Critical Illness Polyneuropathy

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Opinion statement

Critical illness polyneuropathy (CIP) is common among patients in intensive care units (ICUs) [1, Class III]. However, it is rarely diagnosed in patients in most ICUs, because of the lack of knowledge, difficulties in clinical assessment, and failure to perform electrophysiologic studies. Nonetheless, CIP is a significant cause of difficulty in weaning patients from the ventilator and of long-term morbidity in survivors. Although no specific treatment is available, diagnosis is important for the institution of various nonspecific treatments and for prognosis. Moreover, research is important in arriving at a better understanding of the pathophysiologic mechanisms and, hence, possible avenues of specific treatment. Thus, this chapter emphasizes the nature of critical illness and the possible pathophysiology, the clinical and electrophysiologic features, and the differential diagnosis of CIP. Nonspecific and potential specific treatments are also discussed.

Introduction

Recently, "critical illness" has come to be synonymous with sepsis and multiple organ failure syndrome. Thus, it is important to understand this syndrome and, thereby, the polyneuropathy of which it is a complication. *Sepsis* originally meant putrefaction, a decomposition of organic matter by bacteria and fungi. In humans, it increasingly has been associated with a severe systemic response to infection. Because a severe systemic response can be evoked in the absence of infection (*eg*, trauma and burns), the term *systemic inflammatory response syndrome* (SIRS) was coined [2, Class III]. The main features of SIRS are 1) temperature >38° C or <36° C; 2) heart rate >90 beats per minute; 3) respiratory rate >20 breaths per minute or PaCO2 <32 torr (<4.3 kPa); and 4) leukocyte count >12,000 cells/mm^3 or <4000 cells/mm^3 or >10% immature forms. SIRS may be accompanied by hypotension (blood pressure <90 mm Hg).

Cellular and humoral responses are activated in SIRS (Fig. 1) [3••, Class III]. The chief humoral response is the release of cytokines, locally activated mediators, and include interleukins (IL) (IL-1, IL-2, and IL-6), tumor necrosis factor (TNF)-α, arachidonic acid, coagulation factors, free oxygen radicals, and proteases. The cellular response involves lymphocytes, monocytes, and neutrophils. These cellular and humoral factors interact with one another and with adhesion molecules, whose concentration is increased in the blood of patients with sepsis. Adhesion molecules adhere to leukocytes, platelets, and endothelial cells; they also induce rolling neutrophils and fibrin platelet aggregates that obstruct capillary flow. Increased capillary permeability induces edema in local tissue. Activation of nitric oxide, now known to be the endovascular relaxing factor, causes arteriolar dilatation, which may further slow capillary flow. Thus, essential nutrients fail to reach the organ parenchyma. For example, despite adequate oxygenation via mechanical ventilation, the oxygen debt at the parenchymal level is severe, resulting in multiple organ dysfunction [3••, Class III].

SIRS occurs in 50% of patients in ICUs and has several effects on the nervous system (Fig. 2). After SIRS develops—whether the patient is in an ICU or on a gen-

