A framework for diagnosing and classifying intensive care unit-acquired weakness

Robert D. Stevens, MD; Scott A. Marshall, MD; David R. Cornblath, MD; Ahmet Hoke, MD, PhD; Dale M. Needham, MD, PhD; Bernard de Jonghe, MD; Naeem A. Ali, MD; Tarek Sharshar, MD, PhD

Neuromuscular dysfunction is prevalent in critically ill patients, is associated with worse short-term outcomes, and is a determinant of long-term disability in intensive care unit survivors. Diagnosis is made with the help of clinical, electrophysiological, and morphological observations; however, the lack of a consistent nomenclature remains a barrier to research. We propose a simple framework for diagnosing and classifying neuromuscular disorders acquired in critical illness. (Crit Care Med 2009; 37[Suppl.]:S299–S308)

KEY WORDS: intensive care unit-acquired weakness; intensive care unit-acquired paresis; critical illness polyneuropathy; critical illness myopathy; critical illness neuromyopathy; prolonged neuromuscular blockade; electromyogram; nerve conduction studies; direct muscle stimulation

Muscle weakness and atrophy have long been recognized as expressions of severe illness, with Hippocrates describing "spontaneous lassitude" and muscle wasting in patients dying of infection and cancer (1), and William Osler observing how "the loss of flesh and strength is very striking" in life-threatening infections (2). In recent decades, greater survival in critically ill patients has provided the opportunity to identify and characterize a syndrome of neuromuscular dysfunction acquired in the absence of causative factors other than the underlying critical illness and its treatment. Three distinct types of patients were identified: a group with myopathy; another with polyneuropathy; and a group with prolonged pharmacologic neuromuscular blockade.

MacFarlane and 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 (3). These findings were substantiated in subsequent accounts (4, 5), with muscle biopsies demonstrating a spectrum of myopathic changes (6–14). Based on these reports, a variety of terms emerged including "acute quadriplegic myopathy" (6), "acute necrotizing myopathy of intensive care" (10), and "thick filament myopathy" (14) (Table 1). It became apparent that these terms were different expressions of a common syndrome, and in 2000, Lacomis et al proposed the generic term *critical illness myopathy* (CIM) (15).

The first accounts of a peripheral neuropathy complicating sepsis and multiple organ failure were made in the 1980s by Bolton et al, who detailed electrophysiological and morphologic features in intensive care unit (ICU) patients with newly acquired flaccid areflexic weakness and failed attempts to liberate from the ventilator (16–19). The preponderant pattern was an axonal polyneuropathy which, in conjunction with the lack of albumino-cytological dissociation on cerebrospinal fluid analysis, differentiated this condition from the most common form of Guillain-Barré syndrome (GBS) (17, 20). This newly described entity, named *critical illness polyneuropathy* (CIP), was further characterized in a number of ensuing studies (21–31).

During the 1980s and 1990s, there were reports on critically ill patients who had unexpectedly prolonged periods of paralysis after receiving a nondepolarizing neuromuscular blocking agent (NMBA) (32–39). Recovery of motor function was delayed for hours to days after cessation of the causative drug (38). Initial accounts concerned patients who had received large cumulative doses of aminosteroid NMBAs (e.g., vecuronium, pancuronium), often administered in an effort to facilitate mechanical ventilation; prolonged paralysis was subsequently associated with other classes of NMBA (e.g., atracurium or cisatracurium) (40–43). Patients with concomitant organ dysfunction, in particular, renal insufficiency, were found to be at increased risk (44). Many of these accounts did not include detailed neurologic examination or electrophysiological testing, preventing definitive differentiation between these cases and critical illness polyneuropathy and/or myopathy.

The impact of ICU-acquired neuromuscular dysfunction is difficult to overestimate. The functional disability and reduced quality of life described in survivors of critical illness have been linked to neuromuscular complaints including persistent pain (45–47), contractures (48), and muscle weakness acquired

From the Division of Neurosciences Critical Care (RDS, SAM), Departments of Anesthesiology Critical Care Medicine (RDS, SAM), Neurology (RDS, SAM, DRC, AH), Neurosurgery (RDS, SAM); Division of Pulmonary and Critical Care Medicine (DMN), Departments of Medicine (DMN) and of Physical Medicine and Rehabilitation (DMN), The Johns Hopkins University School of Medicine, Baltimore, MD; Department of Neurology (SAM), Uniformed Services University of the Health Sciences, Bethesda, MD; Réanimation Médico-Chirurgicale (BdJ), Centre Hospitalier de Poissy-Saint-Germain, Poissy, France; Division of Pulmonary, Allergy, Critical Care and Sleep Medicine (NAA), Ohio State University, Columbus, OH; and Raymond Poincaré Hospital (AP-HP) (TS), Faculty of Medicine, University of Versailles Saint-Quentin en Yvelines Garches, France.

The opinions expressed in this manuscript belong solely to those of the authors, and they should not be interpreted as representative or endorsed by the Uniformed Services University, U.S. Army, Department of Defense, or any other agency of the federal government of the United States.

For information regarding this article, E-mail: rstevens@jhmi.edu

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181b6ef67

Copyright (c) Society of Critical Care Medicine and Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

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)

ICU, intensive care unit.

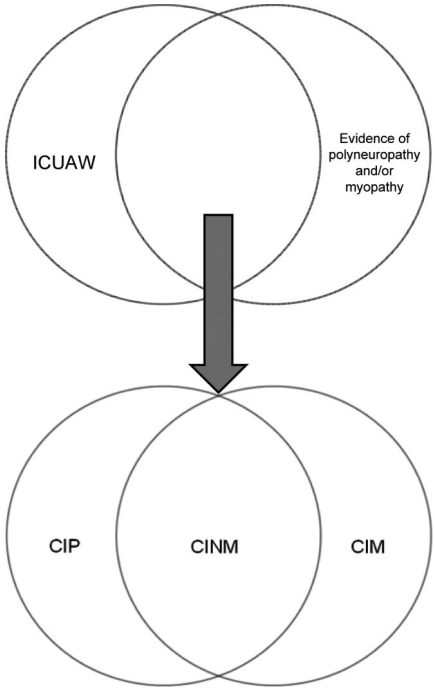


Figure 1. Classification of intensive care unit-acquired weakness (*ICUAW*). *CIP*, critical illness polyneuropathy; *CINM*, critical illness neuromyopathy; *CIM*, critical illness myopathy.

in the ICU (49, 50). Studies have documented clinical and electrophysiologic evidence of focal compressive mononeuropathy (51) and of polyneuropathy and/or myopathy persisting for months to years after the acute illness (52–57). In the ICU acute setting, muscle weakness is associated with prolonged mechanical ventilation and failure to separate from the ventilator (27, 58, 59), delayed discharge from the ICU and hospital (60, 61), and increased costs (62). Higher hospital or ICU mortality rates have been reported in patients with ICU-acquired muscle dysfunction (27, 52, 59, 63), although this association was not found in all studies (22, 24, 30, 61). Recognition of neuromuscular dysfunction as an important and potentially long-term manifestation of critical illness has inspired efforts to identify preventive or therapeutic interventions including glycemic control (64) and programs centered on early mobility, physical, and occupational therapy (65–67).

