Weakness in the ICU

Guillain–Barré Syndrome, Myasthenia Gravis, and Critical Illness Polyneuropathy/Myopathy

Deborah M. Green, MD

Background: Weakness in the ICU may be caused by a number of disorders. Guillain–Barré syndrome (GBS) and myasthenia gravis (MG) are examples of conditions that might lead to an ICU admission. The most likely cause of weakness after ICU admission is critical illness polyneuropathy/myopathy (CIP/M).

Review Summary: Studies have attempted to determine both clinical and pulmonary function criteria for the proper timing of intubation in severe GBS and MG. Optimizing medical management of patients with GBS, MG, and CIP/M is essential in reducing the high morbidity and mortality associated with these conditions. This includes measures to prevent deep venous thrombosis, gastric and decubitus ulcer prophylaxis, and chest physiotherapy. Both intravenous immunoglobulin (IVIG) and therapeutic plasma exchange (TPE) are probably equal in efficacy for the treatment of GBS, although relapse rates may differ. Treatment of MG crisis with TPE or IVIG must be followed by long-term immunosuppression. Studies suggest possible preventative measures for CIP/M such as tighter glycemic control but there are still no definitive treatments.

Conclusion: Research to advance our knowledge of the pathogenesis of GBS, MG, and CIP/M is clearly needed to develop more specific and more effective treatments in the future. In the meantime, measures that optimize medical management can be instituted to improve outcomes in patients with these conditions, preferably in a specialized neuroscience ICU setting.

Key Words: ICU weakness, Guillain–Barré syndrome, myasthenia gravis, critical illness polyneuropathy, critical illness myopathy

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Weakness in the ICU may be caused by a number of conditions, which can be divided into 2 general categories: those that lead to an ICU admission and those that occur after an ICU admission. Guillain–Barré syndrome (GBS) and myasthenia gravis (MG) are examples of conditions that might lead to an ICU admission. Primary central nervous system disorders should be ruled out based on physical examination and neuroimaging of the brain or spinal cord as indicated. Myopathies, botulism, organophosphate poisoning, motor neuron disease, and metabolic causes for weakness such as hypocalcemia or hypomagnesemia are some other potential etiologies that should be considered. The most likely cause of weakness after ICU admission is critical illness polyneuropathy/myopathy (CIP/M).

GUILLAIN–BARRÉ SYNDROME

GBS or acute inflammatory demyelinating polyneuropathy is a rapidly evolving illness that typically consists of fairly symmetric weakness, sensory loss, and areflexia. Diagnosis of typical GBS is based on the criteria of the Ad Hoc National Institute of Neurologic and Communicative Disorders and Stroke Committee.[1] The annual incidence in the United States is close to 2 per 100,000 people. Some patients progress to complete quadriplegia and about 30% require mechanical ventilation. Acute ventilatory failure commonly occurs in GBS (and MG) patients as a result of a combination of hypoventilation, inadequate airway protection, and poor secretion clearance.[2] Hypoventilation is attributed to inspiratory muscle weakness, with the diaphragm being the primary inspiratory muscle. Neck flexor weakness generally correlates well with diaphragm weakness. Weakness of the diaphragm and the intercostal muscles also causes decreased force of coughing and inadequate airway clearance. Weakness of the laryngeal, retropharyngeal, and tongue muscles leads to inadequate airway protection and can cause positional airway obstruction. All of this contributes to atelectasis, decreased pulmonary compliance, and increased pulmonary vascular shunting. This leads to hypoxemia without hypercarbia or dyspnea in the early stages. Weakness and fatigue are usually evident before CO_2 retention occurs. Although dyspnea occurs at different times in different patients, in general, it does not occur until the vital capacity (VC) is less than 30 mL/kg. Finally, the respiratory rate may increase, which increases the workload of breathing, resulting in acute respiratory failure.[3]

From The Queen's Medical Center Neuroscience Institute, University of Hawaii School of Medicine, Honolulu, Hawaii.

Reprints: Deborah M. Green, MD, Associate Director, Stroke Center, Staff Neurointensivist, Assistant Clinical Professor of Medicine and Surgery, University of Hawaii School of Medicine, The Queen's Medical Center Neuroscience Institute, Q.E.T. 5, 1301 Punchbowl Street, Honolulu, HI 96813. E-mail: dgreen@queens.org.

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Serial measurements of pulmonary function tests, combined with clinical examination, allow earlier detection of those at risk for respiratory failure.

Guillain–Barré Syndrome: Intubation Criteria

In an observational series of 19 patients, Ropper and Kehne[4] recommended patients be intubated when there was clinical evidence of fatigue, aspiration, VC dropped below 15 mL/kg, or if PO_2 was less than 70 mmHg on room air. These recommendations have been used ever since as strict criteria for intubation. Earlier predictive factors are needed, however, so that preemptive measures, such as admission to the ICU and elective intubation, may be initiated. Noninvasive ventilation techniques such as continuous or bilevel positive airway pressure are of limited utility in severe GBS patients. If there is bulbar weakness, upper airway collapse would increase airway resistance and there is no airway protection from secretions with noninvasive techniques.

