# orphananesthesia

## Anaesthesia recommendations for patients suffering from

## Pompe disease

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**Disease name:** Pompe Disease

**ICD 10:** E74.0

**Synonyms:** Glycogen storage disease due to acid maltase deficiency, Glycogen storage disease type 2, GSD type 2, acid maltase deficiency, alpha–1, 4–glucosidase acid deficiency, glycogenosis due to acid maltase deficiency, glycogenosis type 2, acid alpha-glucosidase (GAA) deficiency, GAA deficiency

Pompe disease is an autosomal recessive condition with an incidence of around 1 in 40,000 in the general population, and is caused by a deficiency of the enzyme acid alpha-glucosidase. Clinical features occur due to the deposition and accumulation of glycogen within lysosomes, most notably those within the cardiac and skeletal muscles. The extent of this enzyme deficiency affects both the age of onset and severity of symptoms, and allows for clinical stratification into distinct subgroups.

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Medicine in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong

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**Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net**

# Disease summary

Clinical classification:

## 1) Infantile-onset Pompe disease

Classic infantile-onset Pompe disease has a reported incidence of 1 in 100,000 and will usually present in the first two to six months of life with hypotonia and muscle weakness, feeding difficulties and failure to thrive, respiratory distress or infections and cardiac problems. Clinical examination and investigation will frequently reveal hypotonia and motor developmental delay, macroglossia, cardiomegaly, generalised hypertrophy, a murmur, cardiomyopathy, conduction disturbances (short PR interval with a broad QRS complex), respiratory distress and hepatomegaly (usually as a consequence of heart failure).

Children with classic infantile-onset Pompe disease will usually have a severe deficiency of the acid alpha-glucosidase enzyme [1].

Without treatment, these symptoms will progress rapidly and the hypertrophic cardiomyopathy may develop a left ventricular outflow tract obstruction or compress adjacent respiratory structures. These cardiac features together with significant weakness of the diaphragmatic and respiratory muscles will lead to death from cardiorespiratory failure within the first year of life.

## 2) Non-classic infantile-onset Pompe disease

This variant will usually present within the first year of life with motor developmental delay and weakness. Cardiomegaly is less a feature, and cardiac involvement is not present in some definitions of non-classic infantile-onset Pompe disease. The rate of clinical progression is slower in these children and without treatment, death will usually occur in childhood as a result of respiratory insufficiency.

## 3) Late or adult onset Pompe disease

This variant can present at any age, although typically an earlier presentation is associated with more severe symptoms. Clinical features include proximal muscle weakness that progresses slowly, and the involvement of the respiratory muscles and diaphragm. A lower limb weakness, poor exercise tolerance and fatigue are usually present, and affected patients may become wheelchair bound in later life. Orthopnoea, sleep apnoea, and respiratory failure may also be present.

Unlike the infantile-onset forms of Pompe disease cardiac involvement is not a feature, although some adults have been reported to have arteriopathy which may be associated with raised blood pressure and occasionally aortic dilatation.

Those affected by late-onset Pompe disease will usually have a partial deficiency of the enzyme acid alpha-glucosidase. (2 – 40% normal enzyme activity) 1

Without treatment, morbidity and mortality occur mainly as a result of respiratory insufficiency and failure, with death occurring anytime from the third decade onwards.

Diagnosis and treatment

Early diagnosis and treatment is vital in the management of infantile-onset Pompe disease and delays can significantly affect the outcome. The anaesthetist will often be called on to

assess, assist and anaesthetise for procedures such as central venous access, which facilitate the institution of enzyme replacement therapy.

The diagnosis of Pompe disease requires the measurement of acid alpha-glucosidase enzyme activity. Reduced enzyme activity is diagnostic of the disease. This was classically obtained from muscle biopsies or cultured skin fibroblasts, but because of the significant risks associated with anaesthesia for these procedures most centres are now able to rapidly analyse enzyme activity from a whole blood leukocyte assay. Dried blood spots is a promising tool for newborn screening [2].

