Practical approach to respiratory emergencies in neurological diseases

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5	Corresponding Author	Family Name	**Vita**
6		Particle	
7		Given Name	**Giuseppe**
8		Suffix	
9		Organization	University of Messina
10		Division	Unit of Neurology and Neuromuscular Diseases, Department of Clinical and Experimental Medicine
11		Address	Messina, Italy
12		Organization	Nemo Sud Clinical Centre for Neuromuscular Disorders
13		Division	
14		Address	Messina, Italy
15		e-mail	vitag@unime.it
16	Author	Family Name	**Racca**
17		Particle	
18		Given Name	**Fabrizio**
19		Suffix	
20		Organization	Sant'Antonio e Biagio e Cesare Arrigo Hospital
21		Division	Department of Anaesthesia and Intensive Care
22		Address	Alessandria, Italy
23		e-mail	
24	Author	Family Name	**Vianello**
25		Particle	
26		Given Name	**Andrea**
27		Suffix	
28		Organization	University of Padoua
29		Division	Respiratory Pathophysiology Division
30		Address	Padoua, Italy
31		e-mail	

Author	Family Name	**Mongini**
	Particle	
	Given Name	**Tiziana**
	Suffix	
	Organization	University of Turin
	Division	Neuromuscular Center, Department of Neurosciences
	Address	Turin, Italy
	e-mail	
Author	Family Name	**Ruggeri**
	Particle	
	Given Name	**Paolo**
	Suffix	
	Organization	University of Messina
	Division	Unit of Pneumology, Department BIOMORF
	Address	Messina, Italy
	e-mail	
Author	Family Name	**Versaci**
	Particle	
	Given Name	**Antonio**
	Suffix	
	Organization	Intensive Care Unit, AOU Policlinico "G. Martino"
	Division	
	Address	Messina, Italy
	e-mail	
Author	Family Name	**Vita**
	Particle	
	Given Name	**Gian Luca**
	Suffix	
	Organization	Nemo Sud Clinical Centre for Neuromuscular Disorders
	Division	
	Address	Messina, Italy
	e-mail	

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Abstract

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REVIEW ARTICLE

Practical approach to respiratory emergencies in neurological diseases

Fabrizio Racca[1] · Andrea Vianello[2] · Tiziana Mongini[3] · Paolo Ruggeri[4] · Antonio Versaci[5] · Gian Luca Vita[6] · Giuseppe Vita[6,7]

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Abstract

Many neurological diseases may cause acute respiratory failure (ARF) due to involvement of bulbar respiratory center, spinal cord, motoneurons, peripheral nerves, neuromuscular junction, or skeletal muscles. In this context, respiratory emergencies are often a challenge at home, in a neurology ward, or even in an intensive care unit, influencing morbidity and mortality. More commonly, patients develop primarily ventilatory impairment causing hypercapnia. Moreover, inadequate bulbar and expiratory muscle function may cause retained secretions, frequently complicated by pneumonia, atelectasis, and, ultimately, hypoxemic ARF. On the basis of the clinical onset, two main categories of ARF can be identified: (i) acute exacerbation of chronic respiratory failure, which is common in slowly progressive neurological diseases, such as movement disorders and most neuromuscular diseases, and (ii) sudden-onset respiratory failure which may develop in rapidly progressive neurological disorders including stroke, convulsive status epilepticus, traumatic brain injury, spinal cord injury, phrenic neuropathy, myasthenia gravis, and Guillain–Barré syndrome. A tailored assistance may include manual and mechanical cough assistance, noninvasive ventilation, endotracheal intubation, invasive mechanical ventilation, or tracheotomy. This review provides practical recommendations for prevention, recognition, management, and treatment of respiratory emergencies in neurological diseases, mostly in teenagers and adults, according to type and severity of baseline disease.

Keywords Neurological diseases · Respiratory failure · Hypercapnia · Hypoxemia · Invasive mechanical ventilation · Noninvasive ventilation

Fabrizio Racca and Andrea Vianello contributed equally to this work.

✉ Giuseppe Vita
vitag@unime.it

[1] Department of Anaesthesia and Intensive Care, Sant'Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy

[2] Respiratory Pathophysiology Division, University of Padoua, Padoua, Italy

[3] Neuromuscular Center, Department of Neurosciences, University of Turin, Turin, Italy

[4] Unit of Pneumology, Department BIOMORF, University of Messina, Messina, Italy

[5] Intensive Care Unit, AOU Policlinico "G. Martino", Messina, Italy

[6] Nemo Sud Clinical Centre for Neuromuscular Disorders, Messina, Italy

[7] Unit of Neurology and Neuromuscular Diseases, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

Abbreviations

ALS	Amyotrophic lateral sclerosis
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
AT	Ataxia telangiectasia
CNS	Central nervous system
CPEF	Cough peak expiratory flow
DM	Dermatomyositis
DM1	Myotonic dystrophy type 1
DMD	Duchenne muscular dystrophy
ER	Emergency room
ETI	Endotracheal intubation
FSHD	Facioscapulohumeral muscular dystrophy
FVC	Forced vital capacity
GBS	Guillain–Barré syndrome
GCS	Glasgow coma scale
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
IOPD	Infantile-onset Pompe disease

