RECENT ADVANCES IN CRITICAL ILLNESS NEUROMUSCULAR WEAKNESS

DR DIPESH MASKEY

SENIOR RESIDENT

DEPT OF PULMONARY & CRITICAL CARE MEDICINE

Critical illness neuromuscular weakness

- One of the most profound and relatively invisible legacies of critical illness
  - Affect patient management and outcome during the ICU stay
  - May contribute to functional disability for years after hospital discharge

- Consistently seen in
  - Sepsis and/or MODS and/or
  - Acute respiratory failure requiring mechanical ventilation
    - May begin within hours of mechanical ventilation

Intensive Care Med (2009) 35:1–3
DOI 10.1007/s00134-008-1305-3

Critical illness neuromuscular weakness

Syndrome of neuromuscular dysfunction acquired in the absence of causative factors other than the underlying critical illness and its treatment

Crit Care Med 2009; 37[Suppl.]:S299 –S308

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)

Crit Care Med 2009; 37[Suppl.]:S299 –S308

Critical illness neuromuscular weakness

- Number of barriers that hinder the study of this clinical entity
- No consensus on
  - risk factors or modifiers,
  - how and when it should be diagnosed,
  - how to name and categorize these nerve and muscle lesions according to the severity or heterogeneity, and
  - limited data on very long-term outcome
- No guidance to risk stratify this dysfunction
- Impaired ability to tailor specific interventions with appropriate timing and intensity during the recovery continuum

Intensive Care Med (2009) 35:1–3
DOI 10.1007/s00134-008-1305-3

Prevalence of CINMA

Reference	No. of patients enrolled	No. (%) without CINMA	No. (%) with CINMA	No. (%) with CIP	No. (%) with CIM	No. (%) with mixed CIP/CIM	No. (%) with NMJ defect	No. (%) with unclassified CINMA
Amaya-Villar, 2005 [24]								9 (35%)
Bednarik, 2003 [8]						4%)		
Bednarik, 2005 [22]						5%)		
Bercker, 2005 [48]								27 (60%)
Berek, 1996 [34]								
Campellone, 1998 [35]								7 (9%)
Coakley, 1998 [36]								37 (84%)
De Jonghe, 2002 [7]								24 (25%)
De Letter, 2001 [52]						%)		2 (2%)
Druschky, 2001 [38]								16 (57%)
Garnacho-Montero, 2001 [25								50 (68%)
Garnacho-Montero, 2005 [51								34 (53%)
Hund, 1997 [50]								20 (71%)
Kupfer, 1992 [40]							2 (2%)	5 (50%)
Lefaucheur, 2006 [41]						%)		
Leijten, 1995 [43]								29 (58%)
Leijten, 1996 [42]	38	20 (53%)	18 (47%)					18 (47%)
Mohr, 1997 [44]	33	26 (89%)	7 (21%)					7 (21%)
Rudis, 1996 [49]	20	10 (50%)	10 (50%)	2 (10%)	6 (30%)	1 (5%)	1 (5%)	
Tepper, 2000 [45]	22	3 (14%)	19 (86%)					19 (86%)
Thiele, 1997 [50]	44	37 (84%)	7 (16%)					7 (16%)
Thiele, 2000 [46]	19	7 (37%)	12 (63%)					12 (63%)
Van den Berghe, 2005 [54]	405	250 (62%)	155 (38%)					155 (38%)
Witt, 1991 [47]	43	13 (30%)	30 (70%)					30 (70%)

655/1421 (46%; 95% CI 43–49%)
median (range) prevalence 57% (9–87%)
CIP = 51 (7.8%)
CIM= 49 (7.5%)
Mixed CIP/CIM = 44 (6.7%)
Unclassified CINMA = 508 (77.6%)

Intensive Care Med (2007) 33:1876–1891
DOI 10.1007/s00134-007-0772-2

Framework for diagnosing and classifying intensive care unit-acquired weakness → Herculian task!!!

- Traditional nosological schemes based on etiology or pathogenesis are not possible because of no concrete evidence
- Overlap between CIM and CIP
- Semiological classification is of questionable significance as the symptoms and signs of polyneuropathy and myopathy are neither sensitive nor specific
- Diagnosis based of EMG/NCS has limitations too
- Absence of a consistent nomenclature of neuromuscular disorders in critical illness constitutes a serious barrier to research in this field

Crit Care Med 2009; 37[Suppl.]:S299 –S308

Intensive Care Med (2007) 33:1876–1891
DOI 10.1007/s00134-007-0772-2

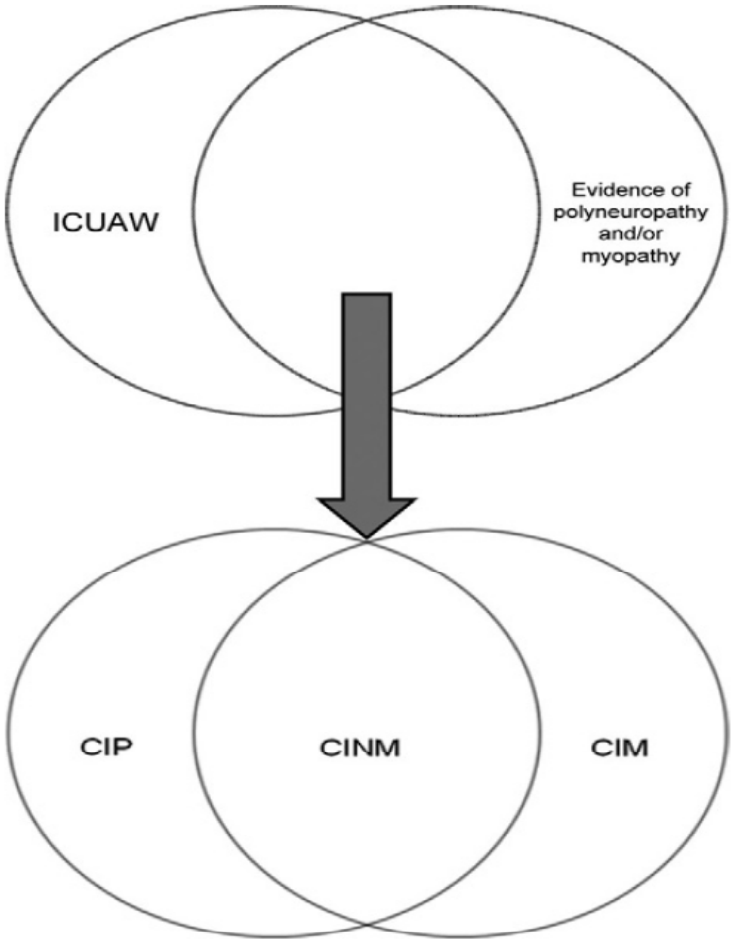
SYSTEMATIC REVIEW

Robert D. Stevens
David W. Dowdy
Robert K. Michaels
Pedro A. Mendez-Tellez
Peter J. Pronovost
Dale M. Needham

