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ORIGINAL ARTICLES

The role of rehabilitation in the management of late-onset Pompe disease: a narrative review of the level of evidence

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Late-onset Pompe disease (LOPD) is characterized by progressive muscle weakness, respiratory muscle dysfunction, and minor cardiac involvement. Although in LOPD, as in other neuromuscular diseases, controlled low impact sub-maximal aerobic exercise and functional ability exercise can improve general functioning and quality of life, as well as respiratory rehabilitation, the bulk of evidence on that is weak and guidelines are lacking. To date, there is no specific focus on rehabilitation issues in clinical recommendations for the care of patients with Pompe disease, and standard practice predominantly follows general recommendation guidelines for neuromuscular diseases. The Italian Association of Myology, the Italian Association of Pulmonologists, the Italian Society of Neurorehabilitation, and the Italian Society of Physical Medicine and Rehabilitation, have endorsed a project to formulate recommendations on practical, technical, and, whenever possible, disease-specific guidance on rehabilitation procedures in LOPD, with specific reference to the Italian scenario. In this first paper, we review available evidence on the role of rehabilitation in LOPD patients, particularly addressing the unmet needs in the management of motor and respiratory function for these patients.

Key words: endurance and resistance training, late-onset Pompe disease, motor function, rehabilitation, respiratory function

Introduction

Glycogen storage disease type II, also known as Pompe disease, is an autosomal-recessive lysosomal storage disorder caused by the deficiency of the lysosomal acid α-glucosidase, which results in the accumulation of glycogen deposits inside lysosomes within the muscular tissue. Pompe disease manifests clinically across a broad spectrum based on age of onset, progression rate, genetic mutation(s), and disease distribution, and is classified as early- (infantile, classic) or late-onset (non-classic) (1, 2).

Late-onset Pompe disease (LOPD) may present at any age after the second year of life and is characterized by progressive weakness in lower limbs and trunk, with only minor cardiac involvement (3, 4). Respiratory muscle impairment, the primary cause of morbidity and mortality in LOPD patients, is also common and involves both inspiratory and expiratory skeletal muscles (1). To this end, and ahead of the current available enzyme replacement therapy, rehabilitation might be proposed as an effective intervention in improving physical function-

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ing of these patients, however supporting evidence and guidelines to support this are lacking (5).

To date, there are no specific guidelines on rehabilitation issues in clinical recommendations for the care of patients with Pompe disease, and standard practice predominately follows more general recommendations or, where available, guidelines for neuromuscular disease (NMD) (1). This lack of treatment guidelines has led to variable and often limited standards of interventional protocols in clinical practice. Moreover, the low prevalence of Pompe disease has hindered the development of a national or international consensus on the appropriate management of musculoskeletal and respiratory impairment in affected patients (1).

The Italian Association of Myology (AIM), the Italian Association of Hospital Pulmonologists (AIPO), the Italian Society of Neurorehabilitation (SIRN), and the Italian Society of Physical Medicine and Rehabilitation (SIMFER), have endorsed a project to formulate recommendations on practical, technical, and, whenever possible, disease-specific guidance on rehabilitation procedures in LOPD, with specific reference to the Italian scenario. In this first, narrative paper, we review available evidence on the role of rehabilitation in the management of LOPD, and define the bases for standardized protocols for the assessment and rehabilitation of musculoskeletal and respiratory impairments in patients with LOPD.

Methods

A multidisciplinary collaboration of 10 clinicians, members of the AIM, AIPO, SIRN, and SIMFER, was established to review current evidence in the field of rehabilitation in Pompe disease. This open forum agreed that two working groups, one on musculoskeletal rehabilitation and a second on pulmonary rehabilitation, should be developed to evaluate available studies and try to standardize patients' assessment and exercise plan. To date, evidence as to whether rehabilitation is effective in LOPD seems poor and contradictory. Therefore, the authors proposed a literature review based on a search of the EMBASE, CINALH, PubMed, PsychINFO, and Scopus databases, using the following keywords: LOPD and guidelines, rehabilitation and LOPD, training and LOPD, physical activity and LOPD, exercise and LOPD. English language papers published between 2000 and 2017 were considered. Papers were selected for inclusion on the basis of their relevance to the topic, according to Authors' judgment.

