Pompe Disease: Diagnosis and Management. Evidence-Based Guidelines from a Canadian Expert Panel

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ABSTRACT: Pompe disease is a lysosomal storage disorder caused by a deficiency of the enzyme acid alpha-glucosidase. Patients have skeletal muscle and respiratory weakness with or without cardiomyopathy. The objective of our review was to systematically evaluate the quality of evidence from the literature to formulate evidence-based guidelines for the diagnosis and management of patients with Pompe disease. The literature review was conducted using published literature, clinical trials, cohort studies and systematic reviews. Cardinal treatment decisions produced seven management guidelines and were assigned a GRADE classification based on the quality of evidence in the published literature. In addition, six recommendations were made based on best clinical practices but with insufficient data to form a guideline. Studying outcomes in rare diseases is challenging due to the small number of patients, but this is in particular the reason why we believe that informed treatment decisions need to consider the quality of the evidence.

RÉSUMÉ: La maladie de Pompe est une maladie de surcharge lysosomale due à un déficit en alpha-glucosidase acide. Les patients présentent une faiblesse des muscles squelettiques ainsi qu’une atteinte respiratoire, avec ou sans cardiométrie. Le but de notre revue était d’évaluer systématiquement la qualité des données de la littérature sur ce sujet et d’élaborer des lignes directrices fondues sur des données probantes pour le diagnostic et la prise en charge des patients atteints de la maladie de Pompe. Nous avons procédé à une revue de la littérature incluant les essais cliniques, les études de cohorte et les revues systématiques. Sept lignes directrices de traitement ont été élaborées concernant les décisions fondamentales de traitement et nous les avons classées au moyen de la méthodologie GRADE (Grading of Recommendations Assessment, Development and Evaluation) évaluant la qualité des données de la littérature. De plus, nous avons émis 6 recommandations fondues sur des pratiques cliniques exemplaires, mais pour lesquelles les données étaient insuffisantes pour établir une ligne directrice. L’étude des résultats du traitement de maladies rares constitue un défi à cause du petit nombre de patients atteints de ces maladies. Cependant c’est la raison pour laquelle nous croyons qu’il est important de considérer la qualité des données disponibles afin de prendre des décisions de traitement éclairées.

Keywords: Pompe disease, guidelines, review

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INTRODUCTION

Pompe disease (OMIM 606800) is a lysosomal storage disease characterized by deficiency of the enzyme acid alpha-glucosidase leading to myopathy, respiratory weakness, physical disability and premature death. The symptoms manifest as a continuum from birth through to adulthood, with a recognized severe infantile-onset form that is associated with cardiomyopathy and...
high mortality, to late-onset forms that are primarily characterized as weakness of limb-girdle and respiratory muscles but usually without cardiomyopathy. Pompe disease is rare, and these guidelines evaluate the quality of evidence from the medical literature to provide recommendations for management and to inform practitioners who may not be familiar with Pompe disease on the essential aspects of identifying and caring for patients.

The guidelines were designed by a multidisciplinary panel of Canadian physicians who manage patients with Pompe disease, have knowledge of the resources available throughout the country and draw upon evidence from peer-reviewed literature. The level of evidence was examined based on the Oxford Centre for Evidence-Based Medicine and the international GRADE group approach to clinical guidelines. If there were sufficient data from the literature to rate the quality of evidence, the treatment choices resulted in a Management Guideline (Table 1). Where there were insufficient or inconsistent data from the literature but the issue was considered important to the overall health of a patient with Pompe disease, these were tabled as Recommendations (Table 1). An evidence-based grading approach has not been used in previous recommendations for the treatment of Pompe disease. Patients with the condition and their caregivers are faced with important choices and need to make decisions about which treatments to consider. Disease-modifying or life-sustaining treatments, be they recombinant enzyme therapy or mechanical ventilation, require significant resources, and the evidence for these decisions needs to be carefully evaluated. The guidelines are not intended to be restrictive, to prescribe a standard of management or to serve as a substitute for decision-making by the patients, their families and their care team. They are intended to provide guidance that can inform the care team about the evidence from the medical literature.

### Table 1: Management Guidelines and Recommendations for Pompe Disease

**Management Guidelines**

1. Patients with infantile-onset Pompe disease should be offered enzyme replacement therapy at a dose of 20 mg/kg every other week.
2. Prior to commencement of ERT, it is important to determine CRIM status and whether a clinical trial of ITI should be part of the treatment plan. The child should be assessed in a paediatric centre with expertise in managing infants with Pompe disease.
3. Following diagnosis and in conjunction with starting ERT, patients with infantile-onset Pompe disease should undergo respiratory assessment and that non-invasive respiratory support should be provided where appropriate.
4. Infants should be evaluated for swallowing difficulties, and methods to promote sufficient intake to provide adequate growth should be used.
5. A trial of enzyme replacement therapy should be offered to patients with late-onset Pompe disease at a dose of 20 mg/kg body weight every other week who demonstrate clinical signs and symptoms of the disease, are ambulatory, and are either non-ventilated or on non-invasive ventilation when asleep.
6. Atrial fibrillation may be considered in individuals with late-onset Pompe disease at a dose of 20 mg/kg every other week who are non-ambulatory and/or receive non-invasive ventilation while awake or invasive ventilation if there are predefined skeletal muscle outcomes which can be evaluated and which, if achieved, would improve the functional status of the patient. In such cases, if the trial of therapy does not result in the pre-specified outcomes, then the trial should be discontinued.
7. Patients with late-onset Pompe disease should be monitored for the development of respiratory complications using pulmonary function tests at regular intervals.

**Recommendations**

A. Patients with LOPD who are showing a poor response to ERT, even if they have been using ERT for a number of months to years, should have an evaluation for HSAT, and if HSAT are present, interventions to lower HSAT, including treatments available in clinical trials, prior to continuation of ERT, may be necessary.
B. Patients with LOPD should be on a diet that supplies adequate protein and energy.
C. Vitamin D status should be optimized consistent with recommendations for the general population in Canada. Patients with LOPD should be offered vitamin D supplementation to achieve a level of at least 75 nmol/L.
D. Patients with LOPD should be encouraged to perform both resistance and cardiovascular exercise to improve general conditioning and quality of life. Interventions should be tailored to individual abilities.
E. Periodic quality-of-life assessments and/or motor function tests, which can include questionnaires, should be part of the routine management of patients with LOPD.
F. Goals of care should be reviewed on a regular basis and with interval changes in health. When disease control is no longer an objective, discontinuation of enzyme replacement therapy, supportive care and palliative measures should be available to patients.

