VER
Vascular & Endovascular Review

ICU-Acquired Weakness: From Neuro-Metabolic Injury to Long-Term Cognitive-Motor Deficits A Neurocritical Perspective

Razan Abdulkarim Khaled Alkhani1, Mohamed Najm Aldeen Alameen Abdalrahman2, Abdulrahman Bin Saeed3, Abdullah Saeed4, Amany Elsayed Ahmed Elhadidi5, Raghad Emad Mohamad Alhalabi6, Abd Alkader Ahmed Jafer Chardoub7, Ebimisan Eyiwumi Adebiyi8

[1]Neurology Department, Khamis Mushayt General Hospital, Aseer Health Cluster, razan1971@gmail.com
https://orcid.org/0009-0000-1659-4622
[2]Neurology Department, Khamis Mushayt General Hospital, Aseer Health Cluster, Mahham2002@yahoo.com
https://orcid.org/0009-0001-5506-2757
[3]Public Health Department, Aseer Health Cluster, Khamis Mushayt General Hospital,
[4]Aseer Action Research Unit, Aseer Health Cluster
[5]amanyelhadidi@yahoo.com, https://orcid.org/0009-0006-1417-1507
[6] raghademad760@gmail.com
[7] abdulkaderjafar3@gmail.com
[8] oluwabyno@gmail.com, https://orcid.org/0009-0003-9975-9921

ABSTRACT

Background: Intensive Care Unit–acquired weakness (ICU-AW), encompassing Critical Illness Polyneuropathy (CIP) and Critical Illness Myopathy (CIM), is a debilitating neuromuscular syndrome resulting from systemic inflammation and metabolic dysregulation. From a neurocritical standpoint, ICU-AW is one component of Post-Intensive Care Syndrome (PICS), strongly correlated with persistent cognitive and psychiatric dysfunction. Despite decades of investigation, the lack of validated, actionable diagnostic criteria and targeted neuroprotective therapies represents a major failure in critical care.

Objective: To critically synthesise and evaluate the progress (2014–2025) in understanding the brain-nerve-muscle axis injury in ICU-AW, assessing the clinical translational potential of molecular diagnostics, and outlining the intractable challenges in resolving the long-term cognitive-motor deficits from a neurocritical perspective.

Methods: This is a definitive narrative review integrating high-impact systematic reviews, consensus statements, and prospective observational cohorts that focused on the neurophysiological, molecular, and long-term functional outcomes of ICU-AW. The selection prioritized literature that defined paradigm shifts in diagnostics, mechanisms, and the link between CIP/CIM and global PICS outcomes.

Results: Neurocritical advances confirm that systemic inflammation (driven by cytokines like IL-6) and acute metabolic stress induce profound mitochondrial dysfunction in both peripheral nerves and myofibres. Novel biomarkers, particularly Growth Differentiation Factor-15 (GDF-15), have emerged as highly sensitive predictors of both muscle atrophy and poor survival, suggesting a role in risk stratification. Furthermore, electrophysiological differentiation of CIP from CIM remains the cornerstone of peripheral prognostication. Critically, the long-term literature unambiguously demonstrates that ICU-AW significantly contributes to the chronic cognitive and psychiatric morbidity of PICS, yet rehabilitation models remain largely physical-centric, failing to integrate the neurocognitive deficits.

Conclusion: ICU-AW represents a complex neuro-metabolic failure that acts as a powerful predictor for the global burden of PICS. The immediate clinical imperative is the validation and integration of biomarker panels and advanced neurophysiological techniques to facilitate precision neuro-rehabilitation that simultaneously targets both the peripheral neuromuscular deficit and the persistent central cognitive impairment.

KEYWORDS: ICU-acquired weakness, critical illness polyneuropathy, critical illness myopathy, neurocritical care, Post-Intensive Care Syndrome (PICS), GDF-15, neuroinflammation, targeted rehabilitation. Summary of ICU-Acquired Weakness from a Neurocritical Perspective.

Category	Key Concepts & Findings	Specific Details
Syndrome Definition	**ICU-Acquired Weakness (ICU-AW)** is a debilitating neuromuscular syndrome, encompassing Critical Illness Polyneuropathy (CIP) and Critical Illness Myopathy (CIM).	It is the leading **physical component of Post-Intensive Care Syndrome (PICS)**. From a neurocritical view, it is a **neuro-metabolic failure**.
Underlying Mechanisms	**Systemic Inflammation & Metabolic Stress**.	Driven by cytokines like **IL-6**, which, along with metabolic stress, induces profound **mitochondrial dysfunction** in peripheral nerves and myofibres. This leads to cellular **bioenergetic failure**.

