

## NEUROLOGICAL EMERGENCY

## Acute neuromuscular respiratory paralysis

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This article reviews the recognition, diagnosis and management of respiratory failure in acute neuromuscular disease. Respiratory failure requiring artificial ventilation occurs in about 14% of patients with Guillain-Barré syndrome (GBS),<sup>1</sup> a small percentage of patients with myasthenia gravis and polymyositis, and also in acute rhabdomyolysis and a wide range of other less common disorders (tables 1-3). Neuromuscular disorders are responsible for only a tiny proportion of admissions to most intensive care units, 23 (1.1%) of 2097 consecutive admissions to our own unit in the last two years. Of those cases, 15 (60%) required mechanical ventilation and two (8.7) died in hospital. The APACHE III study in North America<sup>2</sup> documented neuromuscular disease as the cause of intensive care unit admission in only 45 patients (0.26%) of the cohort of 17 440 patients with a 15.6% unadjusted hospital mortality rate. These figures exclude those patients who were admitted to the intensive care unit because of operation or systemic disease and then developed neuromuscular disease which caused respiratory failure or delayed weaning off the ventilator. Respiratory failure occurring in the setting of chronic progressive neuromuscular disease, such as, Duchenne muscular dystrophy and motor neuron disease, presents a challenging management problem which is outside the scope of this review.

**Pathophysiology**

Respiratory failure is particularly dangerous when it is caused by neuromuscular rather than lung disease because its development may be insidious and unrecognised until sudden decompensation causes life threatening hypoxia. The arterial hypoxaemia of these patients is the result of both hypoventilation and also microatelectasis arising from the retention of secretions.<sup>3</sup> Hypercapnia occurs only as a late feature in this form of respiratory failure and usually heralds an impending respiratory arrest. Bulbar involvement in the primary disease process may prevent clearing of secretions and cause upper airway obstruction and significant pulmonary aspiration. Infection of the lower respiratory tract may supervene at any stage and contribute to a further deterioration in pulmonary gas exchange. Underlying these changes is the profound respiratory muscle dysfunction which interferes with the usual process of spontaneous breathing.<sup>4</sup>

The severity of respiratory failure is related primarily to the number and nature of the muscle groups disabled by the primary disease. Weakness of the diaphragm has different effects from weakness of the intercostal and abdominal muscles. The diaphragm is inserted at an acute angle into the lower border of the ribcage, pulls the ribcage upwards and enlarges the cross-sectional area of the thorax. At the same time the dome of the diaphragm moves caudally and elongates the thoracic cavity. As the diaphragm descends the anterior abdominal wall is forced anteriorly. Thus the action of the diaphragm is to move both the ribcage and the abdomen outwards. During quiet breathing and sleep nearly all the work of breathing is performed by the diaphragm.

When the diaphragm is paralysed, expansion of the ribcage is performed by the accessory muscles of respiration. When the ribcage expands, the fall in intrapleural pressure moves the flaccid diaphragm cephalad into the thorax and the anterior abdominal wall, being coupled to the diaphragm movement through the abdominal contents, moves passively inwards during inspiration. This "paradoxical abdominal movement" is most marked in the supine posture since gravity assists the cephalad movement of the abdominal contents. The change in volume of the ribcage is partly absorbed by the cephalad movement of the abdominal contents and the volume of air inspired is reduced. In the upright posture gravity partially counteracts the upward movement of the abdominal contents and improves the efficiency of the accessory muscles producing inspiration. Consequently, in diaphragmatic paralysis, patients use the accessory muscles of respiration, become distressed when supine and have smaller supine than erect vital capacities. Furthermore, the majority of neural drive to the respiratory muscles during sleep is directed to the phrenic nerves, so that patients with diaphragm paralysis are particularly prone to hypoventilation during sleep.

Patients with intact diaphragms but impaired intercostal and abdominal muscle function show paradoxical ribcage movement. As the diaphragm lowers intrapleural pressure during inspiration the intercostal spaces and the upper ribcage move inwards because of the lack of intercostal muscle tone. In the upright posture, gravity pulls the abdominal contents caudally and the flaccid anterior abdominal wall bulges anteriorly. The diaphragm is thus flattened and shortened

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Table 1 Peripheral neuropathies which cause respiratory failure

Condition	Specific test	Specific treatment
GBS (demyelinating form) GBS (axonal form)	nerve conduction block small CMAPs relatively normal MCV	PE IVIg? PE IVIg?
CIDP Critical illness polyneuropathy <sup>14 15</sup>	nerve conduction block	PE IVIg? S
Toxins: Organophosphates <sup>77</sup>	red cell cholinesterase plasma pseudo-cholinesterase	atropine, pralidoxime
Thallium <sup>16</sup> Arsenic <sup>17 78 79</sup> Lead <sup>79 80</sup>	whole blood thallium 24 hour urine arsenic whole blood lead	Berlin blue dimercaprol, DMSA sodium calcium edetate, DMSA
Gold <sup>81</sup> Lithium <sup>82</sup> Drugs: vincristine <sup>21</sup> Lymphoma <sup>23</sup>	plasma lithium	haemodialysis withdrawal cytotoxics
Vasculitis: systemic lupus erythematosus <sup>83</sup> Metabolic: acute intermittent porphyria <sup>25</sup>	nerve biopsy nerve biopsy urine porphobilinogen	S cyclophosphamide avoidance of precipitants iv haematin
Hereditary tyrosinaemia <sup>26</sup>	urine d-ALA	high calorie intake liver transplant antitoxin
Diphtheria <sup>84</sup> Buckthorn neuropathy (central America) <sup>85</sup>	throat swab culture	antitoxin

