ICU-ACQUIRED WEAKNESS

X. Wittebole
Critical Care Department

Cliniques universitaires
SAINT-LUC
UCL BRUXELLES

INTRODUCTION

- 1915: Sr W. OSLER – The Principles of Medicine – VIIIth Edition
  « Neuromuscular Dysfunction in patients with sepsis »

LESIONS OF PERIPHERAL NERVES DEVELOPING DURING COMA

Clarence W. Olsen, M.D., Beverly Hills, Calif.

Olsen CW. J Am Med Assoc.1956; 160(1):39-41

SEVERE MYOPATHY AFTER STATUS ASTHMATICUS

MacFarlane IA et al. Lancet.1977; 2(8038):615

Polyneuropathy in critically ill patients

CHARLES F BOLTON, JOSEPH J GILBERT, ANGELIKA F HAHN, WILLIAM J SIBBALD

Bolton CF et al. J Neurol Neurosurg Psychiatry.1985; 47(11):1223-31

INTRODUCTION

Table 1. Terms used for critical illness neuromuscular disorders

Terms	References
Myopathic syndromes	
Thick filament myopathy	Danon 1991 (14)
Acute corticosteroid- and pancuronium-associated myopathy	Sitwell 1991 (118)
Acute quadriplegic myopathy	Hirano 1992 (6)
Acute necrotizing myopathy of intensive care	Zochodne 1994 (10)
Acute corticosteroid myopathy	Hanson 1997 (108)
Critical illness myopathy	Lacomis 2000 (15)
Polyneuropathic syndromes	
Polyneuropathy in critically ill patients	Bolton 1984 (16)
Critically ill polyneuropathy	Bolton 1986 (17)
Critical illness polyneuropathy	Zochodne 1987 (18)
Critical illness neuropathy	Coakley 1992 (119)
Mixed or undifferentiated syndromes	
Critical illness polyneuromyopathy	Op de Coul 1991 (75)
ICU-acquired weakness	Ramsay 1993 (9)
Critical illness myopathy and/or neuropathy	Latronico 1996 (12)
Critical illness neuromuscular abnormalities	De Jonghe 1998 (76)
ICU-acquired paresis	De Jonghe 2002 (30)
Critical illness neuromyopathy	Young 2004 (120)
Critical illness neuromuscular syndromes	De Jonghe 2006 (96)
Intensive care unit-acquired neuromyopathy	Hough 2009 (121)

Stevens RD et al. Crit Care Med.2009; 37: S299-S308

INTRODUCTION

DEFINITION:

ICU-acquired weakness designates clinically detected weakness in critically ill patients in whom there is no plausible etiology other than critical illness.

⇨ 3 sub-categories

Stevens RD et al. Crit Care Med.2009; 37: S299-S308

INTRODUCTION

3 DISTINCT FORMS:

- **CRITICAL ILLNESS POLYNEUROPATHY**
  - Affects the limbs (particularly lower extremities)
  - Symetric pattern
  - Weakness is most notable in proximal neuromuscular areas
  - Facial and ocular muscles are rarely involved
  - No demyelination (≠ Guillain-Barré)

- **CRITICAL ILLNESS MYOPATHY**
  - Primary myopathy
  - Difficult to distinguish from CIP by means of a bedside examination

INTRODUCTION

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- **MIXED**

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INTRODUCTION

2 DISTINCT FORMS:

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- **CRITICAL ILLNESS MYOPATHY**
    - Primary myopathy
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- **VENTILATOR INDUCED DIAPHRAGMATIC DYSFUNCTION (VIDD)**
    - Involvement of the respiratory muscles

INTRODUCTION

HOW TO TRANSLATE ?

- Polyneuropathie des soins intensifs ???
- Myopathie des soins intensifs ???

INTRODUCTION

HOW TO TRANSLATE ?

- Polyneuropathie des soins intensifs ???
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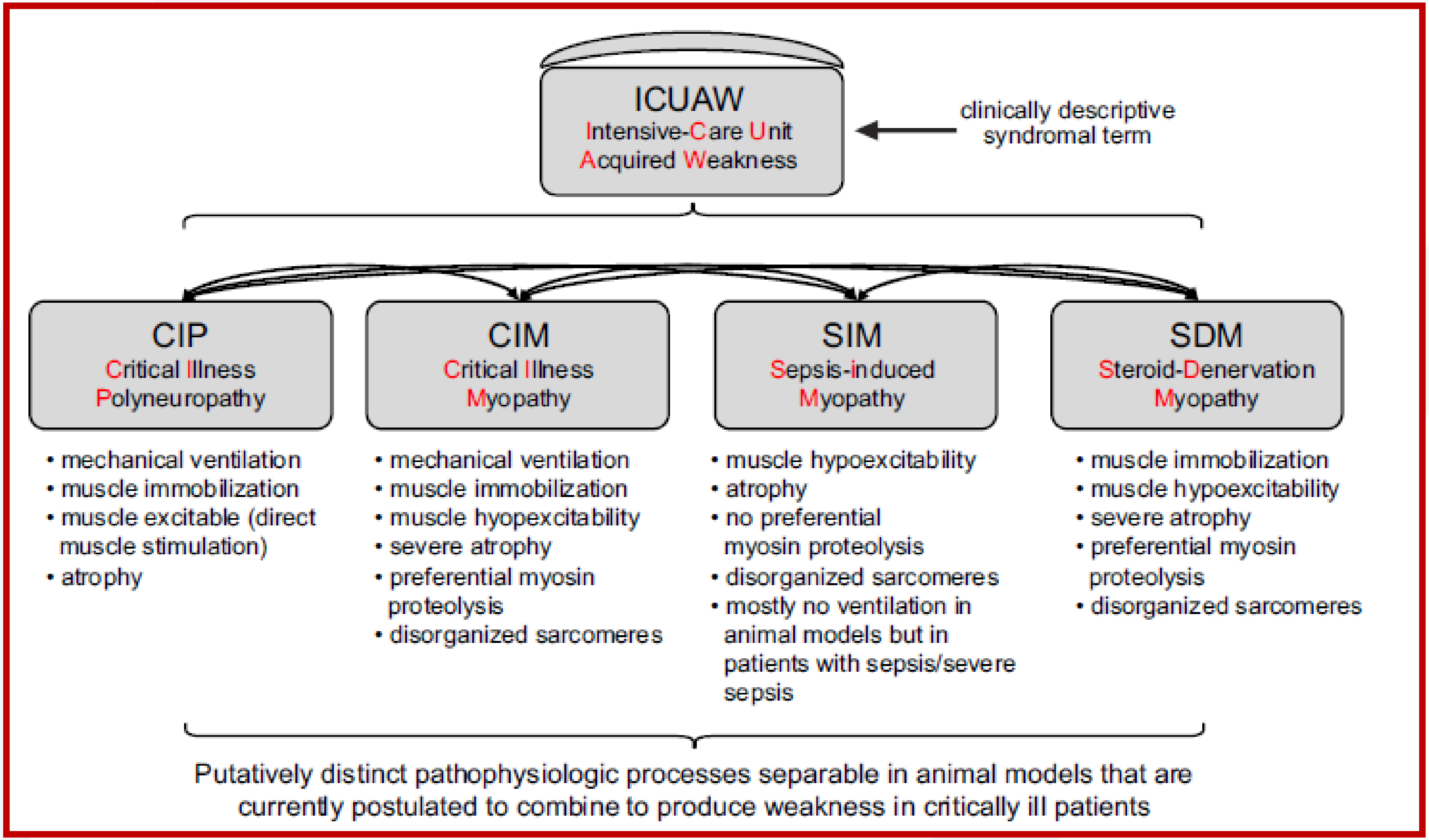
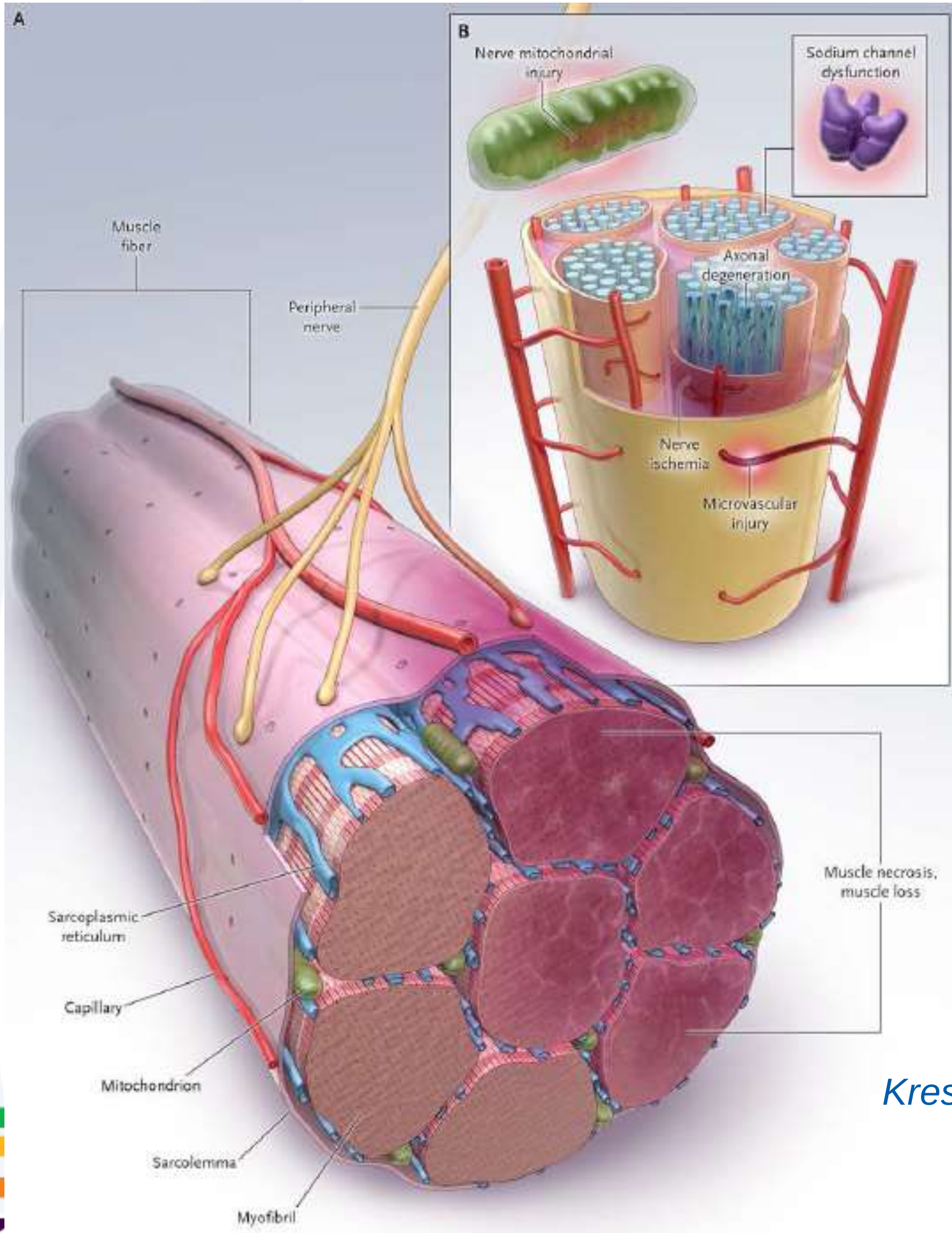
- Critical Illness Polyneuropathy
- Critical Illness Myopathy

NEURO- ou MYOPATHIE
DU PATIENT CRITIQUE



Friedrich O et al. Physiol Rev.2015; 95:1025-1109



NERVE:

Polyneuropathy with axonal degeneration

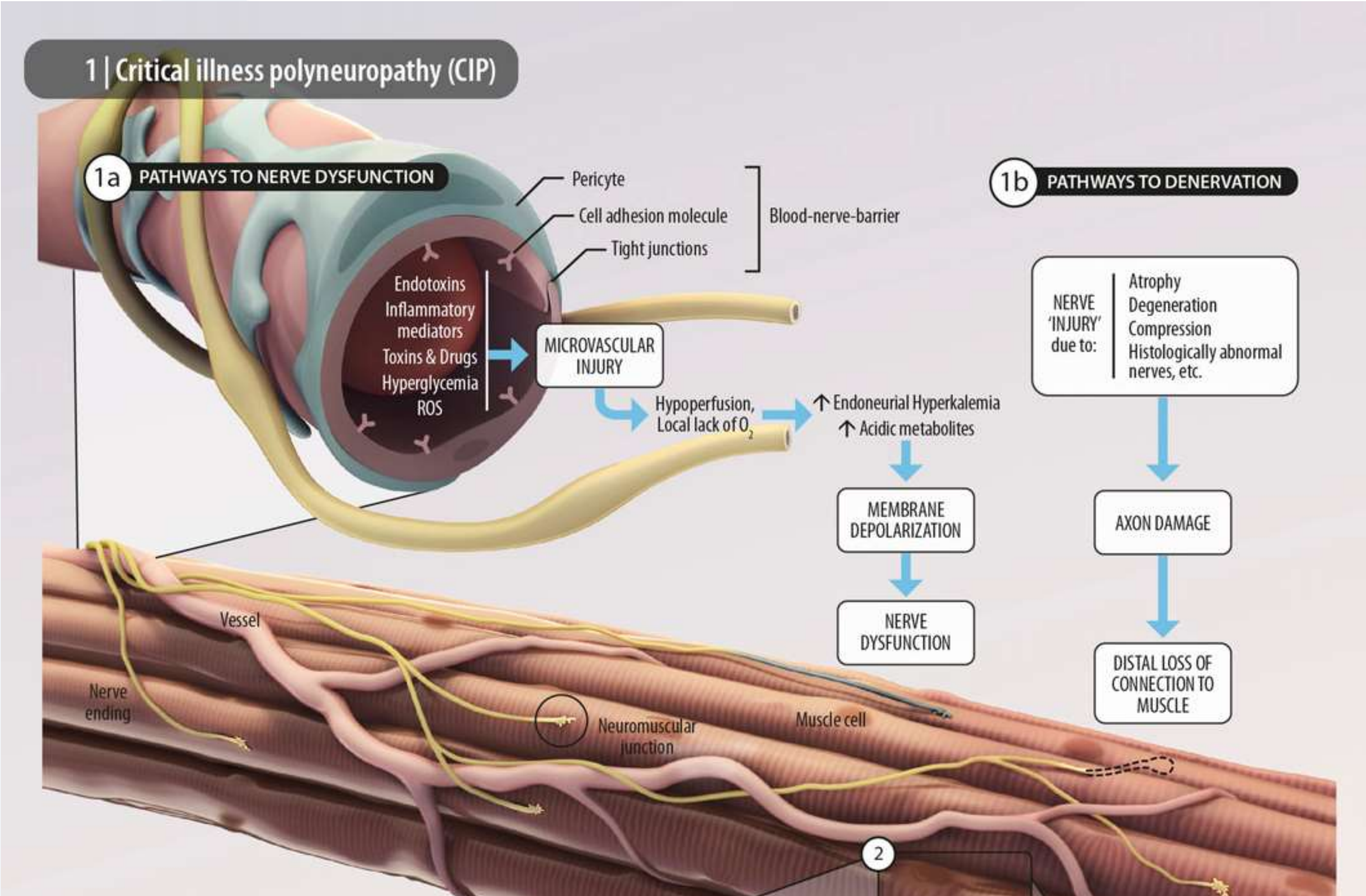
- Microvascular injury with nerve ischemia
- Sodium channel dysfunction
- Mitochondrial injury