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MG	Myasthenia gravis
MIP	Maximum inspiratory pressure
NIV	Noninvasive ventilation
NMDs	Neuromuscular disorders
PD	Parkinson's disease
PM	Polymyositis
RF	Respiratory failure
SCI	Spinal cord injury
SE	Status epilepticus
SMA	Spinal muscular atrophy
TBI	Traumatic brain injury
UAO	Upper airway obstruction

Introduction

Severe cerebrovascular diseases, traumatic injuries of brain and spinal cord, and other toxic, dysmetabolic, infectious, inflammatory, or degenerative diseases involving the central nervous system (CNS) can trigger hypoxic and/or hypercapnic respiratory failure (RF) directly or through major pulmonary complications such as pneumonia, pulmonary edema, and traumatic pneumothorax [1]. Acute respiratory failure (ARF) may often occur in patients with acute or chronic neuromuscular diseases (NMDs) such as Guillain–Barré syndrome (GBS), amyotrophic lateral sclerosis (ALS), myasthenia gravis (MG), spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD), polymyositis (PM), or dermatomyositis (DM). In these patients, weakness of diaphragm, intercostal and expiratory muscles, or concomitant pulmonary complications due to oropharyngeal dysfunction causing aspiration of secretions/food/drink or inefficient cough may lead to respiratory emergencies [2]. In all these neurological disorders, respiratory involvement may increase the burden of the existing disease and mortality.

Respiratory emergencies in neurological diseases may occur at onset or more often along the chronic course of the disease. Emergency room (ER) physicians and consultant neurologists must be aware of the respiratory risks of such patients, be able to recognize early signs, and take action to treat RF adequately. In this context, a competent multidisciplinary team is fundamental including pneumologist, anesthetist, nurse, physical therapist, and speech therapist. Indeed, these cases not infrequently represent a diagnostic challenge in the acute care settings, especially in a busy ER, because of patients' poor ability to communicate and scanty experience of health professionals in caring for patients with neurological diseases [3, 4]. Furthermore, increase in survival of patients with SMA and DMD has emphasized the need for a smooth and successful transition from pediatric to adult healthcare [5, 6]. Unfortunately, many healthcare services are not equipped to provide modified age-appropriate assistance and expertise. This is particularly true at ER, leading to an inadequate medical approach and patients' and caregivers' apprehensiveness with loss of the sense of health protection [7, 8].

This review aims to update and provide practical recommendations to the professionals in emergency medical services for recognition, management, and treatment of respiratory emergencies in neurological diseases mostly occurring in teenagers and adults. Some preventive measures are also reported to decrease morbidity and mortality.

Pathophysiology of respiratory failure

RF is a syndrome in which the respiratory system fails in one or both of its gas exchange functions: oxygenation and carbon dioxide (CO_2) elimination. In practice, patients with RF can be categorized as those with primarily impairment of gas exchange due to intrinsic lung/airways disease, leading to hypoxemic RF ("lung failure"), and those with lung ventilation impairment on the basis of ventilatory pump disorders, leading to hypercapnic RF ("pump failure"). Patients with neurological disease more commonly develop primarily ventilatory impairment causing CO_2 retention, although the probability of occurrence can be different, depending on baseline disease.

Respiratory muscle weakness, defined as the inability of the rested respiratory muscles to generate normal levels of pressure and flow during inspiration and expiration, is a common occurrence in patients with neuropathies or myopathies and provides the condition for the development of acute ventilatory failure [9]. As chest wall and pulmonary compliance may be reduced, mechanical load on weakened respiratory muscles (in particular the diaphragm) can be increased. An imbalance between load and capacity leads to muscle fatigue, which in turn elicits an increase in minute ventilation and respiratory rate and, to a lesser degree, a reduction in tidal volume ("rapid shallow breathing"), causing hypoventilation and ARF [10, 11].

Respiratory muscle weakness is frequently undetected in patients with neurological disease until ventilatory failure is precipitated by aspiration pneumonia or respiratory tract infection [12]. At onset, ventilatory insufficiency leading to failure may only be nocturnal and results from diaphragm failure, with the patient unable to breathe when supine, or from severe generalized respiratory muscle dysfunction. Due to the inadequacy of inspiratory muscle function, a well-known pattern of restrictive ventilatory defect can be detected by pulmonary function tests, with reduced forced vital capacity (FVC).

Effective cough requires deep inspiration followed by glottis closure and appropriate expiratory muscle strength to generate sufficient intrathoracic pressure and obtain high expiratory flows. Clearing airway secretions and airway mucus can be a continual problem for patients with generalized muscle weakness and for those who cannot swallow saliva or food without aspiration. Indeed, in patients with neurological

disorders, inadequate bulbar and expiratory muscle function may cause retained secretions, frequently complicated by pneumonia, atelectasis, and, ultimately, hypoxemic ARF. These conditions can result in hospitalizations, endotracheal intubations, tracheostomy, and death [13]. In rapidly progressing NMDs, ARF due to accumulation of lung secretions ("lung failure") can be the earliest symptom [14]. Cough peak expiratory flow (CPEF) is a measure of the maximum airflow generated during cough and is normally 360 to 1200 L / min; of interest, CPEF may provide valuable information on the ability to clear airway secretions, with values below 160 L/min usually indicating the need for tracheal suctioning and an increased risk of mucous encumbrance at the onset of respiratory infections, contributing to the development of atelectasis and acute hypoxemia [15].