Earlier elective intubation may decrease the high risk of aspiration associated with emergent intubation.[3] In a retrospective study of 67 intubated GBS patients, those who were intubated early with a VC greater than 15 mL/kg were less likely to develop pulmonary complications (ie, chest x-ray abnormalities) than those who were intubated later with a VC less than 15 mL/kg. The benefit was even greater in those who were intubated with a VC greater than 25 mL/kg. Each of the 8 patients intubated emergently had pulmonary complications.[5]

A prospective study looked at serial VC measurements in 10 patients with GBS, 5 of whom progressed to mechanical ventilation.[6] Intubation was decided independently of the pulmonary function tests. A drop in VC of 50% from baseline was associated with intubation within 36 hours, and a drop in VC to less than 1 L was associated with intubation within 18 hours. All those who did not require intubation had stable serial VC measurements that were greater than 40 mL/kg. In contrast to the slow decrease in VC, $PaCO_2$ abruptly increased or only slightly increased in those patients who required intubation, suggesting that VC is an earlier predictor of the need for mechanical ventilation. A clear decrease in tidal volume and an increase in respiratory rate did not occur until less than 8 hours preceding intubation. Inspiratory force measurements were not performed in this study.

The early indicators of subsequent progression to respiratory failure were studied retrospectively in 114 consecutive patients with severe GBS.[7] Sixty patients who had to be mechanically ventilated were compared with the 54 patients who did not. Factors that were not predictive of progression to mechanical ventilation in this study were age, gender, preceding gastrointestinal illness, upper limb paralysis, or preexisting pulmonary disease. Cerebrospinal fluid and nerve conduction studies were similar in both groups, although only a small number of patients had nerve conduction studies performed. Lack of treatment with intravenous immunoglobulin (IVIG) or therapeutic plasma exchange (TPE) was not associated with mechanical ventilation in this study. Mechanical ventilation was highly likely to be required in those patients with rapid disease progression (shorter time to peak disability), bulbar dysfunction (dysarthria, dysphagia, or loss of the gag reflex), bilateral facial paresis, or dysautonomia (unexplained blood pressure or heart rate fluctuations, or significant bowel or bladder dysfunction). Those patients with VC less than 20 mL/kg, maximal inspiratory pressure less than -30 cm H_2O, maximal expiratory pressure less than 40 cm H_2O, or a reduction in any of these values by more than 30%, were more likely to progress to respiratory failure.

In summary, these studies suggest that serial measurements of pulmonary function tests, combined with clinical examination, allow earlier detection of those at risk for respiratory failure. VC and negative inspiratory force (NIF) data should be obtained on admission and approximately every 4 to 8 hours thereafter. Management of the patient needs to include active prevention of secondary pulmonary complications, including chest physiotherapy and incentive spirometry in patients with a VC less than 30 mL/kg. The VC and NIF measurements should be continued until a sustained trend of improvement is recorded. If the patient requires more frequent checks or if there is bulbar or bifacial weakness, or autonomic dysfunction, closer monitoring in the ICU may be indicated. If the VC drops below 20 mL/kg or NIF is less than -30 cm H_2O, or there is a rapid decline of VC or NIF by more than 30% in 24 hours, the physician should be notified immediately for a decision on elective intubation and ICU admission.

Endotracheal intubation should be performed cautiously to avoid bradycardia and large shifts in blood pressure in GBS patients with autonomic instability. The use of succinylcholine is avoided because it may cause a fatal hyperkalemia. Topical anesthesia with short-acting benzodiazepines for sedation is the preferred method of intubation.

For patients with Guillain–Barré syndrome, if the vital capacity drops below 20 mL/kg or the negative inspiratory force is less than -30 cm H_2O, or there is a rapid decline of vital capacity or negative inspiratory force by more than 30% in 24 hours, the physician should be notified immediately for a decision on elective intubation and intensive care unit admission.