MUSCLE:

Skeletal muscle wasting

- Microvascular ischemia
- Catabolism
- Immobility

Kress and Hall. NEJM.2014; 370:1626-35

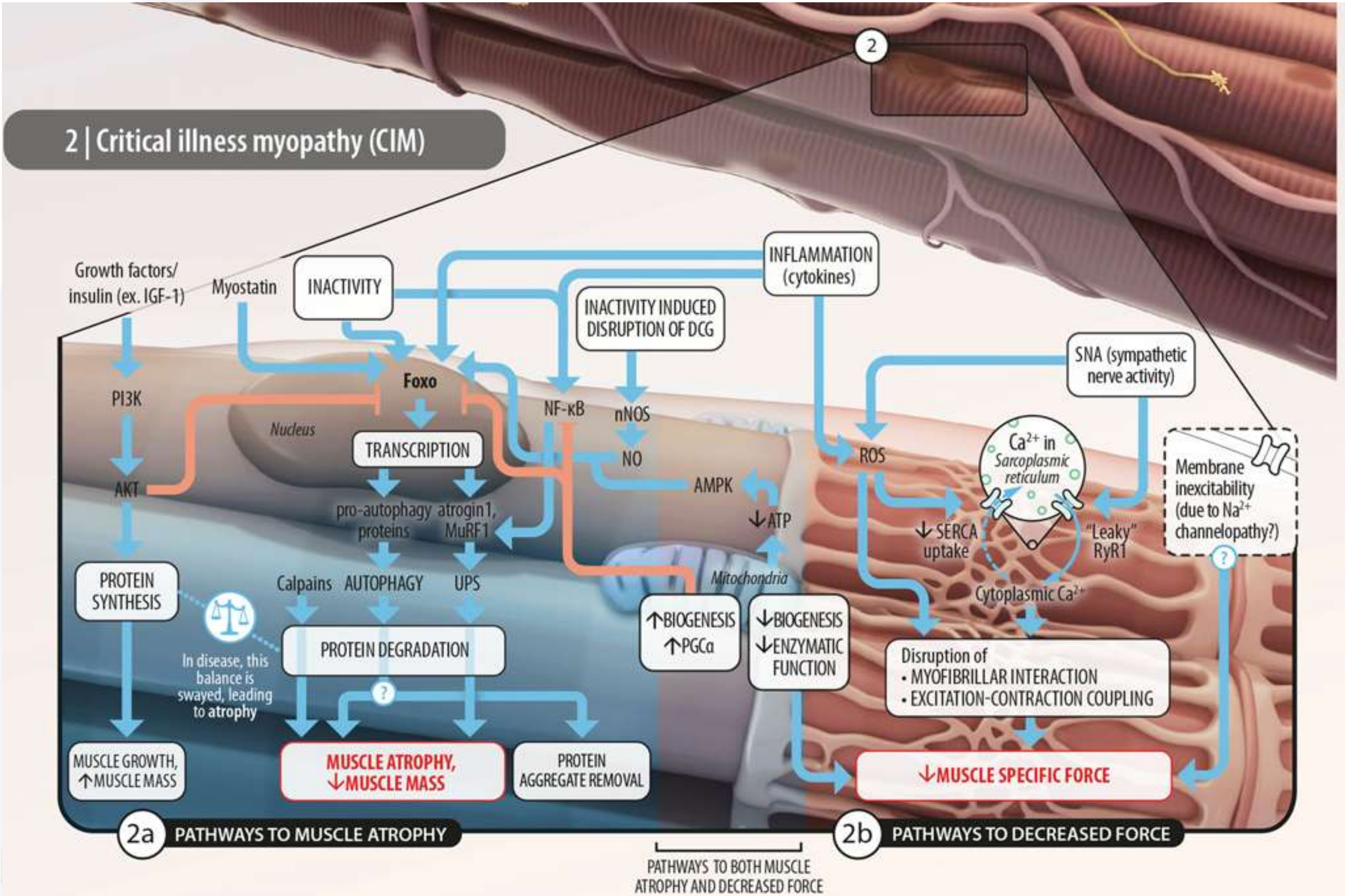


Batt et al. AJRCCM.2013; 187(3):238-246

C.I.N. or C.I.P.

- **Axonal degeneration**
  - Microvascular changes in the endoneuriom
  - Vascular permeability
  - Penetration of toxic factors into the nerve ends
  - Nerve edema
  - Impaired energy delivery to the nerve and axonal death
  - Mitochondrial dysfunction
- **Channelopathy (Natrium)**
- **Small Fiber Neuropathy**
  - Nonlength-dependent small fiber neuropathy
  - Responsible of neuropathic pain, stocking and glove sensory loss, numbness, cold extremities, burning pain.
- **Autonomic dysfunction**
  - Axonal degeneration of the vagal nerve and sympathic chain documented on autopsy findings

Hermans G et al. Crit Care.2015; 19:274



Batt et al. AJRCCM.2013; 187(3):238-246

C.I.M.

Inflammation | Immobilisation | Endocrine stress response | Nutrition Deficit | Impaired microcorculation | Denervation

Protein synthesis / breakdown imbalance

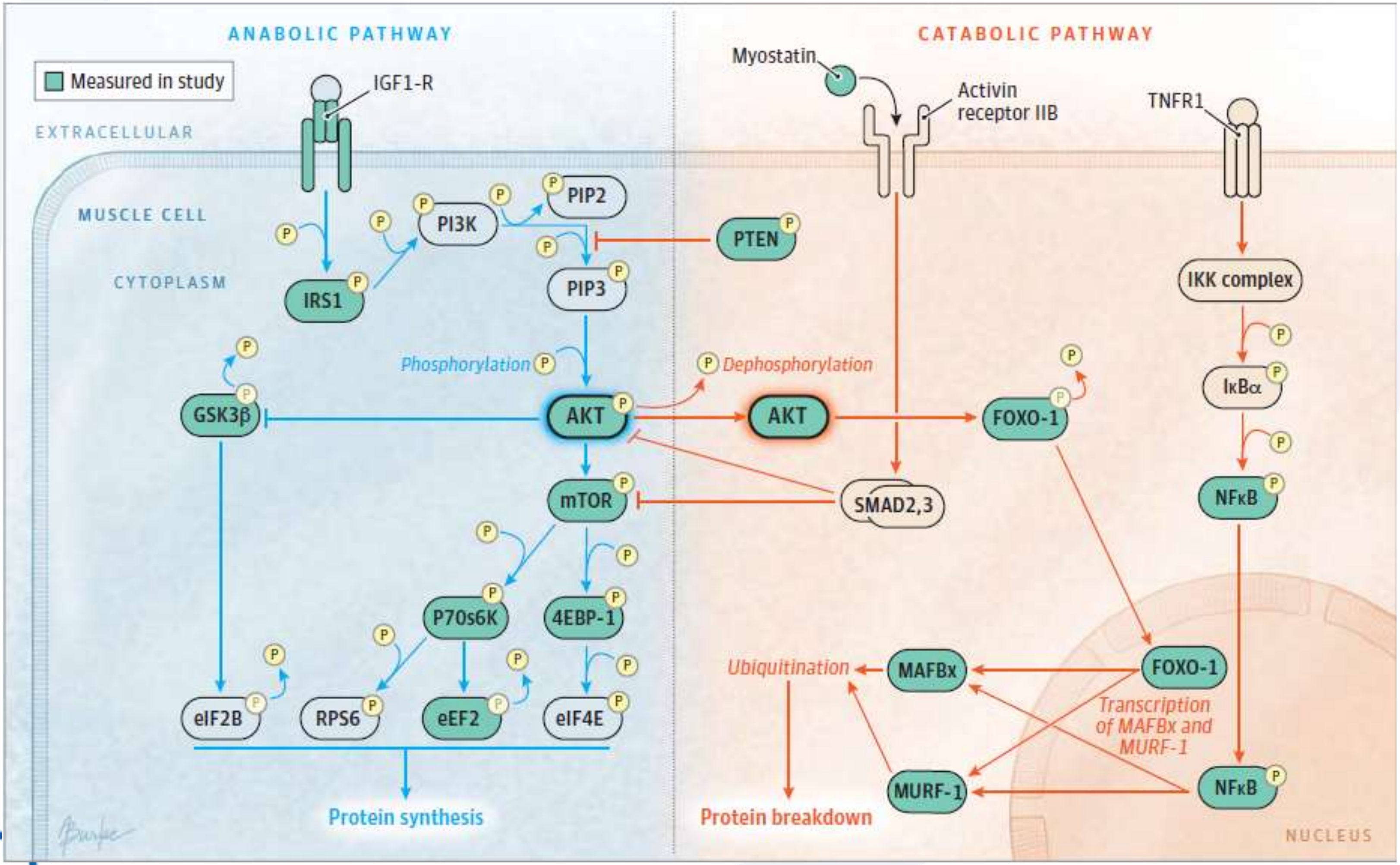
- **Muscle atrophy (**Myosin loss)
- **Disorganisation of sarcomeres**
- **Ultrastructural abnormalities**
- **Electrical hypoexcitability**

Inflammatory Mediator	Molecular Mass, kDa	Effects in Skeletal Muscle
TNF-α (cachectin)	26 (mature secreted form: 17)	Also expressed in type II muscle fibers (550)
		Depolarization of plasma membrane (712)
		Na^+-current inhibition, left shift of Na^+ channel activation and inactivation (274)
		Activation of PKC-mediated Na^+ channel phosphorylation (148)
		Induces muscle proteolysis and atrophy (148)
		Alters resting Ca^{2+} levels (decrease in myotubes) (741)
		No change in tetanic Ca^{2+} amplitudes in muscle fibers (741)
		Decreases Ca^{2+} transient amplitudes by 50% (in myotubes) (741)
		Depresses tetanic force production in limb and diaphragm muscle (571)
		Activates ubiquitin-proteasome pathway (227,428)
		Increase major histocompatibility complex II surface expression (in combination with IFN-γ) in human muscle cells (359)
		Activation of NF-κB (573)
		Downregulation of MyoD inhibits myogenic differentiation (280)
		Induces insulin resistance in muscle (248)
IL-1	13–17 (precursors: 33)	Produced by activated macrophages; also expressed in muscle fibers in health (619), following exercise (101), and in inflammatory myopathies (26)
	IL-1α: primarily membrane-bound	Associates with RyR1, blocks SR Ca^{2+}-release, and decreases SR Ca^{2+} leak in muscle fibers (220)
	IL-1β: secreted form	Upregulates iNOS expression (4)
		Induces skeletal muscle proteolysis [IL-1α (785), but maybe not IL-1β (228)]
		Stimulates IL-6 production in skeletal muscle cells (IL-1β) (445)
		Stimulates prostaglandin E_2 (PGE2) production and proteolysis (250)
		Ubiquitin gene expression ↑ (437) or ⇆ (228)
		Inhibition of protein synthesis (132)
IL-6	23–30 (glycosylation diversity)	Produced by activated macrophages and T-cells, tumor cells, but also produced by muscle fibers (type I > type II) (550)
		No effect on ubiquitin expression (437)
		Promotes infiltration of myocytes with prostaglandins (780)
		Both pro- and anti-inflammatory actions in critical illness (24)
		Induces skeletal muscle protein breakdown (in rats) (259)
		Reduces insulin-stimulated glucose uptake in muscle (364)
IL-10	18 (unglycosylated in humans)	Anti-inflammatory cytokine (780)
		Prevents skeletal muscle from IL-6-induced defects in insulin action (364)
IFN-γ	20–25	Produced by activated T-cells and natural killer cells but also in muscle fibers following muscle injury (118)
		Required for muscle regeneration (118)
		Inhibits protein translation in muscle by stimulating NO synthase activity (223)
		Modulator of TNF-α signaling in muscle (myotubes: downregulation of TNF-R2 and increased NF-κB activity) (710)
		Ubiquitin gene expression ↑ (437)

Friedrich O et al. Physiol Rev.2015; 95:1025-1109

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Acute Skeletal Muscle Wasting in Critical Illness



