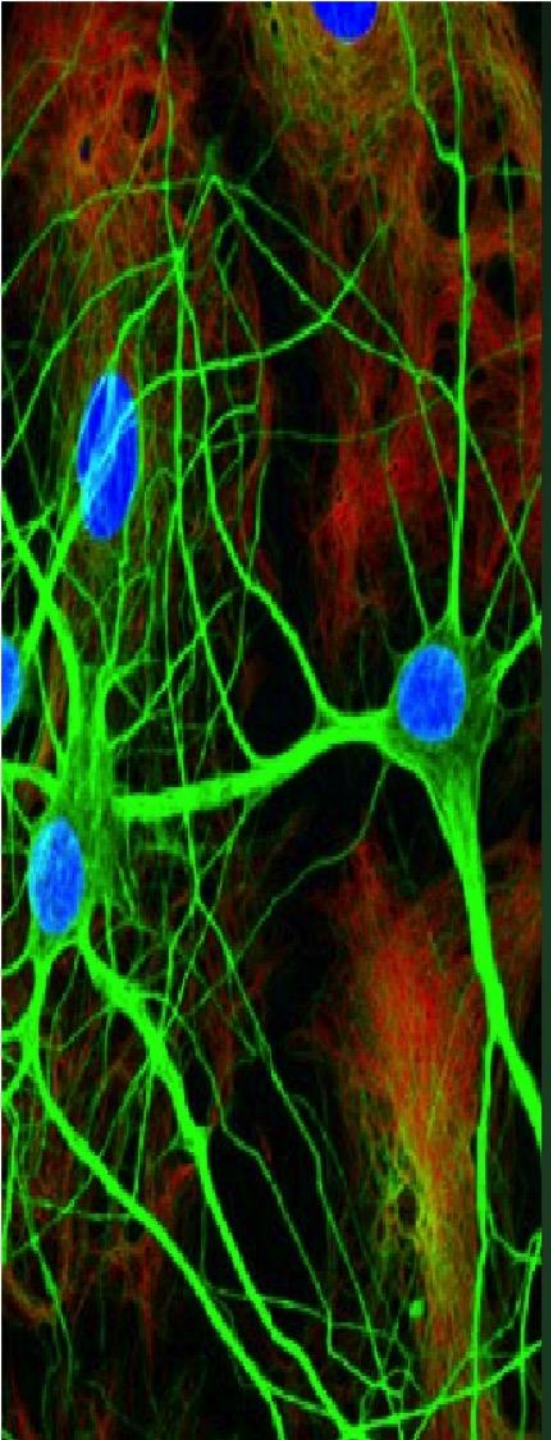

# Critical Illness Neuropathy

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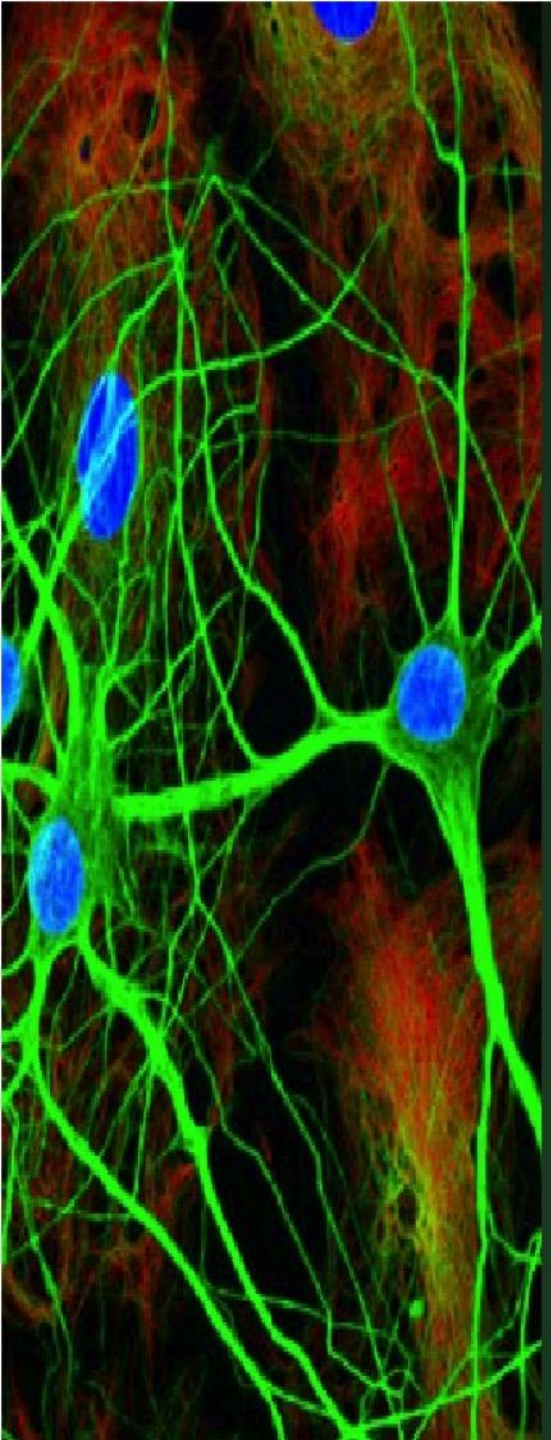
CAEP | ACMU

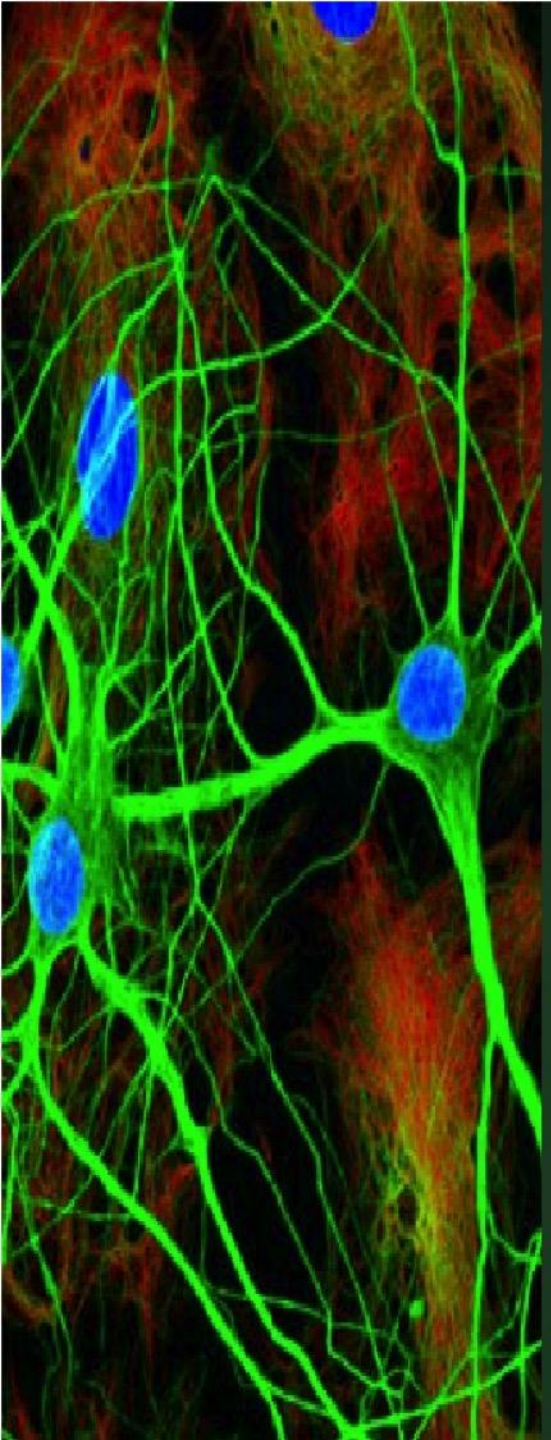

Vancouver Canada


University of British Columbia, Vancouver BC



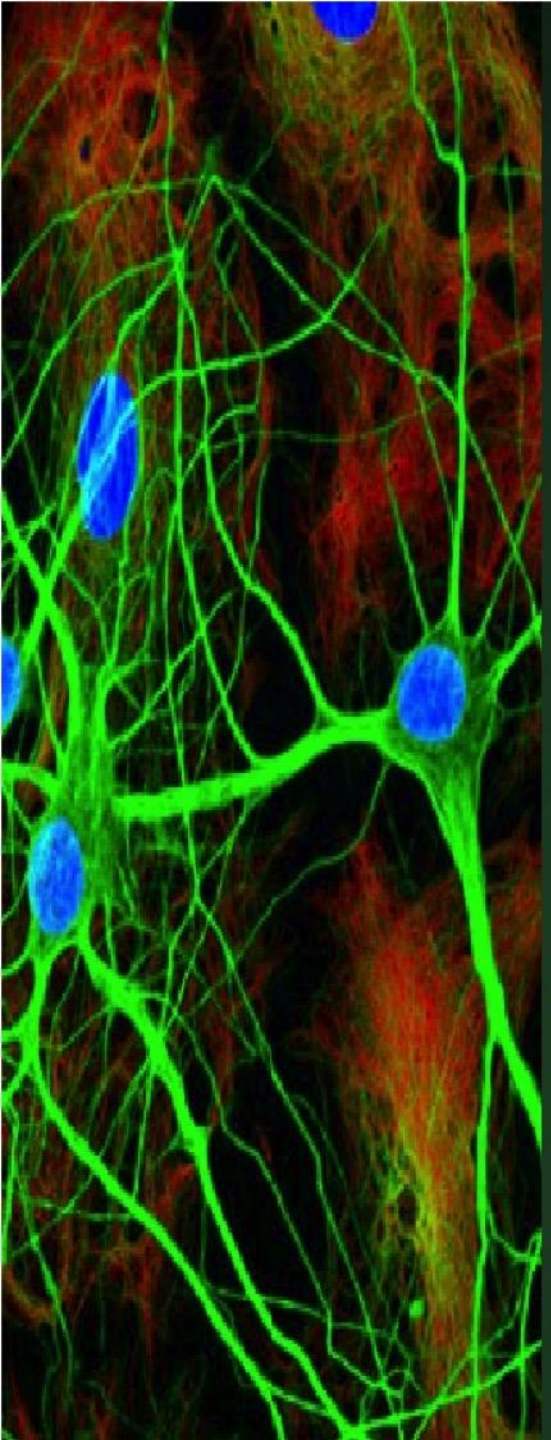
# Disclosure

- No conflict of interest to declare



# Critical Illness Neuropathy Objectives

- Discuss current relevance
- Discuss the spectrum of disorders
- Discuss diagnosis
- Implement preventive measures
- Be aware of the state of current evidence

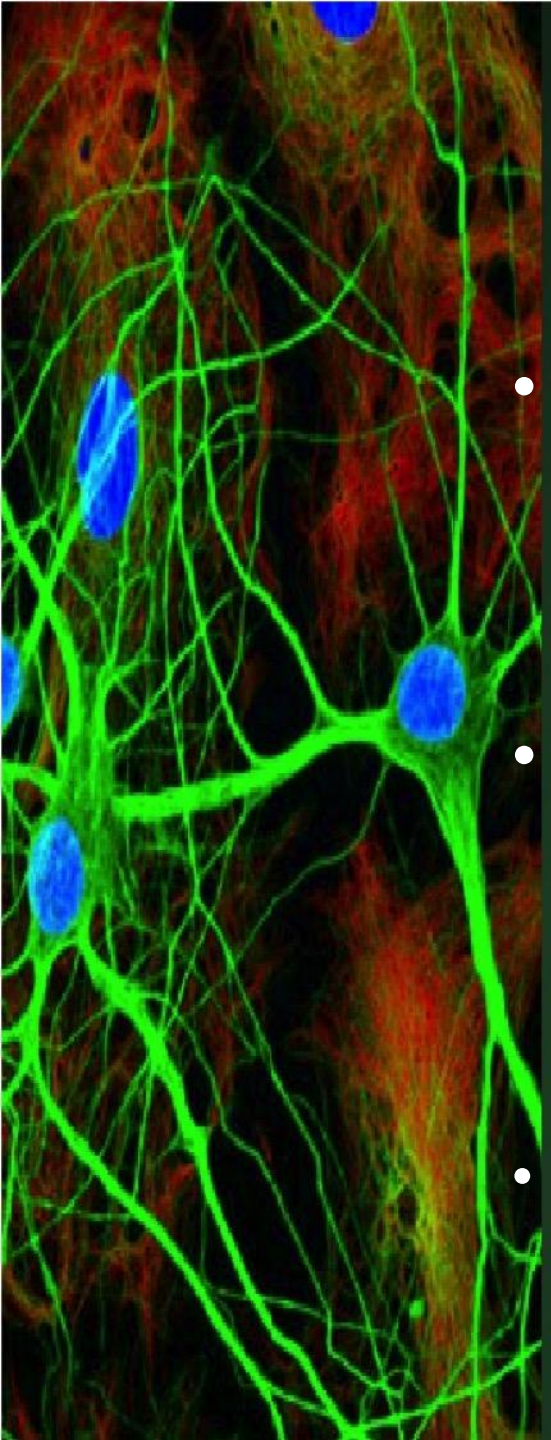


# History

- Osler (1892)
  "*Rapid loss of flesh"* in sepsis
- Bolton et al (1984)
  - ✓ CIN & CIM
- Maher et al (1995)
  - ✓ Common cause of failure to wean from ventilator

