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Founders: Giovanni Nigro and Lucia Ines Comi

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EDITORIAL

Unmet needs on the management of COVID-19 vaccination in patients with neuromuscular disorders

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COVID-19 outbreak has quickly reached alarming morbidity and mortality with vaccines being the only weapon to fight. Although the critical situation, no international guidelines on the vaccination management of patients with neuromuscular disorders (NMDs) has still been issued. We aimed to address some unmet needs about the management of COVID-19 vaccination in patients with NMDs.

Key words: neuromuscular disorders, COVID-19 vaccines, fever

Neuromuscular disorders (NMDs) are a heterogeneous group of genetic conditions characterized by progressive muscle degeneration and weakness. Cardiac and respiratory impairments are a common finding, which severely impact the clinical course of the disease.

There is no current evidence that patients with NMDs have a higher risk of SARS-CoV-2 infection. However, a Forced Vital Capacity (FVC) < 60%, use of invasive/non-invasive ventilation devices, presence of oropharyngeal weakness resulting in inefficient airway clearance, or systemic comorbidities, such as cardiac dysfunction, arrhythmias, diabetes and obesity, treatment with steroids or immunosuppressant drugs, are considered increasing risk factors of severe COVID-19 [1-3].

Also, fever, one of the most frequent signs of COVID-19 infections, could lead to a worse outcome in some NMDs, such as mitochondrial diseases, metabolic myopathies and myasthenia gravis, due to the risk of muscle deterioration or rhabdomyolysis [4,5]; moreover, it might induce adrenal crisis in patients on steroid treatment with a not adjusted dosage[6]. For these reasons, rapid diagnosis, isolation, and intensive clinical management are crucial for patients with NMDs who develop COVID-19.

The European Medicines Agency (EMA) approved two different types of COVID-19 vaccines: mRNA (Comirnaty - BioNTech/Pfizer and COVID-19 Vaccine Moderna) and adenoviral vectored (COVID-19 Vaccine Janssen, Vaxzevria - AstraZeneca). All of them may have several side effects, in particular fever, which accounts up to 28% and 45% after Comirnaty - BioNTech/Pfizer 1st and 2nd dose respectively; 26.7% of patients aged 18-59 and 10% of those aged > 60 years for Janssen. No data are available for Moderna and Vaxzevria - AstraZeneca) [7-10].

Patients with NMDs were not included in the vaccine trials; therefore, efficacy and safety in this population is currently unknown. NMDs are not a contraindication to vaccination for COVID-19 and, on the contrary,

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COVID-19 can take a more aggressive clinical course in some patients in relation, for example, to their degree of disability. Furthermore, there is no reason to believe the vaccine will be less efficacious or safety in patients with NMDs than in the population included in COVID-19 vaccination clinical trials. Some NMDs, such as multiple sclerosis, are autoimmune disorders in which patients are not immunosuppressed, and therefore their efficiency in responding to vaccinations is well known [11]. However, drugs with immunosuppressive action can reduce antibody efficacy even though the cell-mediated response can instead be efficient and therefore guarantee the patient a certain degree of safety both for infectious risk, and for the worse evolution of the disease. At the time, there are no known serious warnings or precautions associated with the vaccines in patients with NMDs.

Italian patients with NMDs have been included by the Health Minister, into the frail category for the COVID-19 vaccination program. The inclusion in this category was also confirmed in the ordinance n. 6/2021 dated 9 April 2021 by the extraordinary Commissioner for the COVID-19 Emergency.

In our view patients with NMDs should preferentially be managed at hospital vaccination centers, so that tailored case management could be guaranteed by the neuromuscular care team, allowing for greater safety and avoiding delays in vaccination.

For patients with mitochondrial diseases, metabolic myopathies or myasthenia gravis, a prophylaxis with paracetamol 1000 mg every 6 hours, or other antipyretics, with dosage adjustment according to age, weight, kidney and liver function, within the first 24-48 hours, has been suggested in order to reduce the risk of fever [5].

For patients with NMDs and severe cardio-respiratory involvement, immunodeficiency or on immunosuppressant agents, hospitalization should be considered following the COVID-19 vaccination, as no current data regarding the efficacy and safety of COVID-19 vaccines in this subgroup of patients are available. However, a case-by-case assessment is recommended considering the age of the patients and how they previously responded to vaccination (Fig. 1).

In a recent observational study that included 658 patients receiving immunosuppressive drugs after solid organ transplantation, 46% developed no antibody response after two doses of SARS-CoV-2 mRNA vaccine [12]. Moreover, among vaccinated patients who showed no SARS-CoV-2 antibody titers after two doses of vaccine, 56% remained antibody-free 4 weeks after the third dose [13].

Anti-COVID-19 vaccination and side-effects

There is no reason to think that the side effects of the vaccine in patients with NMDs could be higher than those expected in the general population, which vary from vaccine to vaccine, and this applies to both common and rarer ones [14]. However, a transient aggravation of pre-existing symptoms during COVID-19, has been reported in patients with NMDs [15] associated with the onset of fever.

The efficacy and long-term persistence of vaccines might be lower than in normal subjects in patients with

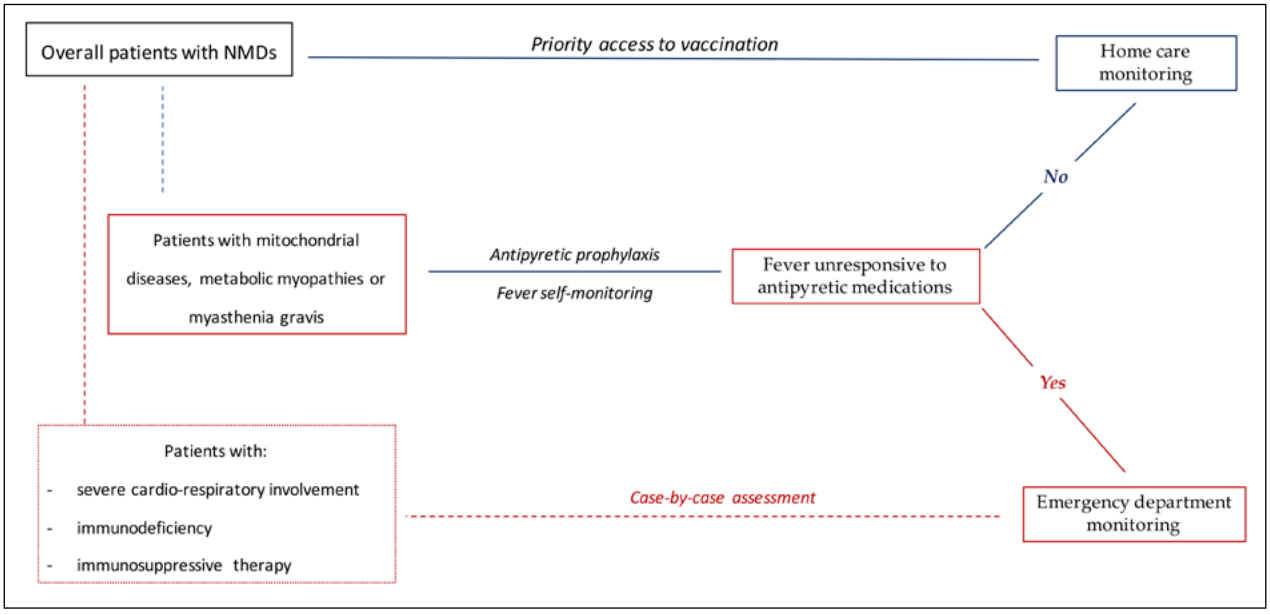

Figure 1. The workflow of the COVID-19 vaccination in patients with NMDs.

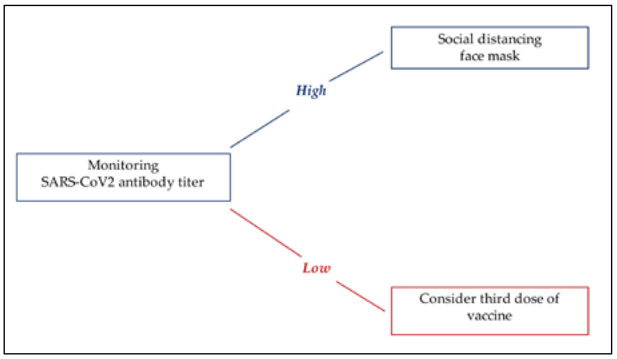

Figure 2. Vaccination monitoring in patients with NMDs and impaired immune system.

NMDs and impaired immune system [15] (Fig. 2). Therefore, we suggest monitoring the SARS-CoV-2 antibody titer to quantify the immune response and to evaluate, in selected cases, the administration of the third dose of vaccine. We also recommend the vaccination of the caregivers and of the other family members in contact with the patients.

In conclusion, we can deduce that the COVID-19 vaccination in subjects with NMDs is safe, does not generate relapses or exacerbations, as on the contrary SARS-CoV-2 infection could do. We believe that achievement of herd immunity may protect this special population as well.

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ORIGINAL ARTICLES

Reproducibility of manual segmentation in muscle imaging

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**These authors have contributed equally to the study*

Purpose. To assess the reproducibility of a manual muscle MRI segmentation method that follows a specific set of recommendations developed in our center.

Materials and methods. Nine healthy volunteers underwent a muscle MRI examination that included a TSE T2 sequence of the thighs. Muscle segmentation was performed by three operators: an expert operator (OP1) with 3 years of experience and two radiology residents (OP2 and 3) who were both given basic segmentation instructions, whereas only OP2 underwent additional supervised training from OP1. Intra- and inter-operator Dice similarity coefficient (DSC) was calculated.

Results. OP1 showed the highest average intra-operator DSC values (0.885), whereas OP2 had higher average DSC (0.856) compared to OP3 (0.818). The highest inter-operator agreement was observed between Operators 1 and 2 (0.814) and the lowest between OP2 and OP3 (0.702). Confidence interval (CI) analysis showed that the most experienced operator also had the least variability in drawing the ROIs, whereas OP2 showed both higher intra-operator reproducibility compared to OP3 and higher inter-operator agreement with OP1. The muscles that showed the least reproducibility were the *semimembranosus* and the short head of the *biceps femoris*.

