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Muscle manifestations and CK levels in COVID infection: results of a large cohort of patients inside a Pandemic COVID-19 Area

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Objective. To investigate both muscular manifestations and CK levels in a large cohort of patients with COVID-19 infection and to determine whether hyperckemia is associated with morbidity and mortality.

Methods. Data of 615 patients discharged from ASST Ovest Milanese (Milan, Lombardy, Italy) with final diagnosis of COVID-19 infection were retrospectively extracted from electronic medical records from 21 February to 1 May 2020. Patients were descriptively analyzed with respect to the following variables: sex, age, muscular manifestations (myalgia and/or arthralgia), fatigue, respiratory involvement (SARS pneumonia or respiratory failure) and history of falls. Association between patients' characteristics and CK levels was investigated. In addition, the proportion of patients who died following access to the ER was calculated. Finally, the effect of CK levels and other patients' features on mortality was estimated using a logistic regression model.

Results. 176 (28.6%) patients had raised serum CK levels. CK levels were significantly associated with history of falls, male gender, SARS pneumonia, respiratory failure and in-hospital death. No correlation was found between hyperckemia and muscular manifestations.

Conclusions. Our study provides preliminary evidence that hyperckemia is associated with respiratory failure and fatal outcome in patients with COVID-19 infection.

In these patients, among other testing, CK dosage is recommended.

Key words: COVID-19, CK, myalgia, coronavirus

Introduction

As of April 15, 2020, Lombardy region accounted for 37% of Italian cases of COVID-19 infection and had 112.9 deaths per 100,000 population, almost six times higher than in the rest of Italy ¹.

Although COVID-19 involves pulmonary system in the first place, in more than one-third of patients it causes neurological manifestations ². Literature data report various symptoms affecting the central nervous system,

the peripheral nervous system and the skeletal muscle^{3,4}. In particular, skeletal muscle injury has originally been defined by muscle pain associated with elevated serum creatine kinase (CK) level above 200 U/L⁵.

During the ongoing pandemics of COVID-19 infection, descriptions of muscle symptoms have been recently reported⁵⁻⁸. However, the correlation between serum CK levels and muscle injury has been poorly investigated^{5,9,10}.

Evidence of possible muscle involvement by coronaviruses dates back to 2003. During Severe Acute Respiratory Syndrome (SARS)-CoV outbreak in March 2003 muscle weakness and raised serum CK levels occurred in more than 30% of the SARS-infected patients¹¹.

In 2005 Leung et al. described a spectrum of myopathic changes associated with a SARS infection. Nevertheless, viral particle was not identified in the muscle¹². SARS-CoV-2 is structurally similar to SARS-CoV, and both bind to the angiotensin-converting enzyme 2 (ACE2) receptor to enter human cells. ACE2 is expressed in various human tissues in addition to the lungs, including muscle, although to a lesser extent¹³, thus postulating a direct muscle involvement by SARS-CoV-2 in addition to immune-mediated muscle damage³. These premises suggest a possible tropism of COVID-19 for muscle.

The primary aim of our study was to investigate both muscular manifestations and CK levels of a large cohort of patients with COVID infection in order to find a possible correlation among them. The secondary aim was to identify the association among CK levels, respiratory failure and in-hospital death.

Materials and methods

Data of 615 patients discharged from ASST Ovest Milanese (Milan, Lombardy, Italy) with final diagnosis of COVID-19 infection were collected from 21 February to 1 May 2020. Clinical data were retrospectively extracted from Emergency Room (ER) electronic records including laboratory findings and they were checked by two neurologists (ADR and EPV).

The institutional ethics board of ASST Grande Ospedale Metropolitano Niguarda, Milan, approved this study and due to the nature of retrospective chart review, waived the need for informed consent from individual patients (Approval number: 411-21072020).

The recorded data included the following: age, sex, muscular manifestations (myalgia and/or arthralgia), fatigue, history of falls (occurred at home before Hospital admission) and CK level. The occurrence of both respiratory involvement (SARS pneumonia or respiratory failure) and in-hospital deaths was collected from hospital discharge forms. CK levels were evaluated at the time of ER arrival. To simplify the results' interpretation, with the aim

of accounting for excessive heterogeneity of the CK level distribution, patients were stratified in four groups according to their CK values as in a previous paper¹⁴: group 0 (CK < 200 U/L), group 1 (CK 200-554 U/L), group 2 (CK 555-1038 U/L) and group 3 (CK ≥ 1039 U/L).

Because CK levels can also raise during cardiac disorders, we selected patients without any reported history of myocarditis or peritonitis and with normal levels of troponin tested in ER.

Statistical analysis

Patients were descriptively analyzed with respect to the following variables: sex, age, muscular manifestations, fatigue, respiratory involvement, and history of falls according to the CK level. In addition, the proportion of patients who died following access to the ER was calculated. The association between patient characteristics, considered individually, and CK level was studied using proportional odds logistic regressions, one for each variable, and estimating the odds ratio and its 95% confidence interval (CI). The proportional odds model has the same structure as the binary logistic regression model but uses an ordinal outcome variable with more than two possible levels (such as the chosen categories of CK level)^{14,15}. It estimates a common odds ratio over all possible cut-offs of the outcome scale.

The association between clinical features and CK levels was also investigated through a multiple regression model. In this way, it was possible to identify the effect of each variable on the CK level accounting for the value of the other variables.

To verify the robustness of our findings and to overcome the arbitrary nature of CK level categorization, in a secondary analysis, the patients with elevated CK levels (≥ 200 U/L) were classified according to the tertiles of the CK level distributions: group 0 (CK < 200 U/L), group 1 (CK 200-288 U/L), group 2 (CK 289-501 U/L) and group 3 (CK ≥ 502 U/L) (see Supplementary material).

Finally, a logistic regression model was fitted to identify the predictors of in-hospital death. CK level was included in the model as a categorical variable. Adjustments were made for the above-mentioned variables.

The Statistical Analysis System Software (version 9.4; SAS Institute, Cary, North Carolina, USA) was used for the analyses. For all hypotheses tested, two-tailed P values less than 0.05 were considered as significant.

Results

Patients

A total of 615 hospitalized patients [mean age: 66.8 (± 16.2); males: 386 (62.8%)] with confirmed COVID-19

Table I. Characteristics of cohort members according to the creatine kinase (CK) levels.

	CK level (U/L)				OR (95% CI)	P-value
	0-199 (n = 439)	200-554 (n = 127)	555-1038 (n = 31)	≥ 1039 (n = 18)		
Sex						
Female	184 (41.9)	34 (26.8)	8 (25.8)	3 (16.7)	Ref.	
Male	255 (58.1)	93 (73.2)	23 (74.2)	15 (83.3)	2.11 (1.44-3.10)	< 0.001
Age (years)						
0-49	69 (15.7)	18 (14.2)	2 (6.5)	3 (16.7)	Ref.	
50-64	115 (26.2)	29 (22.8)	9 (29.0)	3 (16.7)	1.09 (0.60-1.96)	0.780
65-74	92 (21.0)	34 (26.8)	3 (9.7)	5 (27.8)	1.34 (0.74-2.42)	0.336
≥75	163 (37.1)	46 (36.2)	17 (54.8)	7 (38.9)	1.33 (0.77-2.30)	0.300
Muscular manifestations						
No	424 (96.6)	126 (99.2)	30 (96.8)	18 (100.0)	Ref.	
Yes	15 (3.4)	1 (0.8)	1 (3.2)	0 (0.0)	0.34 (0.08-1.45)	0.144
Fatigue						
No	378 (86.1)	112 (88.2)	29 (93.6)	15 (83.3)	Ref.	
Yes	61 (13.9)	15 (11.8)	2 (6.5)	3 (16.7)	0.79 (0.47-1.35)	0.397
Respiratory involvement						
No	78 (17.8)	9 (7.1)	3 (9.7)	1 (5.6)	Ref.	
SARS pneumonia	250 (56.9)	79 (62.2)	8 (25.8)	7 (38.9)	2.15 (1.15-4.04)	0.017
Respiratory failure	111 (25.3)	39 (30.7)	20 (64.5)	10 (55.6)	4.00 (2.08-7.67)	< 0.001
History of falls						
No	429 (97.7)	120 (94.5)	30 (96.8)	14 (77.8)	Ref.	
Yes	10 (2.3)	7 (5.5)	1 (3.2)	4 (22.2)	3.54 (1.60-7.85)	0.002

Abbreviations: CK: creatine kinase; OR: odds ratios; CI: confidence interval; Ref.: reference interval

infection were included in the analysis. Of these patients, 17 (2.8%) had myalgia and/or arthralgia and 81 (13.2%) complained fatigue. Nobody reported cramps.

CK levels were dosed in all patients (11-12328, mean value: 251 ± 658 U/L): 176 (28.6%) patients had CK levels ≥ 200 U/L. Among these patients, 127 (20.7%) were included in group 1, 31 (5.0%) in group 2 and 18 (2.9%) in group 3. The demographic, clinical and laboratory characteristics are shown in Table I according to CK level.

Variables associated with CK levels

Bivariate association analysis results are reported in Table I. Muscular manifestations, fatigue and age were not significantly associated with CK level.

Conversely, sex, respiratory involvement and history of falls were related with hyperckemia. Men prevalence was 58.1% among patients with normal CK level and 83.3% among those with CK level ≥ 1039 U/L.

Among patients with normal CK levels, 25.3% had respiratory failure whereas this figure was greater than 50% among those with CK levels higher than 554 U/L, independently from SARS pneumonia. On the opposite side, the prevalence of SARS pneumonia was higher among patients who had CK levels lower than 555 U/L. A graph-

ical representation of the relationship between respiratory involvement and CK level is provided in Figure 1.

Patients who fell at home before hospitalization had CK levels significantly higher than others. In particular, the percentages of those who fell were 2.3 and 22.2% among patients with CK < 200 and ≥ 1039 , respectively.

Multivariate analysis confirmed these results. Table II shows the adjusted estimates of association between CK levels and the other variables. Respiratory failure was associated with hyperckemia (OR: 3.67, 95% CI 1.86 to 7.24, $p = 0.036$), together with history of falls (OR: 3.66, 95% CI 1.61 to 8.35, $p < 0.001$), SARS pneumonia (OR: 2.00, 95% CI 1.05 to 3.82, $p = 0.002$) and male gender (OR: 1.88, 95% CI 1.26 to 2.79, $p = 0.002$).

CK level and death

One hundred-two patients (16.6%) died. The distribution of deaths occurred within CK level categories is reported in Figure 2. Table III shows adjusted estimates of the risk of death according to the characteristics shown in Table I. CK levels were significantly associated with death. Compared with the normal level group, an increased risk of 51, 172 and 230% was observed among patients with CK 200-554 U/L, 555-1038 U/L and ≥ 1039 U/L, respectively ($p = 0.011$). When patients with el-

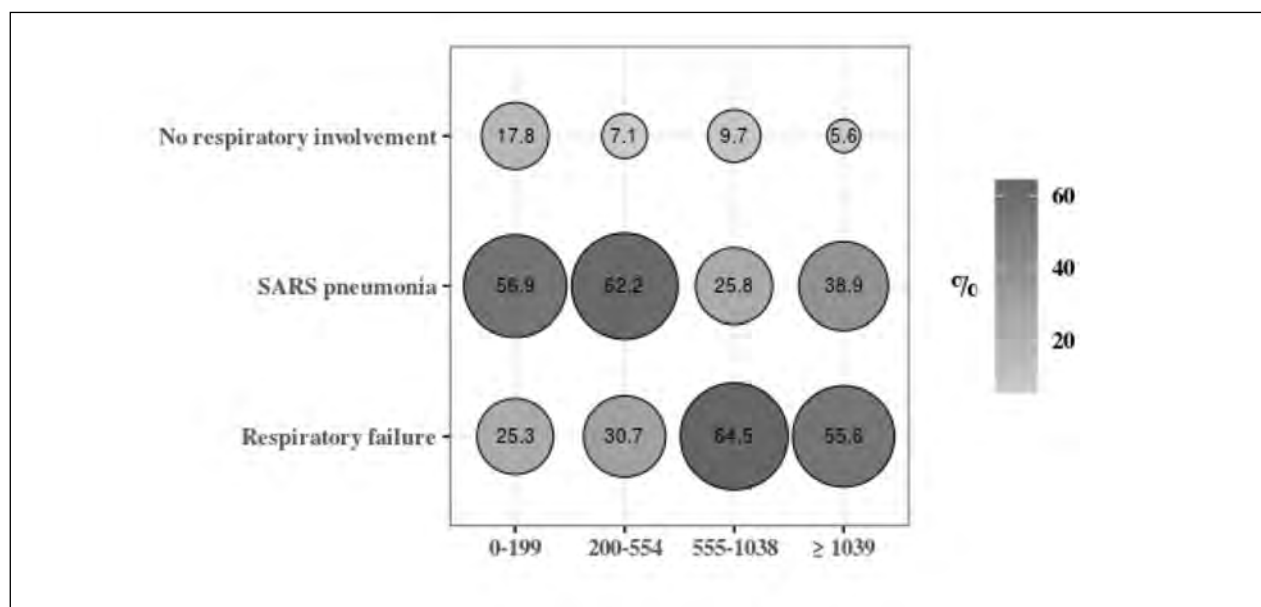


Figure 1. Percentage distribution of respiratory involvement according to CK levels.

Table II. Association between patients' characteristics and CK levels.

	OR (95% CI)	P-value
Sex		
Female	Ref.	
Male	1.88 (1.26-2.79)	0.002
Age (years)		
0-49	Ref.	
50-64	0.87 (0.47-1.60)	0.648
65-74	0.96 (0.51-1.78)	0.890
≥75	0.96 (0.54-1.72)	0.900
Muscular manifestations		
No	Ref.	
Yes	0.44 (0.10-1.96)	0.282
Fatigue		
No	Ref.	
Yes	0.84 (0.48-1.45)	0.531
Respiratory involvement		
No	Ref.	
SARS pneumonia	2.00 (1.05-3.82)	0.002
Respiratory failure	3.67 (1.86-7.24)	0.036
History of falls		
No	Ref.	
Yes	3.66 (1.61-8.35)	< 0.001

Abbreviations: CK: creatine kinase; OR: odds ratios; CI: confidence interval; Ref.: reference interval

Table III. Association between patients' characteristics, including CK levels, and in-hospital death.

	OR (95% CI)	P-value
Sex		
Female	Ref.	
Male	1.94 (1.07-3.50)	0.029
Age (years)	1.17 (1.13-1.22)	< 0.001
Muscular manifestations		
No	Ref.	
Yes	4.08 (0.38-44.34)	0.249
Fatigue		
No	Ref.	
Yes	0.75 (0.32-1.76)	0.509
Respiratory involvement		
No	Ref.	
SARS pneumonia	0.42 (0.17-1.02)	0.055
Respiratory failure	2.71 (1.15-6.41)	0.023
History of falls		
No	Ref.	
Yes	0.78 (0.24-2.52)	0.683
CK level (U/L)		
0-199	Ref.	
200-554	1.51 (0.78-2.92)	0.225
555-1,038	2.72 (1.00-7.42)	0.051
≥ 1,039	3.30 (0.85-12.87)	0.086
P-value trend		0.011

Abbreviations: CK: creatine kinase; OR: odds ratios; CI: confidence interval; Ref.: reference interval

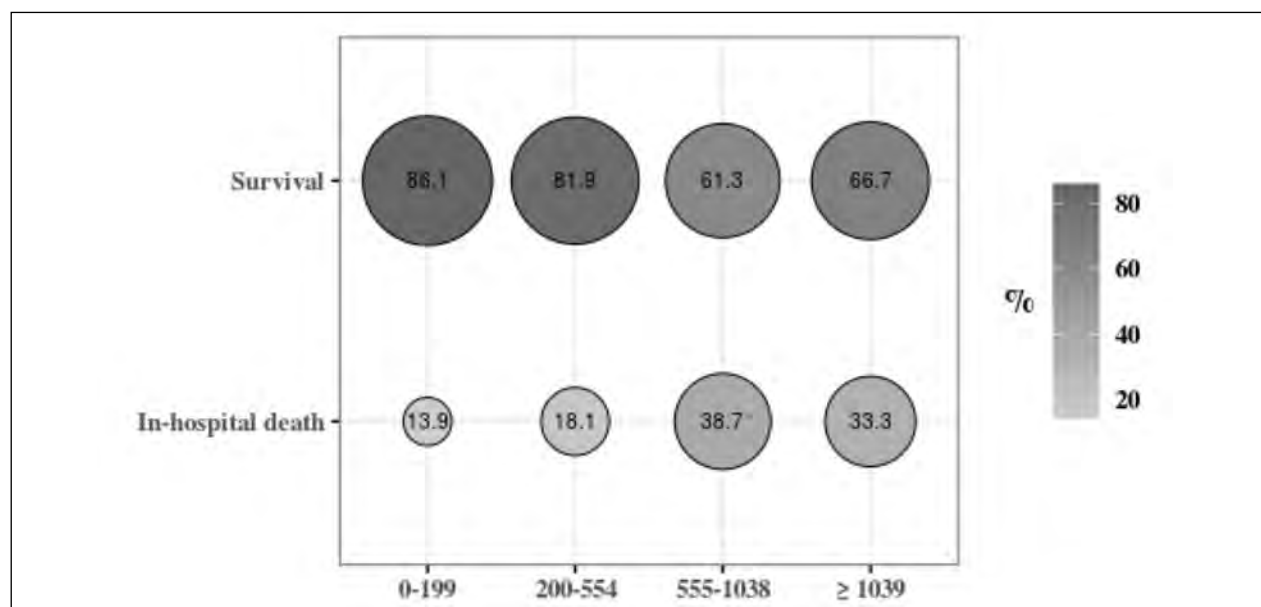


Figure 2. Percentage distribution of in-hospital death according to CK levels.

evaluated CK levels (≥ 200 U/L) were combined into one group, the risk of death was increased by 88% (95% CI, 6-232%).

Sex, age, and respiratory failure were also associated with mortality risk.

These findings did not substantially change by modifying the criteria for categorization of CK levels (Supplementary material, Table S1 and S2).

Discussion

In this study we evaluated the CK levels of a large cohort of COVID-19 patients focusing on muscle symptoms and clinical outcome.

To our knowledge, few studies analysed the correlation between CK levels and muscle injury^{5,9,10}.

Mao et al. studied the neurological manifestations of 214 patients with Coronavirus disease showing that patients with muscle injury (i.e. those with skeletal muscle pain and serum CK greater than 200 U/L) had significantly higher levels of CK (median: 400 U/L [range 203.0-12216.0] vs median: 58.5 U/L [range 8.8-212.0]; $p < .001$) compared with other subjects. Therefore, they speculated that muscle symptoms were owing to skeletal muscle injury and significantly elevated proinflammatory cytokines in serum may cause skeletal muscle damage⁵. Conversely, Vacchiano et al. analyzed 108 COVID-19 patients finding that muscle pain was not associated with CK high levels, supporting the notion that this symptom was not directly accounted for by muscle injury and making a direct viral mechanism unlikely⁹. As the

Italian colleagues, we did not find significant correlation among muscle symptomatology and CK levels. Instead, we found that patients with history of falls (i.e. patients admitted to hospital after falling at home) had CK levels higher than others ($p < 0.002$) even if there was no clinical evidence of muscle trauma on ER reports.

Regarding the clinical aspects, in literature the rate of cases presenting muscular symptoms varies from 63%⁷ to 26%⁸. In our population only 2.8% patients presented myalgia and/or arthralgia. This percentage rises to 15.9% if we include fatigue in the muscular manifestations.

Fatigue is a highly non-specific symptom, and it is hard to assess retrospectively if this figure was related to the infection itself or to a hidden muscle injury.

The low percentage of muscular symptoms observed could be due to the extreme hospital circumstances at the peak of this pandemic for which ER clinicians reported only the prevalent symptoms of the patients. Moreover, a proportion of subjects were unconscious at the time of arrival in the hospital or suffered of previous severe cognitive impairment so it was hard to access if neuromuscular symptoms were present or not. Furthermore, electrophysiological studies that could have been done to evaluate myopathy were infeasible during the COVID-19 epidemic.

In our cohort the mortality rate was 16.6% in line with previous studies¹⁶. Interestingly, we found that elevated CK levels were related with respiratory failure rather than with SARS pneumonia, in accordance with literature data⁵. Although it is impossible to establish a time-dependent relationship between respiratory failure

and hyperckemia because of the retrospective nature of the study, we found that CK levels were significantly correlated to fatal outcome. Previous studies conducted during SARS-CoV outbreak found that CK is an important predictor of oxygenation failure and death in patients with Severe Acute Respiratory Syndrome^{17,18}. In 2007 Chan et al. made a retrospective analysis of 1312 patients affected with SARS showing that CK is one of the predictive elements of oxygenation failure and poor outcome in these patients¹⁹. The most recent literature regarding SARS-CoV-2 infection reported raised serum CK levels in 33% of patients, reaching 46% for Intensive care unit patients⁶. A Chinese retrospective study confirmed that median CK levels (normal values < 190) were higher in deceased patients (189 U/L) than in the other patients (84 U/L)²⁰. Recently, Bonetti et al. found that CK represents one of the laboratory predictors of death from Covid-19²¹ while Pitscheider et al. showed a strong correlation among CK levels, disease severity and markers of inflammation¹⁰. There are currently also a few published case reports of rhabdomyolysis with myalgia and fatigue associated with severe SARS-CoV-2 infection²² with potential implications on renal function²³. Considered all together the above considerations, we thus can conclude that CK levels are correlated with the severity of COVID infection, more likely as an expression of myopathic involvement of skeletal and respiratory muscles during COVID-19 infection, rather than of a distress condition due to the strenuous respiratory muscle effort secondary to SARS interstitial pneumonia.

Conclusions

Our study provides evidence that hyperckemia is associated with respiratory failure and fatal outcome. Muscle manifestations are not associated with the raise of CK levels; however, because of the extreme hospital circumstances, they can be easily misdiagnosed. In patients with COVID-19 infection, among other testing, CK dosage is recommended. Further prospective studies to document the frequency of COVID-associated muscle damage are warranted.

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Supplementary material

Table S1. Association between patients' characteristics and CK levels.

	OR (95% CI)	P-value
Sex		
Female	Ref.	
Male	1.89 (1.27-2.80)	0.002
Age (years)		
0-49	Ref.	
50-64	0.82 (0.45-1.51)	0.525
65-74	0.92 (0.50-1.70)	0.788
≥ 75	0.96 (0.54-1.69)	0.874
Muscular manifestations		
No	Ref.	
Yes	0.44 (0.10-1.96)	0.280
Fatigue		
No	Ref.	
Yes	0.78 (0.45-1.36)	0.389
Respiratory involvement		
No	Ref.	
SARS pneumonia	2.10 (1.10-4.01)	0.025
Respiratory failure	3.66 (1.86-7.23)	< 0.001
History of falls		
No	Ref.	
Yes	4.11 (1.82-9.30)	0.001

Abbreviations: CK: creatine kinase; OR: odds ratios; CI: confidence interval; Ref.: reference interval
Patients were classified into the following groups: group 0 (CK < 200 U/L), group 1 (CK 200-288 U/L), group 2 (CK 289-501 U/L) and group 3 (CK ≥ 502 U/L)

Table S2. Association between patients' characteristics, including CK levels, and in-hospital death.

	OR (95% CI)	P-value
Sex		
Female	Ref.	
Male	1.97 (1.09-3.56)	0.024
Age (years)	1.17 (1.13-1.22)	< 0.001
Muscular manifestations		
No	Ref.	
Yes	4.05 (0.38-43.68)	0.249
Fatigue		
No	Ref.	
Yes	0.76 (0.32-1.77)	0.519
Respiratory involvement		
No	Ref.	
SARS pneumonia	0.42 (0.17-1.04)	0.060
Respiratory failure	2.71 (1.14-6.42)	0.024
History of falls		
No	Ref.	
Yes	0.77 (0.24-2.52)	0.670
CK level (U/L)		
0-199	Ref.	
200-288	1.62 (0.69-3.83)	0.267
289-501	1.37 (0.52-3.59)	0.524
≥ 502	2.62 (1.18-5.80)	0.018
P-value trend		0.019

Abbreviations: CK: creatine kinase; OR: odds ratios; CI: confidence interval; Ref.: reference interval

Management of respiratory complications and rehabilitation in individuals with muscular dystrophies: 1st Consensus Conference report from UILDM - Italian Muscular Dystrophy Association (Milan, January 25-26, 2019)

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Conflict of interest

The Authors declare no conflict of interest

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Respiratory complications are common in the patient with muscular dystrophy. The periodic clinical and instrumental respiratory evaluation is extremely important. Despite the presence in the literature of updated guidelines, patient associations often report lack of knowledge of these pathologies, particularly in peripheral hospitals. The purpose of this work, inspired by the Italian Muscular Dystrophy Association (UILDM) is to improve management of respiratory problems necessary for the management of these patients complex. To this end, the main items that the specialist can meet in the follow-up of these pathologies have been analyzed and discussed, among which the respiratory basal evaluation, the criteria of adaptation to non-invasive ventilation, management of bronchial secretions, situations of respiratory emergency, indications for tracheostomy and the subject of advance directives of treatment (DAT).