Abbreviations: PE = plasma exchange  
IVIg = intravenous immunoglobulin  
CIDP = chronic idiopathic demyelinating polyradiculoneuropathy  
S = steroids  
MCV = maximum conduction velocity  
d-ALA = delta-aminolaevulinic acid  
DMSA = 2,3 dimercaptosuccinic acid<sup>79</sup>

and is inefficient in lifting the ribcage and elongating the thorax. In this situation respiratory distress may be experienced in the upright position. The resultant poor vital capacity and inability to cough contribute to ventilatory failure.

### Clinical diagnosis of neuromuscular respiratory failure

The danger of respiratory failure should be considered in every patient with progressive weakness, especially if the upper limbs and bulbar muscles are involved. The patient complains of weakness and fatigue but, unlike a patient with parenchymal lung disease or airways obstruction, does not appear wheezy or cyanosed. Instead, the patient prefers to sit or lie still in bed, becomes breathless on talking or swallowing, and uses the accessory muscles of respiration (pectoral, scalene, sternocleidomastoid, and levators of the nostrils). Diaphragm weakness may be detected by indrawing of the abdominal wall, that is, paradoxical abdominal movement. Whilst the respiratory rate may be rapid and shallow, and the observation chart may show an increase in heart and respiratory rate over the previous few hours, this is not invariable and some patients present with ventilatory failure

and a normal or reduced respiratory rate. All such patients should be monitored from the outset, especially during sleep, by pulse oximetry for the early detection of arterial desaturation. Clinical assessment however, is better than blood gas analysis in assessing the need for ventilatory support. As respiratory failure worsens, the patient becomes increasingly anxious, and though exhausted, may be unable to sleep. Additional bulbar weakness or insensitivity with the attendant danger of inhalation is particularly hazardous.

Although the decision to intubate and start artificial ventilation depends primarily on the overall clinical assessment, quantitative assessment and monitoring of respiratory muscle function are helpful. The most convenient method is the measurement of vital capacity. A common error is to measure peak expiratory flow because devices for its measurement have always been more readily available on a general medical ward. Fortunately, small portable electronic devices are now available for monitoring respiratory frequency, tidal volume and vital capacity at the bedside in the spontaneously breathing patient. Care is needed to educate the patient to obtain a meaningful measurement since facial weakness may prevent an adequate lip seal around a mouth piece. In such cases, a padded, tightly fitting face mask attached to the measuring device may help. As a rule of thumb ventilatory support of some form should be considered when the vital capacity in an adult falls to less than one litre. The exact figure depends upon the predicted normal vital capacity for the weight and age of the individual concerned.

Maximal static respiratory pressures (maximum inspiratory pressure,  $PI_{max}$ , measured at residual volume; maximum expiratory pressure,  $PE_{max}$ , measured at total lung capacity) obtained whilst breathing against an occluded mouthpiece are said to be more sensitive indicators of respiratory muscle weakness.<sup>5</sup> A  $PE_{max}$  of less than 40 cm H<sub>2</sub>O (adult normal = 100 cm H<sub>2</sub>O) has been associated with an inability to cough and clear secretions adequately whereas a  $PI_{max} > -20$  cm H<sub>2</sub>O (adult normal  $< -70$  cm H<sub>2</sub>O) precludes effective ventilation with the maintenance of a normal arterial CO<sub>2</sub> tension. Nevertheless, a falling vital capacity approximates these changes with impaired clearance of secretions occurring at around a vital capacity of less than 30 ml/kg and frank ventilatory failure at less than 10 ml/kg. Further assessment can be obtained by the measurement of transdiaphragmatic pressure during tidal breathing and on maximal inspiration. Such studies may be coupled with the measurement of the diaphragm EMG, but this is not routinely performed outside research centres.

### Diagnosis of the cause

#### CENTRAL NERVOUS SYSTEM CAUSES

Diseases of the nervous system can cause respiratory failure by damaging the respiratory centre in the medulla or its connections with

Table 2 Disorders of neuromuscular transmission which cause respiratory failure

Condition	Specific test	Specific treatment
Myasthenia gravis <sup>27</sup>	edrophonium test anti AChR antibody	PE S
Anticholinesterase overdose Antibiotic-induced paralysis <sup>30</sup> Hypermagnesaemia <sup>29</sup>	negative edrophonium test — plasma Mg EMG increment on 50 Hz stimulation	drug withdrawal drug withdrawal iv calcium
Botulism <sup>32</sup> Snake, scorpion and spider bite <sup>32</sup> Fish, shellfish, crab poisoning <sup>32 33 86</sup> Tick paralysis <sup>32 34</sup> Eaton-Lambert syndrome <sup>27</sup>	injection of serum into mice identifying the snake identifying the fish finding the tick EMG increment on repetitive stimulation	antitoxin antitoxin varies removal PE S