Discussion. Following specific recommendations such as these ones derived from our single-center experience leads to an overall high reproducibility of manual muscle segmentation and is helpful in improving both intra-operator and inter-operator reproducibility in less experienced operators.

Key words: muscle MRI, segmentation, reproducibility, neuromuscular diseases, qMRI

Introduction

Quantitative magnetic resonance imaging (qMRI) methods are being increasingly used in the field of neuromuscular diseases to assess quantitative features of the muscle such as fat fraction, T1 and T2 relaxation. Additional parameters can also be derived from advanced MRI techniques [1-3], the majority of which are progressively recognized and used as biomarkers for clinical trials [4]. An accurate and reproducible segmentation of mus-

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cles, achieved through the drawing of regions of interest (ROI), is a necessary condition for the technological advancement of qMRI methods, and would allow a wider diffusivity and a broader application of its techniques.

Muscle segmentation has thus far been mostly an operator-dependent, manual operation; however, the process of drawing the ROIs is time consuming, usually needs a dedicated operator, and training times for operators can be quite long before a good performance is achieved [5].

Even though automatic and semi-automatic processes are being developed with promising results through the application of neural networks and machine learning techniques [6,7], the process still needs to be supervised. Furthermore, the availability of an extensive dataset of muscle ROIs realized by expert hand drawing represents a fundamental step in training neural networks, hence the importance of an adequate ROI drawing process.

Few studies described the details of the technique of ROI drawing, and those same studies often apply differing approaches. The differences between the techniques concerned not only the portion of the muscle being segmented – ranging from partial muscle delimitation in the form of circular [8,9] or square-shaped ROIs [10,11] to the complete delimitation of the segmented muscles – but also the number of segmented slices [1,2,12], the level at which the segmentation was performed [4,13] and the MRI sequence used for segmentation [14], although some studies underline the importance of maintaining adequate distance from the muscle fascia [4]. A consensus on the optimal criteria for drawing ROIs over the examined muscles, especially in the case of complete muscle delimitation, is still lacking. In particular, no specific indication exists regarding how the ROI border should be drawn within the muscle area (i.e., the exact distance from the muscle fascia, the inclusion of fatty infiltration or vascular structures), a detail that is particularly important, especially when considering the aforementioned aim of training neural networks.

In this study, we aimed to assess the reproducibility of a manual muscle segmentation method in a small cohort of healthy volunteers using a specific set of recommendations suggested by our single-center experience. The muscle segmentation was centered at the thigh level, as this region is the most commonly examined area in the field of neuromuscular diseases [5,15-17].

Materials and methods

We enrolled 9 healthy volunteers that gave their formal informed consent for the participation in the study, which was approved by the local ethics committee. None of these subjects had significant muscle pathologies, and neurological examination of the muscle function was normal. All subjects underwent a muscle MRI protocol with a 3 Tesla scanner (Skyra Siemens, Erlangen Germany) including a TSE T2 multi-echo sequence with EPG fitting (17 echo times), developed for T2 mapping. Sequences were centered on the thigh muscles. The 32-channels spine coil and a 18-channels phased-array coil positioned upon the thighs were used. The first echo image (TE = 10.9 ms) was arbitrarily used for segmentation.

The drawing of ROIs was performed on the axial slice that was approximately equidistant from the uppermost part of the femoral heads and the lowermost part of

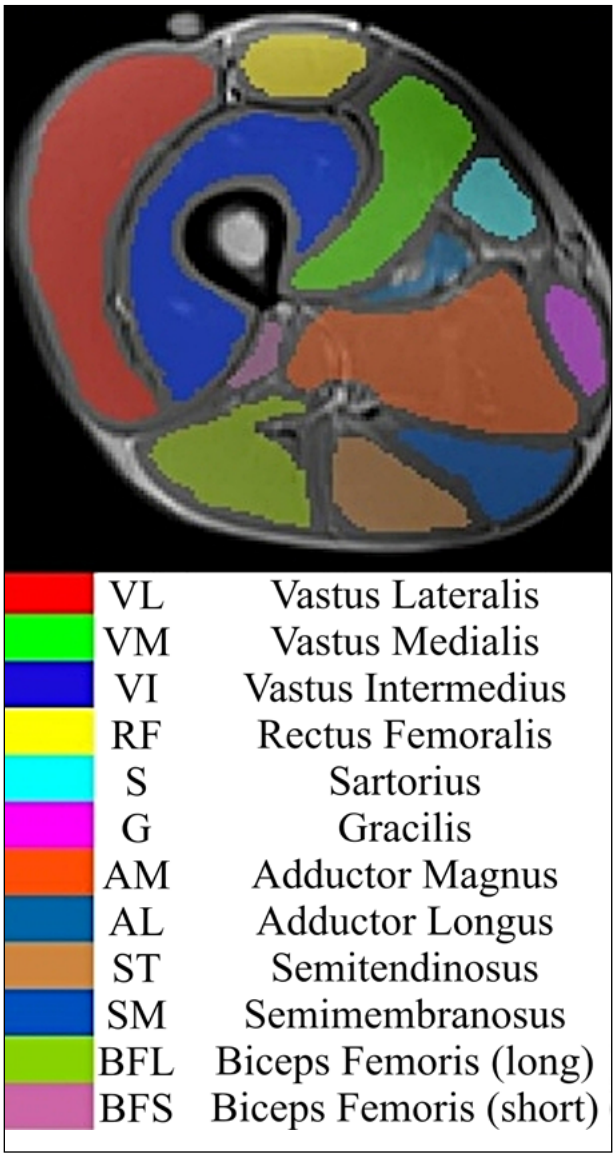

Figure 1. Example of ROIs obtained during manual thigh muscle segmentation superimposed on a TSE T2 weighted image. The color code indicates all 12 ROIs that were considered, which were drawn on both the left and right thigh, with the corresponding muscle indicated in the figure.

the femoral condyles, in order to capture a level where the muscle bellies have a wider spatial representation. Twelve ROIs, one for each muscle of both left and right thigh (Fig. 1), were manually drawn using the ITK-SNAP software (v 3.8.0) [18] by three operators: one operator with 3 years of experience in muscle segmentation (OP1), and two radiology residents. Both radiology residents (OP 2 and OP3), underwent two hours of basic training on muscle segmentation by OP1.

In this study, operators were trained to leave a thin 1-2 mm border of unsegmented muscle tissue between the margins of each ROI and the T2 hypointense fascia and cortical bone of the femur. The same thin border was to be applied between two ROIs of contiguous muscles if no evident anatomical margin was observed (e.g., in the case of the delimitation between the *adductor magnus* and *semimembranosus* in some cases in the young adult subgroup). Secondary instructions for muscle delimitation included avoiding extra-muscular connective tissue, as well as internal fascia invaginations, which at times resulted in a less regular morphology of the ROI but is presumably more representative of the actual muscle tissue. Fatty muscle degeneration within the borders of the muscle fascia in the form of thin, non-confluent internal T2 hyperintensities (though less hyperintense compared to the extra-muscular fat tissue) was to be included as well. In case of doubt, the less experienced operators were instructed to refer to previous segmentations of other patients present in the internal database, for reference. As a last resort, if serious doubts persisted about the location and size of a specific muscle, less experienced operators were trained not to segment that particular muscle.

The instructions also included a review of the anatomy of the thigh muscles, an MRI-based atlas of the lower limbs and hands-on training in the use of the segmentation software. The same radiology residents were also given a reference dataset of muscle MRI studies that were already segmented by the expert operator (OP1). Only OP2 additionally received advanced practical training in the form of twenty practice cases to be segmented independently, with subsequent corrections of the ROIs and further advice by OP1. Such segmentation instructions included leaving a thin border of one to two voxels of muscle tissue while avoiding extra-muscular connective tissue, as well as internal fascia invaginations. All three operators then performed the segmentation process twice on the same slice for each patient, at the beginning of the study and 72 hours after the first segmentation.

Both intra- and inter-operator agreement of the spatial overlap of the ROIs were evaluated with Dice Similarity Coefficient (DSC) (average value between the left and right thigh). The agreement was scored in the range between 0 and 1 as follows: 0 "no agreement", below 0.4 "poor agreement", 0.4-0.6 "moderate agreement", 0.6-0.8 "substantial agreement", and 0.8-1.0 "almost perfect" [19].

Confidence intervals (CI) of intra-operator DSC values were calculated for each operator as a means to define their global reproducibility performance. A non-parametric test for independent samples (Kruskal-Wallis test) was also performed to compare medians of average intra-operator DSC values. An additional more specific analysis was performed comparing pairwise operators in terms of paired differences between average intra-operator DSC of each muscle. The alpha value was conventionally set as 0.05. Considering the low population size, the p values were adjusted with the Benjamini-Hochberg procedure to decrease false discovery rate.

Results

The nine enrolled subjects had a median age of 30 years (20-65 y range, 7 F, 2 M). To assess whether the age of the examined subjects had an impact on the reproducibility of muscle segmentation, we also identified two subgroups based on age: a first group of 6 volunteers between 20 and 30 (4 F, 2 M), hereinafter referred to as the young adult subgrou, and a second group of 3 volunteers aged 45 to 65 years (3F) (the adult subgrou). Inter-operator and intra-operator agreement is expressed as the fraction of the overlapping voxels between two comparisons, ranging from 0 to 1.

Intra-operator agreement

OP1 had the highest intra-operator agreement in drawing the ROIs (0.885, CI 0.8845 ± 0.0093) with high DSC in nearly all the muscles of the thigh of the entire cohort, the only exception being the short head of the *biceps femoris* (BFS)(0.749). Intra-operator DSC values respectively for OP2 and OP3 were also quite high, respectively of 0.856 (CI 0.8558 ± 0.0154) and 0.818 (CI 0.8178 ± 0.0194). When examining muscles separately, OP2 showed the lowest reproducibility again for BFS (0.629), whereas OP3 showed the lowest DSC values for *vastus medialis* (VM) (0.765), *semimembranosus (*SM) (0.719) and for BFS (0.550).