# Relevance of Critical Illness Neuropathy

- Common in ICU Patients
  - 21-74% of critically ill patients
- Increased Morbidity Mortality
  - Short term (in ICU & hospital) &
  - Long term (after discharge)
- Decreased Quality of Living
- Costly
  - Leads to prolonged ICU stay, prolonged hospitalization
  - Prolonged and incomplete post-ICU rehabilitation



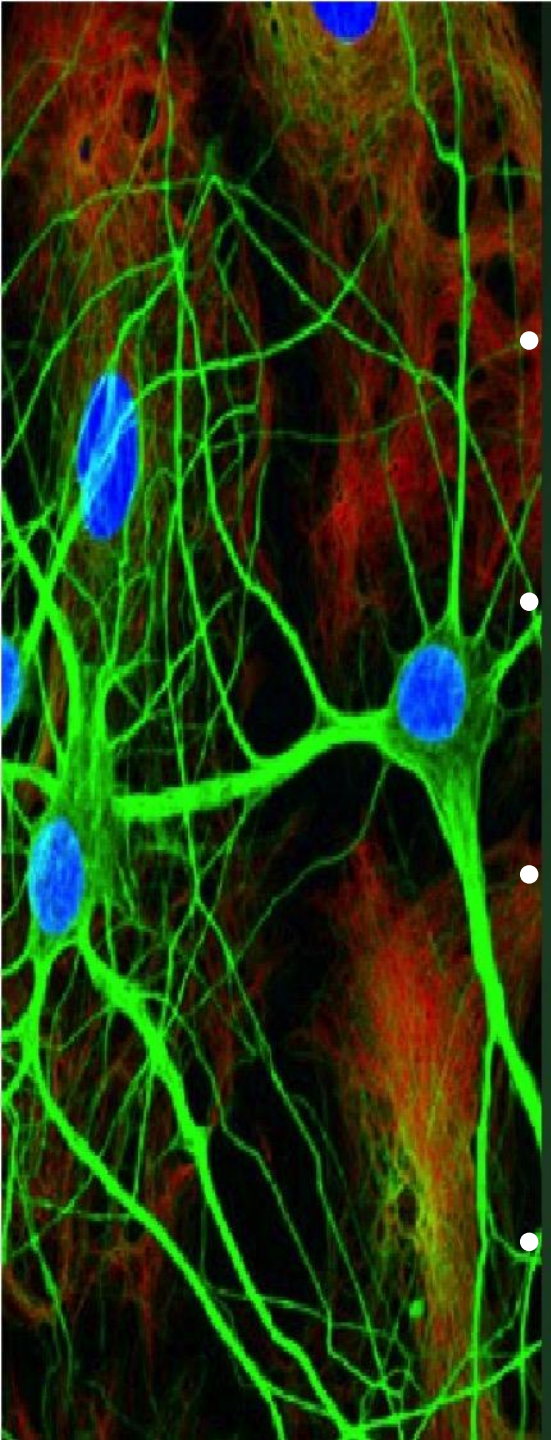
# Prevalence

- Estimates only, due to variability in
  - ✓ Diagnostic criteria
  - ✓ Patient populations studied
- Adults in ICU > 2 weeks
  - ✓ mechanical ventilation & sepsis or multi-organ failure:
    - 43-49%*

* Stevens RD et al. (2007). *Neuromuscular dysfunction acquired in critical illness: a systematic review.* Intens Care Med. 33: 1876-91.

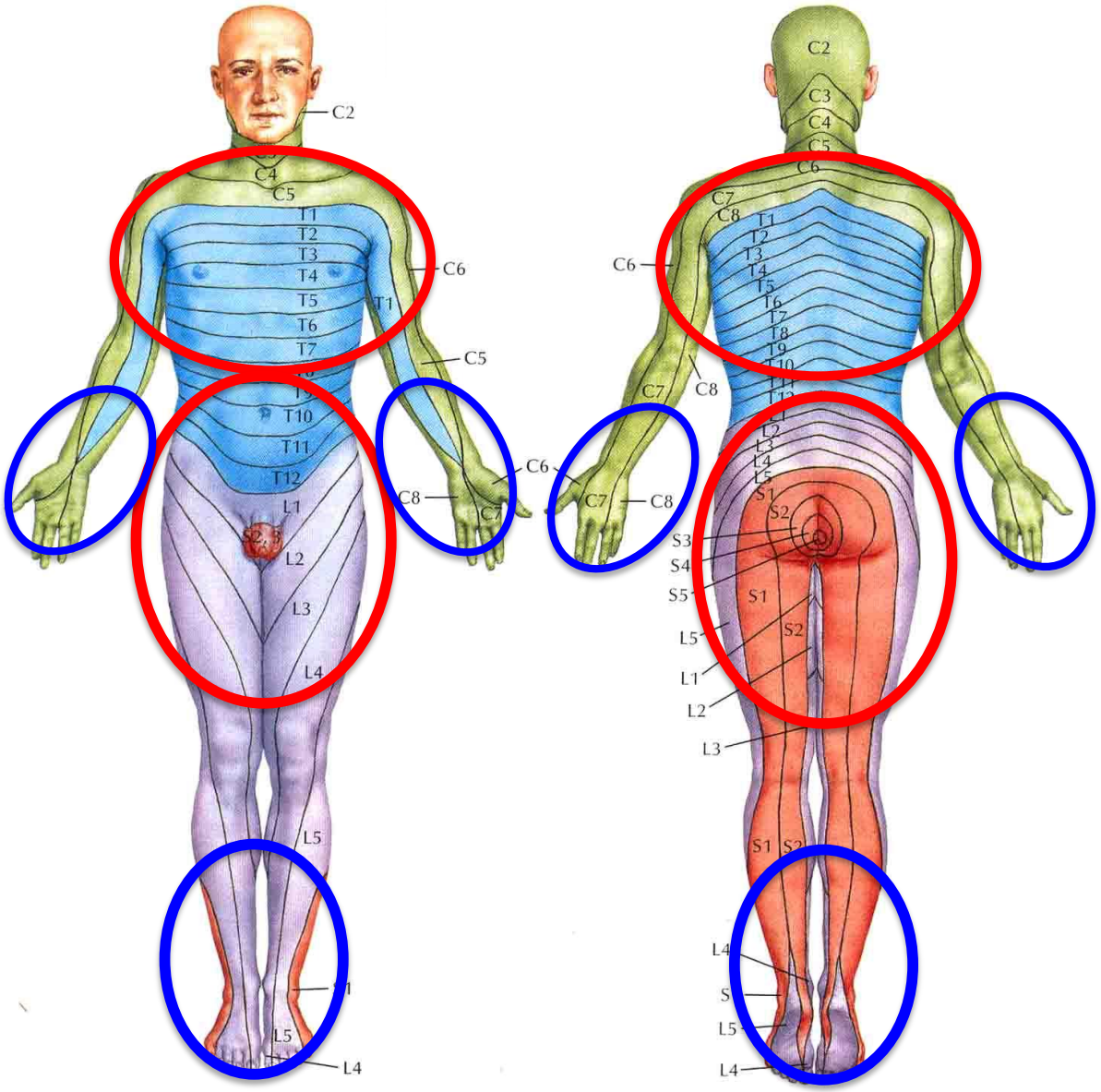
- A review paper 21-74% of ICU patients**

** Farhan H et al. (2015). *Acquired muscle weakness in the surgical intensive care unit: Nosology, epidemiology, diagnosis and prevention.* Anaethesiology 124:1, 207-34.



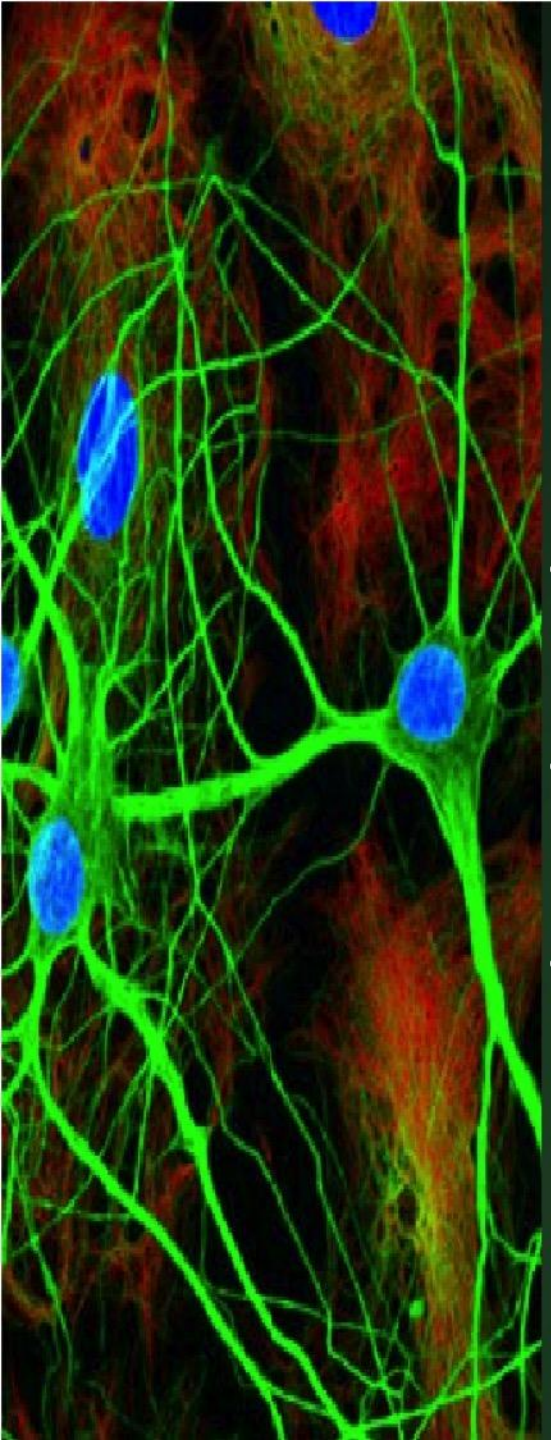
# Definitions

- Critical Illness Polyneuropathy (CIP)
  - ✓ Limb & respiratory weakness
  - ✓ Failure to wean off mechanical ventilation
- Critical Illness Myopathy (CIM)
  - ✓ Primary myopathy (proximal > distal)
  - ✓ Sensory preservation, atrophy
- Critical Illness Polymyoneuropathy (CIPMN) or CI Neuromyopathy (CINM)
  - ✓ Combination weakness & sensory loss
  - ✓ Distal > proximal
- Intensive Care Unit Acquired Weakness (ICUAW)



