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Prevention of Pulmonary Morbidity for Patients With Duchenne Muscular Dystrophy*

John R. Bach, MD, FCCP; Yuka Ishikawa, MD; and Heakyung Kim, MD

Study objective: To evaluate the effects of a new respiratory management protocol on respiratory morbidity and hospitalization rates for patients with Duchenne muscular dystrophy (DMD).

Design: A retrospective cohort study.

Methods: Using a protocol in which oxyhemoglobin desaturation was prevented or reversed by the use of noninvasive intermittent positive pressure ventilation (IPPV) and assisted coughing as needed, the hospitalization rates and days for 24 protocol DMD ventilator users were compared with those of 22 nonprotocol DMD tracheostomy IPPV users.

Results: The 22 conventionally managed patients were hospitalized a mean of 72.2±112 days when undergoing tracheostomy. This included a 16.1±5.4-day period of translaryngeal intubation. The 24 protocol patients were hospitalized a mean of 6.0±2.4 days (p<0.005) when beginning ventilator use. Over their next 126.2 patient-years of ventilator use, the 24 protocol patients had significantly lower rates of hospitalization (p<0.008) and hospitalization days (p<0.005) than had the tracheostomy IPPV users over a 167.2 patient-year period. This is true although 14 of the 24 protocol patients went on to require 24-h noninvasive IPPV for 4.5±3.6 years. Five of the 14 have yet to be hospitalized.

Conclusion: The use of inspiratory and expiratory aids can prolong survival while significantly decreasing the pulmonary morbidity and hospitalization rates associated with conventional resort to tracheostomy IPPV.

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Key words: cough; Duchenne; exsufflation; mechanical ventilation; muscular dystrophy; respiratory failure; respiratory paralysis; respiratory therapy

Abbreviations: DMD = Duchenne muscular dystrophy; IPPV = intermittent positive pressure ventilation; SaO₂ = oxyhemoglobin saturation; PCF = peak cough flows; URTIs = upper respiratory tract infections; VC = vital capacity

It has been estimated that 55% to 90% of Duchenne muscular dystrophy (DMD) patients die from respiratory failure between 16.2 and 19 years of age and uncommonly after age 25 years. For patients with DMD as well as for patients with other progressive neuromuscular diseases, acute respiratory failure most often occurs during otherwise benign upper respiratory tract infections (URTIs). During these episodes, already severe pulmonary dysfunction is further compromised by bronchial mucus plugging and by further weakening and fatigue of inspiratory and expiratory muscles. Such episodes can result in repeated pneumonias, hospitalizations, tracheal intubations, and ultimately, in tracheostomy or death.

Up to 24-h use of noninvasive intermittent positive pressure ventilation (IPPV) has prolonged the survival of over 700 patients with neuromuscular ventilatory failure. For noninvasive IPPV to be effective long term, however, the ability to clear the airway of secretions is critical, especially during intercurrent URTIs. We have found that at least 160 L/min of peak cough flows (PCF) is the minimum required to clear airway debris and that this appears to be possible for the great majority of patients with DMD. Also, in our experience, patients for whom at least 270 L/min of PCF can be generated have little
risk of developing respiratory failure during URTIs. Further, since both hypercapnia and bronchial mucus plugging cause decreases in oxyhemoglobin saturation ($\text{SaO}_2$) below 95%, we hypothesized that if we could identify DMD patients at risk of developing acute respiratory failure on the basis of low PCF and train and equip them to maintain sufficient alveolar ventilation and airway mucus elimination to prevent oxyhemoglobin desaturation, we could prevent pulmonary morbidity and acute respiratory failure.