When examining the young adult subgroup, OP1 outperformed OP2 and even more OP3 in the reproducibility (DSC respectively of 0.901, 0.851 and 0.801). By contrast, when examining the adult subgroup OP3 showed the highest DSC values (0.897), with OP1 and OP2 having only slightly lower values (0.851 and 0.875, respectively). The pairwise analysis showed a significant difference between the intra-operator DSC of OP1 and OP2 ($p = 0.0483$), OP1 and OP3 ($p = 0.0073$), but no difference between OP2 and OP3 ($p = 0.0806$).

Inter-operator agreement

When considering the entire cohort, we found a high (almost perfect) agreement between OP1 and OP2 (0.814) and only substantial agreement between OP1 and OP3 (0.762) and OP2 and 3 (0.702). With regard to single muscles, OP1 and OP2 showed almost perfect agreement in the majority of muscles, with the exception of *semimembranosus* (0.773), *gracilis* (0.747), BFS (0.734) and *sartorius* muscles (0.719). OP1 and OP3 showed a high agreement in most of the muscles, with a substantial agreement of the *gracilis* (0.779), *sartorius* (0.722), *adductor longus* (0.634), *vastus medialis* (0.632), and only fair agreement for BFS segmentation (0.495). OP2 and OP3 had substantial agreement for long head of the *biceps femoris* (BFL) (0.786), *gracilis* (0.700), *adductor longus* (0.626) and *sartorius* (0.626), moderate agreement of the *semimembranosus* (0.599), *vastus medialis* (0.571), and BFS (0.417), as shown in Table I.

When considering the two age subgroups, OP1 and OP2 had slightly higher inter-operator concordance for the young adult subgroup than the adult subgroup (0.827 *vs* 0.775), while higher DSC values were observed in the adult subgroup (compared to young adults) when concordance between OP1 and OP3 (0.775 *vs* 0.751) as well as between OP2 and OP3 (0.785 *vs* 0.680) was evaluated.

Discussion

We aimed to assess the reproducibility of manual muscle MRI segmentation while applying a coherent, well-defined set of drawing recommendations based on our single-center clinical experience. In this experience focused on a small cohort of healthy volunteers we showed that the application of these recommendations leads to not only a high degree of reproducibility in experienced operators, but also to a significant improvement in reproducibility of relatively inexperienced operators, when trained appropriately.

Intra-operator reproducibility

In this study, the highest overall intra-operator reproducibility in ROI drawing was shown for the most expert operator (OP1), which also had the lowest width of the confidence interval. Such a finding reflects the importance of experience in muscle segmentation, which is known to be a strongly operator-dependent process and with a relatively low reproducibility in time.

Among the less experienced operators, OP2 showed higher overall intra-operator agreement compared to OP3, but the pairwise analysis failed to show a significant difference between the distribution of intra-operator DSC values ($p > 0.05$). When examining the confidence intervals for OP2 and OP3, however, we found that they were not overlapping, and that the width of the CI was lower for OP2 compared to that of OP3. If we assume a roughly equal baseline reproducibility between the two less experienced operators, even considering the small dataset, we still can hypothesize that the greater amount of supervised training received actually helped in improving OP2's segmentation reproducibility.

When examining the reproducibility in drawing each muscle separately we found that *semimembranosus* (SM) and the BFS created the higher difficulties to all three operators (also to the expert OP1). We think this might be due to the difficulty in delimitating SM from *adductor magnus* (AM) and, for what concerns BFS, to the small sectional area of the muscle at the considered level for segmentation, compared to other muscles. Arguments could be raised regarding the advantages of omitting certain muscles from the segmentation as BFS in this case, but such decision should follow the purpose of each specific study.

Inter-operator reproducibility

The higher inter-operator DSC was shown between OP1 and OP2 (0.814) compared to OP1 and OP3 (0.762) and OP2 and OP3 (0.702). Even considering the small population, the higher degree of training that Operators 2 received seemed effective in increasing the reproducibility of ROI drawing (though, as aforementioned, the difference between the reproducibility between OP2 and OP3 was not statistically significant).

The two muscles with the worst inter-operator reproducibility (average of all operators) were the *sartorius (*0.689), and the BFS (0.642). Whereas the small sectional area of the BFS undoubtedly makes it difficult to obtain a good reproducibility, we interpreted the low results obtained for the *sartorius* as due to difficult belly delimitation from the adjacent semimembranosus (SM), which also presented low inter-operator DSC values (0.699).

Young versus adult population

The reproducibility of ROI drawing for the young adult group was lower compared to the adult group when examining intra-operator agreement of OP2 and OP3 and the inter-operator agreement between OP2 and OP3 and also OP1 and OP3. By contrast, OP1 had a higher intra-operator reproducibility for the young adult compared to the adult subgroup and also a higher inter-operator agreement with OP2 compared to the adult subgroup. Such a result was not unexpected and seems to confirm our clinical experience suggesting a higher difficulty in drawing replicable muscle ROIs in younger subjects who have more trophic muscles and where muscle borders may

Table I. Average intra-operator and inter-operator DSC test results between ROI segmentation of each thigh muscle at 0 and 72 hours, and average inter-operator DSC test between each operator.

			Single Muscles												All Muscles
			VL	VM	VI	RF	Sa	G	AM	SM	ST	BFL	BFS	AL	
Average intra-operator DSC value	Operator 1	Age 20-30	0.953	0.919	0.923	0.918	0.906	0.887	0.947	0.890	0.927	0.895	0.743	0.909	0.901
		Age 45-65	0.886	0.909	0.890	0.896	0.845	0.822	0.912	0.748	0.884	0.844	0.760	0.814	0.851
		Whole cohort	0.931	0.916	0.912	0.911	0.886	0.865	0.935	0.843	0.913	0.878	0.749	0.877	**0.885**
	Operator 2	Age 20-30	0.934	0.911	0.920	0.926	0.812	0.836	0.916	0.821	0.794	0.853	0.660	0.833	0.851
		Age 45-65	0.941	0.898	0.920	0.924	0.870	0.917	0.949	0.813	0.947	0.906	0.617	0.793	0.875
		Whole cohort	0.937	0.908	0.917	0.925	0.822	0.853	0.924	0.809	0.832	0.863	0.629	0.851	**0.856**
	Operator 3	Age 20-30	0.904	0.714	0.866	0.920	0.790	0.791	0.860	0.740	0.859	0.868	0.550	0.749	0.801
		Age 45-65	0.945	0.906	0.945	0.946	0.872	0.911	0.958	0.733	0.948	0.930	0.807	0.867	0.897
		Whole cohort	0.913	0.765	0.887	0.924	0.807	0.820	0.884	0.719	0.881	0.881	0.550	0.783	**0.818**
Average intra-operator values (all operators)			0.927	0.863	0.905	0.920	0.838	0.846	0.915	0.790	0.875	0.874	0.642	0.837	0.853
Average inter-operator DSC value	Operator 1 and 2	Age 20-30	0.902	0.842	0.911	0.855	0.728	0.780	0.901	0.785	0.833	0.825	0.722	0.837	0.827
		Age 45-65	0.811	0.783	0.829	0.783	0.698	0.686	0.867	0.740	0.833	0.753	0.751	0.766	0.775
		Whole cohort	0.882	0.825	0.892	0.837	0.719	0.747	0.894	0.773	0.834	0.806	0.734	0.828	**0.814**
	Operator 1 and 3	Age 20-30	0.869	0.578	0.820	0.883	0.699	0.750	0.848	0.785	0.855	0.831	0.495	0.602	0.751
		Age 45-65	0.811	0.783	0.829	0.783	0.698	0.686	0.867	0.740	0.833	0.753	0.751	0.766	0.775
		Whole cohort	0.883	0.632	0.838	0.887	0.722	0.779	0.860	0.726	0.866	0.824	0.495	0.634	**0.762**
	Operator 2 and 3	Age 20-30	0.808	0.498	0.780	0.842	0.581	0.672	0.801	0.657	0.766	0.770	0.417	0.575	0.680
		Age 45-65	0.885	0.799	0.883	0.858	0.712	0.787	0.914	0.539	0.903	0.856	0.690	0.591	0.785
		Whole cohort	0.822	0.571	0.805	0.844	0.626	0.700	0.829	0.599	0.800	0.786	0.417	0.626	**0.702**
Average inter-operator values (all operators)			0.862	0.676	0.845	0.856	0.689	0.742	0.861	0.699	0.833	0.805	0.549	0.696	0.760

The latter values represent an average of DSC test results between all combinations of both ROIs of each operator for each muscle and are expressed as an average value between both the left and the right thigh. An average DSC value was provided in the last column as a single value that summarizes spatial overlap of all ROIs. A separate row underneath each sub-table reports the average single-muscle DSC values both for intra-operator and inter-operator tests. The colors represent the agreement class for each value, with dark green representing near perfect agreement (DSC values ranging between 0.8 and 1.0), light green representing substantial agreement (DSC value between 0.6 and 0.8) and yellow representing moderate agreement (DSC value between 0.4 and 0.6). *VL: Vastus lateralis; VM: Vastus medialis; VI: Vastus Intermedius; RF: Rectus femoris; Sa: Sartorius; G: gracilis; AM: Adductor Magnus; SM: Semimembranosus; ST: Semitendinosus; BFL: Long head of Biceps femoris; BFS: Short head of Biceps femoris; AL: Adductor Longus.*

be uncertain between different muscle bellies, leading to a decrease of intra- and inter-operator agreement, especially for less experienced operators. We surmise that the score difference between the two subgroups may be due to inter-muscular adipose tissue being more prominent in the adult group, with fat acting as a natural contrast facilitating the segmentation process. An example of this can be seen in OP3's lower repeatability in segmenting the VM muscle, which is usually clearly distinguishable. Upon further inspection, this error was more pronounced in the younger subgroup, due to the fact that the demarcation between the VM and the vastus intermedius (VI) muscles is less obvious in the younger population.

Initial stages of certain myopathies may have a similar appearance, rendering segmentation slightly easier, whereas advanced stages might have the opposite effect, since the extensive fatty infiltration might render the localization of muscles even more difficult. The most expert operator (OP1) by contrast showed a higher reproducibility in the youngest subcohort, presumably reflecting a higher ability in correctly separating muscle bellies. This finding was also mirrored by the higher reproducibility between OP1 and OP2 in the younger cohort compared to the older one.