Table 3 Disorders of muscle which cause acute respiratory failure

Condition	Specific test	Specific treatment
Hypokalaemia <sup>38</sup> Polymyositis <sup>40</sup>	plasma K + plasma CK EMG muscle biopsy	K + S
Acute rhabdomyolysis <sup>40</sup>	EMG muscle biopsy	urine alkalinisation
Hypophosphataemia <sup>39</sup> Acid maltase deficiency <sup>37</sup> Combined neuromuscular blockade and steroids <sup>28</sup> Barium intoxication <sup>88</sup>	plasma phosphate PAS stain of blood film muscle biopsy  plasma K +	phosphate — withdrawal  iv K + oral magnesium sulphate haemodialysis

the cervical and thoracic spinal cord. In practice the commonest causes are the secondary consequences of central nervous system depression by drugs or metabolic abnormalities or of primary cerebral or brain stem disease. These are important in differential diagnosis but this review is confined to disorders affecting the lower motor neuron, peripheral nerves, neuromuscular junction and muscles. The localisation of the disease process to the brain stem or spinal cord does not usually present the neurologist with any difficulty because of the presence of symptoms and signs at the level of the lesion and involvement of the long tracts.

Poliomyelitis remains a common problem in Eastern Europe, the Middle East and the Indian subcontinent. It should still be considered in the differential diagnosis of acute flaccid paralysis throughout the world, especially when sensory deficit is absent, the onset is asymmetrical and the CSF shows a pleocytosis.<sup>67</sup> The diagnosis may be confirmed by culturing the stool, and sometimes a throat swab or CSF, and by finding a rising titre of neutralising antibody in the serum.

#### PERIPHERAL NEUROPATHY

Peripheral neuropathy causing respiratory failure can usually be diagnosed clinically from the gradual evolution of ascending or sometimes descending weakness associated with paraesthesiae and sensory deficit and reduced or absent tendon reflexes. Difficulties in diagnosis arise in rapidly evolving pure motor neuropathies, especially in the earliest stages when the tendon reflexes may be preserved. Also paraesthesiae occur in occasional cases of toxic neuromuscular conduction block, including botulism.<sup>8</sup>

Guillain-Barré syndrome (GBS) is so much more common than any of the other causes of neuromuscular respiratory failure that there is a danger that other causes and particularly other causes of neuropathy will be overlooked.<sup>19</sup> The diagnosis of GBS cannot be made by any diagnostic test but requires the exclusion of other causes. These are listed in table 1. In most cases the pathological process is inflammatory, demyelinating, and probably autoimmune.<sup>1</sup> The presence of demyelination can be confirmed by the neurophysiological demonstration of multifocal conduction block.<sup>10</sup> However, GBS is a heterogeneous condition whose patholog-

ical substrate also includes an acute axonal form which may have an explosively rapid onset and be associated with a particularly slow and incomplete recovery.<sup>11</sup> The neurophysiological diagnosis of the axonal form of GBS requires the demonstration of reduction in evoked muscle and nerve action potentials without marked slowing or conduction block. If the nerves are already inexcitable by the time of the first neurophysiological study, the distinction between demyelination and axonal degeneration may need to be made by biopsy, preferably of a motor nerve.<sup>12 13</sup>

The other causes of neuropathy (table 1) can be ruled out by a careful history. Critical illness polyneuropathy occurs in the setting of an extremely ill patient who is being ventilated, has had sepsis and multiorgan failure, and cannot be weaned from the ventilator. It is due to an axonal neuropathy and its distinction from the axonal form of GBS may be merely semantic. The aetiology of critical illness polyneuropathy is not known but may be multifactorial.<sup>14 15</sup> Careful enquiry about possible toxin exposure as a cause of polyneuropathy is always necessary. Poisoning with organophosphates or heavy metals severe enough to cause a neuropathy with respiratory failure has usually been preceded by an acute illness with vomiting and an altered level of consciousness. Prominent cutaneous and muscular pain, especially in the feet, and preservation of the reflexes in the early stages should raise the suspicion of thallium poisoning.<sup>16</sup> Painful tingling and weakness begin within one to five days from ingestion of thallium, before the characteristic hairfall. In arsenic poisoning the early clinical picture sometimes closely resembles GBS and neurophysiological changes may initially show partial conduction block and slowing of conduction before giving way to changes suggestive of axonal degeneration.<sup>17</sup> Diphtheria is extremely rare in developed countries but cases were recently reported from Sweden,<sup>18</sup> and the diagnosis should be considered in patients with a recent upper respiratory infection, especially if there is prominent palatal involvement.<sup>19</sup> Buckthorn neuropathy need only be suspected in those who have consumed berries in Mexico.<sup>20</sup> Drugs usually cause an insidiously progressive distal axonopathy without respiratory involvement, but acute paralysis with respiratory failure occurred in a patient being treated with vincristine, possibly due to coincidental GBS.<sup>21</sup> Both T and B cell lymphomas may cause acute neoplastic infiltration of the peripheral nervous system which closely resembles GBS.<sup>22-24</sup> Sometimes acute neuropathy is the presenting feature of the lymphoma. Vasculitic neuropathy rarely causes respiratory failure and usually only does so in the setting of a systemic illness with cutaneous, renal and lung involvement. Acute neuropathy occurs in acute intermittent porphyria, usually after abdominal pain and vomiting, but sometimes as the presenting feature.<sup>25</sup> It may be diagnosed during attacks by detecting increased urine porphobilinogen excretion, a

test which should be undertaken in every case of undiagnosed acute neuromuscular paralysis. Recurrent neuropathy in infants is a feature of hereditary tyrosinaemia.<sup>26</sup>

