrip force, lower respiratory muscle strength, lower 6-MWD and lower physical quality of life with lower physical independence 5 years later (MRC sum score ≤ 55 being most predictive), unlike an abnormal CMAP [77]. Interestingly, evaluation of patients 1 year after ICU discharge suggested that a myogenic origin of ICU-acquired weakness had a better prognosis with virtually full recovery as compared with a neuromyogenic origin that left 50–75% of the patients with persisting muscle weakness or even tetraparesis [84, 85]. This illustrates the importance of a differential diagnosis between CIP and CIM to predict long-term outcome of critically ill patients.

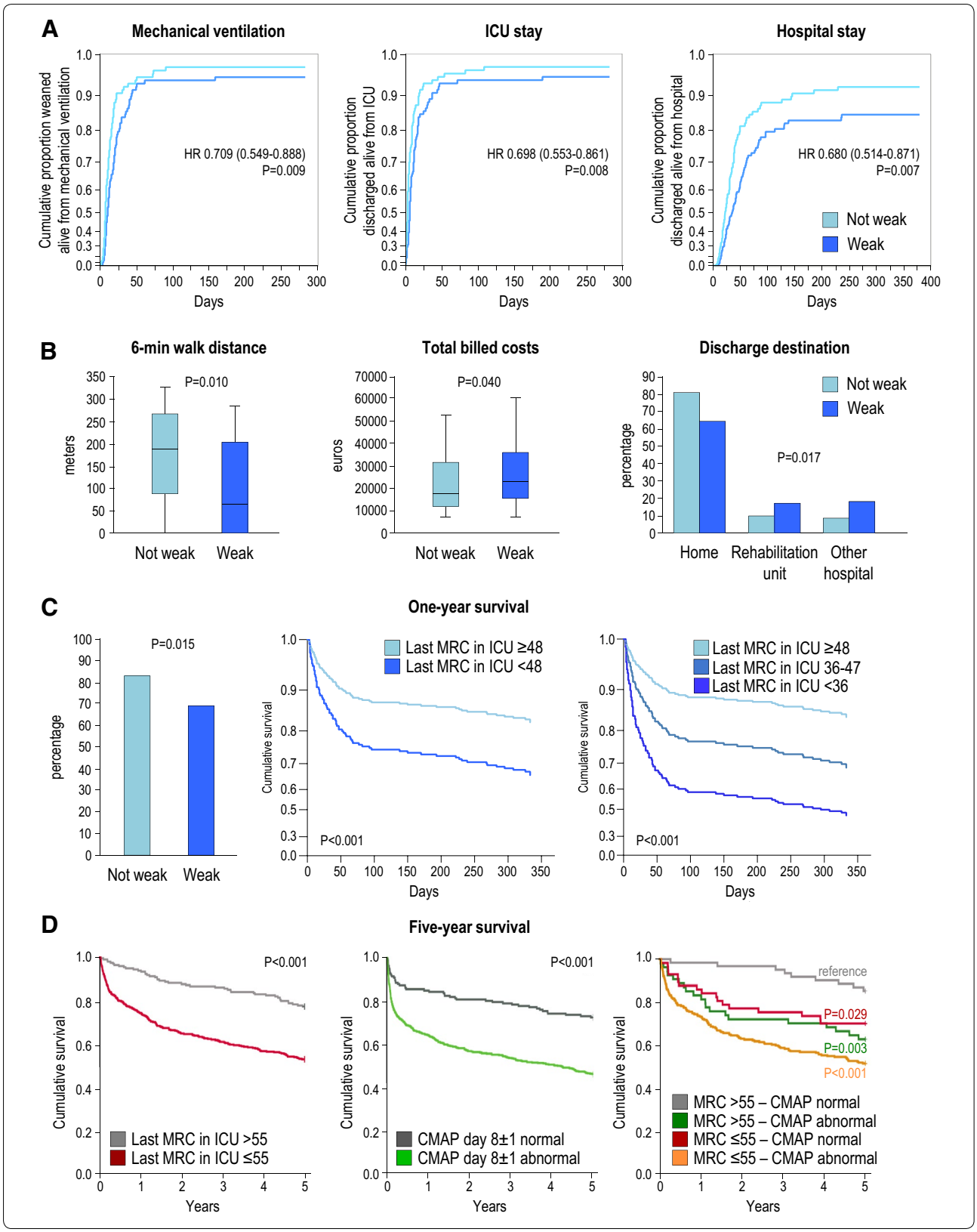
Whether the pathophysiology of the post-ICU weakness is different from that of in-ICU weakness is not clear, given that only few studies explored mechanisms underlying long-term weakness. A study of 11 prolonged critically ill patients assessed 6 months after ICU discharge showed persistent weakness in all tested patients owing to impaired voluntary contractile capacity, whereas quadriceps atrophy had resolved in 27% [86]. Muscle proteolysis, autophagy, inflammation and mitochondrial content had normalized, but patients with sustained atrophy showed less satellite cells, which may impair regenerative capacity. Co-expressed genes associated with the degree of muscle weakness and atrophy showed enrichment in genes involved in skeletal muscle regeneration and extracellular matrix deposition [87]. Interestingly, in mice, engraftment of mesenchymal stem cells improved muscle regeneration and strength after sepsis [88].