In conditions such as severe brain injury due to stroke or trauma, spinal cord injury, multiple sclerosis, tetanus, botulism, GBS, and autonomic nervous system dysfunction may contribute to respiratory complications. They may be the effect of a reduction of airways vagal tone, a decreased bronchodilator effect of anticholinergic drugs, and a diminished ventilatory response to hypoxia and hypercapnia probably caused by dysfunction of aortic and carotid sinus mechanoreceptor transmission [16].

Neurological diseases and acute respiratory involvement

Stroke

After a stroke, the loss of ability to generate normal amounts of force is a major contributor to activity limitation and participation restriction. Weakness after stroke also affects muscles of the respiratory system, and patients typically have altered breathing control, reduced maximal voluntary strength, and decreased endurance of inspiratory and expiratory muscles, as well as altered chest wall kinematics [17, 18]. Associated factors may be impaired vigilance, inefficient cough, aspiration, acute lung injury/acute respiratory distress syndrome (ARDS), pulmonary embolus, and pulmonary edema (neurogenic or cardiogenic) [19]. The risk of respiratory impairment associated to large hemispheric stroke increases after a few days' delay, as cerebral edema intensifies. Sustained hyperventilation in a patient with mass effect can be a manifestation of diencephalic herniation. Ataxic or cluster breathing patterns can be part of brainstem syndromes, and recurrent apnea is a warning sign in patients with basilar artery occlusion. Cheyne–Stokes breathing, characterized by oscillating cycles of hyperpnea alternating with periods of apnea, is a frequent finding after massive hemispheric stroke [20]. Chest infections, such as pneumonia, are the most frequent complications of stroke and occur in up to one-third of patients, resulting in up to a threefold increased risk of death in the first 30 days, longer hospital stay, and poorer post-discharge outcomes [21].

Convulsive status epilepticus

Status epilepticus (SE) is a neurological emergency with high morbidity and mortality requiring neurointensive care and treatment of systemic complications. The estimated annual incidence of SE varies according to studies, with values ranging between 9.9 and 41/100,000 inhabitants. ARF is a frequent complication (about 80%) [22]. It is caused not only by the disease itself but also by the drugs used to treat SE. Aspiration pneumonia is frequent as airway protective reflexes decrease. Another possible respiratory complication is neurogenic pulmonary edema [23].

Traumatic brain injury

Traumatic brain injury (TBI) represents a leading cause of death and disability in adults, thus engaging considerable resources in the health system. ARF is frequent mainly because of airway protective reflex decrease, impaired cough, and altered breathing control. All these factors are related to the severity of consciousness reduction. The incidence of ARF associated with TBI has decreased over the last decade due to improvements in extra- and intrahospital management. However, it still remains one of the main causes of morbidity and mortality, and the incidence of residual respiratory failure at the end of acute hospitalization is approximately 32% [24, 25].

Spinal cord injury

Respiratory complications are the foremost causes of increased morbidity and mortality after spinal cord injury (SCI), with an incidence of 36% to 83%. The pathophysiology is complex, with the level and completeness of phrenic nucleus injury at C3-C5 level with diaphragm paralysis being the greatest determinant. Full cervical lesions (C2-C4) in the absence of mechanical ventilation are incompatible with life. Cervical lesions under C5 (C5-C8) determine weakness or paralysis only of the intercostal and abdominal muscles. In these cases, the diaphragm is preserved, and spontaneous ventilation is usually maintained. Other responsible factors are accessory muscle weakness due to T1-T12 level injury and abdominal muscle involvement due to T5-T12 injury, impaired cough, decreased surfactant production, and increased secretions and bronchospasm due to unopposed vagal activity (C8-L2 sympathetic nerve injury) [26].

Patients may rapidly deteriorate with the need for urgent intubation [27]. In a large prospective study, 67% of 261 acutely injured subjects experienced severe respiratory

complications. Atelectasis (36.4%), pneumonia (31.4%), and ventilatory failure (22.6%) were the most common complications. Ventilatory failure and impaired cough are the main causes of RF. Other responsible factors are pulmonary edema and pneumohemothorax. Ventilatory failure lasted an average of 5 weeks [28]. Transfer to an SCI center specializing in acute management of tetraplegia may significantly reduce the number of respiratory complications.

Inflammatory and infectious diseases of the CNS

Inflammatory and infectious diseases of the CNS are a very heterogeneous group of diseases that can affect CNS function with different patterns of symptoms and signs. Pulmonary complications are related to an altered breathing control system, severity of associated reduction of consciousness, and involvement of respiratory muscles. Pulmonary impairments have long been recognized as major causes of morbidity and mortality in individuals with advanced multiple sclerosis, due to acute or chronic respiratory disorders. Chronic RF involves bulbar dysfunction with swallowing disorders, altered central respiratory drive, motor disorders following corticospinal lesions, or sleep-disordered breathing. Acute conditions mainly involve spinal or bulbar relapse with extensive plaques, neurogenic pulmonary edema, or ARF, often following sepsis [29]. Common pulmonary-related complications in encephalitis are poor gag reflex, pooling of secretion, and loss of swallowing, with risk of aspiration pneumonia and RF development [30].