DEFINITIONS AND CLASSIFICATION

Following the initial descriptions of myopathy and polyneuropathy in critically ill patients, the need to articulate a comprehensive diagnostic nomenclature and classification was hindered by several factors. Traditional nosological schemes based on etiology or pathogenesis were not possible because the latter were (and remain) largely unknown. A semiological classification was of questionable significance as the symptoms and signs of polyneuropathy and myopathy are neither sensitive nor specific (68). Some have recommended that diagnosis and classification must be based on electrophysiological criteria (electromyography [EMG] and nerve conduction studies [NCS]) (29, 69). Others argued that routine EMG/NCS is not needed in clinical practice and should be reserved primarily for research purposes (63, 70–72). Proponents of this latter view assert that the most valuable information is available through a careful history and physical examination, and that EMG/NCS has many limitations (72). Furthermore, accurate electrophysiological differentiation between CIM and CIP is frequently impracticable, particularly in patients who are not able to contract their muscles voluntarily (12).

Nosological efforts were further thwarted by the observation that myopathy and polyneuropathy coexist in ICU patients. This was demonstrated in 1996 by Latronico et al, who found histologic evidence of myopathy in 23 (96%) of 24 patients who had been diagnosed with CIP, using EMG/NCS (12). Other groups have since confirmed that elements of myopathy and polyneuropathy may occur concurrently or sequentially within a single patient, and that these overlapping findings might represent the most prevalent pattern of neuromuscular dysfunction in the ICU (29, 30, 73, 74). Reflecting this construct, and in an effort to remain taxonomically inclusive, a variety of generic terms have emerged, such as *critical illness myopathy and/or neuropathy* (12), *critical illness polyneuropathy* (75), *ICU-acquired paresis* (30), and *ICU-acquired weakness* (9) (Table 1).

The absence of a consistent nomenclature of neuromuscular disorders in critical illness constitutes a serious barrier to research in this field. In a systematic review published in 1998, de Jonghe et al evaluated eight studies enrolling a total of 242 patients, and found major differences in the way ICU-acquired neuromuscular disorders were defined and diagnosed in the populations studied and in the reporting of risk factors and outcomes (76). Such disparities were confirmed in a more recent systematic review of 24 studies comprising 1421 patients (77), and underscore the need to build a consensus on nomenclature and classification (78, 79).

We propose a simple scheme to diagnose and classify these disorders (Fig. 1). The term *ICU-acquired weakness* (ICUAW) designates clinically detected weakness in critically ill patients in whom there is no plausible etiology other than critical illness. Patients with ICUAW and documented polyneuropathy and/or myopathy are classified in three subcategories. *Crit-*

Copyright (c) Society of Critical Care Medicine and Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

ical illness polyneuropathy refers to patients with ICUAW who have electrophysiological evidence of an axonal polyneuropathy, and *critical illness myopathy* indicates patients with ICUAW who have electrophysiologically and/or histologically defined myopathy. The term *critical illness neuromyopathy* (CINM) is reserved for patients who have electrophysiological and/or histologic findings of coexisting CIP and CIM.

DIAGNOSTIC METHODS AND THEIR LIMITATIONS

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

The clinical approach is based on the identification of generalized weakness in the appropriate setting, the exclusion of causes of generalized weakness extrinsic to critical illness, and the measurement of muscle strength. Clinical diagnosis is achieved with a review of medical, neurologic, and familial antecedents; a careful analysis (when possible) of the time course of neuromuscular symptoms, in particular, as they relate to the underlying critical illness; and the search for factors, which have been associated with ICUAW (e.g., sepsis, multiple organ failure, mechanical ventilation, hyperglycemia, exposure to selected pharmacologic agents like glucocorticoids and NMBAs). Neurologic examination should evaluate key functional domains including consciousness and cognitive function, cranial nerves, motor and sensory systems, deep tendon reflexes, and coordination. Motor assessment should include a consideration of tone and bulk in addition to strength.

Although a range of methods exist to measure muscle strength, techniques reported in critically ill patients include manual muscle testing and hand dynamometry. Manual muscle testing is accomplished usually with the Medical Research Council (MRC) score, which grades strength from 0 to 5 in functional muscle groups in each extremity (80). Individual MRC scores obtained from predefined muscle groups can be combined in a sumscore, which yields a global estimation of motor function (81); if three muscle groups are tested in each extremity, the sumscore will range from 0 (complete paralysis) to 60 (full strength). The MRC sumscore has good interobserver reliability in patients with GBS (82) and has been implemented successfully in critically ill patients (30). In several prospective studies of mechanically ventilated patients, an MRC sumscore of <48 (or a mean MRC of <4 per muscle group) was used as the cutoff for defining "ICU-acquired paresis" (30, 31, 58, 63). The MRC is relatively simple and intuitive; however, it requires a patient who is awake, cooperative, and capable of contracting the extremities with maximal force—conditions which many ICU patients fail to meet. MRC scores may be 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). Additional shortcomings of the MRC are that it is expressed on an ordinal scale diminishing sensitivity to subtler changes in muscle function, and that it does not evaluate distal extremity function (e.g., intrinsic hand muscles) which may be the first affected in motor neuropathies.

The standard hand dynamometer, which assesses grip strength with a calibrated device, provides a measurement of force on a continuous scale. In reports of patients in the ICU (63) or recently discharged from the ICU (83), significant decrements in dynamometric measurements of grip strength were noted; in one of these reports, grip strength correlated with MRC scores and was independently predictive of hospital mortality, suggesting that hand dynamometric assessments might be a surrogate for global strength (63). Like the MRC, dynamometry requires voluntary muscle contraction, which may be compromised by concurrent pain, sedation, delirium, or coma. Even in patients who are alert and cooperative, the finding of weakness does not differentiate between a range of possible etiologies (Table 2).

Electrophysiology

Electrophysiological methods routinely used to evaluate the peripheral nervous system include NCS, needle EMG, and neuromuscular junction testing (84). Recently, there has been interest in other parameters of muscle performance, such as isometric force assessment (85, 86).

In NCS, stimulation of a peripheral motor nerve elicits a compound muscle action potential (CMAP), which represents the summated response of all stimulated muscle fibers; alternatively, stimulation and recording are carried out at separate points along a sensory nerve to yield the sensory nerve action potential (SNAP), which represents the summated response of all stimulated sensory fibers. When a nerve is stimulated at two sites separated by a known distance, a nerve conduction velocity may be calculated. The recording of CMAP and SNAP amplitudes and motor and sensory nerve conduction velocity are used to intuit the state of the peripheral nervous system. Normal nerve conduction velocity in conjunction with decreased CMAP and SNAP amplitudes usually indicates an axonal, sensory-motor polyneuropathy (e.g., CIP), whereas markedly reduced conduction velocities with preserved CMAP and SNAP amplitudes usually indicates a demyelinating, sensory-motor polyneuropathy (e.g., the acute inflammatory demyelinating polyneuropathy subtype of GBS).

Needle EMG is recorded in awake, cooperative patients at three states of muscle activity: at rest; with mild voluntary muscle contraction; and with increasing or maximal voluntary muscle contraction (87). The presence of fibrillation potentials and positive sharp waves at rest suggests recent denervation or muscle necrosis. With voluntary muscle activation, motor unit potentials (MUPs) are recorded. Short-duration, low-amplitude MUPs are a sign of reduced functional muscle fibers within each motor unit and usually indicate myopathy. Long-duration, high-amplitude polyphasic MUPs are a sign of collateral reinnervation of denervated muscle fibers and suggest neuropathy in the appropriate setting. With maximal voluntary contraction, an "interference pattern" of overlapping MUPs is recorded; this pattern is reduced in neuropathic processes, whereas in myopathy, there is early recruitment of MUPs and the "envelope" amplitude of the maximal contraction is reduced.