Guillain–Barré Syndrome: Medical Management in the ICU

Figure 1 is a proposed algorithm of guidelines for the management of GBS that is used at The Queen's Medical Center in Honolulu, Hawaii, USA.[8] The algorithm starts with the clinical, electrophysiologic, and laboratory criteria for the diagnosis of typical GBS, and then outlines some of the decision making for ICU admission and the specifics of treatment. A summary of the ICU admission guidelines is in the shaded box on Figure 1. Management of all nonambulatory GBS patients should also include deep venous thrombosis prophylaxis (subcutaneous unfractionated or low-molecular weight heparin with sequential compression boots), gastric ulcer prophylaxis, and monitoring for potential ileus as well as for autonomic instability. A retrospective study of 73 patients with GBS had 5 patients who developed deep venous thrombosis, 3 of whom were on anticoagulation therapy, thereby concluding that patients should also wear sequential compression boots and coagulation studies should be periodically monitored.[9] Serial measurements of R-R interval on cardiac telemetry may be a sensitive method for identifying patients at risk for fatal arrhythmias.[10] Close monitoring of electrolytes is necessary because hyponatremia usually due to the syndrome of inappropriate antidiuretic hormone may occur and should be treated with fluid restriction. Positioning of patients is important to avoid pressure palsies. Splints may be needed early on to prevent tendon shortening. Management of the deep lower back and proximal leg pain, and the peripheral dysesthesias can be challenging, with narcotics frequently used in doses that cause sedation. Epidural anesthesia is an alternative for the lower back pain. One very small study found carbamazepine 100 mg every 8 hours to be helpful in reducing narcotic requirements, but this needs to be followed up with a larger study.[11] Enteral nutritional support with at least 1500 to 2000 kcal/day should be instituted. Intubated patients should also have round-the-clock chest physiotherapy via manual techniques, postural drainage, and bronchial suctioning of secretions at least every 2 hours, keeping in mind, though, that tracheal suctioning can trigger autonomic cardiovascular instability in the patient with GBS. The timing of tracheostomy is controversial, but one study suggests that by waiting until the second week of

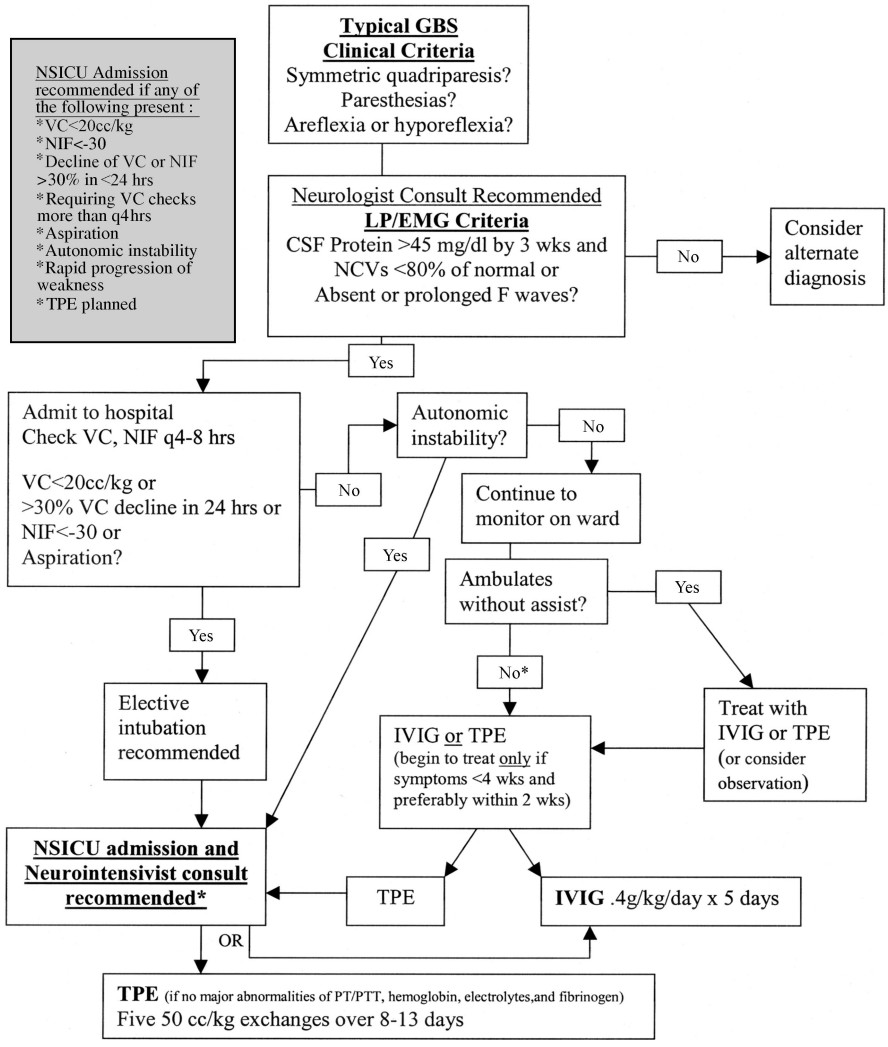

FIGURE 1. Guillain–Barré syndrome management guidelines. *Management of all nonambulatory patients should include subcutaneous heparin and sequential compression boots, bowel regimen, and monitoring for autonomic instability. Abbreviations: CSF indicates cerebrospinal fluid; EMG, electromyography; FVC, forced vital capacity; IVIG, intravenous immunoglobulin; LP, lumbar puncture; NCVs, nerve conduction velocities; NIF, negative inspiratory force; TPE, therapeutic plasma exchange. Reprinted with permission from: Green DM. Advances in the management of Guillain–Barré syndrome. *Curr Neurol Neurosci Rep.* 2002;2:541–548.

mechanical ventilation, one third of patients may be extubated and avoid tracheostomy.[4]

Weaning begins when vital capacity reaches 8 to 10 mL/kg, with slow reduction of the intermittent mandatory ventilation rate.

