Understanding Critical Illness Neuromuscular Disease

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Introduction

- Critical illness myopathy (CIM), critical illness polyneuropathy (CIP), and the overlap, critical illness polyneuromyopathy (CIPNM)
- Impact on neuromuscular weakness and ventilator weaning with longer LOS, more ventilator dependent days and higher hospital mortality
- Most of those who survive have chronic long-term complications

Defining CINM and its Prevalence

- Description of patients progressing to flaccid quadriparesis, preservation of facial expression and ventilator dependency
- Electrodiagnostic findings supporting severe polyneuropathy
- Prevalence rates ranging from 25% to 83% based on underlying critical illness

Bolton CF, Gilbert JJ, Hahn AF, Sibbald WJ. Polyneuropathy in critically ill patients. *J Neurol Neurosurg Psychiatry*. 1984;47

Incidence and Risk Factors of Neuromuscular Weakness in the ICU

- Incidence of neuromuscular weakness varies based on underlying disease process, diagnostic criteria, and timing of evaluation

- **Disease-Specific Rates:**
  - Status asthmaticus requiring intubation: at least 33% develop CIM
  - Sepsis and systemic inflammatory response syndrome: rates up to 70%, reaching 100% with multiorgan dysfunction
  - Acute respiratory distress syndrome: rates reported at 60%

- **Mechanical Ventilation Duration**:
- Patients on mechanical ventilation for 4 to 7 days have CIM/CIP rates ranging from 25% to 33% clinically and up to 58% to 68% on electrodiagnostic testing

Disease Process Associations:

- Higher blood glucose levels associated with CIM/CIP/CIPNM
- Female gender as an independent risk factor for CIPNM
- Increased disease burden as indicated by higher Acute Physiologic and Chronic Health Evaluation III (APACHE III) score and Sequential Organ Failure Assessment (SOFA) score

Medication Associations:

- Conflicting data on glucocorticoids and neuromuscular blockade
- Some studies suggest increased risk with vasopressor drug administration, particularly in cardiothoracic ICU admissions

Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med*. 2007;33(11):1876–1891

Pathophysiology of Critical Illness Neuromuscular Disorders

Clinical Similarities, Pathological Variations

- CIM, CIP, and CIPNM present similarly clinically but exhibit drastic differences in underlying pathology
- Electrophysiological changes can manifest within hours of ICU admission, indicating rapid onset
- Underlying Pathophysiology:
- Microcirculatory, cellular, and metabolic derangements affect muscles and nerves during critical illness

Pathophysiology of Critical Illness Neuromuscular Disorders

Critical Illness Myopathy (CIM)

- Heterogeneous entity with varying pathologic subtypes
- Traditional CIM: Characterized by myosin loss and breakdown of contractile apparatus
- Experimental evidence suggests steroids and other stressors may contribute to myosin loss
- Muscle fiber membrane dysfunction and inactivation of sodium channels implicated in pathogenesis