These data are in line with our data-driven hypothesis of a sort of "U-shaped" curve of difficulty in drawing ROIs in the field of neuromuscular diseases, with higher difficulty presenting when adipose replacement is very low or very high; this observation is in line with our clinical experience.

The ROI-drawing process: our experience

Manual muscle segmentation can be classified into three approaches: segmentation of all muscles as a single ROI, segmentation of each muscle compartment and segmentation of each single muscle separately. The latter approach was the one evaluated in this study. The main disadvantage of single-muscle segmentation is the time required to draw all the ROIs, making it difficult for a single dedicated operator to apply such an approach in routine care (especially when segmentation is applied to several slices to cover a wide range of selected muscles). Multiple operators that are part of the same research (or clinical) center are consequently frequently used to hasten such a procedure. This underlines the importance of establishing clear segmentation criteria to maximize spatial overlap between operators. As software based on machine learning are progressively applied in the segmentation process, segmentation speed might soon, however, not be a relevant issue. In order to develop such algorithms, however, the software must learn from previous adequate and highly reproducible ROI datasets. Algorithms training times are also reduced when datasets received as inputs are more coherent and more representative of the "ground truth" that can be obtained preferably by consensus between human operators with an expert knowledge of muscle segmentation. In this sense, one of the main variables influencing reproducibility of muscle ROIs is the distance of ROI margin from the muscle fascia. Few studies in recent literature specify in sufficient detail the inclusion of anatomical muscle borders or lack thereof [20,21]. One of the exceptions is a recent study [4] that not only explicitly specifies to hold adequate distance to the muscle fascia to avoid chemical shift artifacts but also compared inter-operator and intra-operator agreement [4]. The majority of other studies (including those with segmentation performed by more than one operator) only measured inter-operator agreement, often by measuring the intraclass correlation coefficient (ICC) [22,23]. Even if a high ICC agreement is generally considered to be reliable for follow-up evaluations of fatty infiltration [12,24], we have a stronger interest in the reproducibility of the ROI drawing. The position and the morphology of ROIs, in fact, can be highly relevant when it comes to evaluating the degree of pathology, especially in longitudinal follow-up.

We therefore consider the specification of the distance between the ROI borders and the muscle fascia as the most important factor that influences ROI reproducibility.

Study limitations

Several limitations apply to our study. Firstly, in this study we analyzed the ROI segmentation process of the thigh muscles, as this region is the most frequently studied in the field of neuromuscular disease. Though the focus on a single muscle group represents a limitation of this study, we believe that the presented recommendations are applicable to most muscle groups in several contexts, though we hope to test this hypothesis in future studies.

Secondly, the small number of operators dedicated to ROI drawing and the small numbers of subjects included are certainly to be underlined as limiting factors for generalization of results. Thirdly, the main parameter by which we evaluated the validity of this set of recommendations is reproducibility. Due to the aforementioned lack of a standard set of recommendations concerning manual segmentation, we chose not to perform an accuracy analysis and to concentrate our work on reproducibility by assessing DSC values. A clearly identifiable consensus or guideline for segmentation with muscle volume as its primary objective, is still lacking. As such, a gold standard for comparison with the presented results is missing. A high level of precision and reproducibility is nonetheless highly desirable in the clinical context of ROI drawing, especially when follow-up MRI studies are performed. Such an element becomes particularly relevant in subjects suffering from dystrophic diseases, in which the possibil-

ity to detect even small changes over time have an impact on improving the prediction of the patient's prognosis [25].

Conclusions

In this study we showed how, following specific recommendations, the process of muscular ROI drawing can be highly reproducible and reliable; less experienced operators dedicated to ROI drawing can be trained with specific instructions with promising results in order to gather vast ROI datasets for analysis and as reference. Though only thigh muscles were selected as the target region to be segmented in this study, these same results can be generalized to other anatomical districts and applied to muscles that are more difficult to segment. The measure of distance from the muscle fascia in the drawing process appears, in our opinion, as the main criterion to follow in order to guarantee the reproducibility of ROIs, as well as a major cause of inter-operator low agreement in the cases in which it is not adequately defined. Secondary recommendations include avoiding internal fascia invaginations, while including areas of fatty muscle degeneration within the borders of the muscle fascia. We believe that following these recommendations allows for increased reproducibility of manual segmentation in muscle imaging, especially in the case of young adults, in which the intermuscular connective tissue is less prominent and delimitation between certain muscles is not straightforward.

Ethical consideration

All subjects gave their formal informed consent for the participation in the study, which was approved by the local ethics committee.

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Financial interest

The Authors have no relevant financial or non-financial interests to disclose.

Conflict of interest

The Authors have no conflicts of interest to declare that are relevant to the content of this article.

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Author contributions

A.P. and S.B. contributed to the conceptualization and supervision of this study. F..S, E.B. and R.V. contributed to the investigation, and resource collection. M.P. and N.B. contributed to the methodology, formal analysis, and data curation. S.I.M., M.P. and A.P. contributed to the writing of the original draft, while A.P. and S.B. contributed to the review and editing of the final draft.

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Diagnosis and treatment of pneumonia, a common cause of respiratory failure in patients with neuromuscular disorders

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Patients with neuromuscular diseases, during their illness are more susceptible to respiratory infections due to predisposing factors. Ineffective cough and the presence of atelectasis and hypoventilation, dysphagia and drooling can represent risk factors for the development of respiratory infection and fatal respiratory failure.

Infections of respiratory tract with acute respiratory failure are the most common reason for hospitalizations, and pneumonia is among the leading causes of morbidity and mortality worldwide. The setting in which pneumonia is acquired heavily influences diagnostic and therapeutic choices. We will focus on aetiopathogenesis, diagnosis and treatment of pneumonia in these subjects, particularly considering the disease severity, rates of antibiotic resistance and the possible complications. In this case consultations with specialized physicians are strongly recommended.

Key words: neuromuscular disorders, pneumonia, respiratory infections

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Introduction

Neuromuscular disorders (NMDs) are a large group of inherited and acquired diseases that affect a number of neural structures including motor nerves, neuromuscular junctions and muscles themselves. Despite most of them are rare diseases, however the number of individuals requiring hospital care, often related to cardiac or respiratory complications, is significant.

Sleep disordered breathing, daytime hypoventilation, coughing and swallowing are the most frequent observed symptoms [1,2]. In these cases, non-invasive support with night ventilation with a mask and pressure support device, can be extraordinarily useful to delay daytime ventilatory failure [3].

Dysphagia and difficulty in managing secretions are also common symptoms in neuromuscular diseases due to muscle weakness. Dysphagia may lead to medical complications, such as malnutrition, dehydration, aspiration pneumonia, and other pulmonary complications, causing social isolation and reduced overall quality of life [4]. In particular, patients with Duchenne Muscular Dystrophy (DMD), Myotonic Dystrophy type 1

(DM1), Spinal Muscular Atrophy (SMA), Pompe disease [5] and Amyotrophic Lateral Sclerosis (ALS) [6] develop severe progressive respiratory muscle weakness, with consequent impaired cough and secretion clearance, restrictive lung disease, dysphagia and aspiration [7]. Recurrent respiratory infections, airway obstruction and disordered sleep breathing leading to alveolar hypoventilation and respiratory failure, are a frequent cause of death [1,2].

Sialorrhoea is a common and problematic symptom that arises from a number of neurological conditions associated with bulbar or facial muscle dysfunction. Drooling can significantly affect quality of life both for physical complications such as oral chapping, and psychological complications such as embarrassment, and social isolation.

When saliva is excessive and thick, it can be sucked in and cause cough. If the cough is ineffective, or the patient also has gastroesophageal reflux, it can lead to aspiration pneumonia. These symptoms can be silent for a long time and result in a severe respiratory failure and pneumonia [7-9].

Respiratory tract infections can affect patients with NMDs with severe exacerbations, due to ventilatory insufficiency that results in impaired alveolar ventilation and stagnation of secretions. Furthermore, they can get worse hypoxemia favoring the onset of acute respiratory failure in subjects often suffering from chronic respiratory failure, or dysphagia. Even patients on non-invasive mechanical ventilation can develop severe respiratory failure, sometimes requiring emergency intubation or tracheostomy.

Coordinated multidisciplinary care has led to better survival outcomes over the past decades.

Epidemiology of pneumonia in NMDs

The context in which pneumonia is acquired, heavily influences diagnostic and therapeutic choices. As the causative organism is typically unknown early on, timely administration of empiric antibiotics is a cornerstone of pneumonia management [11].

From an epidemiological point of view, *Streptococcus pneumoniae* is still the most relevant pathogen agent, immediately followed by *Haemophilus influenzae* and *Moraxella catharralis*.

A multiplicity of infectious agents, of a viral and bacterial nature, circulates in the human population and causes, with particular epidemiological relevance, manifestations of respiratory infection in the period between October and April. In other seasonal periods, respiratory forms mostly caused by so-called atypical respiratory pathogens, such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella spp*. (which probably also exert a predisposing function for a second bacterial infection), occupy – in a hypothetical etiological top ten – the positions of immediate reinforcement. About 10% of hospitalized community acquired pneumonia (CAP) requires hospitalization in intensive care units (ICUs), especially for forms mainly sustained by S. pneumoniae and *Legionella spp*.

Similar considerations deserve viral infections that are sustained by a large number of agents such as influenza A and B virus, respiratory syncytial virus (RSV), Rhinovirus (HRV), coronavirus (hCoV), meta-pneumovirus (hMPV), parainfluenza virus (hPIV), adenovirus (ADV), measles virus.

Healthcare-related infections

Healthcare-related infections can be distinguished in a) nosocomial, with onset 48 hours after hospitalization, as the "community infection pneumonia" in patients without previous care contacts; b) non-nosocomial, with onset within 48 h of hospitalization in patients with previous care contacts such as nursing or home IV therapy, wound care, hemodialysis, IV chemotherapy in the last 30 days, hospitalization in the previous 90 days, residence in a nursing home or long-term care.

The pattern of etiological agents is much broader and represented by species resident in the nosocomial environment, with complex resistance profiles.