Puthucheary et al. JAMA.2013

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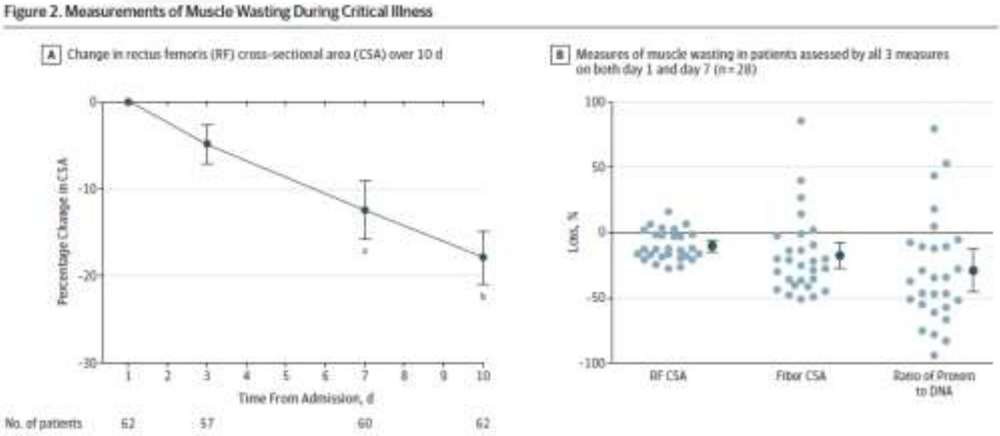
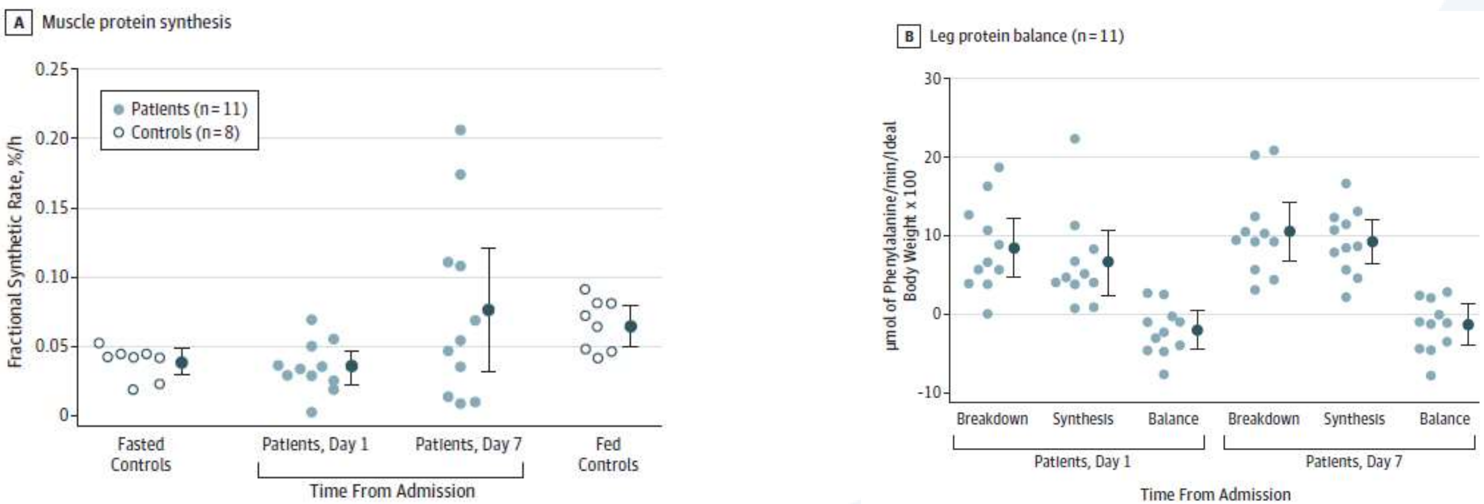
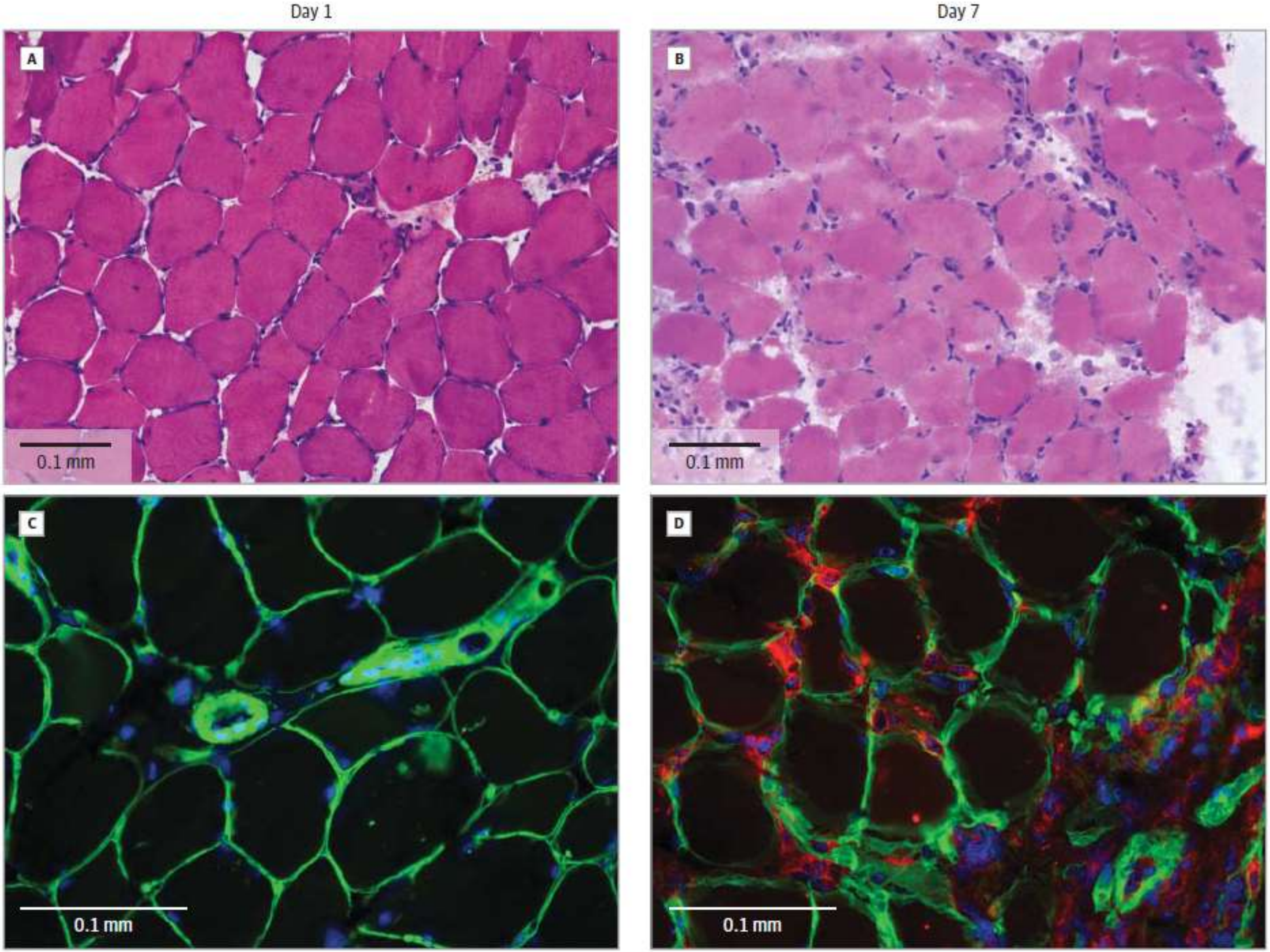




Puthucheary et al. JAMA.2013



Puthucheary et al. JAMA.2013

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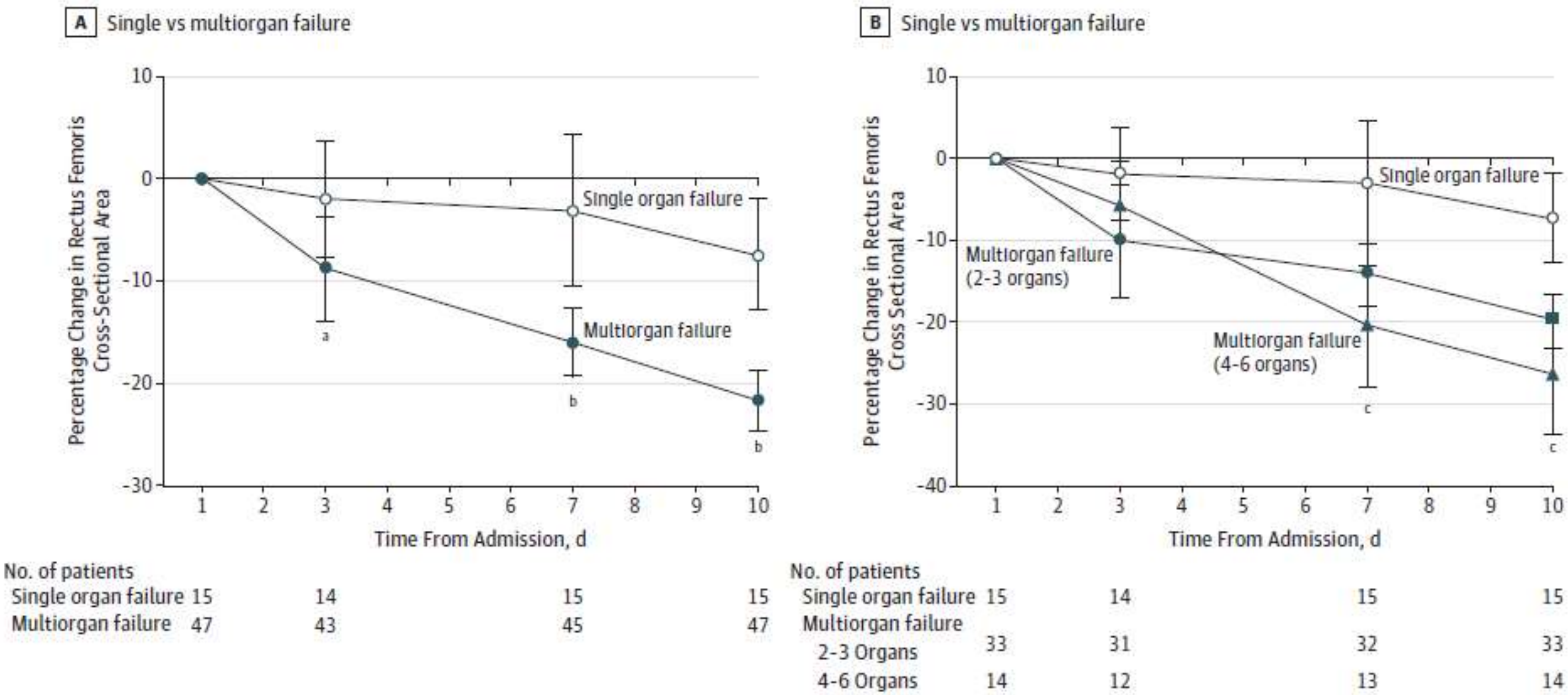
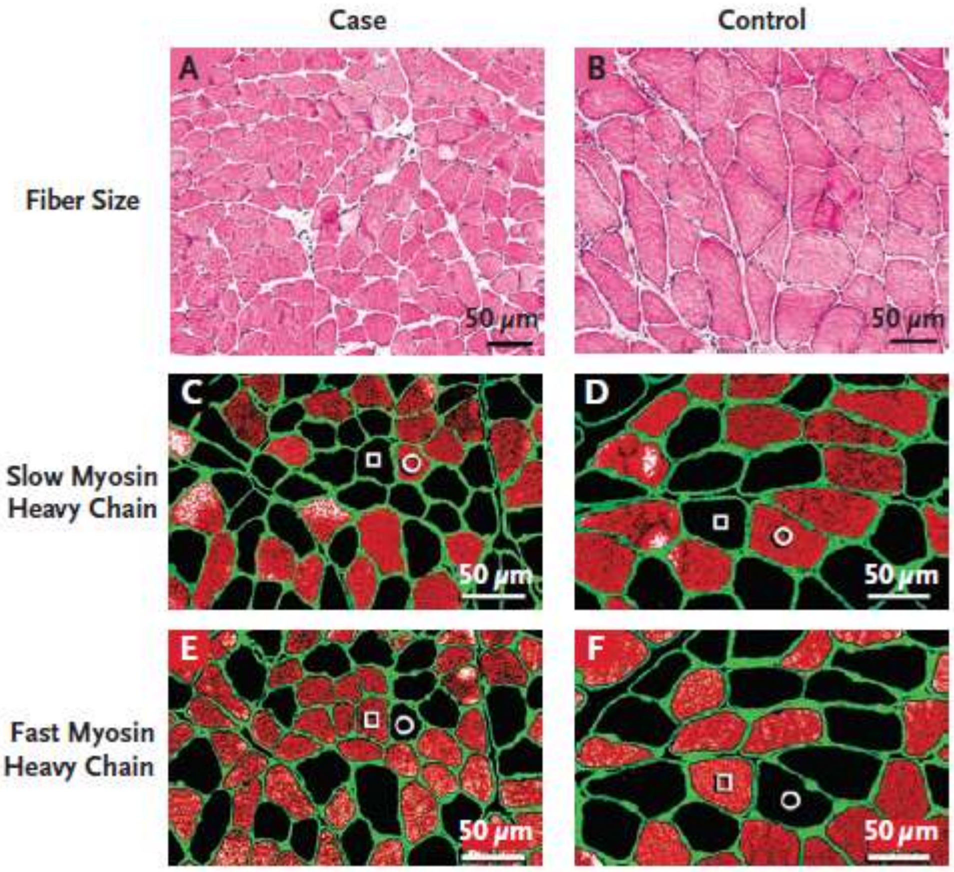
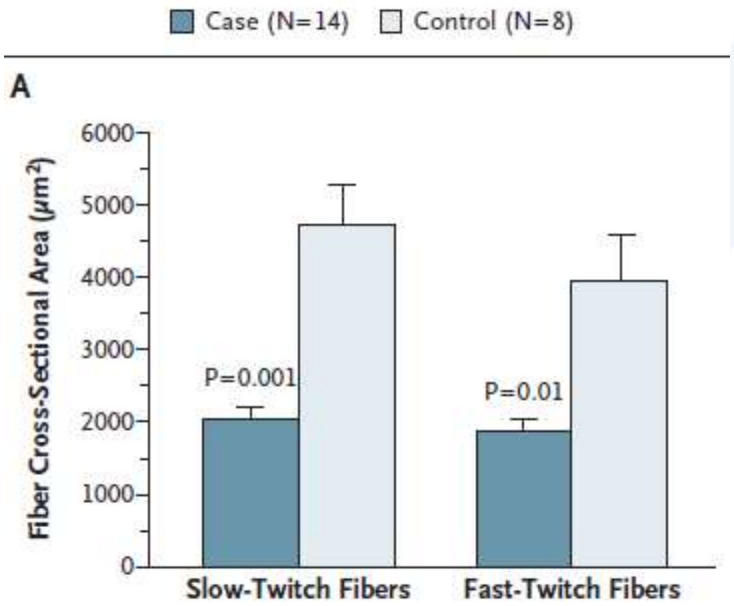