Key words: respiratory failure, muscular dystrophy, cough efficacy, spirometry, polygraphy, non-invasive ventilation, arterial blood gases, cough machine, invasive ventilation, tracheostomy, mechanical ventilation

Introduction

Even though the lungs are not directly involved in the disease process, respiratory problems are common in neuromuscular disease (NMD) patients ^{1,2}. Weakness of inspiratory and expiratory muscles causes decreased ability to expand the lungs and impairs alveolar ventilation leading to low oxygen and high carbon dioxide blood levels ³. Moreover, due to expiratory muscle weakness secretion management is also impaired because of ineffective expiratory flow during cough; saliva and mucus may accumulate in the upper airways and favour local infections, which may then propagate to lower respiratory tract and the lungs ⁴.

The extent to which respiratory involvement occurs and the pattern of the respiratory tests may change according to baseline disease and its progression. A number of diseases such as Duchenne Muscular Dystrophy (DMD) show a slowly progressive disease course and respiratory involvement occurs later on, in the advanced phases of the disease. In other diseases such as Facio-Scapulo-Humeral Dystrophy, acute respiratory insufficiency may be the presenting symptom ⁵. Moreover, other diseases, such as Myotonic Dystrophies (DM), predominantly show breathing disorders during sleep, which may disrupt diurnal gas exchange and aggravate centrally-driven symptoms such as excessive daytime sleepiness ⁶.

Standards of care and care recommendations for respiratory management are now available for DMD ⁷⁻⁹ and DM1 ¹⁰ where death occurs primarily due to respiratory insufficiency and cardiac problems ¹¹⁻¹⁴. This means that clinical centre neurologist and/or pulmonologist may have access to theoretical (pathophysiology) and practical (tests and parameters) information to manage NMD patients at best. However, since muscle disorders are rare, a doctor may happen to manage a very limited number of patients in his/her professional career. In addition, the quality of pulmonary function test and patients' cooperation highly depend on expertise of the technician performing the examination. Finally, access to specialized respiratory centres may be difficult for NMD patients and their families, causing delayed screening and follow-up assessment.

Finally, as research progresses and new treatments for respiratory complications become available, patient and family expectations increase: for this reason, it is crucial that, all patients may be given the possibility to timely access novel respiratory therapies/devices in. Implementation and adherence to standards of care will slow down disease progression and will give the opportunity to include more patients in clinical trials.

The aim of our study was to describe standards of care for the management of respiratory complications in

NMD patients and address some specific issues which are still a matter of controversy.

Materials and methods

Participants

Thirteen pulmonologists, 1 intensivist, 1 paediatrician, 1 psychologist and 2 respiratory physiotherapists with experience in respiratory care of paediatric and adult neuromuscular patients, from 16 different Italian sites, met in Milan to focus on the practical issues of respiratory management in muscular dystrophies in light of the existing standards of care for muscular dystrophies such as DMD and DM. One neuromuscular specialist was also included to integrate the respiratory clinical experience with disease-specific neuromuscular features and representatives from medical groups such as AIPO (Associazione Italiana Pneumologi Ospedalieri), SIP (Società Italiana Pneumologia), SIMRI (Società Italiana Medicina Respiratoria Infantile) as well as a patient representative were also present.

Methods

The method was inspired by the US NIH Consensus Program (<http://consensus.nih.gov>) and adapted from the Methodological Handbook of the Italian National Guideline System ¹⁵. This was the first Consensus Conference organized by the Italian muscular dystrophy association (UILDM). All activities were completed between September 2018 and April 2019. Planning and execution were carried out in 4 stages: (1) assignment, (2) scoping, (3) assessment, and (4) the consensus conference itself. The project included 4 workgroups (Box 1a).

DMD Standards of care implementation survey

In order to assess the level of implementation of respiratory SoC at each of the sites, a survey addressing each item described in the DMD SoC documents was used and given a score from 0 to 2, where 0 indicated that specific aspects were not carried out as described, 1 indicated that the recommendations were only partially addressed as described and 2 indicated that SoC recommendations for that specific item were fully covered. The results of the survey, described in Figures 1-3), showed that sleep studies and specifically nocturnal oximetry and/or capnography and polysomnography were only performed at some sites and, therefore, were not implemented as they should have. In addition, the assessment of maximal inspiratory and expiratory pressures (MIPs and MEPs) was not performed in the more advanced stages of the disease.

Box 1a. Consensus Conference methods Workgroups.

Scientific Committee (4 members): it planned and organized the whole project, nominated the Technical Committee and Workgroup members, chose the questions to be answered by the Workgroups, established the methods and rules of the Consensus Conference and chaired the Consensus Conference.

Technical Committee (9 members): performed the systematic review with evidence mapping and assisted with defining questions; experts (16 members): synthesized and integrated information, provided shared answers to the proposed questions, and presented their findings during the Consensus Conference.

Consensus Development Panel (8 members): established the reviewing and presentation procedures and provided the final evaluation.

¹ Candiani G, Colombo C, Daghini R, et al. Manuale metodologico: come organizzare una conferenza di consenso [online]. Rome: Istituto Superiore di Sanità, Sistema Nazionale Linee Guida SNLG; 2009 (<http://www.psy.it/wp-content/uploads/2018/02/Manuale-Metodologico-Consensus.pdf>).

Outcomes and endpoints

The overall aim of the workshop was to define baseline and follow-up respiratory assessments for children and adults affected by muscular dystrophy, to raise awareness among health professionals working in the acute settings that a specific approach is required for patients with muscular dystrophies having acute respiratory problems, while also providing caregivers with a practical guidelines for respiratory care. Specific aims of the project were: (i) define respiratory tests and procedures to be performed at baseline and at follow-up for all patients; (ii) determine criteria for starting non-invasive ventilation (NIV); (iii) provide indications for tracheostomy (IMV); (iv) define a protocol to manage acute respiratory insufficiency; (v) describe secretion management protocols; (vi) address end-of life protocols.

Unanimous consent was required to approve the care recommendations, protocol or pathway of care. In case of uncertainty, the panel agreed to declare that no consensus was reached and that further data were needed to define management for that specific aspect.

Respiratory management in patients with muscular dystrophies

Muscular dystrophies are characterized by progressive loss of skeletal muscle mass and progressive muscle weakness. In general, for most of them, respiratory decline becomes more obvious when patients lose ambulation. Weakness of the expiratory muscles causes an ineffec-

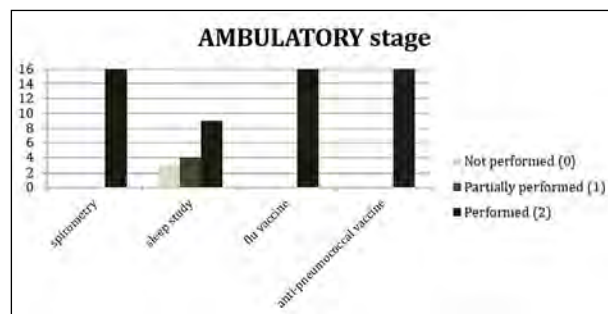


Figure 1. Survey results of participating centres for DMD ambulatory stage patients.

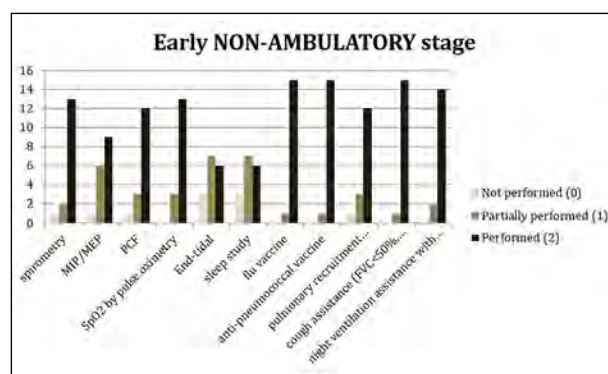


Figure 2. Survey results of participating centres for DMD early non-ambulatory stage patients.

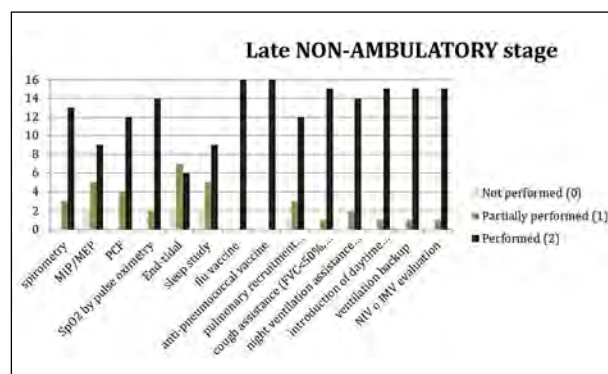


Figure 3. Survey results of participating centres for DMD late non-ambulatory stage patients.

fective cough while weakness of the inspiratory muscles and scoliosis contribute to the restrictive ventilatory deficit, leading to hypoventilation, initially only at night-time and subsequently, even during the day ¹⁶.

a. Respiratory Core data set

Baseline assessments

Look for symptoms of respiratory involvement such as those suggestive of hypoventilation (tiredness, shortness of breath, morning headaches, fragmented sleep,

excessive daytime sleepiness, concentration difficulties) and look for signs of pulmonary impairment (thoracic deformities, facial dysmorphism or paradoxical breathing, abdomen and thorax asynchronous movements suggestive of respiratory fatigue¹⁷.

Test for respiratory function including sitting FVC both as an absolute value and as a percentage of the predicted value; maximal inspiratory and expiratory pressures (MIP, MEP), expiratory peak cough flow (PCF). Assessment of sleep-related breathing disorders (SRBD) such as Obstructive Sleep Apnea Syndrome (OSAS) with nocturnal oximetry or cardio-respiratory polygraphy. Additional tests that can be performed are end-tidal or transcutaneous partial pressure of carbon dioxide and arterial blood gas analysis in adults. These tests should be performed if SpO₂ spot < 95% at RTP (Box 1).

Treat with air stacking exercises if FVC is < of 60% of predicted value using a self-inflating manual ventilation bag (AMBU bag) or mechanical insufflation-exsufflation device twice a day¹⁸.

b. Follow-up assessments

The progression of respiratory involvement is variable within muscular dystrophies; in many of these such as Becker Muscular Dystrophy (BMD), Facio-scapulo-humeral Muscular Dystrophy (FSHD) and most of the Limb-Girdle Muscular Dystrophies (LGMD) it usually occurs over years and a follow-up is recommended every year. However, respiratory involvement may occur early in the disease and may be prominent in LGMD2I (FKRP mutation) or occur only later on in LGMD2C-F e LGMD1B². In these cases, follow-up should be more frequent and similar to the more aggressive approach in DMD (Box 2). Generally, the follow-up should include measurements FVC in sitting and supine and PCF, in addition to symptom and suggestive signs of nocturnal hypoventilation detection. In case of FVC below 50% of the predicted value, or of signs and symptoms of nocturnal hypoventilation, nocturnal pulse oximetry or polygraphy are necessary. The follow-up timeline will also have to be based on the patient's conditions: if the patient is ambulatory, one assessment per year is sufficient, while non-ambulatory patients will have to be assessed every six months^{19,20}.

c. Focus on DMD

Spirometry should be first performed in DMD children from 6 years of age and it should be repeated every year. Sleep studies should be considered if there is weight gain subsequent to steroid treatment or if there are symptoms of sleep-related breathing disorders (decreased attention at school, irritability, excessive daytime sleepiness)²¹. Regular vaccinations (flu and pneumococcal) should be highly recommended. Caregivers should be

Box 1. Respiratory assessment: core data set.

Symptoms (fatigue, dyspnoea, morning headaches, frequent nocturnal awakenings, hypersomnolence, difficulty concentrating)

Objective signs (thoracic deformities, facial dysmorphisms, paradoxical breathing)

Spirometry with FVC, MIP, MEP, PCF

SpO₂ spot measure

Nocturnal SpO₂ or polygraphy

Additional test: end-tidal or transcutaneous partial pressure carbon dioxide

aware of initial signs of respiratory infections so that care can be started promptly.

As disease progresses and adolescents lose the ability to walk at around a mean age of 13-14 years, respiratory monitoring (pulmonary examination, FVC, PCF, nocturnal SpO₂) needs to be more frequent, and repeated every 6 months, specifically looking for symptoms of nocturnal hypoventilation. When FVC drops below 60% of the predicted value, air stacking techniques need to be introduced. Peak cough flow needs to be carefully determined when FVC drops below 50% of the predicted value or MEP is less than 60 cm H₂O and if the PCF is less than 270 L/min, patient needs close monitoring. In the late non-ambulatory stages, the criteria for NIV initiation should be re-evaluated every 6 months⁸.

d. Focus on myotonic dystrophies

Respiratory involvement is a typical feature of Myotonic Dystrophy type 1 (DM1), with pneumonia and arrhythmias being the main cause of death in these patients¹²⁻²¹. Although reports on respiratory involvement and how this progresses over time are scanty in patients with Myotonic Dystrophy type 2²², there is a general agreement that, although similar to DM1, respiratory involvement is less frequent.

Congenital Myotonic Dystrophy (CDM): respiratory insufficiency is the main cause of death in CDM and it

Box 2. DMD and "DMD-like dystrophies" with respiratory involvement.

Duchenne Muscular Dystrophy (DMD)
Limb-Girdle Muscular Dystrophy 2I (LGMD2I)
Myofibrillar Myopathies (MFM)
Facioscapulohumeral Dystrophy (FSH) with:

- small D4Z4 arrays (< 18 kb)
- early onset
- moderate/severe disease

is caused by weakness of the diaphragm and intercostals muscles as well as by the failure of cerebral respiratory control because of the severe cognitive impairment. Furthermore, the weak facial and oesophagus muscles may lead to swallowing inadequacy, and dysphagia mainly for liquids resulting in chronic lung inflammation, and/or aspiration pneumonia²³.

Paediatric onset myotonic dystrophy: respiratory impairment is less frequent in this group of children and adolescents. However, weakness of the respiratory muscles may affect the ability to cough, resulting in atelectasis, chronic lung infections, chronic bronchitis and bronchiectasis. Furthermore, as in new-borns, dysphagia may be present, and children may not be aware of it, so that they may be at risk for aspiration pneumonia.

Adult onset myotonic dystrophy: weakness of the respiratory muscles affects the ability to cough, resulting in atelectasis, chronic lung infections, chronic bronchitis and bronchiectasis. Weakness of the diaphragm and possibly diaphragmatic and respiratory muscles myotonia²⁴ may lead to nocturnal hypoventilation. This condition is worsened by sleep apnoea, leading to disrupted sleep, excessive fatigue, and morning headaches potentially contributing to lethal cardiac arrhythmias. Excessive daytime sleepiness (EDS) is in fact one of the most frequent complaints reported in this patient population reaching a prevalence of up to 88% in some studies²⁵⁻²⁷ and may be the presenting symptom of DM1, not infrequently, years preceding the diagnosis. Although mostly of central origin, EDS may coexist with sleep-related breathing disorders (SRBD) in some patients with DM1²⁸. Symptoms related to chronic respiratory insufficiency such as nocturnal hypoxemia and diurnal hypercapnia may be overlooked by the patients themselves probably because these gas abnormalities develop slowly, allowing brain/brainstem structures to adapt to these changes. It is not infrequent to find patients with unusually high levels of daytime hypercapnia not complaining of respiratory problems and who do not necessarily report EDS²⁹. Both peripheral and central components of EDS can be approached with existing treatment strategies. NIV is recommended to treat nocturnal hypoventilation related to chronic respiratory insufficiency but compliance is limited and despite NIV, EDS may persist. On the other hand, although off-label, modafinil may be used for the central component of EDS.

Late-onset myotonic dystrophy: respiratory impairment is not typically the most frequent complaint although the data on this specific subgroup of patients is scanty. The general impression is that disease progression may be more rapid than in the adult onset, so that respiratory monitoring is recommended despite the lack of symptoms or findings on initial assessments.

Criteria for starting non-invasive ventilation (NIV)

A reduction in vital capacity (VC), total lung capacity (TLC) and functional residual capacity (FRC) determine a respiratory deficiency which has a variable course between different disorders^{30,31}. Nocturnal Hypoventilation (NH) occurring especially during rapid eye movement sleep phase is the first manifestation of chronic respiratory insufficiency in neuromuscular disorders (NMD). It is unclear which definition of NH best relates to prognosis^{32,33}. A correlation between the reduction of VC and progression of sleep disordered breathing has been shown in patients with NMD³⁴. Daytime clinical assessments can be unreliable in early detection of respiratory failure because clinical symptoms of NH can be insidious and not always present³⁵. Early recognition of NH is very important because it can progress to daytime hypercapnia (partial carbon dioxide pressure [PaCO₂] > 45 mmHg in arterial blood) or clinical symptoms related to hypoventilation if it is undiagnosed and therefore untreated with NIV³⁶ (Box 3). Well-timed use of NIV is effective to reduce NH and its progression towards daytime hypercapnia³⁷. NIV should be started in the presence of daytime hypercapnia and/or clinical symptoms as recommended in the current guidelines³⁸⁻⁴⁰. NH diagnosis is not easy in NMD in which hypoventilation is defined as pCO₂ > 50 mmHg for a period longer than 25% of sleep time^{41,42} and this is because it is specifically studied in the paediatric population. Transcutaneous monitoring of pCO₂ levels could detect NH, even in patients that don't show symptoms and significant nocturnal hypoxaemia^{43,44} with similar results reported although the study group included a much wider population of respiratory restrictive disorders other than NMD. Finally, Ognà et al.⁴⁵ demonstrated the usefulness of tcPCO₂/SpO₂ as a NH diagnostic tool and suggested that a better definition of the NH threshold is needed. However, it is still not clear if nocturnal monitoring can be used as an additional tool to decide when to start NIV in clinical setting. Nocturnal polysomnography (PSG) and/or pulse oximetry with carbon dioxide monitoring were recommended in the 2004 by the American Thoracic Society as an indication to NIV for DMD (39). However, PSG has some limits, because it is not universally available, it is expensive, time consuming and not available during routine evaluations⁴⁶. Besides, PSG attributes apneas and hypopneas only to obstructive and central events rather than to inspiratory muscle dysfunction. Assessment of symptoms related to inspiratory muscle dysfunction is often delayed in patients affected by DMD⁴⁷. Unfortunately, night-time ventilation may be insufficient, with development of daytime hypercapnia,

Box 3. Indications for NIV initiation in DMD muscular dystrophy (from Birnkrant DJ et al, *Lancet Neurol* 2018).

FVC less than 50% predicted value

MIP less than 60 cm H₂O

P_{tc}CO₂ or p_{et}CO₂ or p_aCO₂ $\geq$ 45 mm Hg

Baseline SpO₂ less than 95% in room air (post airway clearance)

Box 4. Daytime NIV options.

Multiple interfaces options (nasal, oro-nasal, mouth-piece)

Warning skin lesions prevention

IAPV (intermittent abdominal pressure ventilation)

Negative ventilation

even when appropriate NIV adjustments are made and a vigilant clinical follow-up is done ⁴⁸.

Critical issues with NIV

Age: patient age at initiation of NIV treatment is a prognostic factor, in fact, those patients that require NIV before the age of 17 have a worse prognosis than those starting NIV at an older age. Due to improvements in respiratory care death by cardiac causes has become more common, indicating the need for active cardiology support as this approach may improve outcome.

Facial interface: sometimes, young patients do not easily accept NIV treatment because there is a poor tolerance of the interface, and this can be induced by various factors, such as excessive oral air leakage, excessive pressure of the mask on the face, claustrophobia, anxiety (because sometimes the patient may not be able to call a family member), and patient-ventilator dyssynchrony ⁴⁹. Hence, the interface plays an important role in tolerance and usefulness of NIV use. Interfaces that cover the nose alone or the nose and mouth (oronasal interface) are the most universally used; however, they can cause gastric distension, skin breakdown, conjunctivitis and claustrophobia ⁵⁰. In addition, the application of an oronasal interface can worsen social life, since it makes it difficult to eat, drink and talk. Besides, this type of mask alters the patient's perception of himself and may have negative psychological effects ⁵¹. Mouthpiece ventilation (MPV) via a 15-mm or 22-mm mouthpiece device is the preferable and more comfortable alternative; however, a more active participation of the patient is needed in this case. Patients requiring daytime NIV treatment (Box 4) better accepted the nasal mask treatment during the night hours, probably because the use of MPV during daytime hours made the patients feel safe, and gradually confident enough to be treated with NIV at night. The use of the nasal mask and MPV has enabled the treatment of patients who had formerly refused nasal, oral or oronasal interfaces. The possibility of using a mouthpiece as first choice interface for patients affected by DMD who need to start diurnal NIV treatment should always be kept in mind.

NIV monitoring

Once home mechanical ventilation (HMV) is carried out, it is required a regular follow-up to assess both optimal tolerance and efficiency of the treatment is required. In addition, the measurement of both blood gases and HMV monitoring can be performed with more than one approach with an increasing level of complexity, starting from simple tools, such as oximetry, and moving to the most comprehensive sleep recording systems using in-hospital polysomnography ⁵². Recently a management strategy, with a simple initial screening based on nocturnal oxygen saturation monitoring (SpO₂), followed by additional exams when there are pathological findings was suggested. Non-invasive transcutaneous measure of CO₂ (TcCO₂) has demonstrated to have acceptable accuracy in estimating PaCO₂ over numerous hours in stable patients treated with HMV ^{53,54} showing a higher sensitivity than SpO₂ in finding residual hypoventilation in NMD patients ^{55,56}. Current recommendations regarding settings and monitoring of HMV are based on expert opinions ⁵⁷. The European SOMNONIV Group suggests the use of an algorithm to monitor HMV, which includes oximetry as the first screening step to detect patients who require further nocturnal exams, and advises a mean nocturnal SpO₂ over 90% for at least 90% of the total recording period as a therapeutic goal. The 2010, AASM clinical practice guidelines recommend adjusting the ventilator support if hypoventilation is present for $\geq$ 10 minutes. Recent data showed that TcCO₂ can be an accurate estimation for PaCO₂ in long-term mechanically ventilated patients, with the advantage of finding episodes of transient hypoventilation, not detected by punctual arterial blood gases analyses. The use of TcCO₂ opens the possibility to evaluate the ventilation's usefulness directly and several times at home, allowing a simplification in the management of HMV. However, although capnometry devices have registered technical improvements, TcCO₂ accuracy is strongly dependent on appropriate handling and knowledge of the equipment and procedures. Risk assessment is an important part of discharge planning, and risk will vary according to the use of NIV or invasive ventilation, patient's diagnosis, the degree of ventilator dependency, functional

ability and comorbidities. In a UK study a total of 188 home visits in 6 months were to analyse home problems in 1,200 patients that used predominantly NIV. About one-quarter of these problems were caused by the ventilator, while 43 were caused by technical issues (noisy equipment and recurrent alarms). No patients died or experienced side effects as a result of equipment problems in these studies. More hospitalizations were seen in the “no fault” category, in which patients or caregivers reported a ventilator malfunction. However, when a home visit was performed, a ventilator malfunction was not found; a possible explanation of this is that the patient had become unwell (usually due to an infective exacerbation) and interpreted this event as a ventilator problem⁵⁸. These findings illustrate that patients, families and caregivers require different types of competencies, and shows that a clear problem-solving approach is needed in educating home care teams. In this area, the increasing competence to provide home telemonitoring and to observe data remotely from the ventilator has created great interest⁵⁹.

Focus on DMD: natural history studies in Duchenne muscular dystrophy (DMD), show that patients develop respiratory failure. This usually starts as nocturnal hypoventilation (NH)⁶⁰ and improves with the application of nocturnal non-invasive ventilation (NIV)^{61,62}. If not treated, almost 90% of DMD patients die from pulmonary complications associated with respiratory muscle weakness between 16 and 19 years of age^{63,64}. Nowadays, with the implementation of SoC, it is not infrequent to see that about half of this patient population reaches the age of 25.3-30.4 years as reported in four most favourable nocturnal NIV studies⁶⁵. In DMD patients the vital capacity (VC) peaks are registered between 9 and 16 years of age, and then the VC decreases by 5-10% per year until ventilatory support is needed for survival⁶⁶.

Focus on DM: adaptation to NIV is limited in these patients. Symptoms related to chronic respiratory insufficiency such as nocturnal hypoxemia and diurnal hypercapnia are overlooked by the patients themselves probably because these gas abnormalities develop slowly allowing brain/brainstem structures to adapt to these changes. When NIV is prescribed as a chronic treatment option, compliance is limited mainly because of the lack of symptoms immediately related to respiratory involvement and therefore the benefits of NIV use are not perceived in the short-term nor perceived as effective by the patients. Fatigue and EDS in fact usually persist despite NIV although SRBD improves with NIV constant use. The data on the effects of withdrawal and how this affects prognosis are still scanty⁶⁷⁻⁶⁸.

Indications for tracheostomy

Use of home non-Invasive Ventilation (NIV) in neuromuscular disease (NMD) patients with chronic respiratory failure (CRF) may be expected to extend survival by many years, improve physiologic function and quality of life as well as decrease the frequency of episodes requiring acute care facilities⁶⁴. Based on these considerations and the fact that safety, comfort, satisfactory speech and swallowing have been reported by long-term users, NIV should be regarded as the therapy of choice in supporting breathing in DMD⁶⁹. Nevertheless, a significant proportion of DMD individuals are currently prescribed tracheostomy ventilation (TV) for home ventilatory care. Indeed, recent data published by one of the 14 reference centres for NMD in France, showed that 31 out of 150 DMD patients who had undergone long-term mechanical ventilation (LTMV) between 1997 and 2014 had initiated ventilatory assistance via a tracheostomy, although mechanical ventilation had increasingly started using a non-invasive interface over the course of the study period⁷⁰. In most cases, the decision to perform a tracheostomy is taken when NIV becomes ineffective: according to recent data collected by MD STARnet, the largest population-based surveillance system of individuals with DMD and Becker muscular dystrophy (BMD) in the United States, approximately 90% of patients had received tracheostomy following NIV treatment failure⁷¹.