The level of the evidence of selected studies was defined according to the Scottish Intercollegiate Guidelines Network (SIGN). In addition, the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) method was used to evaluate the quality of evidence with respect to each relevant outcome.

The results of the literature research and the outcomes of the SIGN and GRADE evaluation are summarized in Tables 1 and 2.

Rehabilitation of motor function in LOPD: state of the art

Enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase (Myozyme/Lumizyme) was approved in 2006 for the treatment of Pompe disease and positive effects of ERT on skeletal muscle strength,

Table 1. Level of evidence according to the Scottish Intercollegiate Guidelines Network (SIGN) for studies investigating the role of rehabilitation of motor and respiratory functions in patients with late-onset Pompe disease.

Studies (Author, date, reference)	Level of evidence
Borg 1970 (18)	4
Bach et al. 1996 (48)	2+
Bach 1999 (33)	4
Wasserman et al. 1999 (19)	4
Baydur et al. 2001 (49)	2+
Mellies et al. 2001 (50)	2+
Ragette et al. 2002 (51)	2+
Shneerson et al. 2002 (41)	3
Hill et al. 2004 (40)	4
Slonim et al. 2007 (12)	2-
Mellies et al. 2009 (38)	3
Van der Beek et al. 2009 (34)	2+
Vitacca et al. 2009 (39)	4
van den Berg et al. 2010 (27)	2+
van der Ploeg et al. 2010 (11)	1+
Vitacca et al. 2011 (35)	4
Angelini et al. 2012 (6)	2-
de Vries et al. 2012 (7)	2+
Favejee et al. 2012 (5)	3
van der Ploeg et al. 2012 (46)	1+
Ambrosino et al. 2013 (37)	3
Gungor et al. 2013 (8)	2+
Toscano et al. 2013 (10)	1-
Vianello et al. 2013 (47)	2+
Vitacca et al. 2013 (36)	3
Hundsberger et al. 2014 (45)	2-
Bertoldo et al. 2015 (28)	2-
Crescimanno et al. 2015 (20)	2-
Favejee et al. 2015 (17)	2+
Jevnikar et al. 2015 (43)	2-
Schoser et al. 2015 (31)	4
van den Berg et al. 2015 (13)	2+
Aslan et al. 2016 (42)	2-
Jones et al. 2016 (44)	2-
Schoser et al. 2017 (9)	1-

Table 2. Appropriateness of recommendations according to the GRADE method for outcomes addressed in clinical guidelines for the rehabilitation management of motor and respiratory impairments in patients with late-onset Pompe disease.

Clinical Guidelines (Author, date, reference)	Level of evidence for rehabilitation management	GRADE-like recommendations based on level of evidence
Kishnani et al. 2006 (3)	3	• Submaximal, functional, and aerobic exercise may improve muscle function • Gentle daily stretching, orthotic intervention, splinting, seating systems and standing supports may prevent or minimize contracture and deformity
Barba-Romero et al. 2012 (29)	3	• Aerobic exercise may improve motor function
Cupler et al. 2012 (26)	3	• Submaximal aerobic exercise, incorporating functional activities may increase muscle strength • Daily stretching, orthotic devices, appropriate seating position in the wheelchair, and standing supports may prevent or slow the development of muscle contractures and deformities
Boentert et al. 2016 (1)	3	• Chest physiotherapy and MAC may be sufficient only for patients with mild expiratory muscle weakness • MAC techniques should be implemented by trained physiotherapists or respiratory therapists • Air stacking combined with MAC is recommended if cough assistance is indicated and upper airways are patent in cooperative patients • I/E devices are indicated if MAC/air stacking are not feasible or ineffective • HFCWO is indicated if MAC/air stacking are either not feasible or ineffective and I/E cannot be tolerated
Llerena Junior et al. 2016 (30)	2-	• Aerobic and progressive resistance exercise training, incorporated into daily functional activities, with or without ERT, may improve muscle strength and functioning • Orthotic devices and posture correction while the patient is in the wheelchair and support for when the patient stands may prevent joint contractures
Tarnopolsky et al. 2016 (32)	2+	• Tailored endurance exercise and progressive resistance training, with or without ERT, may improve aerobic capacity and normalize muscle strength, motor function, and lean mass