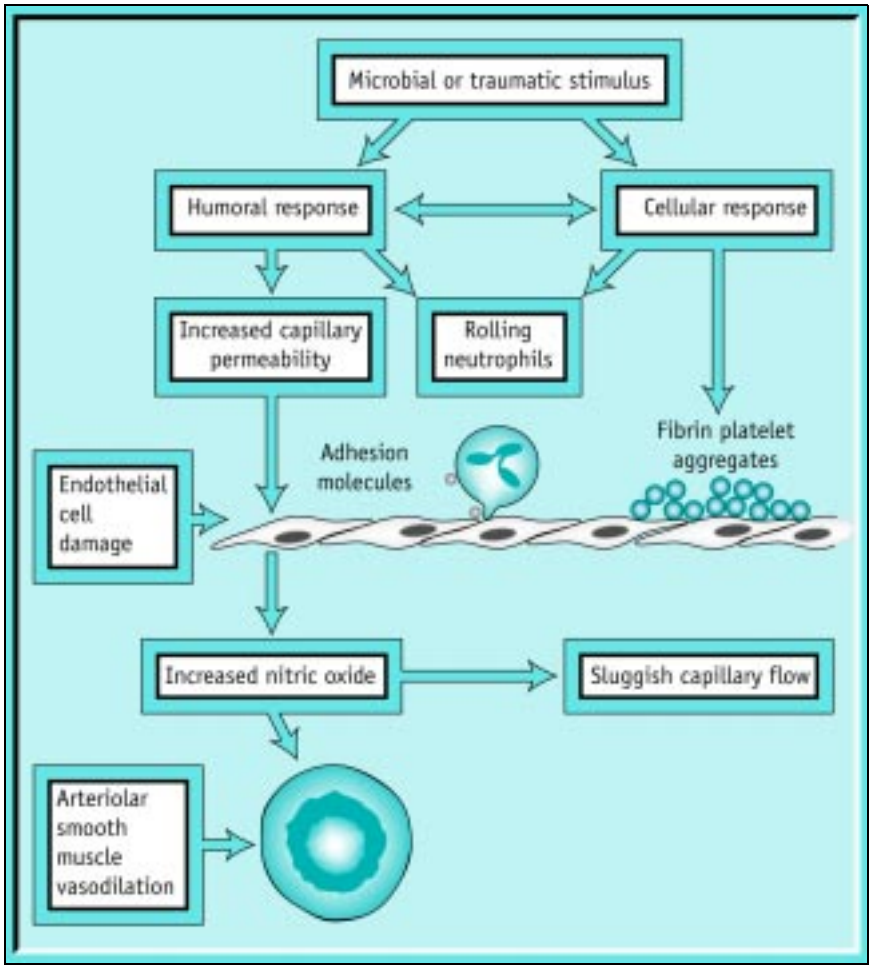

Figure 1. Theoretical presentation of disturbances, caused by sepsis and systemic inflammatory response syndrome, in the microcirculation of various organs, including the brain, peripheral nerve, and muscle. The result is impaired perfusion due to excessive vasodilatation through overproduction of nitric oxide, and aggregation of cellular elements through activation of adhesion molecules. Increased capillary permeability causes edema, and the potential for entry of toxic substances. (*From* Bolton [1]; with permission.)

eral medical ward—the earliest nervous system manifestation is septic encephalopathy, which occurs in 70% of patients with SIRS [4, Class III]. Within hours after a blood culture is positive for sepsis, careful testing may show that the patient has impaired attention, concentration, orientation, and writing. If SIRS continues, the patient gradually slips into deep coma, usually without the development of focal signs, seizures, myoclonus, or asterixis. The electroencephalogram is a sensitive indicator of the presence and severity of septic encephalopathy. The results of computed tomography and cerebrospinal fluid examination are usually unremarkable.

If SIRS is treated successfully, the encephalopathy usually improves rapidly. However, at this time, difficulty in weaning the patient from the ventilator will be noticed. Studies in this author's ICU in London, Canada, indicate that the most common neuromuscular cause for this difficulty, after cardiac and pulmonary causes, is CIP [5, Class III].

CLINICAL AND ELECTROPHYSIOLOGIC FEATURES OF CRITICAL ILLNESS POLYNEUROPATHY

CIP occurs in 70% of patients with sepsis and multiple organ failure [5, Class III], and is a primary distal degeneration of motor and sensory axons [6, Class III]. CIP was so named because sepsis and multiple organ failure were designated critical illness by intensivists. In the last 15 years, cases have been reported from the United States, France, the Netherlands, Austria, Germany, and Spain [5, Class III; 7••, Class III]. It may rarely occur in children. Difficulty in weaning the patient from the ventilator and, less commonly, limb weakness are noted after the first week in the ICU. Because deep tendon reflexes are depressed in only 50% of the patients, electrophysiologic studies are necessary to establish the diagnosis. A more severe polyneuropathy can be suspected when, with deep painful stimulation of the distal extremities, limb movements seem weak, despite strong grimacing by the patient.

The earliest electrophysiologic sign of CIP is a decrease in the amplitude of the compound muscle action potential with minor change in latency. These changes are typical of axonal damage. Fibrillation potentials and positive sharp waves may not appear in muscle until 3 weeks after these early signs. Motor unit potentials, if they can be activated voluntarily by the patient (and may not be due to sedation or septic encephalopathy), often appear normal or somewhat low amplitude and polyphasic, suggesting associated primary involvement of muscle by sepsis. These electro-