Another important diagnostic test is to assess the child's cross-reactive immunologic material (CRIM) status. This requires molecular analysis or quantification of acid alpha-glucosidase protein. CRIM-negative patients are unable to form any acid alpha-glucosidase enzyme, while CRIM-positive patients have some residual enzyme (functional or non-functional). CRIM-negative patients have been shown to have a poorer response to enzyme replacement therapy since they are at higher risk of producing antibodies against the infused enzymes, and will require immunomodulation early or before the commencement of treatment. CRIM status is an important prognostic factor and CRIM-negative children treated with recombinant human acid alpha-glucosidase are more likely to have reduced survival and to require invasive ventilation than those who are CRIM-positive [3].

The treatment of infantile-onset Pompe disease requires the slow infusion of recombinant human acid alpha-glucosidase (Myozyme® or Lumizyme®) intravenously every one or two weeks. This should ultimately be administered through long-term venous access devices. Infusion-associated reactions include rashes, pyrexia, urticaria, flushing, tachypnea and tachycardia amongst others. Anaphylaxis has been reported.

Those treated within the first six months of life showed improved mortality, reduced ventilator-free survival, and an improvement in the cardiomyopathy and motor functions. One investigator showed a 95% reduction in the risk of death and a 91% reduction in the risk of invasive ventilation and death in their study patients over the course of their treatment. Patients who were treated within few weeks of life may achieve normal motor development during early childhood [15]. Long-term outcomes are still unclear [4,5].

## Typical surgery

Typically, patients present for surgery to assist diagnosis or to facilitate the long-term administration of enzyme replacement therapy. These procedures include peripherally inserted central lines, tunnelled cuffed central lines or buried central ports of access and very rarely muscle or skin biopsies [6,7,8,9,10,11].

Children in respiratory distress may require elective intubations for admission to a paediatric intensive care unit (PICU) and once there may require procedures such as tracheostomies, gastrostomies, gastrojejunostomies, fundoplications and bronchoscopies as part of their care.

One case report has described bilateral inguinal hernia repairs in a child with Pompe disease [11].

Adults with late-onset Pompe disease may present for any type of surgery. Case reports in the literature include surgery for a right hemicolectomy and the obstetric management of a mother with Pompe disease [12,13].

## Type of anaesthesia

Anaesthesia for individuals with Pompe disease should be undertaken with the utmost care and precaution. The risk of arrhythmias, cardiac arrest and death as a direct result of anaesthesia should not be underestimated and has been quoted at 6% [11]. Anaesthesia should ideally be undertaken in a specialist institution that has experience in the management of these children and adequate intensive care backup.

All anaesthetic agents have been used for general anaesthesia in children with Pompe disease both with success and with complication. All anaesthetic agents, including those used for purely sedation, should be administered with full monitoring and in an environment that has full access to resuscitation equipment. Agents should be titrated slowly and in reduced doses to make allowance for the prolonged circulatory time caused by the cardiomyopathy.

Agents that cause vasodilatation, decrease the blood pressure and cardiac output and thereby reduce coronary perfusion pressure are most likely to cause cardiac arrhythmias and cardiac arrest. Implicated agents include propofol, halothane, and high doses of sevoflurane. Agents which maintain blood pressure such as ketamine have been recommended, however case reports of arrhythmias on ketamine induction do exist, and in the author's institutions review of 22 Pompe patients one episode of cardiac arrest occurred on induction with ketamine [6,7,8,9,10,11]. Currently no case reports regarding the use of dexmedetomidine in Pompe disease have been published.

Because of the significant risks associated with general anaesthesia many institutions strongly advocate regional anaesthesia as the technique of choice when appropriate for children with Pompe disease. Regional anaesthesia has been used successfully in many case reports and has included femoral nerve blocks, caudal blocks and in two adult cases epidurals. No complications directly related to the regional anaesthetics have been reported, complications have only arisen as a result of sedative anaesthetic agents given along with the block [8,10,12,13]. It is the policy in the United Kingdom for all children presenting with Pompe disease to have an initial placement of a peripherally inserted central catheter awake under local anaesthetic if possible. After 6 months of enzyme replacement therapy and a further cardiac review, they will be considered for a more definitive central venous access under general anaesthesia.