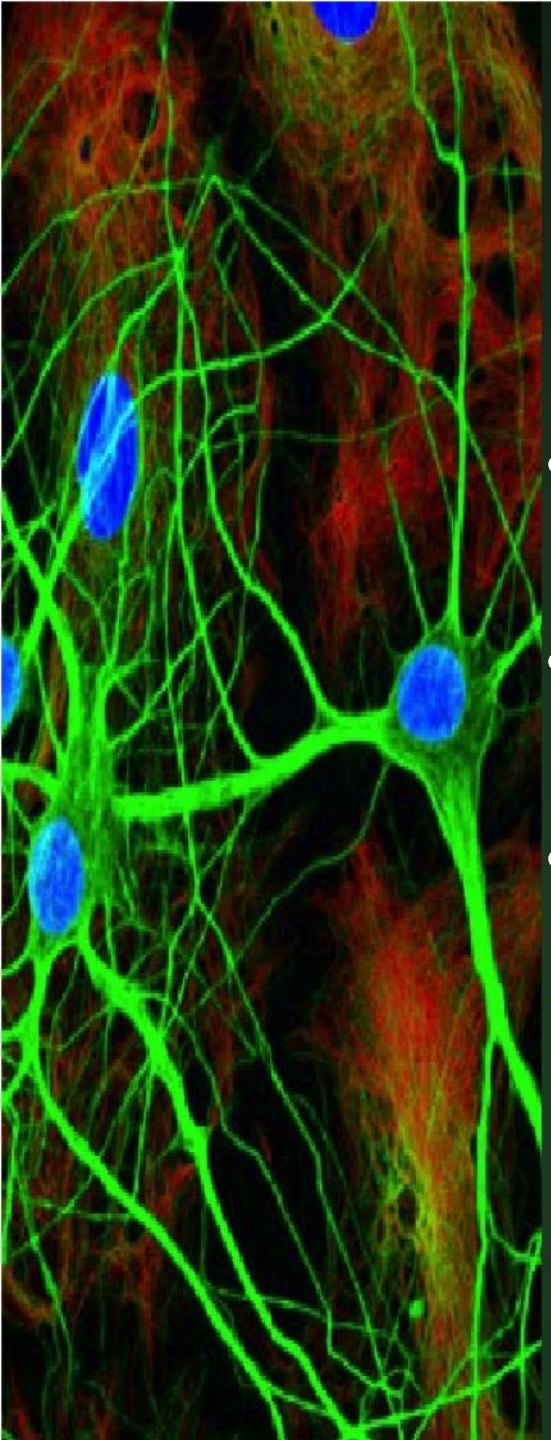

CI Mypoathy – Proximal > distal

CI Polyneuropathy – Distal > proximal



# CIP (Polyneuropathy)

- Diffuse sensory & motor axonal neuropathy
- 50% of patients with severe sepsis & septic shock
- Onset variable 2 days – several weeks after onset of septic shock



# CIM (Myopathy)

- Diffuse inflammatory myopathy that involves muscles of limb and trunk
- Associated with severe sepsis & septic shock
- Also associated with prolonged periods of drug-induced neuromuscular paralysis, particularly if combined with
  - ✓ high dose corticosteroid therapy
  - ✓ status asthmaticus treated with high dose steroids

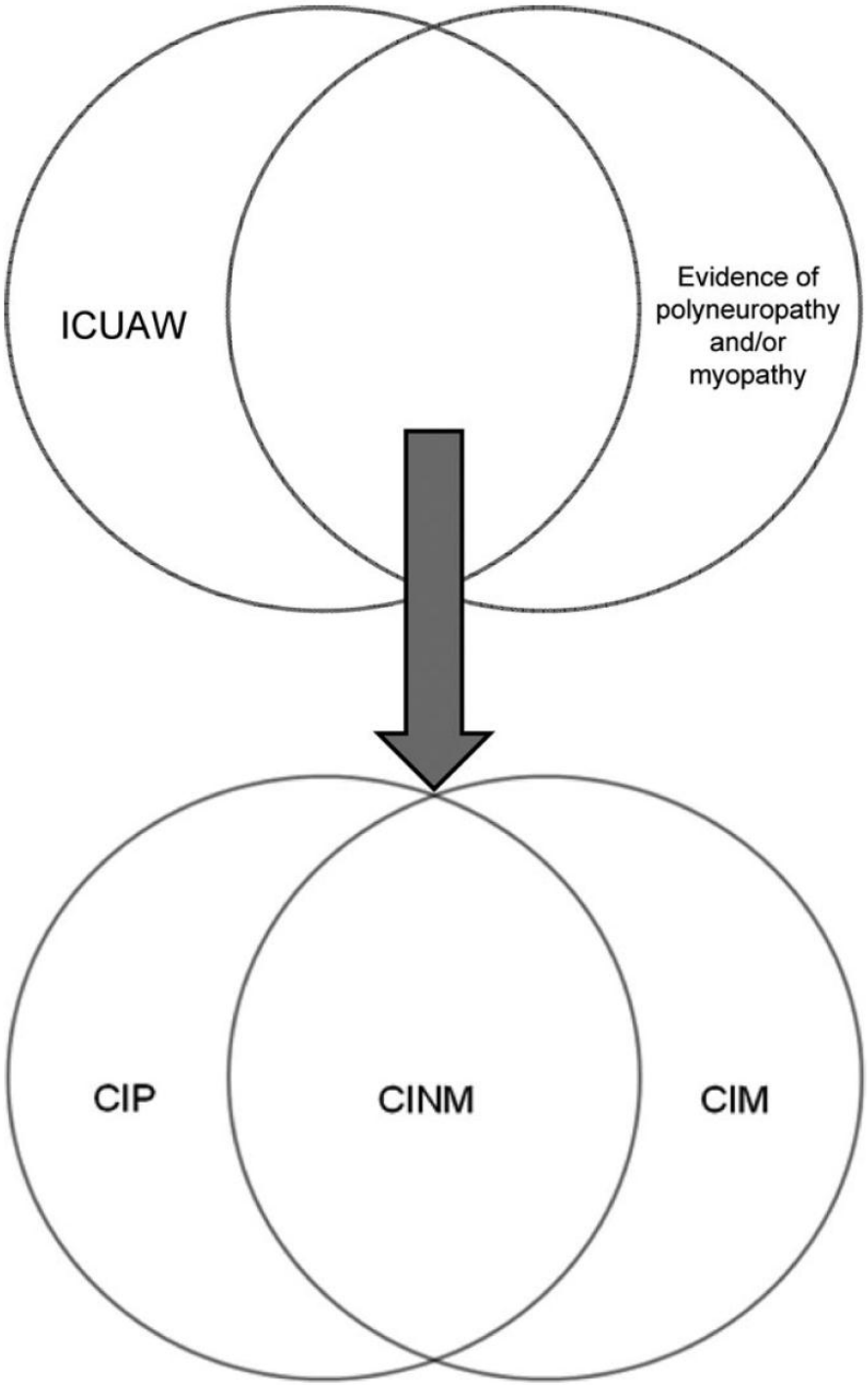
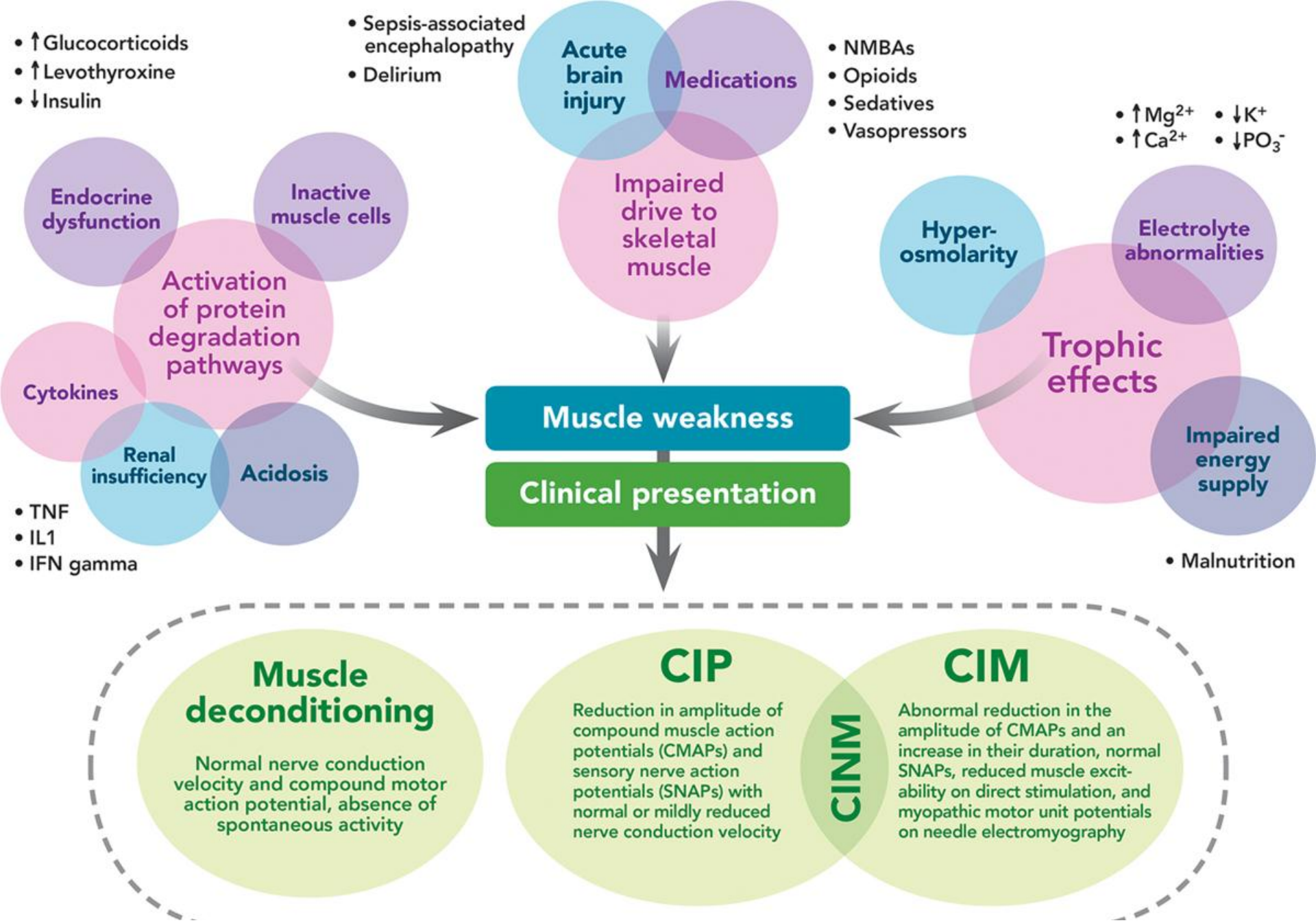
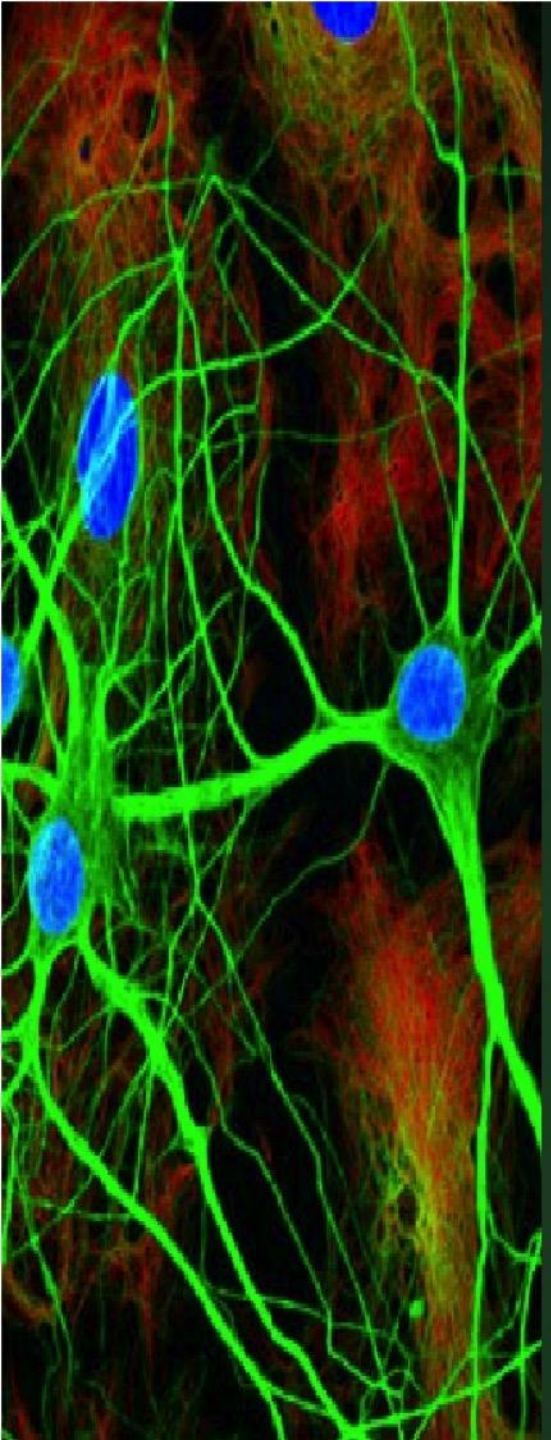



Figure 1. Classification of intensive care unit -acquired weakness (*ICUAW*). *CIP*, critical illness polyneuropathy; *CINM,* critical illness neuromyopathy; *CIM,* critical illness myopathy.

