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REVIEW

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The European reference network for metabolic diseases (MetabERN) clinical pathway recommendations for Pompe disease (acid maltase deficiency, glycogen storage disease type II)

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Abstract

Clinical pathway recommendations (CPR) are based on existing guidelines and deliver a short overview on how to deal with a specific diagnosis, resulting therapy and follow-up. In this paper we propose a methodology for developing CPRs for Pompe disease, a metabolic myopathy caused by deficiency of lysosomal acid alpha-glucosidase. The CPR document was developed within the activities of the MetabERN, a non-profit European Reference Network for Metabolic Diseases established by the European Union. A working group was selected among members of the MetabERN lysosomal storage disease subnetwork, with specific expertise in the care of Pompe disease, and patient support group representatives. The working strategy was based on a systematic literature search to develop a database, followed by quality assessment of the studies selected from the literature, and by the development of the CPR document according to a matrix provided by MetabERN. Quality assessment of the literature and collection of citations was conducted according to the AGREE II criteria and Grading of Recommendations, Assessment, Development and Evaluation methodology. General aspects were addressed in the document, including pathophysiology, genetics, frequency, classification, manifestations and clinical approach, laboratory diagnosis and multidisciplinary evaluation, therapy and supportive measures, follow-up, monitoring, and pregnancy. The CPR document that was developed was intended to be a concise and easy-to-use tool for standardization of care for patients among the healthcare providers that are members of the network or are involved in the care for Pompe disease patients.

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Keywords Pompe disease, Glycogen storage disease (GSD) type II, Acid alpha-glucosidase deficiency, Acid maltase deficiency, Lysosomal storage disease

Introduction and scope of the paper

This article reports about the development of clinical pathway recommendations (CPRs) for Pompe disease (glycogen storage disease type II) by the lysosomal storage disease subnetwork (LSD-SNW) of MetabERN. MetabERN is a non-profit European Reference Network for Metabolic Diseases consisting of 97 nationally certified centers from 27 European Union (EU) Member States. The network was established by the EU in 2016 to facilitate access to the best available care in the Union and to address the needs of patients affected by inherited metabolic diseases. MetabERN covers different activities, divided into work packages, including the development of recommendations for the diagnosis and management of metabolic diseases.

The Pompe disease CPR document developed by the working group was intended to be a concise and easy-to-use tool for standardization of care for patients among the healthcare providers that are members of the network. The document was based on quality assessment and transparent procedures. The approach used to produce this document was based on literature survey, selection of articles that were deemed valuable and essential for Pompe disease care, quality assessment of the literature, and incorporation of information in a template provided by MetabERN.

In this article the document developed by the working group includes minor adaptations and adjustments according by the Journal's editorial requirements.

Methodology

For the development of CPRs a platform was set up on Google Drive and template matrices were made available by the general coordinators of the MetabERN guideline work package.

A working group was selected on a voluntary basis among members of the lysosomal storage disease subnetwork (LSD-SNW). The group was composed by experts from several European countries with specific expertise in the care of Pompe disease, including metabolic physicians, pediatricians, neurologists, child neurologists, endocrinologist, cardiologists, pneumologists, and by patient support group representatives. The work was conducted, according to the workflow indicated by the CPRs platform (Fig. 1), exploiting online resources for exchange of informative materials and correspondence, with periodic reports on advancements and discussions at MetabERN general board conventions or at MetabERN LSD-SNW meetings.

The working strategy was based on a systematic literature search to develop a database, followed by quality assessment of the literature, and by the development of the CPR document according to the matrices provided by MetabERN. An additional file shows the references list evaluated according to the grading system (see Additional file 1).

The literature review was performed in spring 2017 on PubMed, using the following search terms: ["Pompe disease", or "glycogenosis type II", or "acid maltase deficiency", or "acid alpha-glucosidase deficiency"] AND ["guidelines" or "consensus statements", or "reviews"]. No language or data filters were used. Existing guidelines, consensus clinical protocols, or any single published manuscripts with clear clinical relevance for the CPR development were included in the literature database until the end of guideline development process. Studies published in the timeframe 2000–2016 were included in the literature search. Further revisions of literature and updating of the references were performed at the end of 2021, at the end of 2022, and in May 2024, and again circulated for definitive approval.

For the quality assessment of existing guidelines and consensus the AGREE II were used. Whenever primary data were used (clinical trial, clinical research, basic research) the quality of the paper was assessed by the GRADE system. The level of evidence of individual studies was rated from 4 (lowest) to 1 + + (highest). The information about selection of published studies and quality assessment is provided as supplementary material S1.

A draft document was circulated among all members of the LSD-SNW (healthcare providers and patients' association representatives) for evaluation in summer 2019. The document was further discussed at a satellite MetabERN session within the 2019 Annual Meeting of the Society for the Study of Inborn Errors of Metabolism in Rotterdam, the Netherlands, and was revised according to suggestions.

The clinical practice recommendations for Pompe disease

Pathophysiology

Pompe disease, or glycogen storage disease type II, is a lysosomal storage disorder and a metabolic myopathy

caused by deficiency of lysosomal acid alpha-glucosidase (GAA, also referred to as acid maltase).

GAA hydrolyzes the 1,4 and 1,6 glucosidic bonds of glycogen. This function is required for the breakdown of glycogen into glucose in the lysosomes. Biallelic *GAA* gene pathogenic variants result into absent or deficient activity of the GAA enzyme, which leads to the accumulation of glycogen in the lysosomes of several cell types and tissues, particularly cardiac, skeletal, and smooth muscle cells. In addition to glycogen storage, a typical secondary feature of Pompe disease pathology is the accumulation of autophagic material in muscle fibers [1, 2]. Normal intracellular metabolism becomes disturbed, including mitochondrial function with oxidative stress activation [3, 4], and/or cytoplasmic glycogen metabolism impairment. Disruption of lysosomes by itself, with release of proteolytic enzymes into the cytoplasm, may also play a role in the disease pathophysiology [5].

Genetics

Pompe disease is inherited in an autosomal recessive manner and is due to biallelic pathogenic variants in the *GAA* gene. The *GAA* gene is localized on chromosome 17 at the 17q25.2–q25.3 locus and contains 20 exons including the 19 coding ones [6, 7].

There is a high allelic heterogeneity/diversity: missense, nonsense, splice-site variants, partial deletions, and insertions have been reported to be causative of the disease. As of December 2020, Pompe disease *GAA* variant database at the www.pompecenter.nl website included 648 disease-associated variants, 26 variants from newborn screening, and 237 variants with unknown severity [8]. The database is also directly accessible via www.pompevariantdatabase.nl.

The most common pathogenic variant is the intronic mutation c.-32-13T > G (found at the heterozygous state in approximately 80–90% of adult patients and 50% of children) and associated with a slowly progressive course of disease [7]. This splice site mutation results into variable levels of residual activity (up to 20% of normal) and mostly combines in adults with a very severe pathogenic variant on the second allele [8]. Genetic modifiers explaining the broad clinical variability in patients carrying the c.-32-13T > G variant have been identified. For example, the silent, *cis*-acting c.510C > T variant reduces leaky wild type splicing and thereby residual GAA activity [9]. Patients homozygous for the c.-32-13T > G variant rarely express symptoms [10].