Parkinson's disease

Rigidity and hypokinesia of both the upper airway and the chest wall are thought to contribute to upper airway obstruction (UAO) in patients with Parkinson's disease (PD). Restrictive changes are also a common functional abnormality, due to loss of chest wall compliance secondary to severe rigidity [31]. A reduced ventilatory response to hypoxia and hypercapnia related to low ventilatory chemosensitivity and autonomic dysfunction may contribute to the development of ARF [32]. Swallowing impairment exposes PD patients to high risk of aspiration pneumonia that is enhanced by weak cough due to chest wall rigidity, dyskinesia, and upper airway dysfunction. Pneumonia remains the most common frequent cause of death despite the development of effective therapeutic regimen over the past three decades [33]. Although levodopa is the main treatment for PD, improving respiratory and motor functions, development of dyskinesias may affect ventilation inducing dyspnea and chest pain. Moreover, in advanced patients, wearing-off phenomenon may induce pulmonary complaints such as stridor due to UAO and dyspnea due to chest wall tightness.

Ataxias

Subclinical restrictive type of pulmonary dysfunction is present in spinocerebellar ataxias with possible UAO [34]. Particularly in ataxia telangiectasia (AT), respiratory complications may account for 1/3 of deaths. Secondary effects of AT on the lung are related to suboptimal muscle strength due to coordination problem, impaired airway clearance due to weak cough, and abnormal swallow and aspiration [35]. Pulmonary infections are the major cause of RF and death, and associated immune defect can facilitate respiratory infection and contribute to bronchiectasis development. An early diagnosis of pulmonary complications in AT patients is mandatory to significantly reduce morbidity and mortality [36].

Tetanus and botulism

The World Health Organization has announced that in the 2007–2017, period the total number of reported cases of tetanus was 12,000–20,000 cases per year. Tetanus is acquired through the infection of a cut or wound with the spores of the anaerobic bacterium *Clostridium tetani*, and most cases occur within 14 days after initial infection. Spasms and stiffness are hallmarks of the disease. If not treated in time with tetanus immunoglobulins and hospitalization in an intensive setting, it leads to death due to RF in 100% of cases. There is an increased risk of tetanus in adult males and adolescents undergoing circumcision due to decreasing immunity and limited opportunities to receive booster doses in many countries [37, 38].

Botulism is a serious disease caused by a nerve toxin produced by the anaerobic, spore-producing *Clostridium botulinum*, which inhibits the release of acetylcholine at the presynaptic level. Three forms of botulism are distinguished according to the site of production of toxins: food, injury, and intestinal botulism (infant and adult). Clinical manifestations include bulbar symptoms, nasal voice, blurred vision, ophthalmoparesis, and autonomic dysfunctions such as dry mouth, constipations, and urinary retention. In Europe, in the 2007–2017 period, 84 to 125 cases per year were reported, with a mortality rate of 3–9%. Like tetanus, it leads to death due to RF if not treated in time with botulism immunoglobulins and hospitalization in an intensive care unit (ICU). Correct and timely recognition of the infection significantly reduces mortality [39, 40].

Neuromuscular disorders

NMDs are a heterogeneous group of disorders characterized by impairment at the level of motor neurons, peripheral nerve, neuromuscular junction, or skeletal muscle. They include acquired or inherited forms, with very variable age and clinical features at onset and very different courses and prognoses. If

muscle weakness involves the diaphragm and accessory respiratory muscles, it leads to RF more or less early in the patient's life, often also facilitated by a severe scoliosis [41]. Table 1 lists the NMDs constantly associated with very early RF. Table 2 reports the NMDs in which RF develops with a slowly progressive course, requiring ventilatory support at a variable age, and with different rates of occurrence [42–44].

Restrictive RF is the leading cause of death in ALS patients [45]; in some cases it may represent its onset. SMA has a significant impact on the respiratory system, depending on the severity of loss of muscle function [5]. SMA type 1 (non-sitters) and type 2 (sitters) patients need more active surveillance and management, whereas a minority of ambulant SMA type 3 patients (walkers) may have decreased cough effectiveness with upper respiratory infections, sleep apnea, or hypoventilation.

Among acquired polyneuropathies, patients with GBS are often at risk of RF. Predictors are rapid course, severe muscle weakness at hospital admission, bulbar or neck weakness, bilateral facial weakness, or dysautonomia [46]. Respiratory involvement is rare in Charcot–Marie–Tooth disease [47].

MG often causes hypercapnic RF as a manifestation of the disease onset, being diagnosed in the ER or in ICU [41, 48]. Congenital myasthenic syndromes may sometimes present life-threatening respiratory episodes especially in the first decade of life [49].