From: Stevens DR et al. (2009). *A framework for diagnosing and classifying intensive care unit-acquired weakness.* Crit Care Med, 37:10, S299-308.

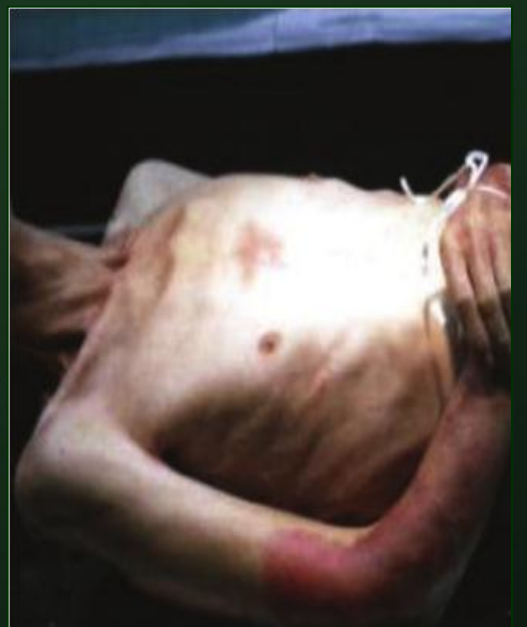



Farhan H et al. (2015). *Acquired muscle weakness in the surgical intensive care unit: Nosology, epidemiology, diagnosis and prevention.* Anaethesiology 124:1, 207-34.

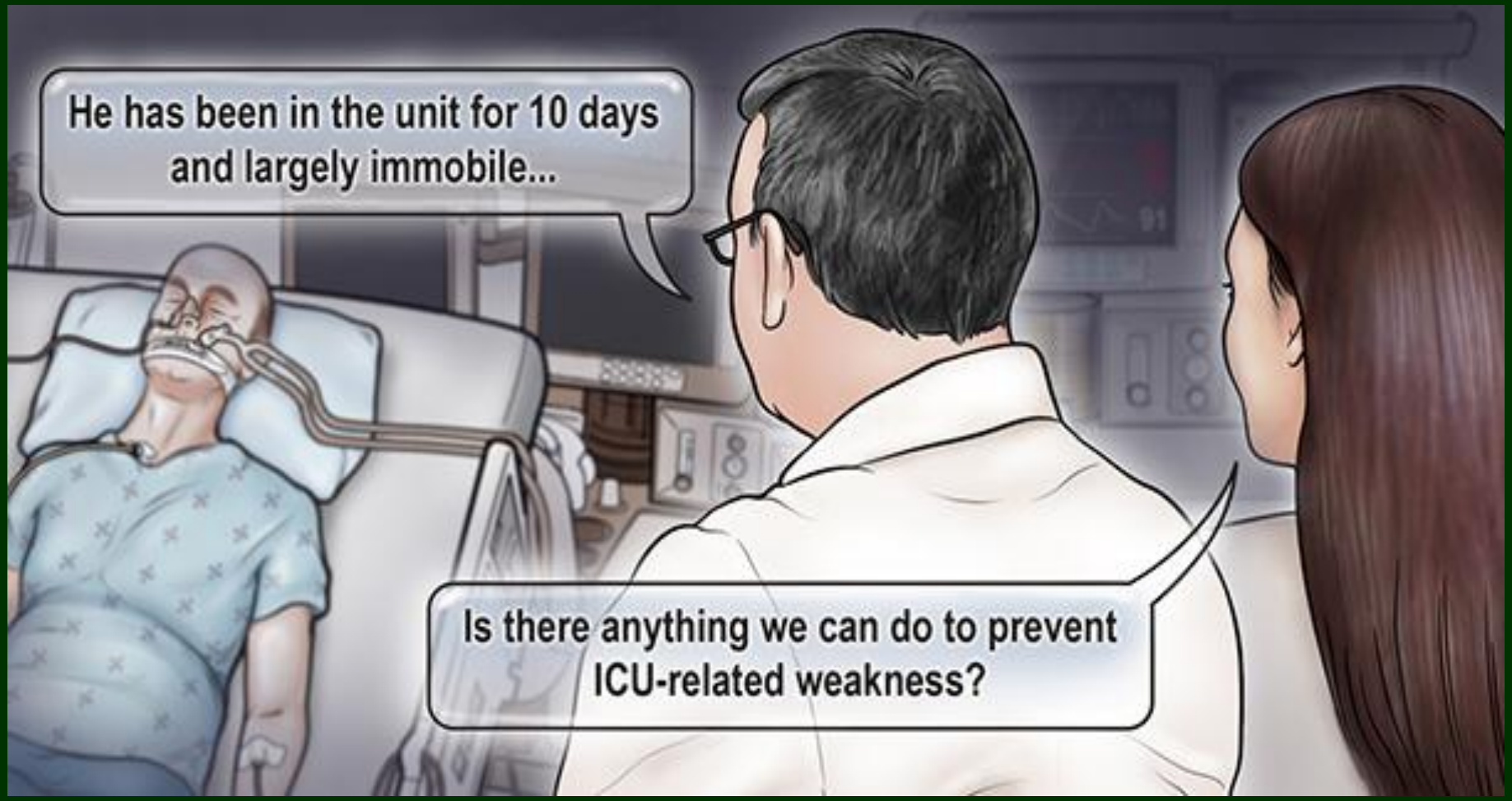


# Clinical Features

- Often undetected until there is an unexplained failure to wean off mechanical ventilation
- Physical exam:  flaccid paralysis with hypo- or a-reflexia

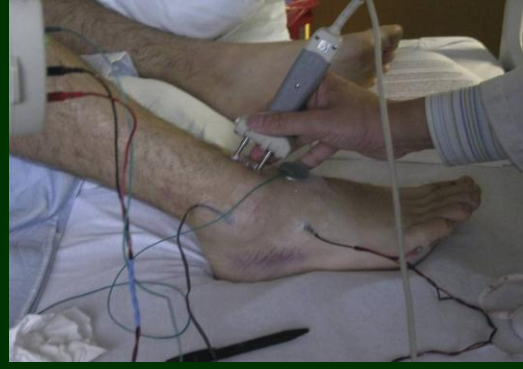


# What can be done?



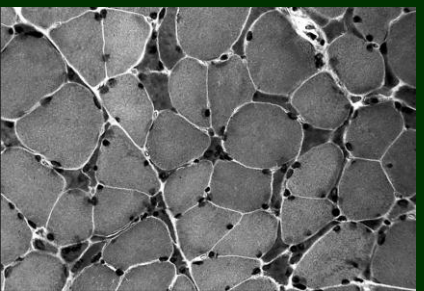

From NEJM Critical Care Challenge: ICU-acquired weakness and recovery from critical illness. doi/story/10.1056/feature.2014.04.15.26

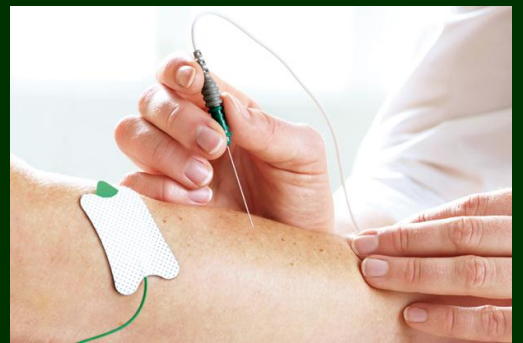
# Diagnosis

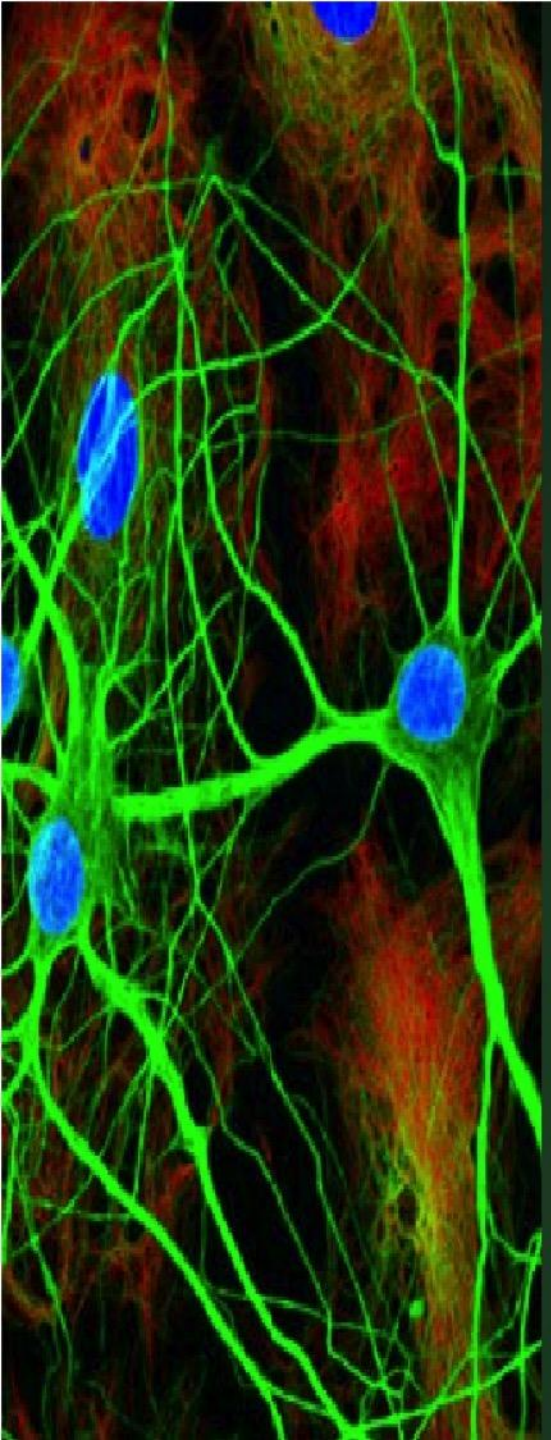


- ✓ CIP
  - nerve conduction studies: slowed conduction in sensory & motor fibres

- ✓ CIM
  - electromyography: myopathic changes
  - muscle biopsy: atrophy, loss of myosin fibrils & inflammatory infiltration







# Differential Diagnosis of Neuromuscular Weakness

Includes:

- Guillain – Barre syndrome
- Rhabdomyolysis
- Cachexic myopathy
- CIN and CIM

# Differential Diagnosis

**Table 1.** 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 |

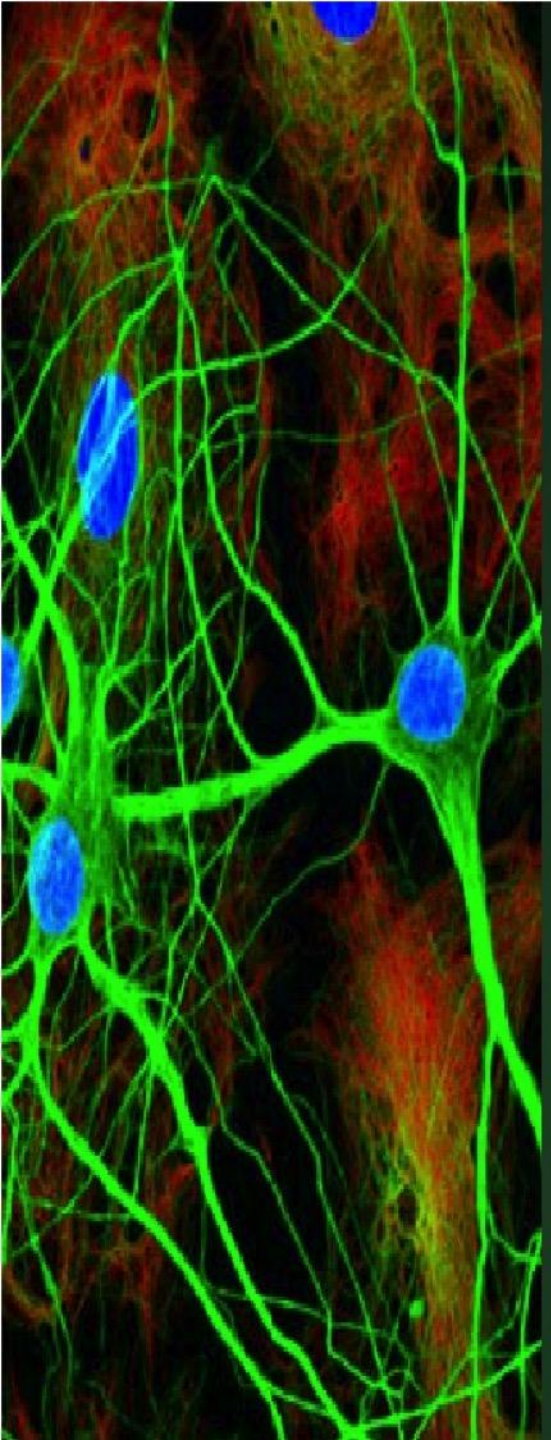
From: Shepherd S et al. (2017). *Review of Critical Illness Myopathy & Neuropathy.* The Neurohospitalist 7:1, 41-48. DOI: 10.1177/19441666329

# Diagnostic Criteria

**Table 2.** Suggested Diagnostic Criteria for Critical Illness Polyneuropathy and Critical Illness Myopathy.[a]

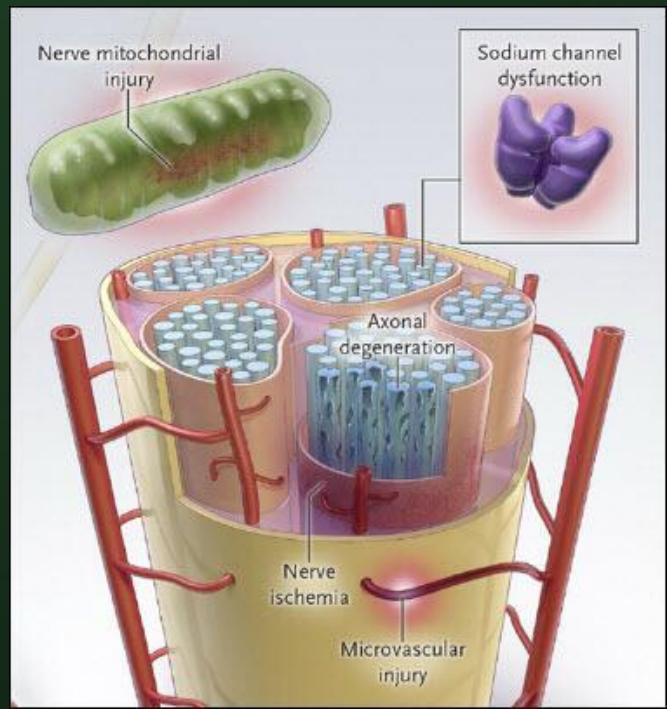
| CIP | CIM |
|---|---|
| Critically ill (sepsis and multi-organ failure) | Not required; typically exposed to variable combination of neuromuscular blocking agent and corticosteroids in the setting of sepsis and multi-organ failure |
| Limb weakness is present | Limb weakness is present |
| Difficulty 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<br>1. Axonal sensorimotor neuropathy | Electrophysiological evidence of<br>1. Preserved sensory response (>80% of lower limit of normal)<br>2. Reduced motor responses (compound muscle action potential <80% lower limit of normal)<br>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<br>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 |

Adaoted from Bolton CF. (2005). *Neuromuscular manifestations of* critical illness. Muscle Nerve: 32:140-63..
Latronico N, & Bolton CF. (2011). *Critical Illness polyneuropathy & myopathy: a major cause of muscle weakness and paralysis.* Lancet Neurol: 10:931-41.

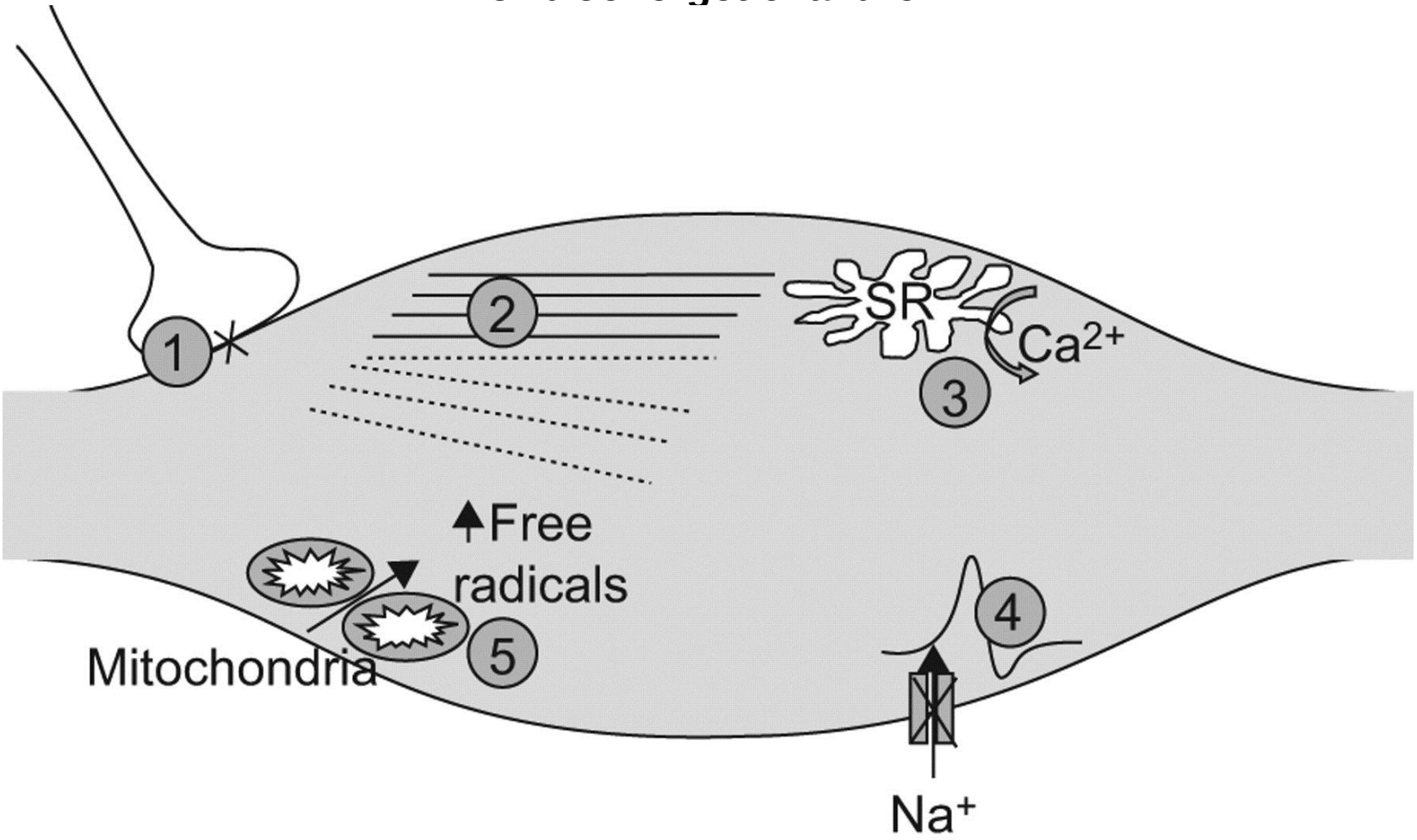


# Pathophysiology

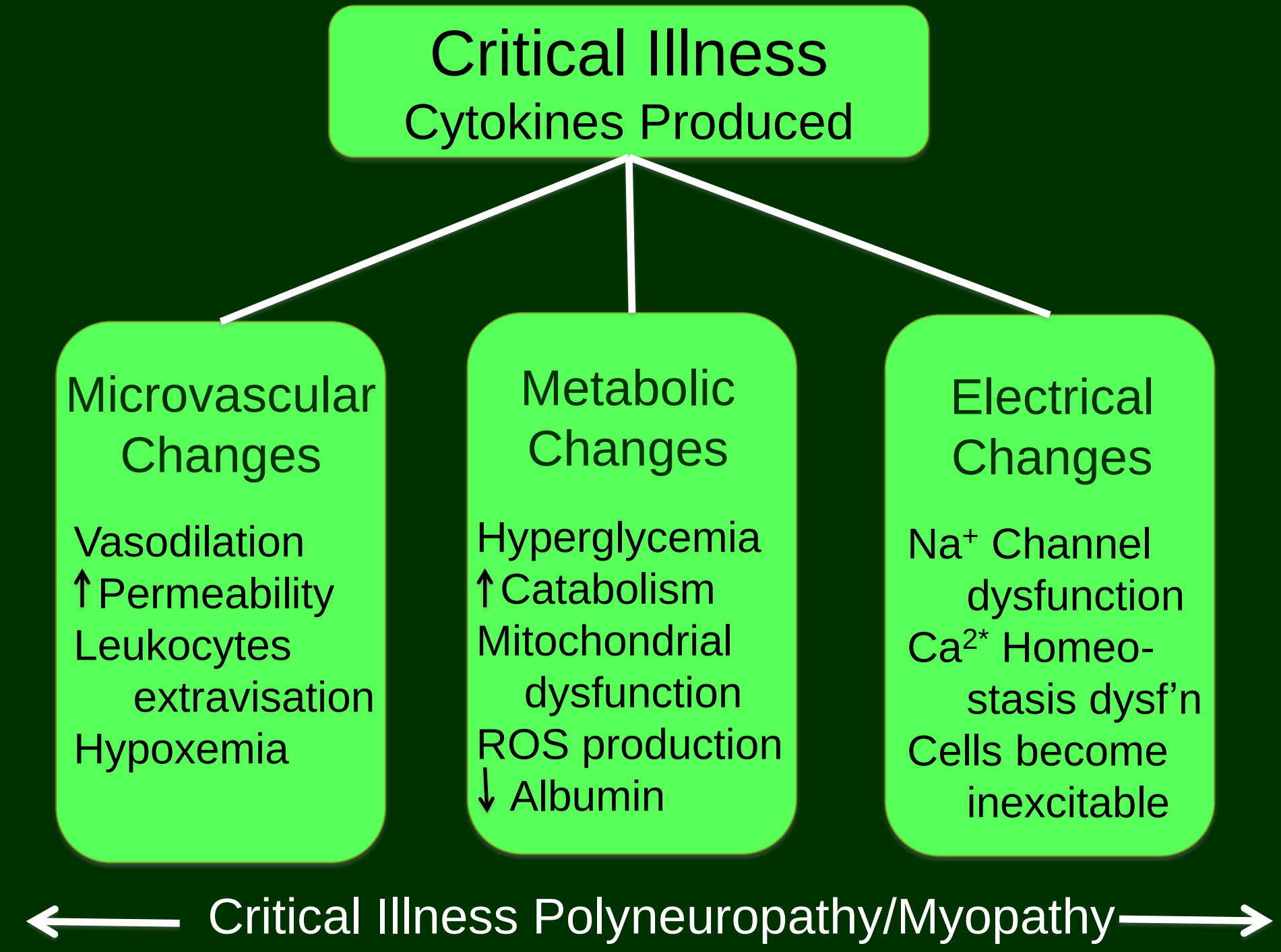
- Unclear
- Involves pathology in the following mechanisms:
  - ✓ Electrical
  - ✓ Microvascular
  - ✓ Metabolic
  - ✓ Bioenergetic