Other relatively prevalent mutations show typical ethnical distribution, such as the p.Glu176Argfs*45 (often referred to as c.525del), p.Gly828_Asn882del, and p.Gly309Arg in the Dutch population, p.Arg854* in Africa, p.Asp645Glu in Taiwan, p.Ser529Val, p.Arg672*, p.Arg600Cys in Japan, p.Trp746Cys in China, p.Gly828_Asn882del in Canada [11, 12].

GAA variants associated pseudo-deficiency of GAA have been described, for example, the variants p.Gly576Ser and p.Glu689Lys, often present *in cis* [13]. Patients homozygous for these mutations have low levels of GAA activity but do not develop clinical signs of the disease.

Most GAA variants lead to production of some (active or inactive) GAA protein. Patients expressing these variants are called CRIM (Cross Reactive Immune Material) positive. About one third of infantile Pompe disease patients, depending on their genotype, do not express any GAA protein and are defined CRIM negative. For example, the mutation p.Glu176Argfs*45 is a CRIM negative *GAA* gene variant. CRIM negative patients have a higher risk of producing antibodies against recombinant

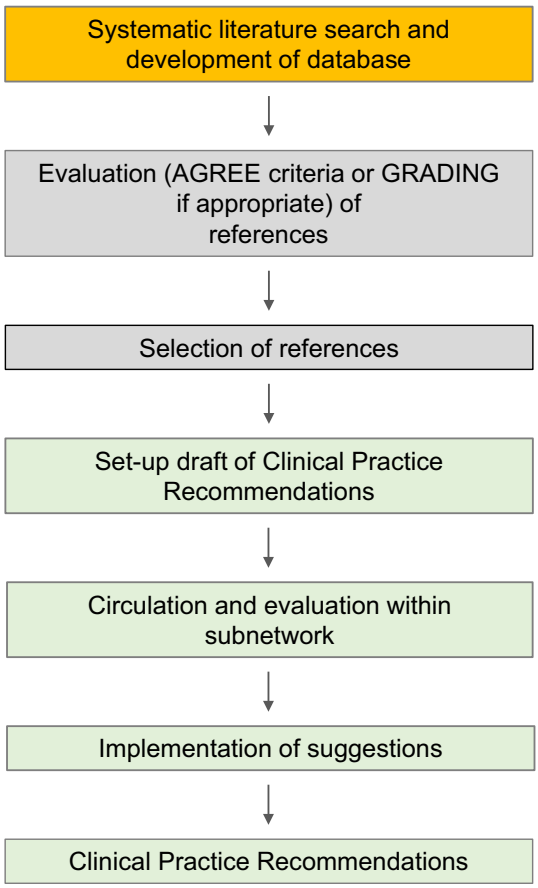

Fig. 1 The working strategy for the development of CPRs for Pompe disease. The process was based on a systematic literature search to develop a database, followed by quality assessment of the literature, discussion within the working group, and by the development of the CPR document according to the matrices provided by MetabERN

enzymes when treated with enzyme replacement therapy (ERT) [14, 15].

Frequency

The estimated incidence of Pompe disease has been reported to vary between 1:40,000 and 1:146,000 [7, 16]. Newborn screening programs implemented in some countries have led to reports of figures between 1:8684 and 1:23,596 [17–19]. Recent studies have revealed a similar incidence in some European countries [20, 21].

The incidence rate is higher in specific countries and ethnic groups, such as Taiwan (1 in 17,000) [19] and French Guiana (1 in 2000) [22].

Classification

Traditionally, different clinical forms of the disease, outlined in Table 1, have been described in the literature depending on age at onset and severity:

1. Infantile-onset Pompe disease.
2. Late-onset Pompe disease or non-classic Pompe disease (childhood, juvenile, adult-onset).

However, the clinical spectrum of Pompe disease is broad and continuous, and symptoms can manifest at any age from infancy to late adulthood.

Skeletal muscle weakness dominates the clinical picture and affects both respiration (including the diaphragm) and mobility. The course of the condition is variable in older children and adults, but it remains relentlessly progressive, resulting in significant morbidity and often in premature mortality. Respiratory failure is the major cause of death [5].

Manifestations and clinical approach

1. Infantile-onset Pompe disease (IOPD).

The classic infantile form is the best delineated form of Pompe disease and at the most severe end of the clinical spectrum. The disease may be present at birth or within the first few months of life with hypotonia, feeding difficulties or respiratory problems. A hypertrophic cardiomyopathy is characteristically present and may already develop in utero. Without therapy the disease progresses fast, and patients do not achieve major motor milestones like sitting, standing or walking and die within the first year of life of cardiorespiratory failure.

Atypical infantile Pompe disease

Rarely patients with infantile Pompe disease present later (beyond 6 months of age). This atypical form of infantile Pompe disease should be suspected in infants that present within the first two years of life with generalized hypotonia, cardiac hypertrophy, mild liver enlargement, recurrent respiratory infections (due to cardiac disease and hypotonia/weakness of respiratory muscles), macroglossia. Cardiac hypertrophy is mostly less prominent than in the classic form. Development of motor milestones is delayed. Some of these children achieve the ability to sit or stand without therapy.

Together the classic infantile form and the atypical infantile form are frequently named infantile onset Pompe disease. Since patients with the atypical form have a better prognosis, it is important to make the differentiation.

ERT has changed the prospects of patients with infantile Pompe disease dramatically. Overall survival has increased, particularly in children with high-dosage treatment regimens (see also section "Therapy"). Many children learn to walk. However, children are not cured. A new phenotype has emerged in long-term surviving patients.

2. Late-onset Pompe disease (LOPD)

The phenotype of late-onset Pompe disease is extremely broad and is generally associated with slower disease progression [23, 24]. Patients may present at any age, but mostly after the age of 1 year during childhood or adulthood. They usually present with proximal (limb girdle) myopathy leading to progressive motor disability (more closely related to disease duration than to the age of the patient), with waddling gait, mostly without cardiac involvement. Respiratory muscle involvement may occur early in the course of the disease. Due to the involvement of diaphragm, pulmonary function in supine position may be more affected than in upright position. Respiratory involvement can be accompanied by headache, somnolence, and/or dyspnea. Respiratory and motor involvement do not necessarily have to progress at the same rate. Rarely patients present with respiratory failure.

Smooth muscles may be involved with, as an example, dolichoectasia of cerebral vessels, but only a very few cases have been described in which an aneurysm has led to intracerebral hemorrhage.