Neuromuscular dysfunction acquired in critical illness: a systematic review

Reference	Timing of first CINMA evaluation	Exclusion of prior NMD	Documentation of weakness	Repetitive stimulation	CMAP	SNAP	MUP	Fibrillation potentials	DMS	No. of patients (%) with muscle biopsy
Amaya-Villar, 2005 [24]	Median (range) 6 (2–12) days of MV	+	+	–	–	–	+	–	–	3 (12)
Bednarik, 2003 [8]	< 3 days after ICU admission	+	+	+	+	+	+	+	+	11 (24)
Bednarik, 2005 [22]	< 3 days after ICU admission	+	+	+	+	+	+	+	+	11 (18)
Bercker, 2005 [48]	NR	+	+	–	–	–	–	–	–	–
Berek, 1996 [34]	14–28 days after ICU admission	+	+	–	+	+	+	+	–	–
Campellone, 1998 [35]	2 weeks after liver transplantation	–	+	+	+	+	+	+	–	5 (7)
Coakley, 1998 [36]	NR	+	+	+	+	+	–	+	–	24 (55)
De Jonghe, 2002 [7]	Mean (SD) 12.4 (6.8) of MV	+	+	+	+	+	–	+	–	10 (11)
De Letter, 2000 [52]	4 days MV	+	+	+	+	+	+	+	–	32 (33)
Druschky, 2001 [38]	4 days of MV	+	+	+	+	+	–	+	–	–
Garnacho-Montero, 2001 [25]	10 days of MV	+	–	+	+	+	–	+	–	–
Garnacho-Montero, 2005 [51]	Onset of weaning from MV	+	–	+	+	+	–	+	–	–
Hund, 1997 [50]	5–7 days of MV	+	+	–	+	–	–	+	–	2 (7)
Kupfer, 1992 [40]	> 24 h after discontinuation of vecuronium infusion	+	+	+	–	+	–	–	–	–
Lefaucheur, 2006 [41]	Mean (SD) 13.7 (7.8) days after awakening from coma	+	+	+	+	+	+	+	+	–
Leijten, 1995 [43]	7–9 days of MV	+	+	+	+	+	–	+	–	–
Leijten, 1996 [42]	7–9 days of MV	+	+	+	+	+	–	+	–	–
Mohr, 1997 [44]	1–2 days before discharge from ICU	+	+	–	+	+	–	+	–	–
Rudis, 1996 [49]	Median 6.5 days after discontinuing NMB	–	+	+	+	+	+	+	–	–
Tepper, 2000 [45]	< 3 days of septic shock	+	+	–	+	+	–	+	–	–
Thiele, 1997 [50]	5–7 days of MV	–	+	–	+	+	–	+	–	–
Thiele, 2000 [46]	5–7 days of MV	–	+	–	+	+	–	+	–	–
Van den Berghe, 2005 [54]	1 week after ICU admission	–	–	–	–	–	–	+	–	–
Witt, 1991 [47]	20 days after ICU admission	+	+	–	+	+	–	+	–	–

Proposed classification



Brussels Round Table Conference, March 2009

DIAGNOSTIC METHODS AND THEIR LIMITATIONS

Diagnostic methods

- Methods to identify ICUAW (and its subcategories) neuromuscular dysfunction include
  - clinical assessment,
  - electrophysiological studies, and
  - morphologic analysis of muscle or nerve tissue.

- No diagnostic gold standard for ICUAW or its subcategories, and therefore little is known regarding the sensitivity and specificity of individual (or clustered) characteristics or test results

Clinical Assessment

- Suspect weakness
  - Failed weaning from mechanical ventilator
  - Unable to move limbs after return of consciouness
- Assess weakness by neurological examination
- Assess sensory deficits
- Exclude other causes of weakness (GBS, Myasthenia,drugs, spinal cord, cortex or brain stem)

Chest 2007; 131:1541–1549

MRC Scale for Muscle Examination

M
a

I
M
a

LIMITATIONS..

1. Awake, cooperative, and capable of contracting the extremities with maximal force—conditions which many ICU patients fail to meet.
2. Affected by differences in the way patients are positioned, and in the availability of limbs for assessment (e.g., limitations in movement due to pain, dressings, or immobilizing devices).
3. Expressed on an ordinal scale diminishing sensitivity to subtler changes in muscle function
4. Does not evaluate distal extremity function (e.g., intrinsic hand muscles) which may be the first affected in motor neuropathies

Crit Care Med 2009; 37[Suppl.]:S299 –S308

Standard hand dynamometer

- Assess grip strength with a calibrated device and provides a measurement of force on a continuous scale
- Grip strength correlate with MRC scores and was independently predictive of hospital mortality, suggesting that hand dynamometric assessments might be a surrogate for global strength *
- Limitations:
  - Need awake and cooperative patient
  - Doesn't differentiate etiology

*Am J Respir Crit Care Med 2008; 178:261–268

RESEARCH Open Access

Manual muscle strength testing of critically ill patients: feasibility and interobserver agreement

Catherine L Hough*, Binh K Lieu, Ellen S Caldwell

Abstract

Introduction: It has been proposed that intensive care unit (ICU)-acquired weakness (ICUAW) should be assessed using the sum of manual muscle strength test scores in 12 muscle groups (the sum score). This approach has been tested in patients with Guillain-Barré syndrome, yet little is known about the feasibility or test characteristics in other critically ill patients. We studied the feasibility and interobserver agreement of this sum score in a mixed cohort of critically ill and injured patients.

Methods: We enrolled patients requiring more than 3 days of mechanical ventilation. Two observers performed systematic strength assessments of each patient. The primary outcome measure was interobserver agreement of weakness as a binary outcome (ICUAW is sum score less than 48; "no ICUAW" is a sum score greater than or equal to 48) using the Cohen's kappa statistic.

Results: We identified 135 patients who met the inclusion criteria. Most were precluded from study participation by altered mental status or polytrauma. Thirty-four participants were enrolled, and 30 of these individuals completed assessments conducted by both observers. Six met the criteria for ICUAW recorded by at least one observer. The observers agreed on the diagnosis of ICUAW for 93% of participants (Cohen's kappa = 0.76; 95% confidence interval (CI), 0.44 to 1.0). Observer agreement was fair in the ICU (Cohen's kappa = 0.38), and agreement was perfect after ICU discharge (Cohen's kappa = 1.0). Absolute values of sum scores were similar between observers (intraclass correlation coefficient 0.83; 95% CI, 0.67 to 0.91), but they differed between observers by six points or more for 23% of the participants.