When to perform a tracheostomy?

Placement of a tracheostomy may be considered both in the event of a life-threatening acute illness that has required invasive management and when a slowly progressive ventilatory failure is present. Indeed, although the non-invasive approach, based on the combination of NIV and assisted coughing techniques, in particular Mechanical Insufflation–Exsufflation (MI-E), should be preferred as a first-line intervention for patients with DMD during an episode of Acute Respiratory Failure (ARF), moving⁷² on to invasive ventilation with intubation becomes unavoidable in case of NIV failure, inability to clear secretions with cough assist and suctioning or the loss of ability to protect the airway with high risk of aspiration. Unfortunately⁷³, once intubated, a substantial proportion of NMD patients may encounter particular difficulties while being liberated from the endotracheal tube after recovery from the acute illness, due to weakness of the inspiratory muscles, inadequate cough and inability to handle oropharyngeal secretions, thereby having to switch to a tracheostomy⁷⁴. Of notice, a large uncontrolled study unexpectedly reported that the standardized use of NIV and cough assistance may lead to an effective extubation of the great majority

of “unweanable” NMD patients who could not pass a spontaneous breathing trial ⁷⁵.

In DMD patients with chronic, progressive ventilatory failure, indications for performing a tracheostomy have not been clearly defined ⁷⁶. According to the consensus conference of the American College of Chest Physicians, and more recently the American Thoracic Society consensus for DMD respiratory care ³⁹, severely impaired swallowing, leading to chronic aspiration and repeated pneumonia, and/or ineffective clearing of tracheobronchial secretions, despite the use of non-invasive manual or mechanical expiratory aids, have been considered to be indications for TV. In current practice, no level of pulmonary function or blood-gas abnormality absolutely mandates tracheostomy over NIV. However, a Vital Capacity (VC) value below 20% predicted, a PaCO₂ level above or equal to 45 mmHg during assisted breathing, a need for increased ventilation time, and a severe clinical status at initiation of NIV, suggest an overall risk of NIV failure and the forthcoming need for a tracheostomy ⁷⁷. Morphologic characteristics of the patient, as difficult intubation prediction, and environmental circumstances determining the ease or difficulty in using emergency service are to be taken into account as well.

In line with the recent German national guideline for treating CRF ⁷⁸ indications for tracheostomy in NMD patients have been summarized in Box 5 and Box 6.

How and where to perform tracheostomy?

Performance of a tracheostomy as an elective procedure by skilled surgeons and follow-up care in specialized centres may reduce the risk of early and/or late post-operative complications ⁷⁹.

In literature, there are no specific indications about tracheostomy implementation, percutaneous or surgical ⁸⁰, but it has been agreed by the participants that, in case of long-term tracheostomy, the surgical technique is preferred. Such indications reflect the need for an easier and safer periodic tube change, a lower risk in case of stable surgical stoma, reduced accidental decannulations, always fearsome when dealing with totally ventilator dependent patients ⁸¹. Risk factors that can complicate the tracheostomy change include obesity, a short neck, anatomical abnormalities, excessive granulation tissue, lack of patient cooperation. In case of tracheostomy recently performed (in the previous 2 weeks) or in case of an anticipated difficult tracheal tube exchange, we suggest using the “railroad” technique with a guiding obturator ⁸².

Impact on patients and family

Once long-term TV is initiated, DMD patients require special considerations for care. Outcome and pa-

Box 5. Indications for tracheostomy in neuromuscular disease patients (from Windisch W et al. *Respiration* 2018;96:171-203, mod.) ⁷⁸.

Inability to fit an appropriate ventilation interface
NIV intolerance
NIV inefficiency
Severe bulbar symptoms with recurrent aspiration
Inefficiency of non-invasive secretion management
Failure to switch to NIV after intubation and invasive ventilation

Box 6. Recommendations for patients who are expected to be on long-term IV (from Windisch W et al. *Respiration* 2018;96:171-203, mod.) ⁷⁸.

Tracheostomy for long term ventilation should be performed surgically and not percutaneously
Patients on NIV ≥ 16 hours a day need to be equipped with 2 ventilators, one acting as a back-up, and need to have an external battery
Patients need to be equipped with an oximetry machine
Patients need to be provided with an extra tracheostomy tube of a smaller diameter than the one in place in case the tube gets removed accidentally and needs to be promptly replaced at home
In order to use a speaking valve, patients' cuff must be deflated
The ventilator needs to be provided with active an humidifier so that the air inspired is sufficiently humidified and warm
2 suction machines are required

tient comfort are improved with the application of a well-conceived management plan including education for patients, families, and health-care providers, and by an active role by home-care agencies in providing care to these patients ⁸³.

Being unable to speak is a major cause of frustration for patients with a tracheostomy tube and their families: a tracheostomy, however, presents opportunities to promote articulated speech. Airflow through the upper airway and vocal cords is necessary for voice production: for this reason, partial cuff deflation may allow the patient to speak in a whisper during the inspiratory phase of the respiratory cycle. Adding a small amount of positive end-expiratory pressure produces a continued air leak and permits audible speech throughout the breathing cycle ⁸⁴. Moreover, subjects with minimal ventilator requirements can be ventilated with cuffless tubes that allow a constant air

leak and the ability to speak. Finally, the use of a one-way valve, such as a Passy-Muir valve, allows airflow through the tracheostomy tube during inspiration but does not permit air to exit the tracheostomy tube during exhalation. When the valve is employed with a cuffless or fenestrated tracheostomy tube, expiratory airflow is directed through the vocal cords and normal speech is facilitated⁸⁵.

A comparison of morbidity and causes of death in a number of DMD patients receiving full-time mechanical ventilation either by tracheostomy or by NIV, showed that the risk of complications was higher in tracheostomized compared with NIV patients, in particular mucus hypersecretion and tracheal injuries⁸⁶. Furthermore, data on mortality showed that the risk of death at 12 years does not significantly differ between DMD subjects undergoing long-term NIV or TV⁸⁷.

In conclusion, the decision to perform a tracheostomy in DMD ventilator-dependent individuals is complex and involves medical, ethical and financial considerations. Patients giving their consent to its application may live at home despite NIV failure.

Secretion management

Respiratory insufficiency and pneumonia are primary causes of mortality and comorbidity in many NMDs². Airway clearance techniques (ACT) are an essential component to the care of people with NMDs. During acute respiratory tract infections, patients with NMDs develop dyspnoea, hypercapnia and a reduction in both respiratory muscle strength and lung function⁸⁸.

What is important to control regularly?

Among, the various measurable parameters, the most useful, when referring to cough efficacy, are:

- Vital Capacity (VC);
- Maximal Insufflation Capacity (MIC);
- Peak Cough Flow (PCF).

VC and MIC can be measured by a simple portable spirometer or flow meter. MIC, the maximum capacity of keeping air in the lungs, starting from vital capacity, through air-stacking manoeuvres, represents the best rib cage elasticity index: it should be measured when VC is below 2000 ml or at 50% of predicted in adults⁸⁹. In the evaluation of cough efficacy, PCF is the most reliable and simple to use assessment at the patient's bedside^{90,91}, reference values are available for children⁹² and adults: cut-off values for cough efficacy in normal adults range from 360 to 840 L/min⁹³. The PCF can be easily measured with a hand-held flow meter or a pneumotachograph/spirometer⁹⁴ using an oro-nasal mask or a mouthpiece⁹⁵. When the values are higher than 270-300 L/min, they are believed to be safe because it is expected that a PCF > 160

can be maintained during episodes of exacerbation⁹⁶. In clinical practice, an efficient cough requests a PCF higher than 160-200 L/min⁹⁷.

What to do when PCF < 270 L/min or VC < 50% or < 2000 ml?

It is important to regularly measure PFC and VC as, even in case of significative muscular weakness, the patient might not experience symptoms in everyday life. If PCF values are stably below 270 Litres/minute or VC < 50% of predicted or < 2000 ml in an adult patient, it is necessary to introduce cough assistance techniques, either manual or mechanical.

a. Manually assisted coughing

Manual cough assistance techniques can assist the inspiratory or expiratory phase, or both.

Assisted inspiration

In order to produce an efficient cough, deep inspiration preceding the expiratory phase is essential. The quantity of inhaled air can be increased by using an AM-BU bag in the air-stacking manoeuvre, or by the use of mechanical ventilator in volumetric mode, with the inhalation of one or more consecutive breaths, without breathing out, in order to obtain a full deep breath. Some patients are able to learn glossopharyngeal breathing (GPB), that allows improved air stacking in the absence of any respiratory device.

Assisted expiration

Manual assistance manoeuvre in the cough expiratory phase consists in chest and abdomen compressions by the caregiver to improve the expiratory flow and promote secretions removal.

b. Mechanical in-exsufflation

Mechanical in-exsufflation (MI-E) is a very popular cough augmentation technique⁹⁸. MI-E devices produce inspiratory and expiratory assistance. MI-E is well tolerated³⁰ and may be delivered by non-invasive or invasive⁹⁹ interfaces. MI-E associated with manual assisted coughing, oximetry feedback and home use of non-invasive ventilation was shown to effectively decrease hospitalizations and respiratory complications and mortality in a program for patients with amyotrophic lateral sclerosis¹⁰⁰.

How to manage deep secretions?

Peripheral ACT incorporates the techniques that aim to improve ventilation and enhance mucus transport from the bronchi to the upper airways. Different techniques

have the potential to loosen secretions and transport them from the peripheral to the proximal airways: these include High Frequency Chest Wall Oscillations (HFCWO), Intrapulmonary Percussive Ventilation (IPV), and Chest Wall Strapping (CWS)¹⁰¹. Peripheral ACT does not require the patient's co-operation. The use of these techniques is possible in infants, children and adults, even in the presence of a tracheostomy and/or bulbar failure or intellectual impairment. Carers must know that peripheral secretions cannot be mobilized in patients who have retained proximal airways secretions. Rather, it is recommended to use peripheral ACT after more central airways are cleaned of secretions by means of proximal ACT. In other words, sessions of airway clearance should first empty the proximal airways and then, if the patient is not too tired, mobilize secretions from the peripheral airways. If patients are exhausted, it is not recommended to approach the patient with peripheral ACT because these will not be tolerated and cough will be ineffective. This could put the patient at risk of having a respiratory arrest because of the excess of secretions without being able to get rid of them using a cough-machine. Recommendations to manage secretions are summarized in Box 7.

Management of acute respiratory failure

ARF most often occurs during otherwise benign upper respiratory tract infections favouring mucous encumbrance, and further weakening of respiratory muscles⁸⁸ or in cases of pneumonia, aspiration or atelectasis⁷³. Other causes of ARF in these patients are pneumothorax, fat embolism and abuse of sedative drugs³⁰. Several muscular dystrophies are associated with dilated cardiomyopathy^{102,103}, which may cause pulmonary edema and favour ARF³⁹.

A proactive clinical approach should be taken to prevent the onset of ARF and allow carers to recognize signs and symptoms potentially leading to ARF early, such as increased respiratory rate, tachycardia, tidal volume reduction in ventilated patients^{9,64,104}.

Admission to the hospital for ARF can be very disruptive for these patients¹⁰⁵, who could be successfully managed at home by experienced and well-trained family members and/or healthcare professionals¹⁰⁶. Bach and colleagues⁹⁶ described a protocol for managing these patients at home in case of respiratory tract infections, reporting a dramatic reduction in the need for hospitalization and a prolongation of life expectancy. More recently, Vianello et al. showed that active treatment provided by healthcare professionals is an effective alternative to hospital admission for selected NMD patients with respiratory infections¹⁰⁷. In particular, during respiratory infection, early

Box 7. Secretion management: recommendations.

PCF and VC assessment are suggested at every follow-up visit

A spirometer or a hand-held flow meter can be used to measure PCF keeping the same type of interface, such as oro-nasal mask or mouthpiece, in the following evaluations

The use of MI-E is safe and effective through both invasive and non-invasive interface, in paediatric and adult patient

Ending the MI-E session during the inspiratory phase is recommended to avoid phenomena of atelectasis, especially in frail patients

To avoid secretion encumbrances in patients with ineffective cough, sessions of secretions removal from central airways must be performed before and after peripheral ACTs

use of antibiotics is mandatory if pulse oximetry is below 95% on room air³⁰. Moreover, according to Bach's protocol⁹⁶, the patients should receive 24-h NIV during the exacerbation. Pulse oximetry should be monitored continuously and when oxygen saturation on room air falls below 95%, secretion removal should be aggressively induced using cough assistance until oxygen saturation returns to the 95% range. Oxygen should not be used to correct hypoxaemia at home, because it can worsen hypercapnia and it does not allow the recognition of a severe hypercapnia with the pulse oximetry. Finally, family members should be trained to use strict criteria leading to urgent hospital admission, and the home treatment protocol should be tailored according to local resources.

If home respiratory management fails, patients must be hospitalized⁷³. Few prospective studies on the management of NMD with ARF¹⁰⁹ and some retrospective studies^{64,109-112} reported the successful use of a non-invasive approach (i.e., NIV combined with assisted coughing) to improve gas exchange abnormalities and avoiding intubation. However, patient selection remains important for the success of this strategy. In particular, severe bulbar dysfunction increases the patient risk for aspiration, and hampers the elimination of airway secretions impeding successful use of non-invasive approach¹⁰⁸. Close monitoring of these patients is mandatory, and NIV should never delay endotracheal intubation for most severe cases⁷³. Monitoring must be tailored and personalized according to the clinical and respiratory severity of each case. In particular, PaCO₂ measurement (i.e., capillary CO₂ in mild disease and indwelling arterial line in most severe cases) must be included if supplemental oxygen is used to correct hypoxemia¹¹³. It follows that these patients should be admitted in a unit where medical and nursing staff is ad-

equately equipped to apply close monitoring and aggressive non-invasive respiratory assistance. Also in this setting the continuous presence of well-trained care-givers is important for the success of the treatment⁷³ Caregivers may provide continuous care, including repositioning of mask and administration of cough machine; otherwise, the presence of a skilled nurse is needed, with a nurse-patient ratio of 1:1¹⁰⁴.

If a non-invasive approach fails or is contraindicated, patients can be intubated as a short-term measure. In this case, assessment for a difficult intubation due to reduced mouth opening, macroglossia or limited mobility of the cervical spine is very important. If any of these conditions are present, intubation should be performed taking into account the guidelines for difficult airway management avoiding emergency intubation¹¹⁴.

After recovery from the acute illness, patients with muscular dystrophies should be promptly extubated. Unfortunately, because of weakness of the inspiratory muscles, inadequate cough, and inability to handle oropharyngeal secretions, a substantial proportion of these patients fail the weaning process¹¹⁵. Preventive application of NIV combined with assisted coughing after extubation provides a clinically important advantage to these patients by avoiding the need for reintubation or tracheostomy and shortening their stay in the ICU¹¹⁶. Moreover, Bach and al. suggest using cough assistance devices before extubation to clear the airways. Once SpO₂ is maintained > 95% on ambient air, patient should be extubated to full NIV support and aggressive cough machine to maintain or return to the SpO₂ ≥ 95%. The indication for a tracheostomy can be evaluated, but it should not be considered in the acute phase. In particular Bach and al. suggest to consider tracheostomy only in case of multiple failures with the application of the discontinuation protocol⁷⁵. Recommendations suggested for patients with muscular dystrophies in case of emergency management are summarized in Box 8.

Care choices and advanced directives

Although NMDs are uniformly fatal, each has a different life expectancy and disease trajectory that potentially influences health care decisions and raises unique ethical concerns. The burden of NMDs is high with consequences requiring repeated and extended hospitalizations, clinical management and frequent interactions with clinicians of many different specialties.

Some of the ethical challenges raised by NMDs include the choice and effectiveness of life-sustaining therapies and advance care planning: these issues involve informed consent and end-of-life care¹¹⁷.

Palliative care (PC) is an “active and global care of patients suffering from diseases that cannot be cured, in order to control pain, dyspnoea and including psychological, social and spiritual aspects”¹¹⁸. The uncertainties that arise in caring for NMDs, coupled with the increasing availability of therapies and technologies, create complex ethical quandaries for families, caregivers, society, school and clinicians. Such quandaries are exacerbated by the certainty

Box 8. Emergency management: recommendations.

Clinicians must know that the development of respiratory tract infections in patients with muscular dystrophies, is a life-threatening event favouring the appearance of mucous encumbrance and further weakening of respiratory muscles that leads to ARF.

A proactive clinical approach should be taken to recognize pulmonary problems prior to the onset of respiratory compromise. Patients who have a FVC <50% of predicted value can be trained to use a protocol that provides indications for the use of NIV, cough assistance and pulse oximetry in case of respiratory infections.

NIV combined with mechanically assisted coughing has been established as standard practice in patients with muscular dystrophies affected by ARF either in the outpatient or in the inpatient (hospital). In particular, techniques to aid secretion removal must be applied aggressively if bronchial encumbrance is present.

During respiratory exacerbations they can be successfully managed at home if family members are well-trained to use NIV, cough assistance and pulse oximetry. Oxygen alone should not be used to correct hypoxemia. Early use of antibiotics is mandatory. Family members should be trained to use a protocol that defines also when patients need urgent hospitalization. This protocol should be tailored according to local resources.

If home respiratory management fails, patients with muscular dystrophies must be hospitalized and they should be placed in a unit where medical and nursing staff is adequately equipped for the aggressive management of these children and close monitoring. Monitoring must be tailored and personalized according to the clinical severity of each case.

The continuous presence of well-trained parents or other care-givers is important for the treatment success also in the critical care setting.

The use of NIV should not delay endotracheal intubation for most severe cases, avoiding emergency intubation.

After recovery from the acute illness, patients with muscular dystrophies should be promptly extubated and started immediately on NIV and cough assistance. Tracheostomy should not be considered in the acute phase and should be considered only in case of multiple failures of weaning protocol.

from the time of diagnosis that these diseases are life limiting¹¹⁷. The most frequent and stressful ethical challenges for NMDs occur in regards to ventilator support, ventilatory support (benefit vs harm), families wishes to receive long-term tracheostomy ventilation¹¹⁹⁻¹²¹, palliative management, differences in opinion between family members and differences in physician opinions. For NMDs there are triggers for referral to palliative care services¹²².

In summary, factors influencing patient/family decisions for ethical concerns are local tradition, level of home assistance, stress, patient's age, where they lived, confusion about disease severity, internet information bias, variability in management across specialties and countries, cases reported in the media, paucity of quality-of-life data, lack of anticipatory care planning (ACP) resulting in critical decision making. NMDs patients frequently die in ICU and acute settings, have a low level of awareness about their disease prognosis¹²³. Italian respiratory units have, only in a minority of cases, a clear ACP and palliative/end of life plan¹²⁴. ACP is the process of communication between individuals and professional caregivers that includes, but is not limited to, options for end-of-life care and the completion of advanced directives. Typically, for NMDs and during an emergency, decisions may be made by clinicians who are unfamiliar with the child, and there is little time for confrontation¹¹⁹. Like other types of preventive medicine, ACP are underutilized even though they are cheap, low-tech, and potentially highly effective¹²⁵. ACP facilitate the application of the proportionality care principle, pain/dyspnoea/anxiety treatment, informed consent, doctor/patient relationship, psychological assistance and trustee administrator presence. On the contrary, ACP could compromise the relationship between doctor and patient due to the mandatory respect of a pure contract; the possibility to refuse incongruous requests in the presence of new undefined therapies, the lack of clear patient informed competence, the risk of conflict between trustee administrator and family and the debate over artificial nutrition and hydration as care treatments, may remain unresolved problems. Recommendations for advanced directives are summarized in Box 9.

Conclusions

There is increasing evidence of a link between respiratory and mental health¹²⁶. In fact, literature suggests that in patients with chronic respiratory diseases, the evaluation of breathlessness perception, psychological disturbances and the recording of any stressful event should be considered as relevant as the physical and functional assessment of respiration¹²⁷.

In severe neurological conditions, ventilator users can present mainly two types of needs: respiratory related needs, including mode of ventilation prescription and

selection, maintenance of lung recruitment and good airway clearance; non-respiratory related needs, including substantial nursing care, adequate nutrition, accessible communication and psychological support. It is relevant to pay attention to all of these needs with the aim to maintain patients' quality of life (QoL)¹²⁸.

A UILDM - Telethon study provides evidence in favour of an integrated care model for muscular dystrophies

Box 9. Care choices and advanced directives.

1. A frank, early and individualized conversation is mandatory:

Listen and talk to your patients
Consider and imagine their preferences and future

2. Timing of conversation with patients/family:

ICU admission
Hospitalization for respiratory reasons
Continuous NIV for more than 16 hours/day
Persisting hypoxemia during NIV use
Severe comorbidities (congestive cardiac failure, gastro-intestinal pseudo-obstruction)
Severe malnutrition
Bulbar symptoms
Recurrent infection and severe malnutrition during tracheostomy ventilation
Cognitive deficit
Poor family network

3. Push for anticipatory care planning (ACP):

Decisions should be made in advance and not during an acute situation
Decisions must be individualized and based on the most objective criteria possible
Extend survival improving quality of life and facilitating the patient spending as much time as possible at home
ACP can be extended to all life support measures including the DNR and withdraw from MV

4. Doctor/team responsibility

The doctor has the legal and ethical responsibility to propose all options treatment including MV
The doctor should avoid personal perception
A multidisciplinary approach is recommended
An ethical committee involvement is welcomed also for moral distress and conflicts of conscience
Team training is needed

5. Taking care of end of life time

Check patient's physical and psychosocial symptoms
Do not unduly prolong life and suffering
Patients who choose not to resort to MV should receive adequate end of life care
Facilitate the presence of family, friendly people and religious comfort
Consider hospice competencies and palliative care consultation services for your patients ("Home hospice" care could be preferred)

that is suitable for: pharmacological treatment, rehabilitative interventions¹²⁹, psychological treatments, welfare and financial support¹³⁰. Medical care of a patient with DMD and his family is not complete without support for their psychosocial wellbeing¹³¹. The families' lives change significantly with the decision to place their child with NMD on HMV because of the experience of a recurrent sense of loss and uncertainty. It would be suitable to improve support by health care professionals, their extended family, and their community, to enable parents to fulfil their vital role¹³².

Interestingly, parents of paediatric neuromuscular patients requiring HMV did not refer significantly higher parental stress compared to parents of non-ventilated children, despite their children having a lower health-related QoL; this data suggests that parents living with a continuous care demand could undergo a progressive adjustment process allowing them to consider respiratory care as a part of "normal" life, thus without the perception of this being an additional source of stress¹³³.

A number of ethical challenges, or dilemmas, can arise alongside treatment progression: the decision-making process regarding whom HMV should be offered to, respect for patient and family wishes, QoL, dignity and equal access to dedicated assistance. Moreover there is uncertainty regarding the impacts of HMV on the patient, the family, the healthcare services and the allocation of resources. A better and broader understanding of these issues is crucial in order to improve the quality of care for both patient and family and to assist HMV professionals to improve the decision-making process and to keep the patient and his or her family highly involved¹²¹.

Improvement and standardization of care pathways, with a better management of comorbidities related to neuromuscular diseases, has led to an increase in life expectancy and an increased number of patients reaching adulthood. Adolescence and adulthood are age groups in which new and challenging problems may develop. Care of children with chronic disorders is often complex, involving a high level of ongoing interaction between caregivers and the multidisciplinary health care team.

The transition from childhood to adulthood has therefore become an emerging problem that involves medical, psychological, social and economic aspects centred on the family. An unmanaged, non-standardized transition increases the risk of adverse outcomes. During this critical period, these patients are at increased risk for interrupted health care and related negative health consequences: They must cohabit with their progressive disability: decreased mobility, decreased independence for hygiene, increased needs of technological support, increased survival rate but at the same time increased morbidity. In

general, the diagnosis is made in paediatric age and the co-morbidities develop starting from adolescence.

It is necessary to develop a standardized multidisciplinary transitional program focused on the needs of the patient around which the various professionals must gravitate. Health care providers and educators are among the best facilitators for discussions around health, education, sexuality, employment, social development and adult living. Therefore, the role of the care coordinator becomes fundamental in obtaining the goal of transition which is to optimize the quality of life and future potentiality of young patients with special health care needs.

Providing guidance on transfer of medical information and developing an individualized care plan for these children becomes essential to draw up a transition policy with planning tools (transition readiness assessment, portable medical summary and transition action plan).

Preparing young adults for the change in health care setting is crucial for a successful transition to adult care: there is no right time, but a timely and organized transfer must be discussed and planned before transitioning to adult health care providers.

The critical aspect of implementing the guidelines/recommendations, present in literature for each neuromuscular pathology, is usually determined by the difficulty in disseminating the scientific contents throughout the country, particularly at the local level of centres working with patients affected by neuromuscular diseases. This assumption was confirmed by the results of the survey, taken by all of the workshop participating specialist centres, from which it appears that not all guidelines on respiratory management of patients affected by DMD are applied in a homogeneous way by these centres.

At the end of the meeting, a flow-chart regarding rapid evaluation of dystrophic paediatric and adult patients, that can facilitate the respiratory classification of the patients, was developed (Fig. 4).