Phrenic nerve conduction studies and needle EMG of the diaphragm have been reported as a valuable adjunct to routine electrophysiological testing in the ICU, particularly in patients who fail to liberate from mechanical ventilation (88). In patients with CIP, a pattern of bilaterally decreased phrenic CMAP amplitudes,

Copyright (c) Society of Critical Care Medicine and Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Table 2. Acute generalized weakness syndromes in critically ill patients

Bilateral or paramedian brain or brainstem lesions[a]
Trauma
Infarction
Hemorrhage
Infectious and noninfectious encephalitides
Abscess
Central pontine myelinolysis
Spinal cord disorders[a]
Trauma
Nontraumatic compressive myelopathies
Spinal cord infarction
Immune-mediated myelopathies (transverse myelitis, neuromyelitis optica)
Infective myelopathies (e.g., HIV, West Nile virus)
Anterior horn cell disorders
Motor neuron disease
Poliomyelitis
West Nile virus infection
Hopkins syndrome (acute postasthmatic amyotrophy)
Polyradiculopathies
Carcinomatous
HIV-associated
Peripheral nervous disorders
Guillain-Barré syndrome[b]
Diphteric neuropathy
Lymphoma-associated neuropathy
Vasculitic neuropathy
Porphyric neuropathy
Paraneoplastic neuropathy
Critical illness polyneuropathy
Neuromuscular junction disorders
Myasthenia gravis
Lambert-Eaton myasthenic syndrome
Neuromuscular-blocking drugs
Botulism
Muscle disorders
Rhabdomyolysis
Disuse myopathy
Cachexia
Infectious and inflammatory myopathies[c]
Mitochondrial myopathies
Drug-induced and toxic myopathies
Critical illness myopathy
Decompensation of congenital myopathies (e.g., myotonic dystrophy, Duchenne muscular dystrophy, adult onset acid maltase deficiency)

HIV, human immunodeficiency virus.

[a]Upper motor neuron signs (increased tone, hyperreflexia) may be absent in the acute setting; [b]includes acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, acute motor and sensory axonal neuropathy; [c]includes polymyositis, dermatomyositis, pyomyositis.

normal phrenic nerve distal latencies (similar to conduction velocities), and EMG evidence of denervation have been reported (26, 89). In CIM, needle EMG of the diaphragm reveals spontaneous "myopathic" potentials (short-duration, low-amplitude MUPs), but these may be difficult to distinguish from normal (90).

Electrophysiological assessment of the neuromuscular junction is accomplished with repetitive nerve stimulation and/or single-fiber EMG. In repetitive nerve stimulation, a train of supra-maximal stimuli is applied at 2 to 3 Hz. A decrement of >10% of CMAP amplitude from the first to fourth response indicates a postsynaptic defect in neuromuscular transmission (e.g., myasthenia gravis or NMBA effects) (91). Single-fiber EMG records the time interval between action potentials in two muscle fibers that are part of the same motor unit; variable interspike intervals (jitter) and absence (blocking) of the second spike are consistent with neuromuscular junction dysfunction (92). Although more sensitive than repetitive nerve stimulation, single-fiber EMG usually requires voluntary muscle contraction; thus, its use in the ICU is more limited.

Electrophysiological tests are invaluable adjuncts to the clinical assessment of patients with ICUAW and yet have important shortcomings. EMG/NCS require dedicated equipment and trained personnel, and recordings can be unreliable because of tissue edema, differences in limb temperature, or electrical interferences in the ICU environment. Even when reliable, these tests frequently lack specificity. NCS consistent with an axonal polyneuropathy might indicate CIP; however, other causes of axonal polyneuropathy (e.g., axonal variants of GBS, or polyneuropathies associated with diabetes mellitus, chronic alcohol use, and chemotherapy) must also be considered (93). The interpretation of EMG/NCS is particularly challenging in patients who cannot voluntarily contract muscle because of concurrent sedation, encephalopathy, or severe weakness. 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 (12, 29, 74), leading many to conclude that definitive electrophysiological differentiation between these entities is frequently not possible (94–96).

The problem of eliciting muscle activity in the absence of voluntary contraction can be overcome with direct muscle stimulation (DMS). DMS compares CMAPs elicited by motor nerve stimulation with CMAPs induced when the muscle itself is stimulated. Neuropathy is suggested when CMAPs produced by muscle stimulation are of normal amplitude whereas motor nerve-elicited CMAPs are reduced or absent; in myopathy, responses to both nerve and muscle stimulation are reduced or absent, indicating the muscle is inexcitable (97). Rich et al proposed a "nerve/muscle ratio," which is the quotient of nerve- and muscle-evoked CMAP amplitudes; a nerve/muscle ratio of >0.5 indicated a neuropathic process, whereas <0.5 suggested a myopathic disorder (98). More recently, nerve/muscle ratios in combination with muscle-evoked CMAP amplitudes have been integrated in ICUAW diagnostic algorithms (29, 73). Concerns have been raised that DMS is semiquantitative and that interpretation is uncertain in patients with combined CIP/CIM (95); however, data have accrued to support DMS as an important new tool in the evaluation of patients with ICUAW, in particular, when voluntary muscle contraction cannot be reliably obtained (29, 73, 74, 98).

Another method to assess muscle performance independently of voluntary contraction is to quantify muscle force generated by high-frequency (tetanic) motor nerve stimulation. Measurements

Copyright (c) Society of Critical Care Medicine and Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

of adductor pollicis force elicited by electrical (85) or magnetic (99) stimulation of the ulnar nerve, or the ankle dorsiflexor force in response to peroneal nerve electrical stimulation (86) 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 (85). 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.

Morphology

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 (16); muscle biopsies from these same patients show changes characteristic of denervation but may also reveal myopathy (12, 18). Muscle biopsies in CIM reveal a spectrum of histologic, immunohistological, and ultrastructural abnormalities frequently coexisting within a single tissue sample (12). These include acute necrosis (6, 9), regeneration (100), type II (fast twitch) fiber atrophy (101), and selective but patchy loss of thick filaments (myosin), which is inferred from a loss of myofibrillar adenosine triphosphate staining on immunohistology (102) and which is directly visualized on electron microscopy (14). This last feature is considered by some to be a hallmark of CIM, leading to the term *thick filament myopathy* (14).

Morphologic studies have increased mechanistic understanding of neuromuscular disorders in critical illness, and the observation of myosin loss, in particular, has spurred key observations on the role of cellular proteolytic systems in experimental models of sepsis (103–105) or in humans with acute quadriplegic myopathy (106). However, the role of muscle (and nerve) biopsies in clinical practice is controversial (72, 107). Clear indications for muscle biopsy in the setting of ICUAW have not been established. The prognostic value of histologic findings remains poorly explored. The place of biopsy within a comprehensive diagnostic algorithm is discussed below.

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

ICUAW, intensive care unit-acquired weakness; MRC, Medical Research Council.
[a]For example, facial grimace is intact.