CRIM = cross-reactive immunologic material; ERT = enzyme replacement therapy; HSAT = high sustained antibody titres; ITI = immune tolerance induction; LPOD = late-onset Pompe disease.

### Clinical Phenotypes

**Infantile Pompe Disease**

Infantile-onset Pompe disease presents during the first few months of life with symptoms of hypotonia, generalized muscle weakness and hypertrophic cardiomyopathy. There is a high mortality rate by one year of age if untreated. At about four months of age, the vast majority of patients show hypertrophic cardiomyopathy, cardiomegaly, hypotonia, respiratory insufficiency, feeding difficulties and failure to thrive. Musculoskeletal abnormalities are also present in about two-thirds of patients by this age and are characterized by proximal muscle weakness in the upper and lower extremities, truncal weakness, macroGLOSSIA, hepatomegaly and hypotonia leading to delayed motor development. Swallowing and feeding difficulties are virtually universal in infants and contribute to poor growth and nutrition. The dysphagia that may occur with Pompe disease presents with aspiration pneumonia. Cardiac involvement is the hallmark of the initial presentation of infantile Pompe disease. A first clinical evaluation can involve a chest X-ray to evaluate for cardiomegaly in its infantile form. Echocardiography is invaluable in assessing ventricular structure and function. Hypertrophy, predominantly affecting the left ventricular posterior wall and interventricular septum, is typically seen in infants at diagnosis and may also be identified postnatally. Left ventricular outflow obstruction may be present. The hypertrophic cardiomyopathy results in systolic and diastolic dysfunction that may progress to congestive heart failure. The dysfunctional left ventricle may be dilated as well as hypertrophied, and there can be underlying myocardial fibrosis detected by cardiac magnetic resonance imaging. Systolic dysfunction, defined as a left ventricular ejection fraction (LVEF) less than 40%, was not seen until after 5 months of age in a cohort of 40 infants. The typical electrocardiographic features of Pompe disease include a shortened PR interval, pronounced ventricular...
voltages and repolarization abnormalities. Arrhythmias can be present, including supraventricular tachyarrhythmias and ventricular ectopy.\textsuperscript{11-14}

Late-Onset Pompe Disease

Late-onset Pompe disease (LOPD) is often used to describe all patients with Pompe disease who do not have a typical infantile (cardiomyopathy) presentation.\textsuperscript{15} The majority of patients with LOPD present with weakness beginning when they are adults, although the history of symptoms in some patients can be traced back to childhood and in some circumstances to less than one year of age.\textsuperscript{16} There have been estimates that the prevalence of late-onset Pompe disease is \textasciitilde 1:57,000, while for the infantile form it is \textasciitilde 1:138,000, but no studies have been performed in Canada.\textsuperscript{17} Compared with the infantile form, LOPD is considered a “milder” phenotype, likely due to higher residual enzyme activity,\textsuperscript{18} but there is still a significant impact on morbidity, quality of life (QoL) and life expectancy.\textsuperscript{19,20} Late-onset Pompe can present in childhood and juvenile forms in the paediatric population, as well as in adulthood. Although these distinctions can be helpful descriptively, there is poor correlation between age of onset and phenotype or disease severity.\textsuperscript{21} The most common presentation is proximal limb-girdle, lower extremity and trunk muscle weakness. Patients may reveal a history of difficulties with such gross motor activities as walking, running, climbing stairs, rising from a sitting position or trying to get up after lying down.\textsuperscript{16,22-24} These symptoms often precede the definitive diagnosis by approximately 7 to 10 years,\textsuperscript{25} with symptom onset occurring at an average age range of 27-35 years of age.\textsuperscript{16,26} Although unique presentations such as rigid spine syndrome have been described in the juvenile age group, these have also been reported in older patients and should be considered regardless of age of presentation.\textsuperscript{27,28} Some patients can also have primary or coexistent atypical patterns of weakness, including ptosis, facial diplegia, ophthalmoplegia, fascio-scapulo-humeral, and scapulo-peroneal or paraspinal muscle atrophy.\textsuperscript{29-31} In addition, some patients can present with respiratory weakness as an initial manifestation of the disease,\textsuperscript{23} with respiratory failure precipitated by infection, aspiration or surgical intervention.\textsuperscript{32-35} Some studies have shown that there may be a group of late-onset patients younger than 15 years of age with prominent respiratory dysfunction and early dependence on continuous ventilation; however, this type of presentation can also occur in adult patients.\textsuperscript{24} With disease progression, greater involvement of upper extremity muscles and respiratory insufficiency may ensue, with respiratory failure being the leading cause of death.\textsuperscript{24}

Hypertrophic cardiomyopathy is a rare finding in LOPD. Electrical abnormalities predominate as the cardiac pathology. In a French registry, an estimated prevalence of 3\% of LOPD patients developed complete heart block.\textsuperscript{13} Supraventricular and ventricular tachyarrhythmias are also relatively common— affecting up to 29\% of patients.\textsuperscript{20} The electrocardiogram of some patients with Pompe disease may suggest ventricular preexcitation (Wolff–Parkinson–White syndrome), but pathologic studies of mouse models show generalized disruption of the annulus fibrosis associated with glycogen storage disease rather than the presence of a myocardial bypass tract.\textsuperscript{36,37} There may be an insulting effect on the cardiac conduction system provided by the glycogen within myocytes that disrupts normal conduction barriers between the atra and ventricles and enhances electrical conduction. This phenomenon has implications in the treatment of supraventricular tachyarrhythmia due to its poor amenability to radiofrequency catheter ablation. There are recent descriptions of dilated arteriopathy of the aorta in patients with late-onset Pompe disease, aneurysm formation and dissection in up to 12.5\% of patients in a German cohort of 40 late-onset Pompe disease patients.\textsuperscript{20,38}