#### NEUROMUSCULAR JUNCTION DISORDERS

Respiratory failure can herald disorders of the neuromuscular junction, which can be distinguished from neuropathic causes by the absence of sensory deficit and preservation of tendon reflexes. In myasthenia gravis respiratory failure usually occurs in the setting of established disease which has failed to respond to conventional treatment. Even in an acute case the diagnosis is usually evident because of ptosis, facial weakness and bulbar palsy with muscle fatigue. The diagnosis can be confirmed by the injection of intravenous edrophonium, neurophysiological tests, and a positive test for acetylcholine receptor antibodies in a reliable laboratory.<sup>27</sup> In treated myasthenia, weakness can be caused by over-dosage of anticholinesterase drugs causing depolarisation cholinergic block. This will be accompanied by diarrhoea, colic, excessive salivation and small pupils and will be worsened rather than improved by intravenous edrophonium.

Other causes of neuromuscular junction blockade are rare and the diagnosis is usually obvious from the clinical setting. Botulism should be suspected when acute descending paralysis has been heralded by autonomic features, dry mouth, constipation, poorly reactive pupils, and ptosis and bulbar palsy. These symptoms have usually been immediately preceded by nausea, vomiting, abdominal pain and diarrhoea from eating foul smelling food contaminated by *Clostridium botulinum*.<sup>28</sup> Severe hypermagnesaemia can be produced by magnesium-containing antacids and aperients in patients with impaired renal function. The increased magnesium interferes with the release of acetylcholine so as to cause weakness which may develop into respiratory failure.<sup>29</sup> The aminoglycoside and polymyxin antibiotics and some other drugs also cause neuromuscular blockade by interfering with the release of acetylcholine.<sup>30</sup> This is usually only significant when weaning infected patients off ventilation.<sup>31</sup> Physicians practising in the tropics have to cope with a much wider range of toxic causes of neuromuscular conduction blockade whose diagnosis will be obvious from the history (table 2).<sup>32</sup> Fish or shellfish toxin poisoning (usually Caribbean or Pacific fish) causes a gastrointestinal upset before the development of weakness.<sup>32-33</sup> In North America paralysis is sometimes caused by the bite of a female tick whose saliva contains an unidentified toxin which probably also interferes with neuromuscular conduction.<sup>32-34</sup> The tick may be difficult to find but its removal is reported to be curative. Respiratory failure occurs in the Lambert-Eaton myasthenic syndrome, but only rarely and then usually in the setting of gradually progressive weakness. The diagnosis may be suggested clinically by autonomic symptoms, including a dry mouth, the finding of

depressed reflexes which are enhanced after exercise, and confirmed by electrophysiological tests showing an increment in muscle action potential amplitude following repetitive nerve stimulation.<sup>27</sup> It may be associated with a small cell lung carcinoma or autoimmune disease.

#### MYOPATHY

Respiratory failure in muscle disease usually occurs insidiously following progressive proximal weakness, which has evolved over months or years, and presents with nocturnal hypoventilation causing morning headache and daytime sleepiness. This form of respiratory failure may develop in the advanced stages of severe muscular dystrophy and also in polymyositis. Sometimes, especially in myotonic dystrophy, the respiratory failure is worsened by depression of central respiratory drive. When the ventilatory reserve has fallen so far that the vital capacity is less than 55% of its predicted normal, there is a grave danger that an intercurrent lung infection will precipitate respiratory failure.<sup>35</sup> In acid maltase deficiency the diaphragm is particularly severely affected and the patient may present with respiratory failure before consulting a neurologist about weakness.<sup>36</sup> Acid maltase deficiency should be suspected if there is proximal upper limb weakness and marked wasting of the paraspinal muscles, and confirmed by seeking glycogen-containing granules in the lymphocytes which stain red with periodic acid Schiff's reagent applied to a blood film.<sup>37</sup>

When a patient presents with flaccid paralysis and respiratory failure over a few hours or days, a correctable electrolyte disturbance should be sought immediately. The feature which distinguishes muscle disease from neuropathy is the preservation of the reflexes and the absence of sensory symptoms or signs. Hypokalaemia induced by potassium loss from the gut or kidneys is the commonest cause and is probably responsible for the muscle fibre necrosis in acute rhabdomyolysis which occurs following some drugs, such as carbenoxolone.<sup>38</sup> Severe hypophosphataemia can also cause paralysis requiring respiratory failure. It is usually precipitated by parenteral glucose infusions in alcoholic patients.<sup>39</sup>

Acute rhabdomyolysis is a rare condition in which acute muscle necrosis causes the very rapid onset of muscle pain, tenderness, swelling and weakness sometimes severe enough to cause respiratory failure. The muscle enzyme concentrations, including creatine kinase, are markedly increased in the plasma, and the EMG shows myopathic changes and spontaneous fibrillation. A muscle biopsy is necessary to confirm the diagnosis and will show massive muscle fibre necrosis and often numerous regenerating fibres but relatively little inflammation. The neurological picture is overshadowed by the development of myoglobinuria and acute renal failure. Causes of acute rhabdomyolysis are alcohol abuse, viruses (influenza, Coxsackie B5, ECHO 9, adenovirus 21, Epstein-Barr), mycoplasma,<sup>40</sup>

and a wide variety of drugs, especially potassium-lowering drugs, amphetamine-like agents, barbiturates, and the combination of the muscle relaxant pancuronium and corticosteroids.<sup>30-41</sup> If the causative agent is withdrawn and the patient can be nursed through the period of respiratory and renal failure, regeneration of the necrotic muscle and full recovery are usual.