Puthucheary et al. JAMA.2013

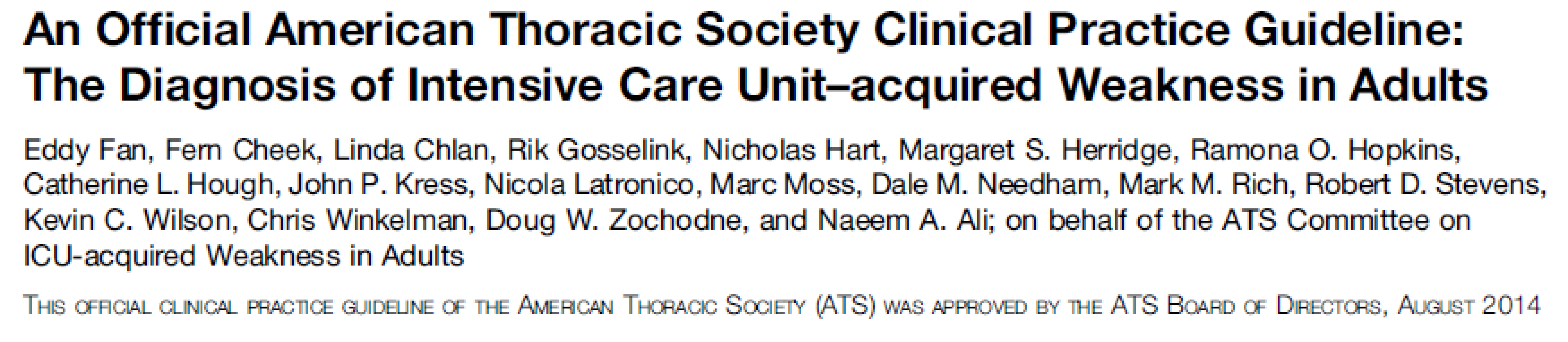
Rapid Disuse Atrophy of Diaphragm Fibers in Mechanically Ventilated Humans





Levine S et al. NEJM.2008; 358:1327-35

DIAGNOSIS


An Official American Thoracic Society Clinical Practice Guideline: The Diagnosis of Intensive Care Unit–acquired Weakness in Adults

Eddy Fan, Fern Cheek, Linda Chlan, Rik Gosselink, Nicholas Hart, Margaret S. Herridge, Ramona O. Hopkins, Catherine L. Hough, John P. Kress, Nicola Latronico, Marc Moss, Dale M. Needham, Mark M. Rich, Robert D. Stevens, Kevin C. Wilson, Chris Winkelman, Doug W. Zochodne, and Naeem A. Ali; on behalf of the ATS Committee on ICU-acquired Weakness in Adults

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, AUGUST 2014

- Physical Examination (Manual Muscle Testing – MRC Score)
- Electromyography
- Nerve Conduction Studies
- Direct Muscle Stimulation
- Muscle or Nerve Biopsy

Fan et al. AJRCCM.2014; 190(12):1437-46

DIAGNOSIS

An Official American Thoracic Society Clinical Practice Guideline: The Diagnosis of Intensive Care Unit–acquired Weakness in Adults

Eddy Fan, Fern Cheek, Linda Chlan, Rik Gosselink, Nicholas Hart, Margaret S. Herridge, Ramona O. Hopkins, Catherine L. Hough, John P. Kress, Nicola Latronico, Marc Moss, Dale M. Needham, Mark M. Rich, Robert D. Stevens, Kevin C. Wilson, Chris Winkelman, Doug W. Zochodne, and Naeem A. Ali; on behalf of the ATS Committee on ICU-acquired Weakness in Adults

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***lack of consensus** on surveillance, diagnostic method, timing of evaluation*

Fan et al. AJRCCM.2014; 190(12):1437-46

DIAGNOSIS

Physical Examination (Manual Muscle Testing – MRC Score)

Table 1 Medical Research Council sum score

Muscle group evaluated
Wrist extension
Elbow flexion
Shoulder abduction
Dorsiflexion foot
Knee extension
Hip flexion
Appointed score
0, no visible/palpable contraction
1, visible/palpable contraction without movement of the limb
2, movement of the limb, but not against gravity
3, movement against gravity
4, movement against gravity and some resistance
5, normal

- The sum score ranges between 0 and 60
- ICUAW when MRC < 48
- Diagnosis of CIP or CIM ???
- Patient needs to be awake and cooperative
- Objectivity ?

Hermans G et al. Crit Care.2015; 19:274

DIAGNOSIS

Physical Examination (Manual Muscle Testing – MRC Score)

Table 3. Diagnostic criteria for ICUAW

1)	Generalized weakness developing after the onset of critical illness
2)	Weakness is diffuse (involving both proximal and distal muscles), symmetric, flaccid, and generally spares cranial nerves[a]
3)	MRC sumscore (82) <48, or mean MRC score (80) <4 in all testable muscle groups noted on ≥2 occasions separated by >24 hrs
4)	Dependence on mechanical ventilation
5)	Causes of weakness not related to the underlying critical illness have been excluded

Minimum criteria for diagnosing ICUAW: 1, 2, 3 or 4, 5

Stevens RD et al. Crit Care Med.2009; 37: S299-S308

DIAGNOSIS

ELECTROMYOGRAPHY and NERVE CONDUCTION STUDIES

EMG Characteristics of ICUAW

Characteristic	CIP	CIM
CMAP	Low amplitude	At least 1 low amplitude Variable duration
Sensory nerve action potentials	Low amplitude or absent	Normal
dmCMAP	Low	Low
Nerve-evoked CMAP-to-dmCMAP ratio	< 0.5	> 0.5
Fibrillation potentials (reflect denervation)	Found in distal and proximal muscles in multifocal pattern with variable severity May be found in 30% of diaphragm	Found in at least 1 muscle in 71% to 100% of patients May be diffuse
Motor unit recruitment	Decreased	Early and full May be of short duration and low amplitude

Zorowitz RD. Chest.2016; 150(4):966-71

DIAGNOSIS

ELECTROMYOGRAPHY and NERVE CONDUCTION STUDIES

Single Fibular Nerve Conduction Study

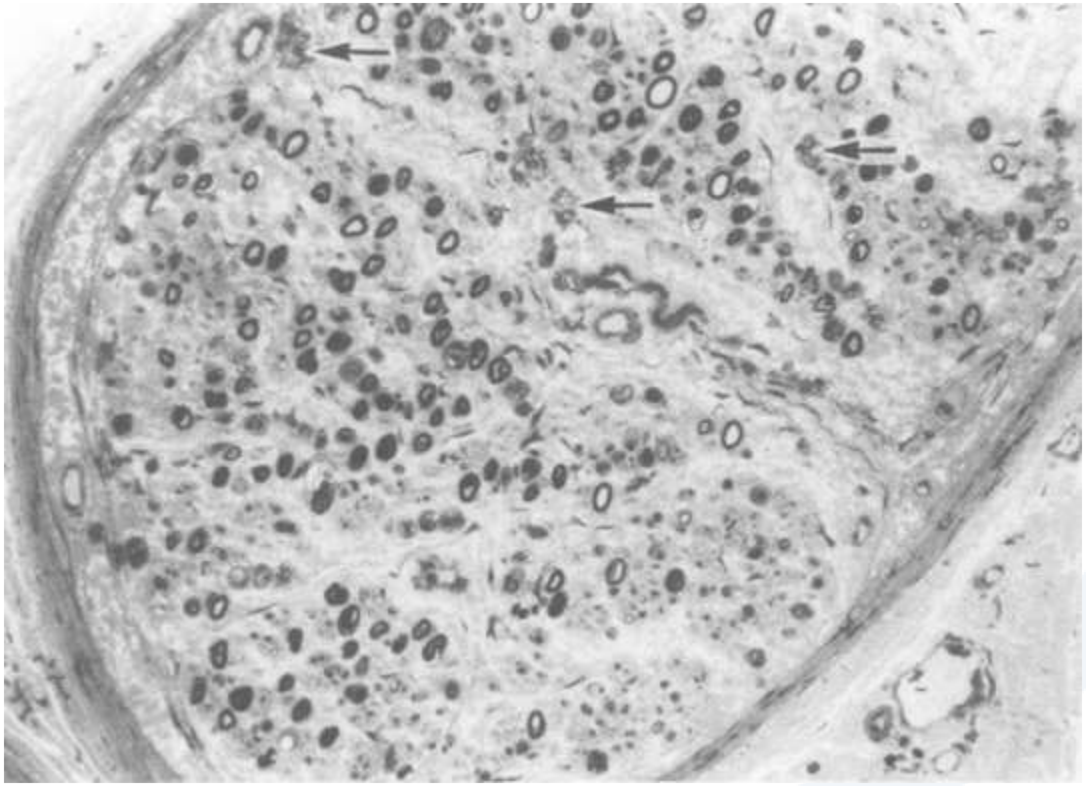
Quick, Safe, Easy

Common peroneal (fibular) compound motoneural action potential is measured using 2 surface electrode;
Progressive increase in stimulus intensity until maximal CMAP is achieved.

Jolley SE. Chest.2016; 150(5):1129-40

DIAGNOSIS

BIOPSY



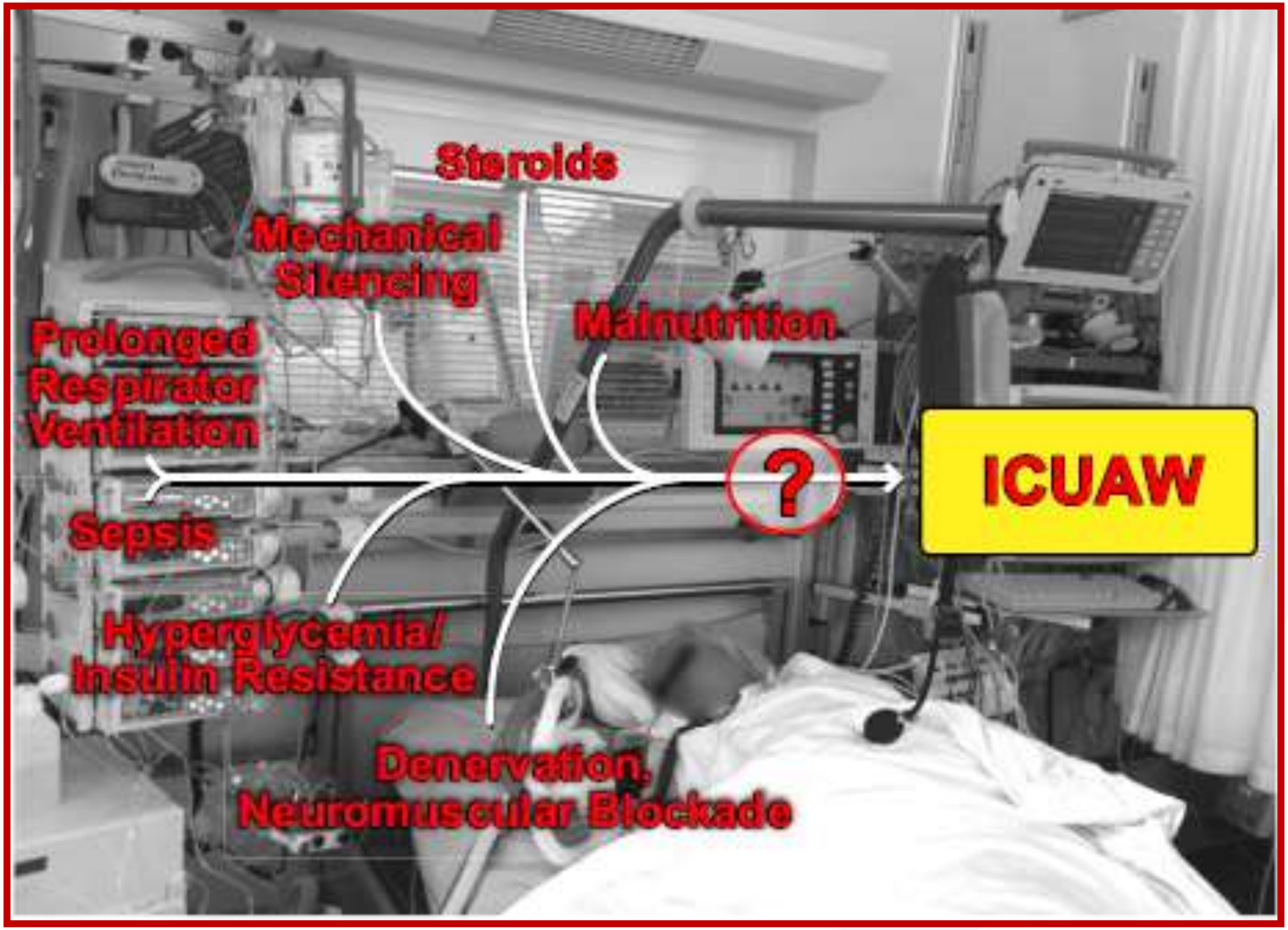
Bolton CF et al. J Neurol Neurosurg Psychiatry.1985; 47(11):1223-31

Modality	Potential Benefits	Potential Limitations
Full NCSs with EMG	• Part of the gold standard definition of CIM and CIP • Associated with functional outcomes	• Time intensive • Expensive • Moderately invasive • Requires technical expertise • Potentially limited by tissue edema or electrical interference • Requires patient participation for full EMG
Single NCSs	• Quick to perform • Minimally invasive • Less cost than full NCS • Associated with functional outcomes	• Requires technical expertise • Potentially limited by tissue edema or electrical interference
Muscle biopsy	• Depicts muscle architecture • Differentiates CIM from CIP • Part of gold standard for diagnosis of CIM	• Invasive • Expensive • Potentially painful • Requires technical expertise • Requires pathologist support for interpretation • Patient refusal common • Risk of bleeding and/or infection
Muscle ultrasound	• Depicts gross muscle architecture • Noninvasive and comfortable for the patient • Does not require patient participation • Inexpensive once ultrasound machine is obtained • Good interrater reliability • Readily available in most ICU settings	• Requires technical expertise • Diagnostic accuracy and functional significance for CIM and CIP not yet clear • May be limited in patients who are obese or severely edematous
MRC manual muscle strength testing	• Easy to administer • Minimal expertise necessary • Cheap • Direct functional significance	• Relies on patient cooperation • Interrater variation • Ceiling effect after hospital discharge

Jolley SE. Chest.2016; 150(5):1129-40

RISK FACTORS

- MECHANICAL VENTILATION
- MUSCLE IMMOBILIZATION
- SEPSIS (SEVERE SEPSIS)
- MULTIPLE ORGAN DYSFUNCTION
- NEURO-MYOTOXIC AGENTS



Friedrich O et al. Physiol Rev.2015; 95:1025-1109

STEROIDS ???

Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome

N Engl J Med 2006;354:1671-84.