Pathology and Pathophysiology

Muscle histochemistry in Pompe disease manifests as glycogen accumulation in membrane-bound vesicles (lysosomes).\textsuperscript{39,40} A secondary mitochondrial cytopathy has also been described.\textsuperscript{39-42} These histopathologic changes are widespread, occurring in many organs and tissues, but skeletal muscle is the most frequently studied tissue. In skeletal muscle biopsies, degenerative myofibres are recognized by their shrunken nuclei with condensed chromatin. Hematoxylin and eosin-stained myofibres in formalin and paraffin-fixed tissue sections show vacuolization; periodic acid–Schiff staining reveals an abundance of glycogen.\textsuperscript{43} Increased lysosomal abundance is demonstrated by acid phosphatase staining.\textsuperscript{44} Ultrastructural examination of muscle using electron microscopy shows vacuolar myopathy, and glycogen granules are observed within some (but not all) vacuoles.\textsuperscript{45} Glycogen granules are also seen in non-membrane-bound free aggregates in the subsarcolemmal sarcoplasm. Though the detection of vacuoles within myofibres can be made at the light-microscopic level, electron microscopy defines the anatomic relations better at a subcellular level. Furthermore, paraffin and frozen sections each have different but significant artefacts that at times might be misinterpreted as vacuoles. The histologic and ultrastructural changes in cardiac muscle are similar, and the smooth muscle of the gastroenteric tract as well as the tunica media of large- and medium-sized arteries can be affected.\textsuperscript{45} Excessive glycogen accumulation has also been noted in cells of the central nervous system, but nervous tissue is not used for diagnostic purposes in patients with Pompe disease.\textsuperscript{46,47} Smooth muscle cells within blood vessel walls also accumulate glycogen and may compromise wall integrity and contribute to the propensity for aneurysm formation.

Diagnosis

The diagnosis of Pompe disease is challenging given the heterogeneous presentation of symptoms, particularly in patients with LOPD.\textsuperscript{48} The wide range of symptoms in Pompe disease can mimic those of other myopathies and neuromuscular junction disorders.\textsuperscript{49} Electromyography can be a clue to the diagnosis, with spontaneous activity (fibrillations, positive sharp waves) and small, brief early recruiting potentials often presenting with greatest frequency in the paraspinous muscles.

The diagnosis of Pompe disease is usually established by demonstrating a deficiency in acid alpha-glucosidase enzyme activity and finding disease-causing mutations using DNA analysis of the G\textsubscript{AA} gene. DNA analysis can involve traditional targeted Sanger sequencing after the enzymatic deficiency result is obtained, but it is recognized that newer methods involving massive parallel sequencing (such as whole or targeted exome sequencing) may be used as the initial test for sequencing of the G\textsubscript{AA} gene. Pompe disease is autosomal recessive. When there are
known disease-causing mutations in a family, finding the mutations on both alleles (trans) in a patient with a known family history of Pompe disease is sufficient for diagnosis without enzyme testing. The finding of one known mutation and a sequence variant (a DNA change with unproven pathogenicity) or two sequence variants of possible pathogenicity requires confirmation using an enzymatic assay from such sources as a dried blood spot, a skin fibroblast culture and a peripheral blood lymphocyte culture, or histological evidence from a muscle biopsy. There was a consensus among the authors that an initial screening test using dried blood spot enzyme analysis is convenient as well as time- and cost-effective, but the risk of false positive tests is high and a positive dried blood spot result requires a confirmatory DNA test in order to make a diagnosis of Pompe disease.

Muscle biopsy as the initial investigation for a patient with a high pre-test probability of Pompe disease is not recommended nor necessary in any age group.49 If the muscle biopsy is suggestive of Pompe disease, a second approved method such as enzyme analysis or DNA testing should be used to confirm the diagnosis. A negative muscle biopsy does not exclude Pompe disease.

**Natural History**

**Mortality and Morbidity**

**Infantile-Onset Pompe Disease**

In a retrospective review of 168 patients with infantile-onset Pompe disease, the median age at symptom onset was 2 months (range 0-12 months),6 the median age at first ventilator support was 5.9 months (range 0.1-31.1 months), and the median age at death was 8.7 months of age (range 0.3-73.4 months). The overall survival rates at 12 and 18 months of age were 25.7 and 12.3%, respectively. Data from the Pompe disease registry showed that 23% of the 742 documented patients had symptom onset at ≤12 months of age.6 A subset of these patients (88%) displayed cardiomyopathy that was consistent with classical infantile-onset Pompe disease. Another review of 225 cases of Pompe disease6 showed that cardiac symptoms primarily occurred in patients with symptom onset at ≤1 year of age.50 Causes of death in patients with symptom onset at ≤12 months of age were respiratory insufficiency and cardiac failure; the median age at death among patients with cardiomyopathy was 0.99 years.

**Late-Onset Pompe Disease**

The rate of disease progression in late-onset Pompe disease is variable. Results from a 12-month study of 58 adult patients with late-onset Pompe disease24 showed that upper and lower extremity weakness, impaired walking ability and respiratory muscle weakness were noted on the basis of predicted values for quantitative muscle testing, a 6-minute walk test (6-MWT) and pulmonary function testing. Significant declines in arm and leg strength as well as a decline in pulmonary function were observed during the study period. Symptom duration was the best predictor of skeletal and respiratory muscle weakness;24,15 while early manifestations of the disease (<15 years of age) implied early wheelchair or ventilator dependence and a rapidly progressive disease course. In a longitudinal study over 16 years,10 50% of patients became wheelchair-bound and 19% of patients became ventilator-dependent. In a prospective international observational study of 268 untreated adults,14 the median age at diagnosis was 38 years of age and median survival after diagnosis 27 years.

Respiratory insufficiency is a cardinal feature of LOPD and the primary cause of mortality. Symptoms include exertion-induced dyspnea, weak cough, frequent episodes of aspiration (particularly with bulbar involvement) and respiratory infections. Sleep-disordered breathing, characterized by hypoventilation or obstructive sleep apnoea, is common51,52 and may be associated with frequent awakenings, nightmares, nocturias, night sweats, morning headache and excessive daytime sleepiness. Nocturnal hypoventilation becomes sustained over time with a decline in vital capacity (VC).51 Moderate-to-severe diaphragmatic impairment is suggested by the occurrence of unexplained orthopnea and/or paradoxical thoraco-abdominal motion while breathing in the supine posture (e.g., inward movement of the abdomen during inspiration), and dyspnea53 when bending over or after immersion into water.54

Respiratory deterioration is related to disease duration rather than to age at presentation.15,55 In most patients with LOPD, symptoms of limb muscle weakness are likely to occur before respiratory symptoms.15,55 This is due to the inherently large reserve of the respiratory system and because patients may reduce their level of physical activity, and hence ventilatory demands, as the disease progresses. Patients with major peripheral muscle weakness are likely to have significant impairment of respiratory function, but the converse is not necessarily true, given that some patients require respiratory support with mechanical ventilation while still ambulatory.56

As noted with other neuromuscular disorders, respiratory impairment in Pompe disease is indicative of a predominantly restrictive abnormality. The rate of decline in VC over time is variable—ranging from 0.9 to 4.6% per year,18,24,55 and the presence of scoliosis may be contributing factor.35,55 Studies have shown that VC declines more rapidly in males than in females regardless of age, disease duration, scoliosis, muscle strength and mobility.55 Deterioration of respiratory muscle function and the decreased effectiveness of cough, which has also been noted in Pompe disease,24,55 predispose patients to recurrent pulmonary infections.