The aim of this document is to facilitate the dissemination and application of essential respiratory care considerations for patients affected by muscular dystrophy, by hospitals and local clinical centres who do not routinely work with, but that could be involved in acute and chronic care of these patients. We are aware of the fact that the management of the respiratory involvement of paediatric and adult patients affected by muscular dystrophy should be as individualized as possible; nonetheless, we believe that patient educational training, and most important of the caregiver, has a significant impact in the course of treatment. For this reason, this paper has some, patient and caregiver cards attached that, describe the management of the most important respiratory issues that occur throughout the life of patients affected by muscular dystrophy such as:

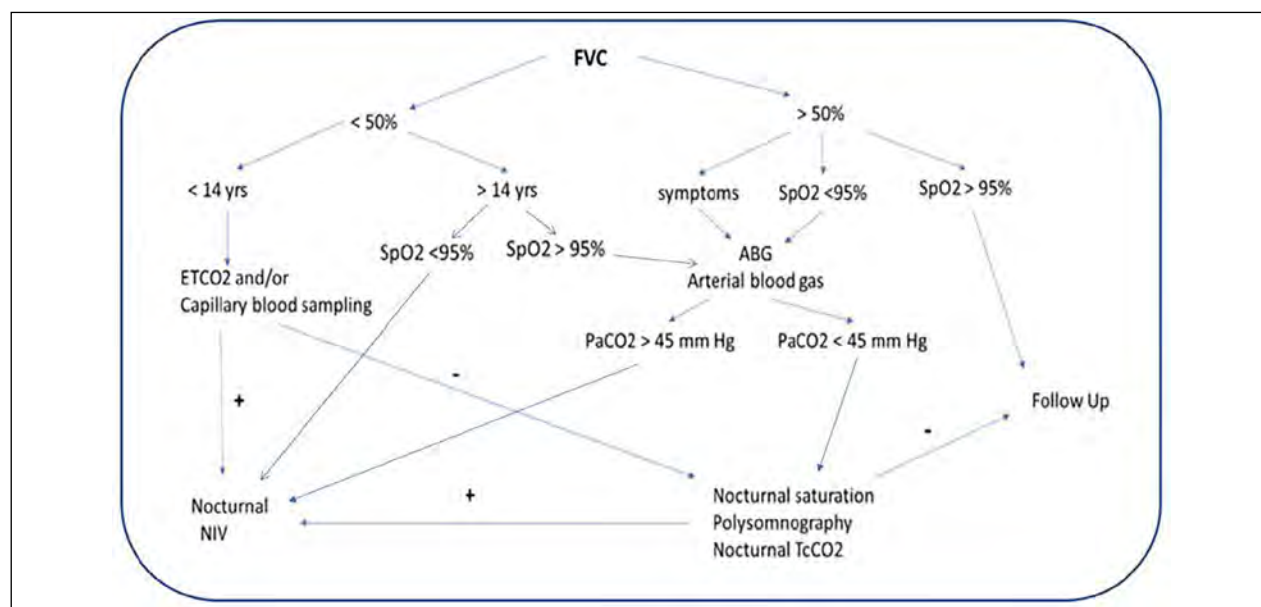


Figure 4. Flow-chart for rapid evaluation of respiratory function in muscular dystrophy.

- air stacking exercises;
- mechanical cough assistance;
- non-invasive ventilation;
- ventilation through tracheostomy critical aspects;
- mouthpiece ventilation.

We hope the result of this work can encourage and facilitate the respiratory care for all the centres that will have to deal, even occasionally, with the respiratory management of patients affected by muscular dystrophy and their families.

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Appendix

Air-stacking and chest expansion exercises: why, how and when to do them

By Vilma Donizetti, Marino Iatomasi, Fabrizio Rao, Giancarlo Garuti

What does air-stacking mean?

In patients with neuromuscular disorders, that have inspiratory and expiratory respiratory muscle weakness, when vital capacity falls below a certain threshold, execution of chest wall expansion exercises is suggested. The objective is to reduce as much as possible acute episodes of secretion build up and maintain chest wall expansion.

When your respiratory therapist and your pneumologist suggest performing “air-stacking” or chest wall expansion exercises, it means that you will be trained to use devices that will permit your chest to expand as much as possible.

The type of expansion you will be trained to perform will help extend your rib cage to an extent allowing it to stretch and maintain all your chest muscles flexible, mobilize your joints as much as possible and allow air to enter all the alveoli present in your lungs.

How to perform it

You can perform this type of stretching and trunk mobilization in two ways, by holding your breath or not (thanks to a big inhale or several consecutive inhales), and by using different devices such as an AMBU bag or a ventilator with a mouthpiece if you are already familiar with this type of ventilation and using it.

Which devices do I have to perform Air-stacking?

AMBU bag

The ambu bag is a self-inflating bag made of PVC/silicone that can hold 1200-1600 mL for adults and about 600 mL for paediatric patients

Air can be delivered to the patient via a mouthpiece or mask.



MPV = Mouth Piece Ventilation

MPV is a modality in which you can use the assistance of the ventilator only if required: when you need it you place your lips on the mouthpiece triggering the ventilator ready to assist you.

You can also use this modality to perform chest wall expansion exercises.



When I store air in my lungs do I necessarily need to hold my breath?

No, not everybody is able to store air inside the lungs. The respiratory therapist will try to adapt the best technique based on your lung function choosing between one of the following options:

1. re-expansion through single insufflation: in re-expansion thru single insufflation you will let as much air as possible into your lungs in one attempt and without necessarily holding it in;
2. Re-expansion through air-stacking. In re-expansion thru air-stacking you will be asked to progressively try to store air inside your lungs through one, two or more consecutive insufflations.

How often and how long do I have to perform this exercise?

Whichever method you are accustomed to using for chest wall expansion, the generally shared indication is to do it for at least around 15 minutes, twice a day.

During each session very frequent and close together expansions should be avoided as they may cause hypoventilation symptoms such as dizziness and tingling of hands and feet.

Try to perform this exercise daily and with due breaks between deep breaths!

When do I have to perform these exercises during the day?

You can perform chest wall expansion exercises when you prefer during the day but with the foresight to avoid the first two post-meal hours as insufflated air can go the wrong way and bloat the stomach and if that is full it may stimulate nausea or even retching.

Is it best to use a mask or mouthpiece when I perform exercise with the AMBU bag?

The respiratory therapist in charge of adapting and training you on expansion exercises will identify the appropriate technique and interface according to your motor function and skills, related to muscles in charge of air flow in the pharynx, larynx and mouth muscles.

For example if you have good motor function of the upper limbs, mouth, larynx, pharynx and mouth muscles the respiratory therapist will probably train you on the use

of the AMBU bag using a mouthpiece to maintain a high level of independence in handling this technique.

If otherwise, when trying the mouthpiece air escapes around the lips, then training with a mask will be performed.

Please note: when using a mask you will need a caregiver to help you keep a tight seal of the mask on your face and to squeeze the resuscitation bag in synchrony with your breathing pattern.

How does air-stacking thru a ventilator and mouthpiece work?

Ventilators often have a dedicated program that can be stored for use with a mouthpiece. The pneumologist or respiratory therapist can set a dedicated program on your ventilator that will provide you with air volumes every time you ask for air from the mouthpiece.

If you are among those patients who already have a ventilator and mouthpiece ventilation then you could use this device to perform chest wall expansion and air-stacking exercises.

A dedicated program that will provide air volume on demand through the mouthpiece will be set on your ventilator.

The instruction you will be given will be to try to get as much air into your lungs through one or several inhales if you cannot hold air with your pharynx/larynx muscles.

This exercise can become ineffective and bothersome when air escape from the nose or mouth.

What if a ventilator does not have the way to store a ventilation through mouthpiece program?

If this is the case or when a patient cannot use this program the therapist will find an alternative solution such as suggesting use of night-time ventilation with a mask but setting the possibility to manually take a large breath on demand on the ventilator or storing a program with greater pressures or volumes to be used for short bouts and with this specific objective.

In conclusion

Chest expansion, using the AMBU bag or mouthpiece ventilator is a fundamental part of the physiotherapy program and should be carried out daily.

The respiratory therapist in charge of your program will try to adapt you to the most adequate modality in terms of efficacy and tolerability.

What is non-invasive ventilation and how can I manage it

By Vilma Donizetti, Marino Iatomasi, Fabrizio Rao, Giancarlo Garuti

What does NIV mean?

NIV is the abbreviation for Non-Invasive Ventilation.

Non-invasive ventilation is a way to help those muscles which make us breathe, and especially ventilate (exchange gases).

Sometimes in neuromuscular conditions, respiratory muscles are or become weak over time. Non-invasive ventilation supports the diaphragm and the other inspiratory muscles to allow the correct volume of air into the lungs and to exhale air from the lungs in a proper way, getting rid of carbon dioxide in the blood.

Carbon dioxide needs to be eliminated during ventilation because it is a gas that normally accumulates in the blood and that becomes noxious if it goes beyond normal levels.

When there is too much carbon dioxide in the blood you may feel excessively sleepy, you may have morning headaches, complain of difficulties concentrating while finding it hard to sleep well.

Non-invasive ventilation helps you sleep better and helps you feel wide awake during the day and to reduce the feeling of shortness of breath during the day if your respiratory muscles are weak.

What is NIV?

Having NIV means that you will be provided with a ventilator, a humidifier and a face mask, all connected by tubes between them.

The air is generated by the ventilator, then it passes through the humidifier so that it is warm enough when it reaches the face and finally the lungs.

The ventilator

There are different types of ventilators, with or without a built in battery, which can start different ventilatory programs.

Your referral centre will choose with you the ventilator best suited to fit your clinical needs.



The mask

The mask is a device that is placed on your face to allow air coming from the ventilator to enter your lungs through the mouth and/or nose. Generally the surface that comes in contact with the face is made of silicon.

There are different types available, all having the same objective that is the tightest fitting interface possible to avoid leaks and making it as comfortable as possible while ensuring the best ventilatory exchange.

On the top of the majority of commercially available masks there are holes from which air can exit: this air flow is very important because it allows carbon dioxide to be expelled thereby avoiding breathing toxic gas.

NEVER CLOSE THE HOLES ON THE MASK!!!

If the mask you are using does not have holes, carbon dioxide is expelled through a different circuit, for example a valve between your mask and the connecting tube. Make sure that blankets or other objects do not obstruct the passage of air outwards. Never add additional layers between mask and valve.

There are different types of masks that can be used depending on the objectives your physiotherapist has shared with you:

- **Nasal mask** = mask that covers the nose only. This can be used to ventilate during the day or night, as needed.
- **Endonasal mask** = mask having two small probes which partially enter your nostrils. This is the smallest possible mask, and it can be used during the day or at night. It allows concomitant use of glasses if needed and has small dimensions. However, it may move out of place more often than the other types of interfaces.
- **Oro-nasal** = this is the best solution for nocturnal non-invasive ventilation especially if you tend to open your mouth while sleeping with a nasal mask and you are not using a chin guard device because you do not tolerate it or it does provide additional help while breathing.



- **hybrid** = oro-nasal mask which does not come into contact with your nasal bone. This may be convenient to avoid pressure lesions in the nasal area and to help you maintain a broader visual field.
- **MPV** (= mouth piece ventilation) = ventilator with a mouth piece. This topic will be specifically addressed in a dedicated section.

We recommend washing your mask every day with water and neutral soap, drying it and placing it in a clean cloth when not in use. There is no need for you to use disinfectants because these may damage the mask itself.

Take care of your mask as best as you can because generally the National Health System provides you with only 2 masks per year.

The humidifier

To help you use NIV at its best you will most probably be given a humidifying system.

The purpose of the humidifier is to humidify air which would otherwise reach the ventilator as a cold and dry gas mixture: a plate warms distilled water to provide warm water droplets which evaporate into the tubes connecting the ventilator to your mask.

The distilled water is kept in a plastic gravity water chamber: never fill the chamber beyond the threshold indicated as the maximum level of water and never leave the water chamber empty as it may burn.

Once at home, you can modify and manage the level of humidification according to your needs and comfort, but avoid water accumulating in the tubes. To ensure this avoid abrupt changes in temperature between the tubes in the circuit and the room where the ventilator is used and kept.



The circuit

This is made up of tubes connecting the humidifier to the mask. Their length is standard: they should not be shortened or lengthened.

Avoid water droplets accumulating in the tubes: this may cause the ventilator to break and facilitates bacterial growth.



FAQ

I only have one mask: am I allowed to have 2 types of masks each year?

Yes, it is actually recommended to have 2 masks of different types so that you can switch from one to the other to avoid pressure lesions on your face where the mask comes into contact.

I cannot remove the facial mask on my own and having an orofacial mask scares me because of the idea of not being able to ask for help or not being able to remove it quickly?

Talk about it with your physiotherapist or your pulmonologist, they will find an alternative solution, maybe using a chin support, a special alarm system or communication device which fits your needs.

I fear I will not be able to talk if I use the ventilator?

No, you will be able to speak, and actually the tone of your voice may sound stronger and of a higher pitch.

Is the air coming from the ventilator pure oxygen?

No, it is simply air taken from your surrounding (which does contain oxygen as well as other gases) which is directed through the circuit into your mask.

If there should be a need to add oxygen to your air supply, the pulmonologist and physiotherapist will provide you with an additional connector which will provide oxygen to the ventilator.

The air coming from the surroundings is full of dust, shouldn't this air be filtered?

Yes, the ventilator has a spongy filter where air from the surroundings enters the ventilator. This needs to be washed weekly and has to be replaced when dry or when worn. Some ventilators also have a white filter against pollen dust which should not be washed but replaced monthly.

If the air that I breathe is the same as the air that the others inhale normally, why should I always use the humidifier with the ventilator?

Because the air which reaches the mask is pushed into the lungs and quickly passes through nose/mouth. The mouth alone cannot provide an adequate humidification and the nose can do this only if air passes slowly and one breathes normally.

May I use demineralized water, osmolarized water or mineral water instead of distilled water?

No, it is recommended to only use distilled water.

In case I travel by plane, how should I carry my ventilator?

The ventilator should always be carried in its original bag as a carry-on luggage and should never be checked in as regular luggage.

There needs to be a pre-printed travel form from the airlines and this needs to be filled out by your pulmonologist.

In case you need to use the ventilator during the flight you need to talk to the airline beforehand and organize your trip with an AMBU bag instead if needed.

Ask the airlines all the information you need before you travel.

May I use indifferently a mask with holes and one with a valve on the circuit?

No, the type of circuit prescribed to eliminate carbon dioxide is a medical prescription and is based on clinical grounds, and on the physiotherapeutic and mechanical features of the ventilator which was chosen. It is very

dangerous for your health to change the parameters and settings that have been chosen specifically for you.



A friend, a technician, a provider, an internet video has prompted me to try a new mask/circuit/humidifier. They seem to be experts in the field. Can I follow their advices?

No, only the pulmonologist or physiotherapist who has experience in ventilation can help you. In case you have additional questions do not hesitate to call them.

I am using the ventilator for more than 16 hours a day. When I leave my house what should I bring with me?

When you leave your house you should definitely have:

- a bag for emergency/accidents (cloth bag which should be hung on the wheelchair) containing the AMBU bag connected to your other mask which should be used in case your ventilator should fail to work and adhesive tape to close potential holes/leaks that may accidentally occur in the circuit;
- saturimeter: if you think you will stay away from home for long (a whole day or longer) you should

also carry your second ventilator and your cough assist machine.



MPV: Mouth Piece Ventilation

By Vilma Donizetti, Marino Iatomasi, Fabrizio Rao, Giancarlo Garuti

What is it?

Mouth piece ventilation is one of the oldest types of non-invasive ventilation born as an alternative to tracheostomy for patients affected by Polio in the Fifties.

For whom

Useful for patients affected by neuromuscular disorders, but also patients with diaphragmatic paralysis, spinal cord injuries, kyphoscoliosis, cystic fibrosis and COPD.

Conditions for use

Patient has to be awake, conscious and cooperative, able to access mouthpiece and with good control of upper airway muscles (no bulbar deficits).

When to use it

A Medical doctor or respiratory therapist will suggest this alternative ventilation technique when:

- your carbon dioxide blood levels during the day increase beyond normal levels (> 45 mmHg) even though they are properly corrected by mechanical ventilation use at night;
- you have during the day episodes of dyspnoea or shortness of breath;
- you cannot talk for long periods of time or have such a low tone of voice that you cannot be heard or scream;
- you use mechanical ventilation with a mask for more than 14/16 hours and are at risk of pressure sores on your face;
- you have shortness of breath while eating and are progressively eating less therefore losing weight;
- you have shortness of breath after a meal or while sitting on the toilet;
- food goes the wrong way if you use the ventilator with a mask while eating or drinking;
- you would like to cough on your own without always having to ask for help;

- you would like to ventilate also during the day without this limiting your vision, speech or social life.

Why use it?

Using mouth piece ventilation improves quality of life and survival. Patients that use this type of ventilation appreciate the independence it provides by reducing fatigue in talking, breathing, eating, coughing sometimes even better than mask ventilation and also allows smelling.

No tube or masks hinder vision or interfere with social interactions. It is the patient that decides when and for how long he/she ventilates, breath by breath, according to his/her needs and is also able to alternate it with glossopharyngeal breathing or air-stacking manoeuvres (holding your breath after consecutive inhales).

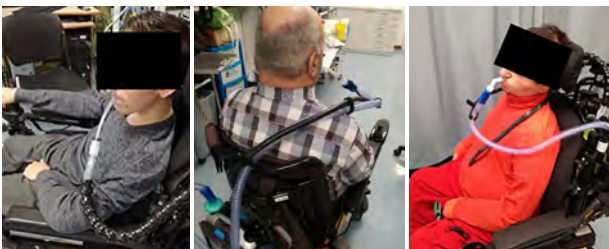
How

Attach the ventilator to the wheelchair, turn it on and choose the MPV setting. After securing the circuit to your preferred support, and the mouth piece or straw close to the lips, come closer as if you were drinking a sip of air or just slightly touch the system (depending on the chosen ventilator): the tube will deliver enough air to fill your lungs to be able to breathe, scream, sing, cough, talk at length. When too much air is delivered, let it escape freely from your mouth without closing your lips too tight on the mouth piece; if too little air is delivered then hold two or three consecutive breaths (air-stacking) and then use the air to cough better or hold your breath longer while for example chewing food in your mouth or yelling.

Frequency, air quantity, regularity of ventilator use is decided by the patient. Normally no one tells us how much air is needed to speak louder or longer for example and everyone self regulates. The same thing happens when using MPV: it has an air reservoir the patient can tap into and he/she can decide when.

Maintenance

Wash and disinfect the mouthpiece daily with neutral detergent, the circuit weekly and the filter monthly.



Important

The mouthpiece has to be always fixed close to the mouth and easily accessed by the patient.



Pay attention to where the circuit support is anchored: if you usually tilt your wheelchair while ventilating, make sure that the mouth piece can follow your movements. There are commercially available supports that can be prescribed or you can adapt other systems such as the ones used to hold smartphones.

Never exhale into the circuit (if it does not have an exhale valve). After drinking from a straw would you then spit again in your glass?

In case of mouth dryness keep some water handy and drink regularly; on the contrary, with excessive salivation, ask for medical advice in regards to drugs that limit saliva production.

Always make sure the ventilator has enough battery charge before going far from an electrical outlet.

Based on your needs and/or for safety reasons, it is possible to program an alarm that is triggered after a set time of failed activation through the mouth piece (voluntary or involuntary).

Remember

Breathing is a vital necessity to survive not an addiction. MPV is needed to live better as it provides independence not addiction.



Cough-assist devices

By Vilma Donizetti, Marino Iatomasi, Fabrizio Rao, Giancarlo Garuti

Cough

Coughing is a physiological mechanism to protect our respiratory airways. We cough to manage secretions or to remove foreign matter in our airways or we may have in our throat.

Stages of cough

First there is a deep inspiration, then for a fraction of a second, the glottis closes and breath is held. Then air is suddenly and explosively expired and with the air any foreign particles of materials found in the airways

Cough efficacy

In order to understand whether cough is effective, the pulmonologist or the physiotherapist measures it with a specific instrument which quantifies the Peak Cough Flow. If this is greater than 270 l/min, cough is effective, if between 160 and 270 l/min cough is weak and if below 160 l/min, cough is definitely ineffective.

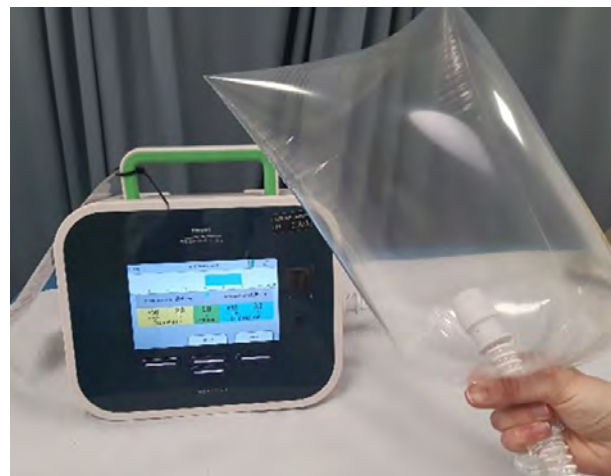
Mechanical cough-assisted devices

If air-stacking techniques and or manually-assisted manoeuvres prove to be inefficient (see document), either due to respiratory muscle weakness, fatigue or lack of compliance, the pulmonologist or the physiotherapist will prescribe a cough-assisted device.

There are different devices which can be prescribed and all are equally efficient. Each patient and caregiver will receive the device prescribed and with it, the specific instructions to use it properly.

What is it?

A cough-assist device is an instrument which mimics the act of coughing by mechanically inflating air within the airways and then by compressing air out of the lungs in the act of expiration. The machine introduces sufficient air within the lungs so as to inflate the lungs and the thorax and then the machine rapidly aspirates the air in the lungs and with it the secretions in the mouth or in the cannula if there is a tracheostomy.



What it does not do?

A cough-assisted device is not an aspirator and it is not a ventilator. It is also not a cough stimulator or cough trainer. One should not expect to hear the typical sound of coughing when in use.

What is the purpose of a cough-assist device?

The purpose is to avoid secretions build-up and to mobilize them in the upper airways when the patient is unable to do so on his/her own. It also exerts action on the respiratory muscles by stretching them and by mobilizing the rib cage while maintaining its elastic properties.

Which techniques can be implemented with the cough-assist device?

To optimize the efficacy of this treatment it is recommended that the patient be asked to try and cough voluntarily when the cough-assist device is beginning to generate negative pressure within the airway system, eventually adding manual assistance (thoracic or abdominal thrust). To avoid tiring the patient in the first sequence, it is recommended to use the passive mode for the first cycles (to recruit and ventilate) and to add



voluntary cough (and manual assistance) for the last cycle. Your therapist will teach you how to coordinate the different manoeuvres so that your participation will be as effective as possible.

Indications for prescription

A cough-assist device is recommended for patients with neuromuscular diseases having a PCF < 160 l/min, or when patients have a PCF < 270 l/min at rest, in a stable condition, but may get easily fatigued in case of acute respiratory disease.

Treatment protocol template

Preventive care: a cough-assisted device should be used even when secretions are within normal range as per quantity and colour. Recommendations are twice a day, five or six cycles for a total of 5 or 6 sequences away from meals. The patient can use the device in any position, while seated, supine or on his/her side. It is recommended to change position even during the same cycle so that air can reach different parts of the lungs. During this treatment the thorax should be monitored to make sure it expands and relaxes regularly as air passes through.

Acute care: in case of a respiratory infection, it is recommended to increase the frequency of the cycles, more than twice a day (even at night-time if needed) and every time saturation goes beneath 95%. Five or six sequences are usually needed for as many times to stabilize the patient. In these cases it is often useful to implement the treatment by asking the patient to try and cough on his/her own and to apply thoracic or abdominal thrusts too. If indicated by the physiotherapist or by your pulmonologist higher pressures may be needed.

If the patient is especially tired there may be the need to place the patient on his/her ventilator between sequences to allow for him/her to recover.

Parameters

Pressure: this is the strength with which air is forced into and out of the airway system. Sometimes the negative pressure is higher than the positive one, the opposite should not be done.

Time: this refers to the time required to insufflate and exsufflate the lungs. In general, the time to inflate is longer than the time needed to exsufflate. There are short intervals of time to recover between each sequence.

Air flow: this is the flow with which air can be delivered: it can be more or less intense or fast.

Trigger: if this is set by the technician, physiotherapist or pulmonologist, the patient can trigger air delivery with a minimum effort. This is of help for some patients because it may help them adapt and synchronize with the machine itself. The patient's strength should be assessed prior to setting this trigger (this is especially true in case of an acute respiratory infection); if this occurs, then the health care professional should be informed and the program should be switched from trigger to automatic mode (if this is already set before hand).

Oscillations: these are vibrations that can be added during the insufflation and/or exsufflation phases.

Modality: a cough-assist device can be automatically shifted to the insufflation and the exsufflation modes or there may be the option to shift manually. At home the

preferred option is the automatic modality (with or without trigger). In case the cough-assisted device is set to the manual mode, you will need to shift the lever to the inhale phase (trying to fill in the lungs as much as possible) and then towards the exhale phase (trying to empty your lungs as much and as quickly as possible).

Number of programs: there is the option to memorize 2 or more programs in the cough-assist device so that one is selected for the usual daily exercises and the other one (or more) can be selected during an acute phase, with higher pressures and different modalities. Precise indications for one or the other program will be provided.

