CINMA

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Points of discussion

- Introduction
- Pathophysiology
- Diagnosis
- Prevention
- Management

Introduction

- At least 25% of patients who are intubated for more than 7 days develop ICU acquired weakness.
- Up to 100% of those who have severe sepsis and SIRS develops CINMA.
- 30% patient who develops CINMA may be left with residual weakness at the end of one year.

De Jonghe B etal, JAMA2002; 288: 2859–2867
Tennila AI et al Intensive Care Med 2000; 26:1360–1363
***Fletcher S etal** Crit Care Med 2003; 31: 1012–1016*

Nomenclature

- The term ***CIP*** was first described by Bolton in 5 critically ill patients with acute flaccid quadriplegia after extensive EP and histological examination.
- MacFarlane & Rosenthal in 1977 documented electrophysiological abnormalities consistent with an acquired myopathy in a young woman with quadriplegia who had received corticosteroids and neuromuscular blocking drugs for status asthmaticus. In 2000 Lacomis etal proposed the generic term ***CIM.***
- Later it was found that overlap was frequent. Hence terms like ***ICUAW/ICUAP/CIPNM*** etc came in use

Bolton etal Journal of Neurology, Neurosurgery, and Psychiatry 1984;47: 1223-1231
MacFarlane IA, Rosenthal FD: Lancet 1977; 2:615
Lacomis D, Zochodne DW, Bird SJ: Muscle Nerve 2000; 23: 1785–1788

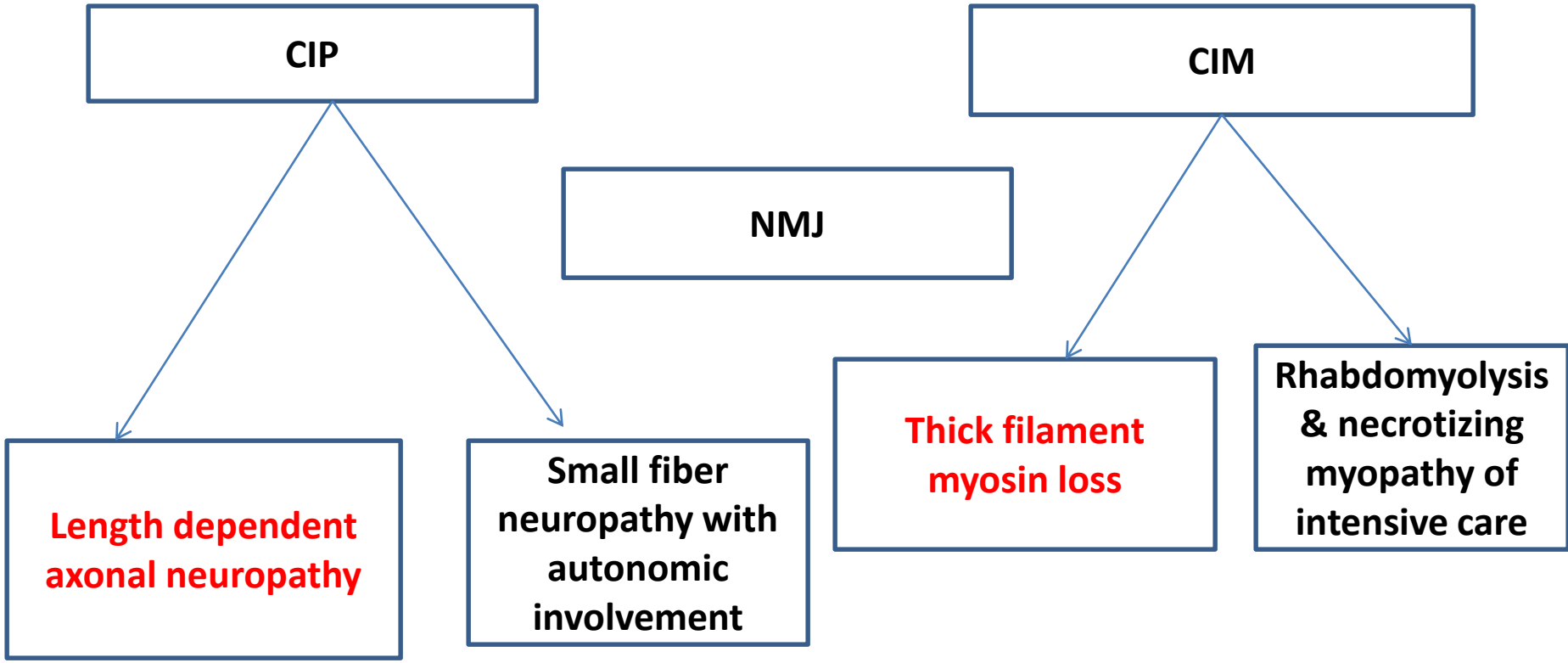
Generalized neuromuscular condition associated with critical care

Table 1. Generalized neuromuscular conditions associated with critical illness*

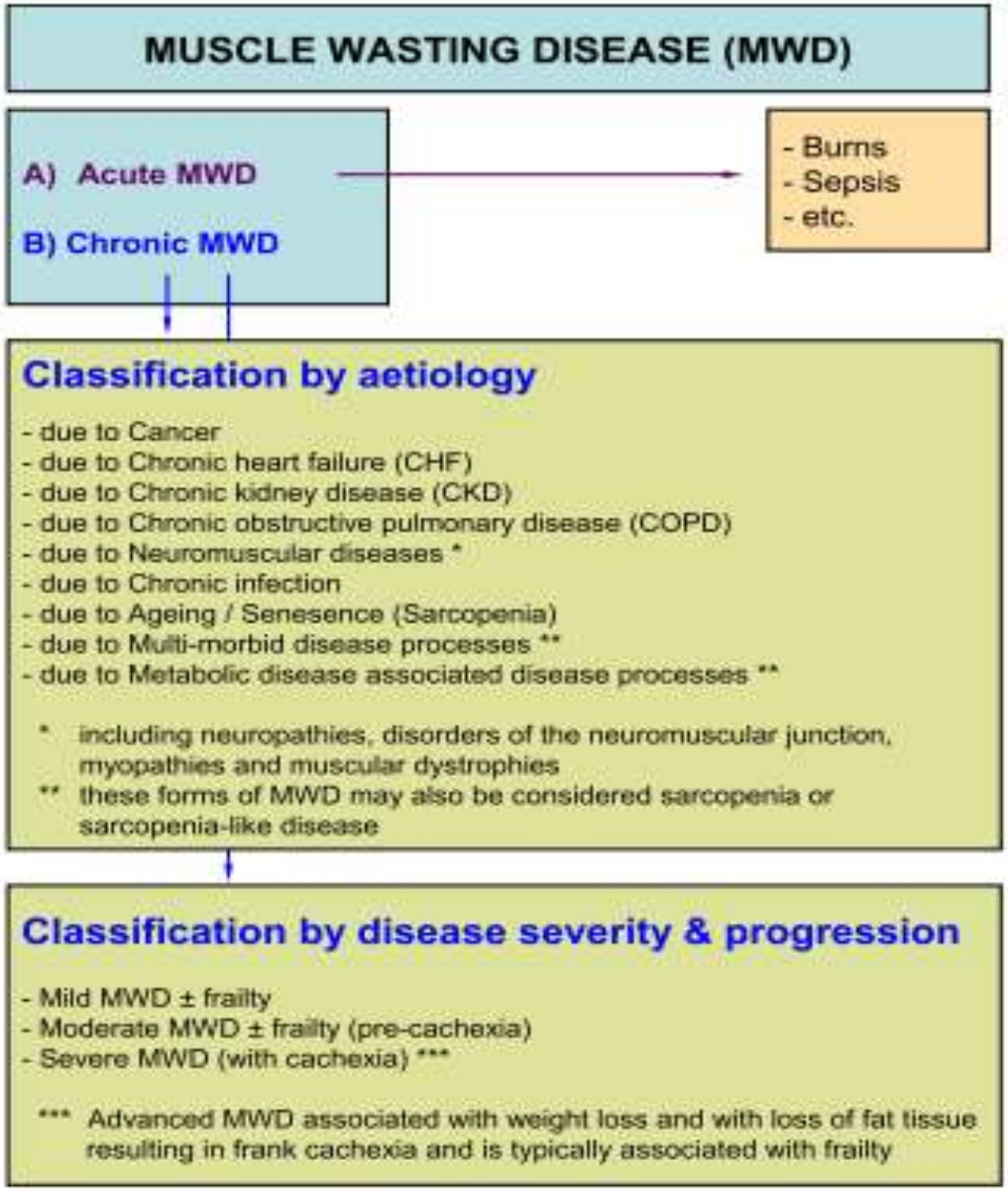
Condition	Incidence	Clinical features	Electrophysiologic findings	Serum creatine kinase	Muscle biopsy	Prognosis
Polyneuropathy						
Critical illness polyneuropathy	Common	Flaccid limbs; respiratory weakness	Axonal degeneration of motor and sensory fibers	Nearly normal	Denervation atrophy	Variable
Neuromuscular transmission defect						
Transient neuromuscular blockade	Common with neuromuscular blocking agents	Flaccid limbs; respiratory weakness	Abnormal repetitive nerve stimulation studies	Normal	Normal	Good
Critical illness myopathy						
Thick-filament myosin loss	Common with steroids, neuromuscular blocking agents, and sepsis	Flaccid limbs; respiratory weakness	Abnormal spontaneous activity	Mildly elevated	Loss of thick (myosin) filaments	Good
Rhabdomyolysis	Rare	Flaccid limbs	Near normal	Markedly elevated (myoglobinuria)	Normal or mild necrosis	Good
Necrotizing myopathy of intensive care	Rare	Flaccid weakness; myoglobinuria	Severe myopathy	Markedly elevated, myoglobinuria	Marked necrosis	Poor
Disuse (cachectic) myopathy	Common (?)	Muscle wasting	Normal	Normal	Normal or type II fiber atrophy	Good
Combined polyneuropathy and myopathy	Common	Flaccid limbs; respiratory weakness	Indicate combined polyneuropathy and myopathy	Variable	Denervation atrophy and myopathy	Variable

Bolton etal Muscle and Nerve 2005 32; 140-163

Classification –updated



Hermans etal Critical Care (2015) 19:274



Anker etal J Cachexia Sarcopenia Muscle (2014) 5:1–3

Diaphragmatic weakness in ICUAP

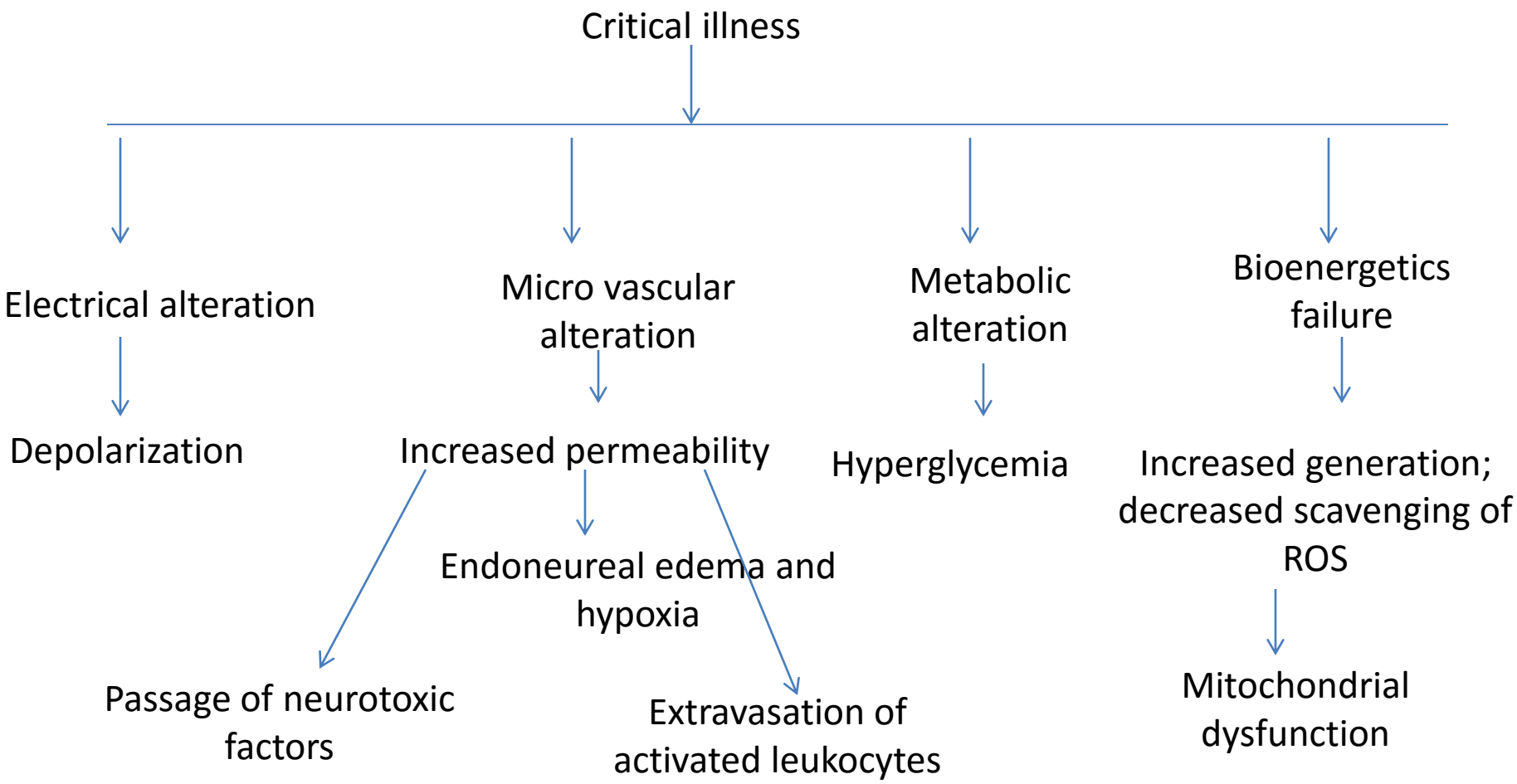
Study	Jung et al (France/2016)	Des etal (France/2016)
Participant	40 patients with MRC <48, ≥2d of MV and undergoing 1st SBT	76 patients who underwent MV for at least 24 hours and were scheduled for 1st SBT
Method	Diaphragmatic dysfunction was assessed with phrenic nerve stimulation and USG	Diaphragmatic dysfunction was evaluated with phrenic nerve stimulation and thickening fraction /excursion by USG. Limb muscle weakness was assessed with MRC
Result	32/40 i.e. 80% of patients with ICUAW had DD. But their severity was poorly correlated.	63% had DD, 34% had ICUAW and 21% had both. DD was independently associated with weaning failure, but ICU AW was not. DD predicted higher mortality whereas ICUAW was associated with longer duration of MV and hospital stay.