**Management**

In general, the monitoring of patients with Pompe disease requires a coordinated approach by a specialist and individuals who have expertise in the care of these patients. Management of care is often coordinated by a neuromuscular physician, neurologist or metabolic disease specialist. Healthcare providers that have expertise in such disciplines as respiratory medicine, cardiology, bone health, nutrition, speech and language, occupational therapy, physical therapy, social work, psychology, community work, and palliative care physicians form an integral part of the circle of care.1,58 The health of patients with Pompe disease can also be affected by issues not directly related to glycogen storage: osteopenia59 and risk from procedures with certain general anaesthetics leading to both cardiac and respiratory complications.60,61

Enzyme replacement therapy (ERT) is the only established drug therapy for patients with Pompe disease that targets the enzyme deficiency. Recombinant human acid alpha-glucosidase (rhGAA; alglucosidase alfa; Myozyme®) is the only approved
ERT currently in Canada and is administered as an intravenous infusion every two weeks. A change in the production process to a larger batch size from 160 to 2000 litres and later to 4000 litres has resulted in the same enzyme product from the larger batch size, alglucosidase alfa, being named Lumizyme® in the United States only. Outside the United States, alglucosidase alfa is named Myozyme® regardless of batch size. Other formulations of ERT are in various stages of clinical development. Although ERT is not curative, it is the only treatment that has been shown to modify the disease course in patients with Pompe disease.62–64 The most significant factor that can influence the bioavailability of recombinant enzyme is the development of anti-GAA neutralizing antibodies that occur after the start of ERT. In cases of infantile Pompe disease, the probability of developing high titres of anti-GAA antibodies is primarily affected by their CRIM status (cross-reactive immunologic material).

**Infantile-Onset Pompe Disease**

**Cardiac Function**

Treatment of Pompe cardiomyopathy is directed by symptomatology. Consultation with a cardiologist is helpful in outlining an appropriate treatment approach. Severe ventricular hypertrophy with concomitant left ventricular outflow tract obstruction is managed with beta blockade and careful manipulation of fluid status. Avoidance of dehydration or hypotension is important, as this may precipitate ventricular arrhythmia and cardiovascular collapse. Systolic function is often hyperdynamic and well preserved initially. Inotropic medications and afterload reduction may worsen outflow tract obstruction and should only be used in the setting of congestive heart failure. Supraventricular tachyarhythmias may be controlled with beta blockade. Careful monitoring for ventricular ectopy is warranted both prior to initiation of ERT and during treatment.11

**Respiratory Function**

Infants and children with Pompe disease are vulnerable to worsening respiratory disease due to muscle weakness, leading to hypoventilation and sleep-disordered breathing. This is compounded by the risk of aspiration and decreased reserve from concurrent cardiac disease. Baseline assessment by spirometry and consideration of non-invasive respiratory support is warranted in all children with a new diagnosis of Pompe disease.65

**Other Parameters**

In patients with infantile-onset Pompe disease who receive intervention and therefore survive infancy, there is a high prevalence of weakness involving oropharyngeal muscles, which can lead to difficulties with speech and swallowing.66 For this reason, assessment of swallowing and speech is critical at the time of diagnosis and at interval follow-up in patients to allow early identification and treatment of any problems.

**Enzyme Replacement Therapy**

Given the rare incidence of infantile Pompe disease, there are only a few studies documenting the efficacy of ERT in these patients. In a pivotal open-label trial in 18 patients with infantile Pompe disease receiving rhGAA for 52 weeks,67 all survived to 1 year of age.67 16 survived to be recruited into a 3-year extension study, 89% survived to 2 years of age, and 39% reached 36 months of age. This compares to a natural history study showing survival at 18 months of only 12.3% and ventilator-free survival of only 6.7%. In these trials, a dose of 20 mg/kg versus 40 mg/kg of rhGAA was used, with no superiority of response to the higher dose. Cardiac muscle responds well to ERT, particularly in asymptomatic patients. A retrospective study68 of 11 long-term survivors with infantile-onset Pompe disease (5.4–12 years of age) who began receiving ERT at ≥6 months of age showed that all patients displayed improvements in cardiac variables and gross motor function. In an analysis of 14 infants with Pompe disease,11 administration of ERT <5 months or ≥5 months after birth partially restored cardiac function in both symptomatic and symptom-free patients, with a less predictable benefit in infants beginning ERT at ≥5 months of age.

Left ventricular (LV) hypertrophy shows significant regression as early as two months after initiation of ERT but may not resolve completely in infants started after five months of age, or those with marked increases in LV mass index.11 The normalization of LV mass index has been shown to be persistent in long-term survivors on ERT.12 In the first two months of treatment, there is a transient decrease in LV ejection fraction that typically returns to baseline by six months of treatment.68 Similarly, the short PR interval and elevated QRS voltages resolve with ERT. In four patients with LV outflow tract obstruction treated with beta blockers, the obstruction resolved after one month of ERT.68 Despite the improvement in cardiac hypertrophy, there continues to be an increased risk of conduction abnormalities and tachyarrhythmias long-term.11

**CRIM Status**

Among patients with Pompe disease, cross-reactive immunologic material (CRIM) status is an important predictor of response to ERT.69 In patients who are identified as having negative CRIM status (CRIM−), no GAA protein is synthesized because of the presence of null GAA alleles. Thus, rhGAA is recognized as a foreign protein by the immune system in these patients, resulting in the development of high neutralizing antibody titres that render ERT ineffective.70 In a retrospective study71 of CRIM+ and CRIM− patients with infantile-onset Pompe disease receiving rhGAA, after 1 year of treatment, 4.8% of CRIM+ and 54.5% of CRIM− patients were deceased. Worse cardiac and gross motor function in CRIM− patients predicted poor ventilator-free survival. In addition, CRIM− patients developed antibodies at a faster rate and had higher antibody titres than CRIM+ patients.71 In another retrospective analysis of infants with Pompe disease,70 clinical outcomes in the high-titre CRIM+ group relative to the low-titre CRIM+ group were poor across all areas evaluated. Interestingly, no significant differences were observed for outcomes in the CRIM− and high-titre CRIM+ groups.70 A mutation analysis study of 243 patients with infantile-onset Pompe disease69 showed that 25.1% were identified as being CRIM+. Most CRIM− patients were either homozygous or compound heterozygotes for nonsense and/or frame-shift mutations, resulting in premature stop codons or multi-exon deletions, and 1 CRIM+ patient was homozygous for a point mutation that abolished the initiator methionine (and no other missense mutations were identified). In contrast, most of the CRIM+ patients had 1 or 2 missense or in-frame deletion mutations that predicted the synthesis of some GAA protein.
swallowing dysfunction. Regular swallowing assessment should be included as part of the follow-up protocol for all infants.66

