

Chronic Respiratory Failure and Neuromuscular Disease

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KEYWORDS

- Noninvasive ventilation • Neuromuscular disease
- Respiratory failure • Child health • Pathophysiology

Over the past 2 decades, there have been significant developments in the understanding of the pathophysiology and management of respiratory complications of neuromuscular disorders (NMDs) in children, resulting in an increase in life expectancy, reduction in hospital admissions, and increase in the quality of life for the patient and his or her caregivers. A major driver of these changes has been the availability of sophisticated technology to investigate and treat affected children. Other important factors include recognition that affected children require close monitoring by a well-coordinated multidisciplinary team, timely use of airway clearance techniques, improved recognition of those at risk for respiratory failure, and the provision of noninvasive ventilation (NIV) for those in respiratory failure. Expert assessment and management of orthopedic, nutritional, and cardiac complications of NMDs have also added to improved prognosis (**Table 1**).

Despite advances in clinical practice and undoubtedly improved prognosis, the evidence on which some management principles are based is relatively sparse, with the number of consensus statements on the use of NIV in children exceeding that of randomized trials of its use. There is, however, no doubt that the outlook for a child with significant respiratory muscle weakness in this decade is markedly improved, with the mean age of survival in Duchenne muscular dystrophy (DMD) increasing by 30% from 19 to 25 years.¹ Even for those with the most severe disorder, type 1 spinal muscular atrophy (SMA-1), the prognosis for those treated in some specialized

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Table 1 Grading of evidence of interventions in respiratory care of children who have neuromuscular disorders			
Assessment/Intervention	Recommendation	Grading of Recommendation	Quality of Supporting Evidence
Symptoms or signs of respiratory failure	Close clinical monitoring of patient	Strong	Strong
FVC <1 L	Urgent respiratory review because survival risk is poor, NIV if not previously started	Strong	Moderate
FVC <40% indicative of nocturnal hypoventilation	Refer for sleep study or polysomnogram	Strong	Weak
Maximal inspiratory pressure <40 cm H ₂ O	Polysomnogram with evaluation of day/night CO ₂ levels	Moderate	Weak
Peak cough flows (PCFs) <270 L/min in older children	Monitor patient closely because there is a risk for respiratory failure with LRTI	Strong	Strong
When wheelchair bound	Overnight sleep monitoring	Moderate	Weak
Intervention: supplemental oxygen	Not recommended	Strong	Moderate
If upper airway obstruction but not significant respiratory muscle weakness	Adenotonsillectomy (or CPAP if no adenotonsillar hypertrophy)	Moderate	Weak
If acute respiratory failure or chronic or nocturnal and diurnal hypercarbia	NIV	Strong	Moderate

Abbreviations: CO₂, carbon dioxide; CPAP, continuous positive airway pressure; FVC, forced vital capacity; LRTI, lower respiratory tract infection; PCF, peak cough flow.

centers has improved from 9.6 ± 4.0 months of age to 65.2 ± 45.8 months of age (range: 11–153 months).² The increase in longevity has and is bringing its own challenges to patients, caregivers, and the health system.³ The picture is further complicated by variation in service provision between and within countries based on available resources and different ethical views.

The primary purpose of this article is to review the principles of pathophysiology, investigation, and management of the respiratory complications of children with NMDs. The management of orthopedic, nutritional, and cardiac complications is not within the remit of this review. NMDs of childhood can be broadly classified into muscular dystrophies, metabolic and congenital myopathies, anterior horn cell disorders, peripheral neuropathies, and diseases affecting the neuromuscular junction. The two disorders that are the most common and exemplify the important principles of assessment, investigation, and management that apply to all these disorders are DMD and SMA. This review concentrates on these two conditions.