The group of myopathies at risk of respiratory emergencies is more complex, including dozens of partly overlapping phenotypes, caused by mutations of different genes, and acquired inflammatory forms such as PM and DM. Dystrophinopathies (especially DMD) invariably need a ventilatory support therapy from a young age [50]. Other myopathies at risk are some limb-girdle muscular dystrophies (especially sarcoglycanopathies) and myotonic dystrophy type 1 (DM1). The latter is a complex multi-systemic disease, in which cardiomyopathy and disturbances of central breathing regulation coexist, which make ventilatory management difficult [51]. The autosomal dominant facioscapulohumeral muscular dystrophy (FSHD), related to the 4q region, may develop ARDS generally in early-onset cases [52]. Among metabolic myopathies, Pompe disease caused by mutations of the acid alpha glucosidase enzyme gene is still at risk of RF, despite the availability of enzyme replacement therapy for over 10 years. About a third of cases with infantile-onset (IOPD) in the first year of life require ventilatory support, as well as a minority of cases with adult form [53]. Some adults start with dyspnea and hypercapnic RF and can be diagnosed after acute ventilatory failure. However, all patients should be carefully monitored for respiratory function. Acute or subacute inflammatory myopathies, especially the autoimmune necrotizing myopathies with positive anti-SRP antibodies, can rapidly evolve into respiratory emergencies.

When physicians working in the ER meet a patient with hypercapnic RF, they must always try to gather detailed information on the exact type of neuromuscular disease already diagnosed, since prognosis and treatment may greatly differ. Furthermore, some patients with NMDs may present with

Table 1 Neuromuscular disorders with respiratory failure at birth or within the first year of life

Spinal muscular atrophy type 1 (SMA1)
Spinal muscular atrophy with respiratory distress (SMARD)
Congenital myotonic dystrophy (CDM)
Infantile-onset Pompe disease (IOPD)
Some mitochondrial diseases
Some congenital myopathies
Some congenital muscular dystrophies
Some congenital myasthenic syndromes
Neonatal myasthenia gravis (transient)

Table 2 Neuromuscular disorders with chronic respiratory failure in infant-to-adult life

Rate of occurrence of respiratory failure	Diseases
Unavoidable	Duchenne muscular dystrophy (DMD) Amyotrophic lateral sclerosis (ALS) Some muscular dystrophies (e.g., sarcoglycanopathies) Some myofibrillar myopathies (e.g., HMERF)
Frequent	Spinal muscular atrophy type 2 (SMA2) Myotonic dystrophy type 1 (DM1) Late-onset Pompe disease (LOPD) Guillain–Barré syndrome (GBS) Myasthenia gravis (MG) Facioscapulohumeral muscular dystrophy (FSHD) Some congenital muscular dystrophies (e.g., Ullrich CMD) Some limb-girdle muscular dystrophies (LGMD) (e.g., calpainopathy, FKRP) Some congenital myopathies (e.g., centronuclear myopathy) Congenital myasthenic syndromes
Occasional	Becker muscular dystrophy (BMD) Some types of Charcot–Marie–Tooth disease (e.g., CMT type 1B and 4) Inflammatory myopathies Spinal muscular atrophy type 3 (SMA3) Some congenital myopathies Some mitochondrial diseases
Rare	Oculopharyngeal muscular dystrophy (OPMD) CMT Chronic inflammatory demyelinating polyneuropathy (CIDP)

acute or subacute RF even before significant limb muscle weakness (Table 3).

Clinical management and treatment

Acute respiratory failure in slowly progressive neurological diseases

Movement disorders

Although advice on the management of ARF in PD is difficult, due to varying and conflicting results of previous studies, a contraindication to noninvasive ventilation (NIV) may exist in the acute setting, and positive pressure ventilation via endotracheal intubation (ETI) may constitute the only choice for treating patients who require ventilatory support. Moreover, abnormally reduced vocal cord movement amplitude, laryngeal tremor, and oropharyngeal dysfunction can produce UAO, which in turn can be associated with difficult intubation and require *bronchoscopy* assistance during the procedure [54].

At ER admission, patients with myoclonus may necessitate invasive mechanical ventilation (IMV) via ETI, in the event of ARDS [55].

In patients with Huntington's disease, death usually results from respiratory complications, in particular aspiration pneumonia which accounts for approximately 55% of deaths, followed by "suffocation" and pulmonary embolism [56]. As these patients commonly suffer from severe dysphagia, ETI and IMV are suggested at the onset of ARF requiring ventilator support, to protect the airways from the risk of inhalation.

Neuromuscular disorders

Development of respiratory infections may be a life-threatening event in NMDs patients, favored by mucous encumbrance and further weakening of respiratory muscles, which lead to ARF [13, 57]. Additionally, several myopathies are associated with cardiac dysfunction such as dilated cardiomyopathy [58], which may contribute to the development of ARF, leading to cardiogenic pulmonary edema (Table 4). Finally, pneumothorax, fat embolism, and abuse of sedative drugs are rare but serious, life-threatening complications in these patients.

The identification of subjects at high risk of RF and timely provision of inspiratory (i.e., NIV) and expiratory aids (i.e., manual and mechanical cough assistance) are critical for preventing severe complications [15, 59–61]. It follows that a proactive clinical approach should be taken to recognize pulmonary problems prior to the onset of respiratory compromise (Table 5). In these patients, the best and easiest parameter used to monitor respiratory muscle strength is FVC. Patients who have an FVC < 50% of predicted value should be trained in protocols that allow successful home treatment managed by well-trained family members or healthcare professionals during respiratory exacerbations [50, 62].