Respiratory muscle involvement was a presenting feature in 4% of 118 patients with polymyositis. More commonly it developed later, contributing to death in 14%.<sup>42</sup> Neuromuscular respiratory failure may be worsened by simultaneous interstitial infiltration and fibrosis of the lungs.<sup>40</sup> Inflammatory changes in muscle are usually so extensive that the diagnosis can be readily confirmed by the increased plasma creatine kinase concentration, myopathic EMG with additional spontaneous discharges, and inflammatory changes in a muscle biopsy.

### **Institution of mechanical ventilation**

The decision to institute respiratory support depends much more on the clinical state of the patient than on any physiological measurement. Arterial blood gas analysis is not particularly helpful. Intervention is required to prevent the development of arterial hypoxaemia and carbon dioxide retention before they become life threatening. Continuous positive airway pressure administered by face mask may be useful in the temporary correction of arterial hypoxaemia but is uncomfortable and poorly tolerated for prolonged periods of time. It has little effect on CO<sub>2</sub> retention although it may reduce the work of breathing by correcting any reduction in functional residual capacity in patients with sputum retention and atelectasis. Nevertheless, it is only a "stop-gap" measure used to avoid tracheal intubation in a small minority of cases in whom some basic treatment, for example, drug therapy or plasma exchange, will reverse the primary disease process. On the whole, it is safer to proceed rapidly to tracheal intubation to ensure control of the airway, adequate oxygenation, ventilation and tracheal toilet (especially in patients with an inadequate cough reflex) and the prevention of pulmonary aspiration.

Intubation is best performed by a skilled operator in the setting of an intensive care unit. This requires referral and involvement of the intensive care medical staff at an early stage to prevent any emergency intervention on a general medical ward. Intubation is best achieved by the oral route following adequate intravenous sedation in combination with muscle relaxation. Whilst it is often said that nasotracheal tubes are a well tolerated alternative, we have found them to be unsuitable because they carry a high risk of sinusitis,<sup>43</sup> and their extra length with the narrow internal diameter makes them more difficult to aspirate adequately and increases the resistance of the ventilatory circuit. Any increase in work of breathing associated with nasotra-

cheal intubation is especially harmful during the weaning period when a weak patient is asked to make some effort whilst receiving graded reductions in ventilatory support. Following pre-oxygenation, etomidate, propofol or a benzodiazepine (midazolam) may be used to render the patient unconscious and this on its own—in the presence of cricoid pressure—may be sufficient for the experienced operator to perform the necessary laryngoscopy and intubation. A non-depolarising muscle relaxant (atracurium, vecuronium) in adequate doses will abolish all remaining muscular tone and can improve the inexperienced operator's ability to visualise the larynx. Suxamethonium should never be used in this setting because of reports of ventricular tachycardia and asystole caused by a sudden rise in serum potassium in patients with denervated muscles.<sup>44-45</sup> Cricoid pressure should always be used since although patients may not have eaten for some time before the induction of anaesthesia, gastric stasis and ileus are common particularly in the early stages of the GBS. Following successful tracheal intubation, a nasogastric tube (if not already present) should be placed to facilitate the initiation of enteral nutrition.

### **Management during mechanical ventilation**

#### **GENERAL PRINCIPLES**

The principles which govern management during mechanical ventilation centre upon three primary concerns—access to the airway with the provision of adequate pulmonary gas exchange, the maintenance of nutrition and the prevention of nosocomial infection. Other issues, very often taken for granted but which require special attention, include the need for scrupulous nursing care to avoid nerve compression syndromes and bed sores; physiotherapy with the provision of splints to prevent irreversible contractures and joint immobilisation; subcutaneous heparin for the prophylaxis of deep venous thrombosis; prevention of deep vein thrombosis; and finally, extensive psychological support throughout the period of their illness when an individual patient with neuromuscular disease is entirely dependent upon his attendants and the mechanical ventilator. Keeping a paralysed but conscious patient comfortable requires careful positioning and frequent gentle repositioning: sitting up, especially out of bed, may help and is good for morale. A particular problem in patients with GBS is the management of autonomic dysfunction which can result in wide fluctuations in pulse and blood pressure as well as a wide variety of atrial and ventricular arrhythmias.<sup>1-45</sup>

#### **AIRWAY ACCESS AND MECHANICAL VENTILATION**

Most patients who develop respiratory failure as a consequence of neuromuscular dysfunction will require a tracheostomy. Whilst mechanical ventilation via an orotracheal tube

can be performed for a limited period of time (usually for 5–7 days in our unit), a tracheostomy simplifies management considerably and allows the withdrawal of all sedation.<sup>46</sup> The tracheostomy tube is well tolerated, gives excellent access for tracheal toilet and chest physiotherapy and since the patient can be placed on and off different forms of respiratory support at will, permits easier “weaning”. Tracheostomy can now be performed at the bedside, using a percutaneous Seldinger technique, and this appears to be the preferred technique.<sup>47</sup> Nevertheless, tracheostomy by whatever method is not without risk (infection of the stoma; primary and secondary haemorrhage).