PHYSIOLOGIC EFFECTS OF RESPIRATORY MUSCLE WEAKNESS

Understanding the physiologic sequelae of evolving respiratory muscle weakness is important because it facilitates the prediction and early recognition of symptoms and physical signs, which are often subtle in slowly evolving neuromuscular conditions.⁴ The normal infant and young child are at a physiologic disadvantage compared with older children and adults, and this is further compounded when respiratory muscle weakness is superimposed. The lung is relatively stiff compared with the highly compliant chest wall in infants and young children,⁵ impeding the generation of adequate tidal volumes.⁶ In those with significant muscular weakness, however, functional residual capacity (FRC) is not maintained because of an even more compliant chest wall and failure to maintain inspiratory muscle tone, predisposing to airway closure and microatelectasis. Upper and lower airways are of smaller caliber in younger children, with a greater amount of intrathoracic airway resistance occurring in the smaller airways.⁷ In addition, the large central airways are more collapsible because of increased compliance.⁷ The respiratory pump power is further challenged by the younger child's horizontal ribs and reduced zone of apposition of the diaphragm.⁸ Thus, any disease of the lower airways in a young child quickly brings added stress to an already stressed system. If challenged, therefore, the infant with severe neuromuscular weakness cannot easily increase minute ventilation and respiratory failure quickly follows. The infant also has poorer collateral ventilation. The pores of Kohn and the other interalveolar pathways are not well developed; therefore any lower respiratory disease adds further to compromise because the collateral channels are less available for compensation.⁹ Add to this the fact that infants have fewer alveoli in total and reduced elastic recoil; thus, it is surprising that the infant with significant neuromuscular disease can breathe at all.

With the ongoing development of neuromuscular weakness, chest wall compliance decreases because of the gradual stiffening of costosternal and costovertebral articulations, which become ankylosed with lack of use.¹⁰ In SMA-1, pectus excavatum develops with concomitant paradoxical respiration because as the diaphragm contracts, the abdomen expands and the anterior chest wall sinks in.¹¹ As patients who have SMA-1 slowly get older, although still in infancy, respiratory muscles that are not functioning at their optimal length tension relations because of weakness undergo significant changes, with resultant loss of normal elasticity and plasticity.¹¹ When scoliosis develops, lung volumes are further reduced, whereas the intercostal muscles are placed at further mechanical disadvantage. The consensus view is that control of breathing is normal in NMD, but in chronic respiratory failure a "blunting" of central chemoreceptors is thought to occur as a result of chronic carbon dioxide (CO₂) retention.¹²

AIRWAY-PROTECTIVE MECHANISMS IN NEUROMUSCULAR WEAKNESS

With loss of expiratory muscle strength, cough power is reduced and is further compromised by inspiratory muscle weakness, because a precough inspiration in excess of 60% of total lung capacity is optimally required.¹³ Transmural airway pressures decrease, thereby reducing the cough flow transients that aid mucus clearance from the airway, and bulbar weakness impairs glottis closure, thereby further impairing cough strength.¹³

If a lower respiratory tract infection is "imposed" on the vulnerable respiratory physiology of a child with NMD, a marked increase in respiratory work occurs at a time when the pump muscles are further weakened by the viral infection itself.^{14,15} Airway resistance increases as a result of increased airway secretions that cannot be effectively cleared by an impaired cough. Lung compliance decreases as a result of

increasing mucus plugging and atelectasis. Acute respiratory failure ensues, and the child may succumb if not mechanically ventilated by NIV or an endotracheal tube. A presentation that is an all too common scenario in childhood NMD is rushing the child in acute respiratory failure attributable to a lower respiratory tract infection or pneumonia to the emergency department. Incidences of 0.8 to 1 per year have been reported in NMDs.¹⁶ A similar presentation can also be the result of aspiration secondary to swallowing dysfunction.¹⁷