In the case of ARF, the patients should receive 24-h NIV and pulse oximetry monitoring. When oxygen saturation on room air falls below 95%, secretion removal should be aggressively induced using manual and mechanical cough assistance until oxygen saturation returns to the 95% range. Oxygen should not be used to correct hypoxemia, as it can worsen hypercapnia and does not allow the recognition of severe hypercapnia with the pulse oximetry. A dramatic reduction in the need for hospitalization and a prolongation of life expectancy have been reported in well-trained patients [13, 15]. Moreover, services providing active treatment by healthcare professionals at a patient's home are an effective alternative to hospital admission [62]. Additionally, in the case of suspected respiratory infections, early use of antibiotics is mandatory, in particular if pulse oximetry is below 95% in room air (Table 6).

If home respiratory management fails, patients must be hospitalized, NIV remaining the first-line ventilator strategy. Moreover, if bronchial encumbrance is present, cough assistance must be applied aggressively. Patient selection is very important to the success of this noninvasive strategy. Severe bulbar dysfunction increases patient risk for aspiration, hampers the elimination of airway secretions, and increases resistance to airflow impeding successful use of NIV [59, 63]. Moreover, the use of noninvasive strategies should never delay ETI for patients where this approach has failed [42].

To receive close monitoring and aggressive noninvasive respiratory assistance, patients should be placed in a unit where nurses are adequately trained and a physician is physically present on-site 24 hours a day. Monitoring must be tailored and personalized according to the clinical severity of each case, but it must include $PaCO_2$ measurements if supplemental oxygen is used to correct hypoxemia (i.e., capillary CO_2 in less severe diseases and indwelling arterial line in most severe cases) [42, 64].

If NIV fails or is contraindicated (Table 7), patients with progressive NMDs should be intubated as a short-term measure. In this case, appropriate assessment for a difficult intubation due to reduced mouth opening, macroglossia, or to limited mobility of the cervical spine is very important. If

Table 3 Adult neuromuscular disorders which may present with respiratory failure at onset

ALS
Pompe disease
DM1
Myofibrillar myopathies
Some LGMD (e.g., type 2I)

t4.1 **Table 4** Neuromuscular disorders associated to cardiomyopathy

Neuromuscular disorder	Cardiac disorder
DMD, BMD	Dilated cardiomyopathy (more frequent), conduction disorders, arrhythmias
Limb-girdle muscular dystrophies (rare)	Conduction disorders and arrhythmias (more frequent), dilated cardiomyopathy
Myotonic dystrophy	
Emery–Dreifuss muscular dystrophy	
Myofibrillar myopathies	Conduction disorders and arrhythmias (more frequent), hypertrophic cardiomyopathy, noncompacted myocardium, dilated cardiomyopathy
Mitochondrial myopathies	
Pompe disease	Hypertrophic cardiomyopathy (in IOPD)
Lipid storage myopathies	Dilated cardiomyopathy, hypertrophic cardiomyopathy

any conditions predicting difficult airway management are present, intubation should be performed considering applicable guidelines and avoiding emergent intubation [65].

After recovery from the acute illness, these patients should be promptly extubated. Unfortunately, because of respiratory muscles weakness and inability to handle bronchial secretions, a substantial proportion of patients fail to pass spontaneous breathing trials [66]. Preventive application of NIV combined with assisted coughing after extubation provides a clinically important advantage by averting the need for reintubation and shortening the ICU stay. Indications for a tracheotomy can be evaluated, but it should not be considered in the acute phase, rather only in the case of multiple failures of weaning protocol [67, 68].

De novo acute respiratory failure

Stroke

Following stroke, hypocapnia is associated with poor outcome [69]. Current guidelines produced by European Stroke Organization, American Stroke Association, and National Institute for Health and Care Excellence support oxygen supplementation if SpO_2 falls below 94%. Although, to date, no trial has tested its utility in severe stroke, IMV via ETI is indicated in conditions such as decreased consciousness level (Glasgow Coma Scale, GCS, ≤ 8), evidence of brainstem dysfunction, or any other cause of a threatened airway, to prevent aspiration pneumonia, in the event of ARF due to pulmonary edema (neurogenic or cardiogenic), generalized seizures or status epilepticus, and apneic episodes [19]. Due to the risk of rapid variation of the patient's *clinical status*, continuous monitoring of systemic oxygenation through pulse oximetry is essential. Mechanically ventilated patients should undergo regular arterial blood gas monitoring. The mortality rate of patients with stroke undergoing ETI has been variously reported to be between 40 and 80% regardless of the causes of intubation, with only about 50% surviving 30 days and 30% surviving 1 year [70]. Predictors of death include low GCS at intubation and absent pupillary light reflexes. 15–35 % of stroke patients admitted at the ICU require tracheostomy for difficult weaning. Patients who survive may achieve good functional outcome, with more than two-thirds regaining normal activities of daily living [71].

t5.1 **Table 5** Causes of ARF in patients with chronic neuromuscular disorders

t5.2	Common	Upper respiratory tract infections (influenza, parainfluenza, bacterial infections)
t5.3	Less common	Community-acquired pneumonia Ventilator-associated pneumonia Aspiration pneumonia Atelectasis
t5.4	Uncommon	Cardiogenic pulmonary edema Pneumothorax Lung adipose embolism (in case of bone fractures) Drug abuse or overdose (e.g., benzodiazepines, opiates, alcohol, anesthetics) Pulmonary embolism Tracheo-arterial fistula Gastric or colonic bloating

Convulsive status epilepticus

ETI and IMV allow to maintain the normocapnia and normoxia, to prevent pulmonary aspiration, and also to use intravenous anesthetics to treat epilepsy. Delay in intubation is associated with increased mortality. Therefore, ETI can be avoided only if recovery of consciousness is rapid [72].