Side effects and adverse events

These are usually few, rare and transitory. These are the most common ones:

- ear pain;
- chest pain (due to stretching of the thoracic musculo-skeletal structures);
- abdominal tension with nausea and vomiting;
- secretions with blood striations resulting from bronchial wall mobility;
- desaturation in case of hemodynamic instability;
- cardiac arrhythmias, bradycardia, tachycardia;
- pneumothorax (lung collapse);
- In case of problems, symptoms and signs of uncertain diagnosis please refer them as soon as possible to your physiotherapist or pulmonologist.

Contraindications

- Emphysema
- Barotrauma predisposition
- Parenchymal lesions
- Hemodynamic instability
- Reduced left ventricular function
- Recent cardiogenic pulmonary edema
- Tracheomalacia

Cleaning and maintenance

After each sequence the circuit and the face mask need to be cleaned with liquid detergent and need to be regularly disinfected with cold disinfectant. The catheter-mount needs to be replaced each time and needs to be washed and disinfected with cold disinfectant. Each part should then be dried.

The filter cannot be washed and needs to be replaced with the rest of the material when this is clearly worn out.

The external surface of the cough-assist device needs to be cleaned with a humid cloth.

The spongy machine filter needs to be washed weekly and has to be dried before it can be placed back on.

For any malfunctioning at home, please call the equipment provider.

What should not be done

DO NOT change the parameters without consulting the pulmonologist or your therapist

DO NOT let air leak out from the sides of the mask, but keep this tight on your face

DO NOT try to handle or try to fix the machine on your own

DO NOT prolong the time of treatment for more than 10 sequences in a row or for more than 30 minutes total

DO NOT interrupt the treatment after just one cycle thinking this is enough or that the machine is not doing anything. Stick to the instructions

Frequently asked questions

I have just eaten but I am already full of secretions. May I use my cough-assist device?

Yes, but with caution. It may cause you to vomit. Limit its use and avoid the abdominal thrust and stay seated for a couple of hours after your meal.

I choked myself with a small piece of food. Can I try and get rid of it, using the cough-assist device to remove this foreign material?

Yes, the machine can be used with the highest negative pressures and use it with the manual trusts until you have gotten rid of the foreign material

My chest hurts each time the air gets in and I have never experienced this type of feeling before

Stop using the machine immediately and contact your pulmonologist right away

I am going on holiday, can I leave my cough-assist device at home?

Your secretions do not go on holiday and your ability to cough does not improve on holiday. If you were given a cough-assist device it is because you need it and this means wherever you may be

I need to take a plane, can I bring it with me?

Yes, as hand-luggage and with a medical certificate saying that you need to use it and have it with you. It is best to contact the airline before you leave.

I have a gastrostomy, may I use it anyway?

Yes, with caution. In case of food or excess air in your stomach, let your physiotherapist or pulmonologist tell you what to do.

I was trained while lying, but now I am in my wheelchair, can I use it anyway?/I was trained while seated, but now I am in bed with a high temperature, can I use it anyway?

You can use the cough-assisted machine in any position, according to your needs and situations. Remember however, that it is best to change position to recruit and ventilate your lungs better.

I was trained some time ago and now I am not so sure I remember how it works, what should I do?

If you do not remember how to use it either because you do not remember or because things are still unclear to you, do not wait for an acute episode to occur but read

this document over again and if, this is still unclear, contact your reference centre and ask to review the whole procedure again.

If I do not have trouble managing secretions should I use it anyway?

Yes, this device should not be used to manage secretions only. It also has the purpose of inspiring better and exercise your respiratory muscles. Ask your physiotherapist if you can perform different exercises on days in which you aren't using it (i.e. air-stacking exercises with an AMBU bag for instance).

I have a tracheostomy. Is it enough for my caregivers to suction secretions from my cannula?

No, suction removes secretions if they are in the cannula or just below that. The cough-assist device mobilizes secretions from both lungs and brings them to the cannula and suction is then needed even more.

Invasive ventilation: critical issues

By Vilma Donizetti, Marino Iatomasi, Fabrizio Rao, Giancarlo Garuti

Tracheostomy is an artificial opening at neck level (between the Adam's apple and the sternum) allowing air flow and direct communication between lungs-trachea and the outside, by-passing upper airways (nose-mouth-throat-vocal cords).

It is a respiratory pathway in alternative to the natural mouth/nose one, which is artificially created by a medical doctor (ENT or intensivist doctor) when breathing (even thru mechanical ventilation) and/or obstruction removal by natural means is not possible or no longer effective.

The tracheostomy is a shared decision between the patient and the multidisciplinary team, that can be planned in a stable stage or it can be a patient's or caregiver/legal guardian's decision in an emergency situation.

Tracheotomy or tracheostomy?

These terms indicate procedures performed to ensure better breathing. They are not synonyms although they are used interchangeably.

To be precise:

- tracheotomy: simple incision and opening of the trachea which is usually temporary;
- tracheostomy: surgical procedure that connects the trachea directly with the outside;
- in both cases the result is an opening at throat level (tracheal stoma) with a tracheal cannula.

The cannula

The tracheostomy cannula is a curved plastic tube that crosses the stoma and directly connects the lungs



with the outside, completely by-passing all structures above the vocal cords (nose-mouth-throat).

It can be equipped with:

- cuff: a balloon that when inflated completely blocks air flow from the mouth and nose, preventing the patient from speaking;
- inner cannula: cannula inside the outer cannula. It can be removed daily and temporarily by the patient to facilitate cleaning of the cannula itself;
- fenestration: holes on the angled part of the cannula that in some specific cases can facilitate phonation.

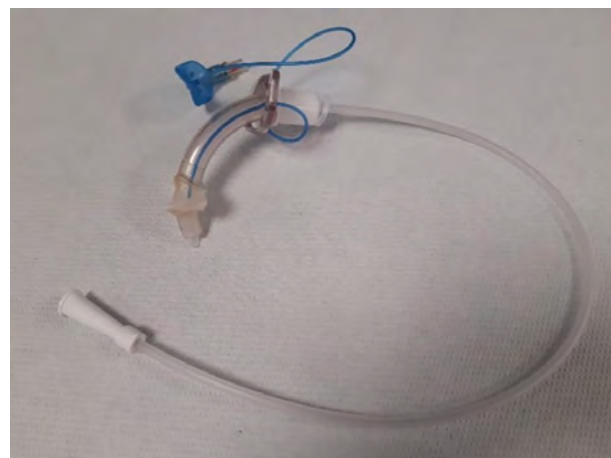


WHAT TO PAY ATTENTION TO DURING DAILY MANUEVERS?

There are some maneuvers to manage the tracheostomy that you might need to perform daily that require much attention.

ALWAYS REMEMBER to safely work with **TWO HANDS**: one hand supports the cannula and the flange to stabilize it, while the other hand connects or disconnects the catheter-mount, tracheal filter, etc.

It is a maneuver that has to be carried out with extreme attention to avoid harming the patient:



- if the catheter-mount is pulled without keeping the cannula still with the fingers, there is a risk of moving or unthreading the cannula, especially if it is uncuffed;
- if the catheter-mount is pushed against the cannula without keeping it still, this pushes directly on the patient's trachea and can cause discomfort.

Always SUPPORT the ventilator circuit with a clip or similar device to avoid pulling the cannula with the tube's weight provoking sores, cannula disconnection or even worse decannulation.

Secretion removal

Suction through tracheostomy cannula

To be performed:

- when needed (for secretion highlighted by the patient or when these are audible inside the cannula);
 - only in cannula e not beyond.
- The safest and most correct method is:
- pre-measure the probe length (equal to the cannula length + ½ cm);
 - enter the cannula, with a sterile tube, only reaching the lower part of the cannula and not further;
 - enter without suctioning and start only when starting to retract the tube from the cannula;
 - suction duration should not last more than about 10 seconds;
 - do not use the same tube for more than two subsequent suctioning unless sanitizing it before each use.

ATTENTION: deeper or prolonged maneuvers may lead to the risk of tracheal mucosa lacerations with possible bleeding and deep desaturations.

Mechanical cough assist

All secretions that did not reach the cannula can be mobilized and moved closer with mechanical cough assistance or AMBU bag. Follow the same directions for cough-assist devices by non-invasive administration simply substituting the mask with a catheter-mount and secretion removal by cough with suction. A cuffed cannula should be preferred when using cough-assist devices.

AMBU bag

The AMBU bag is a useful tool to mobilize secretions when the mechanical cough-assist devices are not available. For ways of using it please refer to instructions from your reference center.

Cleaning above the cuff

Cleaning above the cuff will be performed to avoid secretion or saliva build up above the balloon.

To clean above the cuff briefly deflate the balloon and suction any secretions from cannula and mouth.

This maneuver has to be performed according to the reference center's recommendations. One way is for example to uncuff the cannula after a couple of cycles with a cuffed cannula, in order to use the cough assist machine. Uncuffing during cough assist machine use promotes secretion migration to the mouth, particularly if the patient during insufflation cooperates by scraping his throat.

ATTENTION: this maneuver must be performed with care and attention following all the indications from the physiotherapist in order to avoid patient desaturations and discomfort.

Urgency/emergency: what to do?

PROBLEM: ventilator malfunction



SOLUTION: disconnect patient from ventilator and uncuff cannula and let patient breath on his own (if he is usually able to and is not ventilated continuously) protecting the cannula with a tracheal filter, a phonatory valve or a plug. Call the home care provider's toll-free number to report the malfunction manually ventilate patient with an AMBU bag while waiting for the back-up ventilator or medical assistance. Then call the toll-free number of the Home Care Provider to report the malfunction.

PROBLEM: although the patient is connected to his/her usual ventilator it appears he is not receiving enough air supply and the chest and abdomen do not inflate during insufflation.

This problem has different causes, and below are the ones that can be resolved at home.

Cannula is perfectly clean and free for air flow but there are many secretions below the cannula.



SOLUTION: use the cough assist machine and suction the cannula as needed to bring saturation levels above 94% and observe if the patient breathes better after obstruction removal.

Cannula is completely clogged by a plug of dry secretions that completely blocks the cannula and doesn't allow air flow or the insertion of a suction tube.

SOLUTION: remove inner cannula, if present, substituting it with a clean one if an inner cannula is not used, completely uncuff the cannula and use the cough assist machine on the program with the highest pressure settings or the AMBU bag to try and mobilize the mucous plug.

Insist till removal keeping an eye on patient's saturation and state of consciousness. Between uses of the



cough assist/AMBU bag try to help patient breathe from natural airways using ventilator with mouthpiece or mask.

In the extreme case in which a secretion plug does not move and the patient, although uncuffed cannot breathe properly, **IMMEDIATELY** contact the emergency number and in the meantime, if the patient becomes cyanotic with saturation below 85%, remove the cannula, cover the stoma with a gloved finger and continue to ventilate the patient with a mask or mouthpiece (using mechanical ventilator or AMBU bag).

PROBLEM: if the patient severely desaturates and in a prolonged manner and seems to lose consciousness.

SOLUTION:

- slightly uncuff the cannula;
- start using the AMBU bag checking that the chest/abdomen lift at each AMBU bag squeeze;
- call emergency number to request medical assistance (in case you are unable to resolve the problem in a short period of time).

PROBLEM: patient unplanned decannulation

SOLUTION: if patient usually:

- is not continuously mechanically ventilated, place him in a position that favors spontaneous breathing (usually in sitting) and call the emergency number. Wait for medical assistance and monitor saturation levels;
- is permanently ventilated or desaturates without ventilator assistance: close the stoma with a gloved finger and connect patient to ventilator with a mask, mouthpiece or the free end of the cannula itself used like a straw. Call emergency number as soon as possible.

If airflow is not resumed, the chest/abdomen do not lift and patient desaturates and becomes cyanotic, firmly position the AMBU bag mask on the stoma and try to





ventilate the patient with the AMBU bag thru the tracheal stoma. Call the emergency number IMMEDIATELY

IMPORTANT: do not try to reposition the cannula if you haven't received proper training from medical staff or if you are not in an extreme situation: if this maneuver is performed in a clumsy way it can lead to permanent damage. Should you need, if possible use a cannula without a cuff and with a smaller diameter compared to the usual one.

ADVICE: in the routine daily stoma cleaning maneuvers or change of neckplate avoid undoing or completely unthreading the neckplate. It is wiser to simply loosen the neckplate and keep it attached. If a collar change is needed insert the new collar in the flange and attach it before removing the old one.



Frequently asked questions

Can I use the same tube to first suction the mouth and after the cannula?

NO, the tube that enters the cannula has to be sterile so you can do the opposite and start suctioning in the cannula and then the mouth.

Which is the correct saturation value?

Normally blood oxygen saturation should be above 94%. If it falls below this limit start evaluating the situation: use the cough assist/suction device to remove any secretions, connect patient to ventilator (if not already on ventilation), check for temperature elevation, contact your primary care physician.

Saturation is low or lower than usual. Can I improve it by using a bit of oxygen?

Oxygen is considered a medication and as such should be administered only under medical prescription. Remember anyway that in your disorder pure oxygen



consumption leads to carbon dioxide build up. In case of desaturation even after frequent use of the cough assist device while waiting for antibiotic therapy to become effective, increase hours of ventilation and if prescribed by

a doctor, take oxygen preferably mixed with ventilator air flow. Reduce the time spent breathing pure oxygen thru nasal cannulas but prefer the use of the ventilator. This way you will tire less when breathing and you will avoid rapid carbon dioxide build up.

How many times a day do I have to use the cough assist machine?

At least twice a day, morning and evening and more if needed. Secretion production during the day is variable among different individuals and can be more or less.

Furthermore, most likely, you will need to use the cough assist machine just before or after postural changes such as bed to wheelchair transition, as this mobilizes secretions.

I use the ventilator more than 16 hours a day, when I go out what do I have to bring? When you go out of the house you should absolutely have with you:

- emergency bag (readily available cloth bag attached to the wheelchair that contains an AMBU bag connected to a catheter-mount, adhesive tape to close any

accidental holes in the circuit, a syringe to cuff and uncuff the cannula, a clean inner cannula wrapped in gauze, an uncuffed cannula of smaller diameter compared to the one used for emergencies);

- suction machine (with charged battery, car charging cable) complete with tubes and bottle for water suction;
- pulse oximeter.

If you are away from home for a long time (a whole day or more), it is best for you to also bring the cough assist machine and a back-up ventilator.

My secretions have been drier than usual for a couple of days. What can I do?

In case secretions are very dry it might be necessary to reduce the number of hours on ventilation with just a humidifying filter and/or uncuffed cannula, and increase the number of hours using an active humidifier preferably with a thermoregulated circuit.

It might be useful to use an aerosol dispenser or nebulizer with just physiological water: for practical guidance refer to your clinical center.

Read-through approach for stop mutations in Duchenne muscular dystrophy. An update

Luisa Politano

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Dystrophinopathies are allelic conditions caused by deletions, duplications and point-mutations in the *DMD* gene, located on the X chromosome (Xp21.2). Mutations that prematurely interrupt the dystrophin protein synthesis lead to the most severe clinical form, Duchenne muscular Dystrophy, characterized by early involvement of muscle strength. There is no known cure for dystrophinopathies. In DMD, treatment with corticosteroids have changed the natural history and the progression of the disease, prolonging ambulation, and slowing the onset of respiratory and cardiac involvement and scoliosis by several years. In the last few years, new perspectives and options are deriving from the discovery of pharmacological approaches able to restore normal, full-length dystrophin and potentially reverse the course of the disease. Read-through (RT) of nonsense mutations, thanks to its ability to bypass the premature stop codon and to act on virtually any region of the dystrophin gene, independently of the location in which the mutation resides, is one of these promising approaches. This non-systematic review shows the different steps that, passing from yeast to humans, have made it possible to use this innovative successful approach to treat serious diseases such as Duchenne muscular dystrophy.

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Conflict of interest

The Author declares no conflict of interest

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Key words: Duchenne Muscular dystrophy, nonsense mutations, aminoglycosides, ataluren, translarna

Introduction

Duchenne muscular dystrophy (DMD) belongs to dystrophinopathies, a group of X-linked genetic degenerative disorders affecting striated muscles and caused by mutations in *DMD* gene¹⁻⁴.

Dystrophinopathies present with a variable spectrum of severity ranging from the exercise-induced muscle cramps and myoglobinuria, to the complete loss of muscle function, cardiomyopathy, and respiratory failure. The onset of DMD is in early childhood, characterized by a delay in motor milestones. In about 1/3 of children brain involvement with cognitive impairment and/or behavioural disorders such as ADHD (attention deficit hyperactivity disorder), autism, anxiety and obsessive-compulsive disorder can be associated^{2,3}.

Muscle hypertrophy is evident, especially in the calf muscles. Progression is rapid, so that by the age of 5 waddling gait and positive Gowers' sign appear. In untreated boys, walking is lost by the age of 12 (mean 9.5 years). Following the loss of ambulation, scoliosis, respiratory failure and cardiomyopathy develop²⁻⁵.

The incidence of DMD varies from 1:3.500 to 6.800 male births, according to the more recent estimates⁶⁻⁸.

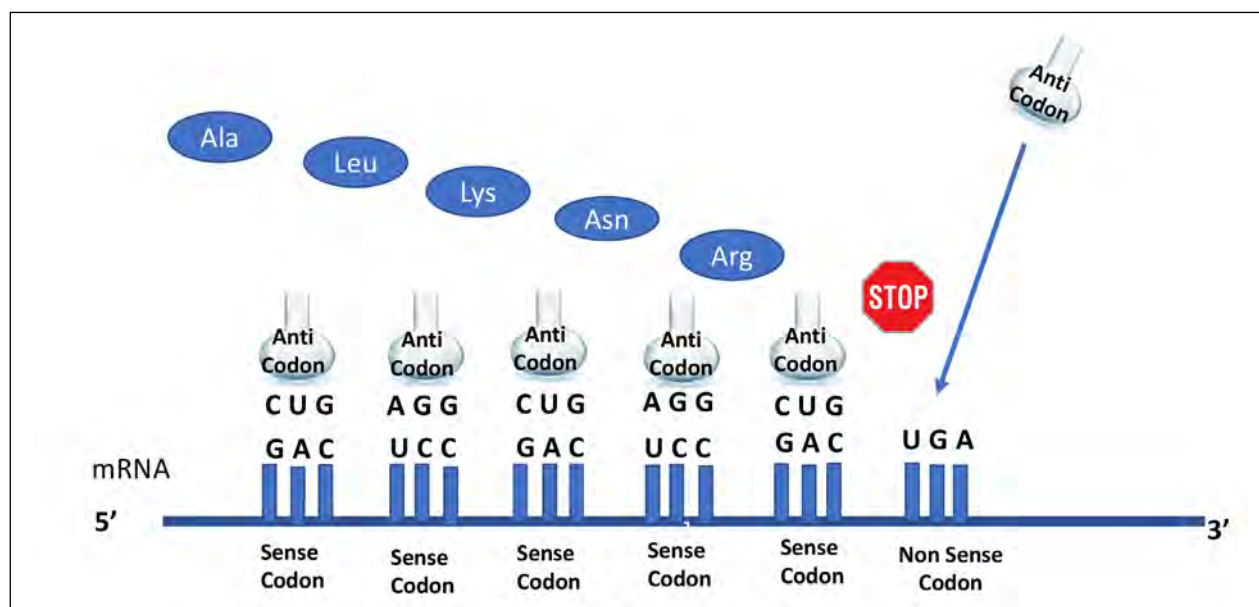


Figure 1. Stop of the protein synthesis, caused by a non-sense mutation (from Roy B, et al. Proc Natl Acad Sci USA 2016;113:12508-13, mod.).

From a genetic point of view, dystrophinopathies are allelic conditions caused by deletions, duplications and point-mutations in the *DMD* gene, located on the X chromosome (Xp21.2). To explain how mutations in the same gene may cause the observed phenotypic variability, the rule of the “Open Reading Frame” (ORF) comes to the rescue^{7,8}. According to this rule, mutations that prevent the ribosome from reading the amino acid sequence correctly (“out-of-frame” or nonsense mutations) result in no functional dystrophin (see Figure 1) and produces the DMD phenotype. On the other hand, mutations that retain the reading sequence (“in frame”), generate a shortened but partly functional protein, leading to the milder BMD phenotype⁷. Exceptions to this rule are observed for up to 9% of dystrophin mutations⁹.

There is no known cure for dystrophinopathies. In DMD, treatment with corticosteroids have changed the natural history and the progression of the disease, prolonging ambulation, and slowing the onset of respiratory and cardiac involvement and scoliosis by several years. Physiotherapy and orthotics delay the onset of joint contractures¹⁰. Symptomatic therapy is available for cardiac and respiratory impairment¹¹⁻¹³. Life expectancy is shortened by cardiac and respiratory involvement but can be substantially improved with regular monitoring and pro-active management^{14,15}.

In the last few years, new perspectives and options are deriving from the discovery of pharmacological approaches able to restore normal, full-length dystrophin and potentially reverse the course of the disease. Read-

through (RT) of nonsense mutations, thanks to its ability to bypass the premature stop codon and to act on virtually any region of the dystrophin gene, independently of the location in which the mutation resides, is one of these promising approaches.

Brief history of read-through approach for stop mutations

The history of readthrough of premature stop mutations in eukaryotes began in 1979, when 2 papers describing suppression of these mutations by aminoglycosides were published^{16,17}. Several of this class of antibiotics were tested for relative capacity to read through premature stop mutations^{18,19}. These observations led to testing of gentamicin, initially in a cystic fibrosis cell line²⁰, then in the mdx mouse, an animal model for Duchenne muscular dystrophy that fortuitously harbors a UAA premature stop mutation in exon 23 of *DMD* gene²¹. This mdx proof-of-concept study demonstrated an about 20% of normal expression of muscle fibre dystrophin in vitro and in vivo, and showed that dystrophin was properly localized to the sarcolemma. These muscle fibres showed an increased resistance to eccentric contraction injury, while a decrease in blood creatine kinase levels suggested a reduced muscle cell fragility¹⁹.

On the basis of these findings, human trials of intravenous gentamicin were undertaken on patients with Duchenne/Becker muscular dystrophies in which read-through strategies may be applicable in about 13% of pa-

tients^{20,21}. With this strategy, small administered molecule drugs producing a conformational change in the mRNA, can allow the ribosome to insert an amino acid at a UGA, UAG, or UAA premature stop codon site during translation¹⁶.

Drugs inducing suppression of these nonsense mutations increase the readthrough of the premature stop signal, and the production of full-length protein. The minimal quantity of full-length dystrophin required to achieve normal muscle function is not known, but a 30% of normal seems to be sufficient to avoid muscular dystrophy in humans. Lesser amounts of dystrophin may ameliorate symptoms or temper disease progression²². Two small pilot studies on gentamicin administration in nonsense mutations DMD (nmDMD) patients appeared in the years 2001-2003. The initial study was performed by Wagner et al.²³. In this trial, 4 patients (2 DMD and 2 BMD) aged 7-16, were daily administered gentamicin intravenously, at a dosage of 7.5 mg/kg, for 2 weeks. Over this short period of drug exposure, drug activity, as assessed by muscle dystrophin expression on biopsies, and muscle strength, was not detected. No renal or ototoxicity was observed.

In 2003, Politano et al.²⁴ reported the results of intravenous gentamicin administration in 4 DMD subjects, 3 ambulant and 1 wheelchair-bound, aged between 4 and 9. They used a gentamicin regimen comprising 2 six-day courses of therapy at a dosage of 6.0 and 7.5 mg/kg respectively, separated by an intervening period of 7 weeks. They demonstrated an increase in dystrophin expression in 3 of 4 subjects in end-of treatment biopsies. The best results were obtained in the younger patient. They also shown a re-expression of sarcoglycan complex consistent with the restore of the sarcolemmal integrity. No renal or ototoxicity was identified.

These reports aroused the attention of many researchers on this new treatment option for patients with nonsense mutations²⁵⁻²⁷.

In 2010, Malik et al.²⁸ published the results of a more extensive study on 34 DMD patients, who were subdivided in four cohorts. Two of them received 14-day gentamicin (7.5 mg/kg/day): Cohort 1, had ten stop codon patients (nmDMD) and Cohort 2, eight frameshift controls. Two additional nmDMD cohorts were treated, at the same dosage for 6 months: Cohort 3 (n = 12) weekly, and Cohort 4 (n = 4) twice weekly. Pre- and post-treatment biopsies were assessed for dystrophin levels, as were clinical outcomes. After 6 months of gentamicin, dystrophin levels significantly increased with the highest levels to 15% of normal (1 in Cohort 3, and 2 in Cohort 4), accompanied by reduced serum CK levels. Stabilization of strength and a slight increase in forced vital capacity (FVC) were also observed. All subjects were carefully monitored for adverse events and no persistent findings of nephrotoxicity or ototoxicity were reported.

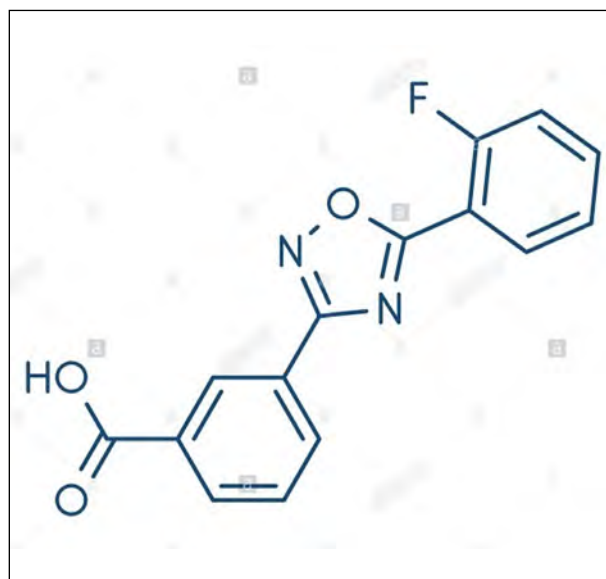


Figure 2. Ataluren chemical structure.