Jung et al Intensive Care Med (2016) 42:853–861

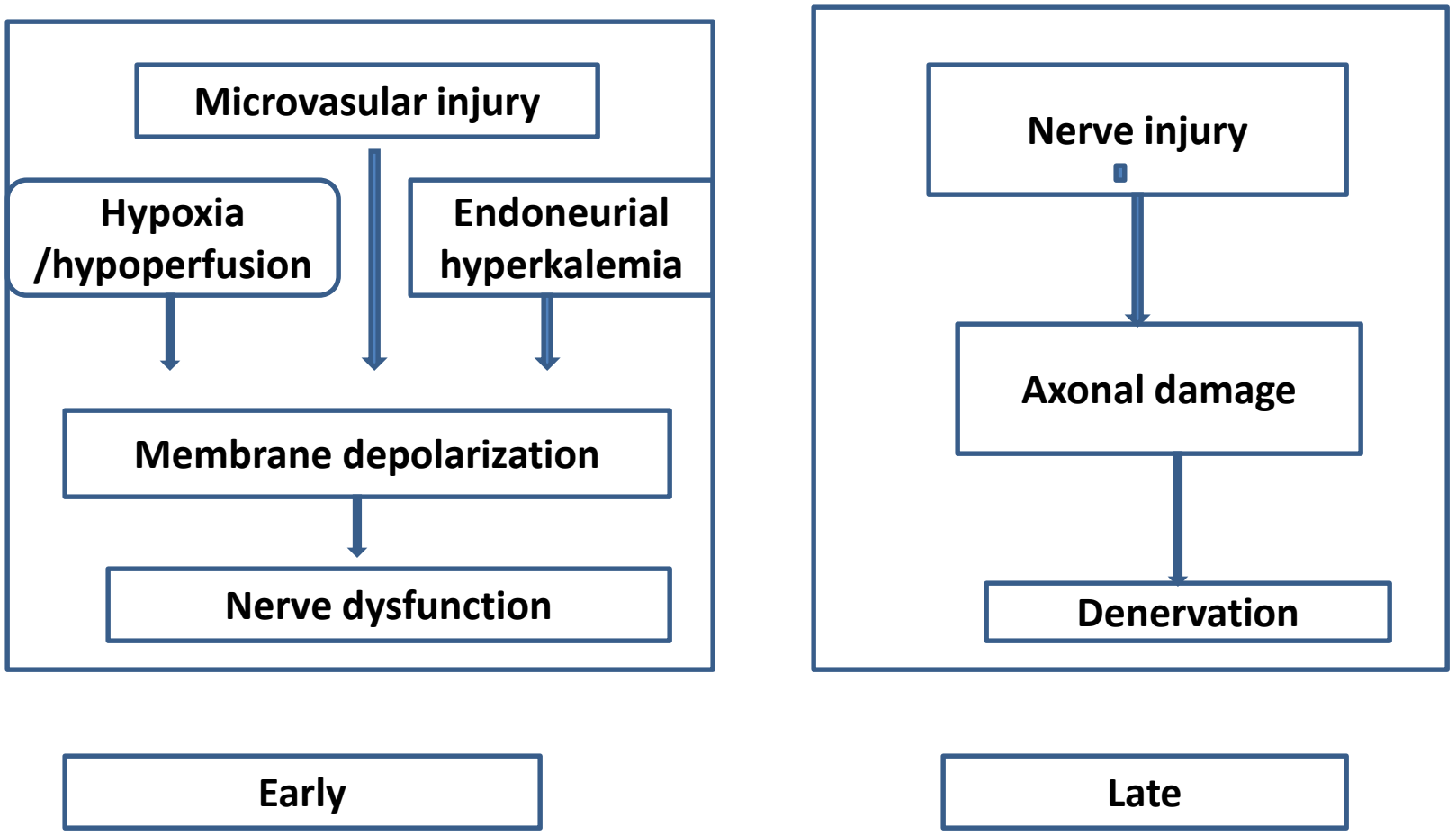
Dres et al AJRCCM Articles in Press. Published on 16-June-2016

- Inference:
  - Diaphragmatic dysfunction has an high incidence in patients with ICUAW (60-80%).
  - Onset of DD may be earlier than onset of ICUAW.
  - And it may predispose to ICUAW by prolonging mechanical ventilation days.

Pathogenesis -CIP

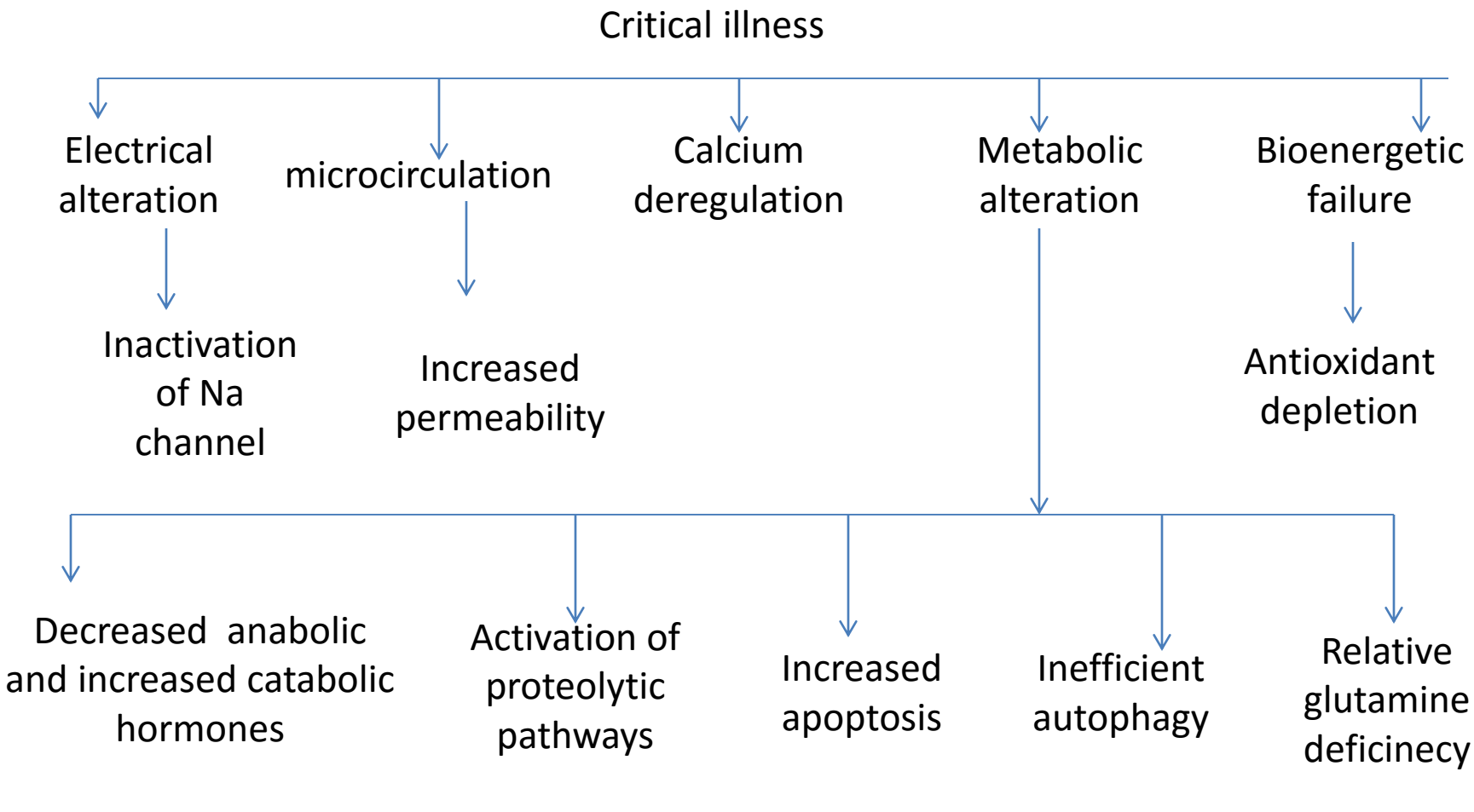


Time course in pathogenesis of CIP



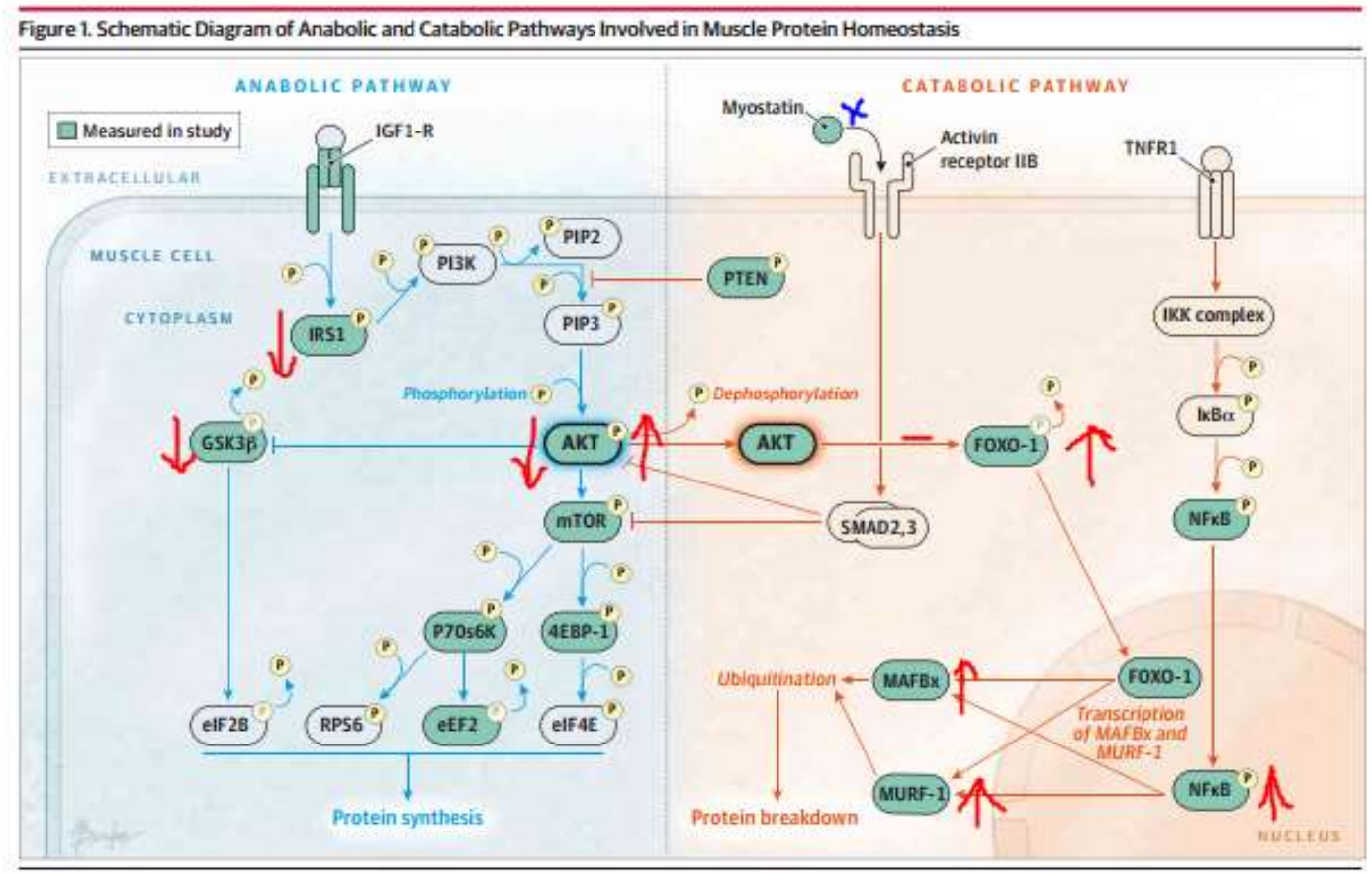
Batt et al Am J Respir Crit Care Med 2013 Vol 187, Iss. 3, pp 238–246,