Traumatic brain injury

In severe TBI (GCS < 9), reduced morbidity and mortality are obtained avoiding secondary brain damage due to low blood pressure, intracranial hypertension, hypoxemia, and hypercapnia. For these reasons, the patient must be intubated, and IMV must be set to maintain

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t6.1 **Table 6** Recommendations for home management of an infectious acute respiratory disease

t6.2	• During the infectious exacerbation, the value of SaO_2 should be continuously monitored using the pulse oximeter with the aim of maintaining an SaO_2 ideally > 95% or at least > 92% in ambient air
t6.3	• It may be necessary to use the ventilator 24 hours a day to avoid hypoventilation and/or SaO_2 < 95%
t6.4	• To avoid the development of pressure sores in the support points of the mask, the use of two different masks should be alternated, and hydrocolloid patches should be used to protect the support points
t6.5	• To reduce dyspnea and enhance the value of SaO_2, the caregiver can increase the respiratory rate by 2–4 points, the positive end-expiratory pressure (PEEP) by 1–2 points, and, in the case of pressometric ventilation, the inspiratory pressure by 1–2 points. To avoid gastric distension, maximum pressure in the airways should not rise above 25 cm H_2O
t6.6	• When the value of SaO_2 falls below 95%, especially when the presence of bronchial secretions is suspected from chest auscultation or due to a sudden change in the parameters of the ventilator (e.g., in the case of reduction of tidal volume if in pressometric ventilation or increase in peak pressure if in volumetric ventilation), manual and/or mechanical cough assistance techniques must be used. In preschool children and in patients with severe dysphagia, it is useful, immediately after using the cough machine, to perform secretion aspiration in the oropharynx with the aid of a mechanical aspirator
t6.7	• To avoid severe desaturation, O_2 can be used but only for short periods (e.g., a few minutes before performing cough assistance maneuvers and/or immediately after). For this purpose, the oxygen source must be connected to the ventilator. However, O_2 must never be used without associating it with NIV
t6.8	• Each febrile episode > 38.5 ° C must be treated with paracetamol and a valid hydration protocol
t6.9	• An antibiotic should be used early, especially if SaO_2 < 95%. It is important that the antibiotic coverage includes atypical bacteria (macrolide or fluoroquinolone). In case of possible inhalation (e.g., in patients with severe dysphagia), a second antibiotic should be associated covering anaerobic bacteria (e.g., amoxicillin associated with clavulanic acid)
t6.10	• In the case of a respiratory tract infection managed at home, a specialist or a general practitioner should visit the patient ideally once a day or at least every 2–3 days. This care is mainly aimed at prescribing antibiotic therapy and excluding the presence of hospital admission criteria. It is desirable that the general practitioner maintains telephone contact with a specialist who is competent in home ventilation in order to share the decision-making process
t6.11	• Hospital admission is recommended if one or more of the following are present:
t6.12	- Desaturation < 92% in ambient air
t6.13	- Need to use O_2 to maintain SaO_2 > 92%
t6.14	- Persistence of dyspnea despite the use of a ventilator
t6.15	- Severe dehydration
t6.16	- High fever unresponsive to antipyretics and antibiotics
t6.17	- No response after 1 week of application of the protocol
t6.18	- Suspected pneumothorax
t6.19	- Suspected cardiogenic pulmonary edema
t6.20	- Suspected pulmonary embolism

Table 7 Contraindications to NIV t7.1

Uncooperative patient	t7.2
Reduced level of consciousness	t7.3
Delirium with restlessness or agitation	t7.4
Severe dysphagia	t7.5
Excessive secretions not managed by mechanical cough assistance	t7.6
Severe hypoxemia (PaO_2 < 60 mmHg with FiO_2 > 0.6)	t7.7
Undrained pneumothorax	t7.8
Coexistence of two other organ failures	t7.9

normal capnia and oxygenation, to allow the patient to be sedated, reducing intracranial pressure and preventing pulmonary aspiration [73]. Moreover, patients with TBI frequently suffer from lung complications and ARDS, which can be multi-etiological (i.e., aspiration pneumonia, pulmonary contusion related to chest trauma, neurogenic pulmonary edema, transfusion-related acute lung injury). These complications represent a further indication for IMV. Unfortunately, ventilator strategies can have effect on cerebral perfusion and represent a potential burden for iatrogenic secondary brain damage [74]. In particular, when a concomitance of TBI and ARDS occurs, the ventilatory management can be very challenging as ventilatory targets are often in conflict among each other. Ventilator strategies commonly used in patients with ARDS induce a relevant increase in intrathoracic pressures, which may reduce cerebral venous return to the right atrium. This phenomenon may cause a significant increase in intracranial pressure and a harmful decrease in cerebral perfusion. In order to avoid iatrogenic secondary brain damage due to these mechanical ventilation consequences on cerebral dynamics, intracranial pressure monitoring is indicated [75].