Guillain–Barré Syndrome: Extubation Criteria

In one small study, 7 intubated, mechanically ventilated patients with GBS or MG had 73 breathing trials performed.[12] The strength of the diaphragm was evaluated using transdiaphragmatic pressure measurements using a multilumen nasogastric tube with a proximal balloon in the esophagus and a distal balloon 10 cm away in the stomach. Maximum voluntary inspiratory effort against an occluded airway at end expiration generated a maximum sustained difference between esophageal and gastric pressures. Several measurements were made during a spontaneous breathing trial and the highest value was called the maximum transdiaphragmatic pressure (Pdi_{max}). Pdi_{max} was found to be significantly higher in successful trials compared with failed weaning trials (specific numbers not given). The study states that airway occlusion pressure at 100 msec correlates well with phrenic nerve and electromyographic activity in normal volunteers, takes into account the secondary ventilatory muscles, and is not subject to electrical interference. Similar to another study,[13] the authors found that successfully weaned patients had more of an increase in airway occlusion pressure with CO_2 rebreathing than those who failed weaning. The investigators argue that cooperative effort is not needed for a CO_2 rebreathing challenge and the results may be more reproducible than voluntary maximum minute ventilation studies.

In a study of 9 patients with GBS or MG, Pdi_{max} correlated with maximal inspiratory force ($P < 0.005$) but not with forced VC.[14] Although it remained low even after weaning, Pdi_{max} was the best predictor of recovery ($P < 0.001$) in this small study. Given that Pdi_{max} measurements are invasive and may not be readily performed at most hospitals, inspiratory force measurements might be an appropriate substitute to guide the weaning process.

In a small prospective study, serial VC measurements were useful not only in predicting the need for mechanical ventilation, but also in predicting a successful weaning procedure.[6] No weaning trial could be performed successfully—that is, the patients could not tolerate even 15 minutes of spontaneous breathing if the VC was less than 7 mL/kg. Based on the values of VC for different spontaneous breathing periods, the authors came up with a prediction equation to compute the maximal tolerable time of spontaneous breathing for a given VC value. For example, a VC value of 6.1 mL/kg was associated with 15 minutes of spontaneous breathing; a VC of 8.5 mL/kg, with 60 minutes; a VC of 10.9 mL/kg, with 4 hours; a VC of 13.6 mL/kg, with 20 hours; and a VC of 14.6 mL/kg, with 24 hours. Patients who were able to breathe for 24 hours consecutively without any mechanical support were extubated or the tracheostomy was closed, and no patient had to be reintubated. Extubation could therefore be safely performed when VC was greater than 15 mL/kg.

Based on 2 large series of GBS patients, Ropper et al[3] recommended weaning beginning when VC reaches 8 to 10 mL/kg, with slow reduction of the intermittent mandatory ventilation rate. Successful extubation can usually occur when the VC is 20 mL/kg, NIF is -35 cm H_2O, and no medical confounding factors exist (see MG: Extubation Criteria).

Treatment with either intravenous immunoglobulin or therapeutic plasma exchange is more efficacious if commenced within 14 days of symptom onset.

Guillain–Barré Syndrome: Treatment Options

Two separate randomized trials of over 200 patients—the Guillain–Barré Syndrome Study Group[15] and The French Cooperative Group on Plasma Exchange in Guillain–Barré Syndrome,[16] both demonstrated that TPE is more effective than supportive care. The Dutch Guillain–Barré Study Group ($n = 150$) found that IVIG and TPE were equally effective.[17] The Plasma Exchange/Sandoglobulin Guillain–Barré Syndrome Trial Group ($n = 383$) demonstrated that TPE alone, IVIG alone, and TPE immediately followed by a course of IVIG were equivalent in efficacy.[18] Therefore, based on this study, adding IVIG after a course of TPE would subject the patient to needless risk and cost without benefit. It also seems counterintuitive to commence TPE after a course of IVIG.

Treatment with either IVIG or TPE is more efficacious if commenced within 14 days of symptom onset and would not be recommended after 30 days.[15–20] IVIG is infused as 5 daily infusions at a dosage of 0.4g/kg/day.[17,18] Giving the same total dose of IVIG over fewer days cannot be recommended based on the current literature. Prior to initiating IVIG, an IgA level may be obtained due to the potential risk of anaphylaxis in patients with IgA deficiency, but it is not considered essential to do so. Prior to starting TPE, blood test results should be reviewed, to include PT, PTT, fibrinogen, electrolytes, BUN, creatinine, hemoglobin, and platelets. TPE may be postponed at the discretion of the neurologist or hematologist for any abnormalities of these laboratory tests. TPE should be performed for 4 to 5 50-mL/kg exchanges over 10 to 14 days, resulting in a total exchange volume of 200 to 250 mL/kg, and replaced with 5% human serum albumin in 0.9% NaCl or a similar colloidal solution. The French Cooperative Group reported that among severe GBS patients, 6 days of TPE were no more effective than 4 days of TPE.[19] To duplicate the optimal study conditions and to

monitor for potential complications, including severe electrolyte derangements, arrhythmias, and hypotension, it is preferable that all patients who will be having TPE be transferred to a neuroscience intensive care unit (NSICU) bed or another ICU bed only if one is unavailable in the NSICU, at least for the first 1 to 2 TPEs.[15]