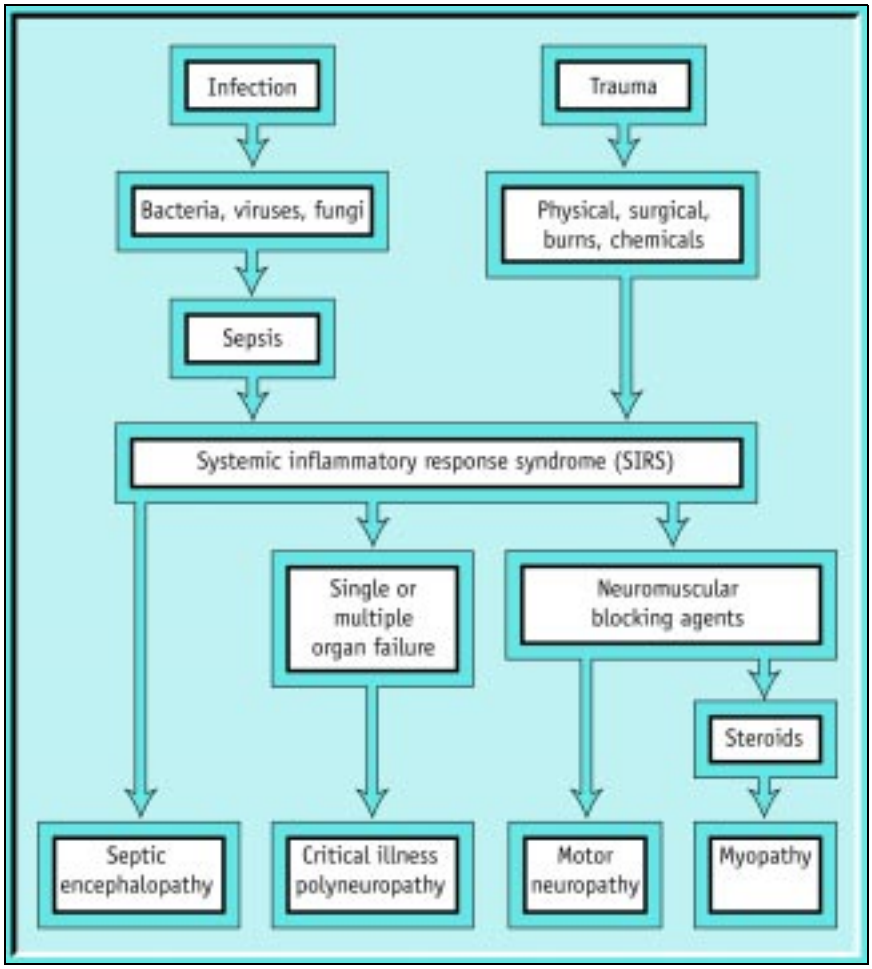

Figure 2. Various factors associated with development of systemic inflammatory response syndrome (SIRS) and its nervous system complications. (*From* Bolton [3]; with permission.)

Table 1. Criteria for the diagnosis of critical illness polyneuropathy

The presence of systemic inflammatory response syndrome (SIRS)
Difficulty weaning patient from the ventilator, or limb weakness
Decreased amplitudes of compound muscle and sensory nerve action potentials
Widespread denervation potentials in muscle
Normal or mildly increased levels of blood creatine kinase

physiologic changes could also be due to a primary myopathy. Hence, before a firm electrophysiologic diagnosis of polyneuropathy can be made, it is important to demonstrate a decrease in the amplitude of sensory compound action potentials [5, Class III].

Criteria for the diagnosis of CIP are summarized in Table 1. Repetitive nerve stimulation studies should be performed to demonstrate a defect in neuromuscular transmission. This defect does not occur in sepsis, but is present if the patient has received treatment with neuromuscular blocking agents. The effects of these agents may persist from more than several hours to several days if the patient has kidney or liver failure. The technique of direct electrical stimulation of muscle developed by Rich *et al.* [8•, Class III] may be valuable in distinguishing between CIP and critical illness myopathy. It is also important to perform phrenic nerve conduction studies and needle electromyography (EMG) of the chest wall and diaphragm to establish that the difficulty in weaning the patient from the ventilator is due to CIP [9, Class III].

THE DIFFERENTIAL DIAGNOSIS

The approach to patients in the ICU who have weakness of limb and respiratory muscles should be systematic. Investigations may include magnetic resonance imaging (MRI) of the spinal cord, neurophysiologic studies, measurement of creatine kinase concentration, and muscle biopsy. The approach is considered in two main categories. The first category consists of patients in whom paralysis develops rapidly before admission to the ICU. Because of the acuteness of the situation, there is not sufficient time to investigate the underlying cause until the patient's condition has been stabilized in the ICU. The following conditions are to be considered: 1) high cervical spinal cord dysfunction due to trauma, neoplasm, or infection; 2) motor neuron disease in

which the respiratory muscles are affected before other muscles; 3) Guillain-Barré syndrome, and other acute polyneuropathies such as prophyria; and 4) acute axonal forms of Guillain-Barré syndrome, including the pure motor variety particularly common in northern China [10, Class III]. Axonal forms of Guillain-Barré syndrome may be difficult to distinguish from CIP if onset occurred after admission to the ICU for severe infection. Yuki and Hirata [11, Class III] have suggested that measurement of certain immunoglobulin G (IgG) class autoantibodies might be used to differentiate the two conditions. Mild chronic polyneuropathies, such as diabetic polyneuropathy, may affect predominantly the nerves of respiration or, after the patient has been admitted to the ICU, sepsis may worsen a pre-existing polyneuropathy. Occasionally, defects in neuromuscular transmission, myasthenia gravis, and Lambert-Eaton myasthenic syndrome present with primary respiratory failure. Finally, there are myopathies caused by various insults and characterized by myoglobinuria and muscle necrosis. They usually have a good outcome, unless the myopathy is severe.