Pseudomonas aeruginosa and methicillin-resistant S. aureus are the most frequent microorganisms, followed by *Enterobacteriaceae*, such as *A. baumannii*. Episodes of pneumonia caused by multidrug-resistant microorganisms (MDRs) - including enterobacteria and mainly Klebsiella pneumoniae carbapenemase-producing (KPC) - are increasingly common in long-term care and hospitals.

Furthermore, the risk of nosocomial pneumonia related to exogenous colonization by environmental pathogens, mainly contaminating the water systems, inhaled after aerosol, should not be overlooked.

Legionella spp represents the archetype of this category of pathogens, but others such as *P. aeruginosa, Aspergillus spp* and fast-growing mycobacteria have non-secondary roles. The mode of transmission in these cases is due to aspiration maneuvers, use of bronchoscopes, contamination of nebulizers, humidifiers and ventilation circuits.

Pulmonary complications are the leading cause of respiratory deaths. Hypoxemia is common and results from both hypoventilation and micro atelectasis.

In patients with NMDs, over 90% of pneumonias are triggered by upper respiratory tract infections. Chest infections pose a serious problem for the treatment of vulnerable patients with muscle weakness and ineffective cough [12]. Pneumonia is the main complication in these pa-

tients due to both inefficient respiratory mechanics and a lack of mucociliary clearance capacity. Though the latter is theoretically preserved, ciliary function is nevertheless often impaired due to chronic aspiration and mucopurulent bronchitis.

Overtime, patients can be colonized by opportunistic pathogens such as *Pseudomonas aeruginosa and methicillin resistant Staphylococcus aureus*. In some cases, irreversible lung damage can occur with the development of bronchiectasis and pulmonary fibrosis [13].

Pneumonia etiology

The etiology of pneumonia can be multifactorial but essentially arises from compromised lung and chest wall function, which produces obstructive and restrictive lung diseases.

The first point is to understand when to treat the patient by distinguishing when he is colonized from when he is in an acute infection; clinical evaluation usually involves measurement of temperature, tracheobronchial secretion volume, culture and purulence assessment of tracheobronchial secretions, evaluation for chest radiograph resolution, white blood cell count, arterial oxygen tension/inspiratory oxygen fraction (PaO2/FiO2) [14].

The most frequent pathogen agents in patients with NMD are *MRSA, Pseudomonas aeruginosa and MDR pathogens* [15]. Prolonged antibiotic treatment is unlikely to prevent this secondary pneumonia but may select for more MDR pathogens. Anaerobes are the etiology in only 0.2 to 0.3% of all patients.

The microbiology of pneumonia after macro aspiration has changed over the last 60 years from an anaerobic infection to an aerobic and nosocomial infection [16].

It has long been known that micro aspiration is the dominant pathophysiologic mechanism behind CAP. Supporting evidence includes the finding that most common CAP causing microorganisms colonize the oropharynx or nasopharynx in non-hospitalized patients. The distinct microbiology of HAP derives from the micro aspiration that occurs after hospitalized patients are colonized with the virulent organisms found in ICUs and hospital settings [16].

Diagnosis

For the microbiological diagnosis, the samples should be collected from respiratory tract, sputum, pleural fluid, endotracheal aspirate, or bronchoalveolar lavage, and blood within 24 hours of hospitalization. The biomarkers determinations may include C-reactive protein (CRP), procalcitonin (PCT), copeptin and adrenomedullin peptide (ADM).

A very important role is now played by the matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) which has become a gold standard for microbial identification in clinical microbiology laboratories. In order to speed up the microbiological diagnostic, the typing of single strains as well as the resistance tests to antibiotics and antimycotics has come into focus, in addition to the identification of microorganisms.

A rapid identification of pathogens is important in the survival of patients undergoing a septic event because it has allowed to shorten the time of access to appropriate antibiotic therapy and has contributed to the improvement of patient outcomes.

Another very important role for the rapid diagnosis of upper and lower respiratory tract infections is now played by the latest generation molecular tests, in particular, *Biofire® respiratory panel RP2.1 plus* for the upper respiratory tract and *BioFire® Pneumonia Plus (Pneumoplus)* for lower respiratory tract. *RP2.1 plus* allows to collect a nasopharyngeal on viral transport, sample volume 300 µL which collects all respiratory viruses including Sars-Cov-2 as well as atypical pathogens responsible for pneumonia (*Bordetella, Chlamidia, Mycoplasma*).

The *Pneumo plus panel*, on the other hand, which provides a sample of about 200 microL of sputum and brochoalveolar lavage (BAL), identifies bacteria, viruses, atypical bacteria and antibiotic resistance genes; this last point is very important for those patients who over time undergo multiple antibiotic therapies [17].

For fungal infections, blood cultures are always important, even those tested with *BioFire® film array panels* that allow the identification of a broad spectrum of yeasts, not least *Candida auris*, as well as antimicrobial resistance genes on the blood. Sputum culture and research of mannan, galactomannan and betaDglucan markers in the blood are of additional help in the diagnostic process.

Treatment

Several trails in the field of hospital pneumonia suggest using a 7-8 days course of antibiotic therapy in patients with VAP without immunodeficiency, and with cystic fibrosis, empyema, lung abscess, cavitation pneumonia or necrosis with a good clinical response to therapy.

Patients with NMDs can be included in these categories as the highest percentage of infection is determined by forms ab ingests, including pneumonia due to continuous aspirations and difficulty in swallowing.

Community-acquired pneumonia (CAP)

CAP has *S. Pneumoniae*, atypical and mycoplasma, in particular *Haemophilus, Moraxella* and in 30% cases

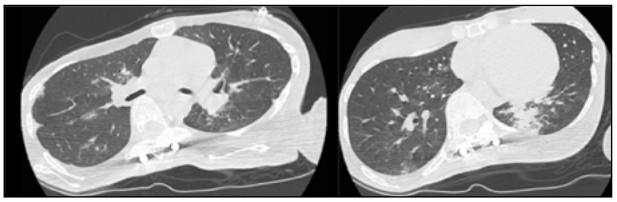

Figure 1. Lung CT scan. Typical picture of pulmonary involvement caused by respiratory syncytial virus, in a patient with congenital myopathy and acute respiratory failure.

to virus Influenza, Parainfluenza, RSV (Fig. 1) and in the last year 2020 Sars-CoV-2 as its prevalent etiologies [18].

Oropharyngeal aspiration is an important etiological factor leading to pneumonia in the elderly and patients with neuromuscular diseases. These disorders are associated with dysphagia and an impaired cough reflex which in turn increases the likelihood of oropharyngeal aspiration. Aspiration pneumonia is difficult to distinguish from other pneumonia syndromes. More than 90% of hospitalized patients have a risk for aspiration; however, some studies do not recommend the routine use of an anti-anaerobic antibiotic coverage [19].

Primary regimen therapy for CAP is summarized in Table I. It is important to discontinue antibiotics with normalization of procalcitonin to 0.1-0.2 mcg/ mL.

Hospital Acquired Pneumonia (HAP)

Antibiotic therapy regimens for hospital-acquired pneumonia are shown in Table II. Each regimen is selected with specific therapy after culture results (sputum, blood, pleural fluid etc.) (Fig. 2).

Aspiration community acquired pneumonia (ACAP)

ACAP is frequent in patients with NMDs; dysphagia, lack of cough reflex, esophageal motility disorders, typical in neurological diseases are considered the most important risk factors for aspiration pneumonia.

Etiologies anaerobes and viridians streptococci group-related are predominant. Primary therapy regi-

Table I. Antibiotic therapy regimens for community-acquired pneumonia.

CAP	Drug	Dose	Route	Duration
Mild CAP	Amoxicillin	1000 mg TID	Oral	5 days
Mild CAP (penicillin allergy)	Doxycycline	100 mg BID	Oral	5 days
Intermediate CAP (comorbidities)	Amoxicillin/clavulanic + Azithromycin OR levofloxacin	875/125 mg BID 500 mg QD 750 mg QD	Oral Oral Oral	7-10 days
Severe CAP (acute respiratory failure, mechanical ventilation)	III generation cefalosporin		Intravenous	7-10 days

Table II. Antibiotic therapy regimens for hospital-acquired pneumonia.

HAP	Drug	Dose	Route	Duration
First line	Cefepime OR piperacillin/tazobactam OR meropenem + macrolide	2000 mg BID 4500 mg TID-QID 1000 mg TID	Intravenous	10-14 days
Methicillin-resistant Staphylococcus aureus (MRSA)	Vancomycin OR Linezolid + macrolide	1000 mg BID 600 mg BID	Intravenous	10-14 days
Vancomycin-resistant Staphylococcus aureus (VRSA)	Ceftarolina OR ceftobiprolo + macrolide	600 mg BID	Intravenous	10-14 days
Pseudomonas A.	IV generation cefalosporin + ciprofloxacin OR amikacin	400 mg BID 15 mg/kg DIE	Intravenous	10 days