Other Diagnostic Tests: Biomarkers and Imaging

Increased serum creatine kinase (CK) has been reported in critically ill patients with acquired myopathy (4, 8, 10, 29, 61, 73, 108, 109), with marked elevations noted in necrotizing myopathy (9, 10). However, 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 (4). In a separate observation of patients remaining in the ICU for >7 days, nearly half had elevated CK but peak levels were considerably lower (200 U/L; range, 17–666). In a more recent prospective study of patients who were alert after >7 days of mechanical ventilation, peak CK levels were mildly increased but not significantly different in patients with and without ICU-acquired paresis (30).

Given evidence of 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 (110–112). 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 (112). Time-dependent decreases in muscle thickness were confirmed in more recent observations made on the quadriceps femoris (111) and upper arm (110). Although these results are captivating, the relationship between ultrasound-defined changes in muscle thickness and clinical or electrophysiological assessments of ICUAW have yet to be delineated.

DIAGNOSTIC CRITERIA

Diagnosis of ICUAW

A diagnosis of ICUAW (Table 3) should be considered in patients with generalized limb weakness developing in the absence of any etiology or condition extrinsic to the underlying critical illness. The weakness must follow the onset of the critical illness; symptoms preceding admission to the ICU should direct attention to other etiologies. The history generally reveals a setting or risk factor, which has been associated with ICUAW, e.g., sepsis, multiple organ failure, mechanical ventilation, exposure to glucocorticoids or neuromuscular blockers, or poor glycemic control (77). Physical examination shows diffuse, symmetric weakness involving all extremities, decreased tone, and deep tendon reflexes which are normal, decreased, or absent (lateralized hyperreflexia might be found if there is a coexisting corticospinal tract lesion). Weakness affects the extremities and the diaphragm with relative sparing of the cranial nerves such that facial grimace is usually preserved. Patients often have concurrent respiratory failure and have undergone unsuccessful attempts to liberate from mechanical ventilation. During spontaneous breathing trials, a rapid shallow breathing pattern is observed; forced vital capacity and negative inspiratory force are characteristically low (26, 58); however, such findings are not specific to ICUAW.

The finding of generalized weakness is extremely common in critically ill patients and warrants a review of etiologies,

Copyright (c) Society of Critical Care Medicine and Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

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.
[a]Modified from Lacomis et al (15).

which may or may not be acquired in the ICU (Table 2). Given that some of these other conditions are treatable, ICUAW should be regarded as a diagnosis of exclusion. Generalized weakness may result from lesions of the brain or brainstem, myelopathies, anterior horn cell disorders, polyneuropathies (from either critical illness or another etiology), neuromuscular junction disorders, and muscle disorders. Weakness may represent the exacerbation or unmasking of a chronic and/or hereditary underlying neuromuscular disease (e.g., acid maltase deficiency, myotonic dystrophy). More commonly, weakness may result from an acute neuromuscular condition of which the etiology and pathogenesis is independent of critical illness) (e.g., GBS or myasthenia gravis). Many of these other etiologies can be excluded with confidence by a careful history and physical examination. In cases of persisting uncertainty, additional tests should be sought—such as neuroimaging to evaluate for brain, brainstem, or spinal cord lesions; infectious and immunologic serologies; cerebrospinal fluid analysis; and EMG/NCS.

Diagnosis of CIP

Pure CIP is identified in patients who meet the criteria for ICUAW and who have electrophysiological evidence of a sensorimotor axonal polyneuropathy (Table 4). Physical examination reveals quadriparesis or quadriplegia, decreased muscle tone, and usually sparing of cranial nerves (i.e., presence of a grimace to noxious stimulus, absence of ptosis or extraocular muscle deficits). Sensory examination, when possible, indicates a predominantly distal loss of pain, temperature, and vibration sense. Deep tendon reflexes are usually decreased or absent, but normal reflexes do not exclude CIP. Cerebrospinal fluid profile (if available) reveals normal cell counts and protein levels that are normal or mildly elevated (17).

Diagnosis of CIP requires differentiation from CIM and from other causes of generalized weakness and, in particular, other polyneuropathies (Table 2). GBS is frequently considered in the differential diagnosis because it is the most frequent neuromuscular disorder requiring ICU admission and because it is treatable with intravenous immunoglobulin or plasmapheresis. GBS is distinguished from CIP by a number of factors including clinical history, cranial nerve involvement, presence of dysautonomia, elevated cerebrospinal fluid protein and, in the case of acute inflammatory demyelinating polyneuropathy, reduced conduction velocities, conduction block, and prolonged or absent F waves, which suggest a demyelinating process. On the other hand, the axonal variants of GBS, such as the acute motor and sensory axonal neuropathy, may be electrophysiologically indistinguishable from CIP and differentiation depends on the time course, setting, and recovery curve (113).

Diagnosis of CIM

A diagnosis of pure CIM is made in patients who meet the criteria for ICUAW and who have myopathic features on EMG recorded during voluntary muscle contraction and/or a myopathic muscle biopsy (Table 5). Physical examination findings have low specificity and do not differentiate CIM from CIP except in fully awake patients in whom the documentation of a new distal sensory loss is suggestive of CIP. In patients who are unable to voluntarily contract muscle, needle EMG/NCS differentiates poorly between CIM and CIP, but preserved SNAP amplitudes are suggestive of CIM without coexisting CIP. In patients unable to voluntarily contract muscle, confirmation of CIM depends on muscle biopsy and/or DMS. Pathologic changes in CIM include thick filament (myosin) loss, type II (fast twitch) fiber atrophy, and necrosis (9, 11). Elevation in serum CK has been detected early in the course of CIM, but the sensitivity of this biomarker for CIM has not been determined (4, 10, 109).

CIM must be differentiated from other causes of acute generalized weakness and, in particular, disuse muscle atrophy, steroid myopathy, cachexia, rhabdomyolysis, and decompensation of primary muscle disorders (Table 2). Cachexia and disuse myopathy are significant causes of weakness and muscle atrophy in patients with chronic illnesses; however, their relationship to muscle dysfunction in the ICU and their potential overlap with CIM remain unexplored (114). Rhabdomyolysis, a breakdown of muscle tissue caused by trauma, ischemia, sepsis, and medication or toxic exposures, is manifested by markedly elevated serum CK, myoglobinuria, and acute kidney injury (95, 115).

Diagnosis of CINM

We propose the use of CINM to designate patients who have features of both CIP and CIM (Table 6). Several groups have documented that CINM is common, possibly more prevalent than CIP or CIM alone (12, 29, 30, 73, 74). The likelihood of identifying CINM is dependent on the diagnostic approach; when a comprehensive diagnostic algorithm is used, incorporating routine electrophysiological testing complemented with muscle biopsy and/or DMS,

Copyright (c) Society of Critical Care Medicine and Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

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.