Conclusions: Manual muscle testing (MMT) during critical illness was not possible for most patients because of coma, delirium and/or injury. Among patients who were able to participate in testing, we found that interobserver agreement regarding ICUAW was good, particularly when evaluated after ICU discharge. MMT is insufficient for early detection of ICU-acquired neuromuscular dysfunction in most patients and may be unreliable during critical illness.

Electrodiagnosis of neuromuscular dysfunction

- Reduced CMAPs & SNAPs in NCS with normal conduction velocity
- Fibrillation potentials and positive sharp waves at EMG

- Reduced CMAPs but preserved SNAPs
- Fibrillation potentials and positive sharp waves at EMG
- Short-duration, low-amplitude MUPs are a sign of reduced functional muscle fibers within each motor unit and usually indicate myopathy

Electrodiagnosis of neuromuscular dysfunction

- Can diagnose neuromuscular dysfunction much earlier than structural changes
- Latronico N et al performed both electrophysiologic and histopathologic investigations in 24 critically ill neurologic septic patients and found divergent results:
  - 14 of 22 EMG/NCS proven axonal neuropathy had normal nerve while 8 demonstrated an axonal changes
  - On the contrary, electrophysiologic and histologic findings were congruent at late biopsies, demonstrating structural axonal damage
- Lead to concept of “bioenergetic failure” during sepsis
- Reduced CMAP is an earliest sign of CIP

Lancet 1996; 347:1579–1582

Electrodiagnosis of neuromuscular dysfunction

- Invaluable adjuncts to the clinical assessment of patients with ICUAW and yet have important shortcomings
- Dedicated equipment and trained personnel,
- Recordings can be unreliable because of tissue edema, differences in limb temperature, or electrical interferences in the ICU environment
- Lack specificity
- Interpretation of EMG/NCS is particularly challenging in patients who cannot voluntarily contract muscle because of concurrent sedation, encephalopathy, or severe weakness
- Electrophysiological differentiation between CIP & CIM is frequently not possible
  - Reduced CMAPs with normal motor nerve conduction velocities and fibrillation potentials with positive sharp waves on resting EMG may be observed in both CIP and CIM

Crit Care Med 2009; 37[Suppl.]:S299 –S308

Direct muscle stimulation (DMS)

- Important tool though semiquantitative
- Doesnot require voluntary muscle contraction
- Compares CMAPs elicited by motor nerve stimulation with CMAPs induced when the muscle itself is stimulated
- Rich et al proposed a “nerve/muscle ratio*,” which is the quotient of nerve- and muscle-evoked CMAP amplitudes;
  - ratio of >0.5 = neuropathic process
  - ratio of <0.5 suggested myopathic process

**Muscle Nerve 1997; 20:665–673*

High frequency motor nerve stimulation

- Another method to assess muscle performance independently of voluntary contraction is to quantify muscle force generated by high-frequency (tetanic) motor nerve stimulation.
- Measurements of adductor pollicis force elicited by electrical or magnetic stimulation of the ulnar nerve, or the ankle dorsiflexor force in response to peroneal nerve electrical stimulation have demonstrated reduced force in significant proportions of critically ill patients.
- In one investigation of 13 patients with sepsis and multiple organ failure, reduced adductor pollicis muscle force was noted in ten patients, only five of whom met the criteria for CIP.
- Although the demonstration of reduced muscle force does not allow differentiation between neuropathy or myopathy, these preliminary results suggest a promising new complement to physical examination and EMG/NCS, in particular, when effective patient cooperation is lacking

Intensive Care Med 2006; 32:251–259
Can J Neurol Sci 1994; 21:S28–S34

Morphology: CIP

- Nerve histology in patients with electrophysiological characteristics of CIP reveals a primarily distal axonal degeneration involving both sensory and motor fibers with no evidence of demyelination or inflammation
- Muscle biopsies from these same patients show changes characteristic of denervation but may also reveal myopathy

Lancet 1996; 347:1579–1582
*J Neurol Neurosurg Psychiatry 1984; 47:*1223–1231
Brain 1987; 110:819–841

Morphology: CIM

- Reveal spectrum of histologic, immunohistological, and ultrastructural abnormalities frequently coexisting within a single tissue sample
- Acute necrosis, regeneration, type II (fast twitch) fiber atrophy, and selective but patchy loss of thick filaments (myosin), which is inferred from a loss of myofibrillar adenosine triphosphate staining on immunohistology and which is directly visualized on electron microscopy
- This last feature is considered by some to be a hallmark of CIM, leading to the term *thick filament myopathy*

Role of creatine kinase as diagnostic biomarker

- Increased serum creatine kinase (CK) has been reported in critically ill patients with acquired myopathy with marked elevations noted in necrotizing myopathy
- The time course, sensitivity, and specificity of serum CK in the diagnosis of ICUAW and its subcategories are poorly studied.
- In a series of patients receiving mechanical ventilation for acute asthma exacerbation, 76% had increased CK with a median peak level of 1575 U/L (range, 66–7430), occurring a mean of 3.6 days after admission; these findings were not corroborated by EMG/NCS and clinically detectable weakness was noted in less than half of the studied patients

Am Rev Respir Dis 1992; 146:517–519

Role USG in assessing muscle mass

- Dramatic muscle wasting in critically ill patients, there is mounting interest in the use of ultrasound to image muscle thickness and make inferences on muscle mass
- Clinical assessments of muscle mass in this population may be confounded by concurrent tissue edema
- An early study of patients with multiple organ failure demonstrated that ultrasound measurements of muscle thickness in the anterior thigh, forearm, and biceps correlated well with lean body mass and declined significantly over time
- Time-dependent decreases in muscle thickness were confirmed in more recent observations made on the quadriceps femoris and upper arm
- Relationship between ultrasound-defined changes in muscle thickness and clinical or electrophysiological assessments of ICUAW have yet to be delineated

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*
3) MRC sumscore <48, or mean MRC score <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

**For example, facial grimace is intact*

Crit Care Med 2009; 37[Suppl.]:S299 –S308

Table 4. Diagnostic criteria for CIP

1) Patient meets criteria for ICUAW
2) Compound muscle action potential amplitudes are decreased to <80% of lower limit of normal in ≥2 nerves
3) Sensory nerve action potential amplitudes are decreased to <80% of lower limit of normal in ≥2 nerves
4) Normal or near-normal nerve conduction velocities without conduction block
5) Absence of a decremental response on repetitive nerve stimulation

CIP, critical illness polyneuropathy; ICUAW, intensive care unit-acquired weakness.

Table 5. Diagnostic criteria for CIM[a]

1) Patient meets criteria for ICUAW
2) Sensory nerve action potential amplitudes are >80% of the lower limit of normal) in ≥2 nerves
3) Needle electromyogram in ≥2 muscle groups demonstrates short-duration, low-amplitude motor unit potentials with early or normal full recruitment with or without fibrillation potentials
4) Direct muscle stimulation demonstrates reduced excitability (muscle/nerve ratio >0.5 [98]) in ≥2 muscle groups
5) Muscle histology consistent with myopathy
Probable CIM: criteria 1, 2, 3 or 4; or 1 and 5
Definite CIM: criteria 1, 2, 3 or 4, 5

CIM, critical illness myopathy; ICUAW, intensive care unit-acquired weakness.