**Materials and Methods**

Of all patients referred to a regional Jerry Lewis Muscular Dystrophy Association clinic since 1977, 92 were diagnosed as having DMD on the basis of onset and progression of weakness before age 5 years, calf muscle pseudohypertrophy, loss of unassisted ambulation before age 13 years, and characteristic elevations of serum creatinine kinase, muscle biopsy in the patient or male relative, and electrodiagnostic examination. More recently, documentation of a Duchenne-type mutation or identical haplotype involving closely linked markers in other family members has been established to eliminate the need for a biopsy or electrodiagnostic examination to confirm the diagnosis. In addition, all 92 patients were seen in our clinic after 11 years of age. No patients had substance abuse problems or chronic lung disease.

Of these 92 patients, 5 had not experienced acute respiratory distress before 26 years of age and were subsequently unavailable for follow-up, and 39 patients were between 11 and 26 years of age but, although 4 were using nocturnal nasal IPPV to reverse symptomatic chronic alveolar hypoventilation and seven patients in all had PCF below 270 L/min putting them at high risk for respiratory failure, none as yet had any episodes of acute respiratory distress. These patients were no longer considered in our data analysis.

Prior to 1983, no respiratory muscle aids were used to prevent respiratory failure. Since 1983, patients were routinely screened every 3 to 6 months for symptoms of chronic alveolar hypoventilation and the following were measured: vital capacity (VC), maximum insufflation capacity (maximum volume of air stacked breaths) (Collins Survey Spirometer; Collins Inc; Braintree, Mass), assisted and unassisted PCF (Access Peak Flow Meter; HealthScan Inc; Cedar Grove, NJ), and $\text{SaO}_2$ (Ohmeda Model 3760; Louisville, Colo). An oral-nasal interface or lipseal (Nelcor, Cambridge, Mass) was added to the screening. Patients were considered part-time use, and $>16$ h/d was considered full-time use. Most patients used noninvasive IPPV for the first time, however, during an URTI.

Patients were considered to be at risk for URTI-associated respiratory failure when they had maximum assisted PCF below 270 L/min. Since their VCs were below 1,000 mL at this point, they were trained in air stacking manual resuscitator delivered volumes to their maximum insufflation capacities. They were also prescribed oximeters and trained in manually assisted coughing and in mechanical insufflation-exsufflation (mechanically assisted coughing). If not already using noninvasive IPPV, they were provided with rapid access (<2 h) to a portable volume ventilator, to various mouthpieces and nasal interfaces, and to a mechanical insufflator-exsufflator (In-Exsufflator; J. H. Emerson Co; Cambridge, Mass). The patients and care providers were instructed to monitor $\text{SaO}_2$ whenever patients were fatigued, short of breath, or ill. They were instructed that any decreases in $\text{SaO}_2$ below 95% indicate either hypoventilation or bronchial mucus plugging and that these must be corrected to prevent atelectasis, pneumonia, and respiratory failure. Thus, the protocol consisted of using noninvasive IPPV and manually and mechanically assisted coughing as needed to maintain normal $\text{SaO}_2$, particularly during intercurrent URTIs. No supplemental oxygen was provided for any patient in the community. No patients who were regularly evaluated failed to be properly trained and equipped or refused the protocol.

Averted hospitalizations were defined as acute episodes of respiratory distress relieved by 24-h ventilator use along with the use of assisted coughing and mechanical insufflation-exsufflation to expel mucus and to immediately reverse oxyhemoglobin desaturation-associated mucus plugging. When baseline $\text{SaO}_2$ decreased below 92% or dyspnea persisted despite continuous ventilator use and aggressive assisted coughing, or when clinical dehydration was suspected, high fever persisted, or lethargy occurred, the patients were instructed to present for evaluation and possible hospitalization.

High-risk ventilator use periods were defined by the period of time following an initial episode of acute respiratory failure or averted hospitalization until the onset of daily definitive ventilator use. These periods were compared for hospitalization rates and days for the protocol and nonprotocol patients. Patients requiring daily ventilator use from the first episode of respiratory failure or averted hospitalization were not considered to have had high-risk ventilator use periods. Likewise, hospitalization rates and days were compared for nonprotocol tracheostomy and protocol noninvasive IPPV users. The Mann-Whitney nonparametric T-test was used to compare hospitalization rates and days for the protocol and nonprotocol groups. p<0.05 was considered to represent statistical significance.