Abbreviations: ERT, enzyme replacement therapy; GRADE, Grades of Recommendation, Assessment, Development and Evaluation Working Group; HFCWO, high frequency chest wall oscillation; I/E, Insufflation/Exsufflation; MAC, manually-assisted cough.

walking distance, respiratory function and survival have been demonstrated in adult patients with LOPD (6-11). Importantly, additional treatments, such as physiotherapy or exercise training, may also benefit patients' fitness and physical functioning, however, evidence of such beneficial outcomes is limited (12, 13). Indeed, the need for guidance and standardization in the use of physiotherapy in clinical practice was highlighted in a Dutch survey of 88 patients with Pompe disease and 31 physiotherapists, which demonstrated a lack of uniformity in the type of physical therapy training programs applied (5). It has also been debated as to whether exercise is beneficial or harmful for patients with myopathic disorders (14-16). To date, only a few studies have investigated the benefits of exercise training in adult patients with Pompe disease. An uncontrolled, prospective study demonstrated that adherence to a high-protein/low-carbohydrate diet and exercise therapy slowed the progressive deterioration of muscle function in LOPD patients (12), and a combination of aerobic, resistance and core stability exercises were shown to be feasible and safe (13) and to improve pain, fatigue and functioning (17) in 23 adult patients with Pompe disease who were receiving ERT and were not dependent on ventilators and/or walking devices.

Adherence to a combination of nutrition and exercise therapy (mean 4.5 ± 2.5 years, range 2-10 years) in 34

patients (aged 25-66 years), ambulatory except for one patient, slowed deterioration of muscle function and improved the natural course of LOPD (12). Progressive worsening of muscle function was significantly slower in 26 patients who were compliant with the treatment regimen whereas progressive impairment of muscle function was reported in 8 noncompliant patients (mean difference between pre- and post-therapy Walton score was -0.29 [95% Confidence Interval (CI) -0.36, -0.19; $p < 0.001$] for compliant patients, and -0.01 [95% CI -0.36, 0.34; $p = 0.95$] for noncompliant patients) (12).

Endurance, core stability and muscle function improved following a 12-week exercise program, which included 36 sessions of standardized aerobic, resistance, and core stability exercises, in 23 adult patients (aged > 17 years) with Pompe disease not dependent on ventilators and/or walking devices and receiving ERT for at least 52 weeks (13). Significant increases in aerobic exercise capacity and distance walked on the 6 minute walking test (6MWT) were demonstrated after training compared with before training (maximum workload capacity 122 *vs* 110 Watt; peak oxygen uptake 75.9% *vs* 69.4% of normal; 6MWT 508 *vs* 492 meters, respectively; all $p < 0.01$). Core stability, and muscle function and strength all improved after 12-weeks' training, with no safety issues reported. Despite being statistically significant, only modest increases were demonstrated in the 6MWT and peak workload capacity, however exercise training appears to be an effective and safe adjuvant therapy for patients with Pompe disease offering added value to treatment with ERT alone (13).

Significant reduction in fatigue ($p = 0.001$) and pain ($p = 0.04$) were also demonstrated after 12-weeks of exercise training in the same cohort, but the motor function and amount of physical activity did not change significantly after training (17). However, these clinical improvements were not correlated with changes in aerobic fitness, muscle strength or core stability.