Mild myopathic features, creatine kinase (CK) levels < 1000 U/L in adults and up to 2500 IU/l in childhood

Table 1 Pompe disease spectrum of manifestations

	infantile-onset	infantile-onset long-term surviving	late-onset
Age at onset	Onset <6 (-12) months	Longest survivors 24 years	Any age during childhood and adulthood
Heart	Hypertrophic cardiomyopathy; ECG: short PR interval; high QRS complex voltage; arrhythmias; cardiac failure	Cardiomyopathy responds well to treatment; arrhythmias may occur, WPW, supra-ventricular tachicardia	
Pulmonary function	Ventilation may be required; recurrent respiratory infections; repiratory failure	Nighttime ventilation may be required due to diaphragmatic weakness; recurrent respiratory infections	Involvement of the diaphragm; respiratory failure and sleep disordered breathing
Skeletal muscle	Severe and progressive hypotonia (floppy baby)	Distal myopathy; no heal strike when walking; residual muscle weakness.	Progressive proximal myopathy; muscle soreness/cramps; muscle atrophy; Gower's sign; hypertrophic calves (in some); scapulae alatae/scapular winging (33%); difficulties to lift the head when lying on the back (weak neck flexors, especially in children); lumbar lordosis (66%), scoliosis (33%).
CNS involvement	No clinical signs of CNS involvement at presentation; neurological signs appear later in the first years	Mental development normal or mildly delayed until the age of 6-10 years; thereafter (variable) decline in most children especially in processing speed. White matter abnormalities (first noted around 2 years of age). Epilepsy may occur in some.	
Motor development	Motor delay or regression	Many children achieve major motor milestones like walking; Motor delay or regression from age of 4-6 years	Delayed motor development (in some); Normal in most Many need walking aids and become wheelchair dependent at some point
Other	Hepatomegaly (moderate) Macroglossia Conductive hearing loss	Speech problems (nasopharyngeal incompetence). earing loss; refractive errors (myopia and astigmatism).	Fatigue Hepatomegaly (rare) Macroglossia (rare) Ptosis (frequently asymmetrical) – 22% Hypotonia of facial and tongue muscles (Myopathic face) Bulbar muscle weakness (28%)- Dysarthria Diarrhea - Gastrointestinal (GI) discomfort Pelvic muscle weakness may result in urinary and fecal incontinence Bone involvement with the risk of osteopenia/osteoporosis (potentially secondary to impaired mobility) Kyphoscoliosis (myopathy) Vascular involvement [Intracranial dolichoectasias may occur (anterior and vertebrobasilar circulation) and aortic aneurysms described in some patient – rarely lead to symptoms]
Laboratory	Increased CK, AST, ALT, LDH levels		
	Increased glucose tetrasaccharide (GLC4); increased Brain Natriuretic Peptide (BNP) or pro-BNP; increased neurofilament light chain		

onset patients and proximal limb girdle weakness and/or axial muscle weakness with or without reduced pulmonary function, in particular when in supine position should be considered as red flags for LOPD patients [25].

Diagnosis

Newborn screening

Newborn screening (NBS) for Pompe disease is possible by measuring GAA activity in dried blood spots with

different methods (tandem-mass spectrometry, fluorometry, microfluidics) [17–21, 26]. Newborn screening is essential for timely identification and treatment of patients with the infantile-onset forms of the disease.

Targeted next generation sequencing (NGS) could provide additional information and confirmation of the diagnosis for people identified by biochemical screening [27].

However, some limitations of the newborn screening should be considered. First, the assay in dried blood spots is only a screening test and is not sufficient for definitive diagnosis. Second, the NBS screening in its current form cannot discern IOPD from LOPD. LOPD patients are thereby patients in waiting requiring long term follow-up and monitoring which may create uncertainty and a psychological burden for families [28, 29].

NBS programs are already active in several countries (for example, in the US, Taiwan, Japan, some Italian regions) [19, 20, 27]. Pompe disease was added to the US Recommended Universal Screening Panel (RUSP) in 2015 [30].

GAA enzyme assay

A GAA enzyme assay in dried blood spot assay can be used as a first line test. However, this test is not sufficient for a definitive diagnosis. The diagnosis of Pompe disease should be confirmed by GAA enzyme assay in at least one of the following: peripheral leukocytes/lymphocytes, cultured fibroblasts from skin biopsy, muscle biopsy. Common biochemical assays are based on the use of the artificial fluorogenic substrate 4-methylumbelliferyl-α-D glucopyranoside (4MUG) [13]. The discovery that acarbose is a selective inhibitor of maltase glucoamylase allows acid alpha-glucosidase to be selectively assayed in white blood cells and dried blood spots [31].

The possibility of GAA pseudo deficiency should be considered for the interpretation of the GAA biochemical assay (see section "Genetics") [32]. The use of glycogen as natural substrate enhances the resolution between affected and unaffected; however, the GAA2 pseudo deficiency that occurs in the Caucasian population, can be excluded using 4MUG rather than glycogen [13].

GAA residual enzyme activity in general correlates with phenotype severity, with the lowest activities (< 1%) found in classic infantile patients, and activities from 2 to 40% in late-onset attenuated phenotypes [5].

Molecular analysis of the GAA gene

The molecular analysis of the GAA gene should follow the enzyme assay. This test is useful for further diagnostic confirmation and is necessary for the genetic counseling. Variant classification should follow the American College of Medical Genetics and genomics and Association for Molecular Pathology (ACMG-AMP) system of variant classification which includes 5 classes: benign, likely benign, variant of unknown significance (VUS), likely pathogenic, and pathogenic (class 5 providing ultimate proof of pathogenicity, see for guidance www.pompevariantdatabase.nl). In addition, considering current knowledge about genotype–phenotype correlations, molecular analysis of the GAA gene may provide information about prognosis [7, 33].

The combination of a pathological GAA assay and a genetic confirmation represents the gold standard for Pompe disease diagnosis. This approach is supported by expert consensus statements published in the literature [34, 35], with a moderate-high level of evidence.

Recently, NGS approaches have been exploited in cohorts of patients with skeletal muscle diseases and limb-girdle muscle dystrophies and have allowed for identification of misdiagnosed Pompe disease patients [36].

When clinical suspicion is strong and standard procedures are insufficient, additional molecular methods may be required to validate the diagnosis of Pompe disease, such as a generic splice assay (consisting of exon-flanking RT-PCR and exon-internal RT-qPCR), MLPA, minigene analysis, SNP array analysis, and targeted Sanger sequencing [37].

Complementary laboratory tests

Routine blood chemistry usually shows increased serum levels of AST, ALT, CK, LDH.

A rapid and simple complementary test to identify affected subjects is based on the detection in peripheral blood smears of PAS-positive vacuoles in lymphocytes [38].

In patients with infantile Pompe disease it is important to test for cross-reacting immunologic material (CRIM) status of patients through a Western blot analysis or DNA analysis. Studies in multiple cohorts of patients support the concept that CRIM status may be informative as a prognostic factor and as a predictive element of response to ERT since CRIM negative patients are more likely to develop antibodies against GAA [14, 15].

Analysis of some biomarkers, when available, may be performed, for example the brain natriuretic peptide (BNP) or pro-BNP, reflecting improved cardiac function [39]; the urinary glucose tetrasaccharide (Glc4) [40]; specific skeletal muscle-enriched microRNAs [41, 42]; neurofilament light chain [43, 44].

Multidisciplinary evaluations at diagnosis

Clinical multidisciplinary evaluations at the time of diagnosis or as an initial assessment should include:

For infants with classical IOPD (see also Table 2):
General

- Physical examination.
- Growth parameters.

Neuromuscular evaluation

- Motor and functional assessments compatibly with patients' clinical conditions, age and participation.

Neurodevelopmental assessment (specifically in infantile patients)

- Neuropsychological evaluation and developmental tests (as appropriate for age).