**Results**

Forty-eight patients required treatment for respiratory failure. Two patients became dependent on 24-h noninvasive IPPV without being equipped with oximeters or the expiratory aids of this protocol. Both died from pneumonia and respiratory failure complicating intercurrent URTIs. They are no longer considered. The remaining 46 patients included the following: (1) 22 nonprotocol tracheostomy IPPV users who were referred before 1983, referred already using tracheostomy IPPV and for whom the tube had not been removed, or patients who were not trained in noninvasive methods because of failing...
to return regularly to the clinic; (2) 10 protocol noninvasive IPPV users; and (3) 14 patients who had experienced multiple hospitalizations before being referred to us and were then placed on our protocol. The latter included three patients who were extubated and one whose tracheostomy tube was removed, all despite requiring continuous ventilatory support.

The 22 nonprotocol patients experienced initial episodes of respiratory failure at 23.7±5.0 years of age and underwent tracheostomy at 24.6±4.9 years of age. It was not always possible to separate tracheostomy IPPV use into part-time or full-time use. However, most patients continued to use tracheostomy IPPV 24 h/d from the point at which they underwent tracheostomy. The 10 protocol patients first had acute respiratory failure prevented at 19.8±4.4 years of age, began ongoing part-time noninvasive IPPV at 19.9±4.4 years of age, and full-time IPPV at 24.6±6.1 years of age. The 14 initially conventionally managed patients initially experienced respiratory failure at 16.9±2.8 years of age, began ongoing part-time noninvasive IPPV at 19.4±3.8 years of age, and full-time noninvasive IPPV at 23.3±6.1 years of age.

Although three of the protocol patients had gastrostomy tubes to supplement paraoral intake, bulbar muscle function was always sufficient to permit speech, assisted PCF over 160 L/min, and continued oral intake except for one patient who could no longer swallow. Although no DMD ventilator user had PCF measurements before 1983, only three tracheostomy IPPV users had indwelling gastrostomy tubes, all received nutrition by mouth and could speak clearly; and clinically, this group had comparable bulbar muscle function to the protocol patients.

Seventeen nonprotocol patients were hospitalized 2.4±1.8 times for 35.4±66.3 days over 3.6±2.7 years before six underwent tracheostomy and 11 were placed on the protocol. Three protocol only patients had one hospitalization avoided, each by using the protocol over a mean 9±3-month period before using ongoing noninvasive IPPV.

At the time of undergoing tracheostomy, the 23 tracheostomized patients were hospitalized a mean of 72.2±112 days, and translaryngeally intubated for 16.1±5.4 days before tracheostomy. This can be compared to the 24 noninvasive IPPV users who were hospitalized 6.0±2.4 days (p<0.0005) at onset of definitive daily ventilatory assistance. In addition, over their next 65.4 patient-years of part-time use, and 60.8 years of full-time use of noninvasive IPPV, these 24 patients were intubated a mean of 0.3±0.2 times for 4.0±3.6 days over 5.5±3.8 total years per patient. On extubation, the patients returned to noninvasive ventilatory assistance. The rates of hospitalizations, hospitalization days, and averted hospitalizations of the protocol noninvasive IPPV users and nonprotocol patients are noted in Tables 1 and 2.

Life was prolonged a mean of at least 7.9±6.3 years for the 22 long-term tracheostomy IPPV users, 13 of whom are still alive, to a current age of 33.7±7.4 years. Life was prolonged at least a mean of 4.5±3.7 years for the 14 full-time noninvasive IPPV users, 11 of whom are still alive, to a current age of 28.0±6.1 years.