Preventive and therapeutic measures

Several interventions have been tested with the aim to prevent or treat ICU-acquired weakness, though with very limited success [15]. Unfortunately, there is currently still no effective treatment though prevention has been shown to work by targeting specific risk factors.

Avoiding hyperglycemia

Tight glycemic control, targeting normal fasting levels with insulin infusion, as compared with tolerating pronounced hyperglycemia, reduced morbidity and mortality of surgical, medical and pediatric ICU patients in the context of early use of parenteral nutrition [89–91]. However, the optimal glucose target remains controversial, as the largest multicenter RCT showed that intermediate blood glucose levels may be safer [92]. Nevertheless, strictly targeting fasting normoglycemia in surgical and medical ICU patients reduced the risk of developing electrophysiological signs of critical illness polyneuromyopathy [48, 49]. Achieving normoglycemia, rather than the administration of insulin, explained this lower risk. The polyneuromyopathy prevention in turn


A
Mechanical ventilation
Cumulative proportion weaned alive from mechanical ventilation
HR 0.709 (0.549-0.888)
P=0.009
Days
ICU stay
Cumulative proportion discharged alive from ICU
HR 0.698 (0.553-0.861)
P=0.008
Days
Hospital stay
Cumulative proportion discharged alive from hospital
HR 0.680 (0.514-0.871)
P=0.007
Not weak
Weak
Days
B
6-min walk distance
meters
P=0.010
Not weak
Weak
Total billed costs
euros
P=0.040
Not weak
Weak
Discharge destination
percentage
Not weak
Weak
P=0.017
Home
Rehabilitation unit
Other hospital
C
One-year survival
percentage
P=0.015
Not weak
Weak
Cumulative survival
Last MRC in ICU ≥48
Last MRC in ICU <48
P<0.001
Days
Last MRC in ICU ≥48
Last MRC in ICU 36-47
Last MRC in ICU <36
P<0.001
Days
D
Five-year survival
Cumulative survival
P<0.001
Last MRC in ICU >55
Last MRC in ICU ≤55
Years
P<0.001
CMAP day 8±1 normal
CMAP day 8±1 abnormal
Years
reference
P=0.029
P=0.003
P<0.001
MRC >55 – CMAP normal
MRC >55 – CMAP abnormal
MRC ≤55 – CMAP normal
MRC ≤55 – CMAP abnormal
Years

partially explained less need of prolonged mechanical ventilation, which suggested an impact of this intervention on clinically relevant ICU-acquired respiratory muscle weakness.

Avoiding early parenteral nutrition

The severe caloric deficit that arises from critical illness-associated anorexia and gastrointestinal dysfunction has been associated with muscle atrophy and weakness [93]. Muscle atrophy has long been regarded a major myogenic component of muscle weakness. Based on observational studies and expert opinion, to prevent muscle atrophy nutritional guidelines hence advocated early full nutrition, preferentially via the enteral route but otherwise supplemented via the parenteral route [94]. Major emphasis was put on giving enough protein as substrate for building muscle mass. However, large RCTs showed lack of benefit or even harm by early full nutrition and hence no longer support such aggressive feeding strategies. Indeed, supplementing insufficient enteral nutrition with early parenteral nutrition to caloric targets increased complications and delayed recovery of critically ill adults and children as compared with accepting the macronutrient deficit by withholding parenteral nutrition in the 1st week in ICU [28, 95]. Harm evoked by early parenteral nutrition comprised more ICU-acquired weakness and impaired recovery thereof, longer dependency on mechanical ventilation and a longer stay in the ICU [20, 28, 95]. Early parenteral nutrition to caloric targets also did not reduce muscle atrophy [20]. Macronutrient doses, and not the route of administration, explained the harm. More specifically, the early administration of amino acids, but not glucose or lipids, appeared to be the culprit [96, 97]. Rather than being used for synthesis of muscle proteins, the amino acids appeared to be largely broken down and shuttled to ureagenesis, possibly explaining the lack of benefit in RCTs investigating increased amino acid supplementation [97–100]. Amino acids also suppress autophagy in muscle, which has shown to be a mechanism contributing to ICU-acquired weakness [20]. Importantly, in these studies, micronutrients were infused in recommended doses in both groups to avoid deficiencies [28, 95] that have also been linked to muscle weakness, among other complications of critical illness [101]. In another RCT, also early full enteral feeding was unable to improve impaired physical function 1 year after ICU admission as compared with early hypocaloric feeding [102]. Further research is needed to establish the ideal timing of initiation beyond the 1st week, optimal dose and composition of artificial nutrition for critically ill patients [93].