Although these promising results, the need for regular intravenous administration, and safety laboratory parameters discouraged the clinical practical application. Furthermore, multiple forms of gentamicin were identified, with significant variation in their potential to promote dystrophin expression²⁵. Hence, the need to study new pharmacological molecules with the same pharmacological characteristics.

Ataluren (PTC124)

Ataluren (formerly known as PTC124) is a small molecule (Fig. 2) developed by PTC Therapeutics as an orally bioavailable product able to bypass nonsense mutations (Fig. 3) and avoid potential renal- and ototoxicity of aminoglycosides. It was originally developed by means of an optimized high-throughput screening campaign. A dose dependent readthrough of all three nonsense codons (UGA, UAG, UAA) was observed, with the highest readthrough at UGA, followed by UAG and then UAA²⁹. PTC124 soon proved to be a more potent nonsense-suppressing agent than gentamicin³⁰⁻³².

When administered in mdx mice, treatment with PTC124 restored dystrophin production in all skeletal muscles examined, including the diaphragm, and cardiac muscle. The dystrophin levels were found to be 20-25% those of control mouse muscles, and partially restored force generation and resistance against eccentric exercise were observed suggesting that PTC124 was able to reduce muscle fragility³³. PTC-treated mdx mice also exhibited increased levels of sarcoglycans, consistent with stabilization of the dystrophin-associated proteins. The

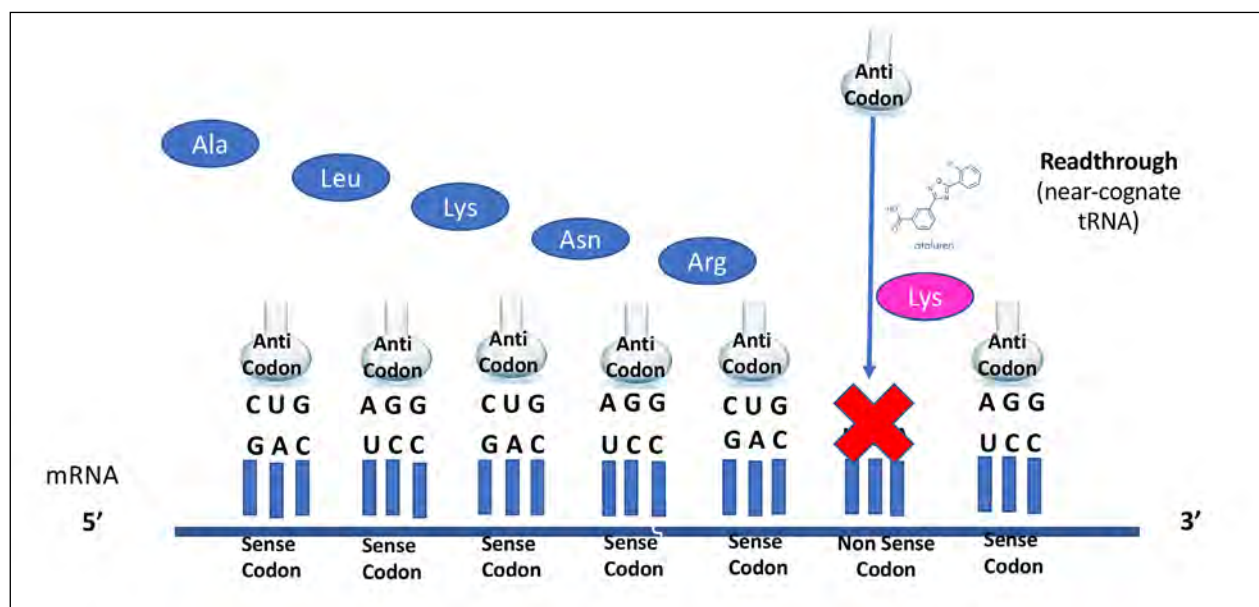


Figure 3. Ataluren's mechanism of action (from Roy B, et al. Proc Natl Acad Sci U S A 2016;113:12508-12513, mod.).

rescue of skeletal muscle was seen within 2 to 8 weeks of exposure. Readthrough by PTC124 was selective and specific to disease-causing premature termination, without evidence of changes in the ribosomal readthrough of normal stop codons. These encouraging results led to the initiation of studies in humans ³⁴⁻³⁹.

Hirawat et al. ³⁴ assessed safety and tolerability of PTC124 in a Phase 1 study enrolling 62 healthy adult volunteers and concluded that the drug was well tolerated, except for mild headaches, dizziness, and gastrointestinal discomfort at high dose.

Finkel et al. ³⁶, in a Phase 2a open-label, sequential dose-ranging trial recruited 38 boys with nonsense mutation DMD, subdivided in three cohorts according to the administered dosage of Ataluren: 16 mg/kg/day (6 patients); 40 mg/kg/day (20 patients); and 80 mg/kg/day (12 patients). Treatment duration was 28 days. Change in full-length dystrophin expression, as assessed by immunostaining in pre- and post-treatment muscle biopsy specimens, was the primary endpoint. They found that dystrophin expression was increased in 61% of subjects post-treatment, associated neither with nonsense mutation type nor exon location. Ataluren was generally well tolerated, supporting the evaluation of ataluren 40 mg/kg/day and 80 mg/kg/day in a Phase 2b, double-blind, long-term study, having 6-minute walk distance (6MWD) as primary endpoint. This phase IIb double-blind, placebo-controlled, dose-ranging, efficacy and safety study failed to demonstrate improvement in the 6MWT.

However, further detailed analysis of the Phase IIb data suggested the possibility of a bell-shaped dose-re-

sponse with clinical benefit to DMD boys receiving low dose, and in high-dose patients in whom serum levels of PTC124 were low ^{37,38}.

In 2014, Bushby et al. ³⁹ published the results of a randomized, double-blind, placebo-controlled study enrolling 174 DMD patients ≥ 5 years with nm-dystrophinopathy who received orally, 3 times daily, ataluren 40 mg/kg/day ($n = 57$); ataluren 80 mg/kg/day ($n = 60$); or placebo ($n = 57$) for 48 weeks. The primary endpoint was change in 6-Minute Walk Distance (6MWD) at Week 48. Ataluren was generally well tolerated. Unexpectedly, both the primary and secondary endpoints (timed function tests) favoured ataluren versus placebo, at the lower dosage.

As a consequence, the European Medicines Agency (EMA) reviewed ataluren for the treatment of ambulant patients aged 5 and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene ⁴⁰⁻⁴⁴.

In 2017, McDonald et al. ⁴⁵ published the results of a major international multicentre, randomised, double-blind, placebo-controlled, phase 3 trial carried out on Ataluren, including 54 sites in 18 countries located in North America, Europe, the Asia-Pacific region, and Latin America. Two-hundred-thirty boys aged 7-16 years, with nonsense mutation DMD and a baseline 6MWD of ≥ 150 m and 80% or less of the predicted normal value for age and height, were enrolled and randomly assigned (1:1) between March 26, 2013 and Aug 26, 2014. Randomisation was stratified by age (< 9 vs ≥ 9 years), duration of previous corticosteroid use (6-12 months vs ≥ 12 months), and baseline 6MWD (< 350

m vs ≥ 350 m). The primary endpoint was change in 6MWD from baseline to week 48. The results showed that changes in 6MWD did not differ significantly between patients in the ataluren group and those in the placebo group. However, a significant effect of ataluren in a subgroup of patients with a baseline 6MWD between 300 m and 400 m was observed. Baseline 6MWD values within this range were in fact associated with a more predictable rate of decline over 1 year. The preliminary patient registry data also indicated a longer ambulatory period in ataluren-treated patients compared with published natural history⁴². Because the phase 2 clinical trial results were not satisfactory in terms of meeting the primary endpoint, ataluren was first rejected for approval by the European Medicines Agency (EMA)⁴³. However, as the conclusions drawn from further analysis suggested ataluren to be effective in terms of slowing down the disease course, EMA has subsequently granted ataluren a conditional marketing authorization in 2014^{43,44}. Ataluren is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older in the European Member States and Iceland, Liechtenstein, Norway, Great Britain, Northern Ireland, Kazakhstan, Israel, and Republic of Korea, and aged 5 years and older in Chile, Brazil, and Ukraine (under special state registration). The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing (Ref Translarna⁴³ Summary of Product Characteristics (SmPC) for respective countries) whereas ataluren is still an investigational drug in the United States⁴⁴.

In 2018, Ebrahimi-Fakhari et al.⁴⁶ reported their experience in 4 *non-ambulatory* nmDMD patients. Routine investigations included cardiac function, pulmonary function tests and muscle strength. They compared changes in left ventricular fractional shorting (LVFS), FVC and BMI from two defined time periods (18–26-month period prior to and after Ataluren start). There were no adverse clinical effects or relevant abnormalities in routine laboratory values. They conclude that Ataluren appears to mildly ameliorate the clinical course in their patients with a good safety profile.

In the same year, Ruggiero et al.⁴⁷, describing how the best results at 1 year were seen in the younger of the 3 DMD patients, aged 5, 8 and 10 and treated with Ataluren, suggested earlier initiation of therapy. D'Ambrosio et al.⁴⁸, broadening the spectrum of patients potentially benefiting from this type of treatment, reported the promising results obtained in a 24-year-old nmDMD symptomatic carrier who took ataluren for a period of 9 months.

Several papers were published in the last 3 years stressing that a new era is emerging for the treatment of DMD patients with nm mutations^{49–59}.

Among these, some deserve to be reported: 1) the paper by Landfeldt et al.⁵² who published a targeted

mini-review of the literature from 1995 to 2018, which included cohort studies, guidelines, randomised clinical trials, clinical commentaries and reviews. The review covered the pathophysiology, epidemiology, and burden of nmDMD and the clinical programme for ataluren. Based on the current evidence, and their experiences, they recommend patients with nmDMD should be given ataluren as soon as possible after diagnosis; 2) that of Muntoni et al.⁵³ who presented patient demographics and characteristics of nmDMD patients treated with ataluren, included in the STRIDE registry. STRIDE (Strategic Targeting of Registries and International Database of Excellence) is a multicentre registry providing real-world evidence regarding ataluren use in patients with nmDMD in clinical practice. Patients should be followed up from enrolment for ≥ 5 years or until study withdrawal. As of 9 July 2018, 213 DMD boys have been enrolled from 11 countries. Mean (standard deviation) ages at first symptoms and at study treatment start were 2.7 (1.7) years old and 9.8 (3.7), respectively. Mean (standard deviation) ataluren exposure was 639.0 (362.9) days. Six patients withdrew. STRIDE represents the first drug registry for patients with DMD and the largest real-world registry of patients with nonsense mutations; 3) the paper by Mercuri et al.⁵⁷ who examined the safety and effectiveness of ataluren, comparing the results from the STRIDE Registry and CINRG DMD Natural History. A propensity score matching was performed to identify STRIDE and CINRG DNHS patients who were comparable in established disease progression predictors (registry cut-off date, 9 July 2018). The results confirmed those of previous clinical trials, showing a series of benefits in nmDMD patients treated with ataluren + Standard of Care (SoC), compared with DMD patients receiving SoC only. Patients receiving ataluren plus standard of care (SoC) in STRIDE had a significantly delayed age at loss of ambulation, worsening of performance in timed function tests and worsening of pulmonary function versus patients receiving SoC alone in the CINRG DNHS (all $p \leq 0.0386$), over a mean treatment period of 632 days. Ataluren plus SoC was also associated with delayed deterioration of cardiac function versus SoC alone, although this did not reach statistical significance likely due to the short period of observation. No correlation was observed between DMD genotype (type and location of nonsense mutation) and disease progression or treatment benefits; 4) the paper by Campbell et al.⁵⁸ who combined data from the two completed randomized controlled trials (ClinicalTrials.gov: NCT00592553; NCT01826487) of ataluren in nmDMD and examined the intent-to-treat (ITT) populations and two patient subgroups (baseline 6-min walk distance [6MWD] ≥ 300 – < 400 or < 400 m). The meta-analyses evaluated 6MWD change from baseline to week 48.

The Authors found statistically significant differences in 6MWD change with ataluren versus placebo across all three meta-analyses, supporting previous evidence for ataluren in slowing disease progression versus placebo in patients with nmDMD over 48 weeks. Treatment benefit was most evident in patients with a baseline 6MWD ≥ 300 -< 400 m (the ambulatory transition phase).

Conclusions

DMD is a genetic degenerative disorder affecting muscles, caused by mutations in the dystrophin gene, the biggest gene described in humans. They can be deletions of one or more exons in prevalence (65-75%), or duplications (10-15%). The remaining are due to nonsense mutations that prematurely stop the protein synthesis. DMD boys present with motor delay and usually loss ambulation before the age of 12. Death is due to respiratory or heart failure. Treatment consists in steroid administration and cardiological and respiratory support. Gene therapy is under consideration.

Ataluren is a treatment for patients with nmDMD, designed to promote ribosomal readthrough of an in-frame premature stop codon and thereby enable the production of full-length dystrophin protein, which has the non-negligible advantage of being orally administered. All the scientific papers published so far have shown that ataluren is a drug capable of slowing the evolution of the disease in patients with nmDMD. Respiratory and cardiac parameters also appear to be positively influenced by treatment with ataluren, though they have not reached statistical significance, probably due to the short period of observation. Early diagnosis and treatment appear to be a key point. The expansion of treatment to female symptomatic carriers of the disease seems a viable option.

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Daytime alternatives for non-invasive mechanical ventilation in neuromuscular disorders

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Mechanical ventilation in recent years has benefited from the development of new techniques and interfaces. These developments allowed clinicians to offer increasingly personalised therapies with the combination of different complementary techniques for treating respiratory insufficiency in patients with neuromuscular diseases. The mouthpiece ventilation, intermittent abdominal pressure ventilator and the negative pressure ventilation can offer many patients alternative therapy options when ventilation is required for many hours a day. In this non-systematic review, we will highlight the use of alternative methods to non-invasive mechanical ventilation at positive pressure in neuromuscular patients, to ensure the optimal interface for each patient.

Key words: mouth-piece ventilation, negative pressure ventilation, daytime non-invasive ventilatory support

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Conflict of interest

The Authors declare no conflict of interest

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Introduction

The birth of non-invasive mechanical ventilation (NIV) occurred in the late 1920s, following the poliomyelitis epidemic that was notable for respiratory muscle paralysis and subsequent death in many children. Mechanical ventilation was in the form of the iron lung, a non-invasive negative-pressure respirator developed by Philip Drinker and Charles McKhann¹. Motley et al. investigated the use of intermittent positive pressure ventilation in the form of expiratory positive airway pressure (EP-AP) and continuous positive airway pressure (CPAP) via a rubber mask for the treatment of acute pulmonary edema, pneumonia, Guillain-Barre syndrome, near-drowning, drug overdose, and acute asthma^{2,3}. In 1980, Sullivan et al. described the successful use of CPAP via nasal mask in the management of obstructive sleep apnea⁴. Subsequently, its use was extended to the chronic respiratory failure from neuromuscular disease (NMD) and symptomatic worsening nocturnal hypoventilation⁵. During the 1990s, the Consensus Conference recognized non-invasive ventilation as a valuable and essential strategy in the managing of subjects with acute respiratory failure⁶⁻⁸.

Acute respiratory failure is a frequent life-threatening problem of acute onset NMD and may exacerbate chronic hypoventilation in patients with NMD or chest wall disorders^{9,10}.

Respiratory care is of high importance because it is a main determinant of quality of life and survival¹¹. NIV is one of the limited modali-

ties that has shown a survival benefit in the NMD patient population. Newer modes with smart technologies are being developed to assist in better ventilation¹². These developments allowed clinicians to offer increasingly personalised therapies, with the combination of different complementary techniques for treating respiratory insufficiency in these patients, who often require 24 hours non-invasive mechanical ventilation or tracheostomy⁹⁻¹⁰.

MouthPiece Ventilation (MPV)¹³, Intermittent Abdominal Pressure Ventilator (IAPV)¹⁴ and Negative Pressure Ventilation (NPV)¹⁵ can offer many patients the option of an alternative therapy when ventilation is required for many hours a day. The ability to alternate complementary techniques to NIV, may be a viable alternative to tracheotomy.

Various conditions such as claustrophobia, skin lesions induced by the mask, rhinitis, or no tolerance to the face's pressure may be responsible for the failure of NIV, therefore alternative NIV techniques should be considered in highly dependent ventilator patients, besides the traditional ventilation with a mask.

The aim of this non-systematic review is to highlight the use of alternative methods of non-invasive respiratory support to positive pressure NIV in neuro-muscular patients.

Mouthpiece ventilation

MPV is a type of non-invasive ventilation delivered – as the name implies – via a mouthpiece. It is used for many years, and there is already evidence in literature documenting the effectiveness of the treatment and greater patient compliance¹³.

The use of the mouthpiece was first described in 1953 in patients with polio, and to date many cases have been documented in the literature of successful treatment. However only one center has documented 500 cases of long-term survival for daytime use in patients requiring 24-hour ventilator support up to 1993^{16,17}. Surprisingly, this technology is still not commonly used. There were no evidence-based guidelines for this technique, that is applied on the basis of the experience of few centers until 2020, when the European Neuromuscular Centre (ENMC) Respiratory Therapy Consortium, during the 252nd ENMC International Workshop developed the “best practice guidelines for management of mouthpiece ventilation in neuromuscular disorders”¹⁸.

The mouthpiece ventilation is used with single non-vented circuit ventilators in pressure-controlled or, more frequently, in volume-controlled mode to allow air stacking¹⁹. The patient can achieve mouthpiece ventilation, breathe passively using the backup rate set on the ventilator, or actively trigger the breath, retain a part or all, of the delivered volume. Different types of triggers are

available. In addition to the traditional flow or pressure trigger, normally used for NIV, the “Kiss trigger” is available on a portable ventilator (Trilogy, Philips Respironics, Murrysville, PA, USA). Such a dedicated MPV trigger allows for activation of inspiration when the patient's lips touch the mouthpiece. It is possible to use a simple single-tube circuit or a circuit with a valve²⁰. The valve is preferred for patients who cannot disconnect to exhale outside the circuit and in this way can remain connected for a long time in succession, avoiding the rebreathing of carbon dioxide. Dedicated MPV mode has been introduced on many portable devices; it is possible to set the type of circuit selected and then select the pressure or volume mode, and the parameters chosen for the patient. In this way, the patient is able to independently remove the mouthpiece to speak, eat, cough, or call a family member. Its use presents no risk of skin breakdown, conjunctivitis, does not induce claustrophobia while causing a lower probability of gastric distension²¹.

Despite these obvious advantages, this modality of ventilation is not commonly used. Mouthpieces for daytime use may cause salivation and more rarely vomiting while prolonged use can cause orthodontic deformities after 20 years²².

However, the same problem was found with the traditional interface in pediatric patients. Nasal pledges or nose clips can prevent air leak through the nares for patients using lip cover interfaces for the NIV mouthpiece while sleeping¹³. During the nighttime sleep, most patients use a mask because the mouthpiece requires collaboration and is uncomfortable. Moreover, though rarely, the air can also be ingested causing gastric distension¹⁹.

Different angled replacement mouthpiece 22 and 15 mm, and MPV straw kit are available²⁰. Mouthpiece and nasal NIV are open systems of ventilator support; the low-pressure alarms of ventilators not having mouthpiece NIV modes can often be inactivate. Backpressure from a 15 mm angled mouthpiece is sufficient to prevent a low-pressure alarm set at 2 cmH₂O.

Carlucci et al. studied how to set different types of the ventilator when using the mouthpiece¹². They found that a proper alarm setting, and a combination of VT and TI would allow most ventilators to be used for mouthpiece ventilation without the alarm activation²¹.

The patient triggers the breath by placing lip on the mouthpiece and generating a small negative pressure in the circuit, by tasting or inspiring. The mouthpieces are very useful as additional daytime ventilation in patients with neuromuscular diseases, who do not have the capacity to preserve acceptable diurnal blood gas without frequent intermittent periods of care^{16-18,22-24}.

Some authors report that patients that used MPV were satisfied and preferred the mouthpiece to the nasal

mask²². Though this aspect can favour NIV adherence, however, it exposes the patient to the risk of underventilation because of frequent disconnection from the mouthpiece¹⁴. Underventilation with hypoxemia and hypercapnia can be tolerated by the patient for a short time, for which he himself feels the need to reconnect. The mouthpiece allows support ventilation with the possibility of consecutive detachments, for speaking or eating. Desaturations during MPV are possible, as well as for mechanical mask ventilations, due to increased resistance (secretions) and excessive system leaks. For example, MPV-dedicated mode without backup respiratory rate may be beneficial in less-dependent patients (frequent disconnections), while severe ventilator-dependent patients may take greater advantage of a more reactive ventilator, with greater rapidity in adjusting tidal volume and setting back up rate²⁵.

Just like masked NIV, the patient should be monitored periodically to identify any progression of the disease and the need for therapeutic changes. The time of interruption is probably the major limitation of this approach to NIV. It has been documented that the periods of disconnection are associated with > 5 mmHg paCO_2 increase and $> 2\%$ spO_2 decrease, but no medical complication occurred before or after the monitoring time. Few patients accepted prolonged disconnections without developing hypercapnia²³.

The most common type of asynchrony was an ineffective effort, suggesting a need to improve trigger sensitivity. The newly introduced MPV software that allows the insufflation to be triggered only by positioning the pa-

tient's lips appears to be a useful option for patients with severe muscle weakness²³. The most commonly used ventilation mode is assisted volume- and pressure-controlled with no expiratory positive airway pressure, with the low-pressure alarm set to apnea minimum and maximum duration²³⁻²⁵.

The MPV characteristics, such as the intermittent disconnection of the patient and the presence of continuous leaks, may represent a challenge for turbine-based home ventilators. There are considerable differences in the ability of the different life-support ventilators to cope with the rapidly evolving respiratory load features that characterise MPV, which can be further accentuated by choice of ventilator settings. It is always needed to carefully monitor the patient during the adaption phase as MPV requires a real patient's collaboration. Not all ventilators guarantee a rapid adaption to the patient's breaths²⁵.

The physician should also evaluate the patient's ability to synchronise with the mouthpiece held in the mouth, and whether or not to exhale outside the mouthpiece. Depending on the ability to turn the neck, the subject can uninterruptedly keep the mouthpiece between lips or leave it for a variable time¹⁸. Patient's limiting factors include inability to close one's mouth to seal the interface, inability to move the neck, impaired bulbar function, non-acceptance to try MPV, lack of available interfaces / equipment, absence of caregivers who can guarantee the change with NIV if necessary (Tab. I). For these reasons, and because of its specific features and drawbacks such as air leaks, MPV must be managed by expert hands, and well-monitored (Tab. II).

Table I. Indication and contraindication of MPV use.

Indication	Contraindication
Diurnal respiratory support needed	Inability to close mouth to seal the interface
Dyspnoea persistent	Inability to move the neck
Weight loss	Impaired bulbar function
Adaptation to any NIV	Non-acceptance to try MPV
Daytime fatigue or hypercapnia	Poor compliance
Weaning from invasive mechanical ventilation	Lack of available interfaces/equipment
Request for autonomy by the patient	absence of caregivers who can change with NIV

Table II. Mode and setting of MPV.

Pressure mode	Volume mode
ST, PSV	ACV
With dedicated mode	With or without dedicated mode
Pressure 10-14 cmH ₂ O	VC 700-1500 ml
EPAP 0	EPAP 0
Back up frequency (as needed)	Back up frequency (as needed)
Inspiratory time 0.8-1.3 sec	Inspiratory time 0.8-1.3 sec

Some authors described the use of mouthpiece in a cohort of patients affected by kyphoscoliosis and acute respiratory failure. They showed an improvement in clinical symptoms, blood gases and nocturnal ventilation, sleep related parameters, and HRQL scores. These improvements were accompanied by a significant increase in lung volumes and respiratory muscle function following diurnal ventilation via angled mouthpiece, alternated with nocturnal ventilation via mask ²⁶.

Applications in clinical practice

Amyotrophic lateral sclerosis (ALS)

ALS is a progressive neuromuscular disease characterised by lower motor neuron and upper motor neuron dysfunction. Although clinical presentations can differ, there is no therapy for ALS, and the disease is generally terminal, with most patients dying of respiratory problems. Patients die within 3 to 5 years of diagnosis, unless they choose to undergo tracheostomy, in which case, they may live, on average, 2 additional years ^{27,28}.

Data in literature confirmed the usefulness of MPV in ALS ²⁹. Bach et al. ³⁰ reported that mouthpiece ventilation was an effective alternative to tracheostomy in patients with adequate bulbar muscle function. In patients using NIV many hours a day or showing low NIV tolerance with oronasal and nasal masks, or skin lesions, eye irritation, or gastric distention, mouthpiece ventilation should be taken into account ³¹. Patients using ventilation even during the night can alternate between daytime MPV and a sleeping interface. Use of mouthpiece in ALS patients may be limited by the involvement of bulbar muscles, or by deterioration of cognitive status; furthermore, disease progression may render MPV ineffective ³². However it has been reported that MPV, while having no impact on survival, improves the quality of life of the patient with ALS ³³.