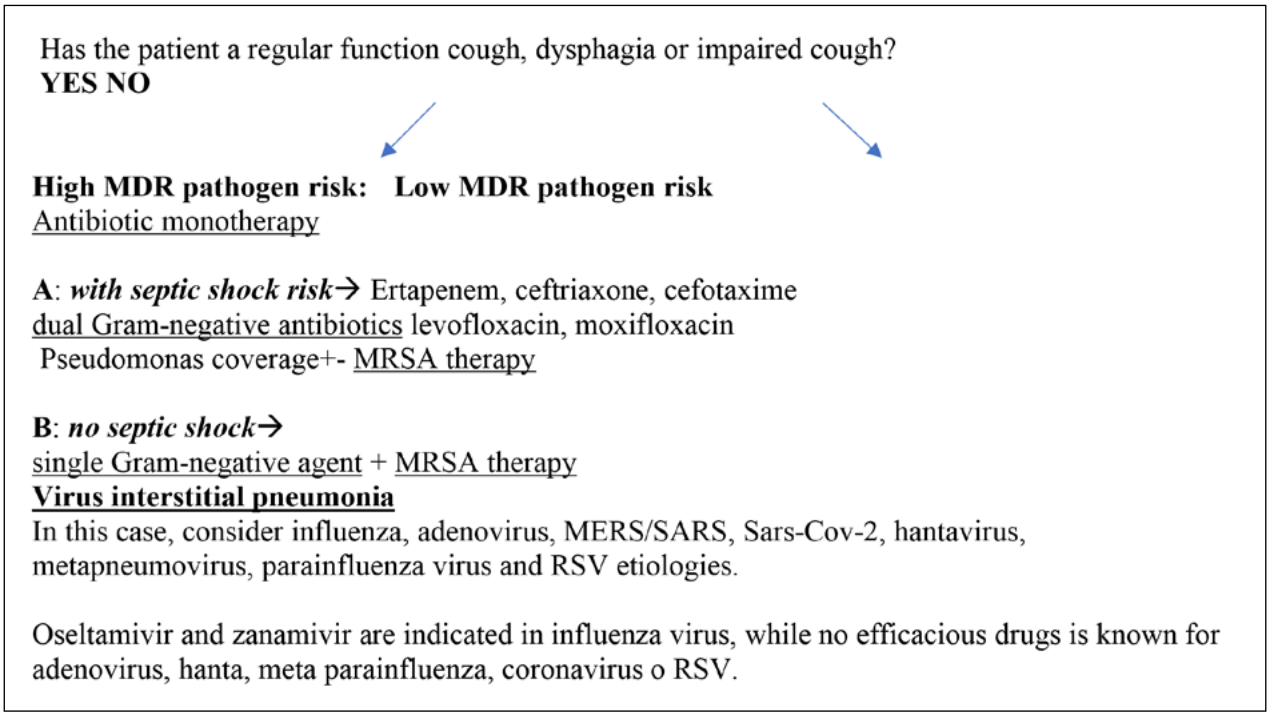

Fig. 2. CAP or HAP in patients with NMDs. Risk assessment for MDR pathogens and mortality (from 2017 European HAP/ VAP guideline, mod.). [23].

men is with Amp/sulb 3 gr ev/6 h or ceftriaxone 1 gr in 24 h plus metronidazole 500 mg ev every 6 hours [20,21]. Infections associated with anaerobes do not evidence pathogenic role [21] and Gram-Negative bacteria were more prevalent in patients with severe ACAP, with higher prevalence of *Pseudomonas aeruginosa* and Enterobacteriaceae (Other GNB). Oral cavity is considered the principal source of pathogens responsible for aspiration pneumonia. Microbiology data from patients with other comorbidities suggested that *P. aeruginosa, K. pneumoniae* and *E. Coli* were frequently isolated from oral samples (Figs. 3-4). For the more appropriate therapeutic choice, it is essential to keep always in mind the local epidemiology of antimicrobic resistance, which varies according to geographic areas [22,23].

Pulmunary Fungal infections (PFIs)

PFIs occur mostly as pulmonary nodules and aspergillosis is the most frequent cause. Interstitial pneumonia is caused by Pneumocystis. Histoplasmosis and aspergillosis can also be presented as ground glass pictures.

In this case, the first therapeutic choice is represented by echinocandins, especially if patients are unstable or have already taken azoles. Voriconazole is the drug of choice for aspergillosis. Amphotericin B is recommended as an alternative [24,25].

Recommendations

Infection surveillance should not be limited to the respiratory system, but other sites of possible infection such as generalized bacteremia or sepsis, urinary tract infections, catheter infections should also be considered; therefore, adequate source control with culture tests such as blood cultures, urine culture, nasal swabs and catheter culture tests is essential.

Other possible sites of first infection can be any bedsores, very common in patients with NMDs, often in a wheelchair, bedridden or on continuous non-invasive mechanical ventilation. If an infection is suspected, a pressure sore swab should be done.

In any case, an antimicrobial stewardship program is fundamental in the therapeutic choice of antibiotics according to local microbiological epidemiology, to prevent antimicrobial resistance. It should be noted that combination therapy was associated with a significantly lower risk of death compared to monotherapy.

Conclusions

Diagnostic tests play a fundamental role in healthcare: they help to further improve antimicrobial stewardship by optimizing the use of antibiotics, a more delicate therapy in vulnerable patients; they also help prevent the

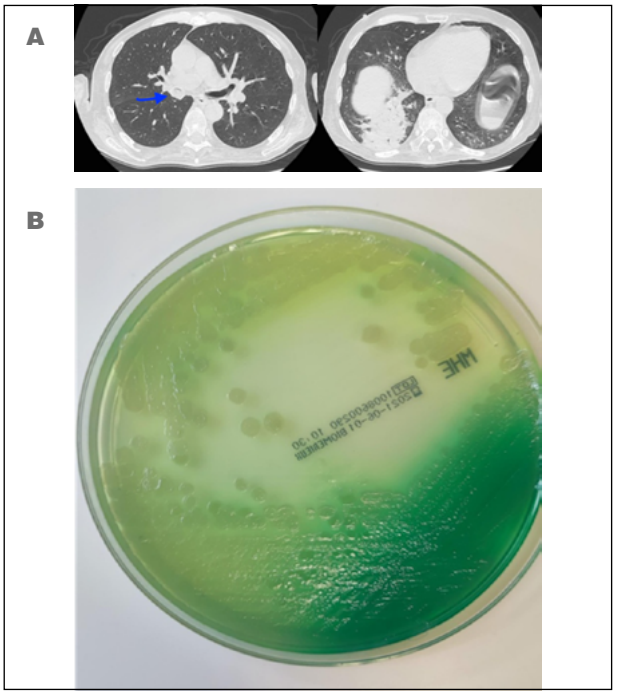

Figure 3. A) Lung CT scan. Typical picture of pulmonary involvement caused by Pseudomonas aeruginosa (sputum isolation) in a patient with amyotrophic lateral sclerosis, dysphagia and respiratory failure. Evidence of food ingestions in the middle lobe bronchus and right lower lobe; B) Pseudomonas aeruginosa in Mueller-Hinton agar plate. Evidence of Pyocyanin or fluorescin production.

appearance of bacterial resistance. However, it should be remembered that antibiotic administration can also adversely affect respiratory muscle function. Numerous studies have assessed that penicillin-type drugs are rarely associated with the development of a myopathy. It is therefore very important to choose a targeted antibiotic therapy, which, on the one hand, must eradicate infections, and, on the other, must not cause damage to the muscles or neuromuscular plaque. Disease severity and antibiotic resistance rates should carefully be considered, when choosing an empirical regimen. If complications occur, further investigation and consultation with a pulmonary specialist may be necessary.

The correct use of the available weapons can contribute to change the patients prognosis and quality of life.

Practical suggestions

- Dysphagia is often the "primum movens" of a number of complications.
- Targeted dietary interventions for patients with dysphagia secondary to neurodegenerative diseases are currently available.

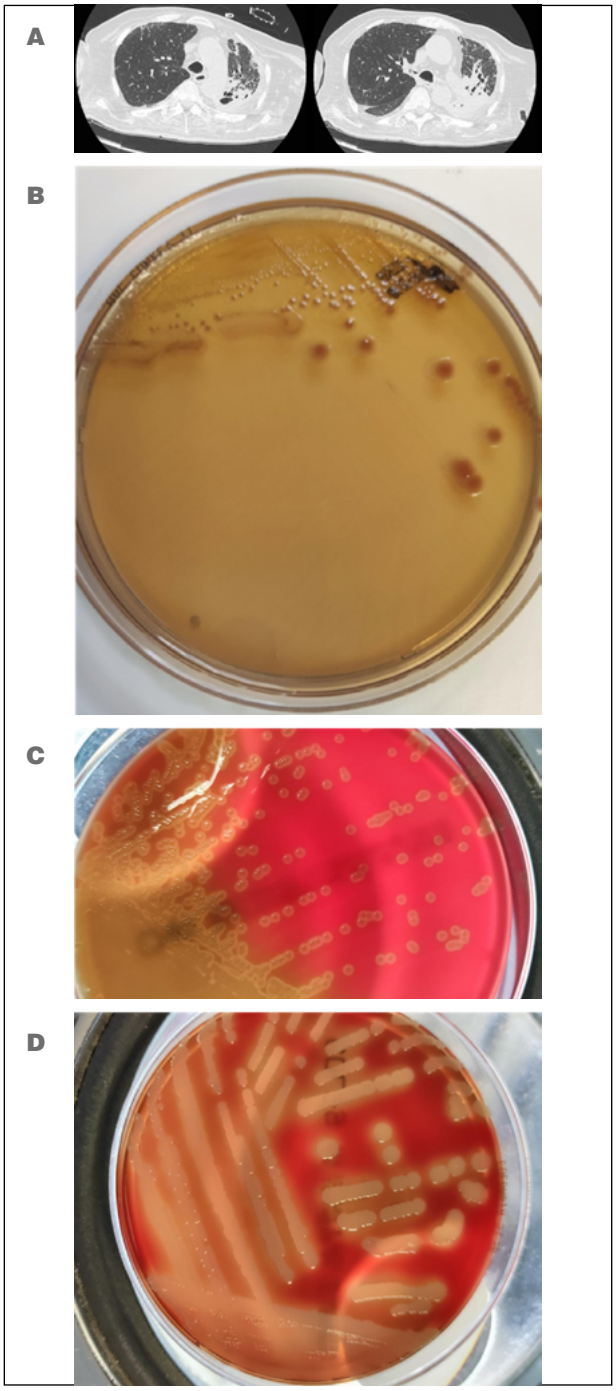

Figure 4. A) Lung CT scan. Picture of pulmonary involvement caused by Stenotrophomonas malthophilia Staphylococcus aureus and Streptococcus pneumoniae (bronchoaspirate isolation) in a patient with muscular dystrophy, tracheostomy and acute respiratory failure; B) Stenotrophomonas malthophilia in MacConkey agar plate; C) Streptococcus pneumoniae in blood agar plate. Evidence of mucoidal colonies and characteristic production of alpha-hemolysis zones; D) Staphylococcus aureus in blood agar plate. Evidence of characteristic production of clear beta-hemolysis zones.

- Once chronic damage has established, bronchiectasis and atelectasis may appear, which favor the triggering of infectious exacerbations.
- The use of antiviral and antibacterial filters during mechanical ventilation is an indispensable safeguard for patients. In some cases, it may be necessary to sanitize the mechanical ventilator.
- Vaccinations play an important role in disease management for prevention. The 23-valent pneumococcal vaccine, *Haemophiles* vaccine, annual influenza vaccine and respiratory syncytial virus antibody prophylaxis for infants are strongly recommended.