For infants at high risk of aspiration and for those who display a suboptimal growth rate, evaluation for swallowing difficulties, dysphagia and gastroesophageal reflux can impact nutritional intake. Jones and colleagues8 studied 13 infants, and all had swallowing dysfunction. Regular swallowing assessment should be included as part of the follow-up protocol for all infants.66 Infants should be monitored by a nutritionist to ensure that they meet the dietary reference intakes (DRI).75

Immune Tolerance Induction (ITI)

To counteract the development of neutralizing antibodies to rhGAA, several agents that can potentially mitigate the immune response to ERT (e.g., promote immune tolerance) are under investigation. The immune-modulating protocols can involve a combination of rituximab, methotrexate, and support with gamma globulins during the period of induced immunocompromise. In small case series, some patients have responded with reduction of anti-GAA titres after the use of ITI or have failed to develop high antibody titres when treated with ITI prior to commencement of ERT. There is growing evidence that high antibody titres in cases of infantile Pompe disease are highly predictive of a failure of response to ERT and that ITI can improve the response to ERT.72-74 At this time, ITI is an investigational therapy used in the context of clinical trials and ongoing studies. While ITI is currently not considered part of standard clinical care in infantile-onset Pompe disease, there is strong evidence that ignoring the contribution of CRIM status can lead to a failure of therapy with ERT. Therefore, the management of these infants should only be initiated after consultation with a medical centre with expertise in paediatric care and who can provide access to CRIM testing and counsel families whether a clinical trial involving ITI may need to be considered before starting ERT.

Late-Onset Pompe Disease

Enzyme Replacement Therapy

The strongest evidence for the benefits of ERT in late-onset Pompe disease comes from a randomized, placebo-controlled, prospective trial of rhGAA,53 in which 90 patients aged ≥ 8 years were randomly assigned to receive treatment with either rhGAA or placebo, every 2 weeks for 78 weeks. These were ambulatory patients with the exclusion of patients that needed either invasive mechanical ventilation or non-invasive ventilation while awake. Subjects on active treatment showed significant improvements in forced vital capacity (FVC) and 6-minute walk test (6MWT) distance compared with patients who received placebo. A subgroup analysis of patients with less severe clinical disease (baseline 6MWT distance ≥ 300 metres and FVC ≥ 55% of predicted values) showed better outcomes.63 Observational and open-label cohort studies of ERT76-82 corroborate the findings noted in the randomized trial. Predictors of response to ERT noted in an open-label prospective study83 of 69 patients who received ERT for up to 23 months were: female sex, younger age and less severe disease. Female sex was associated with improvements in muscle strength after ERT; younger age and less severe disease predicted a better supine FVC response.63 Improvements in muscle function were noted in patients with mild or moderate muscle weakness who were not wheelchair-dependent but not in patients with severe muscle weakness who were wheelchair-bound.84 Notably, 2 of 27 patients who used walking aids at the time of ERT initiation could walk without assistance following ERT.84 In general agreement with the aforementioned outcomes, a recently published literature review79 reported stabilization of motor and respiratory function as well as improvements in QoL in patients who received ERT. An increasing number of patients are receiving their ERT in their own home through home infusion programs. In Canada in 2016, approximately 30% of patients with late-onset Pompe disease have home enzyme infusions and this number is expected to rise (data from Genzyme Canada, a Sanofi company).

Results from a cross-sectional survey of 124 adult patients with Pompe disease84 showed that 84% of patients experienced pain in multiple sites, including the back, shoulders and upper leg/thigh regions. In another study of 225 adult patients,85 78% reported pronounced levels of fatigue (e.g., scores ≥ 4 on the Fatigue Severity Scale). Both pain and fatigue were reported to have an adverse effect on mood, performance of daily activities, sleep, and ability to enjoy life.84,86 Although the effects of ERT on pain have not been elucidated, improvements in fatigue and depression scores were observed in patients on long-term ERT.86 Some comparisons have been made using higher doses of rhGAA,87 but overall, clinical trials showing a clear benefit using higher doses of rhGAA over the standard dose of 20 mg/kg every other week are lacking.

Overall, these data indicate that early initiation of ERT in patients with less-advanced disease improves outcomes. ERT has less of an impact in patients with advanced disease who are wheelchair-bound or are receiving mechanical ventilation support at treatment initiation. There are no randomized, placebo-controlled trials in such patients, and data comes from observational studies. It is nonetheless clear that patients who are not yet at the stage of requiring mechanical ventilation are more likely to benefit from ERT compared to patients with more severe disease.
Nevertheless, patients enrolled in these clinical trials who showed a response to ERT had some degree of respiratory insufficiency or functional impairment. There is no evidence to show that non-symptomatic LOPD patients (who may have been found to have low acid alpha-glucosidase activity or a DNA mutation through family testing or as an incidental finding) will benefit from ERT. There are also no trials showing that patients who just have an elevation in serum creatine kinase without clinical signs and symptoms benefit from ERT. The general consensus of the authors is that patients with LOPD be considered for ERT only when there are symptoms related to a disease-specific impairment such as pulmonary function or motor weakness. It is reasonable in non-symptomatic patients to monitor their function to see if symptoms develop after a diagnosis is made before considering ERT.

It is clear from the above discussion that not all patients will benefit from ERT. If a patient with LOPD is being considered for ERT, it is important to define the outcome parameters that ERT is intended to target prior to starting therapy. A discussion should be held with the patient about these outcome parameters so that the patient is aware that ERT may be discontinued if the patient does not respond to the therapy. There have been guidelines developed that address criteria for cessation of ERT, but these criteria will vary among jurisdictions. In general terms, patients in whom respiratory dysfunction and/or skeletal myopathy continue to progress at the same rate despite the introduction of ERT should be considered candidates for cessation of therapy. Also, patients experiencing severe allergic reactions not amenable to standard therapy, a severe comorbid condition limiting lifespan, and noncompliance with infusions and recommended assessments are also indications to consider cessation of therapy in most of the jurisdictions of Canada.