Neuromyopathy — no./ total no. (%)			0.18
Retrospective review	10/43 (23)	15/44 (34)	
Prospective review	11/48 (23)	11/44 (25)	0.67
Overall	21/91 (22)	26/88 (30)	0.20

Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis

The HYPRESS Randomized Clinical Trial

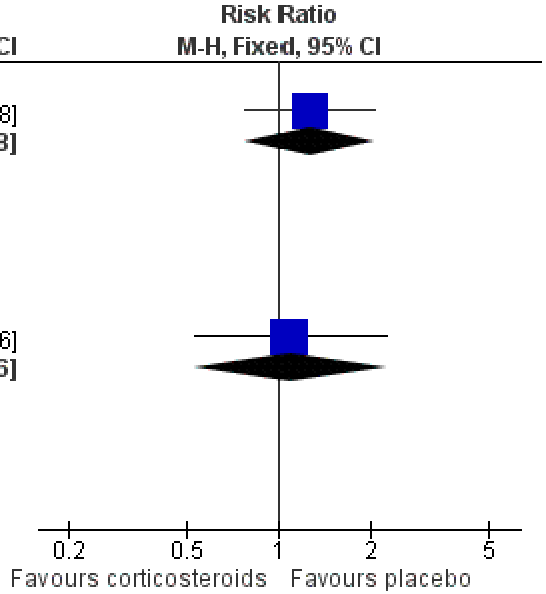
JAMA. 2016;316(17):1775-1785.

MRC Scale for Muscle Strength score available, No. (%)	151 (79.9)	150 (80.6)	301 (80.3)	.86
Muscle weakness, No. (%)[b]	36 (23.8)	46 (30.7)	82 (27.2)	.18

STEROIDS ???

Figure 4. Forest plot of comparison: 2 Corticosteroids versus placebo, outcome: 2.1 Occurrence of CIP/CIM.

Study or Subgroup	Favours corticosteroids Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 In total population randomised						
Steinberg 2006	26	89	21	91	100.0%	1.27 [0.77, 2.08]
Subtotal (95% CI)		**89**		**91**	**100.0%**	**1.27 [0.77, 2.08]**
Total events	26		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
2.1.2 In screened population						
Steinberg 2006	11	44	11	48	100.0%	1.09 [0.53, 2.26]
Subtotal (95% CI)		**44**		**48**	**100.0%**	**1.09 [0.53, 2.26]**
Total events	11		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.81)						



Hermans G et al. Cochrane Database Syst Rev.2014;CD006832

N.M.B.A. ???

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

N Engl J Med 2010;363:1107-16.

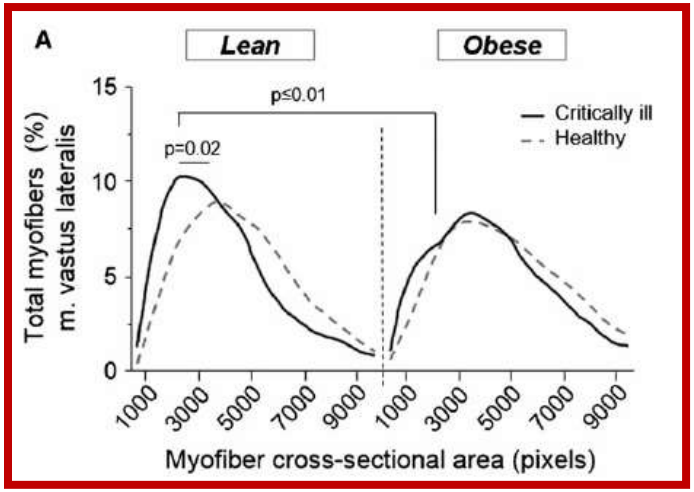
MRC score — median (IQR)§				
At day 28	55 (46–60)	55 (39–60)	1.07 (0.80–1.45)	0.49
At ICU discharge	55 (43–60)	55 (44–60)	0.92 (0.71–1.19)	0.94

NUTRITION STATUS

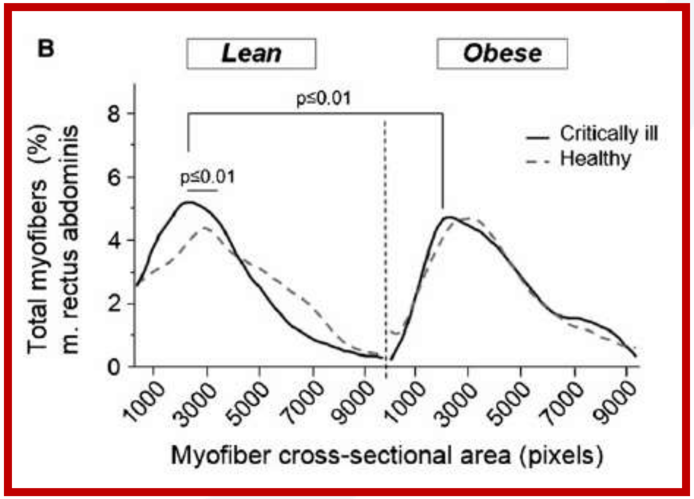
NUTRITION STATUS

Premorbid obesity, but not nutrition, prevents critical illness-induced muscle wasting and weakness

- Mice study
- Critical Care Patients study / D7



In Vivo biopsies of the vastus lateralis

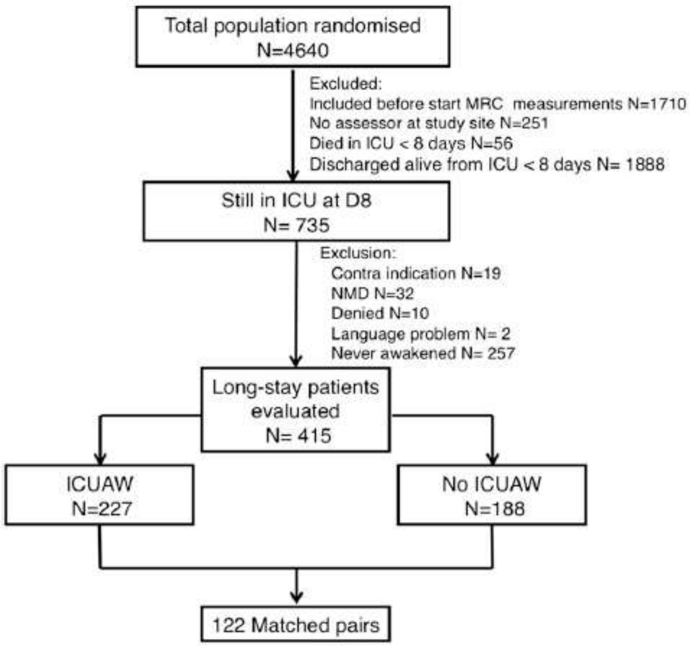


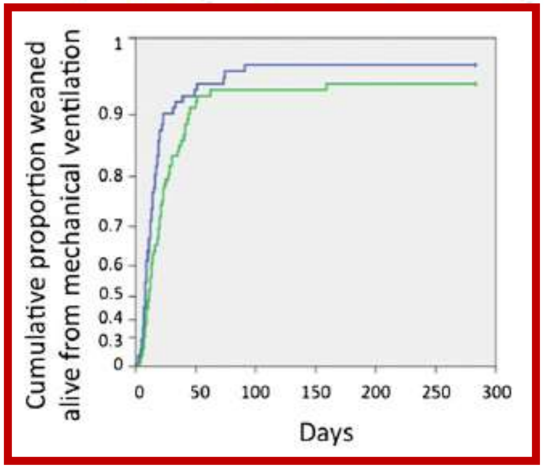
Post mortem biopsies of the rectus abdominis

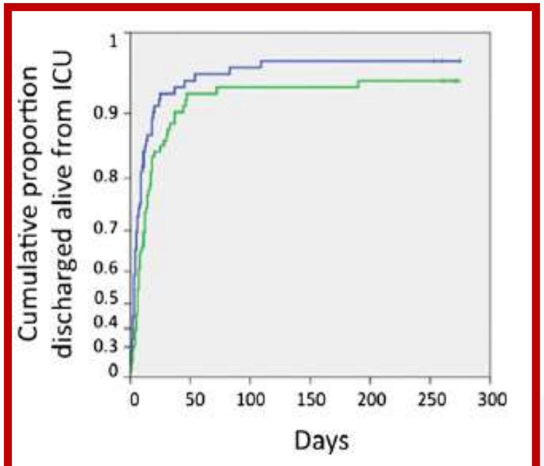
Goossens C et al. J Cachexia Sarcopenia Muscle .2016; in press

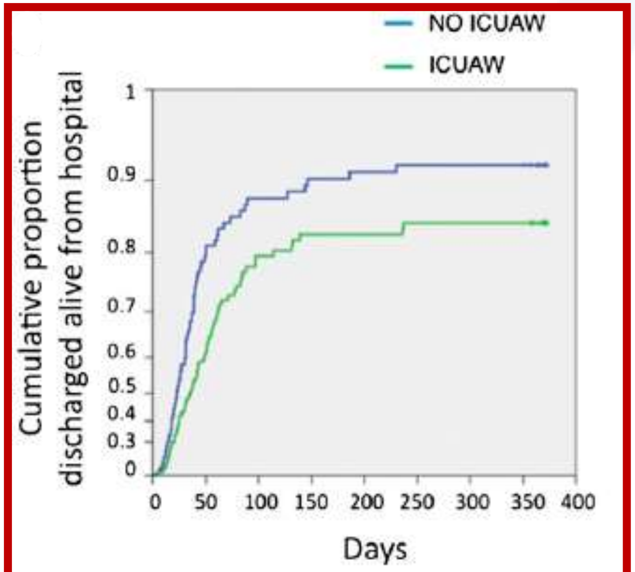
Acute Outcomes and 1-Year Mortality of Intensive Care Unit–acquired Weakness

A Cohort Study and Propensity-matched Analysis









Hermans G et al. AJRCCM.2014;190(4): 410-20

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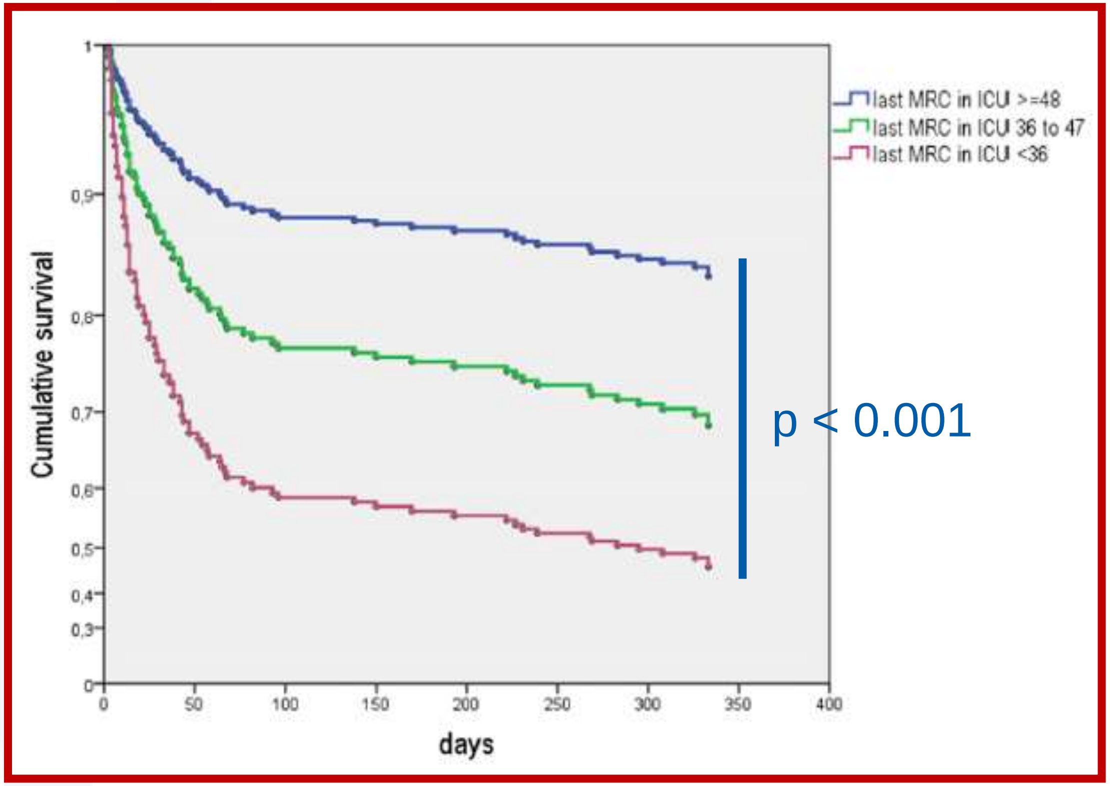
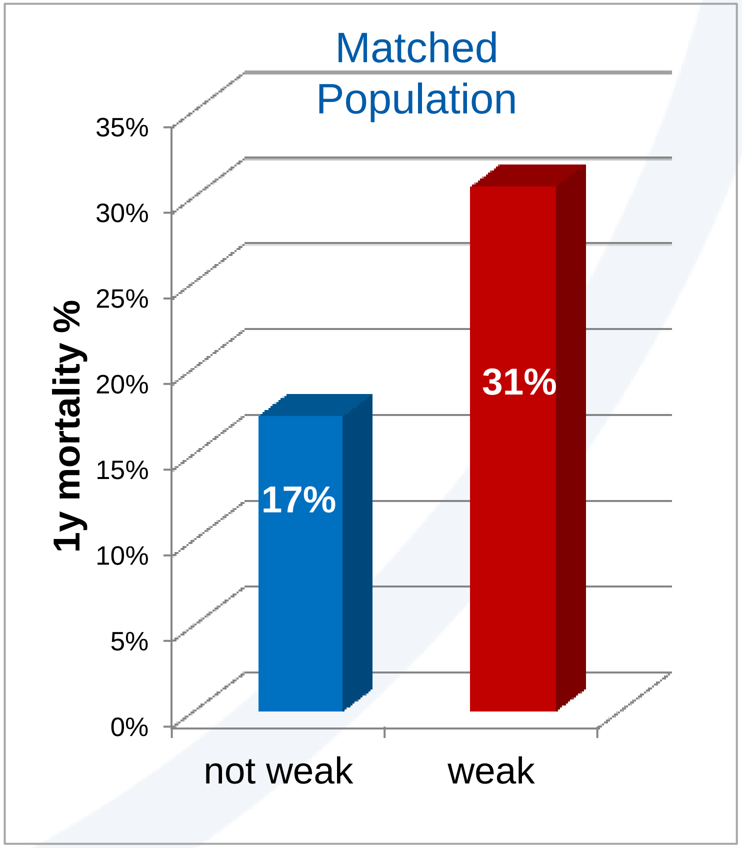
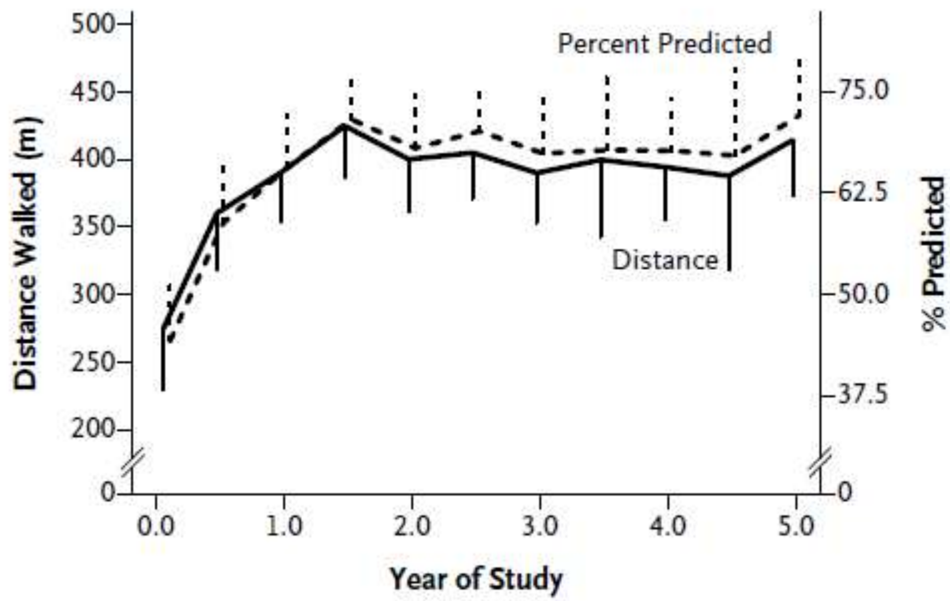