Ethical consideration

None.

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Conflict of interest

The Authors declare no conflict of interest to disclose.

Author contributions

Conceptualization and preparation of the manuscript: NC, AA, A C, FS, AM, GF; data collection: AA, AC, AM, FS, MB, EP, PI data curation AM, PI, EP, AC, writing and editing NC, AA FS MB, PI, GF, revision of the manuscript NC, AA, AC, MB, PI, supervision NC, AA, FS, GF

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Impact of the COVID-19 pandemic on rehabilitation setting. Part 1: professionals' views on the changes in routine care provided by a rehabilitation centre for patients with muscle diseases

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The outbreak of COVID-19 has forced the health care system to undergo profound rearrangements in services and facilities, especially during the periods of lockdown. In this context, inpatient and outpatient services had to rethink and reorganize their activities to meet the needs of severely disabled patients, as those affected by Muscular Dystrophies (MDs).

We present the preliminary results of a survey aiming to explore the staff views on the changes in the care provided by the Gaetano Torre Rehabilitation Centre, and, the impact of these changes on professionals, patients and their families.

The survey was carried out using an open-ended questionnaire including six-items, on the practical and psychological aspects emerged during the pandemic in relation to the healthcare services provided by the Centre and to the patients/caregivers conditions. The participants, most of them physiotherapists, highlighted 169 aspects emerging in the pandemic, 48.5% referring to the resources used to cope with critical issues and 51.5% concerning the difficulties encountered. Emotional aspects prevailed on practical aspects both in resources (52.4 *vs* 47.6%) and in difficulties (57.5 *vs* 42.5%) categories. In particular, with regard to patients' resources, psychological benefits, despite the burden, were greater than practical ones (87 *vs* 13%), in the form of improved intra-family relationships, feeling more cared for, and satisfaction for the received care. As for the patients' relatives, the staff indicated more resources than difficulties (72.8 *vs* 17.2%). Among the former, 75% concerned the emotional sphere, such as the perception of having a point of reference even in such a difficult time.

Key words: pandemic, benefits, difficulties, muscle diseases, rehabilitation setting

Introduction

The outbreak of COVID-19 has forced the health care system to undergo profound rearrangements in services and facilities in Italy, especial-

ly during the first lockdown. In this context, inpatient and outpatient services had to rethink and reorganize their activities to meet the needs of severely disabled patients, as those affected by muscular dystrophies (MDs) [1].

MDs are a heterogeneous group of genetic disorders characterized by progressive wasting of muscle tissue and substitution with fibro-adipose tissue [2]. Age of onset and evolution range from early infantile to adult and late onset forms; loss of ambulation occurs in the first-early second decade in the more severe forms. Most of MDs are multisystemic disorders affecting heart, respiratory and endocrine system, bones, eye. Respiratory insufficiency and cardiac failure are the most frequent cause of death; in some MDs, patients may develop fatal arrhythmias with a high risk of sudden cardiac death. Beside specific drug treatment, motor and respiratory rehabilitation are the mean tools to delay the evolution of the diseases. The most severe MDs require a progressive family involvement in daily care leading to demanding burden [3]. However, psychological benefits related to caregiving are also reported [4].

The Italian Association of Myology has recently conducted an online survey among the affiliated neuromuscular centres, to assess changes in pharmacological therapies provision, outpatient clinical and instrumental services, support services and clinical trials provided to patients with MDs during the first lockdown [5]. On average, 40% of centres reduced outpatient clinical visits (44.5% in Northern Italy centres, 25% in Central Italy centres, and 50% in Southern Italy centres). A postponement of in-hospital therapies provision has been reported in about 20% of cases (23.4% in Northern, 13.0% in Central and 20% in Southern Italy). On average, 57% of centres suspended support services such as physiotherapy, nursing care and psychological support (66% in Northern, 43% in Central and 44% in Southern Italy). The most affected services (in 93% of the centres) were Rehabilitation's services and on-site outpatient visits.

Since May 2020, the gradual resumption of the health activities led to a change in the rehabilitation assistance procedures to guarantee the maximum safety from contagion to the staff, users and their relatives, through individual protection disposals (IPD), environment sanitation, and physical distances.

Here we present the results of a survey aiming to explore the staff views on the changes in the care provided by the centre, and, the impact of these changes on professionals, patients and their families.

Materials and methods

The survey was carried out, at one -year from the beginning of the pandemic, at the Gaetano Torre Centre (G. Torre) for Muscular Dystrophies, a rehabilitation centre, funded by Prof. Giovanni Nigro in 1977, and dedicated to patients with MDs, that operates within the framework of a regular agreement with the Northern Health District of Naples, Italy. The Centre provides a range of outpatient and at-home clinical and rehabilitative care to persons with MDs over their life span.

In the second part of June 2021, the G. Torre staff (N = 30) was invited to complete an anonymous, open-ended questionnaire including six-items, on the practical and psychological aspects emerged during the pandemic in relation to the healthcare services provided by the Centre and the patients/caregivers conditions. The study was approved by the Ethical Committee of ASL NA1 (Prot. 362 of 8/6/2021).

Results

Twenty-four professionals (80%) gave their informed consent and participated in the study. Of these, 79% were physiotherapists engaged in motor and respiratory rehabilitation. Altogether, the participants highlighted 169 aspects emerging in the pandemic. In particular, 48.5% referred to the resources used to cope with critical issues and 51.5% concerned the difficulties encountered. Within the resource category, 47.6% were practical and 52.4% were emotional aspects. Among the practical aspects, the use of IPD (41.0%) and a greater intra-team collaboration in the management of patients (12.8%) prevailed. Among the psychological aspects, the most frequently reported were the perception of a greater sense of protection/affective closeness towards users and family members (28.6%), associated with a sense of gratitude (14.3%) towards the staff.

As far as the difficulties category, 42.5% referred to practical aspects and 57.5% to emotional aspects. Among the practical difficulties, the most frequently reported were the users' reluctance to reach the Centre (13.5%) immediately after the lockdown, and the difficulties in reaching and interfacing with health districts (13.5%). The most frequently reported psychological difficulties were fear of contagion (44.0%) and patients' loneliness (14.0%).

Regarding the impact of the pandemic on staff working, more practical and psychological resources than difficulties (practical: 78.90 *vs* 21.10%; psychological: 76.90 *vs* 23.10%), emerged. In particular, the most emphasized practical resources were teamwork and the use of IPD provided by the centre, whereas the main psychological resources were a greater emotional contact with patients and the ability to reassure them about the fear of contagion.

As far as the difficulties, the participants reported feelings of uncertainty/precariousness in their practices,

related to the need of adhering quickly to the ever-changing regional and national directives. Moreover, the staff reported that the difficulties encountered by the patients were more psychological than practical (84 *vs* 16%), mainly fear of contagion and reduction of social contacts.

Regarding the patients' resources, the participants indicated more psychological than practical benefits (87 *vs* 13%), such as an improvement in intra-family relationships, feeling more cared for, and satisfaction for the received care.

As for the patients' relatives, the staff indicated more resources than difficulties (72.8 *vs* 17.2%). Among the former, 75% concerned the emotional sphere, such as the perception of having a point of reference even in such a difficult time. As for the difficulties, once again, those of an emotional nature prevailed (56.2 *vs* 42.8%), mainly fear of contagion for themselves and the loved ones.

Practical difficulties included contacts with the local health services, such as difficulties in interfacing with the offices, bureaucratic delays, and economic problems.

In line with the significance of the psychological aspects mentioned above, the ability of the G. Torre staff to reorganize services and respond to the new needs of patients during the COVID-19 pandemic emerges. In particular, the initiative of "a virtual coffee point" was appreciated, a weekly online appointment with the psychologist and other professionals during which the difficulties of the period and how to deal with them were discussed with patients and their families.

Limitations of the study

Although this study has many methodological weaknesses, it may provide useful information on the impact of a pandemic in the routine rehabilitation setting. In particular, the findings of this study highlight that, in spite of the difficulties related to COVID-19, healthcare staff, patients and caregivers were able to activate psychological and practical resources.

Future perspectives

We intend to extend this study to the perception of patients and their caregivers on the validity of the changes implemented by the G. Torre Centre during the pandemic. Their view's evaluation will be important in dealing with other events with a potential impact on the daily management of disability.

Ethical consideration

The study was approved by the Ethical Committee of ASL NA1 (Prot. 362 of 8/6/2021).

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Conflict of interest

The Authors declare no competing interests.

Author contributions

G.C.: acquisition and analysis of questionnaires.

MG.E., C.G. and V.T.: acquisition and analysis of questionnaires.

L.M.: study design, writing and critical revision of the manuscript.

L.P.: study concept and design, writing and critical revision of the manuscript.

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CASE REPORT

Non-invasive mechanical ventilation as an alternative respiratory support during gastrostomy tube placement, in a patient with Duchenne muscular dystrophy, 24/24 hours ventilation dependent

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Patients with Duchenne muscular dystrophy may benefit from gastrostomy tube feeding due to progressive dysphagia and malnutrition. However, due to concomitant pathologies, they are often at high risk for anesthesiologic complications. We describe how the non-invasive mechanical ventilation has been an alternative successful respiratory support option during the gastrostomy tube placement in a patient with Duchenne muscular dystrophy, on continuous NIV treatment. This report confirms how the use of NIV can support alveolar ventilation, before, during and after mini-invasive procedures, and prevent respiratory complications.

Key words: Duchenne muscular dystrophy, percutaneous endoscopic gastrostomy, NIV treatment

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Introduction

Patients with Duchenne muscular dystrophy (DMD) may have complications such as dysphagia and progressive weight loss during the end-stages of the disease. As a result, aspiration pneumonia, malnutrition up to severe cachexia, may arise [1]. Often at this stage, patients are also dependent on non-invasive mechanical ventilation (NIV) due to severe muscle weakness. In these conditions percutaneous endoscopic gastrostomy (PEG) becomes necessary to improve the nutritional status of patients. Unfortunately, patients and their families accept PEG only late, when oral feeding becomes impossible due to dependence on continuous NIV.