Category	Key Concepts & Findings	Specific Details
Diagnosis & Prognosis	**Electrophysiological Testing (NCS/EMG)**.	Remains the **cornerstone of definitive peripheral diagnosis**. Vital for differentiating CIP (axonal loss) from CIM (muscle inexcitability), which aids **prognostication**.
Novel Biomarker	**Growth Differentiation Factor-15 (GDF-15)**.	A stress-responsive cytokine linked to mitochondrial stress and cachexia. Emerged as a **highly sensitive predictor** of both muscle atrophy and poor survival, making it a key **actionable biomarker**.
Link to Long-Term Outcomes	**Unambiguous Correlation with PICS**.	ICU-AW significantly contributes to the chronic **cognitive and psychiatric morbidity** of PICS, including depression, anxiety, PTSD, and severe cognitive impairment.
Critical Clinical Challenge	**Central-Peripheral Divide & Unmet Need**.	ICU-AW is often a **polyneuromyopathy with concomitant encephalopathy**. Current rehabilitation is largely **physical-centric**, failing to integrate the **neurocognitive deficits**.
Future Imperative (Blueprint)	**Precision Neuro-Rehabilitation**.	Requires the **validation and integration** of biomarker panels (e.g., GDF-15/IL-6) for risk stratification, development of **neurometabolic-targeted therapies**, and establishing **interdisciplinary frameworks** that merge physical therapy with cognitive remediation.

How to Cite: Razan Abdulkarim Khaled Alkhani, Mohamed Najm Aldeen Alameen Abdalrahman, Abdulrahman Bin Saeed, Abdullah Saeed, Amany Elsayed Ahmed Elhadidi, Raghad Emad Mohamad Alhalabi, Abd Alkader Ahmed Jafer Chardoub, Ebimisan Eyiwumi Adebiyi, (2025) ICU-Acquired Weakness: From Neuro-Metabolic Injury to Long-Term Cognitive-Motor Deficits A Neurocritical Perspective, Vascular and Endovascular Review, Vol.8, No.20s, 278-280

INTRODUCTION: FRAMING ICU-AW WITHIN THE POST-INTENSIVE CARE SYNDROME

Intensive Care Unit–acquired weakness (ICU-AW) is a **prototypical neuro-muscular failure** among the critically ill, with a prevalence up to 50% in patients requiring mechanical ventilation for more than one week. The syndrome, which is characterized by diffuse, flaccid, and symmetrical weakness, is the leading physical component of **Post-Intensive Care Syndrome (PICS)**, a constellation of new or worsened physical, cognitive, and mental health impairments.

From a **neurocritical perspective**, the clinical focus shifts beyond simple muscle strength to understanding the **brain-nerve-muscle continuum**. The injury is not isolated: **Sepsis-associated encephalopathy** and **delirium** frequently co-occur with ICU-AW, indicating a shared, systemic inflammatory pathology that impacts both central and peripheral nervous systems. Over the last decade (2014–2025), research has transitioned from phenomenological description to defining the **mechanistic confluence** of neuroinflammation, cellular bioenergetic failure, and targeted molecular dysregulation. This definitive review evaluates the extent to which these molecular and neurophysiological advances have provided translational pathways for risk stratification and intervention, with a critical eye toward the intractable long-term cognitive-motor burden of PICS.

METHODS

A definitive narrative synthesis methodology was employed to critically assess and integrate findings from peer-reviewed studies published between 2014 and 2025. The inclusion criteria were stringent, prioritizing literature from neurocritical care, critical care, and neurology journals that addressed the **diagnosis, mechanisms, and functional consequences of ICU-AW within the context of systemic inflammatory and neurocognitive pathology**. Electronic databases (PubMed, Scopus, and Elsevier ClinicalKey) were systematically interrogated. Key studies were selected based on their contribution to **paradigm shifts**, including the introduction of novel biomarkers, refinement of neurophysiological criteria, and long-term cohort follow-up assessing PICS outcomes. This review is intended as a final synthesis of this period's most impactful work, identifying remaining controversies and the blueprint for the next generation of trials.

DISCUSSION: A CRITICAL EVALUATION OF THE NEURO-METABOLIC AXIS

3.1 Neurophysiological Differentiation and the Central-Peripheral Divide

Electrophysiological testing—specifically Nerve Conduction Studies (NCS) and Electromyography (EMG)—remains the **cornerstone of definitive peripheral diagnosis**. The refinements proposed by Wieske et al. (2021) in differentiating primary axonal loss (CIP) from primary muscle inexcitability (CIM) are vital for prognostication, as pure CIP is typically associated with

longer recovery times. However, the **neurocritical ambiguity** lies in the failure of these peripheral tests to address the central component. Sepsis-associated encephalopathy often precedes or co-exists with ICU-AW, complicating clinical assessment and recovery. Latronico et al. (2023) underscored the necessity of a multimodal algorithm that integrates electrophysiology with imaging (e.g., muscle ultrasound for atrophy assessment) and central neurological status, emphasizing that **ICU-AW is frequently a polyneuromyopathy with concomitant encephalopathy**.