The second category consists of patients who have been admitted to the ICU because of a severe primary illness or trauma, and in whom neuromuscular disease later develops. Myelopathy affecting mainly anterior horn cells may result from cardiac arrest, atherosclerosis or surgery on the aorta, or severe pulmonary disease. A prime consideration is CIP, as mentioned previously.

Limb weakness that develops suddenly in a patient in the ICU has been termed *acute quadriplegic myopathy* [12, Class III]. Other terms that have been used include *acute myopathy of intensive care* [13••, Class III], *critical care myopathy*, *acute illness myopathy*, *critical illness myopathy* (a more appropriate term), *acute myopathy with selective lyses of myosin filaments*, and *acute necrotizing myopathy of intensive care* [14, Class III]. It often occurs when neuromuscular blocking agents and corticosteroids are used to treat acute severe asthma or patients who have had an organ transplant. The clinical signs are purely motor, and with deep tendon reflexes either decreased or absent. The results of electrophysiologic testing suggest myopathy. Creatine kinase levels vary, but are usually normal or mildly increased, except in acute necrotizing myopathy. Muscle biopsy specimens show a distinctive loss of thick myosin filaments and varying degrees of muscle fiber atrophy and necrosis. Early recovery can be expected, except when necrosis is severe.

The high incidence of myopathy (39 of 92 patients in the ICU) reported by Lacomis *et al*. [15, Class III] may reflect the large number of post-transplant patients receiving high doses of corticosteroids; this is in contrast to the much lower incidence of myopathy in the ICU in London, Canada, which does not manage post-transplant patients. In prospective studies of CIP by this author [7••, Class III; 16•, Class III; 17•, Class III]), and of critical illness myopathy and neuropathy by Latronico *et al*. [18••, Class III], no correlation existed between these conditions and treatment with corticosteroids or neuromuscular blocking agents; instead, SIRS was the underlying factor.

Table 2 outlines how these various neuromuscular complications of sepsis may be differentiated.

ETIOLOGY AND PATHOPHYSIOLOGY

Retrospective [6, Class III] and prospective [16•, Class III] studies have failed to implicate potential causes of CIP, including types of primary illness or injury, Guillain-Barré syndrome, medications (*eg*, aminoglycoside antibiotics and neuromuscular blocking agents), and specific nutritional deficiencies. On the supposition that CIP might have an immune-mediated mechanism, Wijdicks and Fulgham [19, Class III] administered immunoglobulins intravenously to three patients, but without beneficial effect.

This author has speculated that SIRS (sepsis) is the cause [6••, Class III; 16•, Class III]. The severity of the polyneuropathy can be quantified from electrophysiologic data. The polyneuropathy tends to be more severe with increasing time in the ICU and with increasing blood glucose levels and decreasing serum albumin concentrations. All these factors are recognized manifestations of SIRS (sepsis) and multiple organ failure syndrome. Recently, Hund *et al*. [20••, Class III] isolated a humoral factor from the sera of patients with CIP, but the precise nature of the toxin has not been identified.

The morphologic features of CIP have been demonstrated through biopsy of peripheral nerve and muscle tissue and comprehensive autopsy studies of both the central and peripheral nervous systems of nine patients [6••, Class III]. There is primary axonal degeneration in peripheral motor and sensory fibers, but no evidence of inflammation, as may be seen in Guillain-Barré syndrome. Muscle tissue shows scattered atrophic fibers in acute denervation and grouped atrophy in chronic denervation. An associated primary myopathy is suggested by occasional necrotic muscle fibers. The only central nervous system manifestation is central chromatolysis of anterior horn cells because of the axonal damage in peripheral nerves. Loss of dorsal root ganglion cells also occurs on this basis. No change appears to be distinctive for CIP. In the well-designed prospective study of Latronico *et al*. [18••, Class III], in which electrophysiologic studies and biopsies were performed on peripheral nerve and muscle tissue, the primary effects were on both nerve and muscle. Importantly, in some patients, the electrophysiologic results were abnormal, but the biopsy findings were normal, suggesting that functional disturbance of the peripheral nervous system precedes structural change. This probably also involves the central nervous system, because the brains of patients dying of septic encephalopathy may not show any pertinent morphologic abnormality [4, Class III].