Table 6. Diagnostic criteria for CINM

1. Patient meets criteria for ICUAW
2. Patient meets criteria for CIP (see Table 4)
3. Patient meets criteria for probable or definite CIM (see Table 5)
CINM is diagnosed when all three criteria are present

CINM, critical illness neuromyopathy; ICUAW, intensive care unit-acquired weakness; CIP, critical illness polyneuropathy; CIM, critical illness myopathy.

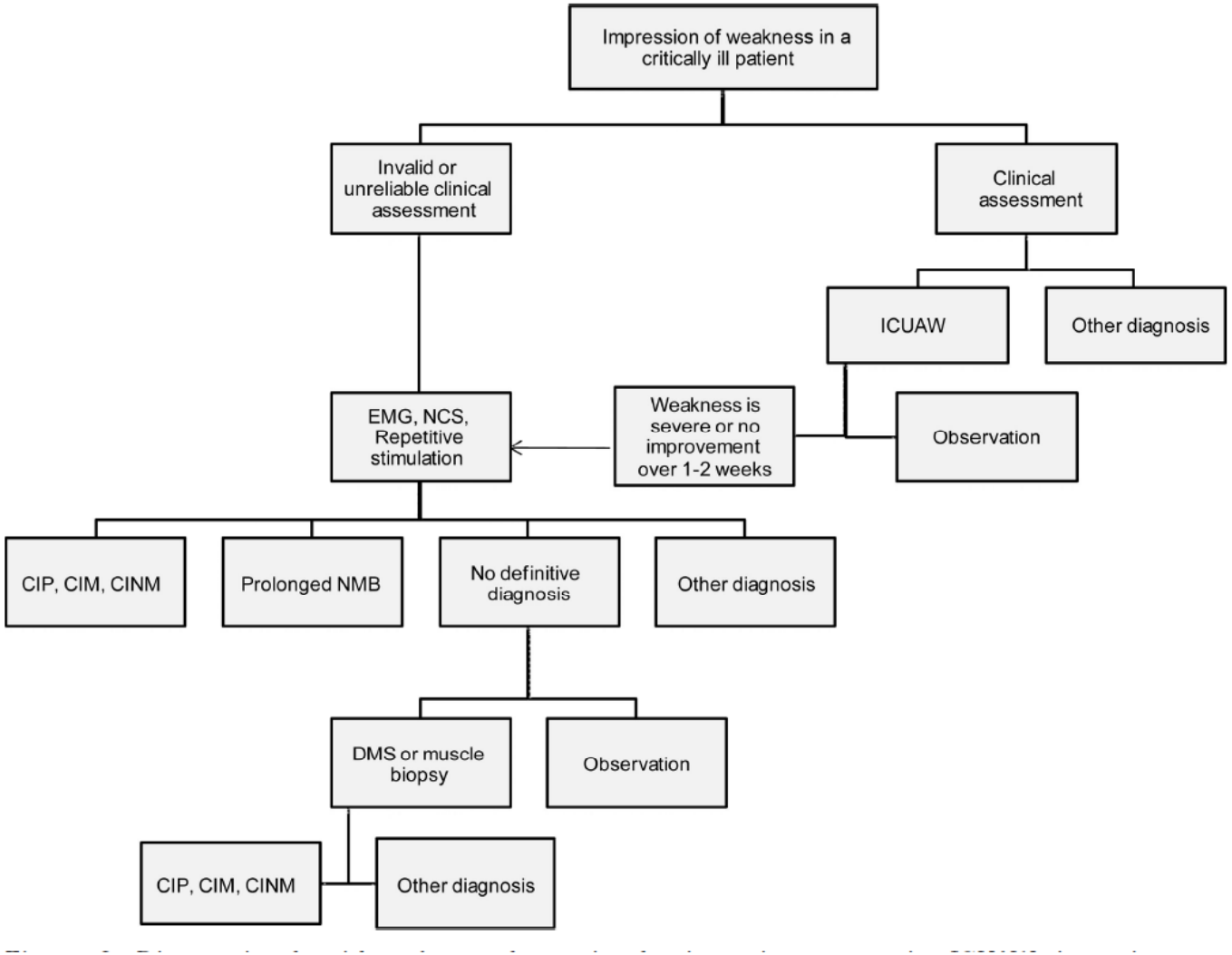
Table 7. Diagnostic criteria for prolonged neuromuscular blockade

1. Patient meets criteria for ICUAW with cranial nerve involvement[a]
2. Exposure to a nondepolarizing neuromuscular blocking agent, usually administered in multiple doses or as an infusion, in the last 10 days
3. Decreased or absent compound muscle action potential amplitudes
4. Presence of a >10% decremental response on 2–3 Hz repetitive nerve stimulation
5. Recovery of motor function over a period of <14 days

ICUAW, intensive care unit-acquired weakness.

[a]For example, facial weakness, ptosis, ophthalmoparesis.

Proposed diagnostic algorithm



Crit Care Med 2009; 37[Suppl.]:S299 –S308

Risk Factors

- Factors such as systemic inflammation, medications, electrolyte disturbances, and immobility have been implicated in the pathogenesis of ICU-AW
- Most risk factors have been identified from prospective observational studies with a multivariate analysis
- In addition, a large body of data is available from two large, prospective, randomized trials comparing the effect of strict vs. conventional blood glucose control on ICU mortality and on secondary outcomes including the occurrence of CINM