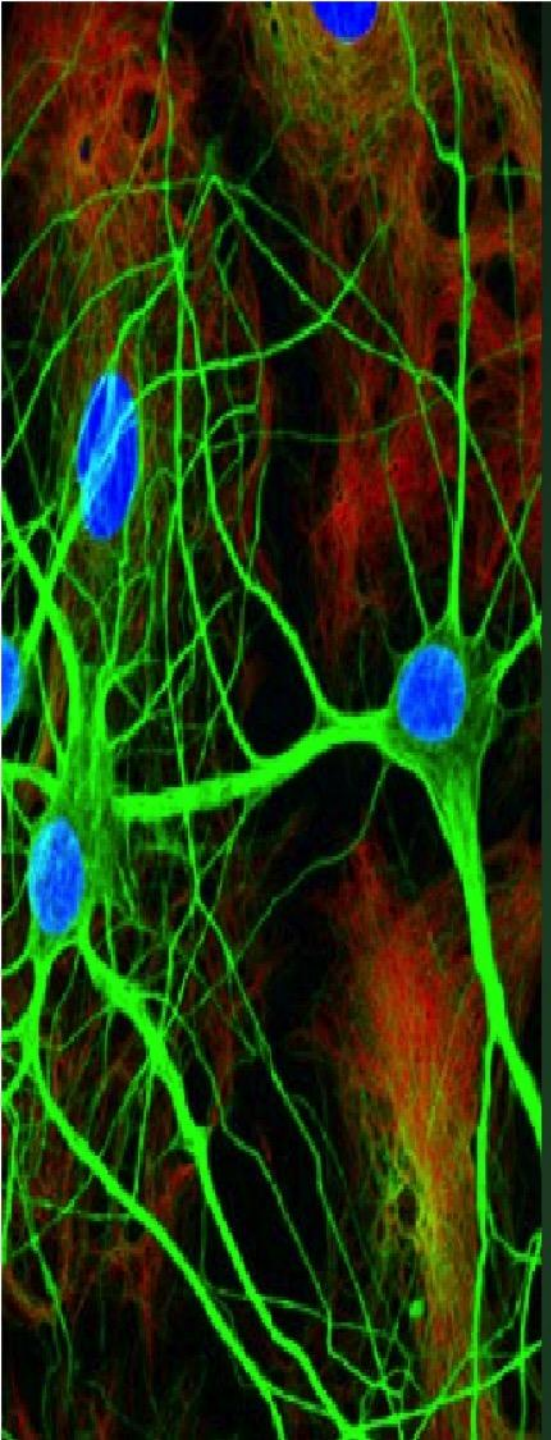


**Representation of potential mechanisms reducing the force-generating potential of skeletal muscle in intensive care unit-acquired weakness. 1: neuropathy; 2: altered myocyte structure and myofilament integrity; 3: sarcoplasmic reticulum (SR) dysfunction; 4: electrical inexcitability 5: bioenergetic failure**




Bloch S et al. Eur Respir J 2012;39:1000-1011

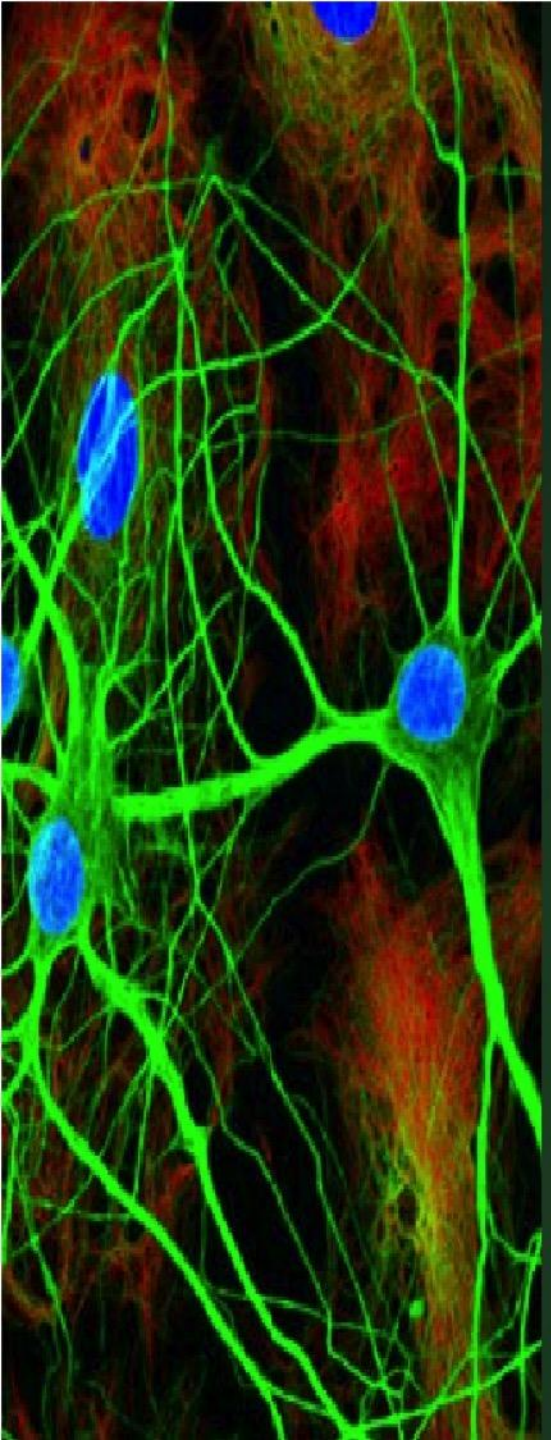

Critical Illness
Cytokines Produced
Microvascular Changes
Vasodilation
↑Permeability
Leukocytes extravisation
Hypoxemia
Metabolic Changes
Hyperglycemia
↑Catabolism
Mitochondrial dysfunction
ROS production
↓ Albumin
Electrical Changes
Na+ Channel dysfunction
Ca2* Homeo-stasis dysf'n
Cells become inexcitable
Critical Illness Polyneuropathy/Myopathy



# Impact

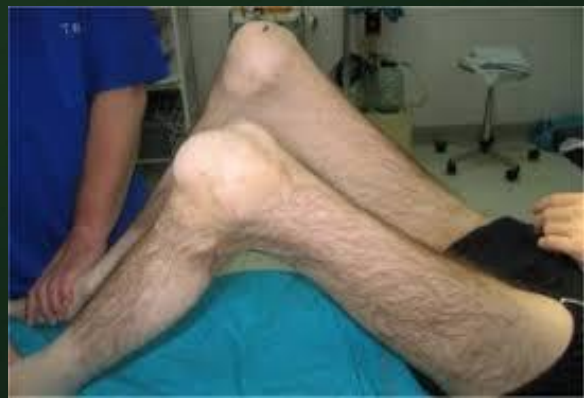
Depends on population

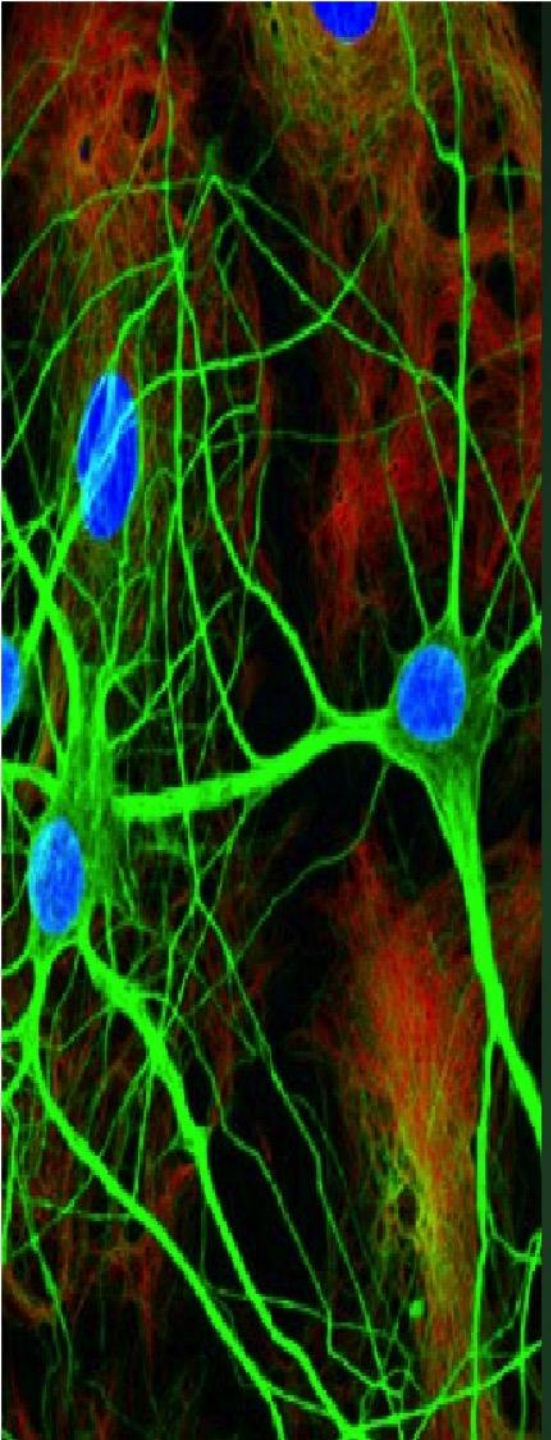
- If mild – can recover in weeks
- Full recovery in 50%
- 10% last > 1 year
- Some have long-term paresis



# Consequences

- Prolonged need for mechanical ventilation
- Longer ICU stay
- Longer hospital stay
- Slower rehabilitation
- Some may develop contractures





# Treatment?

1. Prevent Risk Factors whenever possible
   - ✓ Try to decrease ICU time
   - ✓ Wean off ventilator quickly
   - ✓ Aggressively treat sepsis, ARDS
   - ✓ Avoid hyperglycemia

2. Physical & Rehabilitation Therapy
   - ✓ There are guidelines, however there is limited high quality evidence

# A..B..C..D..E..F..G...For Post-ICU QOL

**A** **B** Awake and Breathing Coordination

**C** Choose light sedation & avoid benzos

**D** Delirium Monitoring & Management

**E** Early Mobility & Exercise

**F** Feeding & Early Adequate Protein

**G** Gain Function & Grow Muscle

From Wischmeyer PE & San Millan I. (2015). *Winning the war against ICU Acquired Weakness – New innovations in nutrition and fitness.* Critical Care, 19:S6

EUR J PHYS REHABIL MED 2015;51:655-61

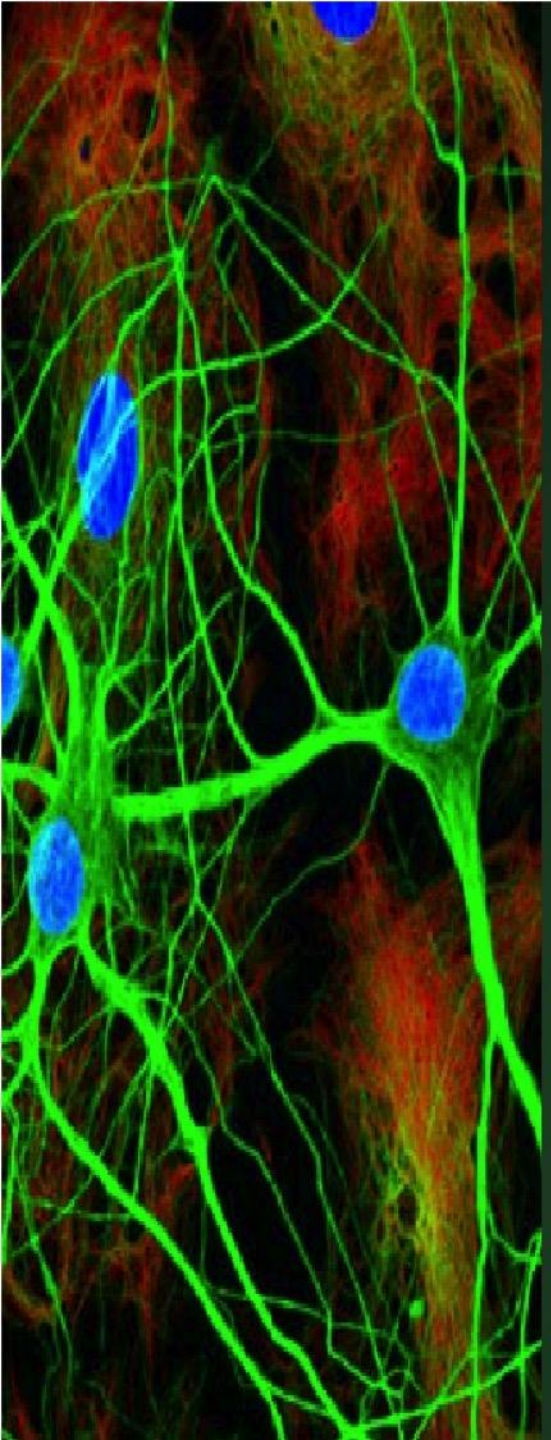
# Physical rehabilitation for critical illness myopathy and neuropathy: an abridged version of Cochrane Systematic Review