## Necessary additional diagnostic procedures (preoperative)

All children with Pompe disease who present for anaesthesia should have a thorough Cardiac assessment. This should include an electrocardiogram (ECG), a recent echocardiogram (ECHO), and a review by a paediatric cardiologist.

Many will most certainly have a significant hypertrophic cardiomyopathy, and although this is not likely to be optimised preoperatively this information will help to direct decisions to pursue regional anaesthesia over general anaesthesia and guide an open discussion about the risks of anaesthesia with the child's family. One recent extensive case series suggests a high risk of death in children with a left ventricular mass index of greater than 350 grams per square meter [11]. Patients who have been treated by enzyme replacement therapy for a period of time may have a normal size heart, but the risk of arrhythmia still persists.

A chest x-ray is important to assess cardiomegaly, as well as the impact of the enlarged heart on surrounding structures including lung volumes and the tracheo-bronchial tree. A pulmonary assessment should be made by a specialist and a baseline sleep study done. Where respiratory symptoms exist as a result of poor cardiac function, muscle weakness or where sleep disturbance is a feature further investigations and interventions should be directed by a specialist.

Routine bloods such as a full blood count, coagulation studies, blood chemistry and blood crossmatch should be taken when indicated and according to the standard requirements of the surgical procedure.

Perhaps the most important preoperative strategy for these children, particularly where left ventricular outflow tract obstruction is a feature of their hypertrophic cardiomyopathy, is to ensure maintenance of their intravascular volume status. Preoperative fasting should be minimised, and where possible, maintenance fluids should run during the peri-operative period. Dehydration can easily exacerbate the dynamic outflow tract obstruction caused by the hypertrophied septum, and these children are particularly vulnerable to cardiac output and mean arterial pressure reductions at the time of induction.

## Particular preparation for airway management

A difficult airway is not classic feature of Pompe disease despite the frequent presence of macroglossia.

In an unpublished review of 22 patients with Pompe disease from the author's institution, 17 general anaesthetics were performed, and 15 sets of noted reviewed. All 15 had uneventful facemask ventilation, and were successfully intubated. In 4 cases the intubation was more challenging, but ultimately successfully managed with external cricoid pressure.

## Particular preparation for transfusion or administration of blood products

Standard management.

## Particular preparation for anticoagulation

Standard management.

## Particular precautions for positioning, transport or mobilisation

Standard management.

## Probable interaction between anaesthetic agents and patient's long-term medication

There have been no reported incidents of anaesthetics drug interactions with alglucosidase alfa (Myozyme® and Lumizyme®).

Children with Pompe disease should only be anaesthetised after a thorough preoperative assessment, careful consideration as to the necessity of the surgical procedure and a detailed and frank discussion with the family regarding the risks of anaesthesia and other options available.

Ideally, two anaesthetists, preferably with experience in anaesthesia for children with hypertrophic cardiomyopathy, should anaesthetise a child with Pompe disease. The child should be fully monitored prior to induction (see 'Particular or additional monitoring' below). The period of preoperative fasting should be minimised and peri-operative maintenance fluids commenced as soon as possible to avoid dehydration, which might exacerbate the left ventricular outflow tract obstruction.

Many centres would consider regional anaesthetic techniques a far safer alternative in these children, and where possible these should be considered. All local anaesthetics and regional techniques can theoretically be used safely in children with Pompe disease with standard precautions and risks applying. Many case reports exist of the successful use of caudal anaesthetics and femoral nerve blocks for muscle biopsies [8,10].

Where sedation is used, it should be administered with extreme caution, and as for a standard general anaesthetic technique with full monitoring and backup resuscitation facilities. In one case series agents including midazolam, ketamine, and propofol were used to achieve sedation in 11 procedures. In one case where midazolam and propofol were used the child developed hypotension and tachycardia which resolved after treatment with 100% oxygen and CPAP [8].