**Discussion**

The initial objective, that of identifying DMD patients at risk of developing acute respiratory failure, appears to have been achieved because no patients with (assisted) PCF above 270 L/min developed acute respiratory distress. All but one patient for whom assisted PCF were below 270 L/min had VCs below 1,000 mL. Despite 14 patients eventually requiring full-time noninvasive IPPV, two with VCs under 100 mL, and three with severe dysphagia necessitating indwelling gastrostomy tubes, assisted PCF of at least 160 L/min were attainable for all protocol patients through the study period. This is consistent with previous studies that indicated the feasibility of managing ventilatory failure without tracheostomy.

Prior to initiating this protocol we informed patients to contact us at the first sign of a URTI, especially in the event of airway encumbrment or respiratory distress, and we would provide them with an oximeter and respiratory muscle aids to avert hospitalization. However, two consecutive patients presented to us only after they had already developed severe oxyhemoglobin desaturation and pne-

| Table 1—Hospitalization Rate Comparisons for Nonprotocol Preventilator Use High-Risk Patients vs Protocol Part-time Noninvasive IPPV Users* |
|-----------------|--------|--------|--------|
|                 | Entire Population | Nonprotocol | Protocol |
| Patients        | 17     | 24     |        |
| Hospitalizations/pt | 2.41±1.84 | 0.5±1.0 | <0.005 |
| Incidence of hospitalizations/ yr/pt | 2.25±4.75 | 0.2±0.5 | <0.005 |
| Hospitalizations avoided/pt | 1.8±1.7 |        |        |
| Hospitalizations avoided/yr/pt | 0.8±1.0 |        |        |
| Hospitalization days/pt | 35.4±66.3 | 3.6±8.7 | <0.005 |
| Average hospitalization days/ yr/pt | 21.4±37.8 | 1.8±5.2 | <0.005 |
| Years           | 3.6±2.7 | 3.1±3.2 | 0.21   |

*This does not include the hospitalizations for introduction of definitive ventilator use. Pt=patient.
This does not include the hospitalizations for introduction of definitive ventilatory support. Pt = patient.

Table 2—Hospitalization Rate Comparisons for Tracheostomy IPPV Users and Protocol Noninvasive IPPV Users

<table>
<thead>
<tr>
<th>Patients</th>
<th>Nonprotocol Tracheostomy</th>
<th>Part-time Noninvasive</th>
<th>Full-time Noninvasive</th>
<th>p Value†</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations</td>
<td>1.6±2.1</td>
<td>0.5±1.0</td>
<td>0.4±0.8</td>
<td>0.008</td>
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</tr>
<tr>
<td>Hospitalizations/yr/pt</td>
<td>6.2±3.6</td>
<td>3.1±2.4</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations avoided/pt</td>
<td>1.8±1.7</td>
<td>1.3±1.4</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations avoided/yr/pt</td>
<td>17.2±22.1</td>
<td>6.2±5.7</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization days/pt</td>
<td>2.3±4.2</td>
<td>1.8±5.2</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization days/yr/pt</td>
<td>7.6±6.2</td>
<td>3.1±3.2</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*This does not include the hospitalizations for introduction of definitive ventilatory support. Pt = patient.
†Comparison with nonprotocol patients.

monia and they required hospitalization and intubation. We, therefore, believed that the presence of an oximeter in the home was especially important for immediate feedback to the patient during URTIs since we have not yet observed any DMD patient to have developed respiratory complications and require intubation when the SaO₂ baseline was maintained above 92%. All of the patients in this study, and their care providers, were properly trained and equipped and used oximetry and the respiratory aids appropriately. However, these patients had very dedicated and capable family members who provided noninvasive IPPV and the cough aids, at times, every 10 to 15 min, and essentially around the clock, during some intercurrent URTIs. Thus, it would be anticipated that patients without dedicated and effective care providers might not succeed in avoiding conventional management.