Spinal cord injury

ETI and IMV are always required in patients with complete lesion above C5, while intubation can be avoided in patients with incomplete injury and lesion below C5. In these patients, to assess the need for invasive or noninvasive ventilatory assistance, it is essential to monitor not only pulse-oximetry but also CO_2, vital capacity and maximum inspiratory pressure (MIP). A reduction in vital capacity to below 15 mL/kg, a maximum inspiratory pressure below − 20 cm H_2O, and an increase in pCO_2 are markers for the need for mechanical ventilation [76]. In the first year after cervical injury, respiratory function may improve spontaneously, often allowing weaning from mechanical ventilation. However, after the first year, improvements in respiratory function are usually minimal or absent.

Diaphragm paralysis

Phrenic neuropathies are a significant cause of respiratory dysfunction. Phrenic neuropathy has been associated with a variety of causes (e.g., brachial plexopathy, infections, amiodarone, chemotherapy agents, thymectomy, cardiac surgery, thoracotomy, internal jugular catheter insertion, interscalene block). However, in many patients, the cause of phrenic nerve damage remains unclear (idiopathic phrenic neuropathy) [77].

Patients with unilateral diaphragm paralysis are often asymptomatic but may develop dyspnea on exertion or when they are supine, particularly if there is abdominal distension (e.g., obesity or pregnancy), or in the case of coexisting heart or lung disease. In the asymptomatic patients, unilateral diaphragm paralysis may be discovered as an incidental radiographic finding of an elevated hemidiaphragm [78]. Patients with bilateral diaphragmatic paralysis develop severe orthopnea with a supine drop in forced vital capacity of more than 30% and progressive nocturnal hypoventilation, which may culminate in acute presentation with hypercapnic RF [79].

Neuromuscular disorders

Myasthenic crisis is observed in approximately 20% of MG patients and may result in ARF caused by the combination of upper airway obstruction and acute hypoventilation due to incapacitating weakness of both bulbar and inspiratory muscles [80]. The evidence for use of invasive ventilation via ETI is strong and has been recommended in most of the series published so far; a mortality rate in patients receiving invasive ventilation has been reported between 4 and 6%. Extubation may fail in up to one quarter of patients, and presence of atelectasis has been reported to be strongly associated with extubation failure [81]. Although NIV may be inappropriate in patients with ARF unless upper airway function is well preserved, this option seems desirable in patients with myasthenic crisis because of the increased risk of prolonged IMV complicated with ventilator-associated pneumonia and other systemic complications [82, 83]. Administering NIV with a relatively low inspiratory-pressure range of 10–16 cm H_2O can be effective in preventing the need for ETI in these patients. Severe hypercapnia ($PaCO_2$ > 50 mmHg) and high serum bicarbonate concentration at admission have been considered predictors of NIV failure [1, 84].

In order to early identify GBS patients at risk for ARF requiring ventilatory support, the "20/30/40 rule" has been proposed: intubation is indicated if the FVC < 20 mL/kg, the MIP < 30 cm H_2O, and the maximal expiratory pressure (MEP) < 40 cm H_2O [9]. The application of NIV in GBS patients is not a safe option for several reasons: (a) patients usually remain extremely weak and require full ventilator assistance for many days, and (b) the manifestations of dysautonomia get worse as RF becomes more severe. Between 25 and 50% of patients require ETI and IMV [85]. Moreover, emergency intubation should be avoided because it can induce life-threatening complications from dysautonomia, including labile blood pressure, cardiac arrhythmias, and fatal hyperkalemia with the use of succinylcholine. The mortality rate of severe GBS causing neuromuscular ARF may still reach 5–10%; in addition, 20% of survivors may suffer from long-term disability [86].

Conclusions

The management of ARF in patients with neurological diseases is a strong challenge and frequently occurs in the ICU setting, a neurological ward, or even at home. Treatment must be tailored on a personalized level by an expert neurointensivist, considering all the past medical history as well as concomitant medical events. Moreover, in the recent years, intensive care medicine has progressed considerably, and new technologies continuously improve ventilatory treatment and survival [87]. In the case of risk of acute-on-chronic RF, appropriate education of caregivers and periodic follow-up are necessary to optimize domiciliary assistance and to remove barriers to its application [88, 89].

Although standards of care have been identified for many acute and chronic NMDs requiring appropriate management of ARF and many guidelines have been elaborated, there are no randomized trials assessing the practice for the use of non-invasive versus invasive mechanical ventilation [90]. There is much work yet to be done in designing and conducting clinical trials to provide evidence-based data to anticipate variations in treatment responses according to disease, onset type (acute onset versus acute exacerbations on chronic NMDs), and presence or absence of bulbar dysfunction.

Finally, increasing recognition of e-health technologies as potential tools in enhancing healthcare quality has recently led to the proposal of innovative technologies and tele-monitoring assistance in the respiratory care of NMDs patients [91, 92]. Although these are pilot applications, encouraging results have been provided, and further studies involving larger cohorts and multidisciplinary teams are needed with the final aim to prevent acute respiratory events.

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