Cardiology

- Chest X-ray.
- ECG.
- Echocardiogram—cardiac ultrasound scan (to evaluate hypertrophic cardiomyopathy).
- 24-h ECG.

Pneumology and respiratory function tests

- Pulse oximetry.
- Polysomnography.
- Assessment of need for ventilatory support by home ventilation experts (if applicable).

Gastrointestinal and nutritional evaluation

- Video fluoroscopic swallowing assessment and evaluation for gastro-esophageal reflux to guide management of feeding (oral/gavage feeding).
- Liver ultrasound scan.
- Nutritional status and nutrient (protein) intake.

Radiology and imaging

- Chest radiography in infants will show an enlarged heart in infants and possible skeletal/spine deformities.

Auditory function

- Hearing tests including otoacoustic emissions, tympanometry, and brain auditory evoked potentials (ABR/BAEP).

Ophthalmological evaluation

- Visual acuity test. Myopia frequently occurs in patients with the classic infantile form.
- Orthoptic evaluation.

Language, speech, and oromotor function

- Assessment batteries for speech intelligibility, disordered articulation, and hypernasality.

For patients with LOPD (see also Table 3)
General

- Physical examination.
- Growth parameters.

Neuromuscular evaluation

- Motor and functional assessments. As LOPD patients may present at any age, depending on their age and level of participation: 6-min walking test (6-MWT) (from the age of 2), Muscular force by Medical Research Council (MMT-MRC) (from the age of 5), timed tests, hand-held dynamometry (from the age of ten), patient-reported outcome measures [39].
- Needle electromyography (EMG). EMG and peripheral nerve conduction studies are optional and may be considered at diagnosis as a supportive element.
- Muscle biopsy (not needed when other biochemical tests are conclusive for the diagnosis).

Cardiology

- ECG.
- Echocardiogram—cardiac ultrasound scan.
- Twenty four-hour ambulatory ECG.

Pneumology and respiratory function tests

- Pulse oximetry.
- Spirometry: forced vital capacity (FVC) sitting; FVC supine; Maximun Inspiratory Pressure and Maximum Expiratory Pressure (MIP/MEP) (from the age of 6).
- Polysomnography.
- Assessment of need for ventilatory support by home ventilation experts (if applicable).

Table 2 Infantile onset Pompe disease—follow-up exams and investigations

Last evaluated (Date)	Basic investigations																
								Cardiology			Neuromuscular evaluation			Radiology			
	History and status	Vital parameters, RR, weight, height, BMI, abdominal circumference	Enzyme activity	Genetics	Metabolic Laboratory	Antibody titer	Routine laboratory	Chest X-ray	ECG, echocardiogram	24 h ambulatory ECG	MMT-MRC(1)	6-MWT(1)	timed test	Lung MRI or chest CT or B-mode ultrasound diaphragm	Skeletal muscle MRI	Cardiac MRI	Brain MRI
First presentation	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	
3 Mo	X	X								X		X	X				
6 Mo	X	X				X	X				X	X	X				
9 Mo	X	X								X		X	X				
12 Mo	X	X			X		X	X(2)			X	X	X	X(3)			
Annual investigations	X	X				X	X	X				X	X	X			
Each 2nd year																	X(1)
Each 3rd year										X					X(3)		
Each 5th year																	
If needed								X	X	X				X	X		

Last evaluated (Date)	Basic investigations												Nice to have		
	Gastroenterology			Pneumology					Ophthalmological evaluation	Language, speech, and oromotor function	DEXA scan				
	Videofluoroscopic swallowing assessment	Liver ultrasound	Nutritional status	Pulse oxymetry	FVC sitting/supine (1)	MIP/MEP (1)	Polysomnography	Hearing tests including otacoustic emission tympanometry				Cognitive assessment/psych	Skeletal x-ray	
First presentation	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3 Mo				X										
6 Mo			X	X										

Table 2 (continued)

Last evaluated (Date)	Basic investigations											Nice to have	
	Gastroenterology			Pneumology									
	Videofluoroscopic swallowing assessment	Liver ultrasound	Nutritional status	Pulse oxymetry	FVC sitting/supine (1)	MIP/MEP (1)	Polysomnography	Hearing tests including otacoustic emission tympanometry	Ophthalmological evaluation	Language, speech, and oromotor function	DEXA scan	Cognitive assessment/psych	Skeletal x-ray
9 Mo				X									
12 Mo	X(3)			X	X		X	X				X	
Annual investigations	X(3)				X	X		X	X	X	X		
Each 2nd year		X										X	
Each 3rd year													
Each 5th year												X	X (4)
If needed	X			X									X

(1) Compatibly with patients' clinical conditions, age and participation

(2) More frequently in the presence of HCMP

(3) More frequent if required, depending on the patient's condition

(4) More frequent if required (eg spine deformities)

Table 3 Late onset Pompe disease: follow-up exams and investigations

Last evaluated (Date)	Basic investigations							Cardiology			Neuromuscular evaluation					Radiology		
	history and status	Vital parameters, RR, weight, height, BMI, abdominal circumference	Enzyme activity	Genetics	Metabolic Laboratory	Antibody titer	Routine laboratory	Chest X-ray	ECG, echocardiogram	24 h ambulatory ECG	MMT-MRC	6-MWT	Hand-held dynamometry	Timed test	Patient-reported outcome measures	Lung MRI or chest CT or B-mode ultrasound diaphragm	Skeletal muscle MRI	Cardiac MRI
First presentation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3 Mo																		
6 Mo	X	X				X	X				X	X	X	X	X			
9 Mo																		
12 Mo	X	X			X		X	X(1)			X	X	X	X	X	X(1)		
annual investigations		X			X	X	X				X	X	X	X	X			
each 2nd year																		
each 3rd year										X							X(2)	
each 5th year																		
if needed								X	X	X						X	X	

Last evaluated (Date)	Basic investigations											Nice to have		
	Gastroenterology			Pneumology										
	Videofluoroscopic swallowing assessment	Liver ultrasound	Nutritional status	Pulse oxymetry	FVC sitting/supine	MIP/MEP	Polysomnography	Hearing tests including otacoustic emission tympanometry	Language, speech, and oromotor function	DEXA scan	Cognitive assessment/psych	Needle elcetromyography (EP)
First presentation	X	X	X	X	X	X	X	X	X	X	X	X		
3 Mo														
6 Mo			X											
9 Mo														
12 Mo	X(1)						X	X	X		X			
annual investigations	X(1)			X(1)	X		X	X	X					
each 2nd year		X									X			
each 3rd year														
each 5th year											X			

Table 3 (continued)

Last evaluated (Date)	Basic investigations									Nice to have		
	Gastroenterology			Pneumology								
	Videofluoroscopic swallowing assessment	Liver ultrasound	Nutritional status	Pulse oxymetry	FVC sitting/ supine	MIP/MEP	Polysomnography	Hearing tests including otacoustic emission tympanometry	Language, speech, and oromotor function	DEXA scan	Cognitive assessment/ psych	Needle elcetromyography (EP)
if needed	X			X								

(1) More frequent depending on the patient's condition

(2) More frequent if required (eg spine deformities)

Gastrointestinal and nutritional evaluation

- Video fluoroscopic swallowing assessment and evaluation for gastro-esophageal reflux to guide management of feeding (oral/gavage feeding).
- Liver ultrasound scan.
- Nutritional status and nutrient (protein) intake.