SLEEP AND RESPIRATORY FAILURE

It is during sleep that physiologic changes are magnified, thereby increasing the likelihood of respiratory compromise. In normal children, while sleeping, the respiratory pattern of wakefulness changes in a characteristic way—ventilatory control inputs from higher centers are lost; chemoreceptor, medullary, and cortical arousal center sensitivity decreases; respiratory muscle power diminishes; and upper airway muscle tone decreases. As a result, tidal volume decreases and there is a mild decrease in oxygen saturation and increase in CO₂.¹⁸ During rapid eye movement (REM) sleep, respiratory control is at its nadir, skeletal muscle atonia is maximal with loss of accessory muscle power, and diaphragmatic function is maintained. Depending on the severity and distribution of respiratory muscle weakness in a child with NMD, the “sleep-induced” effects on muscle power are heightened as NMD-induced diaphragmatic weakness accentuates the normal muscle atonia of REM. Thus, in a child with NMD, sleep does not “knit up the ravell’d sleeve of care” but may, in a true sense, be the “death of each day’s life”.¹⁹

The net result of the physiologic changes outlined previously is the development in NMD of hypoventilation, first during rapid eye movement sleep, then during no rapid eye movement, and, subsequently, during wakefulness. Depending on the distribution of respiratory muscle weakness, however, the pattern may vary. For example, if diaphragmatic function is not significantly impaired while upper airway musculature is weak and tonsils and adenoids are enlarged, upper airway obstruction may predominate during sleep.¹⁸

SYMPTOMS AND SIGNS OF RESPIRATORY COMPROMISE IN NEUROMUSCULAR DISORDERS

In severe early-onset respiratory muscle weakness, as encountered in SMA-1, physical examination may reveal a bell-shaped chest with tachypnea, paradoxical breathing, and head bobbing in the context of severe generalized hypotonia. In more slowly evolving respiratory failure, such as that of DMD, the development of symptoms may be insidious and often missed. Those symptoms that should be specifically sought relate to the effects of nocturnal hypoventilation with resultant hypoxia and sleep fragmentation, including daytime behavioral and neurocognitive problems, hyperactivity or tiredness, morning headaches, nocturnal arousals and frequent repositioning, and daytime sleepiness.^{6,20} Anorexia at breakfast and cyanosis during meals and on transfer from a wheelchair may also occur.²¹ Symptoms may be poorly predictive of sleep breathing difficulties, however.^{22,23} Mellies and colleagues⁴ recently reported that a structured symptom questionnaire was poorly predictive of sleep-disordered breathing (SDB) or nocturnal hypercapnic ventilation in a group of 49 children with NMDs of varying etiologies. The deficit in general intellectual functioning in boys with DMD further complicates ascertainment of significant symptoms, and in the clinical setting of a pediatric outpatient visit, these boys often sit quietly with their parents saying little about their concerns. Thus, in summary, symptoms of respiratory failure are often not reported or are subtle and overlooked.

