# ICU-acquired weakness

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## Definition

Critical illness can severely affect physical function. A condition termed ICU-acquired weakness (ICUAW) is frequently found in critically ill patients, and is characterized by a generalized, symmetric weakness, affecting limb (proximal more than distal) and respiratory muscles[1,2]. Facial and ocular muscles are most often not affected. No demyelination is seen, as is the case in Guillain–Barré syndrome [3]. The condition was first acknowledged in the 1980's and has through the years had a large variety of names, for example: Polyneuropathy in critically ill patients, Acute necrotizing myopathy of intensive care, Critical illness myopathy and/or neuropathy or Critical illness neuromuscular syndrome [4]. Since myopathy and neuropathy often coexist, and since it can be quite a challenge to diagnose and differentiate the two in clinical practice (because it demands electromyography and nerve conduction studies, which are not commonly available in most ICUs), the term ICU-acquired weakness, ICUAW, which focuses on the clinical picture, was agreed on within the critical care community[4]. At present, there is a lack of consensus on the exact diagnostic criteria for ICUAW.

## Extent and consequences

The magnitude of ICUAW is difficult to establish due to the current lack of diagnostic criteria, albeit there is no doubt that it is substantial. In 2002, De Jonghe et al conducted the first prospective study on a mixed ICU-population and found that 25% of patients suffered from ICUAW. In a systematic review, Stevens et al found a median prevalence of 57% (IQR 9%-87%) [5]. Reviews report a prevalence of 25%-100%, varying with the tools and cut-off values used [3,6,7].

Studies show that the consequences of ICUAW can be very severe, as ICUAW is associated with both increased morbidity and increased mortality, also following ICU and hospital discharge [8–10]. Since the majority of critically ill patients are elderly, new or worsened physical impairments can lead to a loss of independence in everyday living, or even necessitate permanent movement to a nursing home facility [11]. The physical impairments have been demonstrated to gradually improve with time, however the most comprehensive prospective follow-up study on the area shows that a substantial number of patients still suffer from ICUAW two years after ICU discharge (36% at hospital discharge and 9% two years later) [12].

Herridge et al studied a young population of ARDS-survivors (median 45 years) and found marked impairments in physical function a year after discharge, illustrated for example by a median score for the physical role domain of the SF-36 at 25, compared to a score in the normal population of 84 [13]. Loss of physical function correlates negatively to quality of life [12–14]. In the aforementioned comprehensive follow-up study, patients suffering from ICUAW only achieved 72% of the estimated premorbid baseline level, two years after discharge [12]. Within the ICU, affection of the diaphragm is found both with and without accompanying muscle weakness, and both muscle weakness and diaphragmatic dysfunction is a predictor for failed extubation and increased mortality [2,15].

## Etiology

Determining the etiology of ICUAW has proven difficult, and currently no specific factor causing ICUAW has been identified, other than critical illness itself (understood as sepsis, multiorgan failure, systemic inflammation)[4,7] and its handling and treatment (see "risk factors"). The catabolic state of critical illness (resulting in reduced protein synthesis along with increased protein breakdown) combined with prolonged bedrest and thereby mechanical unloading of the muscles contribute to muscle wasting [2]. Muscle biopsies have shown necrosis, inflammation and infiltration of muscles with adipose tissue and fibrosis [16]. Microcirculatory disturbances can cause edema, reduced oxygen delivery, leucocyte extravasation, and hypoperfusion, which might lead to mitochondrial dysfunction and neuronal injury [2]. Recently, compromised autophagy (a process meant to clear damaged cellular components) during critical illness has also been identified as a contributing factor [2].

## Risk factors

No effective treatment of ICUAW has yet been established[2], so emphasis is on minimizing exposure to risk factors. The risk factors for ICUAW can be divided into non-modifiable and modifiable. The non-modifiable risk factors can be used as a checklist for points of awareness whereas the modifiable risk factors can be seen as focus points for optimization in patients at risk [2,17,18].