Auditory function

- Hearing tests including otoacoustic emissions, tympanometry, and auditory evoked potentials (ABR/BAEP).

Language, speech, and oromotor function

- Assessment batteries for speech intelligibility, disordered articulation, and hypernasality.

Ophthalmological evaluation

- Visual acuity test.
- Orthoptic evaluation.

Others

- Psychological evaluation.
- Quality of life scales.

Radiology and imaging

- Dual-energy X-ray absorptiometry (DEXA) scan (to screen for osteopenia/osteoporosis) in adult patients.
- Skeletal X-ray in the presence of skeletal dysmorphisms.

Additional evaluations for both IOPD and LOPD

There are several additional imaging techniques that may be available in centers with expertise in the management of Pompe disease and may be advisable to perform both in IOPD and LOPD patients. Even though these tests may be of help in the assessment and evaluation of patient clinical conditions, they require specific experience and skills, and should not be considered as routine or indispensable procedures. These include:

- B-mode ultrasound to assess diaphragm thickness and search for diaphragm paralysis and computed tomography (CT) scan for evaluation of lungs and diaphragm thickness.
- Magnetic Resonance Imaging (MRI). If compatible with patients' conditions (the supine position might be associated with aggravated respiratory failure) and with the need for sedation, brain MRI may provide useful information on:
- Respiratory muscles, position, and thickness of the diaphragm [45].
- Skeletal muscle trophism and fatty degeneration. Whole-body MRI protocols are more inclusive than standard MRI protocols focusing on specific anatomical regions (e.g., paraspinal muscles, tongues, pelvis, thigh), enabling evaluation of relevant muscle groups beyond the pelvis and proximal lower extremities [46].
- Brain involvement (in infants compatibly with patient conditions). Recent evidence indicates that classic infantile patients may show white matter abnormalities [47]. So far, they have not been encountered in patients with the atypical infantile form. As these manifestations are not present until later in life, a brain MRI may not be required at the first assessment.

In LOPD patients cerebrovascular manifestations (e.g., aneurysms, vertebrobasilar dolichoectasia, dilatative arteriopathy) have been reported [48].

For most of the basic evaluations there is sufficient support and good quality evidence in the selected literature. The level of agreement on their importance for an accurate assessment of patients' status is high.

For additional evaluations the indications are somehow less stringent, probably because of a lower number of studies or because some aspects of the disease have been identified only in relatively recent years (for example central nervous system involvement in IOPD patients); thus, the level of evidence in the literature can be assessed as moderate-high.

Differential diagnosis

Depending on the clinical form, differential diagnosis with other disease entities should be considered (Table 4).

Therapy

Therapeutic goals

The therapeutic goals in Pompe disease are:

Infants

Table 4 Differential diagnosis

Late-onset patients	
Muscular dystrophies	Becker muscular dystrophy Limb-girdle muscular dystrophies Scapulo-peroneal muscular atrophy Rigid spine syndrome
Genetic metabolic Diseases	Glycogen storage diseases (debrancher deficiency, branching enzyme deficiency, myophosphorylase deficiency, phosphofructokinase deficiency) Danon disease Mitochondrial disorders (respiratory chain disorders, beta-oxidation defects)
Inflammatory myopathies	Polymyositis
Infantile-onset patients and juveniles	
Spinal muscular atrophy	Acute Werdnig-Hoffman disease
Muscular dystrophies	Congenital muscular dystrophies (Duchenne/Becker, Emery Dreyfuss, limb-girdle)
Congenital myopathies	Nemaline myopathy, fiber type disproportion, central core myopathy
Inborn metabolic Diseases	Glycogen storage diseases Mitochondrial disorders Peroxisomal disorders Congenital defects of glycosylation (CDG) Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency
Congenital cardiac Diseases	Idiopathic hypertrophic cardiomyopathy Myocarditis Endocardial fibroelastosis
Lysosomal storage Diseases	Danon disease
Other	Hypothyroidism

1. Improving survival.
2. Improving or normalizing cardiorespiratory function.
3. Improving or preserving normal motor skill acquisitions.
4. Normalizing growth.
5. Preventing need for ventilator support.

Late-onset patients

1. Reducing or stabilizing musculoskeletal damage in symptomatic patients.
2. Improving or stabilizing respiratory function.
3. Improving the nutritional state of the patient.
4. Preventing skeletal dysmorphisms (particularly kyphoscoliosis).
5. Improving quality of life.

Enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA). (Table 5).

The rhGAA preparation Alglucosidase alfa was approved for the treatment of Pompe disease in 2006 and most of the experience gathered on the efficacy of ERT in Pompe disease has been obtained with this preparation. Alglucosidase alfa has been shown to be effective in improving or stabilizing the disease course both in infantile-onset and in late-onset patients [49–54]. The level of evidence on the effects of ERT both in infantile-onset and late-onset Pompe disease patients is based on long term, high-quality clinical studies in large numbers of patients. The level of evidence is high.

Two other rhGAA preparations, both enriched in their mannose-6-phosphate content and with improved muscle-targeting properties, were granted approval in recent years [55, 56]. Avalglucosidase alfa was approved by Food and Drug Administration (FDA) in 2021 and by European Medicines Agency (EMA) in 2022 for the treatment of late-onset Pompe disease.

Cipaglucosidase received approval by EMA in 2023, also for the treatment of late-onset patients and in the US for ERT experienced patients to be switched from Myozyme to Cipalglucosidase. [57] Each of these preparations were evaluated in large phase 3 studies.

Dose The licensed dose of Alglucosidase alfa is 20 mg/kg body weight, every other week, by intravenous infusion. Published studies have shown that higher rhGAA doses (from 20 mg/kg every other week to 40 mg/kg/week) may be clinically appropriate and safe in infantile-onset patients, improving gross motor outcomes, pulmonary function measures, and biochemical markers [50–53]. Further, a high-dose regimen of 40 mg/kg week

Table 5 Enzyme replacement therapy for Pompe disease

Recombinant human GAA formulation	Licensed dose	Note	Efficacy
Alglucosidase alfa	20 mg/kg/eow	Dose may be increased up to 40 mg/kg/eow or 40 mg/kg/w in patients with classic infantile and in late onset patients showing a suboptimal response, plateau, or clinical decline	Approved in 2006. Since then, a large number of studies on the efficacy of alglucosidase alfa has been published in infantile-onset and in late-onset Pompe disease patients Infantile-onset patients: Long-term alglucosidase alfa treatment substantially improves cardiomyopathy, markedly extends survival and ventilation-free survival late-onset patients: alglucosidase alfa treatment improves motor (6-min-walk test, 6-MWT) and respiratory function (forced vital capacity, FVC). Little or no difference in quality-of-life physical component score
Avalglucosidase alfa	20 mg/kg/eow		Approved in 2021. Still limited evidence based on Avalglucosidase alfa versus alglucosidase alfa studies Avalglucosidase alfa probably improves 6-MWT compared to alglucosidase alfa. Avalglucosidase alfa probably makes little or no difference to % predicted FVC compared to alglucosidase alfa For infantile-onset patients who experience lack of improvement or insufficient response a dose increase to 40 mg/kg/eow may be considered
Cipaglucosidase	20 mg/kg/eow	Approved in association with Miglustat	Compared to alglucosidase alfa plus placebo, cipaglucosidase alfa plus miglustat probably improves % predicted FVC compared to alglucosidase alfa plus placebo Compared to alglucosidase alfa plus placebo, Cipaglucosidase alfa plus miglustat may make little or no difference to: 6-MWT distance; quality of life scores for physical function and fatigue