Proposed protocols for the assessment of musculoskeletal impairments and rehabilitation – The choice of the outcome measure

Evidence supporting the role of musculoskeletal rehabilitation in patients with LOPD remains scant, mainly because it is based on small studies with short follow-up, conducted in a home-based setting. It is therefore difficult to define a standardized protocol for the assessment of motor function for application in the Italian scenario. One of the main related issues, that has to be considered, is the choice of the best clinic-instrumental parameters that are selected as trusted indices to be used to evaluate the efficacy of the motor rehabilitative intervention. However, according to the study conducted in 2015 by Van der Berg and colleagues (13), assessment of motor function should include the following outcome measurements:

Endurance: Aerobic exercise capacity was assessed using an incremental cycle ergometer with progressive increase in exercise intensity until exhaustion (the stepwise load increment was based on the patient's functional capacities within a range of 5-20 Watts/minute), and continuous measurement of patients' heart rates and ventilator parameters using spiroergometry. At exhaustion, the Borg scale (18) evaluated exertional symptoms (scale of 6-20). Measurements of maximum workload capacity and peak oxygen uptake capacity were undertaken, and the ventilatory threshold was assessed using the ventilatory equivalents method (19). Walking distance on the 6MWT was evaluated according to the American Thoracic Society guidelines (20).

Muscle strength: Although muscle force is considered a muscle function parameter with limited relevance in the evaluation of motor performance in myopathic patients, there is no doubt that it can represent a useful index for the construction of motor rehabilitative planning. Maximal voluntary contraction, i.e. maximal isometric segmental muscle strength, the most accepted measurement in exercise laboratories, was measured using a hand-held dynamometry and considered as an index of residual muscle function.

Muscle Function: Muscle function assessment comprised three timed tests (10 meter running, climbing four steps, and rising from supine to standing position), plus the Quick Motor Function Test (QMFT) (21). The QMFT was designed specifically for and validated in patients with Pompe disease, and consists of 16 specific motor skills related to daily activities scored on a 5-point scale (0 "cannot perform" to 4 "can perform with no effort"); a total score, expressed as a percentage of the maximum score, is obtained by adding the scores of all items.

The Rasch-built Pompe-specific Activity (R-PAct) scale was validated to specifically quantify the effects of Pompe disease on patient's ability in activities of daily life and social participation (22). This 18-item scale demonstrated good discriminative ability and external construct validity. Furthermore this assessment tool was recently used in a 5-year prospective study, which aimed to evaluate the long-term benefit of ERT in 102 adult patients with Pompe disease (23).

In addition, an assessment of how musculoskeletal impairments and rehabilitation affect quality of life (QoL) should be undertaken. The Individualized Neuromuscular Quality of Life (INQoL) questionnaire (24), which consists of 45 questions within 10 sections, was designed specifically for NMD and validated for the Italian population (25).

The above assessment methods are in line with guidelines on the diagnosis and management of patients with Pompe disease issued in 2006 by the American College of Medical Genetics (ACMG) (3). Musculoskeletal functional rehabilitation recommendations from the ACMG include: monitoring of cardiorespiratory status; screening for osteopenia/osteoporosis; assessment of musculoskeletal impairments, functional deficits, levels of disability and social participation; enhancement of muscle function; prevention of secondary musculoskeletal impairments; functioning optimization with adaptation and assistive technology; patient and family education about the natural course of Pompe disease and recommendations for intervention (3). With regards to the enhancement of muscle function, the ACMG recommended that guidelines from other progressive muscle diseases were to be followed, including: sub-maximal, functional and aerobic exercise; avoidance of excessive resistive and eccentric exercise; avoidance of overwork weakness; and avoidance of disuse atrophy (3).

The proposal for an International Classification of Functioning, Disability and Health (ICF)-based approach (3), although dated now back to 2006, offers an internationally agreed standard for describing and monitoring functioning, has been endorsed by the World Health Organization, and offers a framework for the identification of the categories of functional damage, structural damage, and limitation of activities of daily living (ADL) and of social participation. In Italy, according to the 2013 national health plan, the ICF has become mandatory to allow access to both physiotherapy and aids. It is therefore important to publish data based on an ICF checklist of items, which recognizes issues specifically related to people affected by LOPD.