Table 1[8,15,16,18,19,21–27] summarizes the relapse rates from several different studies, and the totals at the bottom of the table suggest that the relapse rate is significantly higher for IVIG (10.8%) compared with TPE (4.3%; $P < 0.001$, χ^2 test). There are no data to determine whether a more prolonged course (>5 days) of IVIG would be beneficial in preventing relapses. To help minimize the TPE relapses, it is recommended not to complete the course of TPE in fewer than 10 to 14 days.[20,21,27] Retreatment with either TPE or IVIG may be justified for relapses because most patients seem to respond to a second treatment course.[17,21,23,24] Given that relapses are more likely to occur in treated patients and that one small observational study of mild GBS found no benefit to treatment, consideration could be given to not initiate treatment with TPE or IVIG in a patient who remains ambulatory after 8 days of symptoms, although this is still controversial given the lack of larger studies on mild GBS.[28]

Future research might examine whether IVIG given over less than 5 days would be as effective and whether IVIG given over longer than 5 days would be associated with fewer relapses. Current research is investigating whether newer treatment techniques may be superior to IVIG and TPE. Experimental studies are being performed to determine whether interferon-β may decrease adhesion and transmigration of lymphocytes and be of potential therapeutic benefit to patients with GBS.[29] Cerebrospinal fluid filtration, a method to remove soluble inflammatory mediators and antibodies from a site where myelin or nerve damage might occur, has been studied as a potential new treatment in a small study.[30] A larger trial would need to be performed to make any definitive conclusions and it would be preferable in a future study to investigate combining cerebrospinal fluid filtration with TPE or IVIG (theoretically removing inflammatory mediators and antibodies from both the spinal fluid and the blood). Immunoadsorption using a tryptophan-linked polyvinyl alcohol gel has been investigated, but larger studies are needed.[31,32] Administration of nerve growth factors might enhance axonal regeneration and will be the subject of future research.[33]

The relapse rate of Guillain–Barré Syndrome is significantly higher for intravenous immunoglobulin (10.8%) compared with therapeutic plasma exchange (4.3%).

MYASTHENIA GRAVIS

MG is an autoimmune disorder caused by antibodies against the skeletal muscle acetylcholine receptors. The prevalence is 0.5 to 5 per 100,000 people.[34] There is muscle fatigability and weakness, and the respiratory muscles are frequently involved. The clinical course can be unpredictable, with exacerbations caused by infections, reduction in anticholinesterase medication, initiation of corticosteroids or other medications, stress, or other unidentifiable factors. Table 2 lists medications that can potentially exacerbate weakness in MG patients.[35] Thirty percent of MG patients develop respiratory muscle weakness of some degree, and myasthenic crisis occurs in approximately 15 to 20%.[36] Cholinergic crisis is quite rare, probably due to more judicious use of anticholinesterase medications. In one review of myasthenic crisis, cholinergic medication was discontinued in 50 of 94 crises

TABLE 1. Relapse Rates in Guillain–Barré Syndrome (No. Relapses/Total No. Patients)[8]

Study	No Treatment	TPE	IVIG	TPE + IVIG
GBS Study Group, 1985[15]	2/123	2/122		
French Cooperative Group, 1987[16]	1/111	6/109		
Ropper et al, 1988[21]		4/94 (6/94)*		
Kleyweg et al, 1988[23]			3/8	
Osterman et al, 1988[24]		(6/37)*		
Kleyweg and van der Meché, 1991[25]		6/72	8/74	
Jackson et al, 1993[26]			0/7	
Irani et al, 1993[27]			5/7	
Castro and Ropper, 1993[22]			6/15 (1/15)*	
French Cooperative Group, 1997[19]	0/46	19/510		
TPE/Sando. Group, 1997[18]		7/121	4/130	9/128
Totals (%)	3/280 (1.1%)	44/1028 (4.3%)	26/241 (10.8%)	9/128 (7.0%)

Relapse is broadly defined as initial stabilization or improvement for greater than 3 days followed by worsening by at least 1 functional Hughes grade or by a drop in MRC-sumscore[25] by greater than 5 points.

*Numbers in parentheses include those who worsened but are not included in the totals because neither the change in Hughes functional grade nor the change in MRC-sumscore is reported.