Sources of data on efficacy:

Dalmia S, Sharma R, Ramaswami U, Hughes D, Jahnke N, Cole D, Smith S, Remmington T. Enzyme replacement therapy for late-onset Pompe disease. Cochrane Database Syst Rev. 2023 Dec 12;12(12)

Chen M, Zhang L, Quan S. Enzyme replacement therapy for infantile-onset Pompe disease. Cochrane Database Syst Rev. 2017 Nov 20;11(11)

showed a better effect on survival and also on walking ability than the recommend dose in classic infantile patients [58–60]. High-dose rhGAA may also be a treatment option for late-onset Pompe disease patients showing a suboptimal response, plateau, or clinical decline at the standard dose, in the absence of infusion-associated reactions and clinically significant anti-rhGAA neutralizing antibody titers, but further studies are needed to demonstrate this effect.

While the efficacy of the licensed dose is based on long term experience in large numbers of patients, the evidence supporting the use the higher doses in infantile-onset patients has been obtained in a limited number of clinical studies and the level of evidence is moderate-high.

Avalglucosidase alfa licensed dose is 20 mg/kg body weight/every other week [61]. For infantile-onset patients who experience lack of improvement or insufficient response in cardiac, respiratory, and/or motor function while receiving 20 mg/kg, a dose increase to 40 mg/kg every other week may be considered.

The recommended dosage of Cipaglucosidase alfa is 20 mg/kg every 2 weeks [57] and has been tested in combination with miglustat [56].

For the second-generation recombinant enzymes (Avalglucosidase alfa, Cipaglucosidase) the efficacy has been assessed in a limited number of studies [55, 57, 62–64]. These studies suggest significant improvements or stabilization of some clinical manifestations [54].

Indications Criteria for start and stop treatment in infantile-onset Pompe patients is under evaluation by a European expert panel (EPoC, European Pompe disease Consortium). In these patients treatment should be started immediately after diagnosis, without delay. Early initiation of ERT in infantile-onset patients contributes to a better physical and developmental outcome [60]. Timely start of ERT is associated with preservation of FVC in late-onset patients with better respiratory function and positive effects on walking ability at the time of treatment initiation, but not all patients respond equally well [65].

While the level of evidence for starting early ERT in infantile onset patients is high, evidence for exclusion or stopping therapy criteria is low and is not sufficiently supported by literature. When patients present with extremely severe clinical manifestations, are already invasively ventilated and without any residual respiratory and skeletal muscle function, and no beneficial effects of ERT are expected, it may be reasonable to refrain from starting treatment, or to stop treatment, after extensive discussion with parents. However, the authors are aware that protocols for the start of ERT in classic infantile patients may differ between countries.

Consensus on criteria to start, switch and stop therapy in late-onset patients has been reached by the same expert panel [66]. Specifically, to start ERT a patients should have an established diagnosis of Pompe disease, should present with clinical and supportive paraclinical signs of the disease, should have functionally relevant residual skeletal and respiratory function, should not have another advanced stage life-threatening disease, should be committed to continue treatment. The absence of residual skeletal or respiratory function, the presence of another advanced stage life-threatening disease, an insufficient commitment of patients to treatment may represent reasons for not to recommend the start of ERT. Stopping treatment should be considered for unmanageable severe infusion-associated reactions, high neutralizing antibody titers, lack of any effect of treatment, patient wish, another advanced stage life-threatening disease represent criteria to consider stopping ERT.

Switching to a second-generation ERT can be considered if there is no indication of skeletal muscle and/or respiratory function stabilization or improvements after at least a year on first-generation recombinant alpha-glucosidase, or if the patient suffers from severe infusion-associated reactions that cannot be adequately managed.

The level of agreement is based on published consensus criteria and is considered high.

ERT should be prescribed (and its effects monitored) by centers with specific expertise in the treatment of Pompe disease and/or other lysosomal diseases. rhGAA is approved for hospital administration in different countries and enzyme infusion can take 3–6 h. Home therapy could ameliorate the patient quality of life, although there is the potential for severe infusion reactions and life-threatening anaphylaxis in patients receiving ERT [67, 68].

Immune tolerance induction Immune-modulating protocols have been proposed to counteract neutralizing antibodies to rhGAA in infantile onset forms, mainly in CRIM-negative patients. Recent protocols involve variable combinations of rituximab, methotrexate, bortezomib, rapamycin [15, 69–71], plasma-exchange [72] and support with gamma globulins [73].

Since prophylactic induction of immune tolerance must begin prior to the first rhGAA infusion, it is important to rapidly determine CRIM status. However, this should not delay the start of the ERT. Therefore, it may be advisable that infantile-onset patients with unknown CRIM status are treated as if they were CRIM negative [39]. It should also be noted that 30% of CRIM positive patients develop high sustained antibodies. Although common practice between centers may vary, for the most up-to-date protocols for ERT-naïve and ERT-experienced patients with high sustained antibody titers we refer to Banugaria et al. [15] and Desai et al. [74].

Protocols to desensitize PD patients with infusion-associated reactions due to ERT hypersensitivity have been published [75, 76] but are not generally applied/recommended.

Other therapeutic approaches under development

Beta-2 adrenergic agonist, such as albuterol, has been investigated and tested in clinical trials as an add-on therapy which may enhance the lysosomal uptake of rhGAA [77–79].

In vivo and *ex-vivo* gene therapy approaches are under clinical development [80, 81].

Substrate reduction therapy based on oral administration of small-molecule muscle glycogen synthase (GYS1) inhibitors is currently under investigation [82].

Diet

Recommended diet composition:

25–30% proteins;

30–35% carbohydrate;

35–40% lipids.

It is important to ensure suitable calorie and protein intakes, and to avoid catabolism. It has been advised that adult Pompe patients should consume 1.2–1.4 g/kg protein per day, which is above the intake recommended for the general population (0.8–1.0 g/kg) [35]. The rationale for a high-protein diet is to counteract muscle protein depletion by supplying increased amino acid substrates for protein synthesis.

Supplementation with L-alanine has been proposed as an alternative way to reduce muscle protein turnover and thus possibly improve muscle function [83].

Evaluation of personalized diets is recommended as Pompe patients tend to get more overweight than others.

Other supportive therapies

In addition to ERT, palliative, rehabilitative, supportive, and surgical therapies are needed to manage pulmonary, cardiac, musculoskeletal, neurological, gastrointestinal

and psychological issues. Speech therapy should be considered in infants.

These therapies should be performed in centers with specific expertise in the management of Pompe disease or neuromuscular disorders in general and should be based on multidisciplinary evaluations.