The choice of the protocol

In 2012, the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) convened a consensus committee to create consensus-based treatment and management recommendations for the treatment of LOPD (26). Participants clarified that overall management of musculoskeletal issues in LOPD patients should preserve motor function, prevent secondary complications, maximize benefits of ERT, promote overall health, and improve QoL. Importantly, the AANEM recognized that there were no established guidelines for muscle strengthening or therapeutic exercise for patients with LOPD (26). Although a small number of studies have shown that sub-maximal aerobic exercise may increase muscle function and strength, further studies with larger sample sizes are needed. Moreover, the AANEM recommended the implementation of general precautions regarding strengthening exercises, that are followed for other degenerative muscle diseases, also be applied to LOPD (26). Furthermore, due to the risk of cardiopulmonary compromise in LOPD, it was recommended that LOPD patients were evaluated by a pulmonologist prior to starting an exercise regimen (26).

The frequency and intensity of treatments, from a functional and rehabilitative point of view, was also addressed by the AANEM. It was recommended that therapeutic exercise should start slowly with incremental increases from mild to moderate intensity in order to achieve aerobic levels approximately 60-70% of maximal effort; rest periods should be allowed for and the patients should aim for a frequency of 3-5 treatment days per week (26). A stretching regimen, performed as part of the daily routine, should be implemented.

Patients with Pompe disease may be affected by low bone mineral density (BMD), putting them at risk of fragility fractures. Indeed, 31 out of 46 patients (67%) had BMD Z-score < -1 SD, with the decrease in bone density present in both the infantile and late-onset forms of Pompe disease (27). Moreover, low BMD was correlated with decreased proximal muscle strength. A recent study also identified an increased risk of asymptomatic and atraumatic vertebral fractures in patients with LOPD walking without assistance and not ventilated, who did not have a significant impairment of bone mass (28). The AANEM recommended that patients with LOPD undergo annual screening with dual-energy X-ray absorptiometry (DXA) and fall risk assessment (26).

In 2012, clinical guidelines for LOPD published by the Spanish Society of Internal Medicine, Spanish Society of Neurology, and the Spanish Society of Pneumology and Thoracic Surgery, concluded that nutritional intervention and aerobic exercise can improve motor function in patients with LOPD, albeit with a low level of evidence (29).

More recently, the 2016 Brazilian guidelines for the diagnosis, treatment and clinical monitoring of patients with juvenile and adult Pompe disease were based on the ICF criteria (30). Recommendations for the management of the musculoskeletal impairments in Pompe disease, included: enrolling the patient in the International Pompe Registry; physical examination; physical/occupational therapy; management of contractures; vitamins and minerals supplementation (30).

Other groups have addressed the issue of motor rehabilitation in LOPD. The 208th European Neuromuscular Centre international workshop agreed on a minimal dataset of outcome measures for adult patients with Pompe disease (31). These included; muscle strength (manual muscle testing using the Medical Research Council grading scale, hand-held dynamometry, quantitative muscle testing), muscle function (6MWT, four timed tests including walking 10 meters, climbing four steps, stand-

ing up from the supine position, and standing up from a chair), pulmonary function (forced vital capacity [FVC] standing and sitting, maximal inspiratory pressure [MIP], maximal expiratory pressure [MEP], ventilation status), patient reported outcomes (Rasch-built Pompe-specific activity scale, fatigue severity scale), and other information (treatment and survival status) (31). It was envisaged that the minimal dataset will allow for data sharing purposes in order to address specific research questions.

Evidence-based guidelines on the diagnosis and management of Pompe disease from a Canadian expert panel identified seven management guidelines and made six recommendations (based on best clinical practices but with insufficient data to draw guidelines) (32). Recommendations related to the assessment of musculoskeletal impairments and rehabilitation included the following two statements: "Patients with LOPD should be encouraged to perform both resistance and cardiovascular exercise to improve general conditioning and quality of life. Interventions should be tailored to individual abilities" and, "Periodic quality of life assessments and/or motor function tests, which can include questionnaires, should be part of the routine management of patients with LOPD" (32).