Pathogenesis -CIM



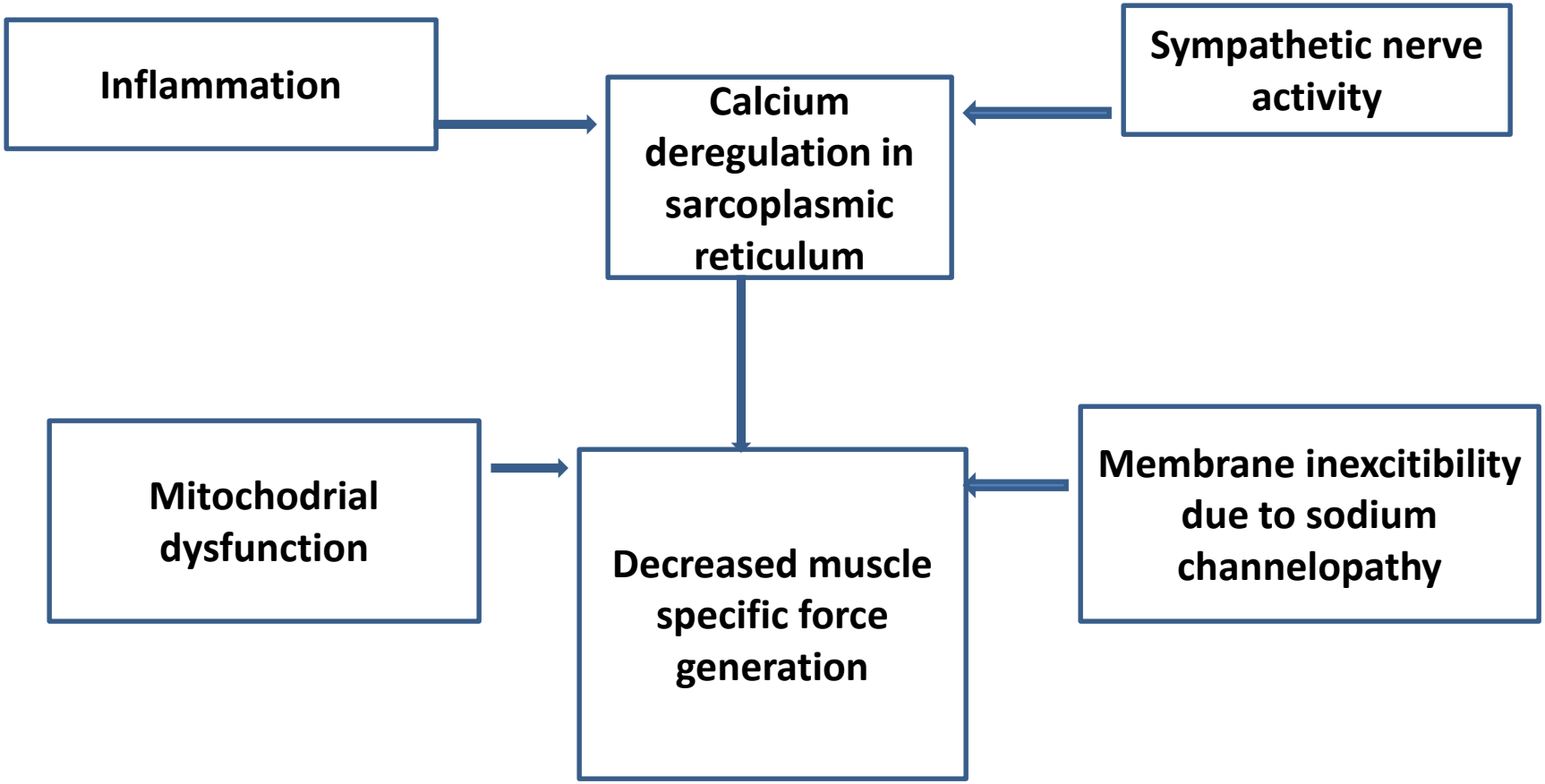
Hermans etal Critical Care 2008, 12:238

Pathway to muscle atrophy -CIM



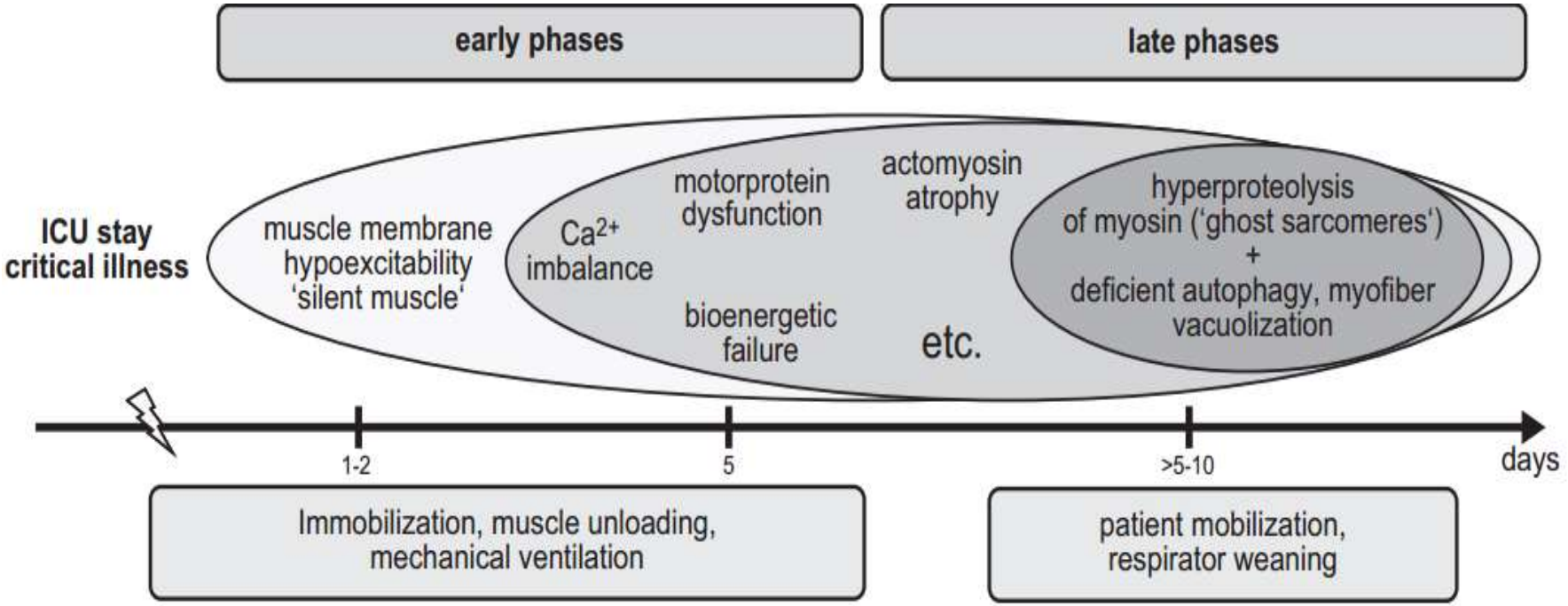
Batt etal Am J Respir Crit Care Med 2013 Vol 187, Iss. 3, pp 238–246

Pathway to contractile failure -CIM



Batt et al Am J Respir Crit Care Med 2013 Vol 187, Iss. 3, pp 238–246

Change in pathogenesis with time frame -CIM



Friedrich etal Physiol Rev 2015; 95: 1025-1109

Pathogenesis –human study

Study	Prospective longitudinal study
Participants	15 patients on for ≥7 days from 3 ICUs in Toronto; 11 of them were followed up at 6 months.
Method	Patients were assessed at 7days and 6 months after ICU discharge. 6MWD, EMG, NCS, muscle bulk by CT, voluntary contractile capacity were measured and percutaneous BX done from vastus lateralis.
Outcome	Compared to day 7, increased ubiquitin proteasome system mediated muscle proteolysis, inflammation, and decreased mitochondrial content all normalized at 6 months. Autophagy markers were normal at 6 months. Patients with sustained atrophy had decreased muscle progenitor (satellite) cell content. Muscle mass reconstitution was not associated with functional recovery due to persistance of contractile dysfunction.

Santos etal AJRCCM article in press published on 8th April 2016

Role of sepsis associated cytokines

Cytokines	Effect on skeletal muscles
TNF alpha	•Depolarization of plasma membrane. •Na^+-current inhibition, left shift of Na^+ channel activation and inactivation. •Induces muscle proteolysis and atrophy by activating ubiquitin-proteasome pathway. •Decreases Ca^{2+} transient amplitudes by 50% (in myotubes). •Depresses tetanic force production in limb and diaphragm muscle. • Induces insulin resistance in muscle.
IL1	•Associates with RyR1, blocks SR Ca^{2+}-release, and decreases SR Ca^{2+} leak in muscle fibers. • Induces skeletal muscle proteolysis. • Inhibition of protein synthesis.
IL6	•Promotes infiltration of myocytes with PGE. • Induces skeletal muscle protein break down. • Reduces insulin stimulated glucose uptake in muscle.

Friedrich etal .Physiol Rev. 2015 Jul; 95(3): 1025–1109

Clinical evidence

Study	Prospective observational study
Participants	40 ICU patients with SAPS score ≥20
Method	Muscle membrane excitability was measured after direct stimulation for 3 successive days. Inflammatory cytokines level, and hemodynamic parameters were measured to look for association.
Result	22 patient showed abnormal muscle membrane excitability. On multivariate linear regression only serum IL6 remained the significant risk factor.

Weber-Carstens et al. Critical Care 2010, 14:R119

Author (year)	Witteven et al (2014)
Aim of systematic review	To investigate whether ICUAW is characterized by local inflammation in muscle or nerve tissue or both.
No of studies	12 animal studies and 20 human studies identified
Population in human studies	ICU patients with acquired weakness
Intervention	Muscle and nerve biopsies
comparator	Control patients include patients with neuromuscular disease, healthy control, or ICU patients without weakness.
Pooled effect	Data on inflammation in the muscle and nerve tissue of all the patients with ICUAW were pooled.
Conclusion	The available literature suggests that local inflammation is found in ICU-AW. However, whether this is specific for ICU-AW, cannot be concluded, because appropriate control samples are lacking.

Witteven etal Journal of the Neurological Sciences 2014; 345: 15–25

	Muscle				Nerve			
	Number of studies	Total ICU-AW patients	Patients with positive finding, n	Percentage with positive finding (95% CI)	Number of studies	Total ICU-AW patients	Patients with positive finding, n	Percentage with positive finding (95% CI)
Any inflammatory cells	*14*	*116*	*29*	*25 (18–34)*	*7*	*46*	*2*	*4 (0–15)*
CD4 positive cells	2	35	21	60 (44–74)				
CD8 positive cells	2	35	11	31 (18–48)				
B-cells	2	34	0	0 (0–12)				
Macrophages	2	35	16	46 (30–62)				
Any antigen presenting molecules	*3*	*44*	*40*	*91 (79–97)*				
HLA-1	3	44	39	89 (76–96)				
HLA-DR	1	29	29	100 (86–100)				
Any complement factors	*3*	*44*	*32*	*73 (58–84)*				
MAC	3	44	32	73 (58–84)				
Any cytokines	*1*	*30*	*28*	*93 (78–99)*	*1*	*22*	*21*	*95 (76–100)*
IL-1 beta	1	28	20	71 (53–85)				
IL-12	1	26	19	73 (54–87)				
IFN-gamma	1	25	10	40 (24–59)				
TNF-alpha receptor	*1*	*30*	*27*	*90 (74–97)*	*1*	*22*	*21*	*95 (76–100)*
IL-10	1	28	27	96 (80–100)				
Any adhesion molecules	*1*	*30*	*21*	*70 (52–83)*	*1*	*22*	*22*	*100 (82–100)*
E-selectin	1	26	0	0 (0–15)	1	22	15	68 (47–84)
ICAM-1	1	26	15	58 (39–74)	1	22	22	100 (82–100)
VCAM-1	1	30	16	53 (36–70)	1	22	17	77 (56–90)

Diagnosis

- Clinical
- Electrophysiology.
- Imaging
- Histopathology

Clinical diagnosis –MRC score

MRC Sum Score Criteria

- Evaluation of adequate awakening
  - Open/close your eyes
  - Look at me
  - Open your mouth and put out your tongue
  - Nod your head
  - Raise your eyebrows when I have counted up to 5
- Muscle groups evaluated (B/L)
  - Wrist extension
  - Elbow flexion
  - Shoulder abduction
  - Dorsiflexion of the foot
  - Knee extension
  - Hip flexion

- Appointed scores
  - 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 force

Friedrich eta; Physiol Rev. 2015 Jul; 95(3): 1025–1109.

Inter observer agreement on MRC

Study design	Cross sectional observational study
Participants and method	2 observers independently measured Medical Research Council (MRC) sum-score (n = 75) and handgrip strength (n = 46) in a cross-sectional ICU sample who had stayed in ICU for ≥7 days.
Result	•The agreement on identifying patients with an MRC sum-score <48 was good (kappa = 0.68 +/- 0.09). •For identifying ‘‘severe weakness,’’ as revealed by an MRC-sum score <36, agreement was excellent (kappa = 0.93 +/- 0.7). •Using equivalent cut-offs for the subtotal scores for the upper and lower limbs separately, there was very good agreement in diagnosing ‘‘significant weakness’’ in the upper limbs (kappa = 0.88 +/- 0.07). •Agreement was also good for handgrip strength.

