Intensive care unit-acquired weakness: early diagnosis, symptomatology and prognosis
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CHAPTER 2

DIAGNOSTIC APPROACH OF INTENSIVE CARE UNIT-ACQUIRED WEAKNESS PRESENT AND FUTURE

Luuk Wieske, Marcus J. Schultz, Janneke Horn

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INTRODUCTION

Since its recognition in the 1980s many different terms and definitions have been used for weakness in critically ill patients. In 2009, a consensus meeting was held to delineate terminology and provide definitions that could be used by clinicians and researchers. Since then, intensive care unit–acquired weakness (ICU–AW) is used as an umbrella term to describe the clinical picture of weakness that develops in the setting of critical illness. Using additional investigations, ICU–AW can be further differentiated into critical illness polyneuropathy (CIP), critical illness myopathy (CIM) or critical illness neuromyopathy (CINM).

Many uncertainties exist about the current diagnostic approach of ICU–AW. It is unknown whether it is beneficial to early diagnose this important complication. An early diagnosis of ICU–AW may have the potential to trigger therapeutic actions. Furthermore, it is uncertain whether there is truly a need for differentiation between CIP, CIM and CINM.

After a short introduction into incidence and impact of, and risk factors for ICU–AW, this chapter focuses on uncertainties in the diagnostic approach of ICU–AW. Finally, this chapter provides a view into new diagnostic techniques for ICU–AW.

INCIDENCE AND IMPACT OF ICU–AW

ICU–AW is a frequent complication of critical illness, occurring in approximately 50% of intensive care unit (ICU)–patients. ICU–AW develops early after onset of critical illness. Signs of nerve and muscle dysfunction have been found as early as 3 days after onset of critical illness. Reliable incidences of the separate syndromes CIP, CIM and CINM are not available, because definitions have only recently been introduced and accurate delineation between these entities is dependent on the extensiveness of additional investigations. It is thought that CINM is the most prevalent. The incidence of ICU–AW is likely to rise due to increased survival after critical illness.

ICU–AW is associated with an adverse short– and long–term outcome. Indeed, ICU–AW is an independent predictor for hospital mortality, increased duration of mechanical ventilation and length of stay in the ICU. After discharge, recovery of patients with ICU–AW is impeded leading to reduced quality of life, mainly attributed to physical disability caused by muscle weakness. Incomplete recovery can be found up to 5 years after ICU–discharge and patients frequently fail to return to work and have high health care expenditures. Weakness due to CIM is thought to have a better prognosis than CIP.

RISK FACTORS FOR ICU–AW

Both sepsis and the systemic inflammatory response syndrome (SIRS) are found to be consistent and important risk factors. Inflammatory mediators, metabolic stress and/or hypoxia occurring in sepsis or SIRS have been suggested to play a role in the pathogenesis of ICU–AW. Other risk factors for ICU–AW include development of hyperglycemia and prolonged, but not short use of neuromuscular blocking agents. Conflicting results have been reported on the role of corticosteroids.
CURRENT DIAGNOSTIC APPROACH OF ICU–AW

The diagnostic process of an ICU–patient with generalized weakness usually follows a two–step approach. First, other disorders than ICU–AW causing weakness are to be excluded. Second, if ICU–AW is diagnosed, it is tried to differentiate between CIP, CIM or CINM.

ICU–AW is considered the most prevalent cause for muscle weakness in ICU–patients but the differential diagnosis is broad. The consensus meeting statement stresses ICU–AW to be a diagnosis of exclusion because some conditions, like Guillain–Barré syndrome or myasthenia gravis, have therapeutic consequences or prognostic implications. A careful medical history (ascertaining when weakness developed) in combination with physical examination (focusing on patterns of weakness, focal signs and brainstem functions) should confidently eliminate most differential diagnoses. Notably, ICU–AW can only be diagnosed if weakness develops after onset of critical illness. In cases where a medical history cannot be obtained or physical examination cannot reliably be performed, appropriate additional investigations are needed. The mnemonic ‘MUSCLES’ has been suggested to address the most prevalent causes for weakness in the ICU (table 1).