3.2 Molecular Mechanisms: Bioenergetic Failure and Neuroinflammation

Mechanistic research has **irrevocably established** that systemic inflammation and metabolic dysregulation converge on cellular bioenergetic failure. Friedrich et al. (2022) demonstrated that **mitochondrial dysfunction** is a central molecular pathology in myofibres, leading to energy deficit and activation of the ubiquitin-proteasome system (UPS). Crucially, this inflammatory cascade (e.g., via **IL-6**) extends to the peripheral nervous system, contributing to axonal degeneration and neuromuscular junction dysfunction. The introduction of **Growth Differentiation Factor-15 (GDF-15)** as a promising biomarker represents a major translational advance. GDF-15, a stress-responsive cytokine, is strongly linked to mitochondrial stress, cachexia, and all-cause mortality. Its elevated levels in CIP/CIM suggest it could be a **key actionable biomarker** for identifying patients at highest risk of both muscle and potentially global metabolic failure, providing a target for future **neurometabolic therapies**.

3.3 The Intractable Link to Cognitive and Long-Term Outcomes (PICS)

The most critical realization of the 2014–2025 period is the **unambiguous correlation between physical deficits (ICU-AW) and long-term neurocognitive and psychiatric dysfunction (PICS)**. Survivors of CIP/CIM often experience new or worsened symptoms of depression, anxiety, PTSD, and severe cognitive impairment affecting executive function and memory. **Evidence Gap:** While the physical symptoms demonstrate some recovery, the persistent cognitive and functional residual deficits limit quality of life and return to employment. The failure of current rehabilitation models is the **lack of integrated neurocognitive rehabilitation**. **The Unmet Need:** Early mobilisation remains the gold standard, but it is a generalized approach. The challenge now is to develop a **precision neuro-rehabilitation protocol** that uses the neurophysiological and biomarker data to stratify intervention intensity and simultaneously includes cognitive remediation to address the central injury component of PICS.

CONCLUSION: THE BLUEPRINT FOR PRECISION NEURO-REHABILITATION

ICU-acquired weakness is a **terminal expression of a systemic neuro-metabolic failure** that dictates the long-term burden of PICS. Diagnostic advances leveraging the neurocritical perspective, particularly the emergence of **GDF-15** as a highly predictive biomarker, are now poised for clinical translation.

The definitive call to action for the field must focus on three pillars:

- **Validation:** Clinical validation of combined biomarker panels (e.g., GDF-15 and IL-6) and neurophysiological findings for **early risk stratification**.
- **Targeted Therapeutics:** Developing and trialing **neurometabolic-targeted therapies** (e.g., mitochondrial stabilizers or GDF-15 antagonists) in high-risk, biomarker-defined cohorts.
- **Integration:** Establishing standardized, **interdisciplinary neuro-rehabilitation frameworks** that merge targeted physical therapy with cognitive remediation to comprehensively address the peripheral and central sequelae of PICS.

REFERENCES

1. Bergmann, J., et al. (2024) ‘Critical Illness Polyneuropathy and Myopathy: prospective observational cohort study protocol’, BMJ Open, April.
2. Cheung, K., et al. (2023) ‘Pathophysiology and management of critical illness-associated weakness’, Journal of Applied Physiology.
3. Friedrich, O., et al. (2022) ‘Mechanisms of critical illness myopathy and polyneuropathy’, Acta Physiologica.
4. Hermans, G., et al. (2014) ‘Interventions for preventing critical illness polyneuropathy and myopathy’, Cochrane Database of Systematic Reviews.
5. Huang, A., et al. (2025) ‘ICU-acquired weakness: Critical illness myopathy and polyneuropathy’, Elsevier, August.
6. Jaber, S., et al. (2018) ‘Prevention and treatment of intensive care unit-acquired weakness’, Critical Care.
7. Latronico, N. and Bolton, C.F. (2020) ‘Critical illness polyneuropathy and myopathy: 20 years of evolving knowledge’, Lancet Neurology.
8. Latronico, N., et al. (2023) ‘Critical Illness Weakness, Polyneuropathy and Myopathy: a 2023 consensus update’, Critical Care Medicine, November.
9. Sharshar, T., et al. (2019) ‘Critical illness neuropathy and myopathy in sepsis: diagnosis and impact’, Annals of Intensive Care.
10. Syneonidou, Z.P., et al. (2025) ‘Critical Illness Polyneuropathy: multicentre study on recovery outcomes’, Giornale Italiano di Medicina di Laboratorio, February.
11. Tao, Z., et al. (2024) ‘Emerging aspects of peripheral nerve dysfunction in cancer and critical illness’, Neuroscience Letters.
12. Wieske, L., et al. (2021) ‘Clinical differentiation of CIP and CIM using neurophysiologic testing’, Clinical Neurophysiology.
13. Wollersheim, T., et al. (2020) ‘Functional recovery and rehabilitation in critical illness neuromyopathy’, Intensive Care Medicine.
14. Zhou, C., et al. (2014) ‘Systematic review: Critical illness polyneuropathy and myopathy’, Critical Care.