Risk factors

Reference	Age (years) CINMA vs. no CINMA	Females (%) CINMA vs. no CINMA	Severity of illness score CINMA vs. no CINMA	Multiple organ failure score CINMA vs. no CINMA	Sepsis (%) CINMA vs. no CINMA
Amaya-Villar, 2005 [24]	62 vs. 66, $p=0.2$	NR	AP2 23 vs. 14, $p<0.001$	NR	67% vs. 6%, $p=0.002$
Bednarik, 2003 [8]	NR	54% vs. 25%, $p=0.09$	NR	NR	NR
Bednarik, 2005 [22]	NR	NR	NR	SOFA score 8 vs. 6, $p=0.04$*	NR
Bercker, 2005 [48]	44 vs. 24, $p=0.01$	NR	SAPS2 35 vs. 32, $p=0.4$	SOFA score 5 vs. 5, $p=0.7$	NR
Berek, 1996 [34]	56 vs. 53, $p=0.44$	17% vs. 50%, $p=0.41$	SAPS1 15 vs. 15, $p=$NS	NR	NR
Campellone, 1998 [35]	NR	NR	AP2 24 vs. 16, $p=0.005$	NR	NR
Coakley, 1998 [36]	NR	46% vs. 42%, $p=0.88$	NR	NR	NR
De Jonghe, 2002 [7]	68 vs. 59, $p=0.02$**	50% vs. 20%, $p<0.004$*	SAPS2 53 vs. 47, $p=0.15$	ODIN score 3 vs. 2.5, $p=0.08$ No. of days with dysfunction in ≥ 2 organs 10 vs. 5, $p<0.001$*	38% vs. 20%, $p=0.08$
De Letter, 2001 [52]	NR	NR	AP3 independently predicted CINMA*	NR	NR
Druschky, 2001 [38]	70 vs. 64, $p=0.02$	38% vs. 33%, $p=0.82$	NR	Goris score 1 vs. 0, $p=0.009$	94% vs. 50%, $p=0.05$
Garnacho-Montero, 2001 [25]	62 vs. 62, $p=0.92$	NR	AP2 17 vs. 18, $p=0.94$	SOFA score 12 vs. 11, $p=0.29$	100% vs. 100%, $p=0.33$
Garnacho-Montero, 2005 [51]	61 vs. 62, $p=0.9$	NR	AP2 19 vs. 18, $p=0.3$	SOFA score 7.2 vs. 7.2, $p=1$	100% vs. 100%, $p=$NS
Hund, 1997 [50]	NR	NR	NR	NR	NR
Kupfer, 1992 [40]	38 vs. 32, $p=0.51$	29% vs. 33%, $p=0.88$	NR	NR	NR
Lefaucheur, 2006 [41]	63 vs. 46, $p=0.143$	33% vs. 44%, $p=0.81$	NR	NR	100% vs. 100%, $p=$NS
Leijten, 1995 [43]	59 vs. 54, $p=0.22$	28% vs. 33%, $p=0.66$	AP2 22 vs. 23, $p=0.74$	22 vs. 11 patients had MOF, $p=0.08$	48% vs. 43%, $p=0.7$
Leijten, 1996 [42]	58 vs. 55, $p=0.49$	33 vs. 30%, $p=0.83$	AP2 22 vs. 23, $p=0.66$	MODS 5.3 vs. 3.6, $p=0.003$	56% vs. 40%, $p=0.34$
Mohr, 1997 [44]	48 vs. 52, $p=0.82$	43% vs. 42%, $p=0.97$	AP2 22 vs. 21, $p=0.34$	NR	100% vs. 35%, $p=0.0027$
Rudis, 1996 [49]	52 vs. 54, $p=0.97$	70% vs. 70%, $p=1$	AP2 61 vs. 62, $p=0.65$	NR	40% vs. 0%, $p=0.001$
Tepper, 2000 [45]	NR	NR	NR	NR	NR
Thiele, 1997 [50]	68 vs. 74, $p=$NS	NR	NR	NR	86% vs. 11%, $p<0.01$
Thiele, 2000 [46]	66 vs. 68, $p=$NS	50% vs. 0%, $p=0.08$	NR	NR	58% vs. 0%, $p<0.05$
Van den Borghe, 2005 [54]	NR	NR	NR	NR	NR
Witt, 1991 [47]	NR	NR	NR	NR	NR

CINMA, critical illness neuromuscular abnormality; *NR*, not reported; *AP2*, Acute Physiology and Chronic Health Evaluation II score; *SOFA*, sequential organ function assessment; *SAPS2*, simplified acute physiology score 2; *ODIN*, organ dysfunction and/or infection score; *AP3*, Acute Physiology and Chronic Health Evaluation III score; *MODS*, multiple organ score; *Goris score*, see ref. [66]; *MOF*, multiple organ failure; * Significant association with CINMA after multivariable adjustment; ** Non-significant association with CINMA after multivariable adjustment