### Non-modifiable risks factors

Patients with a higher illness severity score have consistently shown a higher risk of ICUAW [19–24]. Patients with systemic inflammation or sepsis and patients with multiorgan failure seems to be of particular risk, especially with neurological failure [21,25–27]. High lactate is an independent risk factor [28]. Both prolonged mechanical ventilation and prolonged critical illness has been linked with a higher risk of ICUAW [25,29]. As these risk factors are highly correlated, there is a risk of confounding between the variables.

Female sex and older age indicate a higher risk [25,29]. Disability and overall frailty may be linked with higher severity of illness, whereas obesity is a protective factor [30].

### Modifiable risk factors

Hyperglycemia, both caused by the stress of critical illness and by parenteral nutrition indicates a higher risk of development of ICUAW [17,21–23,31]. Several drugs are associated with higher risk. These are some of the most used drugs in intensive care such as vasoactive drugs (beta-agonists in particular) [23,26,32], some antibiotics [17,22,24,33] and sedatives[34]. Corticosteroids are controversial and their association with ICUAW might be mediated through hyperglycemia [25,35,36]. Neuromuscular blocking agents have been suggested as a risk factor, but the evidence is not unanimous [17,21,23,26,31,37–40]. Sedatives, and deep sedation in particular, is

associated with increased risk, but as use of sedatives is closely related to disease severity, mechanical ventilation and immobility, the direct effect are hard to assess [41]. Immobilization is recognized as a very important risk factor for ICUAW [2]. Several studies have shown that mobilization in the ICU is feasible and safe, even when initiated at an early stage, where the patients might require for example mechanical ventilation, vasopressor infusions or renal replacement [7,42–44]. Studies have suggested that less sedation and more physical activity leads to less ICUAW and better function at discharge [7,42,45].

## Diagnosis

The diagnosis of ICUAW is a diagnosis of exclusions. It will often rely on the typical clinical appearance (generalized, symmetrical muscle weakness involving limb – primarily proximal – and respiratory muscles) and can usually be excluded if there are indications of brain disease (i.e. Babinski sign), if facial muscles are involved or if muscle weakness is asymmetrical [46].

The Medical Research Council has developed a scale, the MRC scale, to diagnose ICUAW. It relies on manual testing of 12 muscle groups, 6 on each side, producing a maximal score of 60, with a score of 48 or below signifying ICUAW [47]. A simplified version of the MRC scale has been published recently and seem to perform as well as the original [48]. The limitation to the MRC scale is that it requires full cooperation from the patient, which can be difficult to achieve in the ICU. A study of an ICU population showed that 75% of patients were unable to participate in the test [49]. Studies also demonstrate low interrater correlation when the MRC scale is used in the ICU [47,49].

Handgrip dynamometry can be used to aid the diagnosis as well. Values below 11 kg in males and 7 kg in females are indicative of ICUAW [46]. The test is simple, but also requires full cooperation from the patient.

A spinal tap is most often not necessary. However, if it is done, it is often normal or with slightly elevated protein level. Blood samples are not specific; creatinine kinase might be normal or moderately elevated, and myoglobin might be elevated. Currently, muscle biopsies are not indicated as findings are not specific [46].

### Electrophysiological diagnosis

In cases where there is doubt concerning the diagnosis, or if there is an interest in establishing the myopathic (critical illness myopathy, CIM) versus neuropathic (critical illness polyneuropathy, CIP) component of ICUAW, electrophysiological diagnosis can be performed in cooperation with the neurological/neurophysiological department. Needle electromyography (EMG) and nerve conduction studies (NCS) are used to differentiate between CIM and CIP [50]. In EMG, short duration and low amplitude motor unit potentials confirm CIM [51]. Additionally, full interference pattern with low amplitude support the myopathy diagnosis. Similar to clinical force measurements, EMG requires patient cooperation. However, in most cases it is possible to perform EMG with passive movements of the joints. Sensory and motor NCS are performed for confirmation of CIP and for differential diagnosis, as for example from Guillain Barré Syndrome. CIP is typically a sensory and motor axonal polyneuropathy characterized by reduced amplitudes of sensory and action potentials. However, reduced amplitudes of motor action potentials are also seen in CIM. Therefore, CIP diagnosis is very much dependent on the sensory NCS, particularly the sural nerve in the legs. Since patients in ICU may have edematous legs, sural NCS may be abnormal due to technical reasons. Reduced motor action potential amplitude due to CIM together with an abnormal sural sensory