In the absence of severe pulmonary aspiration or infection, it is not difficult to achieve adequate pulmonary gas exchange in these patients. Initially, most patients are too weak to generate an adequate negative pressure to “trigger” the ventilator and so require “controlled ventilation”. More modern ventilators, for example, the Siemens Servo 300, have a different method of triggering which requires the patient to change a baseline flow within the machine rather than to reduce a pressure. These machines are much more sensitive to the respiratory efforts of a patient and should theoretically be beneficial in management. In fact, no particular kind of ventilation or ventilator has been shown to be superior in supporting these patients and most intensivists rely on pressure support or some combination of intermittent mandatory ventilation with pressure support to provide an adequate tidal volume and minute ventilation. Positive end-expiratory pressure (with a pressure of 3–6 cm H<sub>2</sub>O) together with physiotherapy is used in the often vain attempt to prevent atelectasis.

#### PROVISION OF NUTRITION

Every effort should be made to feed these patients early via the enteral route.<sup>48</sup> Whilst it is impossible to prevent muscle wasting related to denervation, loss of muscle bulk will only be more exaggerated if an external source of calories and nitrogen is not forthcoming.<sup>49</sup> Muscle wasting is particularly marked in those cases who develop nosocomial sepsis and may contribute to a prolongation of the period of dependence on mechanical ventilation.<sup>50</sup> Use of the enteral route ensures that the gastrointestinal mucosa does not atrophy and the integrity of gut barrier is maintained. Theoretically this should contribute to the prevention of nosocomial infection by reducing the likelihood of translocation of bacteria and endotoxin from the lumen of the gut into the portal venous circulation and lymphatic system.<sup>51</sup> Parenteral nutrition on the other hand, especially that containing large amounts of intravenous fat, may contribute to an increased risk of sepsis and is best avoided.<sup>52,53</sup> It may be difficult to establish enteral nutrition in occasional patients with an ileus. A distended abdomen and large nasogastric aspirates with the absence of bowel sounds are the usual fea-

tures of ileus. In our experience these features have usually been related to the excessive use of sedatives, especially opiates. Early tracheostomy and the subsequent withdrawal of all sedation (other than simple night sedation to ensure an appropriate sleep pattern) will reduce the incidence of ileus. Diarrhoea usually reflects the administration of broad spectrum antimicrobials rather than any effect of enteral nutrition. It should be treated symptomatically and every effort made to withdraw the offending antibiotics.

#### PREVENTION OF NOSOCOMIAL INFECTION

The prevention of hospital acquired infection is at the heart of good intensive care practice.<sup>54</sup> It is especially important in patients requiring prolonged mechanical ventilation since uncontrolled nosocomial sepsis is likely to be an important cause of death in those cases who die in the intensive care unit. Several studies have demonstrated an association between the likelihood of developing a nosocomial pneumonia and the number of days of mechanical ventilation.<sup>55</sup> Prevalence rates vary enormously from unit to unit and reflect local practices and resources. Every intensive care unit should have a written infection control policy developed in conjunction with local microbiological experts. Central issues are local practices of hand-washing, nursing numbers, strict intravenous line/urinary catheter and antimicrobial policies, the avoidance of gastric alkalization with H<sub>2</sub> antagonists and antacids, and an infection surveillance programme. These aspects concerning the organisation of intensive care are fundamental in the prevention of infection in individual cases.

Recently, the practice of “selective decontamination of the digestive tract” has been proposed as another means of reducing the incidence of unit-acquired gram negative infections.<sup>56</sup> This method requires the application of a paste of nonabsorbable antimicrobials (most commonly the combination of tobramycin, polymyxin and amphotericin) to the oropharynx and via the nasogastric tube, to the stomach. It has been best studied in patients following multiple trauma and major surgery. Whilst several studies have demonstrated reductions in the incidence of infection using this technique, no influence on survival has been observed. Many believe that selective decontamination only works well in the setting of a high nosocomial infection rate and we do not use it.

#### AUTONOMIC DYSFUNCTION

In respiratory paralysis due to acute neuropathy, and especially in GBS, autonomic dysfunction is common.<sup>1,45,57–59</sup> Tachycardia with loss of sinus arrhythmia are usual. Rapid fluctuations of pulse and blood pressure and sweating may occur and are sometimes the harbingers of asystole. In particular tracheal suction may cause bradycardia and asystole. This can usually be prevented by hyperoxygenation beforehand but if it persists it may be necessary to use atropine and even an

endocardial pacemaker. Serious arrhythmias usually only occur in patients who need ventilation but we have had a patient with early GBS who developed asystole before needing ventilation. We monitor the ECG from the time of admission in all patients with GBS who have any sign of respiratory or bulbar involvement. Although the bladder is spared in the early stages of GBS, it may be affected in severe cases and bladder catheterisation is often needed as part of the intensive care of the ventilated patient. Postural hypotension is common when the patient is being mobilised so that the blood pressure should be monitored. This is best done with the aid of a tilt table.