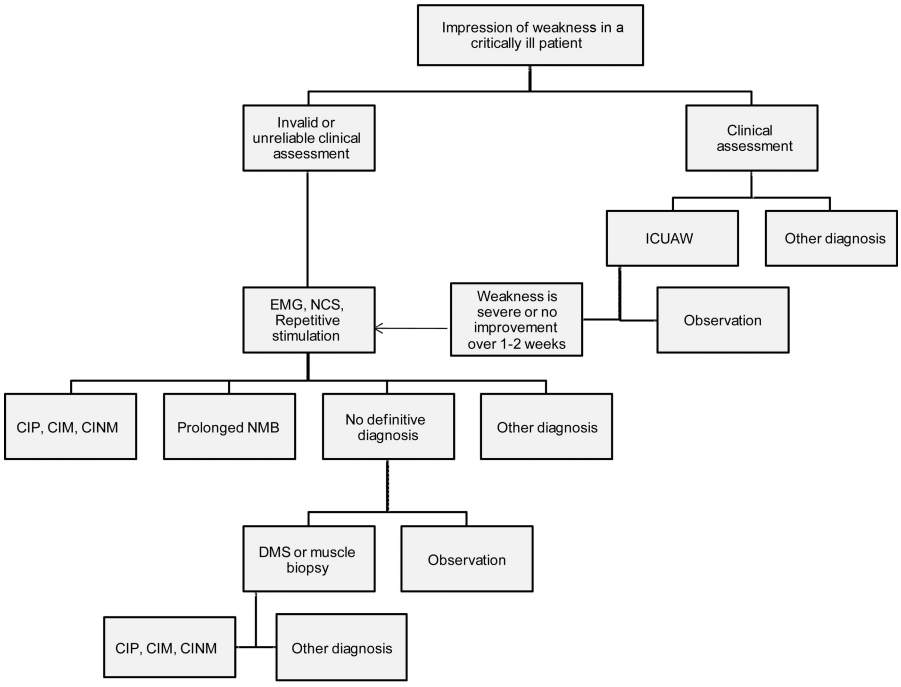


Figure 2. Diagnostic algorithm for weakness in the intensive care unit. *ICUAW*, intensive care unit-acquired weakness; *EMG*, electromyography; *NCS*, nerve conduction studies; *CIP*, critical illness polyneuropathy; *CIM*, critical illness myopathy; *CINM*, critical illness neuromyopathy; *NMB*, neuromuscular blocking; *DMS*, direct muscle stimulation.

the prevalence of CINM may be up to 96% (12, 73).

Diagnosis of Prolonged Neuromuscular Blockade

Proposed diagnostic criteria for prolonged neuromuscular blockade are given in Table 7. This condition is identified in critically ill patients who receive nondepolarizing NMBAs and after cessation of the drug have persistent generalized weakness and dependence on mechanical ventilation (38). Patients with renal failure, liver failure, metabolic acidosis, and hypermagnesemia are at increased risk (44). Examination is notable for flaccid arreflexic quadriplegia and involvement of cranial nerves (facial weakness, ptosis, ophthalmoparesis). Repetitive nerve stimulation shows a decremental response. The "train-of-four" option on widely available twitch monitors measures the decremental response semiquantitatively, allowing serial assessments (38). This condition is reversible and recovery of motor function is usually observed over a period of 2 to 10 days (32, 35, 38). Weakness persisting beyond this duration should elicit other diagnoses. The differential diagnosis includes other neuromuscular junction diseases, in particular myasthenia gravis (Table 2). The distinction from CIP or CIM is not always clear, especially when weakness is prolonged and the results of repetitive nerve stimulation are equivocal.

Diagnostic Strategy

An approach to weakness in the ICU is given in Figure 2. Suspicion for ICUAW should be substantiated with a careful clinical assessment. Whenever possible and appropriate, sedation should be interrupted and the patient should be challenged with a spontaneous breathing trial. Clinical elements suggestive of an etiology unrelated to critical illness should be pursued with ancillary testing (e.g., neuroimaging, cerebrospinal fluid analysis). If no alternative etiology is plausible, a diagnosis of ICUAW can be made. At this stage, it may be reasonable to observe a weak patient with serial neurologic examinations and not seek further tests. However, in cases where weakness is severe and/or no improvement is noted over 1 to 2 wks, electrophysiological testing should be obtained including EMG, NCS, and repetitive nerve stimulation. These tests should also be obtained when clinical assessment is impracticable. Electrophysiological testing will help in the diagnosis of CIM, CIP, CINM, or prolonged neuromuscular blockade, but testing may be nondiagnostic. In these patients, consideration should be given to more specific studies, such as DMS and/or muscle biopsy. The information from these tests, when considered with the prior tests, should allow more definitive identification of CIM or CINM.

AREAS OF UUNCERTAINTY AND THE RESEARCH AGENDA

We have outlined a diagnostic approach and a nosological scheme for neuromuscular disorders acquired in the ICU. Although these elements can serve as a basis for communicating about these disorders, significant areas of uncertainty remain. Many of these questions can be addressed in clinical studies; others will require expert panels and consensus conferences for resolution.

Copyright (c) Society of Critical Care Medicine and Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

The central importance of clinical assessment has been emphasized, but we have also insisted that ICUAW remains a diagnosis of exclusion. If such is the case, minimum requirements (e.g., neuroimaging) to rule out alternative causes of weakness will need to be defined. Another crucial element is the identification of neuromuscular function and functional status preceding critical illness. Subjects with known preexisting neuromuscular diseases have been deliberately excluded from the majority of ICUAW studies for obvious reasons; however, many patients with chronic conditions, such as diabetes mellitus, cancer, congestive heart failure, or chronic obstructive pulmonary disease, have chronic peripheral nerve and/or muscle dysfunction whose potential impact on ICUAW needs to be studied. The natural history of ICUAW is another important and poorly understood issue. In proposing diagnostic criteria for ICUAW, we set 24 hrs as the minimum interval between two separate MRC assessments; yet, these criteria do not address duration of weakness and, in particular, the question—Should a different nomenclature be considered for ICUAW or CINM that resolves in a week as opposed to weakness that persists for 6 or 12 mos?

Regarding physical examination, there is a need to develop and validate techniques to assess strength in patients who are unable to contract muscle voluntarily because of pain, sedation, or brain dysfunction. Research is needed to investigate potential associations between ICUAW and delirium and coma whose prevalence and impact are well established in critically ill patients (116). ICUAW and, specifically, the widely used MRC score and sumscore need to be validated against electrophysiological changes. Are there patients with ICUAW whose electrophysiology is normal? Is there a subset of ICU patients with abnormal neuromuscular electrophysiology who do not have clinically significant weakness?

With regard to electrophysiological tests, specific indications for obtaining EMG/NCS should be articulated, and recommendations should be made on when (or whether) to get repeat testing. Just as studies on the natural history of ICUAW are lacking, so too the time course of electrophysiological abnormalities warrants greater scrutiny. Latronico et al found that unilaterally recorded reductions of >2 standard deviation in peroneal nerve CMAPs predicted EMG/NCS-defined CIP and/or CIM with a sensitivity of 100% and a specificity of 67% (117); the role of such simplified electrophysiological testing needs further validation. Finally, the association between electrophysiological tests and both short- and long-term outcomes needs to be documented prospectively.

A similar set of questions may be directed to muscle biopsies. Indications for biopsies in the setting of ICUAW or electrophysiological abnormalities should be clearly defined. Associations should be investigated between histologic findings and outcomes, in particular, duration of mechanical ventilation, ICU and hospital length of stay, and long-term weakness or disability. The prognostic value of histologic abnormalities should be contrasted with simple clinical parameters or electrophysiological changes.