**High Sustained Antibody Titres (HSATs) in Late-Onset Pompe Disease**

Given the correlation between HSATs in CRIM patients and a poor response to ERT in infantile-onset Pompe disease, a retrospective review revealed a similar correlation in patients with late-onset Pompe disease. After ≥6 months of ERT, 3 of the 6 patients with HSAT (≥1:51,200) developed HSAT that corresponded with a decline in pulmonary function, QoL and motor function. Similarly, in a case report of a patient with LOPD, the antibody titre rose to a high level following ERT, and the patient’s disease progressed. Immunologic assays showed that approximately 40% of the administered rhGAA was captured by circulating antibodies and that GAA uptake by cultured fibroblasts was inhibited by admixture of the patient’s serum. It should be noted that elevations in antibody titre after ERT are not always detrimental, as noted in a case study of a 37-year-old woman with late-onset Pompe disease. The patient was seropositive at baseline, and antibody titres rapidly increased as early as 12 weeks of therapy. However, the antibodies neither inhibited GAA enzymatic activity in the patient’s serum nor interfered with uptake of rhGAA by cultured human fibroblasts. The evidence at present does not suggest routine evaluation of CRIM status in LOPD patients, but baseline antibody status prior to initiation of ERT may prove useful to detect a rise in antibody titres if needed at a later date. It is not clear whether routine measurement of HSAT is necessary after starting ERT. In a patient who has an initial benefit from ERT but is found to show declines at a later date, measurement of HSAT is warranted. The management of patients with HSAT may require enrolling in a clinical trial protocol. Finally, there have been rare cases of IgE-mediated allergic reactions to ERT, and these patients should be assessed by an allergist/immunologist for determination of strategies to mitigate the allergic response.

**Management Guideline**

1. A trial of enzyme replacement therapy should be offered to patients with late-onset Pompe disease at a dose of 20 mg/kg body weight every other week who demonstrate clinical signs and symptoms of the disease, are ambulatory, and are either non-ventilated or on non-invasive ventilation when asleep. Quality of evidence: Grade B.

2. A trial of enzyme replacement therapy may be considered in individuals with late-onset Pompe disease at a dose of 20 mg/kg every other week who are non-ambulatory and/or receive non-invasive ventilation while awake or invasive ventilation if there are predefined skeletal muscle outcomes which can be evaluated and which, if achieved, would improve the functional status of the patient. In such cases, if the trial of therapy does not result in the pre-specified outcomes, then the trial should be discontinued.

**Nutrition**

Nutritional intake should meet the age-appropriate energy and nutrient needs of individuals based on the Dietary Reference Intakes (DRI). Insufficient protein and calories can lead to lower muscle mass. Patients with any progressive neuromuscular disease tend to be less physically active and expend less energy than active individuals. Dysphagia is present in approximately 25% of patients with LOPD, making it challenging to eat. The effects of added protein or modified diets in LOPD has been limited to case study reports and small trials. In general, giving adequate calories and up to 30% of energy intake as protein seemed to preserve muscle mass, protein turnover and respiratory function. Experience from other neuromuscular diseases suggest that patients may benefit from a higher protein intake. Aside from protein and energy, there have been almost no data on whether patients with LOPD have micronutrient deficiencies (vitamins and minerals). The role of vitamin D in muscle and bone health has been studied in a number of different patient groups but not specifically in Pompe disease. However, patients with Pompe disease are at risk for osteopenia and fractures, and this vulnerability appears to be higher if they are not weight-bearing and have muscle atrophy. Recommendations for vitamin D intake range from an acceptable allowance (AI) of 400 IU per day in infants, a recommended dietary allowance (RDA) of 600 IU per day between 1 and 70 years of age, and 800 IU per day for patients 71 years of age and older. In reality, vitamin D supplementation is required for most Canadian patients to achieve a recommended blood level of greater than 75 nmol/L. For adult patients, this usually translates to an additional vitamin D3 (cholecalciferol) supplement of between 1000 and 2000 IU per day. Overall, nutrition in patients with Pompe disease should be optimized.


**Respiratory Function**

Vital capacity remains the best overall indicator of functional impairment and prognosis in LOPD. A postural drop in VC of more than 25% from the sitting to the supine position has been identified as an indicator of diaphragmatic weakness with high sensitivity (79%) and specificity (90%) in various neuromuscular diseases.10–111 Patients showing the largest drops in VC demonstrate more severe hypoventilation and haemoglobin desaturation during sleep.51 Supine VC measurements have been shown to decline more rapidly.24,55,112 Pompe disease patients experience the greatest drops in VC from the seated to the supine position. In general, an upright VC value that is <60% of the predicted value identifies neuromuscular patients at risk for sleep-disordered breathing, while an upright VC <40% of the predicted value indicates an increased risk for sustained nocturnal hypercapnia.113 An upright inspiratory VC of <40% of the predicted value was strongly (sensitivity 80%, specificity 93%) associated with nocturnal hypoventilation in adult Pompe disease patients.51

Maximum inspiratory pressure (MIP) measurements are generally more sensitive than VC for detecting inspiratory muscle weakness, but low values are often related to technical factors and do not necessarily indicate true weakness. Maximal sniff nasal pressure (SNIP) involves measurement of the pressure generated within an occluded nostril during a maximal sniff maneuver.114 In the setting of an equivocally low MIP value or an inability to perform the MIP manoeuvre (e.g., because of bulbar muscle weakness), use of SNIP may be helpful. Although SNIP may be easier to perform, and has a better correlation to VC values than MIP in some neuromuscular diseases,115 this was not shown to be the case in Pompe disease.112 Reducing the degree of coughing effectiveness that are secondary to bulbar dysfunction or respiratory muscle weakness increase patients’ susceptibility to potentially fatal respiratory tract infections.116 The lowest value of maximum inspiratory pressure (MEP) that was consistent with production of a satisfactory cough was in the range of 50-60 cm H2O.116 Peak cough flow (PCF) values below 4.25 L/sec can also identify patients at risk for complications related to impaired clearance of pulmonary airway secretions.117,118

Patients with late-onset Pompe disease should be monitored for the development of respiratory complications and undergo regular pulmonary function tests every 6 to 12 months. Evaluations of forced expiratory and inspiratory VC should be chosen on the basis of the higher of the two measurements.119 Patients and their caregivers should be instructed on appropriate pulmonary airway clearance measures, which might include lung volume recruitment (e.g., breath stacking), manually assisted coughing techniques and the use of a mechanical in-exsufflator device.120 Peak cough flow (PCF) measurements should be included in the routine pulmonary assessment of patients with Pompe disease. Supine VC measurements may be useful in some patients, particularly those in whom upright VC is normal, to detect early pulmonary involvement. However, once the diagnosis of respiratory muscle weakness is established, upright VC values can be used to follow disease progression, and the addition of supine measurements is generally not required.