Rehabilitation of respiratory function in LOPD: state of the art

In LOPD, morbidity and mortality due to progressive respiratory muscle weakness are a major concern and management of respiratory function should include a multidisciplinary approach of neurologists, pulmonologists, and intensive care specialists (1). Clinical presentation of respiratory muscle function impairments in LOPD patients includes restrictive ventilation (hypo-expanding thorax), ineffective cough, alteration of blood gases (from hypoventilation), impaired respiratory muscle strength, alteration of the respiratory pattern (relationship between respiratory rate and current volume), alteration of sleep pattern, and dyspnea in ADL.

The choice of the outcome measure

International guidelines for the management of respiratory function in LOPD patients are well-grounded and defined, and indicate, among other recommendations, essential respiratory function tests to be performed from the onset of the disease to advanced phases (1), including: pulmonary function tests, peak cough flow (PCF), strength of the respiratory muscles, competence of the glottis in the cough, measurement of oxygen saturation (SaO_2) at night, blood gas analysis, and transcutaneous monitoring of paO_2 and $paCO_2$ (Table 3).

These evaluations must be performed initially and repeated over time. Other aspects to be investigated concern stress tolerance, including: incremental tests (with evaluation of desaturation and level of dyspnea); endurance tests (on a treadmill, with evaluation of desaturation and level of dyspnea); study of sleep quality (through standardized scales); 6MWT (with evaluation of desaturation and level of dyspnea); and, evaluation of ADL (from the point of view of both motor and respiratory function).

The pulsed arterial saturation and day time are important to diagnose the development of respiratory failure and to define the timing of the initiation of mechanical ventilation (33). Furthermore, the measurement of oxyhemoglobin saturation is a useful and non-invasive element for monitoring the presence of catarrhal space over time (1).

It is crucial that respiratory function is measured over time since the evolution of respiratory symptoms is highly variable, as demonstrated by a study of 16 untreated patients with LOPD in which only one third of patients presented a rapid respiratory decline over a mean follow-up of 16 years (34). Depending on the rate of disease progression, the authors recommended regular monitoring of LOPD patients every 6-12 months. Consequently, the need to repeat tests of respiratory function over time is extremely variable between patients, which contribute to the heterogeneity of existing approaches in the management of Pompe disease, as confirmed by the results of two surveys recently conducted in Italy (35, 36).

The choice of the protocol

Patients should undergo regular evaluation by a pulmonologist who should initiate respiratory aids as needed so that potentially catastrophic situations during acute chest colds can be avoided (37, 38). Indeed, early diagnosis, aggressive treatment and close follow-up after an acute event are imperative to avoid further deterioration towards acute respiratory failure and hospitalization (1).

Dedicated approaches to pulmonologists' intervention in the management of LOPD have been published by Italian researchers (37). The cornerstones of the respiratory rehabilitative intervention are represented by the treatment of nocturnal hypoventilation and the management of secretions (39). Bronchial disruption must be suggested for preventive purposes and becomes imperative in cases where there is a catarrhal obstruction, which can be detected by auscultation and by clinical signs and symptoms. The main objectives of this therapy are to promote airway clearance, the prevention and treatment of respiratory atelectasis and infections, and the maintenance of a normal ventilation/perfusion ratio. These peripheral disruption interventions act with the purpose of

Table 3. Essential respiratory function tests for the management of respiratory function in patients with late-onset Pompe disease.