RESPIRATORY MONITORING IN CHILDHOOD NEUROMUSCULAR DISORDERS

Role of Lung Function Testing in Predicting Respiratory Failure

Serial monitoring of lung function is mandated for all children with NMD when it is able to be performed—usually after the age of 5 years.^{24,25} The rate of decline in forced vital capacity (FVC) in DMD is variable (2%–39% per year), with a median of 8%, whereas a FVC of less than 1 L in DMD is associated with a median survival of 3.1 years and a 5-year survival rate of only 8%.²⁶ Bourke and Gibson²⁷ suggest that FVC may be a better measure of overall survival in DMD than nocturnal hypoxia. A recent report suggested that a FVC of greater than 60% represented a low risk for nocturnal hypoventilation, whereas a FVC less than 40% was a good predictor of nocturnal hypoventilation in children with NMDs of varying etiologies.²⁵ Daytime P_{aCO_2} levels greater than 45 mm Hg, in combination with spirometry, have also been used to predict SDB,²⁸ whereas Mellies and colleagues⁴ asserted that SDB with nocturnal hypercapnic hypoventilation could be predicted by a P_{aCO_2} greater than 40 mm Hg (92% sensitivity, 72% specificity) and inspiratory vital capacity less than 40% (96% sensitivity, 88% specificity) in a group of 49 children and adolescents who had NMD of mixed etiology (aged 11.3 ± 4.4 years). These researchers also reported that a maximum peak inspiratory pressure less than 4 kPa and less than 2.5 kPa predicted SDB onset and nocturnal hypercapnia, respectively.⁴ Similarly maximum expiratory mouth pressure (MEP) has been used to measure effective cough capacity (MEP >60 cm H₂O is adequate, and MEP <45 cm H₂O is insufficient),²⁹ whereas a maximum inspiratory mouth pressure (MIP) less than 60 cm has been suggested as indicative of the need to consider NIV.³⁰ Peak cough flows (PCFs) are now recognized as important measures of the capacity for mucociliary clearance. Consensus documents have accepted 270 L/min as the acceptable level of flow;^{24,25} at greater than that level, there is a reduced risk for developing respiratory failure during upper respiratory tract infections, whereas a level lower than that target value identifies patients who would benefit from manually assisted cough techniques.³¹ In adult patients who have NMD, however, with PCF values of 270 L/min while well, these values often decrease to less than 160 L/min during acute viral infections,³¹ a level insufficient to clear airway secretions. The target PCF value of 270 L/min may not be appropriate for children because those younger than 13 years of age are often not able to generate values of 270 L/min.¹³ PCFs less than 270 L/min are more likely when FVC is <2.1 L in children who have DMD.³² It is worth noting that PCF can be increased by breath stacking.

In those with the most severe form of NMD, SMA-1, infant lung function testing is technically demanding and untested in this clinical setting, but monitoring with polysomnography (PSG), or with oximetry if the former is not available, particularly during sleep, is extremely helpful in assessing evolving respiratory muscle weakness and resultant hypoventilation.¹⁷ There is a clear consensus in the literature^{24,25,30} that serial monitoring of lung function is mandated for all children who are old enough to perform it. For spirometric evaluation, MIP, MEP, and PCF, this is usually after the age of 5 years.

When to Refer for Specialized Respiratory Review

Although a recent American Thoracic Society consensus statement²⁴ recommended that those who have DMD be reviewed by a pediatric respiratory physician twice yearly after FVC has decreased to less than 80% of that predicted, or if aged 12 years or when confined to a wheel chair, many respiratory pediatricians believe that they should review all children with NMD after the diagnosis has been confirmed. This allows the pediatric respiratory physician and respiratory team to meet with the family

before respiratory complications have developed to discuss their potential evolution and the methods of assessing and treating them. This is important to facilitate before the family undertakes "Internet surfing," wherein management techniques with varying levels of scientific support may be promulgated. The frequency of specialized respiratory assessment depends on clinical progress.²⁵ In children whose respiratory muscle weakness is evolving more slowly, annual monitoring with spirometry and overnight PSG is reasonable initially. The timing of further overnight studies may be varied depending on the PSG results. The more difficult question to answer is when to begin overnight monitoring, although guidelines are outlined elsewhere in this article.

Timing of Polysomnography

In children who have DMD, consensus guidelines²⁴ suggest that overnight monitoring should be considered from the time the child becomes a wheelchair user or when clinically indicated. As outlined previously, symptoms of nocturnal hypoxemia and sleep fragmentation may often be subtle. PSG should be considered annually when FVC is less than 60% and more often if it is less than 40%. A MIP less than 60%³⁰ and daytime P_{aCO_2} greater than 40 mm Hg⁴ are also helpful in prompting a referral for PSG evaluation. These target values are general guidelines only, because not infrequently in clinical practice, one sees children whose FVC is greater than 70% of that predicted but whose PSGs demonstrate significant alveolar hypoventilation.

