

Intensive care unit-acquired weakness

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Intensive care unit acquired weakness (ICU-AW) is a clinical diagnosis characterised by generalised weakness of the limbs and respiratory muscles subsequent to prolonged intensive care. The weakness develops in the intensive care unit and is without another obvious cause. ICU-AW is because of critical illness polyneuropathy or critical illness myopathy or a combination of these two, termed critical illness poly-neuromyopathy. Previously used terms such as steroid denervation myopathy, sepsis-induced myopathy and ventilator-induced diaphragmatic dysfunction have all been abandoned in preference of ICU-AW.

The risk factors for developing ICU-AW are numerous, including patient demographics, premorbid status, drug use in ICU and severity of the disease. The pathophysiology is initiated by an inflammatory response leading to microvascular, muscle and nerve dysfunction or a combination of these factors. The clinical gold standard is the Medical Research Council sum score (MRC-SS) of less than 48 points out of a maximum 60 points. Other modalities used for confirming diagnosis include electromyography, nerve conduction studies and imaging such as ultrasound and magnetic resonance imaging. Nerve and muscle biopsies are rarely performed to confirm the cause of ICU-AW. An integral part in the management of ICU-AW includes limiting or avoiding risk factors, aggressively treating the underlying illness, glycaemic control and early physical rehabilitation. ICU-AW contributes significantly to the development of chronic critical illness and post-intensive care syndrome which affects quality of life of ICU survivors.

Keywords: intensive care unit, acquired weakness, limbs, respiratory muscles

Introduction

Intensive care unit-acquired weakness (ICU-AW) is a clinical diagnosis characterised by generalised, diffuse and symmetrical weakness sparing cranial nerves subsequent to critical illness.³ This diagnosis is made when all other potential causes of weakness have been excluded. ICU-AW develops as a result of critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) or a combination of the two known as critical illness poly-neuromyopathy (CIPNM).² Development of ICU-AW is associated with increased morbidity and mortality, prolonged ICU stay and high cost. It is postulated that chronic critical illness and post-intensive care syndrome may develop as a result of ICU-AW.²

Epidemiology and risk factors

The incidence of ICU-AW varies significantly depending on tools used for diagnosis, population studied and timing of evaluation during critical illness.¹ The estimated occurrence range is between 20% and 55% of patients admitted in ICU; however, incidence as high as 80% has been reported in some centres.^{4,5,12}

ICU-AW has multiple risk factors which may be either modifiable or non-modifiable. These are determined by patient premorbid status, severity of critical illness, management and ICU length of stay.¹³

ICU-AW risk factors include sepsis, multiorgan failure (MOF), high severity score of critical illness, invasive mechanical ventilation (MV), hyperglycaemia, drugs (corticosteroids, muscle relaxants and statin use) and immobilisation.^{7,14,15}

Patient-related risk factors include advanced age, female, frailty, pre-morbid physical status such as malnutrition and patient comorbidities.

Pathophysiology

The development of ICU-AW involves an interplay of multiple factors. Integral to the pathophysiology is the presence of inflammation leading to either microcirculatory disturbance, muscle dysfunction, muscle atrophy, motor nerve dysfunction or a combination of these.^{16,17} The interplay of these component dysfunctions may result in mitochondrial dysfunction, bioenergetic failure and delayed autophagy.^{5,7,9} Figure 1 highlights different contributors to development of ICU-AW.^{2,5,7,9}

Diagnosis and classification

ICU-AW is diagnosed after excluding multiple differential diagnoses. The clinical features of ICU-AW are generalised, diffuse and symmetrical weakness sparing cranial nerves and is associated with failure to wean or dependency on MV.³ Diagnostic tools used may be clinical, electrophysiological, radiological or histological, but all differ in sensitivity and specificity.