Hermans etal. Muscle Nerve , 2012; 45: 18–25

MRC in predicting ICU outcome

Study place/year	Participant and method	Objective	Result
De Jonghe etal (France /2002)	95 Pt on MV assessed with MRC score (MRC<48 as ICUAP) on D7 after awakening.	ICUAP –incidence, risk factors and outcome	Pt with MRC<48 had longer duration of MV(P=0.03)
Nanas etal (Greece/2008)	185 patients assessed after 48-72 hrs after awakening with MRC (MRC<48 as ICUAP)	ICUAP –risk factors	Pt with MRC<48 had a higher ICU mortality (P<0.05)
Naeem etal (USA /2008)	136 pt on MV for ≥5 days were assessed on day of awakening with MRC and hand grip strength	ICUAP -outcome	Both average MRC <4 and hand grip strength were associated with increased hospital mortality

De Jonghe B etal, JAMA2002; 288: 2859–2867

Nanas etal Acta Neurol Scand 2008: 118: 175–181

Naeem etal Am J Respir Crit Care Med Vol 178. pp 261–268, 2008

Electrophysiology

Proponent for routine EP to diagnose ICUAW	Opponent for routine EP to diagnose ICUAW
CIM/CIP may masquerade as coma which is considered a deadly sign in clinical medicine. A confirmed diagnosis may obviate need for pessimistic prognostication.	Limitation of EP study due to technical difficulties.
Clinically muscle weakness cannot be assessed until return of sensorium, but in EP, direct muscle stimulation can overcome the same	EP testing cannot predict reversibility of ICUAW
	EP also cannot predict clinically meaningful outcome e.g. length of mechanical ventilation/ ICU stay etc
	As no specific curative treatment is available, making a highly specific diagnosis doesn't translate into any benefit in decision making

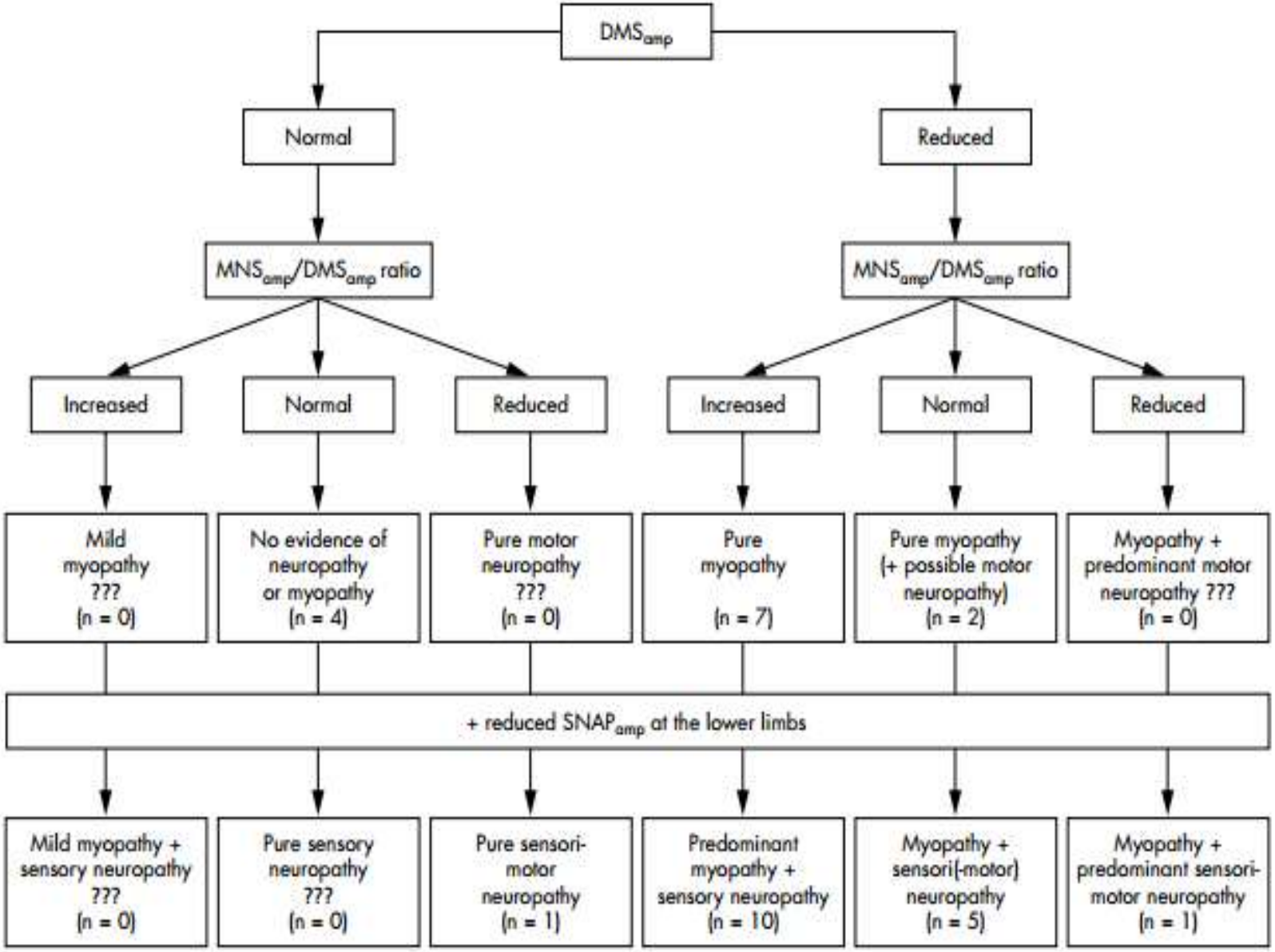
Schweickert et al chest 2007; 131:1541–1549

EP –features

CIP	CIM
On NCS maintained conduction velocity with reduced motor nerve CMAP and sensory nerve SNAP suggestive of axonal polyneuropathy.	.
On EMG presence of fibrillation potentials and positive sharp waves at rest suggests recent denervation.	On EMG during voluntary muscle contraction, short duration, low amplitude motor unit potentials are suggestive of myopathy

•In absence of voluntary contraction direct muscle stimulation can be used to diagnosis myopathy.
•A nerve /muscle ratio (i.e. ration of CMAPs after nerrve stimulation and direct muscle stimulation) <.5 indicates neuropathy and >.5 indicates myopathy.

Schweickert et al chest 2007; 131:1541–1549
Rich etal Muscle Nerve 1997 Jun;20(6):665-73



Lefaucher eta J Neurol Neurosurg Psychiatry 2006;77:500–506

Clinical correlation

Study place/year	Moss et al (USA/2014)	Weiske et al (Netherlands /2015)
Participant	75 patients in ICU with severe sepsis or nonspetic patients with ≥2 organ failure including lung.	40 critically ill pt on MV for ≥2days and RASS <-3
Objective	Diagnostic performance of single nerve NCS for ICUAW	Feasibility and accuracy of EP study for CINM in non awake patient.
Method	NCS and EMG done on 6 nerves b/l if possible within 24 hours of inclusion, then weekly until ICUAW diagnosed on MRC or discharge from ICU.	EP comprised NCS of three nerves and, if coagulation was normal, EMG in three muscles. Upon awakening, strength was assessed (ICU-AW: average Medical Research Council score <4)
Result	Best accuracy were found for peroneal and sural nerve and combining them increase the yield	NCS was feasible for ulnar and peroneal nerves; but cut off values validated in ICU pt is required

Moss et al Intensive Care Med (2014) 40:683–690
Weiske etal Neurocrit Care (2015) 22:385–394

Nerve (recording site)	c-Statistic AUC	Best cutoff amplitude value	Normal nerve amplitude	Sensitivity (with 95 % CI)	Specificity (with 95 % CI)
Sural antidromic ($n = 61$)	0.8611	4.0 μV	>10 μV	94 % (88–100 %)	70 % (59–81 %)
Radial antidromic ($n = 61$)	0.6903	16.2 μV	>20 μV	75 % (64–86 %)	71 % (60–82 %)
Sensory median orthodromic ($n = 61$)	0.7369	5.2 μV	>10 μV	81 % (71–91 %)	67 % (55–79 %)
Peroneal (EDB) ($n = 60$)	0.8856	0.65 mV	>0.8 mV	94 % (88–100 %)	74 % (63–85 %)
Tibial (AHB) ($n = 63$)	0.8315	5.8 mV	>1 mV	94 % (88–100 %)	69 % (58–80 %)
Motor median (APB) ($n = 60$)	0.7209	3.8 mV	>5 mV	63 % (51–75 %)	77 % (65–89 %)

EDB extensor digitorum brevis, *AHB* abductor hallucis brevis, *APB* abductor pollicis brevis

Moss et al Intensive Care Med (2014) 40:683–690

Histopathology

- The definitive diagnosis of muscle involvement requires examination of muscle tissue by biopsy.
- light-microscopic findings
  - ❑ muscle fiber atrophy (preferentially type II fibers),
  - ❑ occasional fiber necrosis, regeneration, and
  - ❑ decreased or absent reactivity in myofibrillar adenosine triphosphatase staining, corresponding to a selective loss of myosin filaments.
- On electron microscopy
  - ❑ Preferential loss of thick filaments with splitting of A band and normal loss of sarcomeric structure.
  - ❑ Mitochondria were often abnormal in size, shape, and distribution, and even in fibers where there appeared to be no loss of myofilaments, mitochondria tended to be elongated in the long axis of muscle fibers

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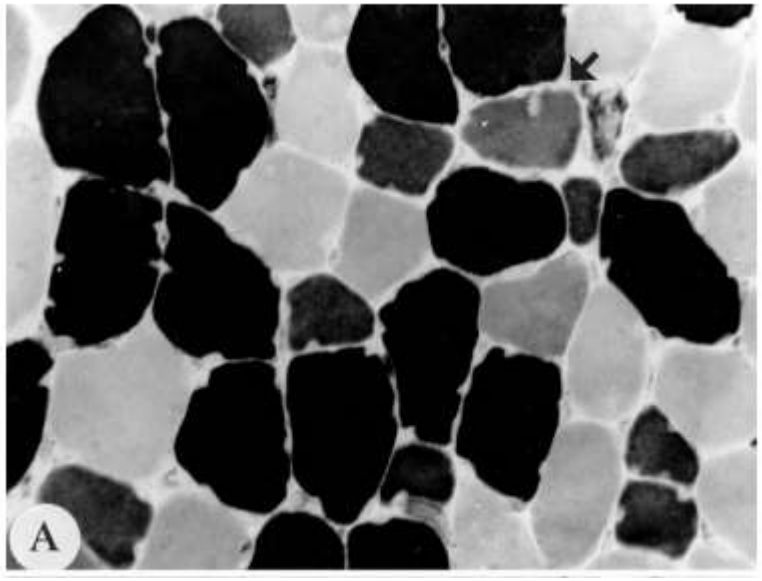
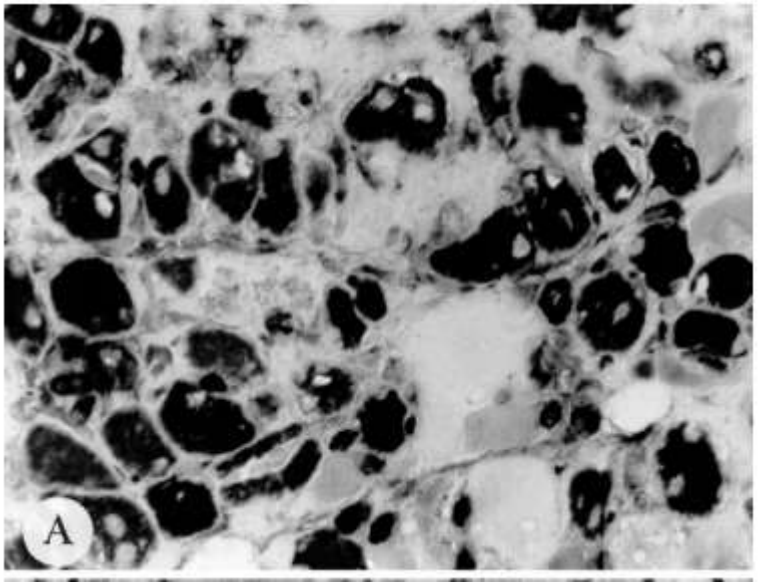
Schweickert et al chest 2007; 131:1541–1549
Danon etal muscle and nerve 1991; 14: 1131-1139



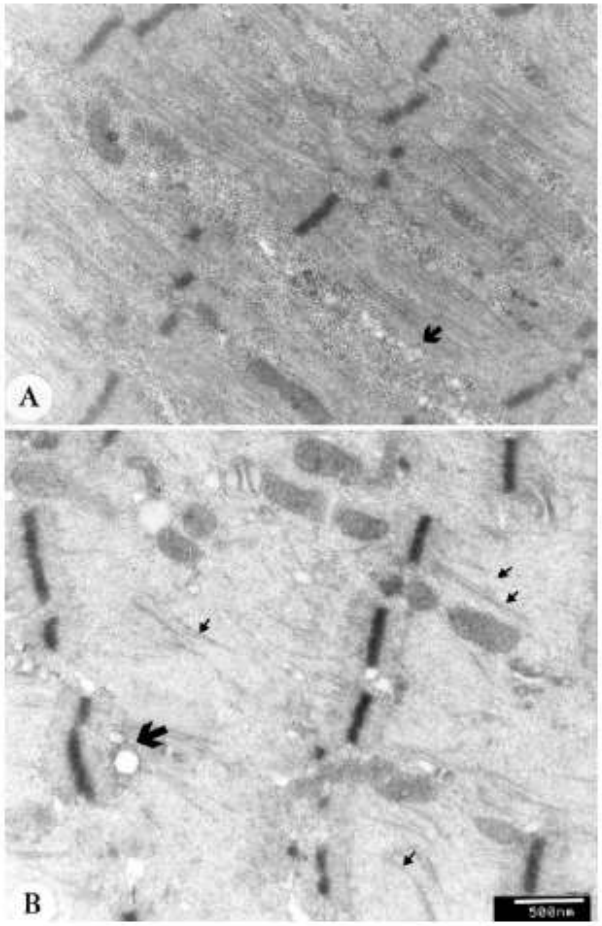


Early in the course of CIM- stained for myosin ATPase

Late in the course of CIM – stained for myosine ATPase

Stibler et al intensive care med (2003) 29:1515–1527

TEM



Stibler et alintensive care med (2003) 29:1515–1527

- On SDS –PAGE
  - Low myosin/actin ratio on SDS PAGE correlates well with optical density of actin or myosin. Hence it has been proposed as an alternative method of diagnosis.

Stibler et alintensive care med (2003) 29:1515–1527

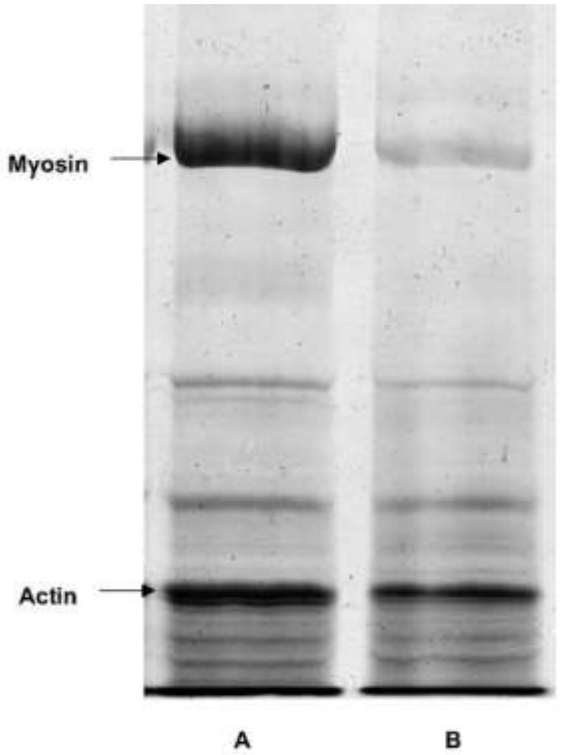


Fig. 5 SDS pore gradient electrophoresis of muscle proteins (diluted 1:2) from a control case (**A**) and a patient with CIM (**B**). Note the much reduced myosin content in the patient with CIM

Stibler et alintensive care med (2003) 29:1515–1527

Neuromuscular ultrasound

Study (place/year)	Puthucheary etal (England/2013)
Population	63 patients were recruited within 24 hours of hospital admission. Patients were included if anticipated to be intubated for >48 hours; to stay in ICU for >7 days and to survive ICU stay.
Intervention	Muscle loss was determined by serial ultrasound measurement of rectus femoris CSA on day 1,3,7 and 10. SOFA was measured as clinical correlate, protein to DNA ratio as biochemical correlate and vastus lateralis biopsy for histopathology
Comparator	8 volunteers in fasting and fed state.
Outcome	Rectus femoris CSA reduced significantly from day1 to day 7 and continued to decrease till D 10, it also correlated with MOF vs single organ failure. Other evidences of muscle wasting also showed same trend.