Pathophysiology of Critical Illness Neuromuscular Disorders

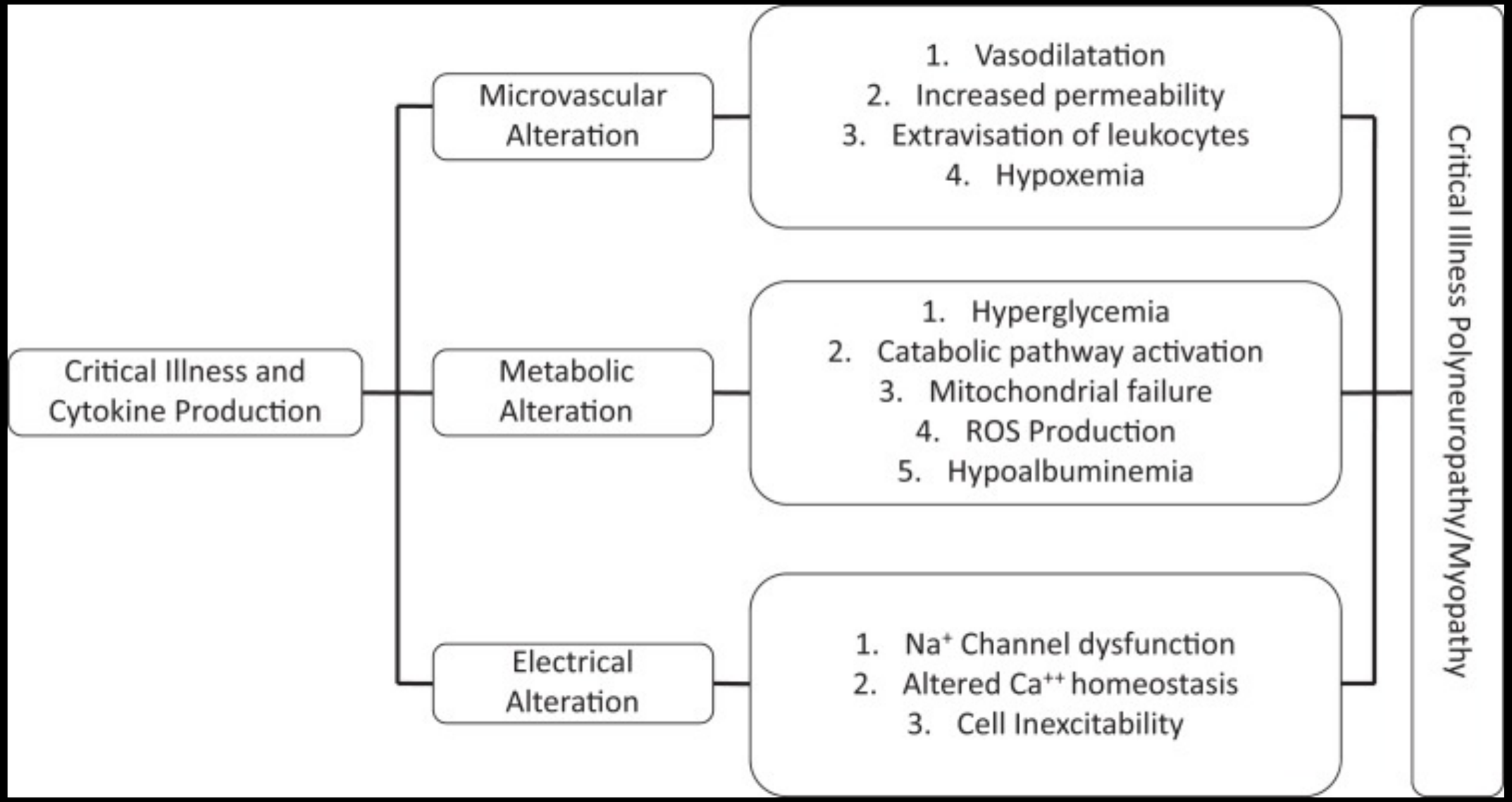
Critical Illness Polyneuropathy (CIP)

- Proposed mechanisms include microcirculatory changes and increased vascular permeability
- Microcirculatory alterations lead to distal nerve ischemia and degeneration
- Increased leukocytes and edema formation contribute to neuronal dysfunction
- Inactivation of sodium channels and alteration of resting membrane potential implicated in pathophysiology

Overlapping Pathogenesis

- Inactivation of sodium channels and changes in resting membrane potential observed in both CIM and CIP
- Coexistence of CIP can exacerbate CIM, supporting the hypothesis of shared underlying disease process

Pathophysiology of Critical Illness Polyneuropathy and Myopathy



Shepherd S, Batra A, Lerner DP. Review of Critical Illness Myopathy and Neuropathy. Neurohospitalist. 2017 Jan;7(1):41-48. doi: 10.1177/1941874416663279. Epub 2016 Aug 23. PMID: 28042370; PMCID: PMC5167093.