Although clinical data are currently still lacking, a series of studies in mice, performed in search of mechanisms underlying protection against ICU-acquired weakness by obesity, revealed that increasing the availability of ketone bodies, either through stimulation of endogenous ketogenesis or through infusion of exogenous ketones, protected against sepsis-induced muscle weakness [103]. This interesting finding still needs to be further explored in patients.

Minimizing sedation and early mobilization

As immobility increases the risk of ICU-acquired weakness, (early) mobilization and physical rehabilitation were tested to reduce this risk. Such interventions evidently require a policy to minimize sedation [3, 9]. Interestingly, daily interruption of sedative infusions was shown to reduce the duration of mechanical ventilation and of ICU dependency [104]. Several modes of (early) mobilization and rehabilitation have been evaluated, but showed inconsistent results. Although several systematic reviews and meta-analyses concluded in favor of this intervention, a low quality of evidence was pointed out [105–109]. Tipping et al. concluded that active mobilization and rehabilitation improved muscle strength at ICU discharge, enhanced the probability of walking without assistance at hospital discharge and resulted in more days alive and out of hospital to day 180 [105]. High dose rehabilitation in the ICU was further suggested to improve some aspects of quality of life at 6 months. A more recent analysis concluded that early rehabilitation improved only short-term physical-related outcomes with low quality of evidence for a decreased risk of ICU-acquired weakness as compared with standard care or no early rehabilitation [106]. Other systematic reviews that compared early mobilization and/or active exercise with delayed exercise emphasized the low quality of evidence in favor of early intervention, given the small sample sizes of these studies, heterogeneity of studied interventions and outcomes, high risk of performance bias, high dropout rates, and inadequate descriptions of usual care [107, 108]. Methodological limitations also explained the low confidence in the observed associations of the improved inspiratory and expiratory muscle strength after inspiratory muscle training with shorter ventilator dependency [109]. However, several additional studies are ongoing which hopefully will shed light on the efficacy of early mobilization and rehabilitation.

Barriers to implementation in clinical practice comprise the patient's capability to perform physical activity, safety concerns for patients, staff and caregivers, lack of expertise and lack of adequate staffing, equipment and funding to provide rehabilitation programs [110]. However, the incidence of potential safety events is low (2.6%) and consequences for patient management are even

more rare (0.6%), provided that consensus guidelines are adequately considered [4, 111].

Neuromuscular electrical stimulation

Because poor alertness and cooperation precludes early active mobilization of a large proportion of patients, neuromuscular electrical stimulation (NMES) has been suggested as an alternative. Several mostly small RCTs have been performed in critically ill patients, with variable use of frequencies, intensities and duration of NMES and widely varying outcomes, limiting pooling and interpretation of data [112, 113]. Although some studies were promising [112], the most recent systematic review and meta-analysis did not reveal significant improvement in muscle strength or dependency on mechanical ventilation and intensive care with NMES as compared with usual care [113].

Drugs

A systematic review of initially promising pharmacological interventions such as the anabolic steroid oxandrolone, growth hormone, propranolol, immunoglobulin and glutamine therapy could not recommend any of these for adoption in routine practice [114].

Rehabilitation beyond ICU stay

Early interventions to prevent or attenuate the debilitating consequences of ICU-acquired weakness are obviously important. It remains unclear, however, whether later exercise-based rehabilitation on regular wards and after hospital discharge are beneficial, as studies have been small. Some studies showed a positive effect related to functional exercise capacity, unlike others, but a systematic review could not support benefits from post-ICU physical rehabilitation given the low quality of available evidence and heterogeneity [115]. Adequately powered RCTs are needed.

Conclusions and clinical implications

Muscle weakness is a frequent complication of critical illness, with devastating short- and long-term consequences and therefore requires prevention and/or treatment. Prevention seems at least in part possible, as avoiding hyperglycemia and postponing parenteral nutrition to beyond the 1st week in ICU, have been shown to reduce the burden of ICU-acquired weakness. Also early mobilization, which requires minimizing sedation, may be promising but several ongoing studies are awaited for to further clarify its impact on clinically relevant outcome measures. Further research is required to design new preventive and/or therapeutic strategies that can be tested in adequately powered RCTs. Based on animal studies [103], a first interesting candidate to explore could be the infusion of ketone bodies or strategies to activate ketogenesis.

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Compliance with ethical standards

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The authors declare that they have no conflict of interest.

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