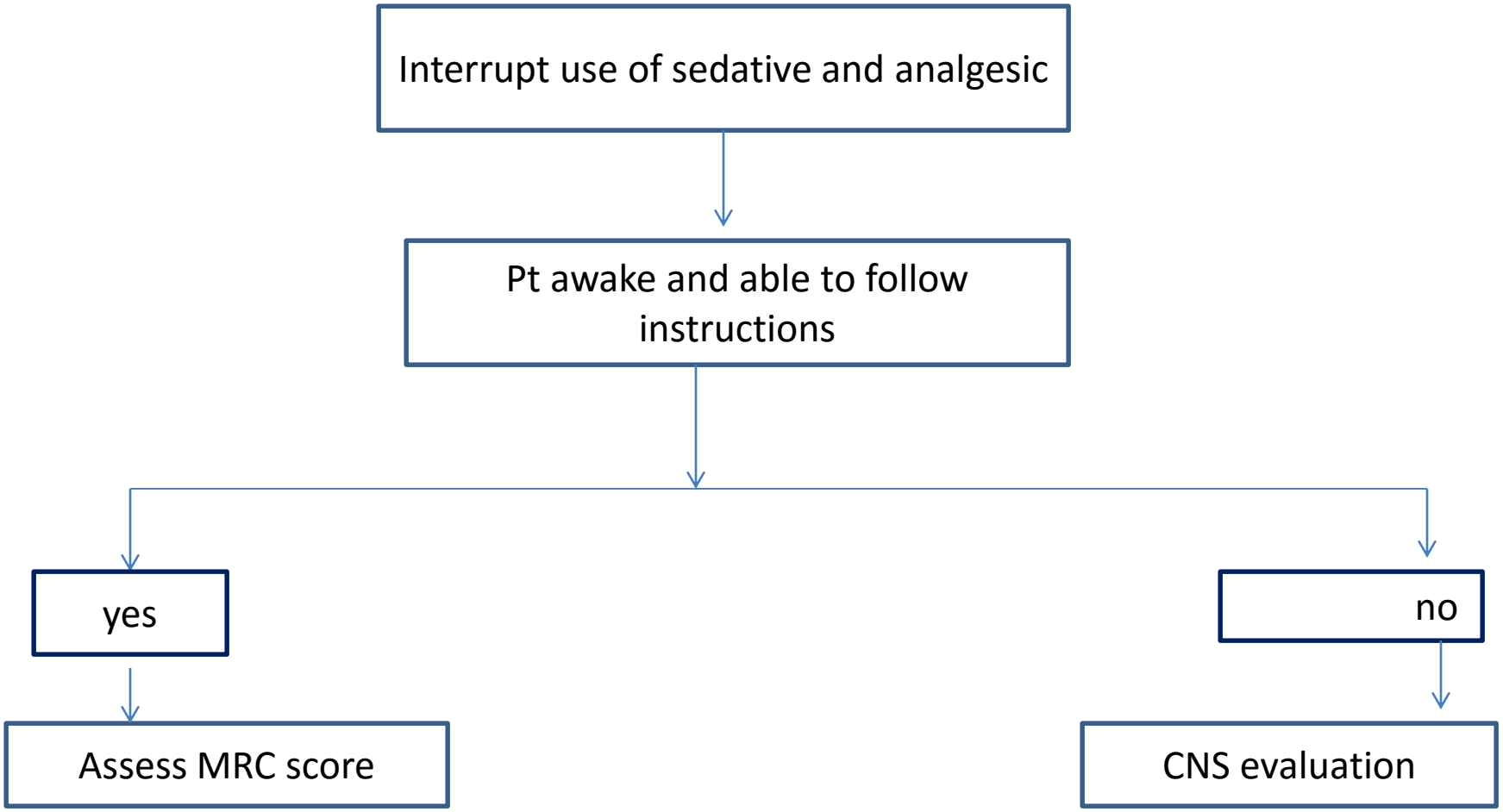
Puthucheary et al JAMA. 2013;310(15):1591-1600.

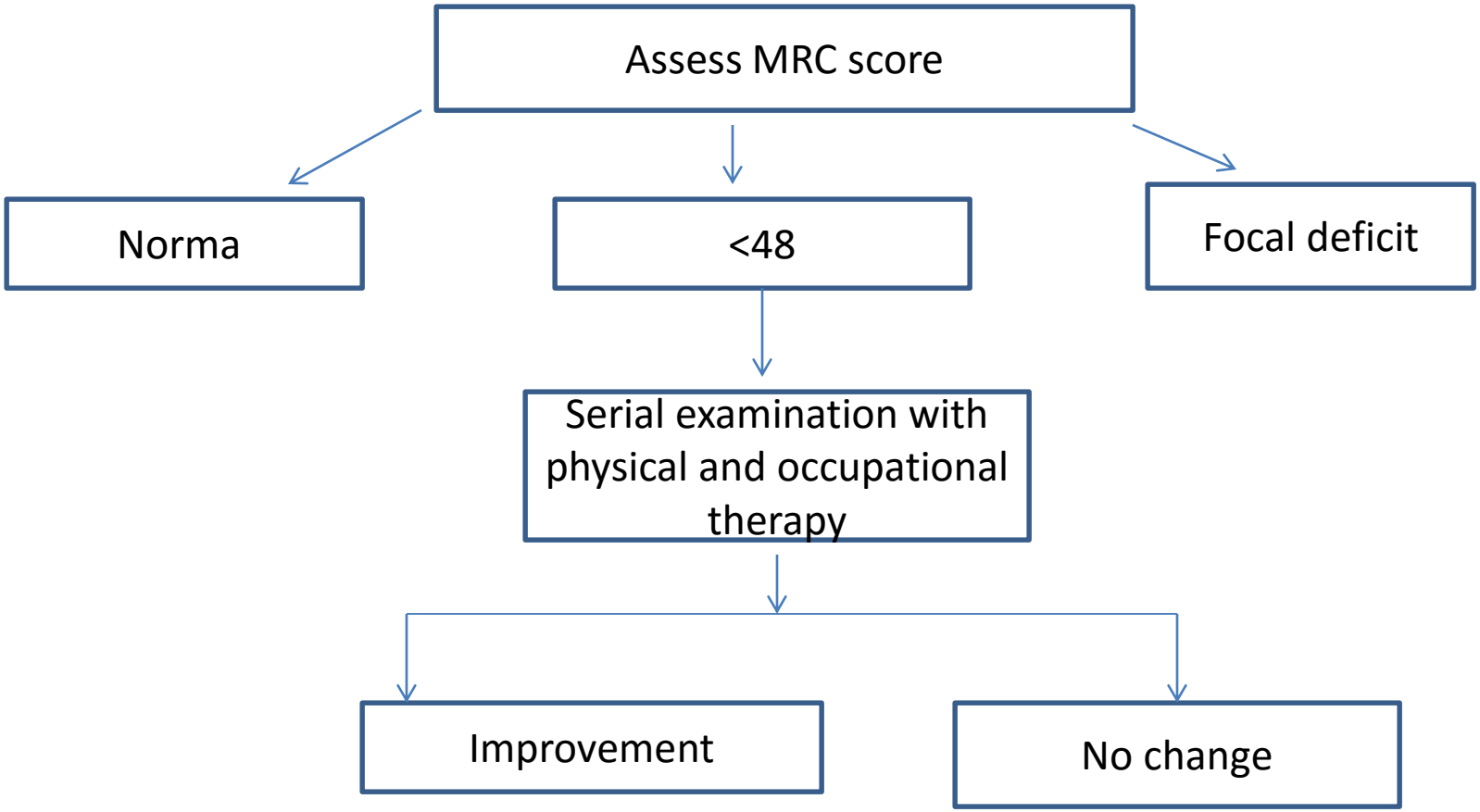
Role in diagnosis

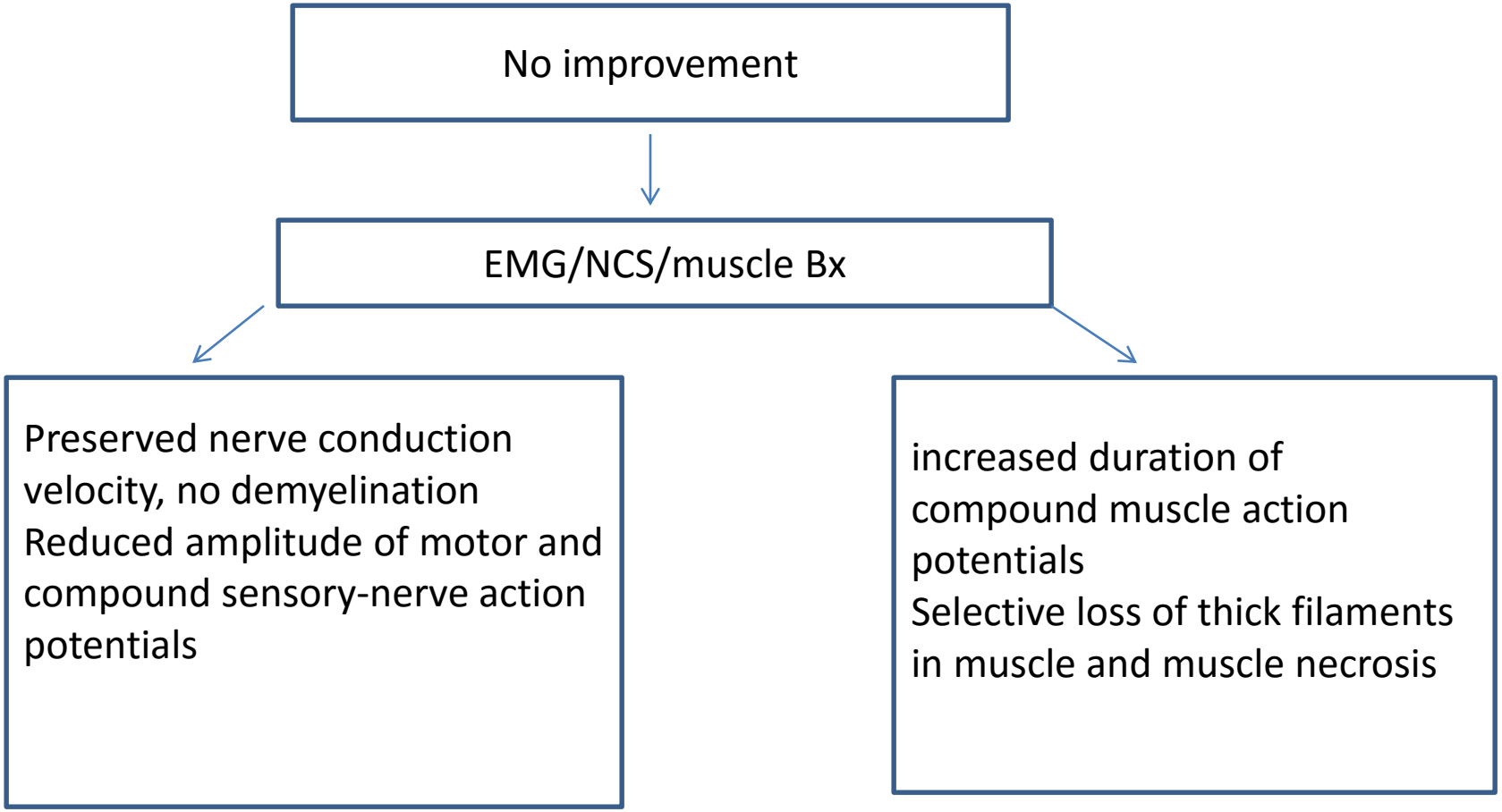
- In a recent systematic review 13 studies were found regarding NMUS in ICU patients.
- Different parameters has been used including
  - Muscle thickness
  - Cross sectional area
  - Gray scale mean/ echogenicity
- NMUS has been used for
  - assessment of muscle mass
  - muscle architecture
  - quantitative measure for study outcome specially in studies of NMES.
- But its place for diagnosis of ICUAW remains speculative and requires further research

Bunnell et al Muscle Nerve 52: 701–708, 2015

Algorithm


Interrupt use of sedative and analgesic
Pt awake and able to follow instructions
yes
no
Assess MRC score
CNS evaluation


Assess MRC score
Norma
<48
Focal deficit
Serial examination with physical and occupational therapy
Improvement
No change


No improvement
EMG/NCS/muscle Bx
Preserved nerve conduction velocity, no demyelination
Reduced amplitude of motor and compound sensory-nerve action potentials
increased duration of compound muscle action potentials
Selective loss of thick filaments in muscle and muscle necrosis

Risk factors as identified in different physiological model

Model (manipulation)	Risk factors reproduced	Pathological changes replicated
Rat steroid denervation (Lesion to the sciatic nerve, daily administration of corticosteroids)	▪Neuromuscular blockade ▪Steroid use	•Muscle atrophy •Disorganization of sarcomere •Preferential loss of myosin Electrical hypo/inexcitability
Rat ICU model (Infusion of neuromuscular blocking agents, mechanical ventilation together with treatments such as LPS and/or corticosteroids)	▪Immobilization ▪Neuromuscular blockade ▪Mechanical ventilation ▪Sepsis ▪Corticosteroid treatment	•Muscle atrophy •Preferrential myosin loss •Disorganization of sarcomere

Friedrich etal Physiol Rev. 2015 Jul; 95(3): 1025–1109.