Respiratory function test	Description
Pulmonary function tests	Slow vital capacity and FVC both in a sitting and supine position where a restrictive ventilator pattern is usually diagnosed [vital capacity values < 50% predicted (49)] or inspiratory vital capacity values [< 60% predictive of sleep-disordered breathing and < 40% predictive of sleep-related hypoventilation (50, 51)] (1)
Peak cough flow	Measurement of air flow generated during the cough evaluates the effectiveness of the mechanism of cough [a value < 160 L/min reflects inadequate airway clearance (48)]
Strength of the respiratory muscles	MIP, MEP, and sniff nasal inspiratory pressure are indicators of diaphragm weakness and are therefore indications for NIV or poor ability to generate cough (1)
Competence of the glottis in the cough	Calculated using the passive maximum intake inspiratory capacity, which is the maximum capacity of the lung to be passively inflated through air boluses delivered by a fan or an Ambu flask (1)
Measurement of SaO_2 at night	Measurement of SaO_2 at night using cardiorespiratory monitoring or polysomnography. Sleep studies are useful to monitor nocturnal hypoventilation (and therefore the need for NIV) by measurement of nocturnal oximetry, use of a CO_2 transdermal tension meter as well as a complete sleep study using polysomnography (1)
Blood gas analysis	Measurement of oxygen and carbon dioxide levels in an arterial blood sample to monitor the adequacy of oxygenation and ventilation. This is the 'gold standard' for the assessment of hypoventilation
Transcutaneous monitoring of paO_2 and $paCO_2$	Provides information on both the CO_2 status and O_2 delivery to the tissues

Abbreviations: FVC, forced vital capacity; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; NIV, non-invasive ventilation; paCO2, partial pressure of carbon dioxide; paO2, partial pressure of oxygen; SaO2, oxygen saturation.

increasing the air flow at the peripheral level and with it promote the recovery of secretions in the upper airways ("Flutter" PEP Mask, autogenous drainage, ELTGOL [total slow expiration, performed at glottis open and in lateral decubitus]).

Cough assistance becomes necessary when PCF values below 270 L/min are reached, and techniques used include manually assisted coughing, air stacking, insufflation/exsufflation, and high frequency chest wall oscillation (1). Selective assistance to the inspiratory phase can be obtained by means of hyperinsufflation (air stacking with fan or an Ambu flask), selective expiratory assistance by manual compression of the rib cage and abdomen (abdominal thrust), and global cough assistance with air-stacking plus abdominal thrust or a specific instrument called an in-exsufflator, which acts by delivering, in rapid succession, a positive pressure of insufflation and a negative expiratory pressure.

Mechanical ventilation is achieved using either non-invasive ventilation (NIV) or invasive ventilation. The indications of the guidelines for NIV are less conservative than in the past, with the intent of recruiting patients earlier to encourage gradual adaptation to these procedures (1). Patients who develop hypercapnic acute respiratory failure should be referred to a specialized center for assessment of long term mechanical ventilation. NIV increases survival, prevents nocturnal hypoventilation, improves nighttime saturation, sleep-related respiratory disorders, and gas exchange, improves QoL, avoids or postpones tracheotomy, and relieves symptoms (40, 41).

Home mechanical ventilation is to be considered when the patient has daytime hypercapnia ($paCO_2 > 45$ mmHg) or orthopnea or symptoms of nocturnal hypoventilation (morning headache, daytime hypersomnolence, disturbed sleep with frequent awakenings) in association with at least one of the following symptoms: vital capacity < 50% of theoretical, MIP/MEP < 60% of theoretical, nocturnal oxygen desaturation (SaO_2 < 88% for more than 5 consecutive minutes), and close exacerbations (1).

Published evidence supports the effectiveness of respiratory muscle training in increasing MIP (42, 43) and improving the strength of both inspiratory and expiratory muscles (the latter being important for the cough function) (44). Inspiratory muscle training for 8-weeks was shown to have a significant ($p = 0.01$ *vs* baseline) positive effect on MIP in 8 patients with LOPD who were receiving ERT (42). This finding was confirmed in 8 patients with LOPD treated with ERT who completed 24 months of respiratory muscle training and showed significant increases in MIP over a period of 24 months ($p < 0.05$ at 3, 6, 9, 12, and 24 months *vs* baseline) (43). Evaluation of MEP over the 24-month treatment period also demonstrated significant increases in MEP from baseline at 3, 6, and 9 months

Table 4. Outcome measures for respiratory function assessment in patients with late-onset Pompe disease based on disease stage. Reproduced with permission from Ambrosino et al. (37).