Challenges in Diagnosis

Symptom Onset

- Uncertainty in onset timing due to concurrent factors like encephalopathy and sedation
- Upto 62% patients with failure to wean from ventilatory support
- Vast differential diagnosis including non-neuromuscular causes.
- Final diagnosis is based on electrophysiologic studies.

National Heart, Lung and Blood Institute (NHLBI) workshop on respiratory muscle fatigue: a report of the respiratory muscle fatigue workshop group. *Am Rev Resp Dis*. 1990;142(2):474–480

Neuromuscular Differential Diagnosis of "Failure to Wean From Ventilator."

Motor neuron	Amyotrophic lateral sclerosis
	Poliomyelitis
	Guillain-Barre syndrome
	Critical illness polyneuropathy
	Critical illness polyneuropathy/myopathy
	Heavy metal toxicity
	Vasculitis
	Sarcoidosis
	Mononeuritis multiplex
Neuromuscular junction	Myasthenia gravis
	Neuromuscular blockade
	Lambert-Eaton myasthenic syndrome
	Botulinum toxicity
	Organophosphate toxicity
	Tetrodotoxin toxicity
Muscle	Rhabdomyolysis
	Mitochondrial myopathy
	Muscular dystrophy (eg, Myotonic dystrophy)
	Critical illness myopathy
	Acid maltase deficiency

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Challenges in Diagnosis

Variability of Clinical Presentation

- Characteristics of CIM: Proximal weakness, sensory preservation, and atrophy
- Characteristics of CIP: Distal weakness, sensory changes, and limited atrophy
- Characteristics of CIPNM: Combination of proximal and distal weakness, sensory loss, and variable atrophy
- Initial preservation of reflexes with gradual loss with progression
- Involvement of most skeletal muscles, including bulbar musculature sparing
- Lack of autonomic instability or pupillary changes
- Impact of sedating medications and intubation status on clinical examination reliability

Challenges in Diagnosis

Clinical Assessment in Ventilatory Failure

- Common findings:
  - Decreased maximal inspiratory pressure >-30cm H2O
  - Decreased maximal expiratory pressure <40cm H2O
  - Decreased forced vital capacity <20mL/kg
- Challenges in differentiating neuromuscular failure from other causes of ventilatory failure
- Spectrum of CINM disease is not restricted to respiratory muscles

Khalil Y, El Din Mustafa E, Youssef A, Imam HM, Behairy AE. Neuromuscular dysfunction associated with delayed weaning from mechanical ventilation in patients with respiratory failure. *Alexandria J Med*. 2012;48(3):223–232

Challenges in Diagnosis

Electrodiagnostic Studies

- Technical Challenges in Nerve Conduction Studies and EMG
- Presence of electronic devices causing 60-cycle artifact
- Physiological changes such as anasarca and hypothermia affecting recordings
- Patient's clinical status hindering cooperation with EMG testing

Electrodiagnostic Findings in CIM:

- Reduced compound muscle action potential amplitudes (<50% of lower limit of normal)
- Possible increased action potential duration within 72 hours of admission
- Sensory nerve action potentials usually normal
- Decreased muscle membrane excitability
- The motor units are short, low amplitude and polyphasic.

Electrodiagnostic Findings in CIP:

- Resemblance to length-dependent axonal polyneuropathy
- Bilateral loss of amplitudes in sensory and compound muscle action potentials
- Initial findings may occur within 72 hours to 2 weeks of critical illness
- Motor unit potentials demonstrate decreased recruitment

Lacomis D. Electrophysiology of neuromuscular disorders in critical illness. *Muscle Nerve*. 2013;47(3):452–463

Suggested Diagnostic Criteria for Critical Illness Polyneuropathy and Critical Illness Myopathy.[a]