Cardiac involvement Therapies for cardiac failure, may be required, mostly in infantile-onset patients.

Infantile-onset patients with cardiomyopathy should initially avoid digoxin or inotropes since they can worsen left ventricular outflow status [84]. Drug therapy with Angiotensin Converting Enzyme inhibitors, calcium antagonists and beta-blockers can be indicated, but these medications should be used with caution and only by a pediatric cardiologist experienced in treating pediatric patients with heart failure [39].

Physical therapy and exercise Active muscle strengthening exercises, aerobic exercise therapy and home exercise program are beneficial [85, 86], depending on patients' conditions. Passive mobilization and physiotherapy may help prevent joint contractures and deformities. Rehabilitation programs should be defined by an experienced team. Splints may help to counteract shortening of the Achilles tendons/clubfoot.

Respiratory therapy and ventilation Oxygen supplementation and/or non-invasive positive pressure ventilation should be prescribed based on underlying ventilatory abnormalities such as hypoxemia, obstructive sleep apnea, and hypoventilation. Treatment modality and need for mechanical ventilation should be based on careful evaluation of respiratory function by home ventilation experts.

In Pompe disease the diaphragm is involved leading to lower pulmonary function in supine position than in upright position and patients may need nighttime ventilation. Patients with an FVC < 40% should be brought to the attention of a home ventilation team [87, 88].

Procedures to facilitate clearance of airway secretions should be routinely performed [89].

Vaccinations Routine immunizations, including pneumococcal vaccination, should be used. Vaccination for influenza may be advisable for patients and other household contacts [90]. Respiratory syncytial virus (RSV) prophylaxis (palivizumab) is indicated in the first two years of life [91].

Management of feeding The management of feeding (oral or gavage) should be guided by the video fluoroscopic swallowing assessment and evaluation for gastro-esophageal reflux [90].

Nissen fundoplication can reduce the risk of aspiration in those with severe gastro-esophageal reflux [35].

Emergency

Acute respiratory failure (ARF)

Acute respiratory failure is the most frequent cause of death independent of the rate of progression of disease. It is more commonly a consequence of respiratory tract infection in patients with known ventilation defect. When hospitalization is needed, the preferable location is a respiratory intensive care unit (RICU).

Management of ARF includes standard measures including the following:

- Mechanical ventilation, preferably Non-Invasive Positive Pressure Ventilation (NPPV) to assist inspiratory muscles.
- It should be noted that most patients have lower FVC in supine position due to poor diaphragmatic function; therefore, they should not lay totally flat, but be positioned in a (slightly) upright position.
- Optimal oxygen supplement when required (maintain saturation between 92 and 94% and monitor $PaCO_2$ and pH).
- Airway secretion clearance through cough assist devices and other physiotherapeutic techniques.
- Endotracheal intubation, only in severe cases.
- Nutritional therapy to reduce aspiration risk.
- Physiotherapy to reduce joint problems.
- Aggressive infection treatment.

ERT should not be suspended [90].

Adverse reactions to ERT

Patients on ERT should be monitored for the possible occurrence of adverse reactions during infusions or in the hours after infusions. Fever, chills, erythema, drop of oxygen saturation and others immune and anaphylactic reactions might occur. Management of adverse effect includes the following measures, according to the standard protocols for infusion-associated reactions:

- interruption of the infusion and restart at a reduced infusion rate.
- H1-antihistamines, corticosteroids and epinephrine, which should be readily available (already prepared in the syringe) when administering infusions [5].

As stated above some desensitisation protocols for the management of infusion-associated reactions due to ERT hypersensitivity have been published [75, 76] but

there is limited evidence in the literature supporting their efficacy.

Follow-up and monitoring of patients

Following diagnosis and baseline full clinical assessment patients should undergo periodic evaluation and examinations to explore heart, respiratory and muscle function (Tables 2 and 3). It is advisable that follow-up programs are individualized and adjusted to the stage of disease.

General evaluation

- Growth parameters should be evaluated at regular intervals in infants and children (every 3–6 months, depending on age and clinical forms).

Musculoskeletal and functional tests

- Motor and functional assessments should be performed every 3–6 months for children under the age of five, every 6–12 months for older children and adults.

Neuromuscular evaluation

A minimum set of tests should be available at the follow-up center [39]:

- Muscular force by Medical Research Council (MMT-MRC) scale (from the age of 5).
- Six-minute walking test and timed tests in ambulant patients (from the age of 2).
- Timed tests.
- Hand-held dynamometry (from the age of 10).
- Fatigue by the fatigue intensity scale (FSS).
- Patient-reported outcome measures.

Motor function in infants can be assessed by the Alberta Infant Motor Scale (AIMS), by the PEDI Pompe test (Pediatric Evaluation of Disability Inventory), or also by Bayley scale depending on patient's age.

Quantitative muscle MRI can be performed in late-onset patients in addition to annual investigations.

Evaluation procedures should be performed by experienced rehabilitation physicians/physical therapists.

Cognitive assessment

Developmental and cognitive assessment in infantile patients at diagnosis and every 12–24 months, using standardized tests appropriate for age.

Cardiology

ECG, Echocardiogram, 24 h-Holter. ECG and Echocardiogram should be performed at diagnosis, and at regular intervals (every 12 months or more frequently, depending on patients' conditions, in the presence of cardiomyopathy).

Respiratory function

- Pulmonary function (FVC sitting, supine) should be evaluated in both sitting and supine position at least once a year or more frequently depending on patients' conditions.
- Pulse oximetry with capnography and/or gas exchange monitored every 6 months in patients with abnormal FVC or if manifestations of intercurrent infections or accelerated worsening become evident.
- Chest radiographs should be performed whenever necessary based on patients' conditions or in case of intercurrent infections.
- Polysomnography and/or oxycapnography should be performed every 12 months.

Evaluation procedures should be performed by an experienced team of ventilation experts.

Gastrointestinal function

Assessment and evaluation for gastroesophageal reflux should be performed at the diagnosis and every 3 years or more frequently in the presence of clinical manifestations such as swallowing difficulties, choking respiratory problems and repeated infections. In the absence of clinical problems, video fluoroscopic exam should be considered every 3 years. Oral feeding in infantile patients with Pompe disease should be stopped if there signs of aspiration on video fluoroscopic exam and be restarted when these signs have disappeared.

Nutritional status should be assessed every 6–12 months in children, 12–24 months in adults.

Auditory function

Hearing tests should be performed at the diagnosis in infants and every 12 months.

Ophthalmological evaluation

- Visual acuity test.
- Orthoptic evaluation.

Bone density

DEXA scans and radiographs should be performed at diagnosis and every 5 years or more frequently in the presence of clinical manifestations indicating progression of bone involvement/fractures.

Anesthesiologic evaluation

General anesthesia should be limited to a minimum, particularly in young infants and should only be carried out by anesthetists with experience in managing general anesthesia in children with heart disease [35].

Antibody status

It is a complementary study. Regular determination of antibody status in patients on ERT, at baseline and after ERT is useful to select patients that could benefit of secondary immunomodulation. Ideally, antibody measurement should be conducted at baseline and then at regular intervals (every 6–12 months), although this may depend upon the patient's clinical status and may be required in case of unexpected worsening of disease course.