<table>
<thead>
<tr>
<th>category</th>
<th>example</th>
</tr>
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<tbody>
<tr>
<td>M</td>
<td>medications</td>
</tr>
<tr>
<td>U</td>
<td>undiagnosed neuromuscular disorder</td>
</tr>
<tr>
<td>S</td>
<td>spinal cord disease</td>
</tr>
<tr>
<td>C</td>
<td>critical illness</td>
</tr>
<tr>
<td>L</td>
<td>loss of muscle mass</td>
</tr>
<tr>
<td>E</td>
<td>electrolyte disorders</td>
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<tr>
<td>S</td>
<td>systemic illness</td>
</tr>
</tbody>
</table>

CIP: critical illness polyneuropathy; CIM: critical illness myopathy; CINM: critical illness neuromyopathy

There is debate whether differentiation between CIP, CIM and CINM is necessary for daily clinical practice. Although prognostication could be a reason for differentiation, evidence for differences in outcome between CIP, CIM and CINM is not yet very supportive. Data so far suggest a longer length of stay in hospital and worse long–term outcome in CIP compared to CIM.

CURRENTLY USED DIAGNOSTIC TOOLS FOR ICU–AW

Several diagnostic modalities are used in the diagnostic process of ICU–AW. The diagnosis of ICU–AW can be made with physical examination alone. Electrophysiological studies and/or muscle biopsies are needed to differentiate between CIP, CIM and CINM.
Physical examination

With physical examination weakness is objectified using the ‘Medical Council Research’ (MRC)–scale, a subjective 5–point rating scale that scores for maximal force produced by voluntary muscle contraction.\(^2\) The scale ranges from ‘no visible contraction’ to ‘normal strength’ (table 2). For the diagnosis of ICU–AW, MRC–scores for 6 different bilaterally tested muscle–groups are summed (the so–called ‘MRC–sum score’ or MRC–SS).\(^2\) A MRC–SS <48 is used as a cut–off for diagnosing ICU–AW.\(^2\) Most often proximal and distal muscle–groups are tested, like deltoid, biceps, wrist extensors, iliopsoas, quadriceps and ankle dorsiflexor muscles. When it is impossible to test all these 6 muscle groups, an average MRC score <4 per muscle group is used as a cut–off. Besides the degree of weakness, distribution of weakness is also important. In ICU–AW, weakness should be present more or less symmetrically in the upper and lower limbs.\(^2\) Of note, facial weakness is usually not present.

Table 2. The Medical Research Council–scale

<table>
<thead>
<tr>
<th>MRC scale score</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>no contraction</td>
</tr>
<tr>
<td>1</td>
<td>contraction palpable</td>
</tr>
<tr>
<td>2</td>
<td>active movement but not against gravity</td>
</tr>
<tr>
<td>3</td>
<td>movement against gravity but not against resistance</td>
</tr>
<tr>
<td>4</td>
<td>movement against some but not full resistance</td>
</tr>
<tr>
<td>5</td>
<td>movement against full resistance</td>
</tr>
</tbody>
</table>

The MRC–scale is an easy to learn and cheap diagnostic tool, which enables repeated monitoring of the neuromuscular status. In addition, the inter–observer agreement of MRC testing is good.\(^18,19\) It requires, though, an awake and attentive patient. The fast majority of ICU–patients is typically sedated for shorter or longer periods. Sedated patients cannot be scored with the MRC–scale. Delirium may also jeopardize the reliability of the MRC scale.\(^18\) Thus, the MRC scale may be far from appropriate for early diagnosis of ICU–AW. A full examination of all 6 bilateral muscle groups may be very demanding for recovering ICU–patients. In those patients, a simple surrogate marker for overall strength could be obtained by assessing handgrip–strength.\(^6,19\) Handgrip–strength is measured using specific devices, like the hand–grip dynamometer.

Nerve conduction studies

Nerve conduction studies (NCS) involve (transdermal) electrical stimulation of a motor or sensory nerve and subsequent recording of the evoked action potential over a muscle or sensory innervated area. With NCS several measures of muscle and nerve function can be studied.

The amplitude of the ‘compound muscle action potential’ or CMAP is a reflection of the number of stimulated axons and the number of muscle fibers that subsequently depolarize.
A reduction in the CMAP–amplitude can be used as a marker of nerve and/or muscle dysfunction. While reduced CMAP–amplitudes in patients with ICU-AW were often interpreted as a sign of neuropathy, this proved to be an oversimplification with the discovery that muscles are also involved in ICU–AW. The amplitude of the ‘sensory nerve action potential’ or SNAP is the sensory homologue of the CMAP but represents solely nerve function.