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TABLE 2. Medications Associated With Exacerbation of Myasthenia Gravis[35]

Definite	Probable	Possible
Penicillamine	Aminoglycoside antibiotics	Anticholinergics
Corticosteroids	Ciprofloxacin	Ampicillin
	Phenytoin	Erythromycin
	β-blockers	Verapamil
	Lithium	Chloroquine
	Procainamide	Neuromuscular blockers

with the diagnosis of cholinergic crisis excluded because no improvement occurred in any of these patients in the following 72 hours.[37]

Myasthenia Gravis: Intubation Criteria

Most recommendations are that frequent VC checks should be performed and that if the VC falls below 15 mL/kg, the patient should be intubated.[38] One very small retrospective study examined serial VC measurements in 5 MG patients with 10 episodes of respiratory failure.[39] There was no difference between patients eventually requiring intubation (4 episodes) and those not requiring intubation (6 episodes). The conclusion was made that repeated VC measurements were a poor predictor of need for mechanical ventilation. Obviously, a study with a larger number of patients would need to be performed before such a conclusion could be generalized. In the meantime, any MG patient with questionable respiratory status should be admitted to the ICU to allow close monitoring of VC, NIF, anxiety, and clinical examination. If the patient chokes when drinking water, then oral intake should be stopped. If there is a wet, gurgling, or stridorous voice, intubation may be necessary for airway protection.[40]

Any patient with myasthenia gravis with questionable respiratory status should be admitted to the intensive care unit to allow close monitoring of vital capacity, negative inspiratory force, anxiety, and clinical examination.

When mechanical ventilation is required, synchronized intermittent mandatory ventilation is recommended. Tidal volumes of 10 mL/kg with pressure support and positive end expiratory pressure of 5 to 15 cm H_2O are used to limit atelectasis. Unlike in GBS, tracheostomy is often not needed because the duration of intubation generally does not exceed 2 weeks.

Myasthenia Gravis: Medical Management in the ICU

Intensive care management of the myasthenic patient is similar to that of the GBS patient, including chest physiotherapy, and deep venous thrombosis and gastric ulcer prophylaxis. Antibiotic treatment of the infection that may have precipitated the crisis should be initiated with care to avoid aminoglycosides and other medications known to exacerbate MG, as noted in Table 2. Approximately 14% of patients in myasthenic crisis have some degree of arrhythmias, and therefore all patients in crisis probably should have continuous cardiac monitoring.[41] Caloric intake must be maintained to avoid a negative energy balance that would interfere with later weaning.

Myasthenia Gravis: Extubation Criteria

Weaning trials should begin early in the day, when the patient is free of crisis triggers, is clearly stronger on clinical examination, VC is greater than 10 mL/kg, NIF is better than -20 cm H_2O, and positive expiratory force is greater than 40 cm H_2O.[40] First the patient is weaned off the fixed rate to a pressure support mode and then the pressure support is gradually decreased by 1 to 2 cm H_2O each day. Medical conditions that can occur in MG patients and that will delay weaning and extubation include fluid overload, electrolyte abnormalities, anemia, infection, hyperthyroidism, cardiac arrhythmias, renal failure, drug-induced sedation or respiratory depression, and malnutrition.

One study of 73 episodes of crisis looked at risk factors for prolonged (greater than 2 weeks) intubation.[42] Patients older than age 50, with a preintubation serum bicarbonate level greater than 30 mg/dL, and with the highest VC less than 25 mL/kg in the first week of intubation, had a 90% likelihood of prolonged intubation. The risk decreased to 50% if only 2 of these factors were present, 20% with only 1 risk factor, and 0% if there were no risk factors. Seventy-seven percent of those who were intubated for longer than 2 weeks had functional dependence at discharge compared with 36% of those intubated for less than 2 weeks.

Therapeutic plasma exchange is generally the first-line treatment of myasthenic patients in crisis because it produces rapid improvement in 75% of patients.

Myasthenia Gravis: Treatment Options

If the patient is intubated, anticholinesterase medication is generally stopped because it is no longer necessary and can cause excessive bronchial secretions and diarrhea. If it is used, pyridostigmine can be given in intravenous form at one thirtieth the oral dose. Symptomatic improvement can be seen within about 20 minutes and lasts for up to 4 hours. Anticho-

linesterase medication is commonly resumed at half the previous dosage when the patient has reached criteria for ventilator weaning.[36]

TPE is generally the first-line treatment of myasthenic patients in crisis because it produces rapid improvement in 75% of patients.[40] It may not, however, decrease the time spent on the ventilator or the morbidity or mortality.[38] Typically, 5 or 6 TPEs are performed, with 2 or 3 L/day exchanged every other day. Some recommend 5 to 8 daily exchanges of 1.5 to 2 L until pulmonary function has reached 80% of the predicted norm.[38] Sometimes a course of TPE is used in preparation for thymectomy in patients with respiratory muscle involvement. One study suggests that IVIG, given over 2 to 5 days at a total dose of 2 g/kg, may be as effective as TPE for myasthenic crisis.[43] A later study found TPE to be slightly more effective than IVIG.[44] It has been my experience and that of others that patients respond more quickly to TPE.[45]