Model (manipulation)	Risk factors reproduced	Pathological changes replicated
Cecum ligation and puncture model (Median abdominal laparotomy, mobilization of cecum, suture-ligation of cecum and needle puncture, relocation and closure)	Various degrees of sepsis (mild, moderate, severe), septic shock, depending on ligation length/level and puncture number	•Muscle atrophy •Myofibrillar protein loss •Disorganization of sarcomere •Decrease in twitch/tetanic forces •Increased sodium channel inactivation •Mitochondrial dysfunction
LPS (Single-dose injections of purified LPS from gram-negative bacteria (e.g., E. coli) sc, ip, or iv)	Various degree of sepsis	do

Friedrich etal Physiol Rev. 2015 Jul; 95(3): 1025–1109

Model (manipulation)	Risk factors reproduced	Pathological changes replicated
Rabbit burn injury model (Third degree burn injury on 15–20% body surface area)	▪Immobilization due to sickness ▪Parenteral nutrition ▪Glucose monitoring/control ▪Hyperinflammation	•Muscle atrophy •Ubiquitin proteosome activation •Impaired autophagy activation with parenteral nutrition
ICU patient in vitro serum challenge model (Serum fractions from ICU patients are applied to skeletal muscle cells (from animals) and acute or long-term effects studied in vitro)	Tests for a putatively myotoxic, systemically circulating factor	•Muscle atrophy •Preferential myosine loss •Muscle membrane depolarization •Ubiquitin proteosome activation

Friedrich etal Physiol Rev. 2015 Jul; 95(3): 1025–1109

Risk factors identified in human studies–patient characteristics

Study (year)	Population (No)	Age (years)	Females %	Severity of illness scores	MOF score	Sepsis %
Amaya – Villar {2005}	AECOPD on MV (30)	NS	NR	23.1vs14 **P<0.001**	NR	6 VS 1 **P=0.002**
Bednarik (2005)	Critically ill With ≥2 OF	NR	NR	NR	SOFA(At admission, delta and summed) **P <0.05**	NR
Bercker (2005)	50 ARDS patients	44 vs 24 **P=0.01**	NR	SAPS 35 vs 32 P=.445	SOFA 5 Vs 5 P=.694	NR
Campello ne (1998)	87 post liver transplant	NR	NR	APACHEII 24 Vs 16 **P=.005**	NR	NR

Stevens etal Intensive Care Med (2007) 33:1876–1891

Study (year)	Population	Age (years)	Female %	Severity of illness score	MOF score	Sepsis
De Jonghe etal (2002)	95 icu pt on MV ≥2 days	68 vs 59 **P=0.02**	50% vs 20% P<0.004	NS	No of days with≥2 organ dysfunction 10.3 VS 4.8 **P<.001**	Septic shock 9 vs 14 **P=0.09**
De Letter etal (2001)	98 ICU patients on MV for ≥4 days	NR	NR	APACHE III P=0.02	NR	Presence of SIRS P=0.04
Nanas etal (2008)	185 patients in ICU for ≥10 days	NR	NR	APACHE III 18.9 VS 15.6 **P=0.004**	SOFA 8.4 VS 7.1 **P=0.013**	Gram negative bacteremia **P =0.014**

Stevens etal Intensive Care Med (2007) 33:1876–1891

Nanas et al Acta Neurol Scand 2008: 118: 175–181

Risk factor –drugs

Study (year)	Serum glucose	Steroid	NMBA	aminoglycoside
A-V (2005)	NR	1649 VS 979 **P=0.05**	4 Vs 3 P=.188	NR
Bercker (2005)	166 vs 144 (mean of daily peak) **P<0.001**	20 vs 12 P=.739	NR	NR
Campellone etal (1998)	312 vs 221 **P=0.007**	2438 vs 1674mg **P=0.02**	NR	NR
De Jonghe etal (2002)	360 VS 259 **P=.001**	13of 54 and 13 of 18 **P=0.01** (but cumulative dose was not significant)	15 vs 29 **P=0.07**	16 VS 30 **P=0.04**

Stevens etal Intensive Care Med (2007) 33:1876–1891

Risk factor –drugs

Study (year)	Serum glucose	Steroid	NMBA	aminoglycoside	Vasopressors
De letter etal	NR	NS P=.67	NS P=.38	significant P=.049	NR
Nanas et al	NR	NS	NS	28vs 52 P=0.002	40 Vs 93 **P=0.003**

Stevens etal Intensive Care Med (2007) 33:1876–1891
Nanas et al Acta Neurol Scand 2008: 118: 175–181

Parenteral nutrition as a risk factor – mechanism

- Consequence of refeeding,
- high amounts of polyunsaturated fats, in the microcirculation were proposed as mechanisms
- Autophagy may also be involved in neuromuscular effects of nutrition in critically ill individuals.
- Nutrients, especially amino acids, are powerful suppressors of autophagy
- Insufficient activation of autophagy was found in muscle biopsies of fed critically ill patients
- higher protein delivery in the first week of critical illness was even associated with greater muscle wasting.

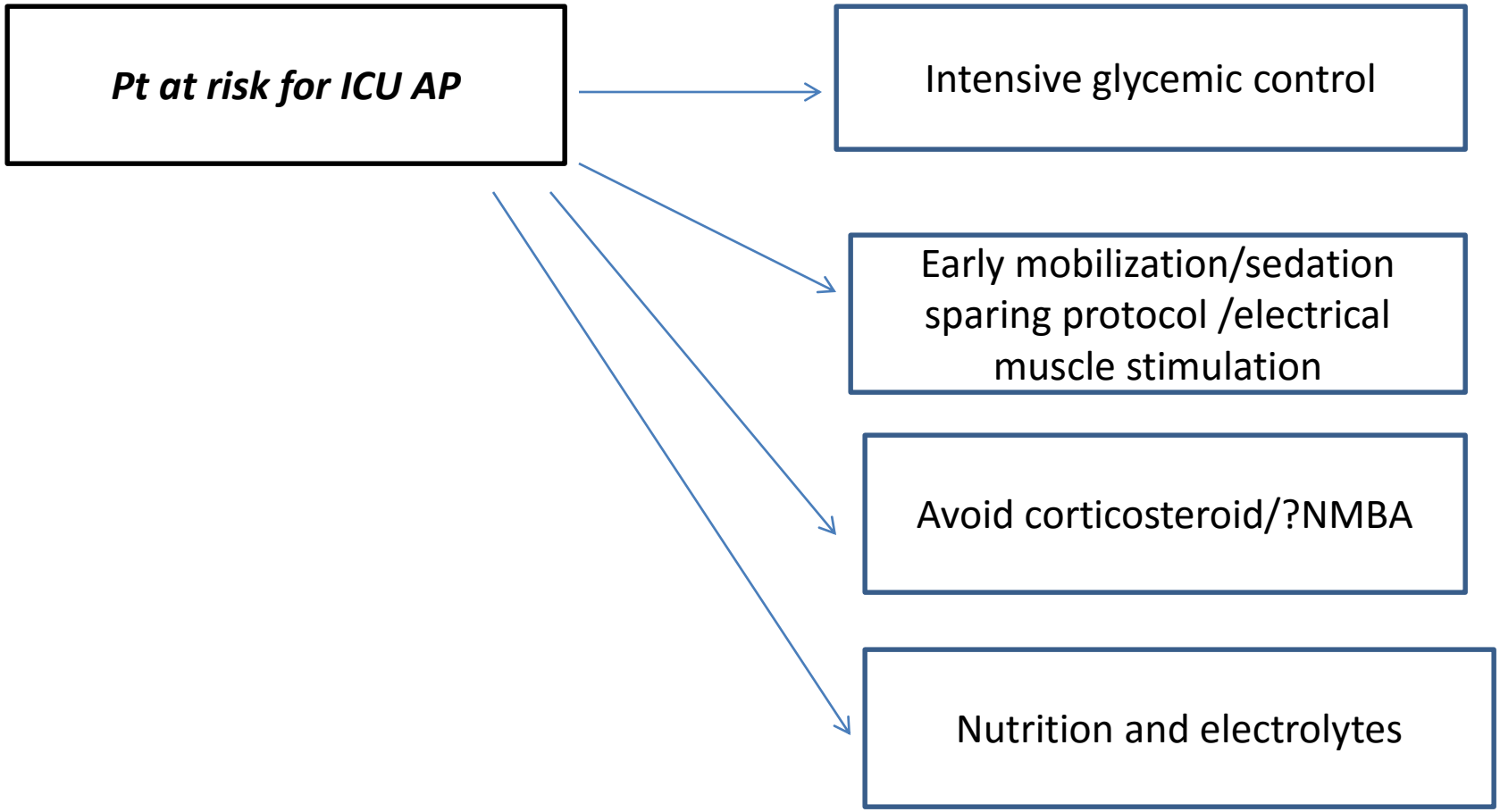
Friedrich etal Physiol Rev 2015; 95: 1025-1109

Evidence

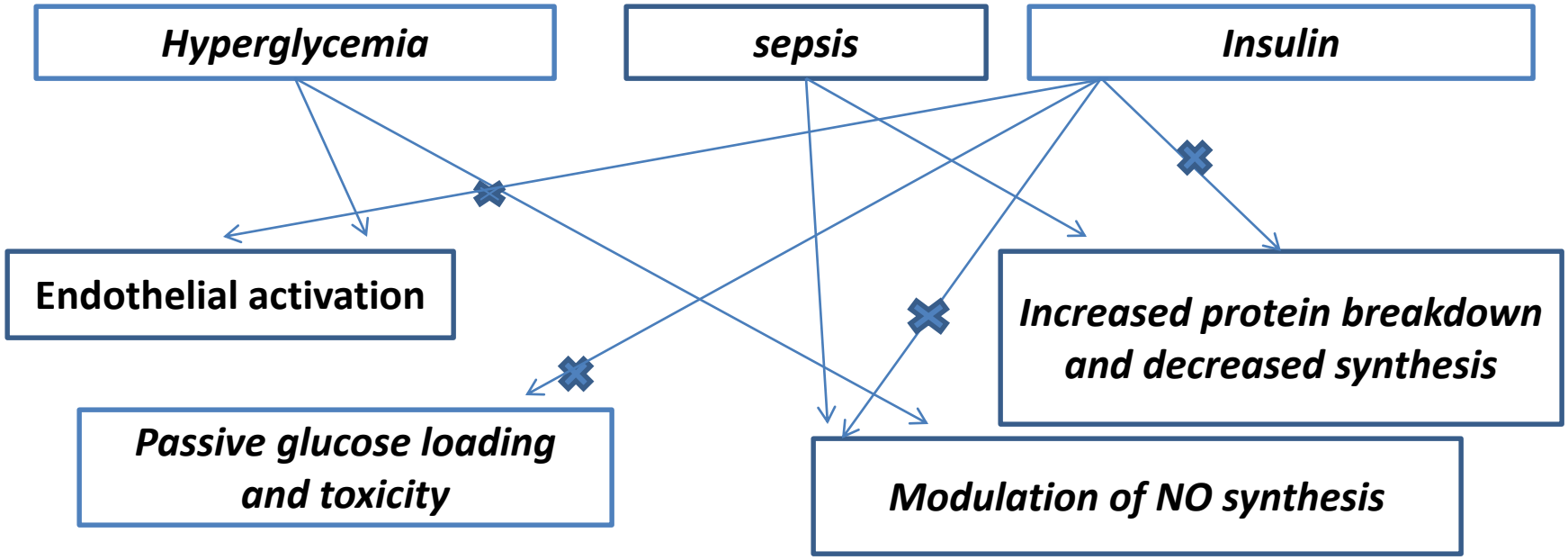
Study	Prospective subanalysis of EPaNIC trial
Population	600 awake patients with ≥8 days of ICU stay. (305 in early PN group and 295 in late PN group)
Method	Weakness was assessed with MRC score thrice weekly. Skeletal muscle biopsy was taken from 122 patients.
Comparator	20 voluntary controls for comparison of muscle biopsy
Outcome	Weakness id significantly more common with early PN and weakness recovered faster in late PN group.