Table 2. Differentiating features of various neuromuscular conditions associated with critical illness

Condition	Antecedent illness	Clinical features	Electrophysiology	Morphology	Treatment	Prognosis
Critical illness polyneuropathy	Sepsis	Absent or signs of mainly motor neuropathy	Consistent with primary axonal degeneration of mainly motor fibers	Primary axonal degeneration of nerve, denervation atrophy of muscle	Treat sepsis syndrome	Good in 40% who survive sepsis and organ failure
Axonal motor neuropathy	Sepsis, neuromuscular blocking agents, neuropathy	Acute quadriplegia	Neuromuscular transmission defect or axonal motor neuropathy	Normal or denervation atrophy on muscle biopsy	None	Good
Critical illness myopathy	Sepsis, neuromuscular blocking agents, corticosteriods	Acute quadriplegia	Neuromuscular transmission defect or myopathy	Thick myosin filament loss	Treat sepsis, stop neuromuscular blocking agents and steroids	Good
Acute necrotizing myopathy of intensive care	Transient infection, trauma, and others	Severe muscle weakness, increased serum creatine kinase, often myoglobinuria	Positive sharp waves and fibrillation potentials on needle electromyogram	Panfascicular muscle fiber necrosis	None or hemodialysis for myoglobinuria	Poor
Cachectic myopathy	Severe systemic illness, prolonged recumbency	Diffuse muscle wasting	Normal	Type II fiber atrophy on muscle biopsy	Physiotherapy, improved nutrition	Good

The microcirculation is disturbed in sepsis (Fig. 1) [3••, Class III]. Blood vessels supplying peripheral nerves lack autoregulation, rendering these vessels susceptible to such a disturbance. Moreover, the cytokines secreted in sepsis have histamine-like properties that may increase microvascular permeability. The resulting endoneural edema could induce hypoxia by increasing intercapillary distance and other mechanisms. Severe energy deficits would result and induce primary axonal degeneration, most likely distal axonal degeneration, if highly energy-dependent systems involving axonal transport of structural proteins are involved. The predominantly distal involvement may explain why recovery in some patients can be unexpectedly short, consistent with the short length of nerve through which axonal regeneration occurs. Also, cytokines may have a direct toxic effect on peripheral nerves, but to this author's knowledge, this has not been demonstrated in either humans or laboratory animals. However, TNF decreases the resting membrane potential of skeletal muscle fibers in vitro and induces muscle proteolysis in animals.

Disturbances of the microcirculation of nerve and muscle tissue may also explain the effects of neuromuscular blocking agents and corticosteroids. Through increased capillary permeability induced by sepsis, neuromuscular blocking agents, notably vecuronium or its 3-desacetyl metabolite, could have a direct toxic effect on peripheral axons. These neuromuscular blocking agents may also cause functional denervation through their prolonged neuromuscular blocking action [3••, Class III]. The result would be denervation atrophy of muscle and relatively pure motor neuropathy.

We suspect that the acute myopathy develops when patients who receive neuromuscular blocking agents and corticosteroids for asthma or post-transplant status have SIRS, because infection is often a precipitating event. Animal experiments by Karpati *et al.* [21, Class III] have shown that if corticosteroids are given after the muscle has been denervated by nerve transection, a thick-filament myopathy can be induced, similar to the myopathy in humans. Thus, in the human condition, CIP, and the additional effects of neuromuscular blocking agents, would denervate muscle and corticosteroids would induce the typical myopathic changes.

It must be recognized that the precise cause is still unknown. Also unknown is why the effects on the peripheral nervous system may vary widely by both site and severity. Because many patients have a combination of effects, Op de Coul *et al.* [22, Class III] proposed the term *critical illness polyneuromyopathy*. Additional investigations, such as biopsy studies of the distal motor axon and neuromuscular junction, are needed, as are further studies of the toxin found in the blood of patients with CIP.

Treatment

- After CIP has been diagnosed, treatment is overseen by a specialist in critical care medicine. The broad areas are the following: 1) treatment of sepsis and multiple organ failure; 2) management of difficulty weaning the patient from the ventilator; and 3) physiotherapy and rehabilitation. The literature on these areas of treatment is extensive and, despite many studies varying from Class I to Class III, the proven value of the treatment is still in doubt [23, Class III]. Thus, only principles are described in the following discussion.