The resulting improvement with TPE or IVIG is usually transient and needs to be followed by long-term immunosuppression with either corticosteroids or another agent such as azathioprine. Corticosteroids should be started in the inpatient setting after the patient is recovering from crisis, because many patients have some exacerbation of their symptoms during the first days of steroid treatment. Prednisone is usually started at 1 mg/kg/day or every other day for at least 4 weeks and is then tapered slowly (by about 2.5 mg every 2 weeks), over months, to the lowest effective dose. Improvement may be seen within weeks of initiation of prednisone. The response to azathioprine is much slower and may take several months to 1 year. Azathioprine can be started at 50 mg/day for 1 week and then increased to 2 to 3 mg/kg/day, but when to start it is subject to debate.[45] Some clinicians start azathioprine concurrently with the prednisone while others use it as a second-line agent after failure on prednisone or if tapering the prednisone is unsuccessful. Other immunosuppressive agents such as cyclosporine or mycophenolate mofetil may have clinical benefit months after initiating treatment.

Thymectomy is usually not performed during a myasthenic crisis. However, after the patient is treated and weakness has improved, thymectomy may be considered. Thymectomy is indicated in cases of thymoma, but in cases without thymoma demonstrated on CT or MRI of the chest, whether to treat with thymectomy is somewhat controversial. This has prompted the planning of a randomized multicenter study of thymectomy.[46] In a retrospective Iranian series of 229 myasthenic clinic patients, there were more patients who had a crisis and those crises were more severe among those patients who did not have a thymectomy compared with those who did.[47] In a review of thymectomy series over 40 years of 8490 myasthenic patients, those who underwent thymectomy were more likely to have clinical improvement, become asymptomatic, or even attain remission.[48] Thymectomy may be less effective in the elderly due to atrophy of the thymus, so many experts do not recommend surgery to patients older than age 60 years.[45] Careful pre- and postoperative care must be carried out to avoid postoperative myasthenic crisis. In a recent retrospective Japanese study, predictors of postoperative myasthenic crisis were preoperative bulbar symptoms, preoperative serum antiacetylcholine receptor antibody level greater than 100 nmol/L, and intraoperative blood loss greater than 1 L.[49] Delaying thymectomy until immunosuppressive treatment has been initiated and bulbar symptoms are resolved may be beneficial in avoiding postoperative myasthenic crisis. Improvement after thymectomy may not be seen for months or even years.

The current treatments for MG are effective but lack specificity, therefore resulting in the side effects caused by overall immunosuppression. Ideally, future research would be directed at finding a treatment that only targets the antibodies to the acetylcholine receptor. Immunoadsorption of acetylcholine receptor antibodies is a technique that may have fewer complications than TPE but has not been studied extensively.

Estimates are that critical illness polyneuropathy occurs in at least 25% to more than 50% of patients in medical and surgical intensive care units.

CRITICAL ILLNESS POLYNEUROPATHY/MYOPATHY

CIP is a syndrome first described in detail in the early 1980s, mostly in patients who could not be weaned from mechanical ventilation.[50] CIP is characterized by fairly symmetric limb muscle weakness, often with sparing of the cranial nerve musculature. In patients on sedating medications, this may manifest as a weak withdrawal of the extremities to painful stimulus with a normal facial grimace. There may be reduced or absent deep tendon reflexes and sensory loss. Involvement of the phrenic nerve, in addition to intercostal muscle weakness, contributes to difficulty weaning these patients from mechanical ventilation. Estimates are that CIP occurs in at least 25% to more than 50% of patients in medical and surgical ICUs, generally in the setting of sepsis and multiorgan failure, and may occur in both adults and children.[51,52] Routine electrophysiologic testing revealed 50 to 100% of patients ventilated mechanically for 5 to 7 days had an axonal polyneuropathy.[53] CIP may even occur as early as within 3 days after sepsis onset.[54] Nerve conduction studies show reduction of the amplitude of the compound motor and sensory nerve action potentials without changes in latency or conduction velocity, consistent with a sensorimotor axonal polyneuropathy.[55] Electromyography shows fibrillation and positive sharp waves consistent with denervation changes. Myopathic changes consistent with critical illness myopathy (CIM) are frequently found on muscle biopsy and, because CIP and CIM are frequently found in combination, it

has been suggested that the syndrome be called critical illness polyneuropathy/myopathy (or CIP/M).

The etiology of CIP/M remains unknown but has been variably associated with hyperglycemia and with the use of neuromuscular blocking agents, corticosteroids, aminoglycoside antibiotics, catecholamines, and parenteral nutrition. One study of 95 medical and surgical ICU patients found that independent predictors of CIP/M were female gender, the number of days with multiorgan dysfunction, duration of mechanical ventilation, and use of corticosteroids.[52] The lowest serum sodium, highest blood glucose, and highest blood urea nitrogen levels were significantly associated with CIP/M in this study.