CMAP and SNAP amplitudes are obtained by distal stimulation (i.e., close to a muscle or sensory area), but can also be obtained by stimulating more proximal along the course of a specific nerve. The delay in CMAP or SNAP onset between distal and proximal stimulation can be used to calculate the conduction velocity of that specific nerve. Conduction velocity is (near) normal with ICU–AW because the neuropathy is axonal, and not demyelinating.

Other useful NCS include repetitive stimulation (RS) and direct muscle stimulation (DMS). RS is used to examine the neuromuscular junction. RS is performed by repeated stimulation of a motor nerve and looking for decremental amplitudes of the CMAP. More than 10 % decrease is considered abnormal. In ICU–AW the neuromuscular junction is not affected. The most frequently occurring neuromuscular junction problem is caused by neuromuscular blocking agents (figure 1).

Figure 1. Repetitive stimulation during and after neuromuscular blockade with a non–depolarizing neuromuscular blocking agent. During neuromuscular blockade, the first stimulation triggers (near)–normal CMAP amplitudes. Ensuing stimuli show a decrease in the amplitudes. After elimination of the neuromuscular blocking agent, repeated stimulation does not decrease CMAP amplitudes. Recorded at the Academic Medical Center, Amsterdam.

With DMS, CMAPs are obtained using two methods of stimulation. A first CMAP is obtained by conventional stimulation of the nerve. A second CMAP is obtained by direct stimulation of the muscle by inserting a needle into that muscle. By comparing both CMAPs localization of the problem could be possible. In case of a neuropathy, decreased CMAPs are found with nerve stimulation and normal CMAPs with muscle stimulation. Decreased CMAPs with both types of stimulation are found in case of a myopathy. For interpretation a nerve–to–muscle CMAP ratio is used. A ratio <0.5 suggests neuropathy, a ratio >0.5 suggests either myopathy or a combination of neuropathy and myopathy.

NCS have the advantage over physical examination that they can be used in patients who cannot be scored with the MRC–scale. NCS are thus proposed to early diagnose ICU–AW. NCS, however, are technologically demanding in the ICU–setting. Indeed, interference caused
by most, if not all ICU equipment (e.g., ventilators, renal replacement therapy–devices) as well as excessive limb edema may importantly hamper all NCS. Moreover, some NCS such as DMS are relatively new and not routinely available in all electrophysiological laboratories.

Myography
With myography a needle is placed inside a specific muscle to capture the electrical activity of that muscle. Electrical activity elicited by voluntary contraction of a muscle is most useful.2
With voluntary contraction, myography visualizes the sequential recruitment of ‘motor unit action potentials’ or MUAPs (a combination of the motor neuron and the muscles innervated by that neuron). Morphology and pattern of recruitment of MUAPs can be helpful in the diagnosis of myopathy. Characteristically, with myopathy MUAPs have a short duration and low amplitude.

For myography an awake and attentive patient is needed to reliably evaluate MUAPs. This of course limits its applicability in sedated, otherwise unconscious or delirious critically ill patients. Clotting disorders may be seen as a contraindication for myography. Alike with NCS most ICU–equipment may cause interference. Notably, interpretation of myography requires more experience and training compared to NCS.

Membrane excitability studies
Several electrophysiological studies other than NCS or myography have been used to investigate ICU–AW, like threshold tracking, velocity recovery cycles (VRCs) of muscle and muscle fiber conduction velocity (MFCV).23–25 All these studies measure excitability properties of nerves or muscles. In ICU–AW, early in the pathogenesis decreased excitability of muscle and nerve develops. This is thought to occur due to a dysregulation of voltage gated sodium channels.26 Threshold tracking measures excitability properties exclusively of nerves, while VRCs and MFCV exclusively give information on muscles. A combination of these techniques may thus allow separation of neuropathy from myopathy. So far, these studies have only been used for research purposes. Clinical feasibility is uncertain.

Muscle biopsy
Muscle tissue can be obtained via open biopsy or needle biopsy techniques. Two structural changes can be identified.27 With ICU–AW total muscle mass can be reduced by atrophy and/or necrosis of muscle fibers. Second, there may be loss of myosin. Loss of these so–called ‘thick filaments’ is a histological hallmark of CIM.2 Myosin and actin are mandatory for contraction of muscle fibers. Selective loss of myosin in ICU–AW is thought to occur due to increased proteolysis and decreased protein synthesis.27 Changes in histology already can be seen within five days of onset of critical illness.28 Analyses of atrophy, necrosis and loss of myosin involves both light microscopy and electron microscopy. Quantification of myosin–to–actin ratio using gel electrophoresis has also been used.29