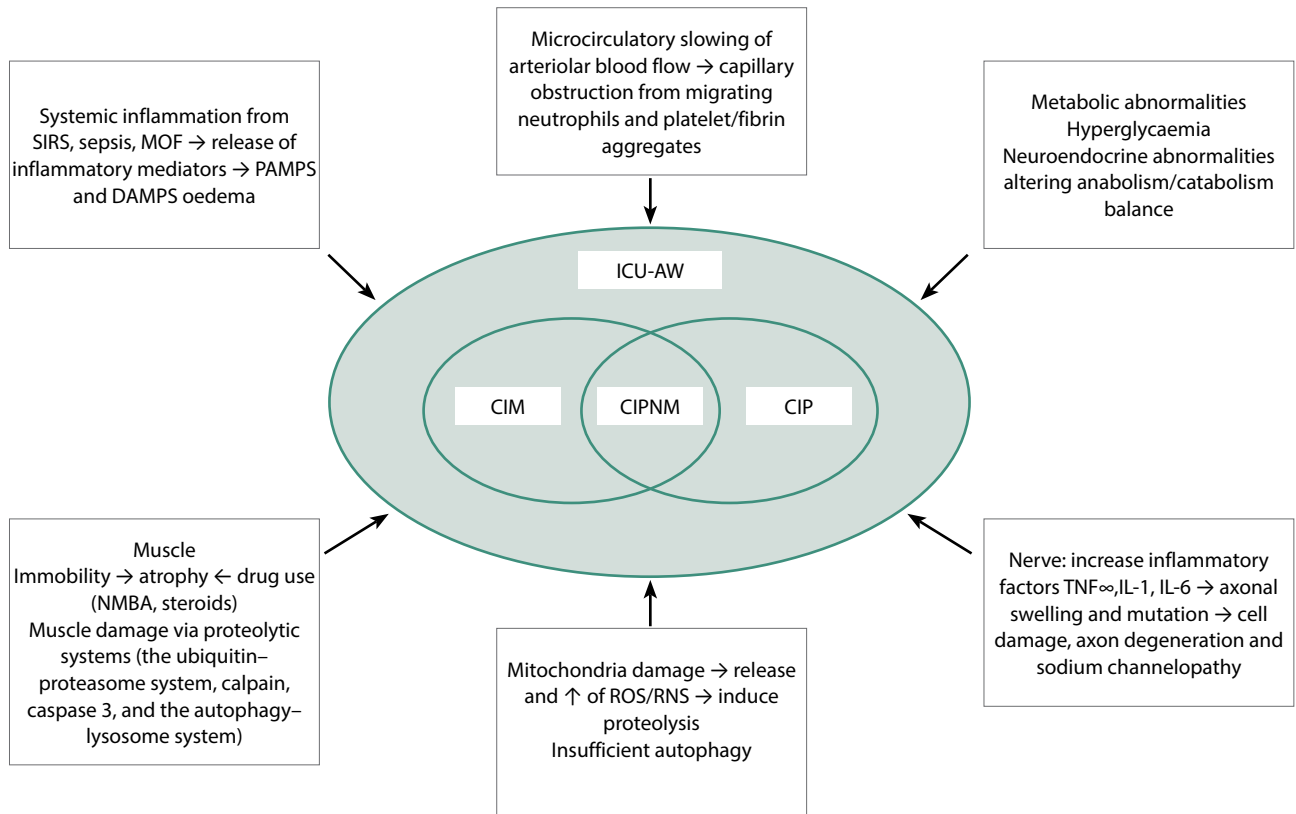


Figure 1: Contributors to development of ICU-AW

ROS – reactive oxygen species, RNS – reactive nitrogen species, NMBA – neuromuscular blocking agents, SIRS – systemic inflammatory response syndrome, CIM – critical illness myopathy, CIPNM – critical illness poly-neuromyopathy, CIP – critical illness polyneuropathy, TNF – tumour necrotic factor, IL – interleukin, PAMPS – pathogen associated molecular patterns, DAMPS – damage associated molecular patterns

Clinical diagnostic tools

The Medical Research Council sum score (MRC-SS) is widely used for the evaluation and diagnosis of ICU-AW. It is non-invasive, easy to administer, cheap and assesses direct functional significance. The limitations of MRC-SS, however, are its requirement of patient cooperation, inter-rater variability and an inability to identify the cause of weakness.

The MRC-SS evaluates the following group of muscle movements bilaterally: wrist extension, elbow flexion, shoulder abduction, dorsiflexion foot, knee extension and hip flexion.^{1,5} The movements for each muscle group is graded 0–5 points for each side; therefore, the maximum score is 60 points.^{1,5} An MRC-SS of 48 points or less is suggestive of ICU-AW. The other available clinical evaluation tools less used include functional status score for the ICU (FSS-ICU), physical function in ICU test-score (PFIT-s), Chelsea critical care physical assessment tool (CPAx).²

Electrophysiological studies

Nerve conduction studies (NCS) of both motor and sensory nerves with electromyography (EMG) is another choice that reduces the subjective errors of healthcare professionals and distinguishes between CIM and CIP. Full nerve conduction studies or single nerve conduction studies can be done. Commonly stimulated nerves are peroneal (motor) and sural (sensory) nerves, comparing amplitudes of compound motor

action potentials (CMAPs) and sensory nerve action potentials (SNAPs).^{6,8} The electrophysiological studies can also be applied to patients who are unconscious/uncooperative.² Both single NCS and full NCS have sensitivity and specificity of 100% and above 80%, respectively.⁶

Hand-held dynamometer

This is a quantitative measure of weakness measuring handgrip strength. It is a non-invasive, easy bedside test with high sensitivity and specificity. Weakness is possible when strength is < 11 kg for men with interquartile range (IQR) of 10–40 and < 7 kg for women with IQR of 0–7.3.¹⁶

Biomarkers

There is no universally-used biomarker for the diagnosis of ICU-AW. Creatine kinase is not the best biomarker, though it might be elevated in patients with ICU-AW. Promising biomarkers such as neurofilament plasma levels has shown good discriminative power for weakness when the diagnosis has been made; therefore, it may be good for confirmation. Other promising biomarkers include growth differentiation factor 15 (GDF-15).¹

Imaging

There are multiple imaging modalities that can be used to aid in excluding differential diagnosis and assist in the diagnosis of

ICU-AW. The chest radiograph has low sensitivity and specificity but may identify diaphragmatic position and other causes of failure to wean from ventilation in ICU-AW.