ACKNOWLEDGMENTS

We are grateful to the participants of the 2009 ICUAW Round Table Conference in Brussels, at which a preliminary version of this manuscript was presented and discussed. We would like, in particular, to recognize the Round Table Chairs, Drs. Jesse Hall and Richard Griffiths, and its Organizer, Dr. Jean-Louis Vincent. Thanks are also owed to Dr. Douglas Zochodne for his careful review of the manuscript.

REFERENCES

1. Hippocrates, Kelly EC: The Theory and Practice of Medicine. New York, Philosophical Library, 1964
2. Osler W: The Principles and Practice of Medicine, Designed for the Use of Practitioners and Students of Medicine. New York, D. Appleton and Company, 1892
3. MacFarlane IA, Rosenthal FD: Severe myopathy after status asthmaticus. *Lancet* 1977; 2:615
4. Douglass JA, Tuxen DV, Horne M, et al: Myopathy in severe asthma. *Am Rev Respir Dis* 1992; 146:517–519
5. Dahlen B, von Scheele C: [Myopathy associated with intensive care]. *Lakartidningen* 1983; 80:3215–3216
6. Hirano M, Ott BR, Raps EC, et al: Acute quadriplegic myopathy: A complication of treatment with steroids, nondepolarizing blocking agents, or both. *Neurology* 1992; 42:2082–2087
7. Blackie JD, Gibson P, Murree-Allen K, et al: Acute myopathy in status asthmaticus. *Clin Exp Neurol* 1993; 30:72–81
8. Coakley JH, Nagendran K, Honavar M, et al: Preliminary observations on the neuromuscular abnormalities in patients with organ failure and sepsis. *Intensive Care Med* 1993; 19:323–328
9. Ramsay DA, Zochodne DW, Robertson DM, et al: A syndrome of acute severe muscle necrosis in intensive care unit patients. *J Neuropathol Exp Neurol* 1993; 52: 387–398
10. Zochodne DW, Ramsay DA, Saly V, et al: Acute necrotizing myopathy of intensive care: Electrophysiological studies. *Muscle Nerve* 1994; 17:285–292
11. Lacomis D, Giuliani MJ, Van Cott A, et al: Acute myopathy of intensive care: Clinical, electromyographic, and pathological aspects. *Ann Neurol* 1996; 40:645–654
12. Latronico N, Fenzi F, Recupero D, et al: Critical illness myopathy and neuropathy. *Lancet* 1996; 347:1579–1582
13. Sander HW, Golden M, Danon MJ: Quadriplegic areflexic ICU illness: Selective thick filament loss and normal nerve histology. *Muscle Nerve* 2002; 26:499–505
14. Danon MJ, Carpenter S: Myopathy with thick filament (myosin) loss following prolonged paralysis with vecuronium during steroid treatment. *Muscle Nerve* 1991; 14: 1131–1139
15. Lacomis D, Zochodne DW, Bird SJ: Critical illness myopathy. *Muscle Nerve* 2000; 23: 1785–1788
16. Bolton CF, Gilbert JJ, Hahn AF, et al: Polyneuropathy in critically ill patients. *J Neurol Neurosurg Psychiatry* 1984; 47: 1223–1231
17. Bolton CF, Laverty DA, Brown JD, et al: Critically ill polyneuropathy: Electrophysiological studies and differentiation from Guillain-Barre syndrome. *J Neurol Neurosurg Psychiatry* 1986; 49:563–573
18. Zochodne DW, Bolton CF, Wells GA, et al: Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. *Brain* 1987; 110:819–841
19. Witt NJ, Zochodne DW, Bolton CF, et al: Peripheral nerve function in sepsis and multiple organ failure. *Chest* 1991; 99: 176–184
20. Lacomis D, Petrella JT, Giuliani MJ: Causes of neuromuscular weakness in the intensive care unit: A study of ninety-two patients. *Muscle Nerve* 1998; 21:610–617
21. Leijten FS, De Weerd AW, Poortvliet DC, et al: Critical illness polyneuropathy in multiple organ dysfunction syndrome and weaning from the ventilator. *Intensive Care Med* 1996; 22:856–861
22. Berek K, Margreiter J, Willeit J, et al: Polyneuropathies in critically ill patients: A prospective evaluation. *Intensive Care Med* 1996; 22:849–855
23. Hund EF, Fogel W, Krieger D, et al: Critical illness polyneuropathy: Clinical findings and outcomes of a frequent cause of neuromuscular weaning failure. *Crit Care Med* 1996; 24:1328–1333
24. Coakley JH, Nagendran K, Yarwood GD, et al: Patterns of neurophysiological abnor-

Copyright (c) Society of Critical Care Medicine and Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