**Sleep and Nocturnal Ventilation**

Sleep evaluation should generally be performed when the upright VC is <60% of the predicted value or earlier if there is clinical evidence of diaphragmatic weakness (e.g., orthopnea, thoraco-abdominal paradox) or symptoms consistent with sleep-disordered breathing. Although complete polysomnography with CO2 monitoring is preferred to distinguish upper airway obstructive events from hypoventilation and to confirm the occurrence of REM sleep, these techniques may not be readily available and may be burdensome for some patients. In such instances, alternative forms of respiratory monitoring during sleep that ideally include both oximetry and CO2 measurements can be implemented.

Correction of nocturnal hypoventilation with non-invasive ventilator support in neuromuscular patients improves blood gas values not only during sleep but also during the daytime while awake and breathing without ventilatory assistance.121 and these findings have been confirmed in Pompe disease patients.122 This appears to be related to reversal of impaired ventilatory drive rather than changes in respiratory muscle properties or pulmonary function.123 Although the optimal timing for initiation of nocturnal ventilation and extending ventilatory support to the daytime has not been established in adults with Pompe disease, data from studies of other neuromuscular disorders124 suggest that a major deterioration in respiratory status occurs if nocturnal non-invasive ventilation is not instituted within one to two years after the onset of nocturnal hypoventilation. Both volume- and pressure-cycled ventilation assist devices have been successfully used.125 If extension of ventilation assistance into the daytime is necessary for symptom relief or due to the presence of diurnal hypercapnia, intermittent mouthpiece ventilation should be considered as an alternative to invasive tracheostomy.126

**Management Guideline**

1. Patients with late-onset Pompe disease should be monitored for the development of respiratory complications using pulmonary function tests at regular intervals. Quality of evidence: Grade B.

**Exercise**

Disuse atrophy and muscle weakness are universal in Pompe disease14 and can have a significant impact on muscle function and QoL. Resistance exercise may enhance mitochondrial capacity and lower oxidative stress.48 It has been suggested that endurance exercise during ERT may enhance GAA uptake by the working muscle by increasing blood flow,82 but evidence from a mouse model revealed no independent or synergistic effects of endurance exercise on GAA activity or glycogen clearance in skeletal or cardiac muscle tissues.127 However, improvements in running speed, endurance, balance and manual dexterity were noted in GAA-deficient mice that received exercise therapy alone or exercise plus ERT.127 The effects of exercise on muscle strength and performance in patients with Pompe disease has been limited to small-scale, uncontrolled, prospective studies.101,128,130 Terzis and colleagues128 used a progressive resistance exercise program for 20 weeks in 5 patients with Pompe disease who had received ERT for a year. Improvements in muscle strength were noted along with a significant increase in arm fat-free mass. Importantly, an increase in 6MWT distance was associated with a strong statistical relationship between hip extension strength and performance of...
the 6MWT. Despite inclusion of an endurance training component, strength outcomes likely resulted from the resistance exercise aspect. In another study, implementation of endurance exercise in five patients with Pompe disease who received ERT did not appear to improve muscle function. Because evaluation of 6MWT and muscle strength in this study occurred after several months of both ERT and exercise, the true effect of exercise could not be determined. Slonim and colleagues examined the potential benefit of endurance exercise in combination with a low-carbohydrate/high-protein diet in 34 patients with Pompe disease over a 2- to 10-year period. In patients who complied with therapy, the Walton and Gardner-Medwin Scale motor function scores had either improved or reached a plateau. However, it is difficult to ascertain whether the benefits in the latter study could be attributed to exercise and/or the nutritional intervention. Exercise may also be useful for pulmonary involvement in that respiratory muscle strength training was shown to improve inspiratory and expiratory muscle strength in two patients with Pompe disease who were also treated with ERT. Overall, data from clinical studies and animal models suggest a possible benefit of endurance and resistance exercise in patients with Pompe disease that is independent of reducing muscle glycogen storage.

In a questionnaire-based assessment of untreated adult patients with Pompe disease, complaints pertaining to motor function were mostly related to mobility problems and limb-girdle weakness. Rising from a chair, climbing stairs and changing to an upright position after bending were either difficult or impossible for more than two-thirds of respondents; 76% were troubled by fatigue and 46% were bothered by pain. Although evidence regarding the potential benefits of exercise in Pompe disease is limited, a review of exercise in neuromuscular diseases, including Pompe disease, and previously published Pompe disease management guidelines suggest that low-impact or submaximal aerobic exercise, targeted training of specific muscles and exercises that improve balance may be prescribed. Exercise must be tailored to the patient’s level of ability; however, the patient may be required to exercise beyond his or her level of perceived tolerance to obtain a benefit. There is no evidence to suggest that systematic activity restriction in Pompe disease is warranted.

### Functional Capacity, Fatigue and Quality of Life

Compared with the general population, patients with late-onset Pompe disease reported significantly lower QoL values on physical functioning, general health, vitality, and social functioning scales. There is a multitude of functional scales for Pompe disease. In an assessment of disability and participation in daily life activities in 257 adult patients with late-onset Pompe disease using the Rotterdam Handicap Score (RHS), individual item scores were lowest for domestic tasks and work/study. The mean RHS score differed significantly between patients with and without respiratory support and patients with and without a wheelchair. Fatigue is a prominent feature among patients with late-onset Pompe disease. In an assessment of 225 adults with late-onset Pompe disease, 67% of patients had Fatigue Severity Scale (FSS) scores >5, indicative of severe fatigue, and markedly higher than those for healthy controls. An normative profile of physical functioning (mobility and self-care) was developed using an expanded version of the Paediatric Evaluation of Disability Inventory (PEDI) for use in infants and in children up to 14 years of age. Twenty-four of the 26 children with late-onset Pompe disease were either at or below the third percentile for their age in mobility function. The 36-item Short-Form Health Survey (SF–36) has been extensively used as a semi-quantitative measure of health-related QoL in many neuromuscular diseases, including Pompe disease. Patients with Pompe disease show marked reductions in SF–36 physical health domains but only marginal decreases in mental health domains. More recently, the Rasch-built Pompe-specific Activity (R–PAct) scale was developed to better quantify the effects of Pompe disease on activities of daily living and social participation. The R–PAct scale consists of 18 items that best met the validity, reliability and responsiveness criteria throughout the spectrum of late-onset Pompe disease.