J. MEHRHOLZ [1, 2], M. POHL [3], J. KUGLER [2], J. BURRIDGE [4], S. MÜCKEL [1], B. ELSNER [2]

A systematic review:

- Does physical rehabilitation improve activities of daily living in patients with CIP & CIM?
- 3587 references >>….. 24……**0** RCTs
  - -22 didn't meet diagnostic criteria & 2 not RCTs

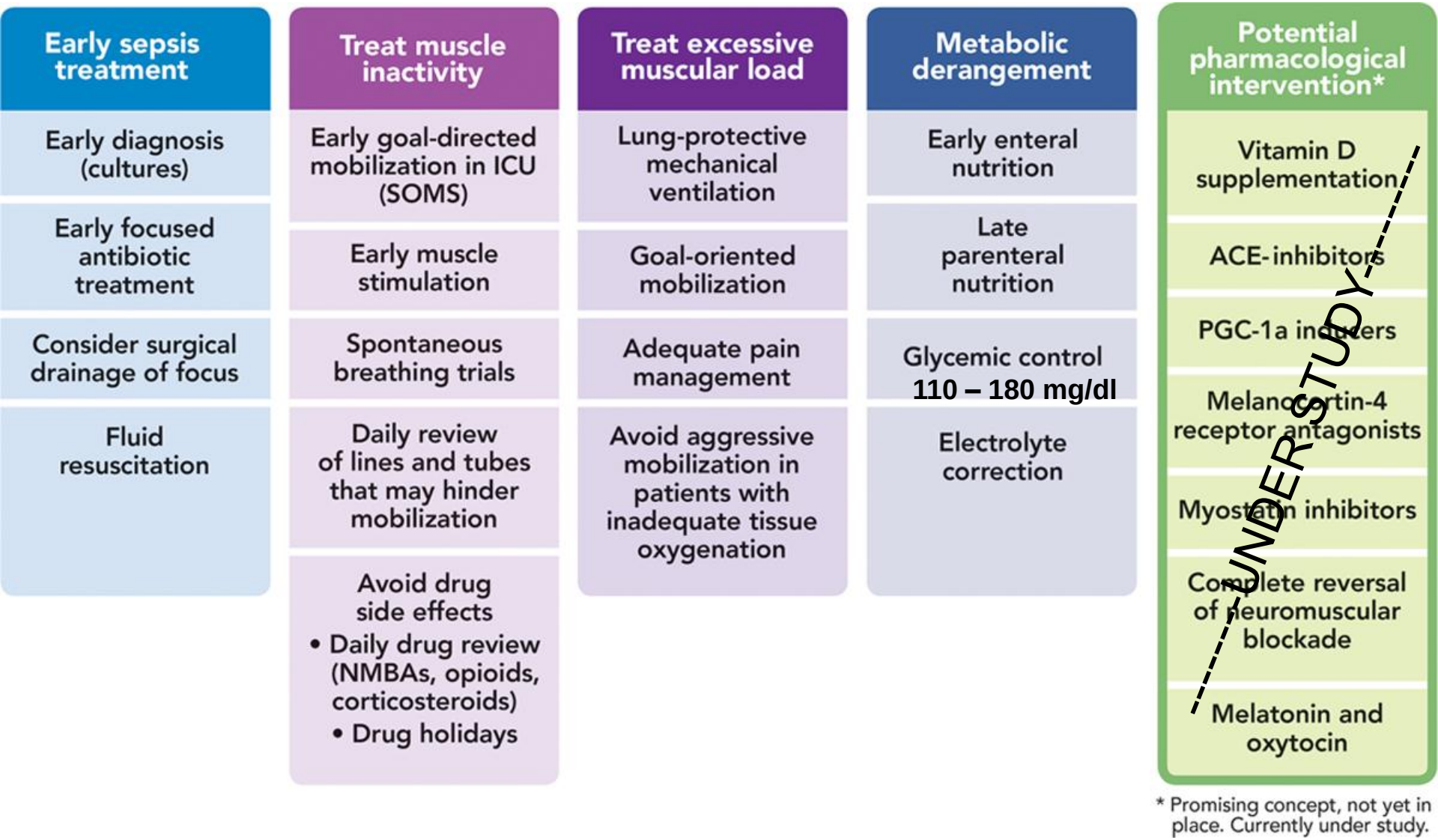
Mehrholz J et al. 2015. European Journal of Rehabilitation Medicine.
Based on a Cochrane Review, (CDSR) 2015. Issue 3
DOI: 10.1002/14651858.CD010942.pub2.



# Problems in rehab literature

- Populations variable
  - ✓ No defined CIP or CIM criteria
- Interventions
  - ✓ Cycling
  - ✓ Sit-to-stand training
  - ✓ Walking & gait training
  - ✓ Neuromuscular electrical vs usual therapy
  - ✓ Muscle strength training

# Prevention of ICU-acquired muscle weakness




Farhan H et al. (2015). *Acquired muscle weakness in the surgical intensive care unit: Nosology, epidemiology, diagnosis and prevention.* Anaethesiology 124:1, 207-34.

# Recommendations for Prevention of ICU-Acquired Weakness p.1

**Table 2.** Recommendations for Prevention of ICU-acquired Muscle Weakness

| | Study Design/ Sample Size | Setting | Intervention | Muscle Weakness | ICU LOS | Hospital LOS | Mechanical Ventilation (Duration or Weaning) | Mortality | Level* | Grade† |
|---|---|---|---|---|---|---|---|---|---|---|
| Aggressive treatment of sepsis | | | | | | | | | | |
| Ranieri *et al.*[200] | RCT/44 patients (37 completed) | Medical and surgical ICU | Protective (low tidal) mechanical ventilation *vs.* conventional | N/R | N/R | N/R | ↓ (8 d less)‡ | ↓ (38 *vs.* 58%) | B | IIA |
| Rivers *et al.*[201] | RCT/263 patients | Mostly medical patients, but also surgical | 6 h of early goal-directed therapy *vs.* standard therapy | N/R | N/R | No difference | No difference | ↓ (30.5 *vs.* 46.5%)‡ | B | |
| Eisner *et al.*[202] | RCT/902 patients | Medical and surgical patients | Protective (low tidal) mechanical ventilation *vs.* Conventional | N/R | N/R | N/R | Proportion of patients achieving unassisted breathing by day 28 (62 *vs.* 52%)‡ | ↓ (31 *vs.* 40%)‡ | B | |
| Trzeciak *et al.*[203] | Historical control trial/38 patients | Medical patients sent to ICU directly from ER | Early goal-directed therapy *vs.* standard therapy | N/R | ↓ (1.8 *vs.* 4.2 d) | ↓ (9 *vs.* 13 d) | N/R | ↓ (18.2 *vs.* 43.8%) | B | |
| Yealy *et al.*[134] | RCT/1341 patients | Mostly medical patients | Protocol-based early goal-directed therapy *vs.* protocol-based standard therapy *vs.* usual care | N/R | No difference | No difference | No difference | No difference | B | |
| ARISE Investigators; ANZICS Clinical Trials Group[204] | RCT/1600 patients | Medical patients sent to ICU directly from ER | Early goal-directed therapy *vs.* usual care | N/R | No difference | No difference | No difference | No difference | B | |
| Optimize the muscular load: early (< 48 h) mobilization | | | | | | | | | | |
| Kangas *et al.*[205] | RCT/50 patients | Surgical patients | Early movement of the ankle in a brace *vs.* Achilles tendon immobilization in tension using a below-knee cast with the ankle in a neutral position for 6 wk | Excellent to good isokinetic calf scores in the early movement group (56 *vs.* 29%) | N/R | N/R | N/R | N/R | B | IIA |
| Schweickert *et al.*[39] | Prospective RCT/104 | Medical ICU | Progressive physical and occupational therapy *vs.* standard physical therapy | ↓ (35 *vs.* 49%) | ↓ (5.9 *vs.* 7.9 days) | No difference | ↓ (3.4 *vs.* 6.1 days)‡ | ↓ (18 *vs.* 25 %) | B | |
| Burtin *et al.*[206] | Prospective RCT/90 | Medical and surgical ICU | Standard PT mobilization plus cycling exercise | Improved quadriceps force at hospital discharge‡ | No difference | ↓ (36 *vs.* 40 d) | No difference | ↓ (8 *vs.* 10%) | B | |
| Routsi *et al.*[42] | RCT/140 patients | Medical and surgical ICU | Electrical muscle stimulation to prevent CIPNM | MRC score improved (58 *vs.* 52)‡ | ↓ (14 *vs.* 22 d) | N/R | ↓ (1 *vs.* 3 d)‡ | No difference | B | |
| Keep the respiratory muscles moving | | | | | | | | | | |
| Spontaneous breaths during mechanical ventilation | | | | | | | | | | |
| Rathgeber *et al.*.[207] | Prospective controlled trial/596 patients | Surgical ICU | Biphasic positive airway pressure ventilation *vs.* synchronized intermittent mandatory ventilation *vs.* assist/controlled mandatory ventilation | N/R | N/R | N/R | ↓ (10.1 *vs.*14.7 *vs.* 13.2 h)‡ | N/R | B | IIA |

Farhan H et al. (2015). *Acquired muscle weakness in the surgical intensive care unit: Nosology, epidemiology, diagnosis and prevention.* Anaethesiology 124:1, 207-34.