Quality of life (QoL)

Pompe disease affects patient quality of life (QoL). Reliable approaches to test QoL and participation are Short Form 36 (SF-36) and the Rotterdam Handicap Scale (RHS) [92].

Behavior

Use of standardized behavioral checklists to better characterize the behavioral, emotional and social functioning of children and adolescents with Pompe disease over time. These measures are useful screening tools for clinicians to identify potential behavioral and emotional problems in children with Pompe disease in a timely manner and to refer them for further evaluation and treatment [93].

Other

When possible, downloadable applications on mobile phone (for example in Italy the AlGkit) may be of help in the clinical management of patients with Pompe disease, to allow continuous remote monitoring of patients by healthcare providers. Such tools can be especially useful in situations such as the COVID19 pandemics to manage related difficulties (reports on patients who have suspended ERT, difficulties in contacting doctors, etc.) [94].

Biochemical markers

- Routine biochemistry.
- Serum CK, CK-MB, AST and ALT.
- BNP or pro-BNP (in patients with cardiac involvement).

When possible, depending on the availability of tests at the follow-up center:

- Urinary Glc4 or Hex4.
- neurofilament light chain (in infantile-onset patients).
- muscle specific microRNAs.

Interaction with patient associations

It is important to inform patients and families about the existence of patients' associations. This contributes to management of the disease by promoting cooperation, exchange, dialogue and even support between patients, patients' associations and caregivers.

Pregnancy

While fertility is not affected, pregnancy may worsen symptoms, or cause initial symptoms to arise. Complications with pregnancy, delivery or birth were not higher, except for an increase in the rate of stillbirths (3.8% compared to the national average of 0.2–0.7%) [95–97]. Pregnancy should be carried out in a referral center with the support of a neonatal ward.

Pregnancy induces a host of adaptive changes that may worsen signs or cause arising of initial symptoms of Pompe disease in the mother, putting at risk both the mother and the fetus.

Although there are no adequate and well-controlled studies in pregnant women about the ERT effects, it has been reported that cessation of ERT in early pregnancy may result in deterioration of maternal symptoms and emergence of allergic reactions on restarting ERT [95, 96].

In animal reproduction studies, no effects on embryo-fetal development were observed in mice or rabbits given daily administration of alglucosidase alfa at the recommended human bi-weekly dose during the period of organogenesis. Although the level of evidence available in the literature is not high, it is advisable to continue ERT during pregnancy as there are several reports on safe

continuation and delivery of healthy offspring of women on ERT during pregnancy.

One other concern for the use of ERT during pregnancy could be the potential drug related immune hypersensitivity reactions [90].

In addition to routine obstetric care, women with Pompe disease should be seen at least once every trimester by a specialist team. Anesthetic input should be discussed and arranged early, with local or regional anesthesia being the techniques of choice, while bearing in mind that muscular skeletal abnormalities may make this difficult. Discussions about mode of delivery and available options should be highlighted to the women, with patient involvement in the development of birth plans.

All investigations (baseline and subsequent) should be made available to obstetrics, neurology and anesthetic colleagues prior to assessment and birth-planning consultations. Input by obstetric, neurology, respiratory, anesthetic and dietician specialists (in addition to metabolic consultant specialist input) should be determined on an individual case basis depending on baseline and progressive symptoms, severity of disease and previous obstetric history.

The use of the home ventilator and the in-exsufflator in the perioperative period should be considered to avoid intubation.

It has been shown that ERT is secreted in low amounts in breast milk after an ERT infusion. Therefore, it is advised not to breastfeed children within the first 24 h after ERT infusion. If preferred, the mother may use previously expressed milk during the 24 h after the last infusion and discard expressed milk during this time [98].

Abbreviations

4MUG	4-Methylumbelliferyl-α-D-glucopyranoside
6-MWT	6-Minute walking test
ABR/BAEP	Auditory evoked potentials
ACMG-AMP	American College of Medical Genetics and genomics and Association for Molecular Pathology
AIMS	Alberta Infant Motor Scale
ALT	Alanine aminotransferase
ARF	Acute respiratory failure
AST	Aspartate aminotransferase
BNP	Brain natriuretic peptide
CDG	Congenital defects of glycosylation
CK	Creatine kinase
CPR	Clinical pathway recommendations
CRIM	Cross reactive immune material
CT	Computed tomography
DEXA	Dual-energy X-ray absorptiometry
EMA	European Medicines Agency
EMG	Electromyography
EPoC	European Pompe disease Consortium
ERT	Enzyme replacement therapy
EU	European Union
FDA	Food and Drug Administration
FSS	Fatigue by the fatigue intensity scale
FVC	Forced vital capacity
GAA	Acid alpha-glucosidase
GL	Guidelines
Glc4	Glucose tetrasaccharide
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GYS1	Glycogen synthase
HCP	Healthcare providers
IOPD	Infantile-onset Pompe disease
LDH	Lactate dehydrogenase
LOPD	Late-onset Pompe disease
LSD-SNW	Lysosomal storage disease subnetwork
MIP/MEP	Maximun inspiratory pressure and maximum expiratory pressure
MMT-MRC	Muscular force by Medical Research Council
MRI	Magnetic resonance imaging
NBS	Newborn screening
NGS	Next generation sequencing
NPPV	Non-invasive positive pressure ventilation
PD	Pompe disease
PEDI	Pediatric evaluation of disability inventory
QoL	Quality of life
rhGAA	Recombinant human GAA
RHS	Rotterdam Handicap Scale
RICU	Respiratory intensive care unit
RSV	Respiratory syncytial virus
RUSP	Recommended universal screening panel
SF-36	Short form 36
VLCAD	Very long-chain acyl-CoA dehydrogenase
VUS	Variant of unknown significance

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13023-024-03373-w.

Additional file 1. Quality Assessment of references: References list evaluated based on the AGREE II criteria and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology.

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The authors confirm contribution to the paper as follows: GP coordinated the working group, selected and evaluated the literature, prepared and revised the manuscript. SF selected and evaluated the literature, contributed to the writing of the manuscript. MA selected and evaluated the literature, contributed to the writing of the manuscript. FA selected and evaluated the literature. AV selected and evaluated the literature. AT selected and evaluated the literature. VG selected and evaluated the literature. AZ selected and evaluated the literature, contributed to the writing of the manuscript, participated in the coordination of the working group. MJG evaluated the literature, revised the text. PRTA evaluated the literature, revised the text. AH, evaluated the literature, revised the text. OA evaluated the literature, revised the text. MAD evaluated the literature, revised the text. BKW evaluated the literature, revised the text. MS participated in the coordination of the working group, evaluated the literature, revised the text. NAMEvdB evaluated the literature, revised the text. MDTR participated in the coordination of the working group, evaluated the literature, contributed to the writing of the manuscript. DPG participated in the coordination of the working group, evaluated the literature, contributed to the writing of the manuscript. HH participated in the coordination of the working group, evaluated the literature, contributed to the writing of the text. JMPvdH participated in the coordination of the working group, evaluated the literature, contributed to the writing of the text. ATvdP coordinated the working group, selected and evaluated the literature, prepared and revised the manuscript. All authors read and approved the final manuscript.

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