Because muscle biopsy is an invasive technique and as such carries the risk of bleeding and/or infection, its use is mostly limited to research settings. In cases of ambiguous clinical and/or electrophysiological findings or when a strong suspicion of myopathy other than CIM exists, muscle biopsy may be mandatory.
**INTERPRETATION OF ELECTROPHYSIOLOGICAL AND HISTOLOGICAL FINDINGS IN ICU-AW**

Table 3 summarizes the diagnostic criteria for CIP and CIM. For CIP decreased CMAP and SNAP amplitudes with a normal conduction velocity (axonal neuropathy) need to be found and RS needs to be normal. CIM is separated in probable or definitive CIM. Probable CIM can be diagnosed when SNAP amplitudes are normal and either MUAPs are myopathic or the nerve-to-muscle ratio is > 0.5 on DMS. Probable CIM can also be diagnosed when myopathic changes are found upon muscle biopsy. Definite CIM is diagnosed when both sets of criteria for probable CIM are present. CINM is diagnosed when a patient fulfills both the criteria for CIP and either probable or definite CIM. Because of incomplete examinations due to technical issues, interpretation of electrophysiological results is frequently not straightforward or even inconclusive. Moreover, the validity of the proposed criteria has not yet been investigated.

<table>
<thead>
<tr>
<th>criteria</th>
<th>CIP</th>
<th>CIM</th>
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<tr>
<td>clinical criteria ICU-AW</td>
<td>+</td>
<td>+</td>
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<tr>
<td>CMAP</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>SNAP</td>
<td>↓</td>
<td></td>
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<tr>
<td>conduction velocity</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>repetitive stimulation</td>
<td>decremental response &lt;10%</td>
<td>nerve/muscle ratio &gt;0.5</td>
</tr>
<tr>
<td>direct muscle stimulation</td>
<td></td>
<td>myopathic MUAPs</td>
</tr>
<tr>
<td>myography</td>
<td></td>
<td>myopathic changes</td>
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<tr>
<td>muscle histology</td>
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</tbody>
</table>

CIP: critical illness polyneuropathy; CIM: critical illness myopathy; ICU-AW: intensive care unit-acquired weakness; CMAP: compound muscle action potential; SNAP: sensory nerve action potential; MUAP: motor unit potential

**POTENTIAL NEW DIAGNOSTIC TOOLS FOR ICU-AW**

Given the limitations of currently used diagnostic tools, new diagnostic tools are highly needed. Ultrasound may be a promising diagnostic tool for ICU-AW. Ultrasound provides information on muscle structures in an easy and non-invasive way. Cross-sectional muscle area decreases rapidly with critical illness, but this has not yet been linked to development of ICU-AW. Ultrasound may also be used to visualize peripheral nerves, though studies of patients with ICU-AW are currently lacking. Biological markers may also be of help in diagnosing muscle and/or nerve injury. It should be noted, though, that creatinine kinase levels in blood were found insufficient as a biological marker of ICU-AW. Biological markers of nerve injury, like neurofilaments, could be useful.

Identification of structural nerve damage may serve as a prognosticator for long-term functional impairment. Assessing structural nerve damage using nerve biopsies seems an
unattractive modality. Histological examination of nerves may also be possible through use of simple skin biopsies. Currently unknown, however, is whether small nerve fibers in the skin are also affected in ICU–AW.

A further understanding of the pathophysiology of ICU–AW may identify new diagnostic tools in the future. Particularly, a better understanding of the transition from dysfunction to structural damage of nerves may be important. Figure 2 illustrates the progression of ICU–AW and possible time points of application of different diagnostic tools. With increasing knowledge on pathophysiological mechanisms in ICU–AW and the causative disorders, the road for possible therapeutic interventions lies ahead. Properly used diagnostic tools can then also be implemented as surrogate endpoints to assess effectiveness in phase II studies.

**Figure 2.** Progression of ICU–AW and possible time points of use of (new) diagnostic approaches. NMD: neuromuscular disorder; NCS: nerve conduction studies; MRC: Medical Research Council; ICU–AW: intensive care unit-acquired weakness.

**CONCLUSION**

Currently used diagnostic tools for ICU–AW include physical examination using the MRC–scale, NCS, myography and muscle biopsy. They all have their limitations. New diagnostic tools are highly needed for daily clinical care and future research of therapeutic interventions aiming at a reduction of ICU-AW. Ultrasound studies and biological markers may be used in the future.
REFERENCES