In patients with neuromuscular pathologies, and especially in those suffering from severe DMD undergoing invasive procedures, it is desirable to minimize sedation to preserve the respiratory function, often already compromised. It should be remembered that anesthetic procedures in such patients become very complex due to difficulty in emergency intubation, and if intubated, the high risk of weaning failure due to invasive venti-

lation [2]. Tracheostomy may be required and/or serious complications such as ventilator-associated pneumonia may occur.

To our knowledge, there are only few reports in literature on the use of NIV in patients with DMD during PEG [3-5].

We describe a 28-year-old patient with Duchenne muscular dystrophy in 24/24h non-invasive mechanical ventilation with a nasal mask, undergoing PEG with the support of NIV.

Case report

Patient 28-year-old, affected by Duchenne muscular dystrophy, chronic respiratory failure and dilated cardiomyopathy (ejection fraction 40%), in treatment with ACE-inhibitors, warfarin, deflazacort, anti-oxidants and micro-nutrients. Despite supplementary nutritional support, the patient continued to lose weight due to the difficulty in eating orally. He was therefore offered to place a PEG, which he categorically refused. During the last 14 months his weight has further reduced from 48 to 35 kg, so much so that the patient himself was finally convinced to ask for PEG. At the time of the admission at our Unit, the serum level of prealbumin was 9.5 mg/dl (normal, 16.7-29.6 mg/dl), indicating severe malnutrition, while forced vital capacity (FVC) was 180 ml (7% of predicted, based on arm-span height estimate). Prior to the procedure, warfarin was replaced with sub-cutaneous low molecular weight.

PEG placement

The anesthetic evaluation assessed the patient as a high-risk subject (ASA IV), with a high probability of tracheal intubation. The patient was sedated with midazolam, 2 mg before and 4 mg during the procedure, with 5' infusion rate.

The overall duration of the procedure was approximately 15 minutes. The patient was ventilated through the controlled assisted ventilation (CAV) mode with 450 ml tidal volume, and 14 back up respiratory rate. During the procedure the tidal volume was increased to 650 ml and the back up rate to 16, to compensate for the losses due to the placement of a mouthpiece for a few minutes to allow the passage of the gastroscope (Fig. 1), a greater alveolar recruitment, and the achievement of 95-96% stable peripheral saturation.

The following clinical parameters were monitored throughout the procedure: heart rate, blood pressure, electrocardiogram, and SpO2. Chest lift was also frequently monitored.

Respiratory support was supplemented with oxygen, 1-2 liters per minute, to avoid sudden desaturations. Tidal volume was titrated to achieve a good chest lift and air exchange, compensating for circuit losses and partial upper airway obstruction.

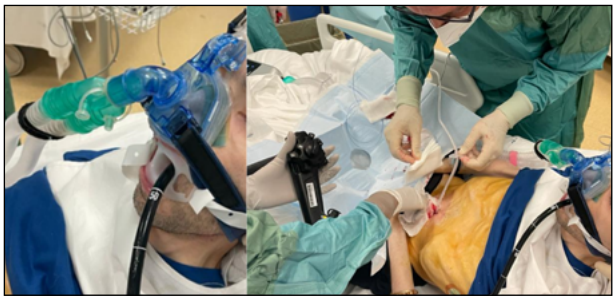

Figure 1. Patient during percutaneous gastrostomy tube placement.

The procedure was successfully completed. At the end of the procedure, the ventilatory parameters were progressively reduced until the initial parameters were restored; the patient continued usual NIV during the post-operative phase and transport to the room. The gastrostomy tube was used for feeding, after 24 hr.

Discussion

In end-stage Duchenne muscular dystrophy, a balanced nutritional approach is essential for patient care. However, in the phase of transition to wheelchair, overnutrition often occurs caused by reduced caloric needs associated with reduced physical activity and energy expenditure at rest [3] The excess caloric intake may also be due to the use of medication (steroids) with a consequent increase in appetite and/or compassion on the part of the parents, who tend to gratify the patient with food [6]. This results in an increased risk of obesity, dyslipidemia, hypertension, and often obstructive sleep apnea. As the disease progresses, loss of muscle strength and dysphagia are the main causes of malnutrition. Gastrointestinal problems (constipation, delayed gastric emptying, gastric reflux) may also arise, resulting in reduced food intake [6]. Prolonged meals and dependent eating are all consequences of muscle weakness and gastrointestinal dysfunction. The presence of respiratory inufficiency, constant in the advanced stages of the disease, further increases energy expenditure.

For these reasons, as respiratory failure progresses and weight loss begins, it is very important to evaluate the usefulness of nutritional support and PEG placement early. Over time, the patient's clinical condition may worsen, respiratory failure may evolve, and the patient may become dependent on NIV, making the endoscopic procedure more complex and life-threatening.

The case here reported is the first case in the litera-

ture describing support with NIV in a patient with DMD, chronic respiratory failure (FVC < 10%), dependent on NIV 24/24 per day.

A case of a patient with DMD and 17% FVC, in NIV, was previously described [3]. The procedure in that case was extremely complex and several attempts were made to settle the patient. The NIV had failed and an alternative method of ventilation was therefore used, manually ventilating the patient through an anesthesia bag connected via a short tube to the patient's NIV mask, with 100% oxygen bled into the circuit. In this way, the anesthesiologist, adjusted the volume of gas delivered with the anesthesia bag to maintain a good chest lift and air exchange.

From a practical standpoint, it is essential to recognize that there is no low-risk method of assisted ventilation for subjects with severe muscle weakness who require sedation for medical procedures.

It is therefore imperative that doctors of patients with severe DMD be aware of this. Furthermore, if a procedure requires sedation, the potential benefits, such as possible prolongation of survival and improved quality of life, and possible risks, such as emergency intubation, potential extubation failure, and the risk of tracheostomy should be carefully and equally evaluated [7].

The benefits of NIV in patients with DMD are recognized in terms of prevention of hospitalization, recovery of alveolar hypoventilation, treatment of acute or chronic secondary respiratory failure, weaning from oro-tracheal intubation, and last but not least increased survival.

The use of non-invasive mechanical ventilation in patients with pre-and post-operative support needs, anecdotally already reported [3-5] in literature, requires further studies to validate its use in extremely fragile patients, at high anesthetic risk.

Ethical consideration

None.

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None.

Conflict of interest

The Authors have no conflicts of interest to disclose.

Author contributions

Conceptualization and preparation of the manuscript: AA, GF; data collection: AA, RC, EDC, writing and editing AA GF, revision of the manuscript RC, EDC, supervision AA, GF.

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NEWS FROM AROUND THE WORLD

AIM

In the period between July and September 2021, four webinars, one for each "Macro Areas" representative of Northern, Central and Southern Italy were held organized by the regional coordinators of the Association with the support of the First Class Events Agency.

The webinars aimed at disseminating and discussing issues related to neuromuscular diseases with local doctors and sharing information that allow an early diagnostic suspicion and the correct sending of the patient to the Reference Centers; they took place on September 16, 2021 for 3 out of 4 Macro Areas: NORTH, Lombardia, Piemonte-Valle D'Aosta, Triveneto; CENTER-SOUTH, Basilicata, Campania, Lazio, Marche, Sardegna and SOUTH, Puglia, Sicilia, Calabria, while that of the macro area CENTER-NORTH (Toscana, Liguria, Emilia-Romagna e Umbria) took place on September 30th. All the webinars, individually MCE accredited, had a great success of participation (further information is available at https://www.aim-fad2021.it/).

Prof. Carmelo Rodolico
Secretary of Italian Association of Myology

MSM

Due to pandemics, the 14th Meeting of the Mediterranean Society of Myology (MSM) is moved to 2022. Proposals to organize and host the event are welcome.

WMS

The 26th WMS congress took place, as a virtual meeting between 20 and 24 September. The 5-day congress week has been an opportunity to catch up on the latest developments in neuromuscular diseases from around the world. Controversial debates, oral lectures and electronic poster presentations were planned through the virtual platform and a series of inspiring industry symposia on a dedicated day. The usual WMS 2021 Virtual Pre-Congress Teaching Course was held on the neuromuscular field. To learn more, please visit the congress website: *https://www.wms2021.com.*

FORTHCOMING MEETINGS

2021

September 15-17

17th Congress of the Italian Association of Cardiac Arrhythmias. Bologna, Italy. Information: website: *www.aiac.it*

September 17-19

260th ENMC Workshop. Congenital Myasthenic syndromes. Information: website: *https://www.enmc.org*

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 1-3

The 3rd ENMC workshop on Dystroglycan and the Dystroglycanopathies. Information: website: *https://www.enmc.org*

October 3-7

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

October 15-16

Mitochondrial Diseases Virtual Conference 2021. Information: website: *www.mitocon.it*

October 15-16

255th ENMC Workshop: Muscle imaging in idiopathic inflammatory myopathies. Information: website: *https://www.enmc.org*

October 19-23

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

October 29-31

261st ENMC Workshop: Management of safety issues arising following AAV gene therapy. Information: website: *https://www.enmc.org*

November 19-21

264th ENMC Workshop: Multi-system involvement in Spinal Muscular Atrophy. Information: website: *https://www.enmc.org*

December 10-12

253rd ENMC workshop. Skeletal muscle laminopathies – natural history and clinical trial readiness. Information: website: *https://www.enmc.org*

2022

January 28-30

254th ENMC Workshop: Formation of a European network to initiate a European data collection, along with development and sharing of treatment guidelines for adult SMA patients. Information: website: *https://www.enmc.org*

February 11-12

262nd ENMC Workshop: Standards of Care for the Dysferlinopathies. Information: website: *https://www.enmc.org*

February 13-17

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

March 25-27

258th ENMC Workshop: Leigh syndrome. Information: website: *https://www.enmc.org*

April 28-May 02

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

May 13-15

263rd ENMC Workshop: Focus on female carriers of dystrophinopathy: refining recommendations for prevention, diagnosis, surveillance and treatment. Information: website*: https://www.enmc.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. Name(s) of the author(s) in full, name(s) of institution(s) in the original language, address for correspondence with email address on the second page.
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