### Specific interventions

#### GUILLAIN-BARRÉ SYNDROME

In two large randomised trials, patients with GBS who received plasma exchange (PE) recovered more quickly than those not so treated.<sup>60-62</sup> PE should therefore be offered to all patients with GBS who have such severe disease that they require assistance to walk. It seems logical to give it as early as possible, preferably during the first week, and its value after the second week is doubtful, although so long as the disease is still progressing it would be worth using PE. In the North American trial continuous flow PE appeared more effective than intermittent flow although intermittent flow was better than none.<sup>62</sup> There is no information concerning the relative merits of filtration compared with centrifugation systems. Albumin is the preferred exchange fluid since fresh frozen plasma caused more reactions and was no more effective.<sup>61</sup> The North American trial exchanged 200–250 ml/kg body weight (four to five plasma volumes) over seven to 14 days, and the French trial two plasma volumes on alternate days for a total of four exchanges. It is not known whether more exchanges would be more effective, but 10–25% of patients show a limited relapse after one to six weeks and usually respond to a further PE.<sup>63,64</sup> We space five 50 ml/kg PEs over 14 days and add further exchanges if there is a subsequent relapse:

Although steroids might have been expected to be beneficial in GBS, neither a small trial of oral prednisolone nor a large double-masked trial of intravenous methylprednisolone 500 mg daily for 5 days demonstrated any benefit.<sup>65,66</sup>

Much interest surrounds the possible use of intravenous immunoglobulin (IVIg) as an alternative to PE. A recent Dutch trial showed that the rate of recovery was similar or possibly slightly faster in patients treated with IVIg 0.4 g/kg daily for 5 days compared with those treated with PE. The median time to walk unaided was 55 days in 75 patients treated with IVIg and 69 days in the same number treated with PE ( $p = 0.07$  two-tailed). Lung and circulatory complications were more common in the PE treated group than the IVIg group.<sup>67</sup> Although IVIg is

expensive, it is not usually more expensive than PE and it is more widely available and simpler to give. Because GBS has such a variable prognosis and results are available from only one relatively small "open label" trial,<sup>68</sup> it would be premature to replace PE with IVIg as the preferred treatment for GBS and we await the outcome of an international trial which is comparing PE alone with IVIg alone and PE followed by IVIg. In the meantime we recommend IVIg whenever PE is impractical.

#### MYASTHENIA GRAVIS

After establishing with an edrophonium test that a patient has respiratory failure due to myasthenia gravis the dose of anticholinesterase drugs should be optimised. The vital capacity should be monitored before and after small (2 mg) doses of intravenous edrophonium. Swallowing is usually impaired and a nasogastric tube is often needed. Pyridostigmine should be given orally or via the nasogastric tube, but when enteral fluids cannot be absorbed, neostigmine should be given intramuscularly, substituting each 60 mg of pyridostigmine with 1 mg of neostigmine.

Patients with myasthenia gravis respond so dramatically in the short term to PE that a controlled trial has never been undertaken. We use 50 ml/kg exchanges on alternate days until an adequate response has been achieved, usually after two to five exchanges. Improvement is usually noticeable after the second exchange and lasts for about four to six weeks. Similar clinical benefit and falls in anti-acetylcholine receptor antibody have been reported following IVIg. The largest published experience is that of Cosi *et al*<sup>69</sup> who reported clinical improvement 12 days after a standard course of 0.4 g/kg in 70% of 37 patients treated which lasted for 60 days in 57%. Arsura *et al*<sup>70</sup> reported improvement in 11 of 12 patients beginning 3.6 days after IVIg treatment began, reaching a maximum after 8.6 days and lasting an average of 52 days. Sustained improvement has been maintained with repeated courses in a small number of cases.<sup>71</sup> Judgement of the relative merits of PE and IVIg must await comparative trials. In the meantime it would be reasonable to try IVIg to treat a myasthenic crisis if PE is not available.

Since PE provides only temporary relief, immunosuppressive treatment should be started, or increased, at the same time. We follow the practice of Newsom-Davis<sup>27</sup> and use prednisolone 120 mg on alternate days. In patients with early respiratory failure steroids should be introduced slowly and cautiously because of the danger of a transient worsening during the first week or two of the course. In patients with established respiratory failure on artificial ventilation, this cautious approach is superfluous and a full dose of steroids can be started immediately. Very large doses of steroids, including boluses of intravenous methylprednisolone, should be avoided because of the danger of inducing necrotic myopathy.<sup>72</sup> For patients who are



inadequately controlled with steroids we add azathioprine. If azathioprine is not tolerated, other immunosuppressive agents, such as cyclophosphamide or methotrexate, and as a last resort, low dose total body irradiation can be tried. When the respiratory failure due to myasthenic crisis has been controlled younger patients and those with thymoma should be assessed for thymectomy.

#### POLYMYOSITIS

Treatment of polymyositis with large doses of steroids is universally recommended and so clearly helpful, at least in the short term, that a controlled trial has never been considered necessary. A typical regime, recommended by Mastaglia and Ojeda,<sup>40</sup> is prednisone 60 to 80 mg/kg daily for 6 to 8 weeks followed by gradual withdrawal at the rate of 5 mg of the daily dose per week. After the dose has reached 30 mg daily further reductions should be made at 2.5 mg per week. However, a wide range of doses are used: some prefer an alternate day dose but others feel that this is not so effective.<sup>40</sup> It is important to bring the disease under control before beginning the reduction and then to monitor the course of the disease closely with serial measurements of muscle strength and plasma creatine kinase concentrations. Although PE combined with cyclophosphamide has been reported beneficial in polymyositis,<sup>73</sup> the usefulness of PE alone was not confirmed in a controlled trial in which three groups of 13 patients were treated with leukopheresis, PE, or sham PE.<sup>74</sup> The authors of that trial claim an 80% power of detecting a minimal improvement in functional capacity. The trial did not answer the question whether PE followed by immunosuppression would provide a more rapid response than immunosuppression alone. Further exploration of this possibility would be worthwhile since the PE group had a highly significant fall in plasma creatine kinase concentration compared with the sham PE group. Intravenous immunoglobulin was dramatically effective in two cases resistant to steroids and immunosuppressive drugs,<sup>75</sup> but its usefulness requires more study. Immunosuppressive treatment with azathioprine, cyclophosphamide or methotrexate have often been tried when steroids have failed,<sup>40</sup> but they probably do not have the rapid effect necessary to prevent or reverse the acute onset of respiratory failure. In desperation, total body low dose irradiation has sometimes been used and remissions have occurred in those cases which have been published.<sup>40</sup>