TREATMENT OF RESPIRATORY FAILURE IN NEUROMUSCULAR DISORDERS

Although one of the major changes in the treatment of respiratory failure in NMDs has been the introduction of NIV, the literature evidence on which its effectiveness is based is not clear-cut. In a recent Cochrane review, the conclusions of Annane and colleagues³³ were that "current evidence about the therapeutic benefit of mechanical ventilation (in NMD) is weak, but directionally consistent suggesting alleviation of the symptoms of chronic hypoventilation in the short term." They suggested that large randomized trials were needed to confirm long-term beneficial effects of NIV on symptoms, quality of life, unplanned hospital admissions, and mortality and, finally, to evaluate its cost-effectiveness. For this review, only eight trials in the literature were deemed eligible for evaluation because entry criteria dictated that they had to be quasirandomized or randomized controlled studies and most patients studied were adults. It is against this backdrop that one needs to consider the pros and cons of NIV treatment in pediatric patients who have NMD.

Although noninvasive positive-pressure ventilation was first used in the 1960s,^{34,35} it was not until the 1980s, after the development of the continuous positive airway pressure mask,³⁶ that Rideau and colleagues³⁷ in Europe and Bach and colleagues³⁵ in the United States suggested that noninvasive positive-pressure ventilation (NIV) be used to treat respiratory failure in NMD. With the subsequent development of suitable children's masks, NIV gained acceptance in pediatric practice during the 1990s. In a recent review of NIV in children, Norregaard⁶ noted that knowledge of NIV application in children depended in the main on reports of case series, with little firm evidence of when to initiate NIV in this age group. It is also salutary to note how far pediatric clinical practice has come since the findings of a consensus conference,³⁸ which reported that "nasal mask ventilation in young children must be considered an investigational technique for research and/or use only by experienced centers." Notwithstanding the conclusions of the Cochrane report outlined previously, NIV is now accepted as one of the major strategies in the treatment of respiratory failure in children who have NMD and is

strongly supported by several consensus statements.^{17,24,25} There is not a clear consensus in the literature as to when one should initiate NIV, however.

EVIDENCE THAT NONINVASIVE VENTILATION IS EFFECTIVE IN RESPIRATORY FAILURE IN NEUROMUSCULAR DISORDERS

The evidence for NIV's effectiveness in NMD is based mainly on case series, non-randomized trials, and comparisons with historical controls. Despite this, the weight of evidence is persuasive. Eagle and colleagues¹ reported that the mean age of death in patients who had DMD and were treated with NIV had increased from 19 to 25 years when compared with historical controls who did not receive this treatment, whereas Simonds and colleagues³⁹ found a one year and five year survival rate of 85% and 73%, respectively, in DMD patients treated with NIV. There are now a series of studies that report improvements not only in survival but in symptoms of nocturnal hypoventilation, gas exchange during the day and night, preservation of lung function, quality of life, and frequency of hospital admissions.^{21,31,39–46} John Bach has been a tireless advocate over many years of NIV in the treatment of respiratory failure in NMD, and his results even in severe muscle weakness, such as SMA-1,^{2,47} are impressive. He reported that as a result of noninvasive management in his clinic (which included monitoring of oximetry, mechanical-assisted coughing techniques, and short-term intubations for acute respiratory infections), 80 of 115 patients who had SMA-1 were still alive without tracheostomy at 4 years, with 8 children older than 8 years of age and 2 older than 10 years of age.⁴⁸ The management of children who have SMA-1 is a highly controversial area, however, and as outlined by Bush and colleagues,⁴⁹ individual physicians may discourage long-term daytime NIV but “many will disagree with this approach in good faith.” What Bach's approach may be demonstrating is that with aggressive management of respiratory failure with NIV, close monitoring of ventilation with oximetry, and the early introduction of mechanical-assisted coughing in acute respiratory infections, the long-term outlook for many children with neuromuscular weakness of varying etiologies may be enhanced.