CIP	CIM
Critically ill (sepsis and multi-organ failure)	Not required; typically exposed to variable combination of neuromuscular blocking agent and corticosteroids in the setting of sepsis and multi-organ failure
Limb weakness is present	Limb weakness is present
Difficulty in weaning from mechanical ventilatory support with the exclusion of cardiac and pulmonary causes	Difficulty in weaning from mechanical ventilatory support with the exclusion of cardiac and pulmonary causes
Electrophysiological evidence of 1. Axonal sensorimotor neuropathy	Electrophysiological evidence of 1. Preserved sensory response (>80% of lower limit of normal) 2. Reduced motor responses (compound muscle action potential <80% lower limit of normal) 3. Normal repetitive nerve simulation, and EMG with short-duration, low-amplitude motor unit potential with early full or normal recruitment of motor unit action potentials 4. Muscle inexcitability with direct muscle stimulation
Other causes of acute neuropathy should be excluded, for example, porphyria, acute massive intoxications of heavy metals, and vasculitis	Muscle biopsy consistent with myopathy and myosin loss

Bolton CF. Neuromuscular manifestation of critical illness. *Muscle Nerve*. 2005;32(2):140–163
Lacomis D, Zochodne DW, Bird SJ. Critical illness myopathy: what's in a name? *Muscle Nerve*
Shepherd S, Batra A, Lerner DP. Review of Critical Illness Myopathy and Neuropathy. Neurohospitalist. 2017 Jan;7(1):41-48. doi: 10.1177/1941874416663279. Epub 2016 Aug

Electrodiagnostic Studies

Diaphragmatic EMG

- Diagnosis assistance in respiratory failure and ventilator weaning
- Findings include fibrillations, positive sharp waves, and reduced motor unit potentials
- Phrenic nerve conduction can demonstrate either prolonged latency or reduced motor unit end potentials.

Diagnostic Studies

Muscle Biopsy

- Utility in cases where electrodiagnosis is inconclusive
- CIM: relative selective loss of myosin and loss of type 2 greater than type 1 fibers.
- CIP: features of denervation and reinnervation with small muscle fibers, fiber-type grouping, and fiber group atrophy
- Nerve biopsy in CIP: widespread axonal degeneration of both motor and sensory nerves.
- Muscle biopsy in CIPNM can have features of both CIM and CIP, typically thick filament loss, denervation and reinnervation changes and nerve biopsy can have axonal degeneration.

Amato AA, Russell JA. Myopathies associated with system disease In: *Neuromuscular Disorders*. New York, NY: McGraw-Hill Companies; 2008:721–736
Visser LH. Critical illness polyneuropathy and myopathy clinical features, risk factors and prognosis. *Eur J Neurol*. 2006;13(11):1203–1212

Prognosis of Critical Illness Neuromuscular Disorders

- Patients with neuromuscular weakness experience prolonged ICU stays and increased ventilator-dependent days
- Mortality rates vary from 16% to 55%, with higher hospital mortality in some reports
- Twenty percent of patients have ongoing weakness or sensory changes at discharge
- CIM patients generally experience faster and more complete recovery compared to CIP or CIPNM

Treatment Strategies and Preventative Measures

- Tight Glucose Control and Immunomodulation
- Deep Vein Thrombosis Prophylaxis and Positioning
- Early Nutrition Initiation and Skin Care
- Importance of Multidisciplinary Approach in Preventing Complications

Importance of Physical Rehabilitation

- Early ICU mobility can decrease length of stay and improve functional outcomes
- Limited evidence suggests intensive physical therapy may enhance discharge to home
- Passive Mechanical Loading and Electrical Stimulation: shows promise in improving muscle function and reducing ICU-acquired weakness

Future Directions and Research Needs

- Opportunities for Further Research in Understanding Pathophysiology
- Development of Targeted Therapies and Personalized Treatment Strategies
- Importance of Continuous Improvement in ICU Management Protocols

Conclusion

- Critical illness neuromuscular disorders pose significant challenges in ICU management
- Comprehensive strategies encompassing rehabilitation, preventive measures, and targeted interventions are essential for improving patient prognosis and quality of life