mality in prolonged critical illness. *Intensive Care Med* 1998; 24:801–807
25. Latronico N, Candiani A: Predominant involvement of motor fibres in patients with critical illness polyneuropathy. *Br J Anaesth* 1997; 79:547–548
26. Zifko UA, Zipko HT, Bolton CF: Clinical and electrophysiological findings in critical illness polyneuropathy. *J Neurol Sci* 1998; 159:186–193
27. Garnacho-Montero J, Madrazo-Osuna J, Garcia-Garmendia JL, et al: Critical illness polyneuropathy: Risk factors and clinical consequences. A cohort study in septic patients. *Intensive Care Med* 2001; 27: 1288–1296
28. Woittiez AJ, Veneman TF, Rakic S: Critical illness polyneuropathy in patients with systemic inflammatory response syndrome or septic shock. *Intensive Care Med* 2001; 27: 613
29. Bednarik J, Lukas Z, Vondracek P: Critical illness polyneuromyopathy: The electrophysiological components of a complex entity. *Intensive Care Med* 2003; 29: 1505–1514
30. De Jonghe B, Sharshar T, Lefaucheur JP, et al: Paresis acquired in the intensive care unit: A prospective multicenter study. *JAMA* 2002; 288:2859–2867
31. De Jonghe B, Bastuji-Garin S, Sharshar T, et al: Does ICU-acquired paresis lengthen weaning from mechanical ventilation? *Intensive Care Med* 2004; 30:1117–1121
32. Smith CL, Hunter JM, Jones RS: Vecuronium infusions in patients with renal failure in an ITU. *Anaesthesia* 1987; 42: 387–393
33. Segredo V, Matthay MA, Sharma ML, et al: Prolonged neuromuscular blockade after long-term administration of vecuronium in two critically ill patients. *Anesthesiology* 1990; 72:566–570
34. Lagasse RS, Katz RI, Petersen M, et al: Prolonged neuromuscular blockade following vecuronium infusion. *J Clin Anesth* 1990; 2:269–271
35. Partridge BL, Abrams JH, Bazemore C, et al: Prolonged neuromuscular blockade after long-term infusion of vecuronium bromide in the intensive care unit. *Crit Care Med* 1990; 18:1177–1179
36. Rossiter A, Souney PF, McGowan S, et al: Pancuronium-induced prolonged neuromuscular blockade. *Crit Care Med* 1991; 19:1583–1587
37. Vanderheyden BA, Reynolds HN, Gerold KB, et al: Prolonged paralysis after long-term vecuronium infusion. *Crit Care Med* 1992; 20:304–307
38. Segredo V, Caldwell JE, Matthay MA, et al: Persistent paralysis in critically ill patients after long-term administration of vecuronium. *N Engl J Med* 1992; 327:524–528
39. Gooch JL, Moore MH, Ryser DK: Prolonged paralysis after neuromuscular junction blockade: Case reports and electrodiagnostic findings. *Arch Phys Med Rehabil* 1993; 74:1007–1011
40. Davis NA, Rodgers JE, Gonzalez ER, et al: Prolonged weakness after cisatracurium infusion: A case report. *Crit Care Med* 1998; 26:1290–1292
41. Bizzarri-Schmid MD, Desai SP: Prolonged neuromuscular blockade with atracurium. *Can Anaesth Soc J* 1986; 33:209–212
42. Hoey LL, Joslin SM, Nahum A, et al: Prolonged neuromuscular blockade in two critically ill patients treated with atracurium. *Pharmacotherapy* 1995; 15:254–259
43. Leatherman JW, Fluegel WL, David WS, et al: Muscle weakness in mechanically ventilated patients with severe asthma. *Am J Respir Crit Care Med* 1996; 153:1686–1690
44. Watling SM, Dasta JF: Prolonged paralysis in intensive care unit patients after the use of neuromuscular blocking agents: A review of the literature. *Crit Care Med* 1994; 22: 884–893
45. Lamer C, Harboun M, Knani L, et al: Quality of life after complicated elective surgery requiring intensive care. *Intensive Care Med* 2004; 30:1594–1601
46. Kaarlola A, Pettila V, Kekki P: Quality of life six years after intensive care. *Intensive Care Med* 2003; 29:1294–1299
47. Schelling G, Stoll C, Haller M, et al: Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. *Crit Care Med* 1998; 26:651–659
48. Clavet H, Hébert PC, Fergusson D, et al: Joint contracture following prolonged stay in the intensive care unit. *CMAJ* 2008; 178: 691–697
49. Cheung AM, Tansey CM, Tomlinson G, et al: Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; 174:538–544
50. Herridge MS, Cheung AM, Tansey CM, et al: One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003; 348:683–693
51. Angel MJ, Bril V, Shannon P, et al: Neuromuscular function in survivors of the acute respiratory distress syndrome. *Can J Neurol Sci* 2007; 34:427–432
52. Leijten FS, Harinck-de Weerd JE, Poortvliet DC, et al: The role of polyneuropathy in motor convalescence after prolonged mechanical ventilation. *JAMA* 1995; 274: 1221–1225
53. Zifko UA: Long-term outcome of critical illness polyneuropathy. *Muscle Nerve Suppl* 2000; 9:S49–S52
54. Fletcher SN, Kennedy DD, Ghosh IR, et al: Persistent neuromuscular and neurophysiologic abnormalities in long-term survivors of prolonged critical illness. *Crit Care Med* 2003; 31:1012–1016
55. Kerbaul F, Brousse M, Collart F, et al: Combination of histopathological and electromyographic patterns can help to evaluate functional outcome of critical ill patients with neuromuscular weakness syndromes. *Crit Care* 2004; 8:R358–R366
56. Guarneri B, Bertolini G, Latronico N: Long-term outcome in patients with critical illness myopathy or neuropathy: The Italian multicentre CRIMYNE study. *J Neurol Neurosurg Psychiatry* 2008; 79:838–841
57. de Seze M, Petit H, Wiart L, et al: Critical illness polyneuropathy. A 2-year follow-up study in 19 severe cases. *Eur Neurol* 2000; 43:61–69
58. De Jonghe B, Bastuji-Garin S, Durand MC, et al: Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. *Crit Care Med* 2007; 35: 2007–2015
59. Garnacho-Montero J, Amaya-Villar R, Garcia-Garmendia JL, et al: Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients. *Crit Care Med* 2005; 33:349–354
60. Bercker S, Weber-Carstens S, Deja M, et al: Critical illness polyneuropathy and myopathy in patients with acute respiratory distress syndrome. *Crit Care Med* 2005; 33: 711–715
61. Amaya-Villar R, Garnacho-Montero J, Garcia-Garmendia JL, et al: Steroid-induced myopathy in patients intubated due to exacerbation of chronic obstructive pulmonary disease. *Intensive Care Med* 2005; 31: 157–161
62. Rudis MI, Guslits BJ, Peterson EL, et al: Economic impact of prolonged motor weakness complicating neuromuscular blockade in the intensive care unit. *Crit Care Med* 1996; 24:1749–1756
63. Ali NA, O'Brien JM Jr, Hoffmann SP, et al: Acquired weakness, handgrip strength, and mortality in critically ill patients. *Am J Respir Crit Care Med* 2008; 178:261–268
64. Hermans G, De Jonghe B, Bruyninckx F, et al: Interventions for preventing critical illness polyneuropathy and critical illness myopathy. *Cochrane Database Syst Rev* 2009; (1):CD006832
65. Schweickert WD, Pohlman MC, Pohlman AS, et al: Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomised controlled trial. *Lancet* 2009; 373:1874–1882
66. Morris PE, Goad A, Thompson C, et al: Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008; 36:2238–2243
67. Bailey P, Thomsen GE, Spuhler VJ, et al: Early activity is feasible and safe in respiratory failure patients. *Crit Care Med* 2007; 35:139–145
68. Leijten F, Poortvliet DC, de Weerd AW: The neurological examination in the assessment of polyneuropathy in mechanically ventilated patients. *Eur J Neurol* 1997; 4:124–129
69. Latronico N, Peli E, Botteri M: Critical illness myopathy and neuropathy. *Curr Opin Crit Care* 2005; 11:126–132

Copyright (c) Society of Critical Care Medicine and Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