NCS due to technical reason may cause a false CIP diagnosis rather than CIM. In a recent study, only few patients with CIP were found, in contrast to a majority of patients with CIM, when the technical considerations are taken into account [52]. Another electrophysiological feature characteristic for CIM is the prolonged duration of the motor action potential [51,53–55]. As a rule, conduction velocities in NCS are normal in CIM while slight decreased velocities may be seen in CIP [56]. On the other hand, demyelination is not seen. Another electrophysiological approach to differentiate CIM and CIP is direct muscle stimulation [51].

## Differential diagnoses

Several specific neurological diseases are relevant to consider, and if any doubt concerning the diagnosis of ICUAW exists, close cooperation with a neurological department is encouraged (in a Danish context see for example https://neuro.dk/wordpress/nnbv/critical-illness-neuropati-og-myopati/). However, specific neurological diseases are the primary cause for less than 0.5% of ICU admissions internationally[57]. The following list consists merely of examples and is not exhaustive.

### Guillain-Barre syndrome

Often involves cranial nerves, bulbar palsy, back pain and neurogenic pain. Increased protein is found in spinal fluid. GBS is most often a demyelinating condition.

### Amyotrophic lateral sclerosis

Findings of initial muscle atrophy, normal or hyperactive deep tendon reflexes along with acute and chronic neurogenic changes on EMG indicate ALS.

### Myasthenia gravis

Often exhibits normal deep tendon reflexes, involvement of cranial nerves, bulbar palsy, and positive acetylcholine receptor antibodies.

### Spinal cord injury

Complete or incomplete loss of muscle function, sensation and autonomic functions only below the level of injury. Diagnosis often heavily supported by the anamnesis.

## Treatment

A systematic review assessed pharmacological intervention for the prevention and treatment of ICUAW[58]. Use of anabolic steroids, growth hormone, propranolol (beta-blocking agent), immunoglobuline and glutamine were investigated. Some of the studies showed promising results, however most studies had a high risk of bias and focused on surrogate outcome measures. Therefore, evidence does currently not support any pharmacological intervention in the treatment or prevention of ICUAW[58].

Several studies on the effect of active mobilization and exercise during ICU admission have been conducted. Some studies found a promising effect[42,59,60], however, others did not [61]. Systematic reviews found that patients might experience at least short term benefit from active mobilization and exercise during ICU admission, but conclude that studies have generally been small and of low quality, so further research is needed [62,63].

Exercise rehabilitation following intensive care unit discharge has also been investigated, however, results have not been promising despite considerable efforts [64]. Systematic reviews report of conflicting results and studies of generally low quality [65].

## Perspective

Patients suffering from ICUAW are numerous, and they are at increased risk of adverse events (re-admissions, loss of independence, increased morbidity and increased mortality), also following discharge from the ICU [2,9]. Currently, systematic screening for ICUAW at ICU discharge is not common in Denmark. Effective prevention, treatment or rehabilitation has not yet been established. An increased focus (both in the ICU, the hospital wards and when discharged) on these patients' individual needs for rehabilitation and increased support is needed, which is why awareness on the existence of ICUAW and its' consequences is important across all medical specialties.

Currently, there is a focus on less sedation and more active mobilization during ICU admission. This could provide the basis for more research into ICUAW, its prevention and possible treatment. Cooperation with colleagues from other areas of medicine, as for example neurophysiology, will allow us to obtain a more detailed knowledge of the pathophysiology and diagnosis of ICUAW. Hopefully, this will eventually allow us to effectively prevent, diagnose and treat ICUAW, to the benefit of almost all critically ill patients.

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