Hermans etal lancet respiratory medicine 2013 62-629

Prevention


Pt at risk for ICU AP
Intensive glycemic control
Early mobilization/sedation sparing protocol /electrical muscle stimulation
Avoid corticosteroid/?NMBA
Nutrition and electrolytes

Intensive insulin therapy mechanism



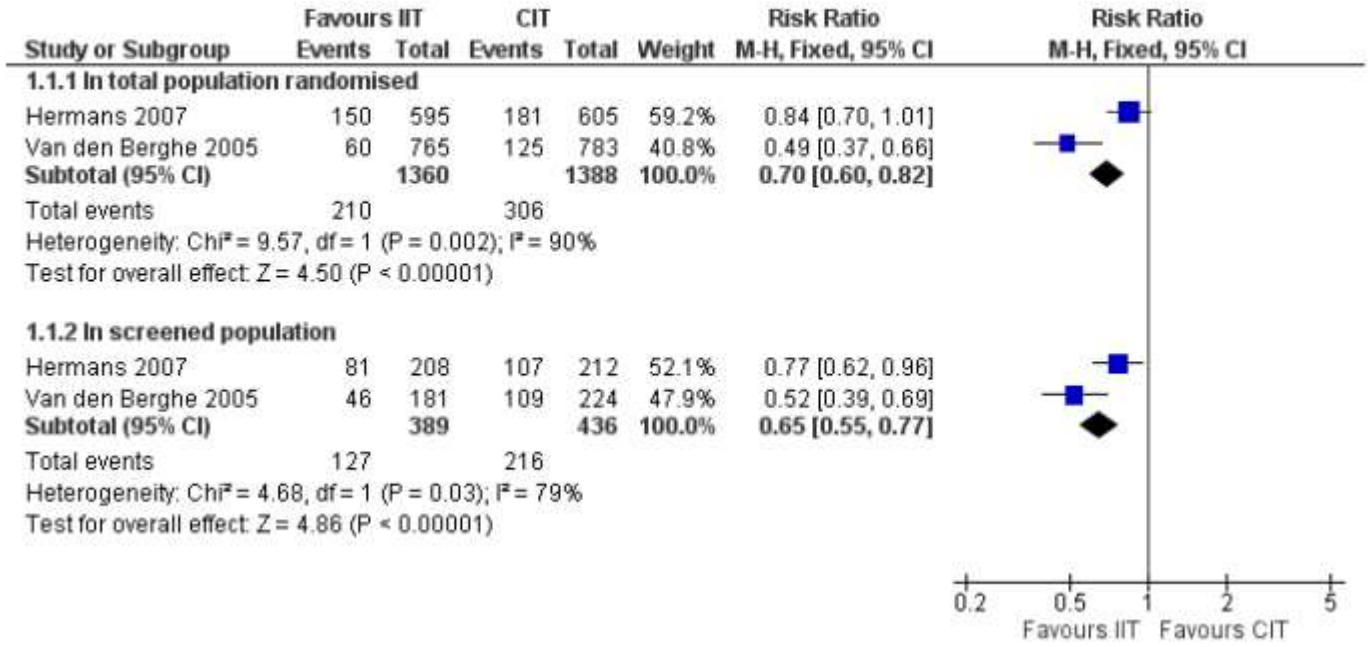
Intensive insulin therapy -RCT

Author (year/place)	Van Den Berghe etal (2001//single centre at LEUVEN, Belgium)	Van Den Bergh etal (2006)
Participants	1548 patients admitted in surgical ICU	1200 patients admitted in medical ICU
Methods	Randomized to 2 group: 1. IIT (80-110mg/dl) 2. Conventional treatment to maintain serum glucose within 180-200mg/dl	do
Objective	To look for effect of IIT on mortality (& morbidity including CIM/CIP as 2ndary outcome).	do
Outcome	32% Risk reduction of mortality with IIIT in ICU as well as in hospital.	No significant reduction in in-hospital mortality.
Dx and Incidence of ICUAP	Weekly EMNG was done for patients who stayed in ICU for ≥7days. Significantly fewer people in IIT group developed CIP/CIM (P=.007)	An ENMG diagnosis of CIP/CIM was significantly more frequent in the CIT group (p=0.02).

Van Den Bergh et al NEJM 2001; 345: 1359-1367
Van Den Bergh etal NEJM 2006; 354: 449-461

Cochrane review -2013

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



Contd

Author year/place	Finfer etal (2009/multi center)	Mikaeili etal (2012/Iran)
Participants	Patients who were expected to stay in ICU for ≥3 days	40 ICU patients.
Methods	Intensive glucose control (81-108 mg/dl) vs conventional approach (i.e. <180mg/dl)	Euglycemic control (80-140 mg/dl) vs conventional approach (<180)
Objective	Death from any cause within 90 days	Incidence of CIP/CIM and duration of MV
Outcome	Deaths were significantly higher in IGC group	Less number of CIP (P=0.01)/and less days on ventilator (P=0.04) with euglycemic control
Dx and Incidence of ICUAP	Not mentioned, but days on MV were similar (P=0.56)	

Finfer etal NEJM 2009; 360: 1283 -1297
Mikaeili etal Bratisl Lek Listy. 2012;113(10):616-9.

Early mobilization rationality

- During moderate to strenuous exercise (60% to 75% of maximal oxygen intake) in unfatigued skeletal muscle, show increased production of antioxidants.
- In addition, moderate exercise leads to a shift toward increased production of anti-inflammatory cytokines, typically IL-6 . It rises up to 100-fold greater than pre-exercise levels, and then declines shortly after discontinuation of exercise (<30 minutes).
- Taken together, antioxidant formation and a shift toward anti-inflammatory cytokines during moderate exercise may play an important role in muscle preservation and protection.

Truong et al Critical Care 2009, 13:216

Early mobilization feasibility

Study	Bailey etal 2007
Population	103 patients on MV for ≥4days
PT/OT	Sitting on the edge of bed, transfer to chair and mobilization
Objective	Safety and feasibility of early mobilization
Adverse events	<1% adverse events as defined priori in 1449 activities including 598 activities in intubated patients
Comment	Most of the pt was able to mobilize 100m at discharge

Bailey etal Crit Care Med 2007; 35:139–145

Early mobilization -RCT

Study	*Schweickert* etal (USA/2009)
Participant	104 adults in ICU; on MV for <72hrs; who were functionally independent at baseline; were randomized
Intervention	In the intervention group patients received early physical and occupational therapy (if not contraindicated); synchronized with daily sedation interruption.
Comparator	Control group received daily sedation vacation with physiotherapy at physician discretion.
Outcome	Primary outcome was independent functional status at hospital discharge as measured by ADL and walk distance.
Safety	PT/OT terminated 19/498 for dysynchrony, 1 event of desaturation and 1 event of radial line displacement.
Result	A strategy for whole-body rehabilitation consisting of interruption of sedation and physical and occupational therapy in the earliest days of critical illness was safe and well tolerated, and resulted in better functional outcomes at hospital discharge, a shorter duration of delirium, and more ventilator-free days compared with standard care.

Schweickert etal Lancet 2009; 373: 1874–82

	Intervention (n=49)	Control (n=55)
Age (years)	57·7 (36·3–69·1)	54·4 (46·5–66·4)
Female	29 (59%)	23 (42%)
Black race	30 (61%)	31 (56%)
Barthel Index score	100 (85–100)	100 (90–100)
Body-mass index (kg/m²)	27·4 (25·1–32·4)	28·0 (23·5–34·1)
APACHE II score	20·0 (15·8–24·0)	19·0 (13·3–23·0)
Sepsis	42 (86%)	45 (82%)
Diabetes	18 (37%)	18 (33%)
Primary diagnosis on admission to intensive care		
Acute lung injury	27 (55%)	31 (56%)
COPD exacerbation	4 (8%)	6 (11%)
Acute exacerbation of asthma	5 (10%)	4 (7%)
Sepsis	7 (14%)	9 (16%)
Haemorrhage	1 (2%)	2 (4%)
Malignancy	2 (4%)	1 (2%)
Other	3 (6%)	2 (4%)

Data are number of patients (%) or median (IQR). APACHE II=Acute Physiology and Chronic Health Evaluation II. COPD=chronic obstructive pulmonary disease. Barthel Index scale 0–100, APACHE II scale 0–71.

Table 1: **Baseline characteristics of the study population**

	Intervention (n=49)	Control (n=55)	p value
Return to independent functional status at hospital discharge	29 (59%)	19 (35%)	0·02
ICU delirium (days)	2·0 (0·0–6·0)	4·0 (2·0–7·0)	0·03
Time in ICU with delirium (%)	33% (0–58)	57% (33–69)	0·02
Hospital delirium (days)	2·0 (0·0–6·0)	4·0 (2·0–8·0)	0·02
Hospital days with delirium (%)	28% (26)	41% (27)	0·01
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
Ventilator-free days*	23·5 (7·4–25·6)	21·1 (0·0–23·8)	0·05
Duration of mechanical ventilation (days)	3·4 (2·3–7·3)	6·1 (4·0–9·6)	0·02
Duration of mechanical ventilation, survivors (days)	3·7 (2·3–7·7)	5·6 (3·4–8·4)	0·19
Duration of mechanical ventilation, non-survivors (days)	2·5 (2·4–5·5)	9·5 (5·9–14·1)	0·04
Length of stay in ICU (days)	5·9 (4·5–13·2)	7·9 (6·1–12·9)	0·08
Length of stay in hospital (days)	13·5 (8·0–23·1)	12·9 (8·9–19·8)	0·93
Hospital mortality	9 (18%)	14 (25%)	0·53

Data are n (%), median (IQR), or mean (SD). ICU=intensive care unit. *Ventilator-free days from study day 1 to day 28. Barthel Index scale 0–100, APACHE II scale 0–71.

***Table 3*: Main outcomes according to study group**

Study	Burtin etal (Belgium/2009)
Participants	90 adult ICU patients (both surgical and medical) who expected to stay in ICU for ≥7 days on day 5. patients were randomized into control and treatment group.
Method	In control group patients received CPT and daily passive or active motion session. In addition treatment group received 20min/day session of passive or active exercise session using a bedside ergo meter.
Outcome	At hospital discharge patients of intervention arm had significantly higher 6MWD, isometric quadriceps force and physical well being as per SF36.

Burtin et al Crit Care Med 2009; 37:2499–2505

Early mobilization –RCT contd

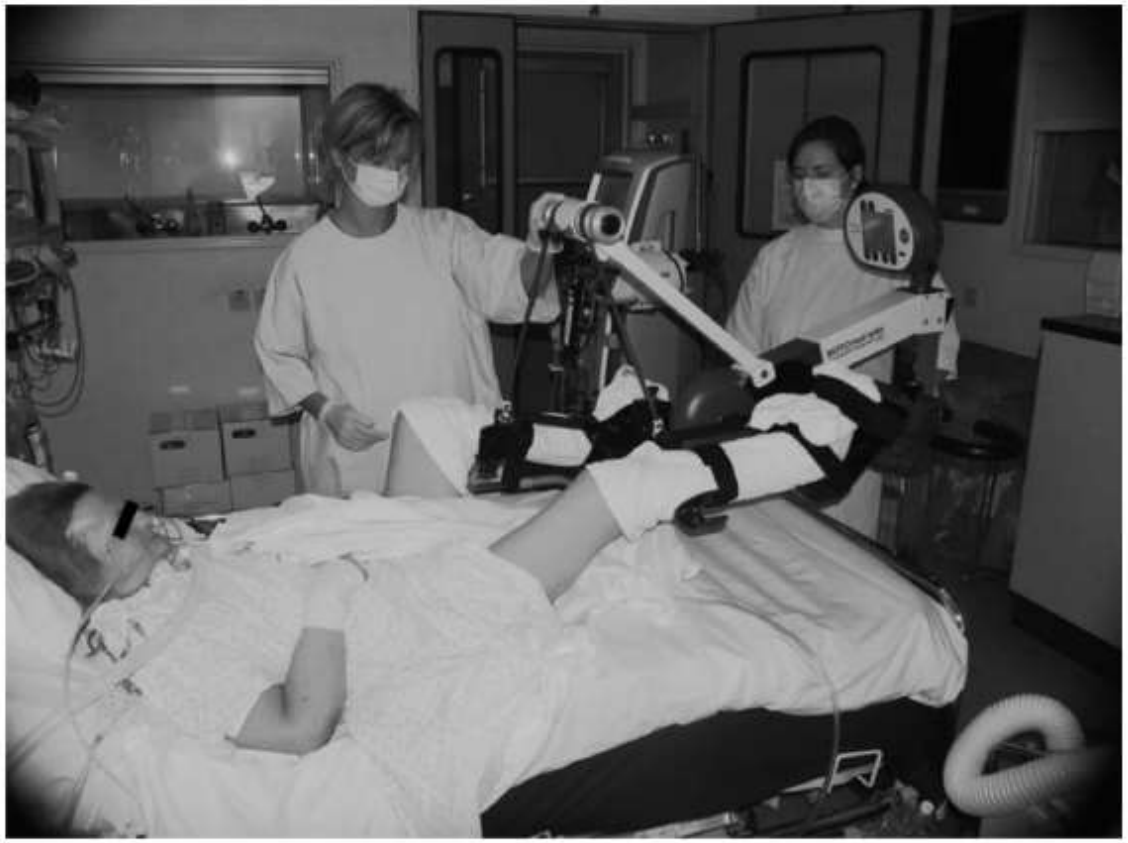


Figure 1. Bedside cycle ergometer (MOTOmed Letto 2, RECK, Betzenweiler, Germany).

Early mobilization –current scenario

Study (place/year)	TEAM study (12 ICU in Australia and Newzelands/2015)
Population	ICU patients who were functionally independent and expected to be ventilated for >48 hrs
Method	Mobilization during first 14 days or extubation/ ICUAW at ICU discharge/ 90 day mortality and return to work at 6 month were measured.
outcome	Of 1288 planned early mobilization episode no mobilization occurred in 1079. the maximum levels of mobilization were exercises in bed (N = 94, 7%), standing at the bed side (N = 11, 0.9%) or walking (N = 26, 2%). In 94 of the 156 ICU survivors, 48 (52%) had ICU-AW. The MRC-SS score was higher in those patients who mobilized while mechanically ventilated (50.0 ± 11.2 versus 42.0 ± 10.8, P = 0.003). Patients who survived to ICU discharge but who had died by day 90 had a mean MRC score of 28.9 ± 13.2 compared with 44.9 ± 11.4 for day-90 survivors (P <0.0001).

The TEAM Study Investigators Critical Care (2015) 19:81

Electrical muscle stimulation

- Non volitional method of physiotherapy hence doesn't require patient co operation.
- Multiple studies and systematic review available with low grade evidence of preservation of muscle strength.

EMS –mechanism

- EMS acts as an anabolic stimulus to the muscle as evident from its effect on improving muscle oxygen utilization and work efficiency.
- As evident by near infrared spectroscopy technique EMS applied on lower limb of critically ill induces a systemic effect on microcirculation possible by increaing local cytokine production.
- IL-6 mRNA has been shown to increase after an EMS session in rat skeletal muscles.
- EMS may improve mitochondrial function in skeletal muscle by activating hitherto unknown bio energetic pathway.
- EMS may improve skeletal muscle metabolism by some ergo/metabolo reflexes enhancing sympathetic dischage..

Abdelaziz Abu-Khaber etal Alexendria journal of medicine, 2013. 49; 309-315

NMES/EMS -RCT

Study place/year	Routsi etal (Greece/2010)	Abu-khabar etal (Egypt/2013)
Population	140 consecutive ICU patients with APACHEIII≥13 were randomized 24 to 48 hrs after ICU admission.	80 patients on MV for >24 hrs.
Method	Patients in N group received daily EMS session of 55 minutes duration with biphasic symmetric pulse of 45 Hz and 400 ms duration.	Patients in EMS group received daily 1hr EMS session with biphasic symmetrical pulse of 50Hz and 200ms duration
Objective	Incidence of ICUAW by MRC, duration of MV and ICU length of stay.	Assessment of ICUAMW with MRC, duration of MV.
Outcome	24 in EMS group and 28 in control group was finally evaluated. On per protocol analysis EMS significantly reduce CIPM (p=0.04);	The MRCS were significantly better in N from day 4 until day 21. The MRCS at day 28 was not significantly different (*P* = 0.091).