$p < 0.001$



Hermans G et al. AJRCCM.2014;190(4): 410-20

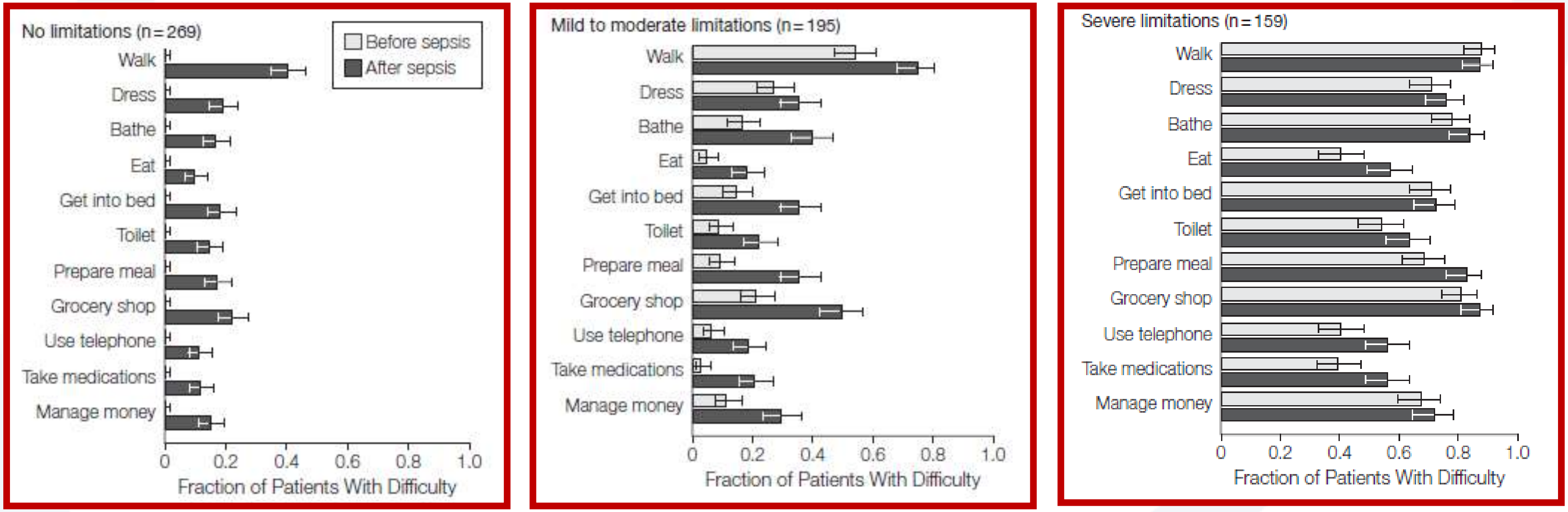
Functional Disability 5 Years after Acute Respiratory Distress Syndrome



Distance walked in 6 min§					
Median — m	422	416	418	406	436
Interquartile range	277–510	285–496	311–474	314–488	324–512
Percent of predicted¶	66	68	67	71	76

Herridge MS et al. N Engl J Med.2011;364: 1293-304

Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis



Iwashyna et al. JAMA.2010; 304(16): 1787-94

Interventions for preventing critical illness polyneuropathy and critical illness myopathy (Review)

Authors' conclusions

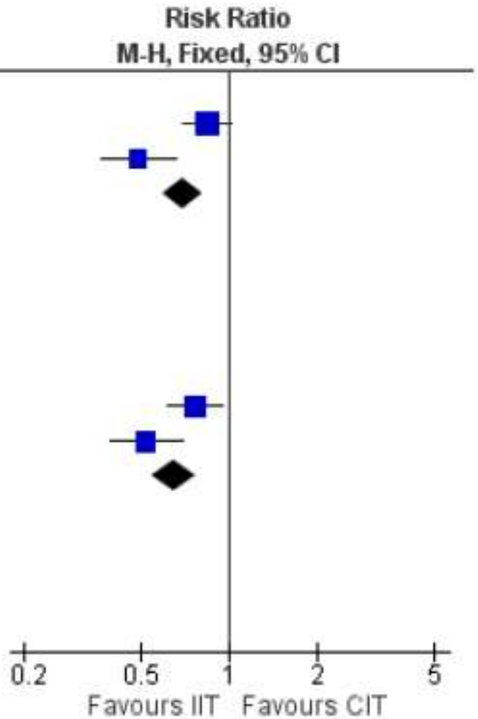
There is moderate quality evidence from two large trials that intensive insulin therapy reduces CIP/CIM, and high quality evidence that it reduces duration of mechanical ventilation, ICU stay and 180-day mortality, at the expense of hypoglycaemia. Consequences and prevention of hypoglycaemia need further study. There is moderate quality evidence which suggests no effect of corticosteroids on CIP/CIM and high quality evidence that steroids do not affect secondary outcomes, except for fewer new shock episodes. Moderate quality evidence suggests a potential benefit of early rehabilitation on CIP/CIM which is accompanied by a shorter duration of mechanical ventilation but without an effect on ICU stay. Very low quality evidence suggests no effect of EMS, although data are prone to bias. Strict diagnostic criteria for CIP/CIM are urgently needed for research purposes. Large RCTs need to be conducted to further explore the role of early rehabilitation and EMS and to develop new preventive strategies.

Hermans G et al. Cochrane Database Syst Rev.2014;CD006832

Interventions for preventing critical illness polyneuropathy and critical illness myopathy (Review)

Figure 3. Forest plot of comparison: 1 Intensive insulin therapy (IIT) versus conventional insulin therapy (CIT), outcome: 1.1 Occurrence of CIP/CIM.

Study or Subgroup	Favours IIT Events	Favours IIT Total	CIT Events	CIT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 In total population randomised						
Hermans 2007	150	595	181	605	59.2%	0.84 [0.70, 1.01]
Van den Berghe 2005	60	765	125	783	40.8%	0.49 [0.37, 0.66]
Subtotal (95% CI)		**1360**		**1388**	**100.0%**	**0.70 [0.60, 0.82]**
Total events	210		306			
Heterogeneity: Chi² = 9.57, df = 1 (P = 0.002); I² = 90%						
Test for overall effect: Z = 4.50 (P < 0.00001)						
1.1.2 In screened population						
Hermans 2007	81	208	107	212	52.1%	0.77 [0.62, 0.96]
Van den Berghe 2005	46	181	109	224	47.9%	0.52 [0.39, 0.69]
Subtotal (95% CI)		**389**		**436**	**100.0%**	**0.65 [0.55, 0.77]**
Total events	127		216			
Heterogeneity: Chi² = 4.68, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 4.86 (P < 0.00001)						

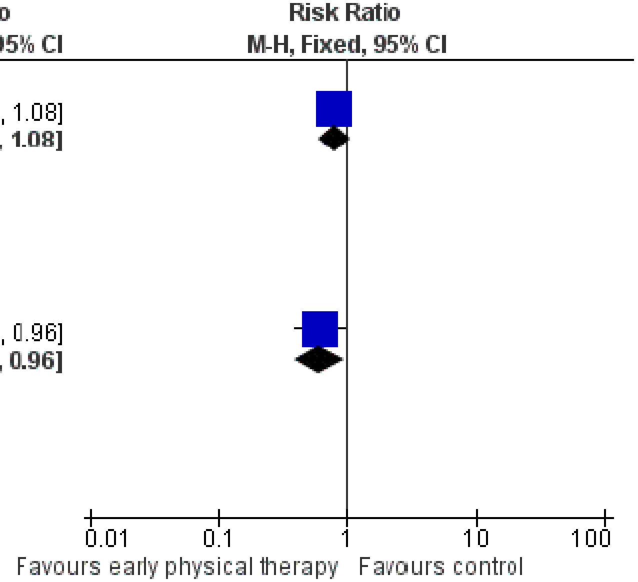


Hermans G et al. Cochrane Database Syst Rev.2014;CD006832

Interventions for preventing critical illness polyneuropathy and critical illness myopathy (Review)

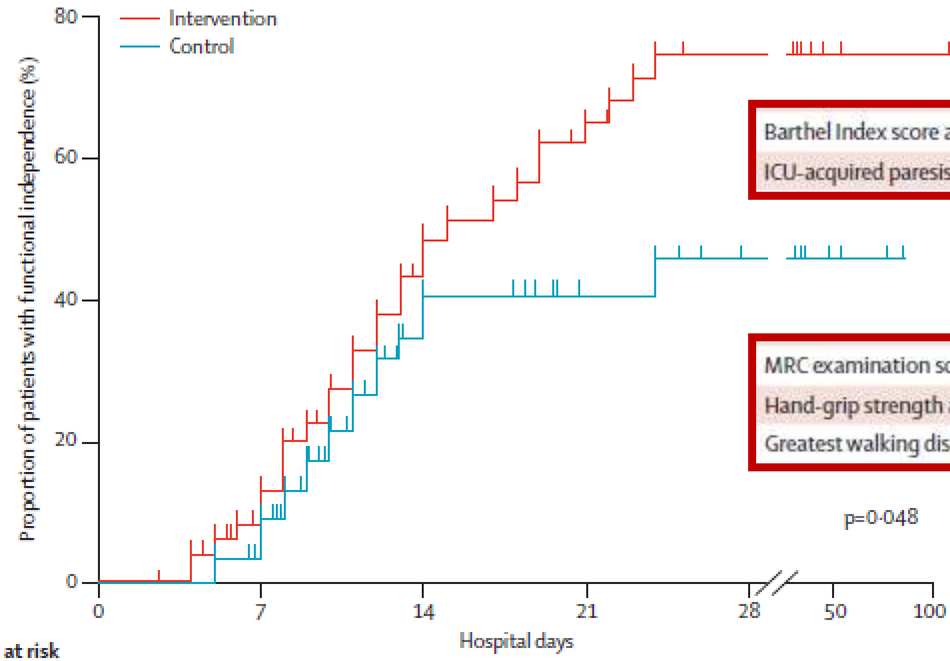
Figure 5. Forest plot of comparison: 6 Early physical therapy versus control, outcome: 6.1 Occurence of CIP/CIM.

Study or Subgroup	Early phsyical therapy Events	Early phsyical therapy Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 In total population randomised						
Schweickert 2009	28	49	39	55	100.0%	0.81 [0.60, 1.08]
Subtotal (95% CI)		**49**		**55**	**100.0%**	**0.81 [0.60, 1.08]**
Total events	28		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						
3.1.2 In screened population						
Schweickert 2009	16	41	26	41	100.0%	0.62 [0.39, 0.96]
Subtotal (95% CI)		**41**		**41**	**100.0%**	**0.62 [0.39, 0.96]**
Total events	16		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.13 (P = 0.03)						



Hermans G et al. Cochrane Database Syst Rev.2014;CD006832

Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial



Barthel Index score at hospital discharge	75 (7·5–95)	55 (0–85)	0·05
ICU-acquired paresis at hospital discharge	15 (31%)	27 (49%)	0·09

MRC examination score at hospital discharge	52 (25–58)	48 (0–58)	0·38
Hand-grip strength at hospital discharge (kg-force)	39 (10–58)	35 (0–57)	0·67
Greatest walking distance at hospital discharge (m)	33·4 (0–91·4)	0 (0–30·4)	0·004

Number at risk

Control	55	51	21	13	9	4	0
Intervention	49	40	21	13	8	2	1

Schweickert t al. Lancet.2009;373: 1874-82.

Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure
A Randomized Clinical Trial

Peter E. Morris, MD; Michael J. Berry, PhD; D. Clark Files, MD; J. Clifton Thompson, RN; Jordan Hauser, MS; Lori Flores, RN; Sanjay Dhar, MD; Elizabeth Chmelo, MS; James Lovato, MS; L. Douglas Case, PhD; Rita N. Bakhru, MD, MS; Aarti Sarwal, MD; Selina M. Parry, PhD; Pamela Campbell, RN; Arthur Mote; Chris Winkelman, PhD; Robert D. Hite, MD; Barbara Nicklas, PhD; Arjun Chatterjee, MD, MS; Michael P. Young, MD

JAMA. 2016;315(24):2694-2702.