Intensive Care Med (2007) 33:1876–1891
DOI 10.1007/s00134-007-0772-2

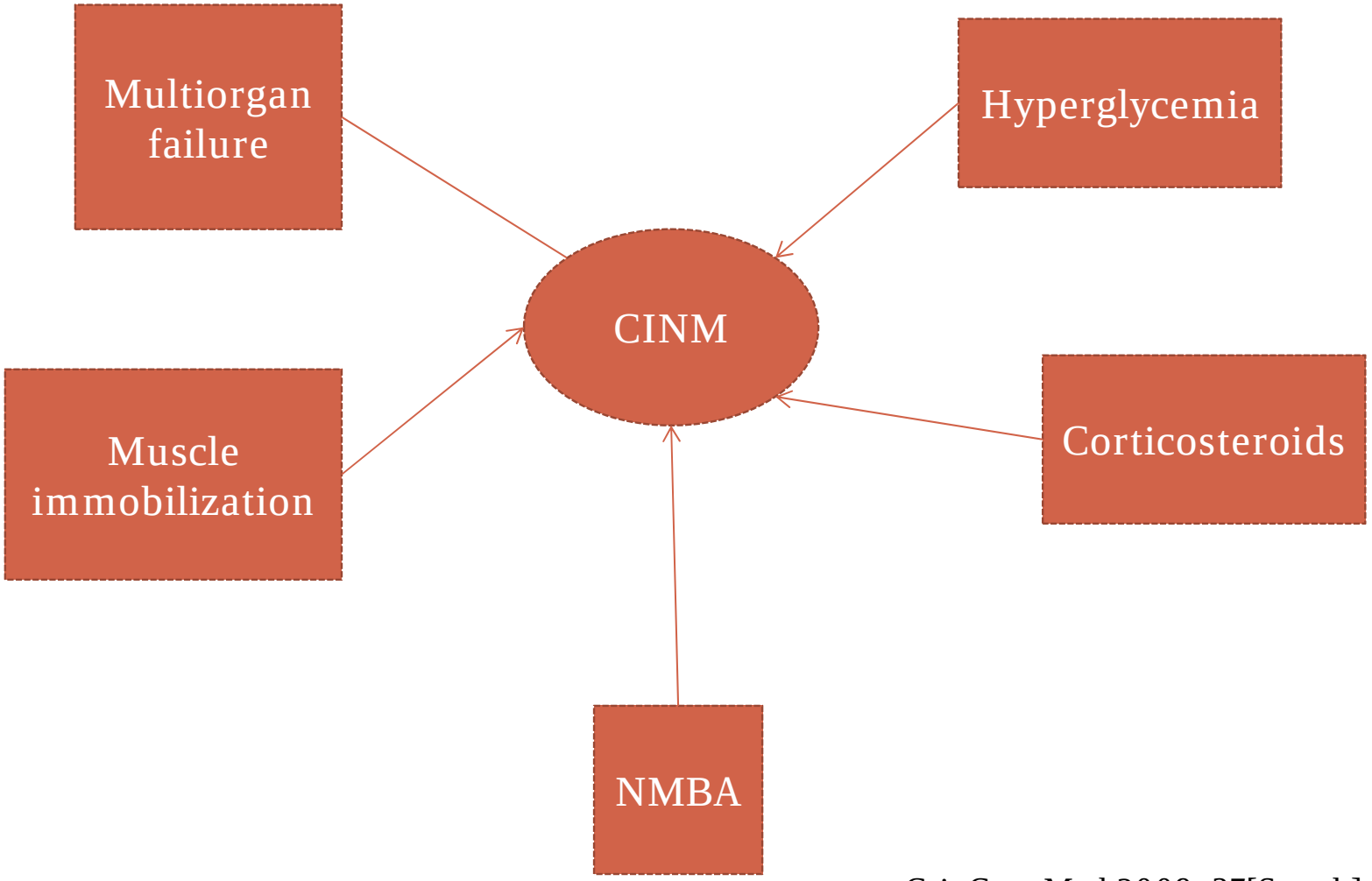
Risk factors

Reference	Serum glucose or hyperglycemia (mg/dL or % patients) CINMA vs. no CINMA	Glucocorticoids (MP total dose or % patients) CINMA vs. no CINMA	Neuromuscular blockers (Total dose or % patients) CINMA vs. no CINMA	Aminoglycosides (% patients or dose) CINMA vs. no CINMA
Amaya-Villar, 2005 [24]	NR	1649 vs. 979 mg, $p=0.05$	44% vs. 18%, $p=0.19$ Vecuronium 13 vs. 11 mg, $p=0.19$	22% vs. 0%, $p=0.1$
Bednarik, 2003 [8]	NR	NR	NR	NR
Bednarik, 2005 [22]	NR	NS association with CINMA	NS association with CINMA	NR
Bercker, 2005 [48]	Peak, 166 vs. 144, $p<0.001$	74% vs. 66%, $p=0.7$	NR	NR
Berek, 1996 [34]		NR	NR	NR
Campellone, 1998 [35]	312 vs. 221, $p=0.007$	2438 vs. 1674 mg, $p=0.02$	NR	NR
Coakley, 1998 [36]	NR	24% vs. 29%, $p=1$	62% vs. 71%, $p=1$	NR
De Jonghe, 2002 [7]	Peak, 360 vs. 259, $p=0.001$**	54% vs. 18%, $p=0.001$* 290 vs. 460 mg, $p=0.32$	63% vs. 41%, $p=0.07$** Vecuronium 13 vs. 16 mg, $p=0.11$	67% vs. 42%, $p=0.04$**
De Letter, 2001 [52]	NR	NS association with CINMA**	NS association with CINMA**	NS association with CINMA**
Druschky, 2001 [38]	NR	Daily dose, 0 vs. 32 mg, $p=0.47$	NR	NR
Garnacho-Montero, 2001 [25]	30% vs. 30%, $p=$NS	14% vs. 17%, $p=0.7$	18% vs. 4%, $p=0.16$*	42% vs. 44%, $p=0.91$