This study demonstrated that, given effective care providers, the use of noninvasive inspiratory and expiratory aids with oximetry feedback can significantly decrease the incidence of respiratory hospitalizations and prolong survival for DMD patients without resort to tracheostomy. There were only three protocol patients who had episodes that would have warranted hospitalization before requiring definitive ventilator use because most protocol patients first used noninvasive IPPV during URTIs and weaned to nocturnal use of noninvasive IPPV after their first averted hospitalization, whereas nonprotocol patients tended to have repeated episodes of respiratory failure until undergoing tracheostomy. The study also demonstrated that hospitalization rates and days can be significantly fewer both at onset of definitive ventilator use and subsequently for part-time and for full-time noninvasive IPPV users than for tracheostomy IPPV users.

Considering the fact that the ages at onset of tracheostomy IPPV and full-time noninvasive IPPV were the same, the noninvasive IPPV users experienced their first episodes of acute respiratory distress before the tracheostomy group, and there were as many protocol as tracheostomy patients who required gastrostomy tubes, one cannot explain the lower morbidity in the noninvasive IPPV users by their being less severely affected than the nonprotocol patients.

Besides guiding the use of respiratory muscle aids during URTIs, oximetry was also useful in guiding the daytime and nocturnal use of noninvasive IPPV.¹³,¹⁶,¹⁷ For patients using only nocturnal noninvasive IPPV, daytime hypercapnia was usually mild and well tolerated when SaO₂ remained within normal limits. Oximetry was also useful for indicating the need for manually and mechanically assisted coughing during oral food intake for patients with severe dysphagia. Although many patients were found to aspirate food to varying degrees, patients were permitted to continue oral intake provided that any aspiration-associated oxyhemoglobin desaturations could be reversed by using manually and mechanically assisted coughing. Mechanical insufflation-exsufflation via an anesthesia mask became particularly important when assisted PCF were marginal (about 160 L/min) and scoliosis prevented optimal abdominal thrusts. Since all patients had normal SaO₂ when awake and using ventilatory assistance as necessary, and all could reverse sudden desaturations, we considered any ongoing aspiration of airway secretions or food to be clinically insignificant.

Although both tracheostomy and noninvasive IPPV can prolong life, tracheostomy IPPV has been reported to be associated with numerous complications and excessive expense.¹⁸ Tracheostomy necessitates more professional medical services than noninvasive ventilation and there are other expenses associated with wound care, tracheal suction catheters, and other supplies. In addition, tracheostomy is associated with an initial mean hospital stay of 72 days, and more hospitalization days subsequently, than is associated with noninvasive management. Further, patients almost invariably prefer noninva-
DMD remains “untreatable.” The invasive nature of tracheostomy IPPV and tracheal suctioning also diminishes patients’ quality of life. This study further suggests that even full-time need for noninvasive IPPV can be safer as well as being less expensive than tracheostomy IPPV. Most of our protocol patients were trained in the use of respiratory muscle aids by a skilled respiratory therapist in the clinic and home settings, and five noninvasive IPPV users went on to require definitive 24-h ventilatory support without as yet ever being hospitalized. Successful use of noninvasive alternatives, however, requires dedicated personal care providers and their effort-intensive interventions during intercurrent URTIs.

Despite the fact that survival can be extended, there continue to be reports declaring that the prognosis for DMD remains unchanged, and DMD remains “untreatable.” This is particularly ironic since medical treatments that are most costly and less beneficial on function and survival are now being widely used to treat amyotrophic lateral sclerosis, another common severe neuromuscular disease. Medications, however, are a familiar modality to physicians and usually are associated with high profile marketing campaigns. Physical medicine applications that can prolong survival and optimize quality of life, however, tend to be misunderstood and underutilized. As a result, the conventional practices of offering elective tracheostomy, treating “sleep-disordered breathing” with oxygen supplementation and minimal-span nocturnal bilevel positive airway pressure, or of simply waiting for acute respiratory failure to develop and then intubating and performing tracheostomy on patients are no longer necessary or advisable.

REFERENCES

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