Because critical illness polyneuropathy and critical illness myopathy are frequently found in combination, it has been suggested that the syndrome be called critical illness polyneuropathy/myopathy.

Critical Illness Polyneuropathy/Myopathy: Intubation and Extubation Criteria

Most patients with CIP/M are already intubated prior to diagnosis. Extubation criteria are the same as for GBS and MG but may take weeks or months. The mean total duration of mechanical ventilation in 1 study of 95 ICU patients was significantly longer in CIP/M patients than in the control group (34.8 days versus 18.4 days, $P < 0.001$).[52] The initial strength score did not correlate with duration of weakness in that study and the weakness resolved within 3 weeks in half of their CIP/M patients. Overall prognosis is uncertain because there are no prospective studies looking at long-term outcome; however, estimates are that there is about a 50% chance of complete recovery depending on the severity of symptoms.[55] Other estimates are that mortality in these patients approaches 50% and are even much higher with 3 or more failed organ systems.[56]

Critical Illness Polyneuropathy/Myopathy: Medical Management

As with GBS or MG patients in the ICU, medical management should include chest physiotherapy, deep venous thrombosis prophylaxis, gastric and decubitus ulcer prophylaxis, nerve pressure palsy prophylaxis, and psychologic support. Tracheostomy may be considered earlier than in MG given the probable prolonged need for mechanical ventilation. Enteral nutritional support is preferable given parenteral nutrition has been suggested as a risk factor for CIP/M.[51] Medications such as neuromuscular blocking agents, corticosteroids, aminoglycoside antibiotics, and vasopressors, especially catecholamines, should be avoided if possible. The use of succinylcholine has been associated with life-threatening hyperkalemia in CIP/M patients and should be used with caution.[55] The effect of neuromuscular blockers may be potentiated by certain drugs given in the ICU, including corticosteroids, aminoglycoside antibiotics, clindamycin, vancomycin, and procainamide.[56] Some have questioned whether preservation of minimal muscle activity either by minimizing sedation or by frequent passive physiotherapy might be beneficial in preventing CIP/M.[52,57]

One prospective, unblinded, controlled study of 1548 patients in a primarily cardiothoracic surgical ICU found that intensive insulin therapy with a continuous intravenous infusion to keep blood sugars between 80 mg/dL and 110 mg/dL was associated with a 44% lower risk of CIP than those treated only to keep the blood sugar at 180 to 200 mg/dL.[58] The intensive insulin therapy patients had lower mortality during ICU and hospital stay, shorter duration of ICU stay, required prolonged mechanical ventilation less often, and had reduced ICU morbidities, including infections. In a posthoc analysis of data from the same study, maintenance of a blood glucose level from 80 to 110 mg/dL was associated with a better outcome than even intermediate blood glucose control of 110 to 150 mg/dL, and the lower the glucose was maintained, the lower was the risk of CIP.[59] Whether intensive insulin therapy is as effective in reducing risk of CIP/M in nonsurgical ICU patients remains to be determined.

Critical Illness Polyneuropathy/Myopathy: Treatment Options

There is no proven treatment of CIP/M other than prevention. Aggressive treatment of sepsis, multiorgan failure, and hyperglycemia (blood sugar >110 mg/dL) may reduce the risk of developing CIP/M. Some suggest that bed rest and immobility due to sedating medications may contribute to the development of weakness, and that sedation protocols designed to minimize the use of sedatives may be a useful preventative measure.[60] There have been mixed results and no large controlled studies on the use of IVIGs in the treatment of CIP/M.[55,56] A retrospective chart analysis of 33 patients with sepsis, multiorgan failure, or both suggested that early treatment with immunoglobulin may prevent or mitigate CIP.[61] However, a small pilot study of patients with CIP found high-dose immunoglobulins did not alter the clinical course.[62]

CONCLUSION

GBS, MG, and CIP/M cause weakness in the ICU. Clinical and pulmonary function criteria are available to guide clinicians in the optimal timing of intubation in severe GBS and MG. Rigorous medical management is essential in preventing infections, deep venous thromboses, and gastric and decubitus ulcers in patients with these conditions. IVIG or TPE are both equally effective in the treatment of GBS, but anecdotal evidence suggests that relapses may be more frequent with IVIG, perhaps due to differences in length of treatment. Either TPE or IVIG may be used in the treatment of myasthenic crisis, but must be followed by long-term immunosuppression. Studies suggest possible preventative measures for CIP/M such as tighter glycemic control and

avoidance of neuromuscular blockers, but there are still no definitive treatments. Research to advance our knowledge of the pathogenesis of GBS, MG, and CIP/M is clearly needed to develop more specific and more effective treatments in the future. In the meantime, measures that optimize medical management can be instituted to improve outcomes in patients with these conditions, preferably in a specialized neuroscience ICU setting.

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