Routsi et al. Critical Care 2010, 14:R74

Abukhabar etal Alexendria journal of Medicine 2013;49: 309-315

NMES on muscle strength [MRC]meta - analysis

Study or subgroup	Electrical stimulation Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Fixed, 95% CI
Abu-Khaber *et al.* (2013)	20.6	5.68	36	21	9.76	34	1.2%	–0.40 [–4.17, 3.37]
Routsi *et al.* (2010) and Karatzanos *et al.* (2012)	56.75	2.25	24	52	4.5	28	4.9%	4.75 [2.86, 6.64]
Zanotti *et al.* (2003)	3.83	0.57	12	3.08	0.51	12	93.9%	0.75 [0.32, 1.18]
Total (95% CI)			72			74	100.0%	0.93 [0.51,1.35]

Heterogeneity: $Chi^2 = 16.76$, df = 2 ($P = 0.0002$); $I^2 = 88\%$
Test for overall effect: Z = 4.36 ($P < 0.0001$)

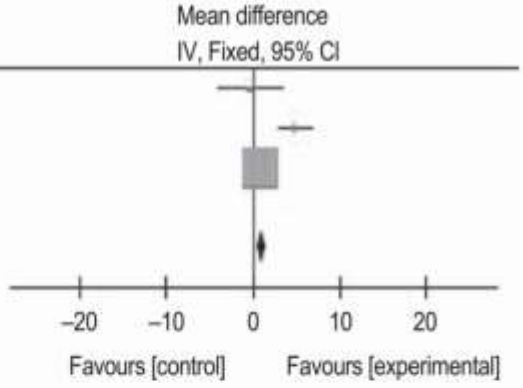


Figure 2. Meta-analysis of muscle strength from included randomised controlled trials (RCTs).

Burke etal meta-analysis. Clin Respir J 2016; 10: 407-420

Study (place/year)	Gruther (Austria/2010)
Population	46 adult ICU pt were divided in acute (<7d) and long term (>2wks) groups. Each group were randomized in N&C .
Method	EMS was given with biphasic symmetrical wave (50Hz and 350ms duration) for 30 min/d in 1st wk and for 60min/d in2nd wk for 5 days/wk X 4wks.
Objective	Muscle layer thickness of quadriceps was measured with USG
Outcome	Only long term patients in EMS group showed significant improvement in MLT.

W Gruther etal J Rehabil Med 2010; 42: 593–597

Corticosteroids

- Proposed mechanisms:
  - inhibition of anabolism.
    - inhibition of amino acid transport within the muscles, limiting protein synthesis.
    - inhibition of the stimulating effect of insulin and the insulin growth factor (IGF-1) on the phosphorylation of the eIF4-binding protein and ribosomal protein kinase S6, two key factors in mRNA translation.
    - Finally, GCs inhibit myogenesis by the low regulation of myogenin, an essential transcription factor for the differentiation of satellite cells in muscle fibers.

- The catabolic action of GCs is mediated by
  - the proteolytic ubiquitin-proteasome, lysosome and calpain-dependent systems. that primarily affect the myofibrillar proteins.
  - In muscle wasting, intracellular mediators such as FOXO, GSK3b, C/EBP beta, p300, REDD1 and ATF4 form part of the catabolic action .

Corticosteroid RCT

Study (place/year)	Steinberg etal (ARDS net/2006)	CORTICUS study (2008)
Participants	180 patients with ARDS of at least 7 days duration.	499 patients in participating ICUs with septic shock of ≥72 hours.
Method	They were randomized to receive either methyl prednisolone IV or placebo for 25 days	Patients were randomized to receive IV hydrocotisone or placebo for 12 days.
Outcome	1ry outcome was 60 day mortality	Mortality at 28 day among patients who did not respond to corticotrophin.
ICU AW	Occurs equally in both group [p=0.2].	Rarely reported [2 patients in treatment arm and 4 in placebo arm].

Steinberg et al N Engl J Med 2006;354:1671-84.
Sprung et al N Engl J Med 2008;358:111-24

NMBA –non RCT

Study (year)	Participant	Steroid use	NMBA use Drug and duration	Incidence of ICU AW	Association with NMBA
Adnet etal (2001)	Asthma patients	All in both group	Pancuronium/ Vecuronium /atracurium/ cisatracurium	10/55 in NMB group and 1/46 in comparator	Strong (on MA P<0.0001). They found hours of NMB use (101vs22) had significant correlation with ICUAW.
Garancho montero etal (2001)	Sepsis with ≥2 organ failure	7/50 with CIP and 4/23 without CIP	Vecuronium & atracurium 9/50 in CIP grpup and 1/23 in non CIP group	50/73; EPS done on D10 and D21	Yes (on multivariate analysis; P< .0008)

Adnet etal Intensive care medicne 2001; 27: 1729-173

Garancho –Montero etal Intensive care medicine2001: 27; 1288-1296

NMBA non RCT

Study (year)	Participant	Steroid use	NMBA use Drugs and duration	Incidence of ICU AW	Association
Leatherman etal (1996)	94 pt with asthma on MV	38/94	69/94 Pancuronium 20 Vecuronium 26 Atracurium 17	20/94 Clinical /EP and biopsy	•weakness was limited to patients who had received both corticosteroids and a NMBA •the risk of weakness increased with the duration of paralysis; •Paralysis with atracurium was associated with as great a risk of weakness as paralysis with an aminosteroid NMBA

Letherman etal; AM J RESPIR CRIT CARE MED 1996;153:1686-90.

NMBA -RCT

Study (plance/year)	Papazian etal (Multicenter study in France/2010)
Participants	340 patient with ARDS
Method	Pt were randomized to receive either cisatracurium for 48 hrs or placebo.
Objective	Primary -90 day mortality. Secondary -28 day mortality and incidence of ICUAW
Outcome	No difference in the rate of ICU AP .

Papazian etal; NEJM 2010. 363. 1107-1116

Therapy

- Pharmacological
- Non pharmacological

Recombinant growth hormone

- proposed hypothesis:
    - Sarcopenia has been proposed as one of key mechanism for ICUAW.
    - Hence rh GH may be effective in critical illness neuropathy/myopathy for its anabolic action..
    - In a RCT GH has shown to be associated with increased protein content and increased protein synthesis in skeletal muscle in critically ill patients in surgical ICU.

Gamrin etal Ann Surg2000; 231:577–586

Recombinant growth hormone: RCT

Study (place/year)	RCT (multinational study in Europe/1999)	RCT (1995)
Participants and method	247 Finnish ICU patients and 285 patients in other European ICUs and who were expected to require intensive care for at least 10 days	20 patients requiring more than 7 days of mechanical ventilation
Method	The patients received either growth hormone or placebo until discharge from ICU or for a maximum of 21 days	Random assignment to receive either recombinant GH or normal saline for 12 days.
Outcome	In hospital mortality was higher in patients receiving growth hormone.	Primary outcome i.e. mortality was not different between groups; though GH group has higher lean body mass but no improvement in muscle strength seen

Takala et al N Engl J Med 1999;341:785-92
Pichard et al Crit Care Med 1996; 24:403-413

IV immunoglobulin

- Proposed mechanism :
  - Studies have shown possible association of CIPNM with the proinflammatory cytokines released during critical illness, the effect of which may be attenuated by the immunomodulating properties of IVIG.
  - In a retrospective chart analysis Mohr etal postulated that early application of IV Ig may mitigiate the occurance of CIP in septic patients .

Mohr et al; Intensive Care Med (1997) 23:1144-1149

IV Ig – RCT

Study (place/year)	RCT (Vienna/2013)
Participant	38 Critically ill patients with MOF (failure of two or more organs), a SIRS/sepsis diagnosis, and first clinical evidence for CIPNM were randomized to receive IVIg or IV albumin (placebo).
Method	CIP was determined and graded by EPS on D0 and D14. CIM was scored semiquantatively depending on histopathology.
outcome	Study was terminated after 1st interim analysis due to futility of the intervention.

Brunner et al. Critical Care 2013, 17:R213

Glutamine

- Glutamine is the most abundant free amino acid in the body and is normally synthesized and stored in skeletal muscle.
- During sepsis and catabolic states, increased glutamine demands may be met in part by increasing breakdown of protein in skeletal muscle but glutamine deficiency can occur.
- In an RCT in general ICU patients Tjader et al found intravenous glutamine can normalization of plasma glutamine concentrations in a dose dependent way whereas muscle glutamine concentrations were unaffected.

Tjader et al Intensive Care Med (2004) 30:266–275

Non pharmacological therapy

- Physical therapy
- Electrical muscle stimulation
- Rehabilitation program etc.

Physical therapy

- Involvement of physiatry is ideally initiated immediately following the recognition of neuromuscular disease in the ICU.
- Initially, only light exercises to promote muscle strength, maintain joint mobility, and prevent contracture should be instituted.
- As the patient improves, progressive strengthening of the major upper and lower extremity muscle groups is followed by training in activities of daily living.
- As the patient improves, therapy can be advanced, with gradual mobilization.
- Most patients benefit from transitioning to an inpatient rehabilitation unit once clinically stable, with the goal of returning home to independent living.

Chawla et al. Neurol Clin 28 (2010) 961–977

Non pharmacological therapies -SR

Systematic review	Kayambu etal 2013	Hermans etal
Aim of the study	Review the evidence base for exercise in critically ill	Review of evidence of any intervention that reduces CIM/CIP
no of studies included/no of patients included	10/790	2/244
Population	Patient receiving physical therapy	Adult ICU patients
Intervention	Physical therapy	PT/EMS/Rehabilitation programme
Comparator	No or minimal physical therapy	placebo
Outcome	Peripheral muscle strength, respiratory muscle strength, physical function, QOL ventilator, ICU and Hospital days, mortality.	Incidence of CIP/CIM; Duration of MV, ICU LOS 20d and 180d mortality/serious adverse events

Connolly B, et al. Thorax 2016;0:1–10

Quality appraisal method	PEDro	Cochrane risk of bias
Pooled effect	Peripheral muscle strength **P=0.03** Respiratory muscle strength **P=0.01** Physical funtion **P=0.01** Quality of life **P=0.01** VFD **P<0.001** ICULOS **P<0.001** Hospital LOS **P<0.001** hospital mortality **P=1.0**	CIP/CIM (for earLy PT) **p=0.03** (for EMS) **P=0.05**
Grade of evidence	Moderate to high	Low to moderate

Connolly B, et al. Thorax 2016;0:1–10.

Systematic review	Wageck etal (2013/Australia)	Calvo –Ayala etal
Aim	Application and effect of NEMS in critically patients in ICU	Identify effective intervention that improve long term PF in ICU survivors
No of studies/ no of patients	8/274	7/678
Population	Adult ICU patients with ≥48 hrs stay	Adult ICU patients
Intervention	Neuro muscular electrical stimulation	exercise/PT; parenteral nutrition, nurse led follow up, IIT, SAT, SBT; absence of sedation, tracheostomy
Comparator	Not specified	Placebo, no treatment or any different treatment
Outcome	Muscle strength, muscle structure ICU LOS Duration of MV	SF36 PF; 6MWD, barthel index, ADL

Connolly B, et al. Thorax 2016;0:1–10

Quality appraisal method	PEDro	Cochrane risk of bias
Pooled effect	Musle power P=0.02	Not mentioned
Grade of evidence	Very low	

Connolly B, et al. Thorax 2016;0:1–10

NAVA for CINMA –feasibility study

Study (place /year)	Tuchscherer etal (Bern/2011)
Population	Mechanical ventilation for longer than 48 hrs, presence of at least 1 risk factor associated with CIPM, clinical diagnosis of CIPM
Method	Peripheral and phrenic nerve electrophysiology studies were performed in 15 patients with clinically suspected CIPM and in 14 healthy volunteers. In patients, an adequate NAVA level (NAVAal) was titrated daily and was implemented for a maximum of 72 h. Changes in tidal volume (Vt) generation per unit of EAdi (Vt/EAdi) were assessed daily during standardized tests of neuroventilatory efficiency (NVET).
Result	NAVA al could be calculate in al but 2 patients.

Tuchscherer etal Intensive Care Med (2011) 37:1951–1961

Tracheostomy

- Early vs late Tracheostomy has not been studied directly for prevention or management of CINMA.
- A recent systematic review and meta-analysis had shown reduced ventilator days, reduced sedation requirement, reduced ICU stay and reduced long term mortality with early Tracheostomy.
- Considering association of prolonged MV with CINMA early Tracheostomy may be considered.

Systematic review	Hosokawa et al (2015)
Aim	To clarify potential benefit of early vs late tracheostomy
No of studies/ no of patients	12/2689
Population	Adult ICU patients
Intervention	Early tracheostomy (<4 vs>10 days/ <4 vs>5 days and <10 vs >10 days)
Comparator	Late tracheostomy
Outcome	Tracheostomy rates, Ventilator free days, duration of ICU stay, sedation requirement

Hosokawa et al. Critical Care (2015) 19:424

Method of appraisal	Cochrane tool for assessing Bias
Pooled effect	The Tracheostomy rate was significantly higher with early than with late tracheotomy (87 % versus53 %, OR 16.1 (5.7-45.7); p <0.01. Early tracheotomy was associated with more ventilator-free days (WMD 2.12 (0.94, 3.30), p <0.01), a shorter ICU stay (WMD -5.14 (-9.99, -0.28), p = 0.04), a shorter duration of sedation (WMD -5.07 (-10.03, -0.10), p <0.05) and reduced long-term mortality (OR 0.83 (0.69-0.99), p = 0.04) than late Tracheostomy.

Hosokawa et al. Critical Care (2015) 19:424

Take home message

- Clinical identification of CINMA should be a routine clinical practice in all critically ill patient.
- Early mobilization should be a priority in critically ill [as early as 48 hrs].
- NMBA/steroid use in ICU should always be kept at minimum.
- Electrical muscle stimulation may be used with therapeutic intent.

Thank you