WHEN TO START NONINVASIVE VENTILATION

There is little consensus in the literature regarding when to start NIV, with some advocating its introduction if the patient is hypercapnic or hypoxic during sleep or wakefulness (in DMD).⁵⁰ Others (in congenital muscular dystrophies, SMA-2, and congenital myopathies) advocate its initiation in those with acute respiratory failure, symptomatic diurnal hypercapnia or symptomatic nocturnal hypoventilation in the absence of daytime hypercapnia, failure to thrive, or more than three chest infections per year, with its use in nonsymptomatic nocturnal hypercapnia or hypopnea being considered on an individual basis.²⁵ As outlined previously, symptoms are often subtle.

Mallory⁵¹ suggests that its use should commence early, that is, before the onset of respiratory failure. The American Thoracic Society consensus statement²⁴ suggests that NIV be used to treat “sleep-related upper airway obstruction and chronic respiratory insufficiency” in DMD, although no definitive guidelines are given as to levels of severity that would mandate NIV. A second consensus statement³⁰ suggests NIV use in NMD if the patient has symptoms, such as fatigue, morning headache, and one of the following: (1) Paco_2 of 45 mm Hg or greater, (2) nocturnal oxygen saturation of 88% or less for 5 consecutive minutes, or (3) maximal inspiratory pressures less than 60 cm H_2O or FVC less than 50% of that predicted. Ward and colleagues⁴⁴ make the point that these recommendations are not based on controlled studies and that the oxygen saturation guidelines were not based on evidence but partly on

Medicare guidelines for oxygen therapy in chronic obstructive pulmonary disease.⁵² These researchers performed one of the few randomized controlled trials of NIV in a group of patients who had NMD (of mixed etiology).⁴⁴ They randomized 26 subjects, aged 7 to 51 years, with an FVC less than 50% of that predicted with nocturnal hypercapnia (peak $T_{ccO_2} > 6.5$ kPa) but normal daytime CO_2 levels to nocturnal NIV or to a control group without NIV. Nocturnal ventilation improved in the treated group, but 9 of 10 controls needed NIV after a mean of 8.3 months (SD = 7.3). These findings support the conclusion that once nocturnal hypoventilation is present, NIV treatment should be considered.⁴⁰ A recent index, the “Breathing Intolerance Index,” was developed by Koga and colleagues⁵³ calculated from the formula of inspiratory time (T_i) divided by total respiratory time (T_{tot}), multiplied by the result of tidal volume (V_t) divided by vital capacity (VC) [ie, $(T_i/T_{tot}) \times (V_t/VC)$]. These investigators found that a value greater than 0.15 was noted for all subjects on NIV.

One of the studies often quoted in the literature as demonstrating the possible hazard of initiating NIV early is that of Raphael and colleagues.⁵⁴ Its importance lies in its being one of the few randomized trials of NIV use in children. These researchers’ aim was to evaluate the use of “prophylactic” NIV in a group of 70 teenaged patients who had DMD with a FVC from 20% to 50% of that predicted and who had not developed diurnal hypercapnia by randomizing them to NIV or standard treatment. The worrying result was a fourfold increase in mortality in the NIV group, with most resulting from respiratory infections. These investigators thought that the putative reason for the increase in mortality was the false sense of security in patients using NIV, thereby resulting in a delay in seeking medical help during a significant respiratory infection. The study has subsequently been criticized by many investigators for limitations in design and analysis, including failure to document patient compliance with NIV or to use assisted cough techniques, a higher proportion of patients with cardiac dysfunction in the NIV group,⁵² and the absence of PSG data before and after NIV initiation.⁵⁵

The initiation of NIV should optimally be electively planned after discussions with family and patients. Unfortunately, in practice, this is not always what happens. Sritipayawan and colleagues⁵⁶ reported that of 73 children who had NMD of mixed etiologies, only 21% had NIV commenced electively. Some authorities have suggested that the reticence to discuss long-term ventilatory support with patients might be because of health providers’ assessments of the patients’ poor quality of life.^{57,58} As outlined by Kohler and colleagues,⁵⁹ however, even patients who have DMD with advanced muscle weakness report a high quality of life despite their illness, which was not correlated with physical limitation or need for NIV.