Disease stage	Outcome measures
Stage 1	• Improvement/stabilization of vital capacity (% expected) and respiratory muscle strength tests (MIP/MEP)
Stage 2	• Improvement/stabilization of vital capacity (% predicted) and respiratory muscle strength tests (MIP/MEP) • Reduction of stress dyspnea • Increased CPEF (manual/mechanical assistance) • Reduction in number, frequency and duration of pulmonary infections (bronchopneumonia episodes or atelectasis proved with radiologic examination) • Reduction of exacerbations that require antibiotics • Sleep quality improvement • Life quality improvement
Stage 3	• Reduction in number, frequency and duration of pulmonary infections and bronchoaspirations • Reduced ventilation hours (< 8/day) • Change of the type of ventilation assistance (from controlled to assisted) • Tracheostomy removal • Improved ability in common daily activities after MV • Sleep quality improvement • Life quality improvement

Abbreviations: CPEF, cough peak expiratory flow; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MV, mechanical ventilation.

(all $p < 0.05$) but not at 12 and 24 months; FVC remained stable throughout the study period (43). In addition, Jones et al. showed improved inspiratory and expiratory muscle strength in 8 adults with LOPD receiving ERT following a 12-week respiratory muscle training program, with positive changes largely persistent after 3-months detraining (44). The authors concluded that respiratory muscle training offers a potential adjunctive treatment for respiratory weakness in patients with LOPD.

However, a survey on attitudes and practices in Italy for the management of NMD found that rehabilitative approaches used in clinical practice include mainly mechanical ventilation (96.5%) and bronchial disruption (84.2%), while respiratory muscle training was used in only 36.6% of cases (36).

Ambrosino and colleagues divided the possible outcome measures for patients with LOPD into three groups based on the level of progression and disease severity (Table 4) (37). This is a clinical-functional classification, and it would be of interest to link with the ICF criteria. Studies on the use of ERT in LOPD use FVC, MEP and MIP as the main outcome measures (6, 7, 10, 11, 45, 46), however these endpoints are characterized by high variability, which reduces the reliability of such spirometric data. An alternative endpoint can be represented by the number of hours of mechanical ventilation required (47).

Lastly, considerations on the palliative setting should be performed, which are in line with position papers referring to the Italian setting (35, 39). For end-stage LOPD patients, the wishes of the patient should be respected, decisions must be based on a shared process, and medical treatment must be proportionate; if the patient chooses to not use mechanical ventilation, they must receive adequate palliative care.

Unmet needs in the rehabilitation of LOPD patients and future perspectives

On the bases of the criticisms discussed in the first paper produced by this multidisciplinary group, a number of unmet needs have been identified in the rehabilitation of motor and respiratory function of LOPD patients (Table 5).

The next step of the working group will be to investigate which functioning categories, according to the ICF, are most impaired in patients with LOPD, and to propose a practical approach to address specific management strategies, including physical activity, therapeutic exercise programs for global and specific motor function impairments, patients' education for healthy lifestyle, enhancement strategies to improve social participation, and QoL.

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Table 5. Unmet needs in the rehabilitation of motor and respiratory function of LOPD patients.

Unmet needs
Lack of definitions for adapted physical activity
Clinical and functional heterogeneity of LOPD patients
Poor identification of patients to whom protocols can be applied
Lack of guidelines based on well-grounded evidence
Poor identification of impairment and disability, also according to ICF classification
Lack of consensus on outcomes for clinical studies
Lack of different protocols for different clusters of patients
Modification of rehabilitation procedures on the basis of ERT
Evaluation of the influence of nutrition/supplementation on rehabilitation outcomes
Evaluation of the influence of the severity of pulmonary function impairment on rehabilitation programs for motor impairments
Lack of evidence on the safety of the specific rehabilitation procedures during the course of LOPD
Lack of definition of the rehabilitation approach according to current regulations – for instance, in Italy and in many European countries, ICF classification is required

Abbreviations: ERT, enzyme replacement therapy; ICF, International Classification of Functioning, Disability and Health; LOPD, late-onset Pompe disease.

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