70. Morris C, Trinder JT: Electrophysiology adds little to clinical signs in critical illness polyneuropathy and myopathy. *Crit Care Med* 2002; 30:2612
71. De Jonghe B, Finfer S: Critical illness neuromyopathy: From risk factors to prevention. *Am J Respir Crit Care Med* 2007; 175: 424–425
72. Schweickert WD, Hall J: ICU-acquired weakness. *Chest* 2007; 131:1541–1549
73. Lefaucheur JP, Nordine T, Rodriguez P, et al: Origin of ICU acquired paresis determined by direct muscle stimulation. *J Neurol Neurosurg Psychiatry* 2006; 77:500–506
74. Trojaborg W, Weimer LH, Hays AP: Electrophysiologic studies in critical illness associated weakness: Myopathy or neuropathy—A reappraisal. *Clin Neurophysiol* 2001; 112: 1586–1593
75. Op de Coul AA, Verheul GA, Leyten AC, et al: Critical illness polyneuromyopathy after artificial respiration. *Clin Neurol Neurosurg* 1991; 93:27–33
76. De Jonghe B, Cook D, Sharshar T, et al: Acquired neuromuscular disorders in critically ill patients: A systematic review. Groupe de Reflexion et d'Etude sur les Neuromyopathies En Reanimation. *Intensive Care Med* 1998; 24:1242–1250
77. Stevens RD, Dowdy DW, Michaels RK, et al: Neuromuscular dysfunction acquired in critical illness: A systematic review. *Intensive Care Med* 2007; 33:1876–1891
78. Herridge MS: Building consensus on ICU-acquired weakness. *Intensive Care Med* 2009; 35:1–3
79. Deem S: Intensive-care-unit-acquired muscle weakness. *Respir Care* 2006; 51: 1042–1052; discussion 1052–1053
80. Aids to the Examination of the Peripheral Nervous System. London, Philadelphia, Bailliere Tindall on behalf of the guarantors of Brain, 1986
81. van der Meche FG, Kleyweg RP, Meulstee J, et al: High-dose intravenous gammaglobulin in Guillain-Barre syndrome. *Ann Neurol* 1988; 24:588
82. Kleyweg RP, van der Meche FG, Schmitz PI: Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barre syndrome. *Muscle Nerve* 1991; 14:1103–1109
83. van der Schaaf M, Dettling DS, Beelen A, et al: Poor functional status immediately after discharge from an intensive care unit. *Disabil Rehabil* 2008; 30:1812–1818
84. Oh SJ: Clinical Electromyography: Nerve Conduction Studies. Baltimore, University Park Press, 1984
85. Eikermann M, Koch G, Gerwig M, et al: Muscle force and fatigue in patients with sepsis and multiorgan failure. *Intensive Care Med* 2006; 32:251–259
86. Ginz HF, Iaizzo PA, Urwyler A, et al: Use of non-invasive-stimulated muscle force assessment in long-term critically ill patients: A future standard in the intensive care unit? *Acta Anaesthesiol Scand* 2008; 52:20–27
87. Preston DC, Shapiro BE: Electromyography and Neuromuscular Disorders: Clinical-Electrophysiologic Correlations. Boston, Butterworth-Heinemann, 1998
88. Bolton CF: Assessment of respiratory function in the intensive care unit. *Can J Neurol Sci* 1994; 21:S28–S34
89. Maher J, Rutledge F, Remtulla H, et al: Neuromuscular disorders associated with failure to wean from the ventilator. *Intensive Care Med* 1995; 21:737–743
90. Bolton CF, Grand'Maison F, Parkes A, et al: Needle electromyography of the diaphragm. *Muscle Nerve* 1992; 15:678–681
91. Jablecki CK: Electrodiagnostic evaluation of patients with myasthenia gravis and related disorders. *Neurol Clin* 1985; 3:557–572
92. Stalberg E, Trontelj JV: The study of normal and abnormal neuromuscular transmission with single fibre electromyography. *J Neurosci Methods* 1997; 74:145–154
93. Bolton CF: Electrophysiologic studies of critically ill patients. *Muscle Nerve* 1987; 10:129–135
94. Latronico N: Neuromuscular alterations in the critically ill patient: Critical illness myopathy, critical illness neuropathy, or both? *Intensive Care Med* 2003; 29:1411–1413
95. Bolton CF: Neuromuscular manifestations of critical illness. *Muscle Nerve* 2005; 32: 140–163
96. De Jonghe B, Lacherade JC, Durand MC, et al: Critical illness neuromuscular syndromes. *Crit Care Clin* 2006; 22:805–818; abstract xi
97. Rich MM, Teener JW, Raps EC, et al: Muscle is electrically inexcitable in acute quadriplegic myopathy. *Neurology* 1996; 46:731–736
98. Rich MM, Bird SJ, Raps EC, et al: Direct muscle stimulation in acute quadriplegic myopathy. *Muscle Nerve* 1997; 20:665–673
99. Harris ML, Luo YM, Watson AC, et al: Adductor pollicis twitch tension assessed by magnetic stimulation of the ulnar nerve. *Am J Respir Crit Care Med* 2000; 162: 240–245
100. Showalter CJ, Engel AG: Acute quadriplegic myopathy: Analysis of myosin isoforms and evidence for calpain-mediated proteolysis. *Muscle Nerve* 1997; 20:316–322
101. Gutmann L, Blumenthal D, Schochet SS: Acute type II myofiber atrophy in critical illness. *Neurology* 1996; 46:819–821
102. Sher JH, Shafiq SA, Schutta HS: Acute myopathy with selective lysis of myosin filaments. *Neurology* 1979; 29:100–106
103. Williams AB, Decourten-Myers GM, Fischer JE, et al: Sepsis stimulates release of myofilaments in skeletal muscle by a calcium-dependent mechanism. *FASEB J* 1999; 13: 1435–1443
104. Tiao G, Hobler S, Wang JJ, et al: Sepsis is associated with increased mRNAs of the ubiquitin-proteasome proteolytic pathway in human skeletal muscle. *J Clin Invest* 1997; 99:163–168
105. Voisin L, Breuillé D, Combaret L, et al: Muscle wasting in a rat model of long-lasting sepsis results from the activation of lysosomal, Ca2+ -activated, and ubiquitin-proteasome proteolytic pathways. *J Clin Invest* 1996; 97:1610–1617
106. Di Giovanni S, Molon A, Broccolini A, et al: Constitutive activation of MAPK cascade in acute quadriplegic myopathy. *Ann Neurol* 2004; 55:195–206
107. Deem S, Lee CM, Curtis JR: Acquired neuromuscular disorders in the intensive care unit. *Am J Respir Crit Care Med* 2003; 168: 735–739
108. Hanson P, Dive A, Brucher JM, et al: Acute corticosteroid myopathy in intensive care patients. *Muscle Nerve* 1997; 20:1371–1380
109. Zochodne DW, Ramsay DA: Acute quadriplegic myopathy. *Neurology* 1994; 44:988–989
110. Reid CL, Campbell IT, Little RA: Muscle wasting and energy balance in critical illness. *Clin Nutr* 2004; 23:273–280
111. Gruther W, Benesch T, Zorn C, et al: Muscle wasting in intensive care patients: ultrasound observation of the M. quadriceps femoris muscle layer. *J Rehabil Med* 2008; 40:185–189
112. Campbell IT, Watt T, Withers D, et al: Muscle thickness, measured with ultrasound, may be an indicator of lean tissue wasting in multiple organ failure in the presence of edema. *Am J Clin Nutr* 1995; 62:533–539
113. Chen R: Electrophysiological studies in the critical care unit: Investigating polyneuropathies. *Can J Neurol Sci* 1998; 25:S32–S35
114. Herridge MS, Batt J, Hopkins RO: The pathophysiology of long-term neuromuscular and cognitive outcomes following critical illness. *Crit Care Clin* 2008; 24:179–199
115. Melli G, Chaudhry V, Cornblath DR: Rhabdomyolysis: An evaluation of 475 hospitalized patients. *Medicine (Baltimore)* 2005; 84:377–385
116. Ely EW, Shintani A, Truman B, et al: Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004; 291:1753–1762
117. Latronico N, Bertolini G, Guarneri B, et al: Simplified electrophysiological evaluation of peripheral nerves in critically ill patients: The Italian multi-centre CRIMYNE study. *Crit Care* 2007; 11:R11
118. Sitwell LD, Weinshenker BG, Monpetit V, et al: Complete ophthalmoplegia as a complication of acute corticosteroid- and pancuronium-associated myopathy. *Neurology* 1991; 41:921–922
119. Coakley JH, Nagendran K, Ormerod IE, et al: Prolonged neurogenic weakness in patients requiring mechanical ventilation for acute airflow limitation. *Chest* 1992; 101: 1413–1416
120. Young GB, Hammond RR: A stronger approach to weakness in the intensive care unit. *Crit Care* 2004; 8:416–418
121. Hough CL, Steinberg KP, Taylor Thompson B, et al: Intensive care unit-acquired neuromyopathy and corticosteroids in survivors of persistent ARDS. *Intensive Care Med* 2009; 35:63–68. Epub 2008 Oct 23

Copyright (c) Society of Critical Care Medicine and Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.