Interventional procedures

Sepsis and multiple organ failure

- The initial insult should be identified, if possible, and treated. Antibiotics should be administered appropriate for the organism, if isolated. If a septic focus can be identified, it should be drained surgically. Episodes of septic shock should be treated vigorously. Low intravascular volume should be treated with fluid replacement and with various inotropes and other drugs. Any coagulopathies should be corrected. Cardiac arrhythmias are common in shock and also should be corrected.
- If there is upper respiratory insufficiency, the airway should be protected by intubation, and adequate amounts of oxygen delivered, although sufficient oxygen may not reach the parenchyma, because of the severe oxygen debt caused by dysfunction of the microcirculation. This early and aggressive treatment may prevent development of multiple organ failure, but when it does develop, treatments are instituted for each organ, with varying results. These may be directed specifically at dysfunction of the gut and kidneys. For example, dysfunction of the gut may be prevented by early treatment with enteral feedings; if rest periods between enteral feedings are used, this may allow acidity to return in the stomach, thus killing bacteria and reducing the incidence of nosocomial infection in the gut. In the kidney, fluid resuscitation and treatment with inotropes and diuretic drugs in various combinations may prevent kidney failure.
- Despite these measures, the mortality rate in sepsis and multiple organ failure in the ICU is approximately 50%.

Difficulty in weaning from the ventilator

- Patients with CIP typically have a period of difficulty in being weaned from the ventilator. This usually occurs after sepsis and multiple organ failure has been controlled, and there is no apparent cardiac or pulmonary cause for the difficulty in weaning. At this point, neurologic examination and electrophysiologic tests, measurement of creatine kinase, and, if necessary, muscle biopsy are performed to define the neuromuscular cause for difficulty in weaning. This author believes that phrenic nerve conduction studies, and needle EMG of the chest wall and diaphragm are valuable in proving that the cause for respiratory insufficiency is neuromuscular.
- After a neuromuscular cause has been established, weaning is unsuccessful if, after discontinuation of ventilator support, the respiratory rate becomes unacceptably high (<35 per minute), title volumes become unacceptably low (<5 mL/kg), and respiratory acidosis develops. Several types of ventilators, ventilator settings, and other measures may be used. Weaning is

considered successful if breathing becomes spontaneous without ventilator support after 2 days. Measurements such as vital capacity, ratio of respiratory rate to tidal volume, peak negative inspiratory pressure, maximum voluntary ventilation, and occlusion pressure are useful for assessing respiratory function before, during, and after weaning.

- Whether or not respiratory muscle strengthening exercises should be used is a controversial area. If the patient has CIP, these exercises are not likely to be helpful until significant reinnervation of the respiratory muscles occurs. However, if there is little evidence of CIP and the respiratory weakness is due to disuse atrophy of the diaphragm, muscle strengthening exercises are valuable. Finally, if the patient is thought to have the phenomenon of diaphragmatic fatigue (almost impossible to prove in clinical situations), theoretically, the best method of management is continued ventilatory support, rest of the diaphragm, and more gradual attempts at weaning without the use of vigorous muscle training exercises.

Physical/speech therapy and exercise

Physiotherapy and rehabilitation therapies

- CIP may first be identified when the patient is in the ICU or after the patient has been transferred to a general medical ward, where limb weakness will be noted because the patient will have difficulty sitting, walking, feeding, dressing, etc. In either case, formal consultation with physiotherapy and rehabilitation should be arranged. Initially, only light exercises should be instituted to promote muscle strength, to maintain joint mobility, and to prevent contracture. As the patient becomes stronger, greater strengthening exercises should be prescribed. The program of rehabilitation, which may be lengthy, involves consultation with occupational medicine and the use of various assistive devices.

Specific treatments

Specific treatment of CIP

- The rationale for the treatment of CIP is to treat SIRS. Retrospective and prospective studies have shown a strong association between CIP and SIRS [5, Class III; 6••, Class III; 16•, Class III; 17•, Class III; 24, Class III]. It has been observed that if the above-described nonspecific methods of treatment are successful, CIP improves within weeks in mild cases and within months in severe cases. Clinical and electrophysiologic studies indicate there is progressive reinnervation of muscle and restoration of sensory function. However, in rare circumstances, extremely severe cases of CIP may not have recovery [16•, Class III].
- However, more specific methods of treating SIRS and the complicating CIP have been considered. Still, no specific treatment has proved effective, but several avenues have been explored.

Specific treatment of SIRS

- Many studies, several with carefully controlled trials (Class I to Class II evidence), have focused on the treatment of gram-negative sepsis, including searching for a “magic bullet” to interrupt the septic cascade at its early stages, for example, monoclonal and polyclonal antibodies directed against bacterial endotoxins, monoclonal antibodies to TNF-α, fusion protein constructs of soluble TNF receptors, IL-1 receptor antagonists, BN5202

(platelet-activating factor receptor antagonist), and N-acetylcysteine (a drug that acts as an oxygen-radical scavenger). None has been effective [3••, Class III; 25, Class III]. A small preliminary trial of a novel approach using detoxification plasma filtration, which clears several cytokines from the plasma, has shown promise [26, Class III]. However, a recent review by Vincent and Tielemans [27, Class III] of various hemofiltration techniques and plasma exchange indicated that the treatment has not proved effective.