Garnacho-Montero, 2005 [51]	NR	NR	29% vs. 10%, $p=0.06$	NR
Hund, 1997 [50]	NR	NR	NR	NR
Kupfer, 1992 [40]	NR	NR	Vecuronium 1352 vs. 528 mg, $p=0.05$	NR
Lefaucheur, 2006 [41]	NR	58% vs. 25%, $p=0.31$	19% vs. 25%, $p=0.78$	NR
Leijten, 1995 [43]	NR	NR	NR	NR
Leijten, 1996 [42]	NR	NR	NR	NR
Mohr, 1997 [44]	NR	NR	100% vs. 77%, $p=0.26$	100% vs. 35%, $p=0.6$
Rudis, 1996 [49]	NR	70% vs. 50%, $p=0.65$	70% vs. 90%, $p=$NS Vecuronium or pancuronium 1080 vs. 1165 mg, $p=0.76$	70% vs. 80%, $p=1$
Tepper, 2000 [45]	NR	NR	NR	NR
Thiele, 1997 [50]	NR	100% vs. 11%, $p<0.01$ 16 vs. 20 mg/kg, $p<0.01$	86% vs. 30%, $p=$NS Vecuronium or pancuronium 0.37 vs. 0.52 mg/kg, $p=$NS	14% vs. 5%, $p=$NS Total netilmycin 23 vs. 16 mg/kg
Thiele, 2000 [46]	221 vs. 215, $p=$NS	NR	NR	NR
Van den Berghe, 2005 [54]	OR (95% CI) of CINMA 1.26 (1.09; 1.46) per mmol/l of AM blood glucose level*	NR	NR	NR
Witt, 1991 [47]	NR	NR	NR	NR

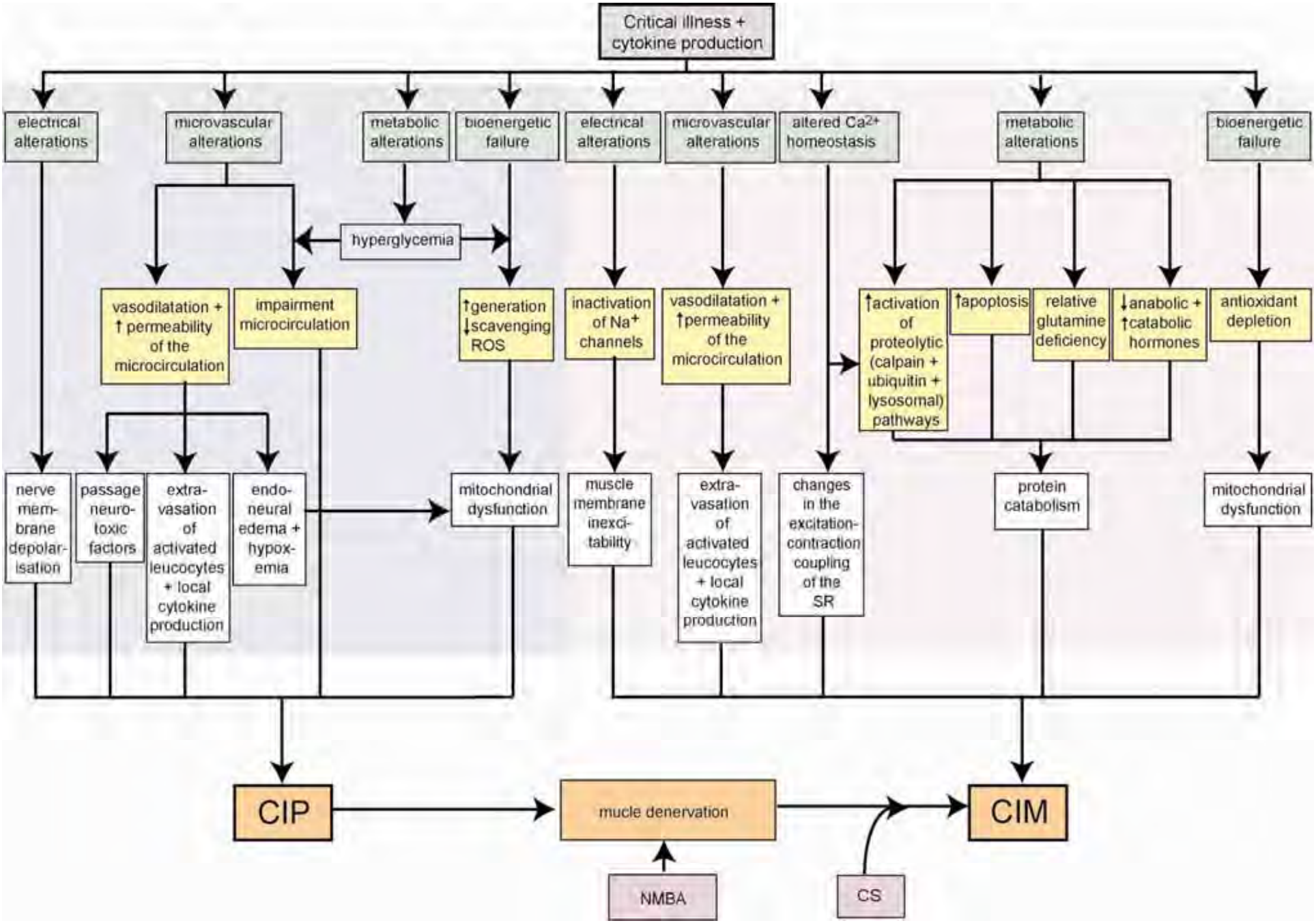
CINMA, critical illness neuromuscular abnormality; *MP*, methylprednisolone; *NR*, not reported; *NS*, not significant or non significant; *HT*, intensive insulin therapy; * Significant association with CINMA after multivariable adjustment; ** Non-significant association with CINMA after multivariable adjustment