Ultrasound is the most used imaging modality used in identifying ICU-AW. It is non-invasive, available at the bedside, relatively cheap and easy to use. Ultrasound of the diaphragm can be done to assess diaphragmatic excursion and diaphragmatic thickening fraction of less than 11%.^{2,3} Ultrasound of peripheral skeletal muscles is topical in research for ICU-AW.¹⁸

Magnetic resonance imaging, although accurate and highly reliable, especially in fluid overloaded patients, is limited in its use for diagnosing ICU-AW. The main challenges with its use include high cost, need for patient transport, highly specialised staff and software use.²

Histology

Nerve and muscle biopsies are part of the gold standard for the diagnosis of ICU-AW. Biopsies show tissue architecture and histologically differentiates CIM from CIP. The use of biopsies is limited by its invasive nature, pain, requirement of technical expertise, pathologist support and overall expense associated with it.⁶

The differences between CIM and CIP are described in Table 1.

Prevention and treatment

A coordinated multidisciplinary effort that includes the intensivist, nurses, dieticians as well as the physical, occupational and respiratory therapists, is needed. The key to treating ICU-AW is the aggressive treatment of the primary disease such as sepsis.

The review of drugs used in the ICU such as corticosteroids, daily assessment of sedation needs and paralytics (NMBA) use, together with planned sedation holidays assist in management of patients with ICU-AW.¹⁵

Glucose control using insulin-based protocols is essential to prevent both hyperglycaemic and hypoglycaemic episodes. All abnormal electrolytes need prompt correction.

Immobilisation is reduced by early, progressive, targeted physiotherapy for critically ill patients, even those on ventilators.^{14,19} Prevention of diaphragmatic weakness is reduced by the transition of mechanically-ventilated patients from mandatory modes to spontaneous breathing-based modes when it is safe to do so. Additionally, use of a bedside cycle ergometer for 20 minutes as early as day 5 following ICU admission for five days per week, has shown good results.¹² Electrical muscle stimulation for immobile patients has not shown a significant improvement in mechanical ventilation dependency and muscle strength.^{2,20}

Prognosis and outcomes

ICU-AW can have short-term and long-term effects on the ICU survivor. The post-ICU syndrome may result in physical impairment, cognitive and/or mental impairment which all have significant negative impacts on quality of life.^{4,10} Short-term effects of ICU-AW include prolonged ICU and hospital stay, prolonged mechanical ventilation, failure to extubate and swallowing abnormalities.² In the long-term, weakness may persist and progress to disability; up to 30% of survivors have severe quadriparesis, quadriplegia or paraplegia. One year mortality is higher in previous ICU-AW survivors and is further increased if patients were still weak when discharged from ICU (MRC-SS < 48).¹¹

Table 1: Differences between CIM and CIP

	Critical illness myopathy (CIM)	Critical illness polyneuropathy (CIP)
Weakness distribution	Generalised, mainly proximal, symmetric weakness Flaccidity	Generalised or distal weakness Flaccidity
Sensation	Normal sensation	Distal sensory deficits
Cranial nerves	Usually spared	Spared
Muscle atrophy	Possibly absent in early stages with normal or reduced deep-tendon reflexes, possibly absent in severely affected muscles	Muscle atrophy with reduced or absent deep-tendon reflexes (reflexes recovery in one third of patients)
Mechanical ventilation	Dependency with reduced vital capacity, tidal volume, negative inspiratory force	Dependency with impaired respiratory mechanics
Creatine kinase levels	Elevated or normal CK levels	Usually normal CK levels
Cerebrospinal fluid (CSF)	Normal CSF	Normal CSF
Electrophysiological features		
Compound muscle action potentials (CMAP)	Amplitude decreased/duration increased	Amplitude decreased/duration normal
Sensory nerve action potential (SNAP)	Amplitude normal	Amplitude decreased
Nerve conduction velocity	Normal	Normal
Muscle/nerve biopsy	Acute muscle fibre degeneration and thick filament loss without inflammation in muscle biopsy, abnormal myosin ATPase activity	Neurogenic atrophy in muscle biopsy; possible presence of critical illness myopathy characteristics. Primary distal axonal degeneration of sensory nerve fibres, no demyelination

Conclusion

The development of advanced care and modern technology in the ICU over the years has improved critically ill patient survival. ICU-AW, however, is among the critical illness legacies that needs to be better understood in terms of its pathophysiology and risk factors so as to use available tools of diagnosis. Multidisciplinary teamwork is critical in implementing prevention and management strategies of ICU-AW and to improve the long-term outcomes.

Conflict of interest

The author declares no conflict of interest.

Funding source

No funding was required.

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