Specific treatment of CIP with intravenous immunoglobulins

- This method of treatment has been widely used as a supplemental treatment of sepsis, septic shock, and systemic inflammation in critically ill patients [28, Class III]. Although it is not a "magic bullet," and its effect has not been clearly proved, it shows promise in decreasing the morbidity associated with sepsis. In an open trial of three patients, Wijdicks and Fulgham [19, Class III] did not show improvement in CIP. However, in a more recent and extensive (albeit retrospective study of 33 patients, Mohr *et al.* [29, Class III] reported that early treatment of gram-negative sepsis with intravenous immunoglobulins may have prevented the development of CIP.

The role of total parenteral and enteral nutrition

- On the basis of clinical observations, Waldhausen *et al.* [30, Class III] have proposed that enteral nutrition may cause CIP. They surmised that the enzyme activity for the oxidation of glucose is reduced and, with the accumulation of glucose, phosphorylated glycolytic intermediates accumulate, thus blocking the energy cascade and causing peripheral axonal degeneration. Marino and Millili [31, Class III] have theorized that with total parenteral nutrition and enteral nutrition, polyunsaturated fatty acids, which are oxidized more rapidly in sepsis, may damage the vascular endothelium and various cell membranes, including those of the nervous system. Also, these acids may increase the production of inflammatory cytokines, all of which would tend to cause a CIP. However, Bolton and Young [32, Class III] and Leijten *et al.* [33, Class III] have argued that prospective studies [16•, Class III; 33, Class III] have not shown a statistical relationship between the administration of enteral or parenteral nutrition and the development of CIP. Moreover, we believe that many of the nutrients in these treatments are essential for the health of the nervous system, notably the various B vitamins and vitamin E. Currently, it would seem unwise to limit the use of whatever methods are necessary to improve nutrition in critically ill patients.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Bolton CF: Critical illness polyneuropathy. In *Peripheral Nerve Disorders 2*. Edited by Asbury AK, Thomas PK. Oxford: Butterworth-Heinemann; 1995:262-280.
2. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: **Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis.** *Crit Care Med* 1992, **20:**864-874.

3.•• Bolton CF: **Sepsis and the systemic inflammatory response syndrome: neuromuscular manifestations.** *Crit Care Med* 1996, **24:**1408-1416.

A review of the literature and the author's experience (Class III) relating how SIRS may have widespread effects on the human neuromuscular system.

4. Young GB, Bolton CF, Austin TW, *et al.*: **The encephalopathy associated with septic illness.** *Clin Invest Med* 1990, **13:**297-304.

5. Zifko UA, Zipko HT, Bolton CF: **Clinical and electrophysiological findings in critical illness polyneuropathy.** *J Neurol Sci* 1998, **159:**186-193.

An update on the experience with CIP in London, Ontario, Canada. Despite utilizing respiratory electrophysiological studies in their prospective study (Class III) it was not possible to prove a relationship with respiratory abnormalities and duration of ventilation or stay in the ICU.

6. Zochodne DW, Bolton CF, Wells GA, *et al.*: **Critical illness polyneuropathy: a complication of sepsis and multiple organ failure.** *Brain* 1987, **110:**819-841.

7.•• Leijten FS, de Weerd AW: **Critical illness polyneuropathy. A review of the literature, definition and pathophysiology.** *Clin Neurol Neurosurg* 1994, **96:**10-19.

A major paper based on Leijten's thesis, critical illness polyneuropathy. This is a comprehensive review of the literature and results of a Class III study of 50 patients, examining relationships to organ dysfunction, weaning from the ventilator, and the clinical and EMG spectrum.

8.• Rich MM, Bird SJ, Raps EC, *et al.*: **Direct muscle stimulation in acute quadriplegic myopathy.** *Muscle Nerve* 1997, **20:**665-673.

A fine study describing a new technique for directly studying the electrical function of muscle membrane in critically ill patients.

9. Bolton CF: **AAEM minimonograph #40: clinical neurophysiology of the respiratory system.** *Muscle Nerve* 1993, **16:**809-818.

10. McKhann GM, Cornblath DR, Griffin JW, *et al.*: **Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China.** *Ann Neurol* 1993, **33:**333-342.

11. Yuki N, Hirata K: **Relation between critical illness polyneuropathy and axonal Guillain-Barré syndrome [letter].** *J Neurol Neurosurg Psychiatry* 1999, **67:**128-129.

12. 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.

13.•• Lacomis D, Giuliani MJ, Van Cott A, Kramer DJ: **Acute myopathy of intensive care: clinical, electromyographic, and pathological aspects.** *Ann Neurol* 1996, **40:**645-654.