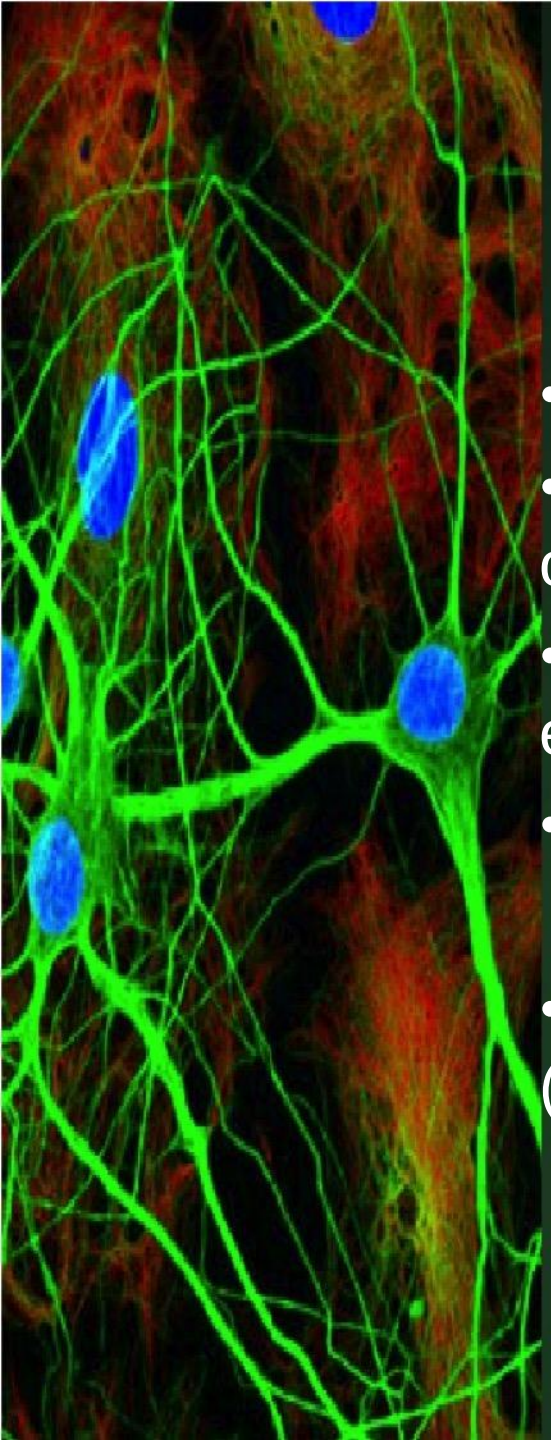
| | Study Design/ Sample Size | Setting | Intervention | Muscle Weakness | ICU LOS | Hospital LOS | Mechanical Ventilation (Duration or Weaning) | Mortality | Level* | Grade† |
|---|---|---|---|---|---|---|---|---|---|---|
| Putensen *et al.*[208] | RCT/30 patients | Trauma ICU | Airway pressure release ventilation with spontaneous breathing *vs.* pressure support controlled ventilation | N/R | ↓ (23 *vs.* 30 d)‡ | N/R | ↓ (15 *vs.* 21 d)‡ | No difference | B | |
| Protective mechanical ventilation | | | | | | | | | | |
| Amato *et al.*[209] | RCT/53 patients | Medical and surgical ICU | Protective (low tidal) mechanical ventilation *vs.* conventional | N/R | N/R | N/R | Early weaning (66 *vs.* 29%)‡ | ↓ (38 *vs.* 71 %)‡ | B | I |
| ARDS Network[210] | RCT/861 patients | Medical and surgical ICU | Protective (low tidal) mechanical ventilation *vs.* conventional | N/R | N/R | N/R | ↓ (2 d less)‡ | ↓ (31 *vs.* 39.8%)‡ | B | |
| Maxwell *et al.*[211] | RCT/63 patients | Surgical or trauma ICU | Low tidal volume ventilation *vs.* APRV | N/R | ↓ (14.18 *vs.* 16.47 d) | N/R | ↓ (8 *vs.* 10.49 d) | No difference | B | |
| Holiday periods | | | | | | | | | | |
| Kress *et al.*[212] | RCT/128 patients | Medical ICU | Daily interruption *vs.* standard interruption of sedative drug infusion | N/R | ↓ (3.5 d less)‡ | ↓ (13.3 *vs.* 16.9 d) | ↓ (4.9 *vs.* 7.3 d)‡ | ↓ (36 *vs.* 46.7%) | B | I |
| Girard *et al.*[66] | RCT/336 patients | Medical ICU | Daily spontaneous awakening trial followed by a spontaneous breathing trial *vs.* sedation per usual care plus a daily spontaneous breathing trial | N/R | ↓ (9.1 *vs.* 12.9 d)‡ | ↓ (14.9 *vs.* 19.2 d)‡ | Ventilator-free days within 28-d study period): ↑ (14.7 *vs.* 11.6 d; mean increase 3.1 d)‡ | ↓ (44 *vs.* 58%)‡ | B | |
| Robinson *et al.*[213] | RCT/143 patients | Surgical ICU | Daily interruption *vs.* standard interruption | N/R | ↓ (4.1 *vs.* 5.9 d) | ↓ (12 *vs.* 18 d)‡ | ↓ (1.2 *vs.* 3.2 d)‡ | ↓ (14.7 *vs.* 17.6%) | B | |
| Papazian *et al.*[41] | RCT/340 patients | Medical and surgical ICU | Short period of cisatracurium besylate *vs.* placebo | No difference | N/R | Days outside the ICU:↑ (47.7 *vs.* 33.5 d)‡ | Ventilator free days (at 90 d): ↑ (10.6 *vs.* 8.5 d)‡ | At 90 d: ↓ (30.8 *vs.* 44.6%)‡ | B | |
| Mehta *et al.*[214] | RCT/430 patients | Medical and surgical ICU | Protocolized sedation plus daily sedation interruption *vs.* protocolized sedation | N/R | No difference | No difference | In surgical and trauma patients: ↓ (6 *vs.* 13 d)‡ | N/R | B | |
| Optimal nutrition | | | | | | | | | | |
| Enteral nutrition | | | | | | | | | | |
| Singh *et al.*[215] | RCT/43 patients | Surgical ICU | Feeding jejunostomy from 12 h postoperatively *vs.* control | N/R | N/R | No difference | N/R | No difference | B | IIB |
| Marik and Zaloga[216] | Systematic review/15 RCT | Surgical or trauma ICU | Early *vs.* delayed enteral nutrition | N/R | N/R | ↓ (2.2 d less; in trauma/ head injury/ burn patients 4.04 d less)‡ | N/R | ↓ (8 *vs.* 11.5%) | B | |
| Minard *et al.*[217] | RCT/30 patients | Trauma ICU | Early *vs.* delayed enteral feedings | N/R | No difference | No difference | No difference | ↓ (8 *vs.* 27%)‡ | B | |

| | Study Design/ Sample Size | Setting | Intervention | Muscle Weakness | ICU LOS | Hospital LOS | Mechanical Ventilation (Duration or Weaning) | Mortality | Level* | Grade† |
|---|---|---|---|---|---|---|---|---|---|---|
| Lewis *et al.*[218] | Systematic review and metanalysis/ 837 patients | Surgical patients | Enteral feeding started within 24 h after surgery *vs.* nil by mouth management in elective gastrointestinal surgery | N/R | N/R | ↓ (10.4 *vs.* 12.9 d)‡ | N/R | ↓ (7 *vs.* 13%) | A | |
| Braunschweig *et al.*[219] | Metanalysis/ 27 studies; 1,828 patients | Medical and surgical patients | Parenteral nutrition *vs.* tube feeding *vs.* standard care | N/R | N/R | N/R | N/R | ↑ In standard of care | A | |
| Heyland *et al.*[220] | Systematic review/8 RCT | Medical and surgical ICU | Early *vs.* delayed enteral nutrition or intravenous fluids | N/R | No difference | No difference | N/R | ↓ (6.3 *vs.* 14.6%) | B | |
| Dvorak *et al.*[221] | RCT/23 patients (17 patients included in analysis) | Trauma ICU | Early *vs.* late enteral feeding | N/R | N/R | ↑ (53 *vs.* 37.9 d) | ↑ (763 *vs.* 502 h) | N/R | B | |
| Peck *et al.*[222] | RCT/95 patients eligible (data analyzed from 27 patients) | Trauma (burn) ICU | Early *vs.* late enteral feeding on postburn metabolism | N/R | ↑ (40 *vs.* 37 d) | No difference | ↑ (32 *vs.* 23 d) | ↓ (28 *vs.* 38%) | B | |
| Artinian *et al.*[223] | Retrospective cohort/4049 patients | Medical ICU | Early *vs.* delayed enteral nutrition | N/R | ↑ (10.9 *vs.* 10.2 d)‡ | N/R | No difference | ↓ (28.7 *vs.* 33.5%)‡ | C | |
| Harvey *et al.*[224] | RCT/2400 patients | Medical and surgical ICU | Parenteral *vs.* enteral nutrition | N/R | No difference | No difference | No difference | ↓ (33.1 *vs.* 34.2%) | B | |
| Parenteral nutrition | | | | | | | | | | |
| Casaer *et al.*[162] | RCT/4640 patients | ICU | Late *vs.* early parenteral nutrition | N/R | ↓ (3 *vs.* 4 d)‡ | ↓ (14 *vs.* 16 d)‡ | Requiring > 2 d of mechanical ventilation: ↓ (36.3 *vs.* 40.2%)‡ | No difference | B | IIB |
| Hermans *et al.*[131] | RCT/600 patients | Mostly surgical but also medical ICU | Late *vs.* early parenteral nutrition | ↓ (34 *vs.* 43 %)‡ | ↓ (11 *vs.* 13 d)‡ | ↓ (27 *vs.* 32 d) | ↓ (6 *vs.* 7 d) | ↑ (11 *vs.* 9%) | B | |
| Heidegger *et al.*[164] | RCT/305 patients | Surgical and medical ICU | Supplemental parenteral nutrition with enteral nutrition *vs.* enteral nutrition alone from day 4 to 8 in the ICU | N/R | No difference | No difference | No difference | ↓ (13 *vs.* 18%) | B | |
| Doig *et al.*[225] | RCT/1,372 patients | Surgical and medical ICU | Early parenteral nutrition within 24 h after ICU admission *vs.* standard therapy | N/R | ↓ (8.6 *vs.* 9.3 d) | No difference | ↓(7.26 *vs.* 7.73 d per 10 patient × ICU days)‡ | ↓ (21.5 *vs.* 22.8%) | B | |
| Tight glycemic control | | | | | | | | | | |
| van den Berghe *et al.*[193] | RCT/1548 patients (preplanned subanalysis of patients still in ICU on day 7: 405 patients) | Surgical ICU | Intensive insulin therapy *vs.* conventional management | ↓ (25 *vs.* 49%)‡ | ↓ (14 *vs.* 15 d)‡ | N/R | ↓ (11 *vs.* 13 d)‡ | ↓ (12 *vs.* 21%)‡ | B | III |

| | Study Design/ Sample Size | Setting | Intervention | Muscle Weakness | ICU LOS | Hospital LOS | Mechanical Ventilation (Duration or Weaning) | Mortality | Level* | Grade† |
|---|---|---|---|---|---|---|---|---|---|---|
| Brunkhorst *et al.*[226] | RCT/537 | Medical and surgical ICU | Intensive insulin therapy *vs.* conventional management | N/R | ↑ (16 *vs.* 14 d) | N/R | No difference | ↑ (39.7 *vs.* 35.4%) | B | |
| Wiener *et al.*[227] | Meta-analysis/ 34 trials; 29 RCTs contributed data | Medical and surgical ICU | Intensive insulin therapy *vs.* conventional management | N/R | N/R | N/R | N/R | ↓ (21.6 *vs.* 23.3%) | A | |
| Griesdale *et al.*[228] | Meta-analysis/26 trials | 6 trials in medical ICU | Intensive insulin therapy *vs.* conventional management | N/R | N/R | N/R | N/R | ↓ in the surgical ICU,‡not in the others | A | |
| Finfer *et al.*[229] | RCT/6104 patients | Medical and surgical ICU | Intensive insulin therapy *vs.* conventional management | N/R | No difference | No difference | No difference | ↑ (27.5 *vs.* 24.9%)‡ | B | |
| Preiser *et al.*[230] | RCT/1101 | Medical and surgical ICU | Intensive insulin therapy *vs.* conventional management | N/R | No difference | No difference | No difference | ↑ (17.2 *vs.* 15.3%) | B | |
| Marik and Preiser[231] | Systematic review + meta-analysis/7 trials | Medical and surgical ICU | Impact of tight glycemic control | N/R | N/R | N/R | N/R | No difference | A | |
| Kansagara *et al.*[232] | Systematic review/21 trials | Medical and surgical ICU | Benefits and harms of IIT in hospitalized patients | N/R | ↓ (1.484 d less) in the surgical ICU | No difference | N/R | No difference | A | |
| Hermans *et al.*[43] | Systematic review/2 trials | Medical and surgical ICU | IIT on incidence of CIM/CIP | ↓‡ | ↓ (1.48 d less)‡ | N/R | ↓ (2 d less)‡ | No difference | A | |

* American Heart Association levels of evidence: A (multiple populations evaluated, data derived from multiple randomized clinical trials or meta-analyses), B (limited populations evaluated, data derived from a single randomized clinical trial or nonrandomized studies), and C (very limited populations evaluated, only consensus opinion of experts, case studies, or standard of care). † Recommendation: I (benefits greatly surpass risks, procedure/treatment should be performed or administered), IIA (benefits surpass risks, additional focused studies needed, it is reasonable to perform procedure/treatment), IIB (benefit surpasses risks, additional studies with broad objectives needed, procedure/treatment may be considered), and III (risks surpasses benefit, procedure/treatment should not be performed. ‡ Statistically significant.

APRV = airway pressure release ventilation; ARDS = acute respiratory distress syndrome; ARISE = Australasian Resuscitation in Sepsis Evaluation; CIM = critical illness myopathy; CIP = critical illness polyneuropathy; CIPNM = critical illness polyneuropathy and myopathy; ER = emergency room; ICU = intensive care unit; IIT = intensive insulin therapy; LOS = length of stay; MRC = Medical Research Council Scale for muscle strength; N/R = not reported; PT = physical therapy; RCT = randomized controlled trial.



# Summary of Interventions

- Aggressive treatment of underlying problem
- Minimize paralytic agents, sedation & duration of mechanical ventilation
- Institute early active & passive mobilization even during mechanical ventilation
- Optimize nutrition
  - enteral early, parenteral later
- Target glycemic levels 110-180 mg/dl (140 target)
  - not “tight” 80-110mg/dl


Thank you!
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