Duchenne muscular dystrophy

Duchenne muscular dystrophy is a rare genetic neuromuscular disorder, due to mutations in the *DMD* gene, that affects skeletal and heart muscles causing muscle wasting and cardiomyopathy. Chronic respiratory failure is a constant feature in patients with DMD ³⁴, who often require continuous ventilation and need respiratory support 24h a day. McKim et al. ³⁵ argue that 24h NIV should be considered a safe alternative to tracheostomy in these patients, especially in those presenting skin lesions, gastric distension, or eye irritation. They examined the impact of diurnal mouthpiece intermittent positive pressure ventilation and concluded that it is safe, stabilises vital capacity and improves survival. The mouthpiece can be

very valuable, in patients who use NIV many hours a day, alternating between nasal masks and full-face masks. It is also useful to promote adherence to NIV. ²⁴

Myotonic dystrophy type 1

Myotonic dystrophy type 1 (DM1) or Steinert disease is the most common type of muscular dystrophy in adults, and presents multiple organ symptoms, including respiratory dysfunction. As a cause of respiratory dysfunction in DM1, a restrictive ventilatory pattern due to respiratory muscle weakness and central nervous system's involvement has been reported, requiring non-invasive mechanical ventilation ³⁶.

There are few data on the use of MPV in patients with Steinert disease. It could be useful for patients who previously refused NIV for tightness, claustrophobia, and poor compliance interface. MPV was successfully used in our practice in patients who yet refused nasal, oral or oro-nasal interface ³⁷.

Other neuromuscular diseases

Bach et al. reported a large number of patients with neuromuscular diseases, long managed with 24hours NIV ³⁰. They describe non-invasive acute and long-term management of patients with quadriplegia due to high spinal cord lesions. This includes full-setting, continuous ventilatory support by non-invasive intermittent positive pressure ventilation to sustain inspiratory muscles and mechanically assisted coughing to support inspiratory and expiratory muscles. Even patients previously ventilated 24h/24h via tracheostomy were converted to non-invasive mechanical ventilation with MPV ^{30,35}. Bilateral diaphragmatic paralysis (BDP) is usually associated with dyspnoea that worsens when the patient is recumbent, increasing breathing and exercise intolerance. With the BDP progression, there is an increase in ventilatory failure with hypoxaemia and hypercapnia, which can further worsen due to atelectasis and ventilation-perfusion mismatch. Reports are showing that MPV is a clinically beneficial treatment to improve exercise tolerance and exercise-induced dyspnoea in patients with BDP ³⁸. MPV may also be useful for weaning from orotracheal tube or tracheostomy (Fig. 1).

Intermittent abdominal pressure ventilator (IAPV)

Intermittent abdominal pressure ventilator was first described in 1935 by R.W. Paul for adults and young patients who require continuous respiratory support ³⁹. In 1938 it was described for the treatment of post-diphtheritic respiratory paralysis or respiratory paralysis due to anterior poliomyelitis ⁴⁰. Over the years, an alternative approach to NIV with IAPV was described in patients with spinal cord injury ⁴¹. Later Bach, in 1991, described the



Figure 1. MPV for weaning from tracheostomy.

long-term use of IAPV in 209 patients diagnosed with myopathy, Duchenne dystrophy and spinal cord injury ¹⁴.

This approach was used in several types of neuromuscular patients: ventilator-dependent traumatic quadriplegic patients, spinal cord injured, non-Duchenne myopathy, Duchenne muscular dystrophy, myelopathy, polymyositis and Friedreich's ataxia for long-term respiratory support ^{14,42-45}. The Authors conclude that, in general, patients with traumatic high level spinal cord injury are the best candidates to benefit from these techniques because of their youth, intact mental status and bulbar musculature, absence of obstructive lung disease.

The new IAPV (LunaBelt, Dima, Italia) consists of a corset with an elastic inflatable bladder that fits over the abdomen. A hose attaches the bladder to a ventilator that gives up to 2.5 liter of air to the bladder and the abdominal wall (Fig. 2). This raises the diaphragm to cause expiration below the functional residual capacity. The new models that prevent clothing taking on the corset buckles, are more comfortable, lightweight, suitable, easy to make and put on and use Velcro for fastening ⁴². The following IAPV parameters can be set: Pressure inside the bladder, Tinsp (real inspiratory time when the diaphragm moves down), Frequency (respiratory rate), and Rise Time (time to inflate the bladder). The IAPV only works efficiently when patients are in sitting position, at an angle of 30° or greater with the optimum at 75°. No guidelines are available on the use of IAPV and on the parameters to be set, the indications usually derive from case reports and experience (Tab. III).



Figure 2. Patient during IAPV.

Applications in clinical practice

The use of IAPV is reported with success in patients with a post-ischemic cervical myelopathy ⁴² and in ALS patients with tracheostomy by De Mattia et al. ⁴⁴ IAPV permitted optimal speech, efficient diurnal ventilatory pattern, good pulmonary gas exchange without dyspnoea, and a significant improvement in the management of salivary secretions, with a reduction in the number of tracheal aspirations. Furthermore, the Authors reported the resumption of the spontaneous respiratory activity, which demonstrates an improvement in the patient's respiratory condition ⁴²⁻⁴⁴. IAPV facilitates diaphragmatic

Table III. IAPV indications and contraindications.

Indications	Contraindications
Daytime respiratory support needed	Inability to posture trunk of at least 30°
Adaptation to any NIV	Intolerance of corset
Diaphragmatic weakness	Severe sacral decubitus
Weaning from invasive mechanical ventilation	Hiatal hernia with regurgitation during meals
Request of autonomy by patient	Recent abdominal surgery

Table IV. NPV indications and contraindications.

Indications	Contraindications
Severe facial decubitus	Sleep-apnoea syndrome
Mask intolerance	Severe obesity
Facial deformity	Severe kyphoscoliosis
Inability to fit mask	Rib fractures
Severe hypercapnic encephalopathy	Recent abdominal surgery
Severe respiratory acidosis	Claustrophobia or poor compliance

motion and may be particularly useful in patients with bilateral diaphragmatic weakness or paralysis, and allows for plugging of the tracheostomy tube with the cuff deflating for several hours during the day, thus preventing tracheal damage.

Pierucci et al. described the case of a young patient with late onset Pompe disease who was successfully treated with nocturnal NIV and daytime IAPV⁴⁵.

IAPV can also be used in patients who require NIV many hours a day. Patients with gastric distension may benefit from the abdominal compression exerted by the device during the exhalation phase⁴². Disadvantages can be food regurgitation during meals (rarely), locking of clothing on straps and Velcro fasteners, redness of bony prominences, and inability to shower or bathe while using it^{46,47}. Indications and contraindications are described in Table IV. Furthermore, regular follow-up is required as it can become less effective over time^{42,47}.

IAPV can be less effective for the appearance of gastric complications, the worsening of respiratory function due to the evolution of the disease, and the need for invasive support.

Negative pressure ventilation

Negative pressure ventilation (NPV) has played a crucial role in the history of ventilatory support for patients with neuromuscular diseases and respiratory failure. A full-body type ventilator was the first description of a negative-pressure ventilator. The first “tank ventilator” was described by Dalziel in 1838. It was an airtight box, where the patient remained in a sitting position⁴⁸.

A pinnacle of negative-pressure ventilation appears with the development of the iron lung, originally designed and built by Drinker and Shaw⁴⁹, but manufactured and sold by Emerson during polio epidemics around the world, from 1930 to 1960. Numerous other types were developed over time, such as the “raincoat” and the “chest cuirass”. However, due to several factors, in the 1960s, there was a movement away from negative-pressure ventilation (excessive leaks; difficult time to maintain effective ventilation, inability to sustain high airway pressure or establish EPAP, limited access to the patients)⁵⁰.

This technique has some strengths as it is able to guarantee a breathing completely analogous to the natural one, consisting of an inspiratory phase followed by the expiratory phase. Both phases are applied by means of a negative pressure ventilator and some accessories connected to it, such as a cuirass or a poncho. The ventilator first applies a negative pressure forcing the movement of the diaphragm downwards while the rib muscles tend to enlarge the thorax: this process generates lung expansion by generating a lower intrathoracic pressure than the external one; subsequently, the ventilator exerts positive pressure forcing the air inside the chamber, to compress the chest and empty the lungs⁵¹. The cuirass negative pressure ventilators were primarily beneficial in children with neuromuscular disorders. Children had their own cuirass built from a plaster prototype of the chest and abdomen. This was important when there was a severe thoracic scoliosis. The cuirass is a plastic model of the front and sides of the trunk, the edges are padded with airtight material and the cuirass attached to the patient with a back strap. Cuirass pressure injuries are also possible. Cuirass ventilators are easy to put on and suitable for home use (Fig. 3).

The last new soft cuirass (Dima Italia, Negavent - Pegaso Vent) is an accessory for negative ventilation, designed to ensure a good quality of life and normal daily activities. It is a structure that creates a ventilation chamber on the chest. On the edges, it is covered with a soft gasket to ensure patient comfort and low pressure losses. It is available in various sizes and the choice of size depends on the size of the chest, body structure, weight, and height of the patient, and of any deformities of the chest such as scoliosis. Generally new cuirasses are necessary as the patient grows⁵².

Kavanagh et al. hypothesized that, compared with positive pressure ventilation, negative pressure translates in a greater functional residual capacity at the same transpulmonary pressure, and results in a greater oxygenation with the same residual capacity. NPV may distend lungs fundamentally differently to positive pressure, resulting in more homogeneous ventilation, less injury, and superior oxygenation^{51,53}.

The data showed that negative-pressure ventilation produces superior oxygenation unrelated to lung perfusion which may be explained by more effective lung volume inflation during both inspiration and expiration⁵³.

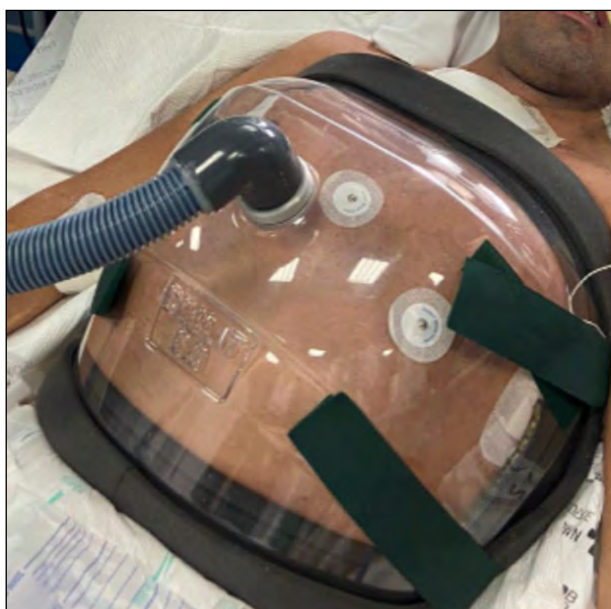


Figure 3. Negative pressure ventilation.

NPV may preserve physiological functions, such as speech, cough, swallowing and feeding and its major advantage is the prevention of endotracheal intubation and its related problems.

A limitation is the lack of upper airway protection, particularly in comatose and/or neurological patients, which may result in aspiration, considering the described impact of NPV on the lower esophageal sphincter^{50,54}. Upper airway obstruction can occur in unconscious patients, in patients with neurologic disorders with bulbar dysfunction, and in those with sleep apnea syndrome. This event can be prevented by using concomitant nasal continuous positive airway pressure, although switching

to non-invasive positive pressure ventilation may be more helpful in this situation.

Those who cannot tolerate a facial mask due to facial deformity, claustrophobia or excessive airway secretion, or young children, and in particular in children undergoing complex cardiac reconstructive surgery considering the beneficial effects on the cardiopulmonary circulation, and patients in whom excessive airway secretion or difficulty in wearing a mask limits the application of NIV are the best candidates for this type of ventilatory support⁵⁴.

The choice of the best negative pressure mechanical ventilation device depends on the indications and contraindications and varies among subjects. The main indications and contraindications are listed in Table V. There are no guidelines on the use of NPV nor on the parameters to be set (Tab. VI).

Conclusions

The use of MPV, IAPV and NPV is limited to a few centres, likely for the long time required to adapt and monitor the patients. The different possibilities of non-invasive mechanical ventilation to ensure the optimal interface for different patients should be known and applied.

Our goal must be to ensure the best possible quality of life for our patients. However, lack of local resources can also interfere with the diffusion of innovative technologies. MPV and IAPV are comfortable alternative to NIV, but more active participation than traditional masks is required when using MPV. For subjects with chronic disease who need to initiate NIV, both systems should be considered. In fact, they are useful for promoting a positive approach to NIV or for alternating the interface in patients who require 24-hour ventilatory support^{24,31,37,43,45}.

Table V. IAPV parameters; we suggest starting: Pbelt 0-70 Hpa (at the beginning 30-40 Hpa); select desired Ti (during the Ti settled, the PBAir will be deflated, while the patient will be able to inhale); back up rate as desired; rise time usually 1.0s; Expiratory time (abdominal compression) will be linked to the back up rate and inspiratory time settled. For example: settled inspiratory time 1.5 sec, Fr 15 bpm, derivative expiratory time will be 2.5 sec.

Intermittent abdominal pressure ventilator (LunaBelt)		
Mode	Timed	Spontaneous/timed
Pression belt	0-70 hPa	0-70 hPa
Time inspiratory	0.3-5.0 sec	na
Time inspiratory minimum	na	0.3-3.0 sec
Time inspiratory maximum	$[(60/\text{Freq}) - 0.6 \text{ sec}]$	$[(60/\text{Freq}) - 0.6 \text{ sec}]$
Time expiratory minimum	na	0-1.5 sec
Back-up Frequency	1-60 bpm	1-60 bpm
Frequency maximum	$[60/(\text{Tinsp} + 0.6 \text{ sec})]$	$[60/(\text{Tinsp} + 0.6 \text{ sec})]$
Rise time	0.1-1.0 sec	0.1-1.0 sec
Trigger inspiratory (nasal cannula)	na	Auto
Trigger expiratory (nasal cannula)	na	Auto

Table VI. NPV parameters; we suggest start: Inspiratory pressure of -20, Expiratory pressure from 0 to 5, I:E Ratio from 1:1 to 1:2, back up frequency: set frequency at 2-4 breaths above patient's own spontaneous rate.

Negative pressure ventilation (Negavent)			
Mode	T (timed)	ST (spontaneous/timed)	Syncro (synchronized)
Inspiratory pressure	Da -5 a -90 hPa	Da -5 a -90 hPa	Da -5 a -90 hPa
Expiratory pressure	Da +25 a -25 hPa	Da +25 a -25 hPa	Da +25 a -25 hPa
Back-up frequency	5-60 bpm	5-60 bpm	5-60 bpm
I/E ratio	1.0:9.9 - 9.9:1.0	1.0:9.9 - 9.9:1.0	1.0:9.9 - 9.9:1.0
Trigger inspiratory (nasal cannula)	na	1;9	1;9
Trigger expiratory (nasal cannula)	na	1;9	na

NPV, alternating with other techniques or in addition in case of patients with congenital or acquired facial deformities or not tolerating positive pressure, may have still a role in the treatment of patients with neuromuscular disorders⁵²⁻⁵⁴.

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CASE REPORTS

Genotype phenotype analysis in a family carrying truncating mutations in the *titin* gene

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We report a family carrying a previously described truncating mutation, NM_001267550.2(TTN):c.107889del p.(Lys35963Asnfs*9) in exon 364, and a novel truncating mutation, NM_001267550.1:c.100704C > A p.(Tyr33568*) in exon 358 in the *titin* gene. The c.107889del mutation, which was maternally transmitted, has been previously described in patients from the Iberian Peninsula. The mother was of Peruvian descent suggesting a potential European ancestral origin of this mutation. In this family, a daughter, who is a compound heterozygote carrying both these mutations, developed a peripartum cardiomyopathy during her second pregnancy. Subsequently, she was diagnosed with a myopathy following electro-myography testing and a muscle biopsy which showed fiber type disproportion. Her brother, who carries only the paternally inherited c.100704C > A mutation, developed a cardiomyopathy following a suspected viral illness. Their father, who transmitted this mutation, has no evidence of a cardiomyopathy. We hypothesize that the c.100704C > A mutation confers susceptibility to the development of cardiomyopathy which may be brought on by cardiovascular stress. Our study of this family expands the genotype and phenotype spectrum of disorders that can be associated with mutations in the *titin* gene.

Key words: *TTN* gene truncating mutations, cardiomyopathy, susceptibility mutation

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Conflict of interest

The Authors declare no conflict of interest

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Introduction

The *titin* gene, *TTN*, is the largest known polypeptide in humans and has multiple functions that include participating in myogenesis and contributing to the elasticity of muscle tissues. There are a variety of clinical and pathological phenotypes that have been described ranging from early onset myopathy with fatal cardiomyopathy, congenital centronuclear myopathy to adult onset muscular dystrophy. The pattern of inheritance can also vary from autosomal recessive to autosomal dominant ¹. We present a family with siblings suffering from cardiomyopathy, one of whom also developed a myopathy.

Case history

The index patient is a 37-year-old woman who was admitted for delivery of her second pregnancy and was diagnosed with toxemia of pregnancy. Her first pregnancy had been uneventful. As part of the investigations for the toxemia, an echocardiogram was performed and revealed a left ventricular ejection fraction of 30-35% (normal range 55-70%) with impaired relax-

ation of left ventricular diastolic filling. She was treated for a global cardiomyopathy and delivered by cesarean section. At age 39 years, the ejection fraction had improved to 45% and she continued to follow up with a cardiologist. Over the next four years it was noted that she had reduced exercise tolerance and for several years she was having difficulty climbing stairs. These issues were attributed to the cardiomyopathy. At age 43 years she developed an episode of plantar fasciitis and was evaluated by a physical therapist who noted weakness. She was sent for an initial neurological consultation and subsequently referred for a neuromuscular evaluation. Her neurological review of systems revealed no complaints of difficulty chewing, swallowing, speaking, double vision or sensory loss. She had complaints of imbalance and difficulties climbing stairs and arising from a deep seated chair. Physical examination revealed normal vital signs and neurological examination showed no abnormalities of the mental status, cranial nerve examination, cerebellar system and sensation assessing light touch, pin prick, vibration and proprioception. Testing her power revealed normal strength in her arms evaluating the biceps, triceps, internal rotation, external rotation, wrist flexion and extension. She had no scapular winging. In her right leg, she had weakness with Medical Research Council (MRC) scale of 3/5 testing hip flexion, extension and abduction, knee extension and foot dorsiflexion. On the left, power in these muscles was diffusely MRC Grade 4/5. She had normoactive reflexes in her arms and reduced reflexes in her legs. Her plantar reflexes were flexor and she had a “waddling” gait.

Follow up with the cardiologist at age 44 years showed an ejection fraction of 50% and a negative nuclear stress test.

A family history revealed that her two children do not suffer from a neuromuscular disorder. She has 5 siblings who are all healthy with no complaints or ongoing diagnosis of a neurological or cardiac disorder. However, a brother, age 53 years, was diagnosed with non-ischemic cardiomyopathy at age 43 years when he presented with symptoms of congestive heart failure following a prodrome of a presumed viral infection. Investigations revealed a left ventricular ejection fraction of 10%. Currently he is well controlled with medical management and has an ejection fraction of 55%. He has no symptoms of muscle weakness. Her mother, who was the product of a consanguineous marriage between first cousins died at age 46 years from an unclear cause. Her father, age 84 years, has no neuromuscular complaints and no history or clinical evidence of a cardiomyopathy. Both of her parents are from Peru and are not related to each other.

Routine serum chemistries including a cell count and differential, comprehensive metabolic panel, aldolase and inflammatory markers such as erythrocyte sedimentation

rate and C-reactive protein were normal. Her creatine phosphokinase was 976 U/L (nl-24-173 U/L) and after discontinuing fenofibrate came down to 477 U/L. Magnetic resonance imaging (MRI) of the pelvis with and without contrast showed atrophy of the right piriformis and gluteus maximus muscles with no enhancement. This was interpreted as showing evidence suggestive of a neurogenic process. An MRI of the lumbosacral spine showed no significant abnormalities.

She had an electromyography (EMG) done which showed normal motor nerve conduction parameters testing bilateral ulnar, median, peroneal and tibial nerves. Evoked sensory nerve action potentials were normal testing the ulnar, median, radial, sural and superficial peroneal nerves. A concentric needle EMG showed no spontaneous activity in any muscle sampled of her arms or legs. Low amplitude polyphasic motor unit potentials and a full interference of submaximal effort was noted in the proximal muscles of her arms. These abnormalities were noted to a greater degree in analyzing the muscles of her legs.

Muscle biopsies of the left deltoid and tibialis anterior were obtained, and show moderate myopathic changes (Fig. 1). H&E stained frozen section (1A) show an increase in variation of fiber size, with several smaller/hypotrophic fibers, and an increase in the internally and centrally placed nuclei. NADH-TR (1B) illustrate several ring and lobulated fibers. ATPase Ph-4.3 (1C) in which the type 1 myofibers show darker staining, and ATPase Ph-9.4 (1D) where the type 2 myofibers show darker staining. Both stains show that the type 1 myofibers are small/hypotrophic and are more numerous, comprising more than 60% of the myofibers, compared with type 2 fibers. Based upon these non-specific pathological changes, the differential diagnosis includes fiber type disproportion, limb-girdle muscular dystrophy, myotonic dystrophy and centronuclear myopathy.

Genetic analysis

The patient underwent commercial genetic analysis by performing whole exome sequencing of eighty genes known to cause genetic myopathies. This analysis included negative test results of myotonic disorders DM1 and DM2. All testing was done with the patient and family members following local IRB approved policies and procedures.

In the index patient, the results showed a c.617G>A variant (rs373108373) in exon 4 of the *TRPV4* gene resulting in an R206H protein alteration. This variant is reported in the ExAC database in a heterozygous state in three individuals (https://gnomad.broadinstitute.org/variant/12-110240891-C-A?dataset=gnomad_r2_1)².

This R206H change involves a conservative amino acid substitution which is not likely to impact secondary protein structure. Our protein modeling analysis with

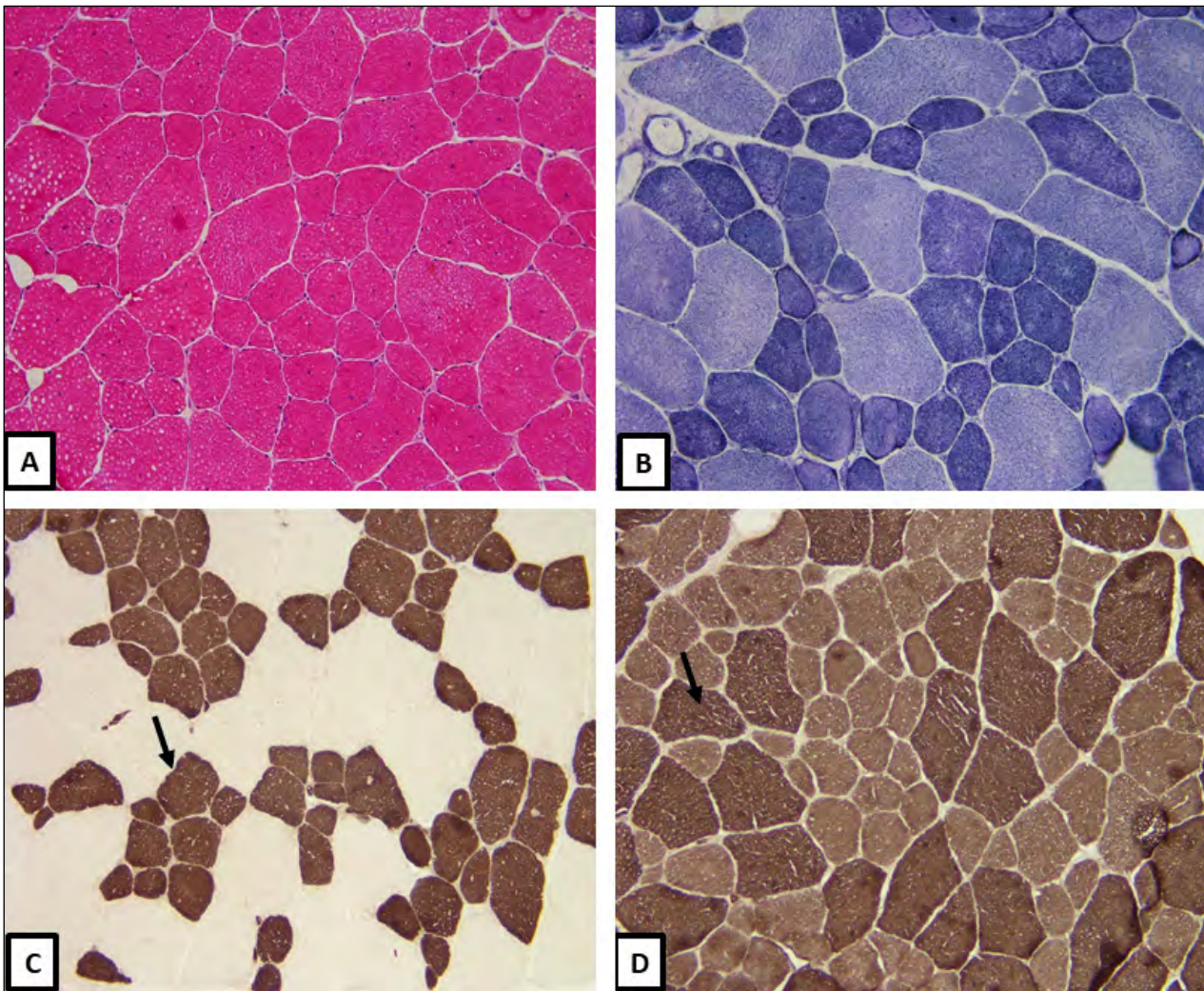


Figure 1. (A) H&E, Frozen section 200X, show an increase in variation of fiber size and internally and centrally placed nuclei. (B) NADH-TR, Frozen section 200X, ring fibers. (C) ATPase Ph 4.3, Frozen section 200X, type 1 myofibers (arrow) are hypotrophic and more numerous (> 60%). (D) ATPase Ph 9.4, Frozen section 200X type 2 myofibers (arrow) are of normal size and fewer in number.