A well-designed retrospective (Class III) study detailing the clinical, electrophysiologic, and histopathologic features of the acute myopathy associated with intensive care. Exposure to neuromuscular blocking agents and corticosteroids in the setting of critical illness was prominent.

14. Zochodne DW, Ramsay DA, Saly V, *et al.*: **Acute necrotizing myopathy of intensive care: electrophysiological studies.** *Muscle Nerve* 1994, **17:**285-292.

15. 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.

16.• Witt NJ, Zochodne DW, Bolton CF, *et al.*: **Peripheral nerve function in sepsis and multiple organ failure.** *Chest* 1991, **99:**176-184.

A perspective study (Class III) relating peripheral nerve function to a variety of factors that might cause neuropathy in critically ill patients. The evidence pointed to sepsis (SIRS).

17.• Berek K, Margreiter J, Willeit J, *et al.*: **Polyneuropathies in critically ill patients: a prospective evaluation.** *Intensive Care Med* 1996, **22:**849-855.

A well-designed Class III prospective study using clinical and electrophysiologic methods. The incidence of CIP was 70%, with no relationship to the use of neuromuscular blocking agents or corticosteroids.

18.•• Latronico N, Fenzi F, Recupero D, *et al.*: **Critical illness myopathy and neuropathy.** *Lancet* 1996, **347:**1579-1582.

A Class III study using clinical, electrophysiologic, and nerve and muscle biopsy findings to study critically ill patients with acute, severe weakness. The incidence of combined neuropathy and myopathy was high, but some patients had normal morphologic findings, suggesting early "functional" derangement of nerve and muscle.

19. Wijdicks EF, Fulgham JR: **Failure of high dose intravenous immunoglobulins to alter the clinical course of critical illness polyneuropathy [letter].** *Muscle Nerve* 1994, **17:**1494-1495.

20.•• Hund E, Herkert M, Becker C-M, Hacke W: **A humoral neurotoxic factor in sera of patients with critical illness polyneuropathy [abstract].** *Ann Neurol* 1996, **40:**539.

An example of a neurological experimental design to elucidate the course of CIP.

21. Karpati G, Carpenter S, Eisen AA: **Experimental core-like lesions and nemaline rods: a correlative morphological and physiological study.** *Arch Neurol* 1972, **27:**237-251.

22. Op de Coul AA, Verheul GA, Leyten AC, *et al.*: **Critical illness polyneuromyopathy after artificial respiration.** *Clin Neurol Neurosurg* 1991, **93:**27-33.

23. Baue AE, Berlot G, Gullo A: *Sepsis and Organ Dysfunction: Epidemiology and Scoring Systems: Pathophysiology and Therapy.* Milano: Springer; 1998.

24. Leijten FS, Harinck-de Weerd JE, Poortvliet DC, de Weerd AW: **The role of polyneuropathy in motor convalescence after prolonged mechanical ventilation.** *JAMA* 1995, **274:**1221-1225.

25. Opal SM, Yu RL Jr.: **Antiendotoxin strategies for the prevention and treatment of septic shock. New approaches and future directions.** *Drugs* 1998, **55:**497-508.

26. Levy H, Ash SR, Knab W, *et al.*: **Systemic inflammatory response syndrome treatment by powdered sorbent pheresis: the BioLogic-Detoxification Plasma Filtration System.** *Asaio J* 1998, **44:**M659-M665.

27. Vincent JL, Tielemans C: **Continuous hemofiltration in severe sepsis: is it beneficial?** *J Crit Care* 1995, **10:**27-32.

28. Werdan K: **Supplemental immune globulins in sepsis.** *Clin Chem Lab Med* 1999, **37:**341-349.
29. Mohr M, Englisch L, Roth A, *et al.*: **Effects of early treatment with immunoglobulin on critical illness polyneuropathy following multiple organ failure and gram-negative sepsis.** *Intensive Care Med* 1997, **23:**1144-1149.
30. Waldhausen E, Mingers B, Lippers P, Keser G: **Critical illness polyneuropathy due to parenteral nutrition (letter).** *Intensive Care Med* 1997, **23:**922-923.
31. Marino PL, Millili JJ: **Possible role of dietary lipids in critical illness polyneuropathy [letter].** *Intensive Care Med* 1998, **24:**87.
32. Bolton CF, Young GB: **Critical illness polyneuropathy due to parenteral nutrition [letter].** *Intensive Care Med* 1997, **23:**924-925.
33. Leijten FSS, De Weerd AW, Harinck-De Weerd JE, *et al.*: **Critical illness polyneuropathy due to parenteral nutrition [reply to letter].** *Intensive Care Med* 1997, **23:**925.