Intensive Care Med (2007) 33:1876–1891
DOI 10.1007/s00134-007-0772-2

Risk factors of ICU acquired paresis

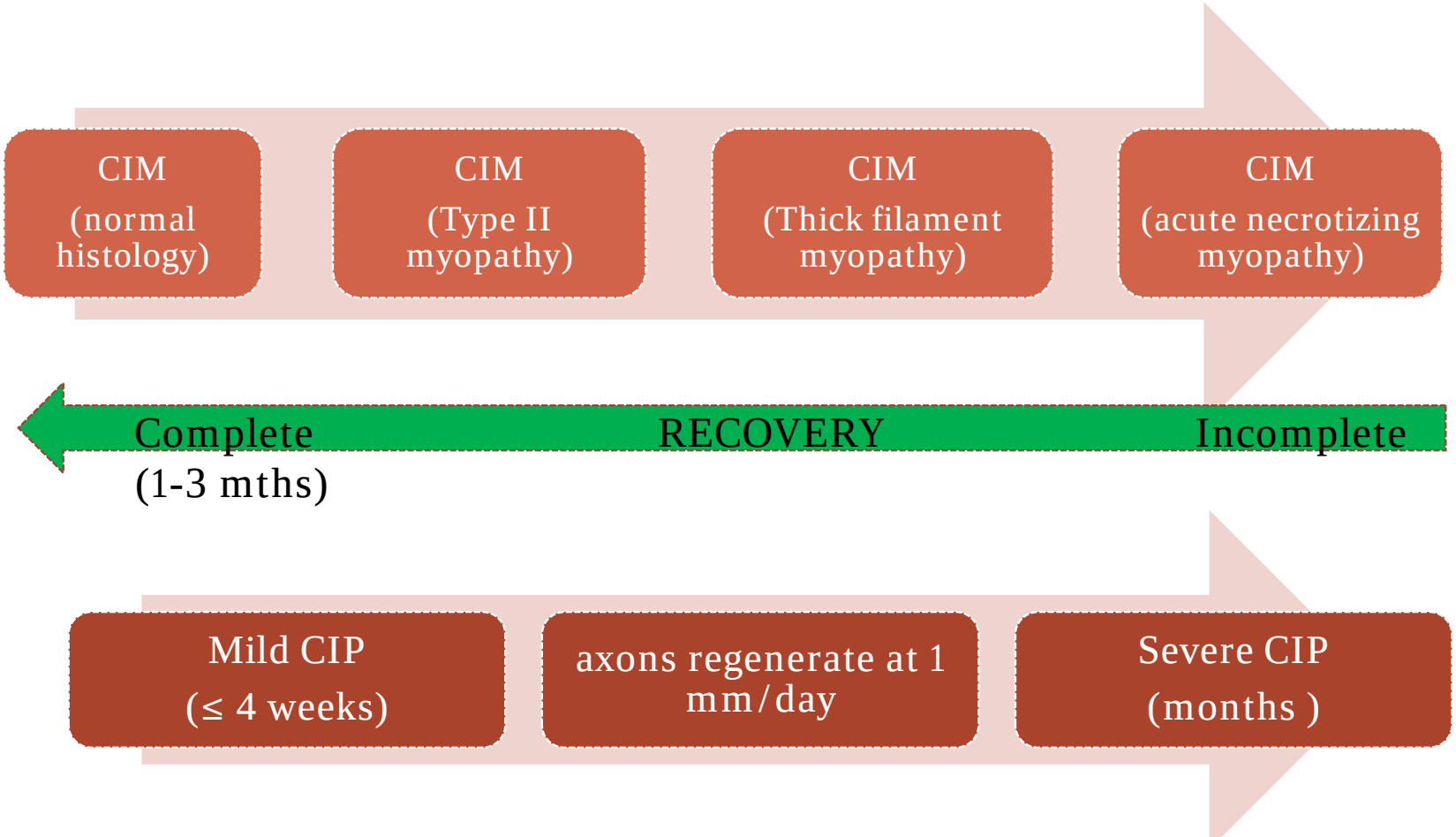


Crit Care Med 2009; 37[Suppl.]:S309 –S315



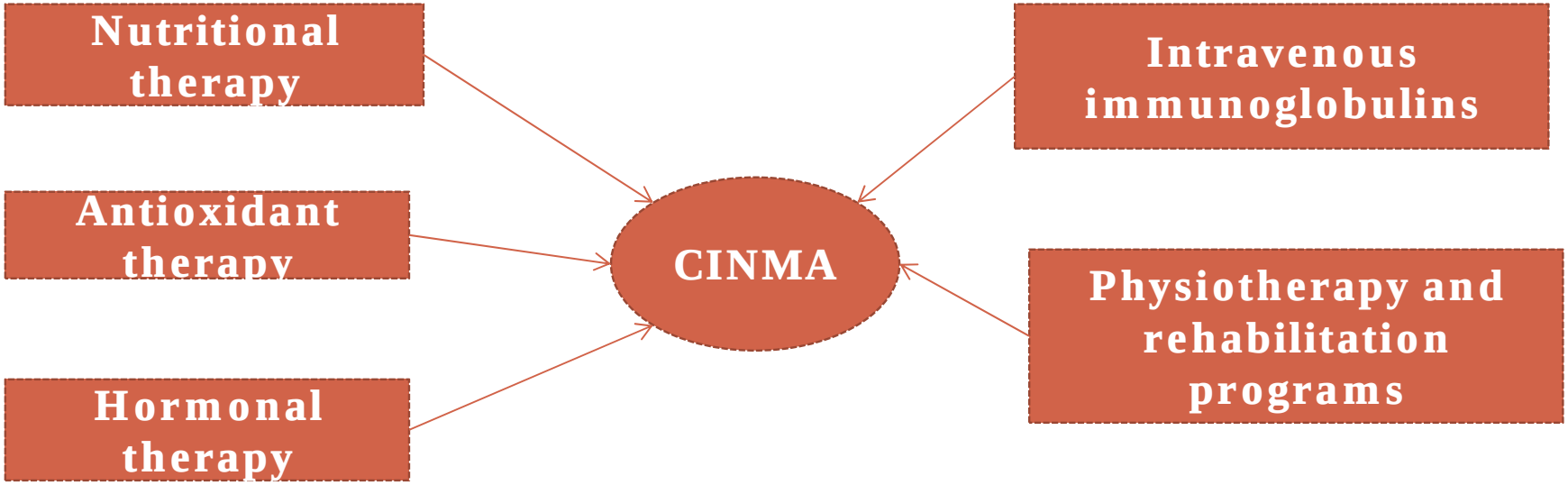
Critical Care 2008, 12:238 (doi:10.1186/cc7100)

Natural course



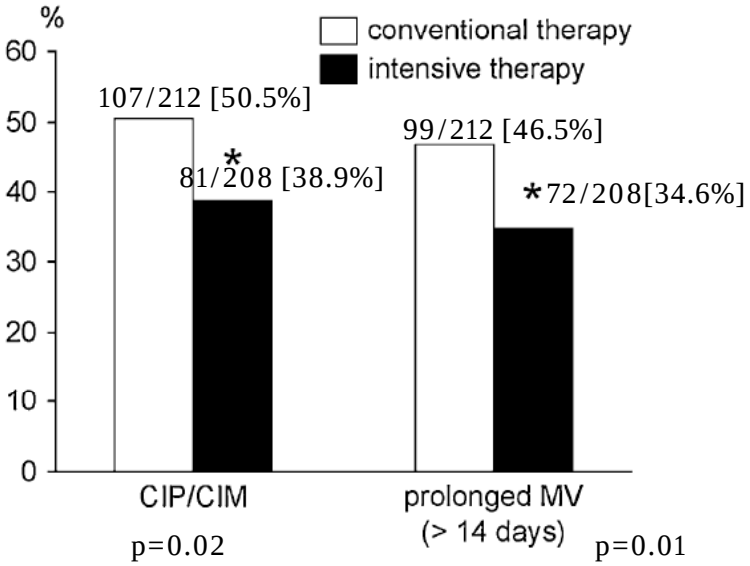
Crit Care Med 1999, 27:2544-2547
JAMA 1995, 274:1221-1225
Crit Care Med 2003, 31:1012-1016

Interventions studied



Impact of Intensive Insulin Therapy on Neuromuscular Complications and Ventilator Dependency in the Medical Intensive Care Unit

Greet Hermans[1], Alexander Wilmer[1], Wouter Meersseman[1], Ilse Milants[2], Pieter J. Wouters[2], Herman Bobbaers[1], Frans Bruyninckx[3], and Greet Van den Berghe[2]



- 420/1200 analysed
- Diagnosis based of ENMG
- 212 CIT vs 208 IIT
- no difference in incidence of known risk factors
- Median AM blood glucose levels were
  - 159[IQR 132-172] in CIT
  - 102 [IQR 97-115] in IIT

Am J Respir Crit Care Med Vol 175. pp 480–489, 2007

Impact of Intensive Insulin Therapy on Neuromuscular Complications and Ventilator Dependency in the Medical Intensive Care Unit

Greet Hermans[1], Alexander Wilmer[1], Wouter Meersseman[1], Ilse Milants[2], Pieter J. Wouters[2], Herman Bobbaers[1], Frans Bruyninckx[3], and Greet Van den Berghe[2]

TABLE 5. INCIDENCE OF KNOWN RISK FACTORS FOR CIP/CIM IN PATIENTS IN THE SURGICAL AND MEDICAL ICU FOR AT LEAST 7 DAYS

	SICU (*n* = 405)	MICU (*n* = 420)
Treatment with norepinephrine	72.1%	74.8%
No. days, median (IQR)	4 (0–10)	4 (0–8)
Treatment with aminoglycosides	15.6%	17.8%
No. days, median (IQR)	0 (0–0)	0 (0–0)
Treatment with NMBAs	36.0%	63.3%
No. days on NMBAs, median (IQR)	0 (0–0)	1 (0–3)
Prolonged treatment with NMBAs, defined as on continuous infusion	NA	18.1%
Prolonged treatment with NMBAs, defined as > 3 d on bolus injections	5.2%	NA
No. days of NMBAs when on prolonged treatment, median (IQR)	5 (4–6)	3 (1–8)
Treatment with glucocorticoids	33.8%	72.8%
No. days, median (IQR)	0 (0–0)	7 (0–13)
Dialysis, yes	21.7%	31.4%
Mean daily total carbohydrate intake, g/d, median (IQR)	223 (192–248)	235 (206–268)
Mean daily total caloric intake, kcal/d, median (IQR)	1,542 (1,314–1,736)	1,581 (1,407–1,797)
Duration of ICU stay, no. days, median (IQR)	15 (10–26)	15 (11–24)
Bacteremia	22.2%	18.6%

The absolute reduction by IIT of the risk for CIP/CIM was even greater in the surgical population (24%) than in the medical population (11.6%)

Am J Respir Crit Care Med Vol 175. pp 480–489, 2007

Consensus to build...

- Incorporate a systematic and daily surveillance for weakness into our routine medical assessment
- Prioritize an awake, communicative and mobile culture in our intensive care units to improve case ascertainment
- Reach consensus on working diagnostic criteria, nomenclature and taxonomy for ICU-acquired weakness to facilitate future research work
- Prioritize longer-term natural history studies to facilitate risk stratification, and determination of what is reversible and amenable to rehabilitative intervention, and ascertainment of optimal timing and intensity of treatment
- Promotion of study of the biology and basic science of muscle and nerve injury associated with critical illness