#### Withdrawal of mechanical ventilation

The course of respiratory failure related to neuromuscular disease is extremely variable. Various factors such as the primary diagnosis, chronic health status, treatment and the presence or absence of supervening complications dictate the rate of recovery. It eventually becomes evident that an individual patient has regained adequate neuromuscular func-

tion to be placed on a spontaneous mode of ventilation. At this stage, lung compliance and spontaneous minute ventilation should be relatively normal with a stable cardiovascular system. We prefer pressure support as a weaning mode and it is our practice to reduce gradually the amount of pressure support while monitoring the clinical appearance of the patient, respiratory rate, tidal volume, and arterial saturation by pulse oximetry. Daily measurements of vital capacity are also performed but it is not clear how helpful these are in the assessment of the recovery of respiratory muscle function. One study has clearly demonstrated that tidal volume rather than vital capacity is more closely related to recovering diaphragm function.<sup>76</sup> However, we have not found the more complex assessments of diaphragmatic performance such as maximum transdiaphragmatic pressure ( $P_{Di\max}$ ) or inspiratory time fraction ( $T_i/T_{tot}$ ) useful in the withdrawal of ventilatory support in these cases.

As respiratory muscle strength increases, it is possible to ask the patient to breathe for longer periods off the ventilator, either on continuous positive airways pressure or a T-piece. A relatively low level of pressure support (10 cm H<sub>2</sub>O) is usually maintained overnight to allow a patient to rest and to prevent nocturnal hypoxaemia. Many patients find that this period of ventilator withdrawal provokes extreme anxiety because of psychological dependence on the presence and the sound of the ventilator. Careful assessment of respiratory function and extensive psychological support are required to meet the physical and emotional needs of the patient.

#### The aftermath

Prevention of death from respiratory failure is merely the first stage in treatment of an illness such as GBS. Maintenance of morale and recognition and treatment of depression are important and difficult tasks which call on all the resources of the intensive care team. For some conditions patient support groups exist which offer counselling services (for example, Guillain-Barré Syndrome Support Group International, PO Box 262, Wynnwood, Pa 19096, USA; Guillain-Barré Syndrome Support Group, Foxley, Holdingham, Sleaford, Lincs NG34 8NR, UK). There are no easy guidelines. The patient and the family need clear information about what is happening and what may be expected. Over-optimistic prognoses may be greeted eagerly at first but reap a grim harvest of dashed hopes later. Above all, a conscious patient festooned with monitoring equipment in a modern intensive care unit needs a sympathetic caring approach tailored to his or her own needs.

We thank our colleagues and the nursing staff of Russell Brock and Starling Wards for their help, Dr L. Loh, Radcliffe Infirmary, Oxford, Dr D F Moore, Guy's Hospital Poisons Information Service, and Professor CM Wiles, University of Wales, Cardiff for advice, and the Medical Research Council and Guillain-Barré Syndrome Support Group for financial support.



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## Neurological stamp

### Emanuel Swedenborg (1688–1772)

Swedenborg, best known for his mystic and religious beliefs, also made important contributions to science. He received his formal education in Uppsala, where his father (Jesper Svedberg) was Professor of Theology. Soon after Swedenborg's death, his devoted followers created Swedenborgian societies dedicated to the study of his work.

He produced a new design for a dry dock, machinery for working salt springs and a system for moving large boats overland. He devised a method of calculating longitude at sea by the stars, invented an ear trumpet, began the science of crystallography, drew up plans for a machine gun, a submarine and an aeroplane. As assessor for the Royal Bureau of Mines he also devoted himself to the improvement of the Swedish metal mining industry.

His concepts of representation of the cerebral cortex were astonishingly modern. He observed that the muscles of the extremities were controlled by the upper frontal convolutions, those of the abdomen and thorax by the middle frontal convolutions, and those of the head and neck by the lower frontal convolutions. Swedenborg also studied the cerebrospinal fluid, the pituitary gland (which he called the arch gland) and proposed the concept of upper and lower motor neuron. He constructed a type of neuron theory based on the observations of Malpighi and Leeuwenhoek.

Swedenborg died on 29 March 1772 in London and was buried there in the Swedish Lutheran church. In 1908 the Swedish Government brought his remains back to Sweden, and they now lie in a large tomb in the



Cathedral at Uppsala, not far from that of Linnaeus. He was initially reburied with the wrong skull which had, until then, remained in England. In 1936 Swedenborg was honoured with this stamp to mark the 250th anniversary of his birth (Stanley Gibbons 201, 202; Scott 266, 267).

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