From a practical standpoint, at a minimum during clinic visits, inquiries should be made about specific activities of daily living that reflect the underlying major aspects of the disease pathology (limb and respiratory weakness). Areas of inquiry should include difficulties associated with getting in and out of bed, meal preparation and eating, toileting, bathing, ambulation (level walking and climbing stairs) and falls, dressing, shortness of breath on exertion, orthopnea, morning headaches, sleep symptoms (e.g., apnoea, snoring, paroxysmal nocturnal dyspnea), muscle pain and fatigue, speech and swallowing difficulties, and heart palpitations.

### Biomarkers

Glucose tetrasaccharide (GLC4; Glcα1-4Glcα1-6Glcα1-4Glcα1-4Glc) is a tetramer identified in the urine and recently applied in Pompe disease as a biomarker associated with skeletal muscle glycogen content. Higher levels of urine GLC4 are found in 94% of patients with Pompe disease. However, there is a strong relationship with urinary GLC4 and age that must be considered when interpreting the results. Urinary GLC4 is positively correlated with age in children under 1 year of age and negatively correlated with age in patients ≥18 years of age. There is no correlation with age between 1 and 18 years of age, but limited data. In infantile patients, urinary GLC4 levels decrease within four weeks of treatment with rhGAA. Glucose tetrasaccharide is not specific to Pompe disease, and elevations in urine can also be seen in other types of genetic muscle diseases, trauma, acute pancreatitis and malignancies, and can also be increased with pseudodeficiency alleles in the GAA gene. There currently are no studies published that evaluate prospectively the specificity of GLC4 as a screening test when used to distinguish Pompe disease from other sources of elevation of this marker. GLC4 may be useful to monitor a biochemical response to ERT with consideration of age-specific norms, but there is currently insufficient data to evaluate its utility in relationship to a clinical response. This panel does not recommend the use of GLC4 as a diagnostic test.

### Discontinuation of Enzyme Replacement Therapy (ERT)

Pompe disease is a progressive neuromuscular disorder. Therefore, if a patient is treated with ERT and their muscle strength and respiratory parameters remain stable over time, this is contrary to the natural history of the disease, and therapy should be continued even if no improvement in function is seen with
initiation of ERT. It is important to document the rate of decline of skeletal and pulmonary function over time through patient history and review of past health records at the time that the diagnosis of Pompe disease is made. Treatment discontinuation may be considered if:

a. Patients have severe infusion-related reactions that are not amenable to therapy and that compromise patient safety.

b. Patients have an estimated life expectancy, either due to co-morbidities or advanced stages of decline from Pompe disease, that appears to be short and where the outcome is unlikely to be improved with continued use of ERT.

c. Patients have a rate of decline in skeletal and/or pulmonary function after ERT initiation that is similar to that seen prior to the use of ERT.

In Canada, where the cost of the enzyme is provided largely by public healthcare, there are general requirements that patients maintain adherence to a certain frequency of enzyme infusions, supportive therapies and other aspects of medical monitoring of their disease in order to continue receiving enzyme replacement therapy. In certain cases, providers have stopped providing coverage for ERT if compliance becomes an issue. Sporadic or intermittent use of ERT is not justified.

**Palliative Care**

As in other severe neuromuscular disorders, patients with Pompe disease may evolve into a state of advanced respiratory insufficiency as well as severe disability, at which point many forms of treatment may become futile. When patients reach this stage, the medical team involved will offer treatments to relieve or prevent suffering and therefore improve quality of life. The goals of care should be discussed prior to start of treatment, periodically during the course of treatment, and when the goal does not involve aiding recovery from the disease. Palliative care teams can facilitate communication between families and medical teams to clarify treatment goals and make difficult medical decisions. They can also address issues related to grief, loss and bereavement, as well as provide expertise in the management of discomfort and end-of-life care.

**Future Therapeutic Considerations**

Although rhGAA remains the current targeted therapeutic option, there are pre-clinical and clinical trials involving potential new products. Two strategies involve modifications to the GAA molecule itself to enhance uptake. One method involves the addition of extra mannose-6-phosphate residues on the GAA protein to enhance mannose-6-phosphate-mediated cellular uptake (carbohydrate remodelling: oxime-neo-rhGAA). Although this strategy did enhance muscle uptake and glycogen clearance, we are not aware of any data from clinical trials using this type of product. Another strategy involved the creation of a fusion protein where GAA is linked to the insulin-like growth factor II to take advantage of the glycosylation-independent lysosomal targeting (GILT-tagged) to enhance muscle uptake. A murine study has shown that the GILT tag enhanced muscle uptake and glycogen clearance as compared with non-tagged GAA. There is currently a phase 3 trial of GILT-tagged GAA in LOPD (www.clinicaltrials.gov). A murine study has shown that clenbuterol does enhance mannose-6-phosphate receptor expression in vivo and that this enhances muscle enzyme uptake and glycogen clearance. We are not aware of any clinical trials with this compound. Finally, studies have shown that the stability of the GAA enzyme in blood during infusions and the residual enzyme activity in muscle can be enhanced using the molecular chaperone AT2200 (1-deoxynojirimycin hydrochloride; duvoglustat hydrochloride). A phase 2 trial using AT2200 in LOPD patients was completed, but there are no published manuscripts as of the date of submission of the present manuscript.

**DISCLOSURES**

These guidelines represent a consensus opinion of a pan-Canadian, multidisciplinary panel of healthcare professionals who are involved in the care of patients with Pompe disease. The concept of a working group to develop Canadian guidelines for the management of Pompe disease was initiated by members of the expert committee. The working group has been led by Dr. Aneal Khan. Financial contributions have been made by Genzyme Canada (Mississauga, Ontario, Canada) in the form of travel grants, and the authors have received honoraria as speakers and consultants, and some authors (AK) have received research grants from Genzyme. None of the authors have disclosed a financial interest in Genzyme. None of the authors have received financial remuneration for development of these guidelines. This document is not intended to be a comprehensive guide to the diagnosis and management of patients with Pompe disease but represents general guidelines based on evidence in the available published literature, which in the opinion of the authors can inform care providers about the needs of patients with Pompe. The authors have written the manuscript on their own without any input from Genzyme Canada or other service organizations, and the content of this document has been kept strictly confidential among the authors prior to its publication in the literature.

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REFERENCES