A Randomized Trial of an Intensive Physical Therapy Program for Patients with Acute Respiratory Failure

Marc Moss[1], Amy Nordon-Craft[2], Dan Malone[2], David Van Pelt[3], Stephen K. Frankel[4], Mary Laird Warner[4], Wendy Kriekels[2], Monica McNulty[5], Diane L. Fairclough[5], and Margaret Schenkman[2]

Am J Respir Crit Care Med Vol 193, Iss 10, pp 1101–1110, May 15, 2016

Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial

*Stefan J Schaller, Matthew Anstey, Manfred Blobner, Thomas Edrich, Stephanie D Grabitz, Ilse Gradwohl-Matis, Markus Heim, Timothy Houle, Tobias Kurth, Nicola Latronico, Jarone Lee, Matthew J Meyer, Thomas Peponis, Daniel Talmor, George C Velmahos, Karen Waak, J Matthias Walz, Ross Zafonte, Matthias Eikermann, for the International Early SOMS-guided Mobilization Research Initiative**

Lancet 2016; 388: 1377–88

Original Investigation

Increased Hospital-Based Physical Rehabilitation and Information Provision After Intensive Care Unit Discharge
The RECOVER Randomized Clinical Trial

Timothy S. Walsh, MD; Lisa G. Salisbury, PhD; Judith L. Merriweather, PhD; Julia A. Boyd, PhD; David M. Griffith, MD; Guro Huby, PhD; Susanne Kean, PhD; Simon J. Mackenzie, MBChB; Ashma Krishan, MSc; Stephanie C. Lewis, PhD; Gordon D. Murray, PhD; John F. Forbes, PhD; Joel Smith, PhD; Janice E. Rattray, PhD; Alastair M. Hull, MD; Pamela Ramsay, PhD; for the RECOVER Investigators

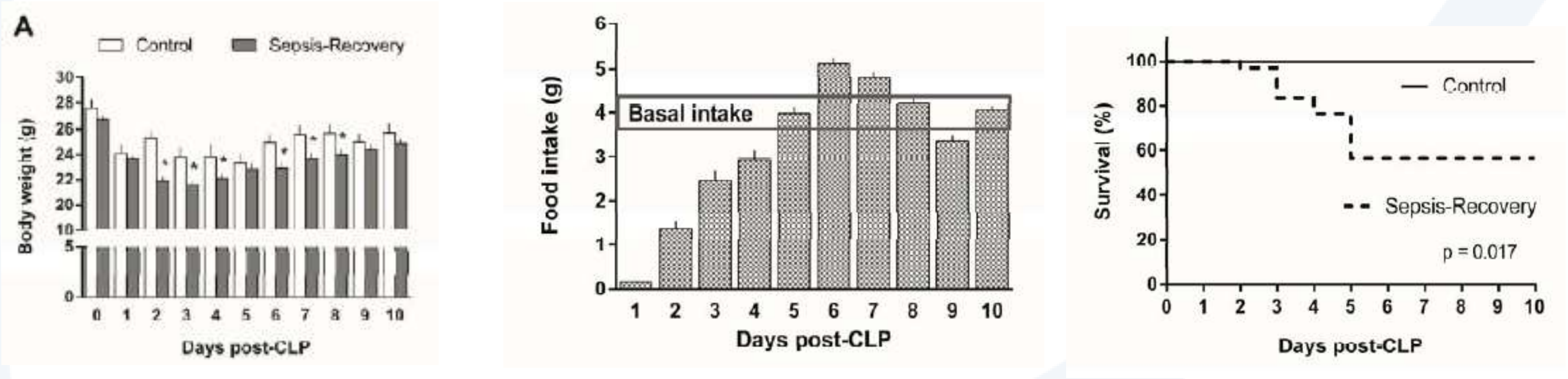
CONCLUSIONS AND RELEVANCE Post-ICU hospital-based rehabilitation, including increased physical and nutritional therapy plus information provision, did not improve physical recovery or HRQOL, but improved patient satisfaction with many aspects of recovery.

JAMA Intern Med. 2015;175(6):901-910.

Restorative mechanisms regulating protein balance
in skeletal muscle during recovery from sepsis

Sepsis recovery mouse model

- Male C57BL/6 mice
- Polymicrobial peritonitis induced by Cecal Ligature and Puncture
- H24: antibiotics
- H48: surgery
- D10: in vivo protein synthesis measurement
  - Ubiquitin proteasome activity



Crowell KT et al. Shock.2016; in press

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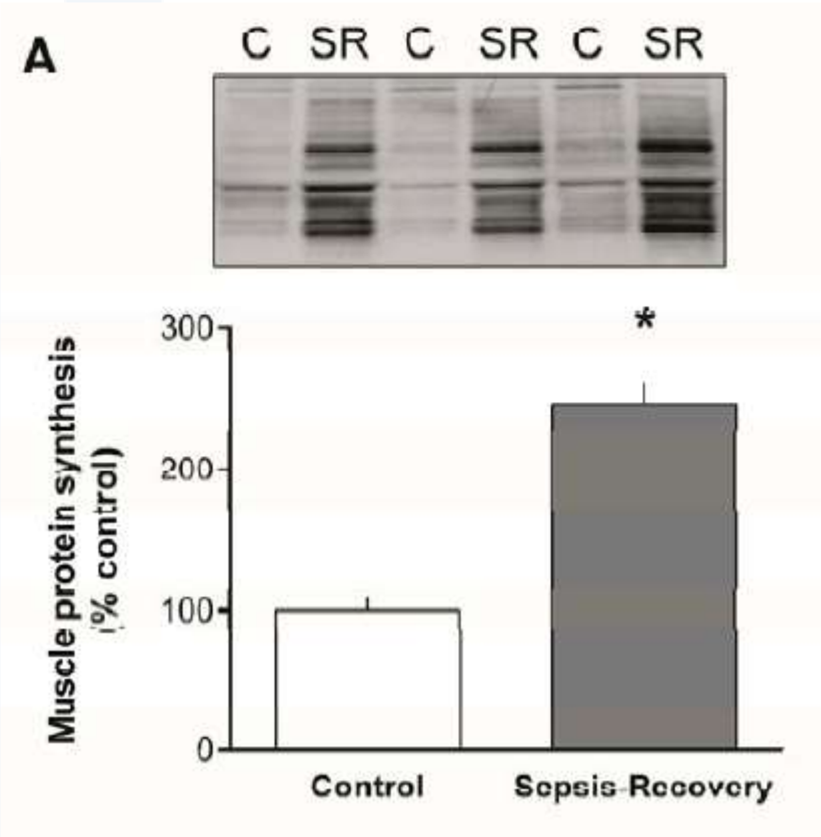
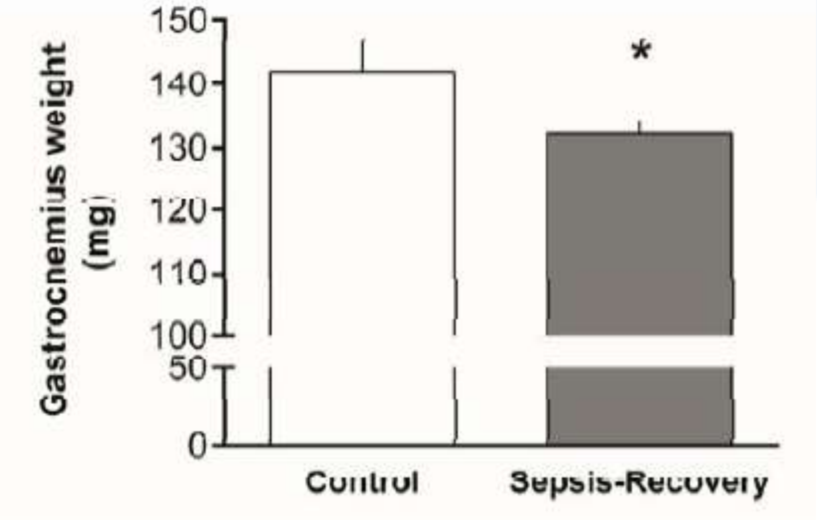




Crowell KT et al. Shock.2016; in press

Restorative mechanisms regulating protein balance in skeletal muscle during recovery from sepsis

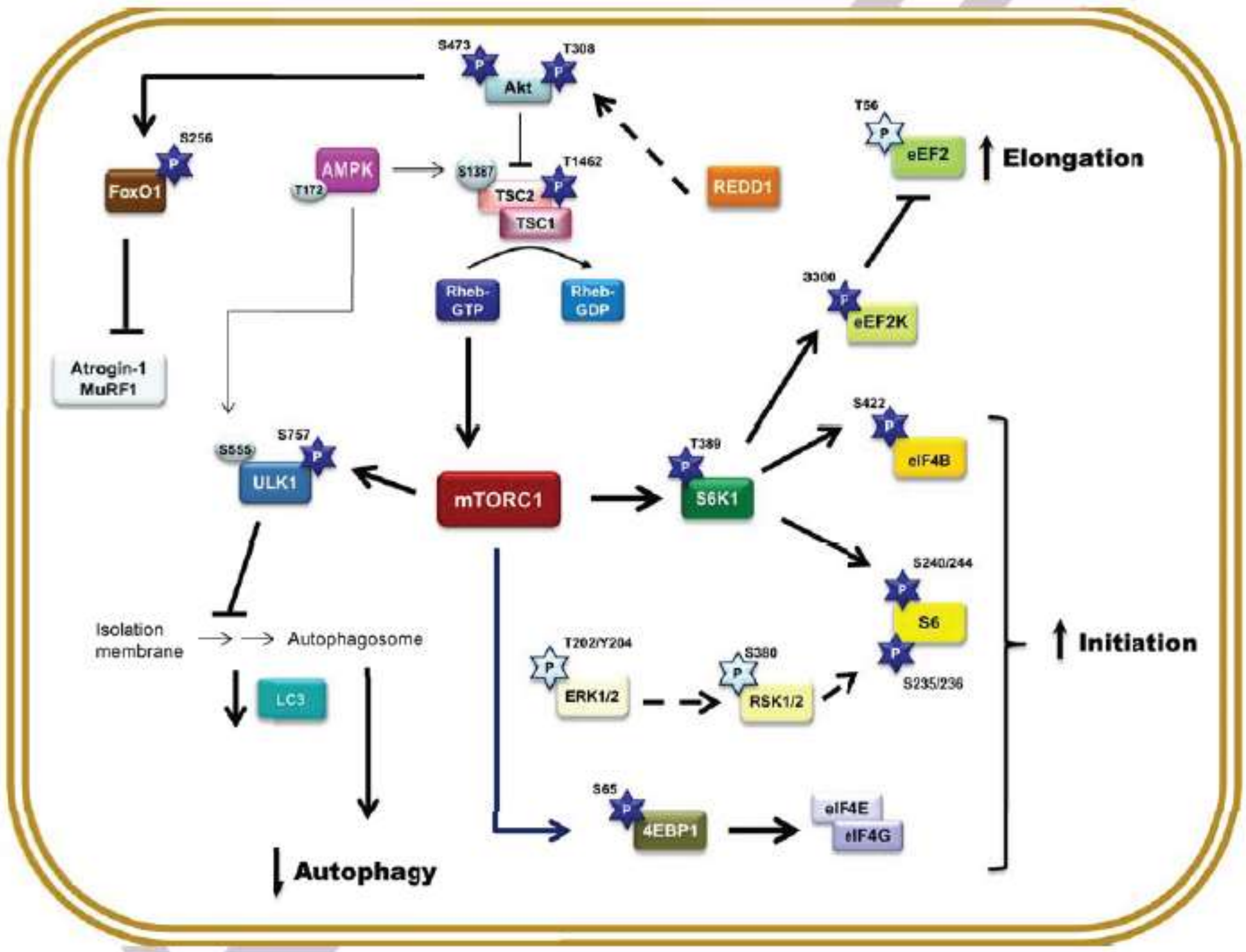
During recovery:

1. Period of over-compensation (muscle protein synthesis is above normal value)
   This increase is mediated by a activation of the Akt-TSC2-mTORC1 transduction system.

2. Divergent effects on the pathways modulating the protein breakdown.

3. Decrease in autophagy

Crowell KT et al. Shock.2016; in press



Crowell KT et al. Shock.2016; in press

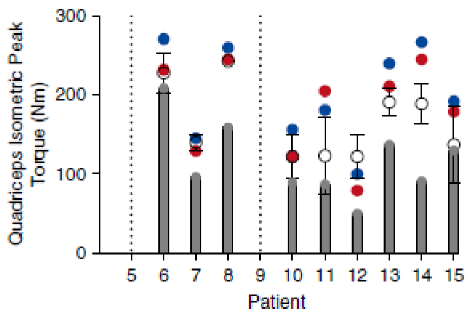
Mechanisms of Chronic Muscle Wasting and Dysfunction after an Intensive Care Unit Stay

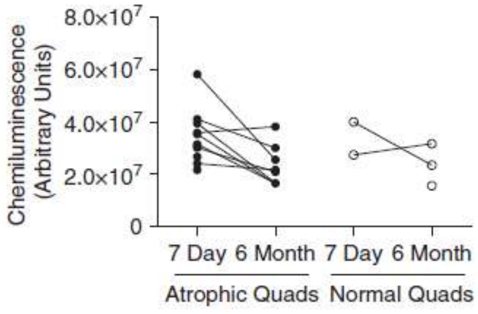
A Pilot Study

Nested, prospective, study of patients on MV for at least 7 days. Evaluation at D7 and M6 post ICU discharge.