The long-term positive effects of NIV in children who have NMD have been demonstrated in two recent studies. Mellies and colleagues⁴³ reported that in 30 patients who had NMD of varying etiologies, NIV normalized nocturnal and daytime gas exchange and sleep and that the effects persisted over 25.3 ± 12.7 months. In 15 children who had varying types of NMD, Katz and colleagues⁴⁵ found that over at least a 1-year period, NIV resulted in an 85% reduction in days in the hospital and a 68% reduction in days in intensive care. The physiologic reasons for this improvement in respiratory failure parameters have been recently explored by Nickol and colleagues,⁶⁰ who found that increased ventilatory response to CO_2 was the main contributor. An intriguing aspect of NIV use is its possible positive effects on lung and chest wall growth. Bach and Bianchi¹¹ have advocated its use for this purpose, suggesting “high span positive inspiratory pressure plus positive end-expiratory pressure” to improve lung compliance and prevent pectus excavatum in SMA-1. The effectiveness of NIV in promoting lung and chest wall growth awaits further elucidation. The long-term potential effect of NIV on facial development also needs to be remembered because a recent study of

40 children using NIV (cystic fibrosis [$n = 10$], obstructive sleep apnea [$n = 16$], and NMD [$n = 14$]) found a prevalence of global facial flattening in 68%. No correlation was found with age or daily or cumulative use of NIV.⁶¹

The increasing use of NIV in neuromuscular disease in children must be seen against the background of other developments that have, in concert, improved the quality and quantity of life for affected children. The importance of airway clearance methods using manual-assisted techniques (manual-assisted coughing with increased inspiratory capacity facilitated by glossopharyngeal breathing, breath stacking, or self-inflating bag and mask) has been highlighted in recent studies and consensus statements.^{24,25,31} In addition, mechanical insufflator-exsufflators play an important role in mobilizing airway secretions, especially in those whose PCFs are ineffective, and their efficacy in NMD has been highlighted in several recent studies.^{31,62–64} Chatwin and colleagues⁶⁵ demonstrated in 22 patients with NMD, 8 of whom were children, that the insufflator-exsufflator produced a greater increase in PCFs than voluntary unassisted cough or cough assisted by physiotherapy or noninvasive positive-pressure ventilation. Two newer mucus clearance devices whose benefit awaits clarification include high-frequency chest wall oscillation and intrapulmonary percussive ventilation.^{66,67}

The continued improvement in outlook from a respiratory point of view for children who have NMD has also been aided by the early use of antibiotics in acute respiratory infections, influenza, and pneumococcal vaccinations; improved intensive care techniques; and specialized regional care centers. Nonrespiratory interventions, such as the use of oral steroids in DMD to improve muscle strength and respiratory function⁶⁸ (although not uniformly accepted),²⁴ surgical correction of scoliosis,⁶⁹ early intervention and treatment of cardiac dysfunction,^{70,71} recognition and treatment of gastroesophageal reflux and aspiration,¹⁷ close monitoring of nutritional status, and intervention with gastrostomy in those failing to thrive²⁴ are all integral to optimal management of these complex patients.

In summary, the management of respiratory complications of children who have neuromuscular disease has markedly improved in the past 15 years. The reasons for this are many and include a better appreciation of the symptoms of hypoventilation during sleep, which are often subtle; a greater understanding of the importance of close monitoring by a respiratory pediatrician with serial lung function testing and overnight monitoring; the acceptance of the importance of NIV in treating acute and chronic hypoventilation; and improved airway clearance techniques, including assisted coughing and insufflator-exsufflators. The role of the respiratory pediatrician is vital in coordinating all these aspects of care.

Further improvements in the quality and quantity of life for children who have NMD are likely in the years ahead with gene- and cell-based treatments. This should also have a significant impact on patients' families and health systems. Governments need to be made aware of the demands that are likely to be made on the health systems as a result. There is an urgent need for improvement in the home care and respite opportunities provided in addition to education and skills training for young adults. We have come some way, but there is much to be done.

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