PolyPhen³ suggests that this is a benign variant. In addition, a c.409G > A variant was detected in exon 4 of the *LAMA2* gene. This A137T variant (rs368349321) is predicted to be deleterious to the protein by SIFT⁴, PolyPhen and Mutation taster analysis⁵. Although it has not been reported in the ClinVar database, pathogenic variants in *LAMA2* gene typically cause an autosomal recessive disorder and a second variant was not detected by sequencing and deletion/duplication analysis. It is unlikely that this is a disease producing variant in this patient.

Two variants were observed in the *TTN* gene (NM_001267550), a previously reported pathogenic variant in the ClinVar database, rs281864930, c.107889del in the last exon (364/364), resulting in frameshift and premature truncation of protein (Lys35963Asnfs*9) (Na-

tional Center for Biotechnology Information. ClinVar; [VCV000038439.5], <https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000038439.5>). This variant is located in the portion of the *TTN* gene encoding the M-band region of the protein. A second variant, c.100704C > A in exon 358 (358/364) of *TTN* gene results in a nonsense variant Tyr33568*. This is a novel variant not reported in either the 1000 Genome⁶ or gnomAD (ExAC) databases² and is predicted to cause loss of normal protein function through protein truncation or nonsense-mediated decay. This variant is located in that portion of the *TTN* gene which encodes the A-band of the titin protein and, overall, our analysis suggest that it is pathogenic.

Her father agreed to directed testing for the *TTN* gene and results show he is a carrier of the c.100704C > A vari-

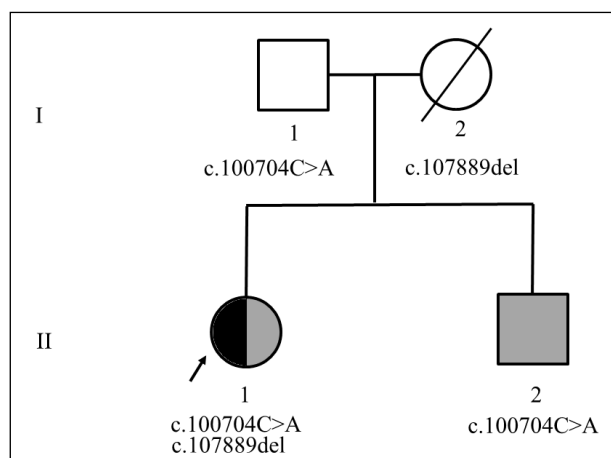


Figure 2. Pedigree showing the inheritance of the *titin* variants in this family. Dark fill indicates muscle phenotype and grey fill indicates cardiac phenotype. Index patient (arrow) inherited two variants one from each parent and shows both muscle and cardiac phenotype.

ant. This indicates that the mutations in the index case are in trans confirming that she is a compound heterozygote inheriting the c.100704C > A mutation from the father and the c.107889del mutation from her mother. Her brother with the history of cardiomyopathy, also underwent directed testing which showed that he inherited the c.100704C > A paternal allele (Fig. 2).

Discussion

The first description of a titinopathy resulting from mutations in the *titin* gene was published in 2002 by Hackman et al.⁷ This was a study of Finnish patients with tibial muscular dystrophy and there was evidence for a founder effect in this population. In a follow up study in 2008⁸ by this same group, the first report of the c.107889del is described in two unrelated Spanish families and designated as g.29337delA. This report described adult patients developing muscular dystrophy in an autosomal dominant fashion. In 2013, this mutation was again described but following an autosomal recessive pattern of inheritance in a 7 year old boy who initially developed symptoms at age 3⁹. The ethnic origin of this patient's mother who carried the c.107889del mutation is not indicated. Interestingly, in follow up study of the patients involved in the prior publication by Hackman et al.⁸, a second mutation is described confirming an autosomal recessive mode of transmission¹⁰. Evila et al. published an additional paper in 2016 describing another Spanish family carrying this mutation¹¹. In 2020, Savarese et al. reported six individuals with this mutation one of whom is from France and the remaining five

are from Spain¹². Our genetic analysis demonstrates the presence of this c.107889del mutation in the *TTN* gene in our family which is of Peruvian descent, a population that has an admixture of genes from Spain. This strongly suggests a founder effect for the c.107889del mutation in this admixed population that may have originated in Spain. Alternatively, this mutation could be the result of a separate mutational event at this site. The second mutation, c.100704C > A in exon 358 of *TTN* gene is novel and following the ACMG/AMP guidelines¹³ the variant is pathogenic (or probably pathogenic). These results, in combination with the neurological examination, EMG testing and muscle biopsy provide strong evidence that the index patient has a titinopathy.

Our patient can be compared to others carrying biallelic protein truncating variants described in recent report by Savarese et al.¹. In this report, analysis of five patients indicates onset in the thirties with distal lower limb weakness and walking difficulties in three of them. Our patient shows proximal and distal lower extremity weakness which was described in the two of the patients with biallelic truncating mutations but unlike our patient, their onset was in infancy and childhood. The presence of the c.107889del causes the production of a 'quasi-normal' protein, resulting in an adult-onset myopathy. The muscle biopsy of our patient demonstrates fiber type disproportion. This is a common pathologic feature of not only those patients with biallelic truncation mutations but also those carrying missense and monoallelic truncating mutations¹.

The role of truncating mutations in the etiology of cardiomyopathy was initially reported in 2012 based upon analysis of 312 patients with dilated cardiomyopathy¹⁴. More recently, a large population study supports the role of truncating mutations in patients affecting heart function¹⁵. In four patients with biallelic truncating mutations described by Savarese et al., the presence of a dilated cardiomyopathy was noted in one and some abnormality of cardiac function in two others¹. One patient had no evidence of cardiac involvement indicating the cardiac abnormalities are an inconsistent feature of those with titinopathy. In our family, it is interesting to note that the index patient and her brother carrying the c.100704C > A truncating mutation both developed a cardiomyopathy. Their father, in his eighties, who passed this mutation to both siblings remains without evidence of a cardiomyopathy. It appears that this mutation may represent a susceptibility gene for the development of cardiomyopathy. It is important to note that the index patient did not develop the cardiomyopathy until the hemodynamic stress brought on by her second pregnancy. In her brother, it is likely that the viral illness the patient suffered contributed to the development of his cardiomy-

opathy. There is experimental evidence of studies in rats carrying a single truncating *TTN* mutations on the impact upon heart physiology during cardiac stress¹⁵. These experiments provide support that these mutations contribute to a susceptibility to the development of cardiomyopathy which manifests after cardiac stress. In this family, the c.100704C > A mutation encodes the A-band region of the titin protein. It has been reported that mutations associated with dilated cardiomyopathy were overrepresented in the titin A-band and were absent from the Z-disc and M-band regions of titin¹⁴. The authors concluded that *TTN* truncating mutations are the most common known genetic cause of dilated cardiomyopathy, occurring in approximately 25% of familial cardiomyopathy cases and 18% of sporadic cases^{15,16}. We hypothesize that in this family, the c.100704C > A represents a susceptibility variant that requires the presence of an additional cardiac stressor for the development of cardiomyopathy.

Our genetic analysis of this family strongly suggests the possibility of a founder effect of the c.107889del mutation originating in the Iberian Peninsula and spreading to South America. In addition, our study reports a novel truncating mutation, c.100704C > A, that expands the spectrum of mutations that can cause a titinopathy. Furthermore, we provide evidence that this mutation may confer carrier susceptibility to the development of dilated cardiomyopathy. Finally, our report confirms that in individuals with a titin related cardiomyopathy, the clinician must monitor such patients for the development of myopathic symptoms prompting further genetic analysis for a second *TTN* mutation.

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Coexistence of myasthenia gravis and amyotrophic lateral sclerosis in a Bosnian male: an unusual clinical presentation

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Purpose. Myasthenia gravis (MG) and amyotrophic lateral sclerosis (ALS) are two different diseases. The coexistence of both of them is extremely rare and represents a diagnostic challenge which requires thoughtful interpretation of clinical characteristics.

Case report. We present the case of a 46-year-old Bosnian male who developed ALS five months after MG. Diagnosis of MG was based on elevated titers of anti-AchR antibodies, positive edrophonium test, and decremental responses on a repetitive nerve stimulation test while the diagnosis of ALS was based on clinical and neurophysiological findings: upper motor neuron signs in the lumbar region, lower motor neuron signs in the bulbar and cervical regions, generalized fasciculations and muscle atrophy and progressive asymmetric muscle weakness together with active and chronic denervation in the cervical and lumbosacral region determined by electromyoneurography.

Conclusions. The coexistence of MG and ALS is rare and request an adequate interpretation of clinical symptoms. The relationship between these two diseases in as interesting phenomenon to present.

Key words: myasthenia gravis, amyotrophic lateral sclerosis, coexistence

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Introduction

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction that is usually caused by antibodies against nicotine acetylcholine receptors (AChR) and occasionally by antibodies against muscle-specific kinase (MuSK). Clinical characteristics of MG are fluctuating muscle weakness and easy fatigability of voluntary muscles. MG follows a slowly progression course. By contrast, amyotrophic lateral sclerosis (ALS) is as a progressive neurodegenerative disorder affecting motor neurons in the cerebral cortex, brainstem, and spinal cord. Studies of ALS have revealed defects in expression of acetylcholine receptors (AChRs) in skeletal muscle that occur even in the absence of motor neuron anomalies¹. The co-occurrence of MG and ALS has been described in a few reports, suggesting a possible association of the two diseases^{2,3}. A recent study reported that 0,75% of patients with ALS were also affected by MG⁴. We report the case of a patients with seropositive MG who within 5 months developed ALS.

Case report

A 46-year-old Bosnian male developed difficulties in swallowing, and dysarthria in April 2019. Difficulties with swallowing and chewing as well as pronouncing words were getting worse with more activities and in the evening and improved with rest. These symptoms he noted five months before he was referred to Department of Neurology. He had no family history of neuromuscular disorders. On neurological examination, his pharyngeal reflex was reduced. Eyelid ptosis, ocular and facial motility deficits were not evident on neurological examination. There was no muscle weakness, atrophy, or fasciculations in any of his extremities. Deep tendon reflexes were normal, and Babinski signs were absent. Sensory abnormalities were not detected. His biochemical investigations, thyroid function test and tumor markers were normal. Acetylcholine receptor antibodies (AChR level 2.85 nmol/l; normal values < 0.5 nmol/l) were elevated. The MuSK antibodies were not tested. Computed tomography scans of the chest did not reveal remarkable abnormalities (Fig. 1). An edrophonium test showed improvement in a way that patient could speak better and swallowed better without any side effects. Repetitive nerve stimulation performed on the ulnar nerve at 3 Hz showed a 25% decrease in musculus abductor digiti minimi amplitude after 1 minute, and 60% after 3 minutes compared to baseline. The compound muscle action potential (cMAP) after first stimulation was 2.5 mV, after second 1.8 mV and the value of the highest cMAP was 4mV. We discharged our patient from the hospital with diagnosis of Myasthenia gravis based on elevated titers of anti-AChR antibodies, positive edrophonium test, and decremental responses on a repetitive nerve stimulation test. We prescribed oral prednisolone, pyridostigmine and

azathioprine. Our patient was feeling much better during the follow-up. Quantitative Myasthenia gravis score before therapy was 8, and on therapy was 4. Five months later, he was again referred to our institution because he developed new symptoms such as initial tongue atrophy and fasciculations, moderate muscle weakness detected in the neck and all extremities as well as fasciculations in the upper limbs. On neurological examination, jaw jerk and snout reflex were hyperactive, and Babinski reflex was positive. An edrophonium test was again positive while titer of anti-AChR antibodies decreased to 0.85 nmol/l. Repetitive nerve stimulation showed a decrement response in the abductor digiti minimi muscle (25%). Needle electromyography showed fibrillation potentials, positive sharp waves, and fasciculation potentials with chronic denervation in the triceps brachii, biceps brachii, first dorsal interosseus muscles and chronic denervation in the lumbosacral regions. Needle electromyography of the tongue could not be done since it caused discomfort to the patient and he could not stand this diagnostic procedure. Brain MRI (Fig. 2) and cervical spine MRI showed no abnormalities (Fig. 3). He was diagnosed with clinically probable ALS, according to the revised El Escorial criteria⁵. We prescribed him Riluzole and so far he shows no progression.



Figure 1. CT scan of the thorax.

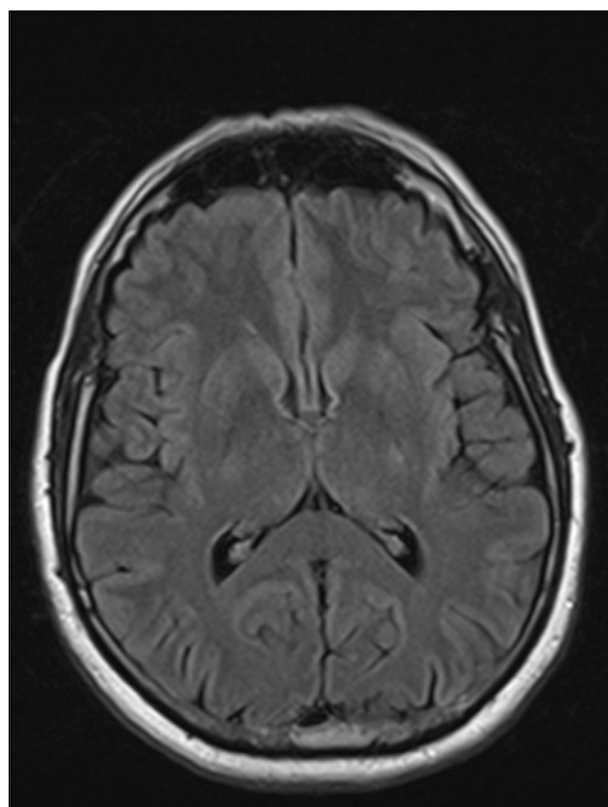


Figure 2. MRI of the brain.



Figure 3. MRI of the cervical spine.

Discussion

We present the case of a Bosnian patient who developed ALS symptoms five months after MG. Diagnosis of MG was based on elevated titers of anti-AchR antibodies, positive edrophonium test, and decremental responses on a repetitive nerve stimulation test. We did not test for MuSK antibodies; however the coexistence of AchR and MuSK antibodies is rare⁶. Diagnosis of ALS in our patient was based on clinical and neurophysiological findings: upper motor neuron signs in the lumbar region, lower motor neuron signs in the bulbar and cervical regions, generalized fasciculations and muscle atrophy and progressive asymmetric muscle weakness together with active and chronic denervation in the cervical and lumbosacral region determined by electromyoneurography. It has been suggested that autoimmune diseases, including MG, are associated with a small but increased risk for ALS⁷. The prevalence of MG and ALS are 11.8⁸ and 7-11⁹ cases per 100.000 people, respectively. Therefore, co-occurrences of MG and ALS are extremely rare. Males were affected twice compared with females, which might reflect a higher incidence of ALS in the male population³. The onset period between MG and ALS is variable, ranging from 3 months to 41 years^{3,4}. Despite of their rarity, co-occurrence of these two diseases have been presented in several case reports. The cases can be divided into two groups: first group in which MG patients developed ALS symptoms, and second where ALS patients developed myasthenic symptoms. Naik et al reported the development of ALS in a patient with established seropositive MG, 38 years after the onset¹⁰. Sawic-

ka et al. showed the case of ALS that developed 3 months after thymectomy in a patient with MG¹¹. Virmot et al. investigated if muscle dynein is involved in neuromuscular junction (NMJ) formation and in ALS. They found that the overall muscle differentiation process and differentiation of the post-synapse and the maintenance of NMJs are dependent on dynein. They conclude that the NMJ loss in ALS or in dynein-related neuromuscular disorders can be due in part to a defect in MuSK turnover at the NMJ¹². We can conclude that clinicians should not exclude the involvement of ALS when patients with MG show aggravated symptoms.

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NEWS FROM AROUND THE WORLD

AIM

In the period between January and March 2021, the activities of the Italian Association of Myology were reduced due to the pandemic related to SARS-CoV-2.

The activities concerned two web meetings with the Regional Representatives of the Association, and the organization of webinars on topics discussed within the Advisory Board and addressed to general practitioners, neurologists, pediatricians, physiotherapists, nurses. These events are listed below with their respective dates:

- May 6-7, 2021: Hereditary neuromuscular diseases: management in developmental age and continuity of care in adulthood;
- May 20, 2021: Muscular dystrophies with infantile and late onset;
- May 27, 2021: Metabolic myopathies with childhood and late onset;
- June 10, 2021: Spinal muscle atrophies;
- June 17, 2021: Autoimmune diseases of the muscle and of the neuromuscular junction, in childhood and adults;
- June 24, 2021: Instrumental and laboratory diagnostics of neuromuscular diseases: the role of the general practitioner after diagnosis.

The association has given the patronage for the “Fourth day of the neuromuscular diseases” which took place on March 13, 2021 – simultaneously in online mode with various topics – in 16 different Italian cities, representative of Centers belonging to the Italian Association of Myology (www.giornatamalat-tieneuromuscolari.it)

Prof. Carmelo Rodolico
AIM Secretary

MSM

Due to pandemic, the 14th Meeting of the Mediterranean Society of Myology has been moved to the next year. Proposals to organize and host the event are welcome.

WMS

The 26th WMS congress will take place, as a virtual meeting between 20 and 24 September 2021. The 5-day congress week will be an opportunity to catch up on the latest developments in neuromuscular diseases from around the world. The Programme Committee has done a fantastic job to come up with an exciting scientific programme and they expect the quality of the submitted abstracts on all aspects of neuromuscular disease to be as outstanding as always. Controversial debates, oral lectures and e-poster presentations through the virtual platform and a range of stimulating industry symposia on a dedicated day are expected. The usual WMS 2021 Virtual Pre-Congress Teaching Course will be held on the neuromuscular field, so everyone who is interested is encouraged to register and participate. Abstract submission and registration are now open!

Early Bird Registration Deadline: 12th March 2021 (Midnight BST/GMT+1)

Abstract submission deadline: 9th April 2021 (Midnight BST/GMT+1)

To learn more, submit an abstract and register for the congress, please visit the congress website: <https://www.wms2021.com>

FORTHCOMING MEETINGS

2021

January 13-15

IRDiRC Conference and RE(ACT) Congress. Virtual Edition. Information: website: <https://www.react-congress.org>

February 19-20

253th ENMC International Workshop on Skeletal Muscle Laminopathies. Virtual Meeting. Information: website: www.ENMC.org; email: enmc@enmc.org

February 28

Rare Disease Day. Information: website: <https://ern-euro-nmd.eu>

March 5-11

ICHG 2021 – International Conference of Human Genetics. Cape Town, South Africa. Information: website: www.ichg2021.com

March 22-24

ACSC | Genomics of Rare Diseases. Virtual Conference. Wellcome Genome Campus, Hinxton, UK. Information: website: <https://coursesandconferences.wellcomegenomecampus.org>

April 15-17

ESC Preventive Cardiology 2021. Virtual Edition. Information: website: <https://www.escardio.org/Congresses-&-Events>

May 15-18

Heart failure 2021. Virtual edition. Information: website: <https://www.escardio.org/Congresses-&-Events>

May 21-24

European MTM-CNM Family Conference, Bad Nauheim, Germany. Information: website: <https://ern-euro-nmd.eu/event/european-mtm-cnm-family-conference>

May 21-29

16th International Congress on Neuromuscular Diseases, Valencia, Spain. Information: website: www.icnmd.org

June 12-15

The European Human Genetics Conference. Glasgow, United Kingdom. Information: website: <https://eshg.org>

June 19-22

7th Congress of the European Academy of Neurology (EAN), Vienna, Austria. Information: website: www.ean.org

July 20-22

12th Annual Congress of Cardiology-2021 (ICC-2021), Lisbon, Portugal. Information: website: www.bitcongress.com

September 20-24

International Course and Conference on Neuromuscular Imaging 2021, Rotterdam, The Netherlands. Information: website: <https://iccnmi2021.com>

September 20-24

26th Congress of World Muscle Society. Virtual Meeting. Information: website: <https://www.wms2021.com>

October 3-7

XXV World Congress of Neurology (WCN 2021), Rome, Italy. Information: website: <https://wfneurology.org/world-congress-of-neurology-2021>

October 19-23

ASHG Annual Meeting. Montreal, Canada. Information: website: www.ashg.org

2022

February 13-17

International Conference on Human Genetics. Cape Town, South Africa. Information: website: www.ichg2022.com

April 28-May 2

14th European Paediatric Neurology Society Congress, Glasgow, UK. Information: website: www.epns.org

October 10-15

27th Congress of World Muscle Society. Halifax, Canada. Information: website: <https://worldmusclesociety.org>

INSTRUCTIONS FOR AUTHORS

Acta Myologica publishes articles related to research in and the practice of primary myopathies, cardiomyopathies and neuromyopathies, including observational studies, clinical trials, epidemiology, health services and outcomes studies, case report, and advances in applied (translational) and basic research.

Manuscripts are examined by the editorial staff and usually evaluated by expert reviewers assigned by the editors. Both clinical and basic articles will also be subject to statistical review, when appropriate. Provisional or final acceptance is based on originality, scientific content, and topical balance of the journal. Decisions are communicated by email, generally within eight weeks. All rebuttals must be submitted in writing to the editorial office.

Starting from 2020, a publication fee of 200 Euros is required. The Corresponding Author must fill in the appropriate form and send it with the corrected proofs. 50% off is offered for members of Associazione Italiana di Miologia (AIM) and/or Mediterranean Society of Myology (MSM) in good standing with dues. A copy of the payment receipt for the current year is mandatory to prove the membership).

On-line submission

Manuscript submission must be effected on line: www.actamyologica.it according to the following categories:

Original articles (maximum 5000 words, 8 figures or tables). A structured abstract of no more than 250 words should be included. **Reviews, Editorials** (maximum 4000 words for Reviews and 1600 words for Editorials). These are usually commissioned by the Editors. Before spontaneously writing an Editorial or Review, it is advisable to contact the Editor to make sure that an article on the same or similar topic is not already in preparation.

Case Reports, Scientific Letters (maximum 1500 words, 10 references, 3 figures or tables, maximum 5 authors). A summary of 150 words may be included.

Letters to the Editor (maximum 600 words, 5 references). Letters commenting upon papers published in the journal during the previous year or concerning news in the myologic, cardio-myologic or neuro-myologic field, will be welcome. All Authors must sign the letter.

Rapid Reports (maximum 400 words, 5 references, 2 figures or tables). A letter should be included explaining why the author considers the paper justifies rapid processing.

Lectura. Invited formal discourse as a method of instruction. The structure will be suggested by the Editor.

Congress Proceedings either in the form of Selected Abstracts or Proceedings will be taken into consideration.

Information concerning new books, congresses and symposia, will be published if conforming to the policy of the Journal.

The manuscripts should be arranged as follows: 1) Title, authors, address institution, address for correspondence; 2) Repeat title, abstract, key words; 3) Text; 4) References; 5) Legends; 6) Figures or tables. Pages should be numbered (title page as page 1).

Title page. The AA are invited to check it represents the content of the paper and is not misleading. A short running title is also suggested.

Key words. Supply up to six key words. Wherever possible, use terms from Index Medicus – Medical Subject Headings.

Text. Only international SI units and symbols must be used in the text. Tables and figures should be cited in numerical order as first mentioned in the text. Patients must be identified by numbers not initials.

Illustrations. Figures should be sent in .jpeg or .tiff format. Legends should be typed double-spaced and numbered with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, each should be explained clearly in the legend. For photomicrographs, the internal scale markers should be defined and the methods of staining should be given.

If the figure has been previously published a credit line should be included and permission in writing to reproduce should be supplied. Color photographs can be accepted for publication, the cost to be covered by the authors.

Patients in photographs are not to be recognisable

Tables. Tables should be self-explanatory, double spaced on separate sheets with the table number and title above the table and explanatory notes below. Arabic numbers should be used for tables and correspond with the order in which the table is first mentioned in the text.

References. Indicate all Authors, from 1 to 3. If their number is greater than 3, indicate only the first 3, followed by “et al.”. Arabic numbers in the text must be superscript. References in the list must be numbered as they appear in the text, with the reference number superscript. **DOI number must be included with each reference** (when available). If not available, indicate the PMID number.

Examples of the correct format for citation of references:

Journal articles: Shapiro AMJ, Lakey JRT, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000;343:230-238. doi.org/10.14639/0392-100X-1583

Books and other monographs: Dubowitz V. Muscle disorders in childhood. London: WB Saunders Company Ltd; 1978.

Please check each item of the following checklist before mailing:

- Three-six index terms, short title for running head (no more than 40 letter spaces) on the title page.
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- Figures submitted actual size for publication (i.e., 1 column wide or 2 columns wide).
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