RESULTS:

- Decreased strength at D7;
- Improvement at M6 (w/o normalisation)
- Sustained muscle atrophy at M6 in the majority of patients
- Persistent myopathy detected by EMG at M6 in 3/8 patients
- Inflammatory cells infiltration present at D7 resolves at M6
- The UPS-related proteolysis returns to levels comparable to healthy individuals despite persistent quadriceps atrophy



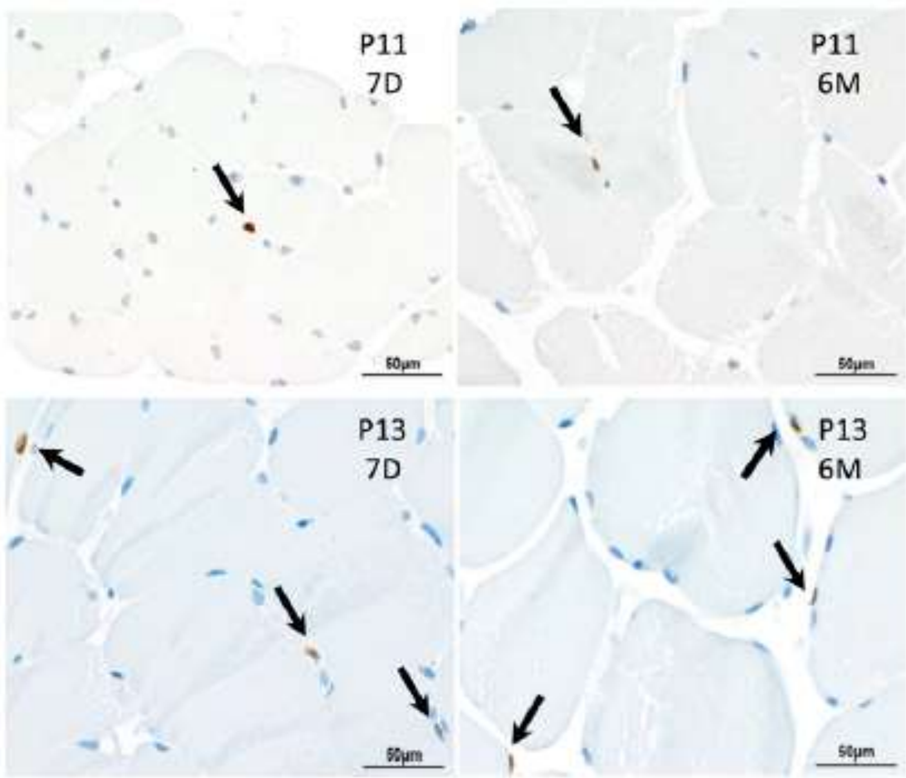


dos Santos et al. AJRCCM.2016;194: 821-30

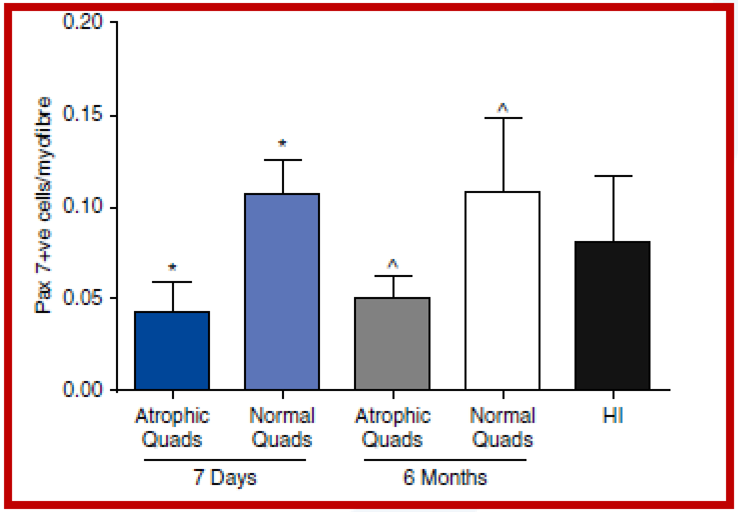
Mechanisms of Chronic Muscle Wasting and Dysfunction after an Intensive Care Unit Stay
A Pilot Study

SATELLITE CELL CONTENT

Persistent atrophy (CSA)



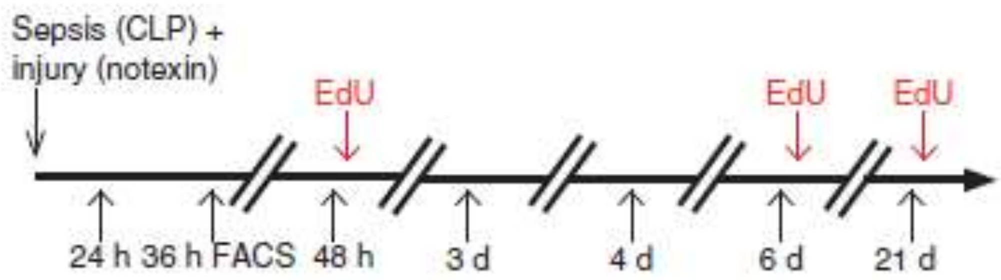
Normalized CSA



dos Santos et al. AJRCCM.2016;194: 821-30

Sepsis induces long-term metabolic and mitochondrial muscle stem cell dysfunction amenable by mesenchymal stem cell therapy

Male C57BL/6RJ mice
Polymicrobial peritonitis induced by Cecal Ligature and Puncture



D21:

- Marked anisocytosis and small atrophic myofibers
- Endomysial fibrosis
- Persistence of chronic endomysial inflammation
- Calcification of necrotic myofibers
- Increased CPK

Rocheteau P et al. Nature Med.2015;

Sepsis induces long-term metabolic and mitochondrial muscle stem cell dysfunction amenable by mesenchymal stem cell therapy

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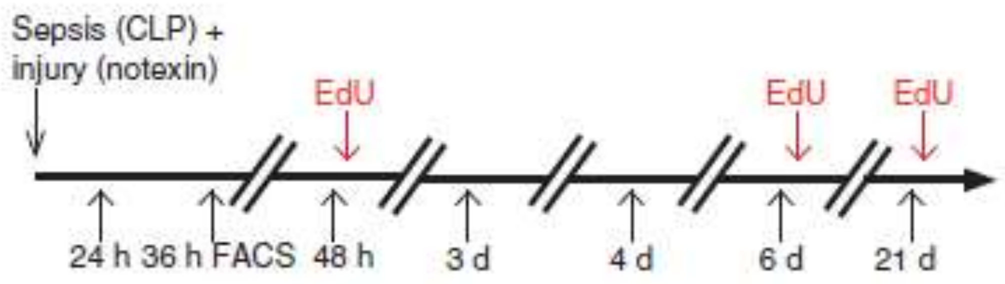

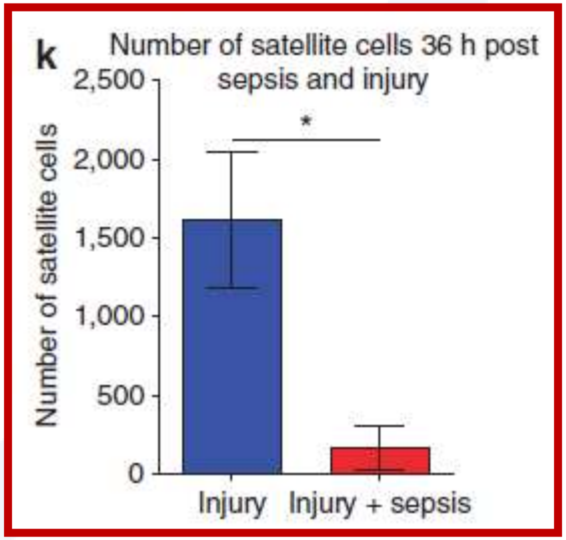

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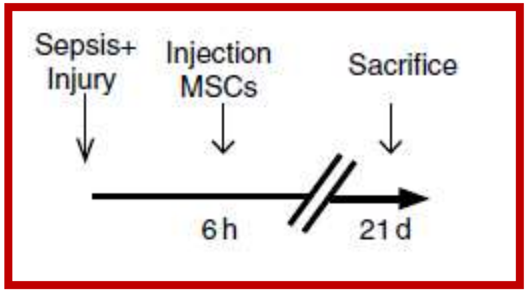
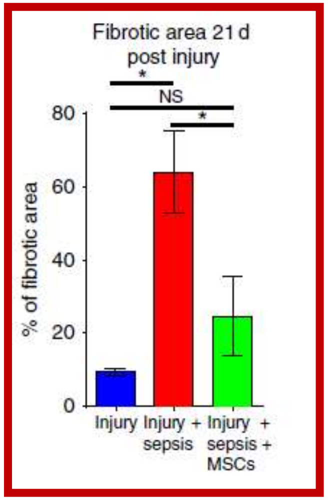
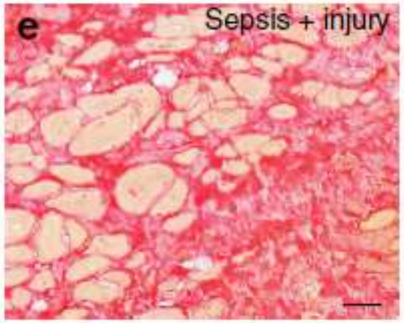
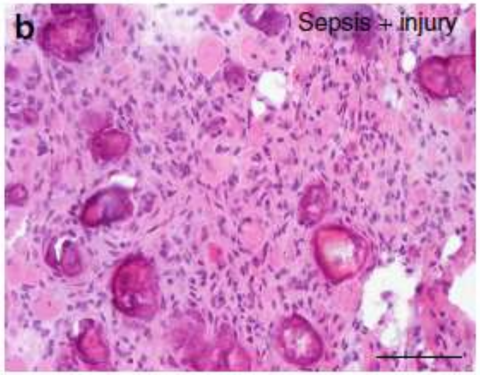
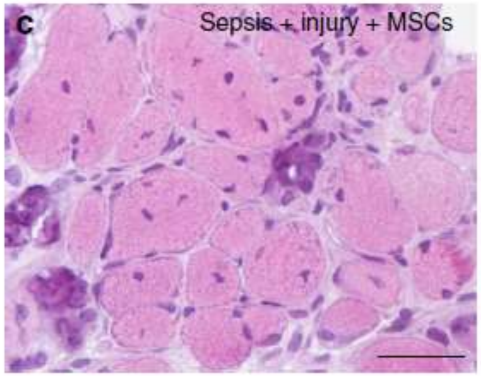
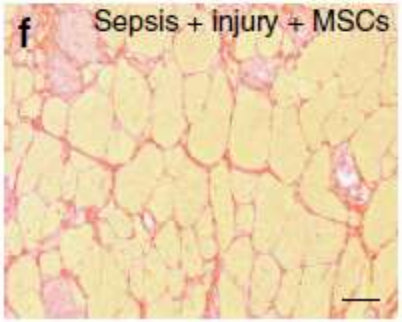






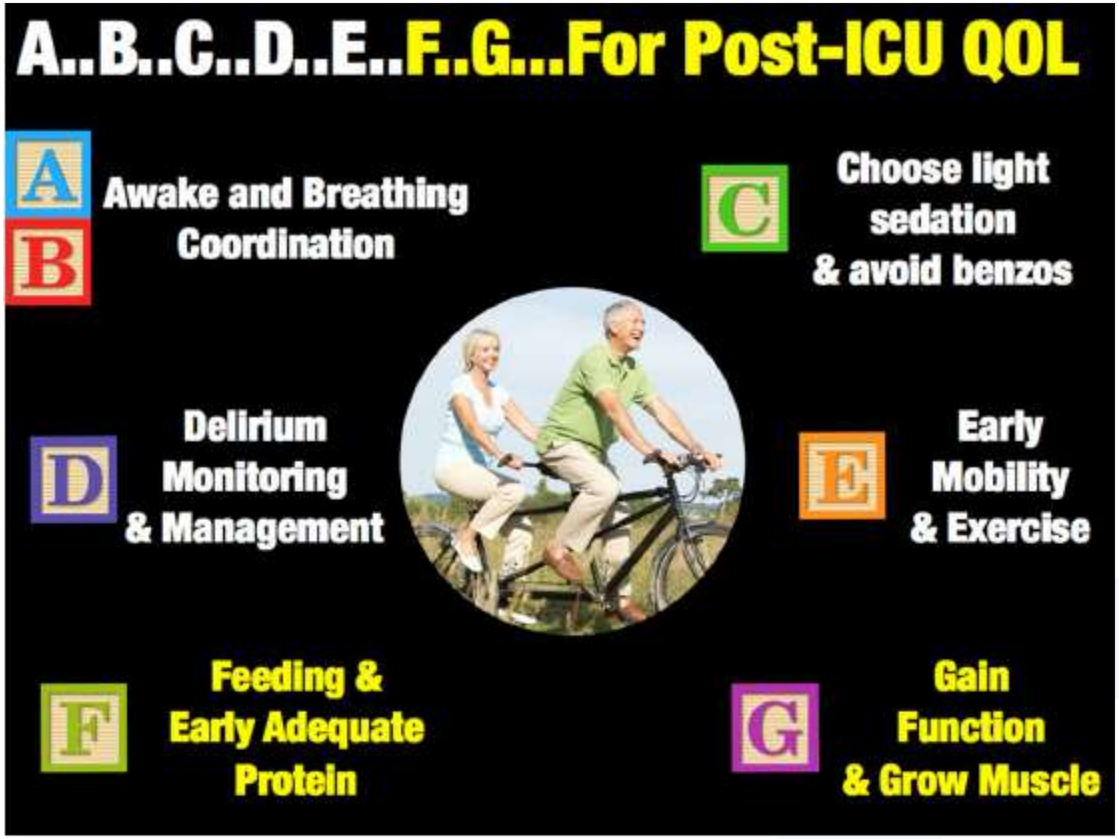






Rocheteau P et al. Nature Med.2015;

Winning the war against ICU-acquired weakness: new innovations in nutrition and exercise physiology



Wishmeyer P et al. Crit Care.2015; 19:S6

Winning the war against ICU-acquired weakness: new innovations in nutrition and exercise physiology

Recovery from ICU via Surveillance, Exercise, and Nutrition (RISEN) protocol

Day 1 (ICU admission)

Baseline nutritional and metabolic evaluation

- Nutrition risk score (NUTRIC score?)
- Metabolic evaluation with indirect calorimetry

Baseline muscle evaluation

- Lean body mass ultrasound
- Muscle glycogen ultrasound
- Markers of muscle injury?
  - CPK-MM (creatine phosphokinase-muscle component)
  - Myoglobin
  - LDH-(lactate dehydrogenase)

Every 3-7 days post ICU admission

Ongoing nutritional evaluation

- Indirect calorimetry to guide feeding and assess recovery and mitochondrial function along with lactate measurements.

Muscle evaluation

- Lean body mass ultrasound
- Muscle glycogen ultrasound
- Markers of muscle injury?
  - CPK-MM
  - Myoglobin

Physiologic exercise evaluation (when able)

- Diagnose exercise/mitochondrial function
- Individualized exercise prescription including resistance training to improve metabolic and musculoskeletal function.

Wishmeyer P et al. Crit Care.2015; 19:S6

TAKE HOME MESSAGES

ICU-AW

- Frequent complication
- Morbidity / Mortality
  Age, Comorbidities, Organ failure,
- Slow recovery and ongoing decline
- May warrant closer follow-up during and *after* ICU stay
- Potential therapies (MSC ? Nutrition? Mobilisation?)