Regardless of the agent used, general anaesthesia should be induced with reduced agent doses (on average a quarter to half of the calculated dose) and over double the conventional time period. The ideal induction agent would be one that does not alter haemodynamic parameters, particularly maintaining mean arterial blood pressure, cardiac output, diastolic filling, and avoiding tachycardia. Agents including ketamine, propofol, sevoflurane, halothane, etomidate, thiopentone and midazolam have all been used to induce and maintain anaesthesia in these children.

Ketamine has been used successfully to induce anaesthesia in many children with Pompe disease [6,7,10,11]. The advantageous properties of ketamine include its sympathetic stimulation, which increase blood pressure, cardiac output and coronary perfusion, and maintain systemic vascular resistance and contractility. The disadvantage of ketamine is the tachycardia induced by this sympathetic stimulation. Where there is a risk of myocardial ischaemia it is desirable to maintain a normal heart rate to allow for better coronary perfusion. This effect is particularly relevant where there is left ventricular outflow tract obstruction. In these circumstances when ketamine is used it is important to have drugs available that can reduce the heart rate, and to maintain normovolaemia through adequate fluid therapy. Of the case series of 22 Pompe children treated at the author's institution, only one child suffered a cardiac arrest and in this case it was a ketamine induction. Despite some case series also reporting arrhythmias on induction with ketamine [9,10] most feel that this is the most suitable drug currently available for the induction of children with Pompe disease.

Midazolam may cause vasodilatation, but is a useful adjunct to limit the dose requirements of other anaesthetic drugs.

Propofol reduces afterload, systemic vascular resistance, diastolic blood pressure and mean arterial pressure. Numerous case series report arrhythmias upon administration of propofol [6,8,11] and therefore suggest that this is the least appropriate choice for induction of children with Pompe disease.

Sevoflurane can cause vasodilation and reduce myocardial contractility. It must be used with care, slowly and in low concentrations, but is an acceptable anaesthetic agent for induction. In many cases cardiac arrhythmias have been associated with the use of higher concentrations of sevoflurane [6,11].

Suxamethonium should be avoided in patients with Pompe disease. In the presence of the hypotonia and myopathy in these children there is a theoretical risk of potassium efflux, hyperkalaemia and rhabdomyolysis, although no case reports of such a reaction exist in the literature.

Non-depolarising muscle relaxants should be avoided if possible or used in reduced doses since these patients will be sensitive to neuromuscular blockade due to their hypotonia and weakness.

Opiates should be used with caution in the presence of respiratory insufficiency that often exists in association with respiratory muscle weakness. A multimodal approach to pain, which includes regional techniques, is preferable in these children.

The role of agents such as etomidate, remifentanil and dexmedetomidine in patients with Pompe disease has poor coverage in medical literature, but may offer safer alternatives to current anaesthetic agents in the future.

Maintenance of anaesthesia requires equal care and attention as induction, particularly if the anaesthetist switches from one agent to another. In case reports patients are most frequently managed. Of the literature reviewed, the most common agents used for maintenance are ketamine or volatile anaesthetic agents, such as sevoflurane, in combination with nitrous oxide. The vasodilatory and myocardial depressant effects of volatile agents require that they are titrated in slowly and that low concentrations are maintained. Volatiles such as sevoflurane are acceptable to use in Pompe disease, but to maintain a low concentration they are best used in conjunction with other agents. In one case report a patient developed ventricular fibrillation on commencement of 2% sevoflurane maintenance following a stable induction with etomidate [11]. In the author's institution series of 22 Pompe patients, gentle sevoflurane/nitrous oxide inhalational inductions were achieved in 60% of cases and maintenance with sevoflurane occurred in all but one case without complication.

Emergence from anaesthesia should occur with full monitoring, taking care to avoid tachycardia. The patient should be monitored in the post-anaesthetic care unit until fully awake or transferred to an intensive care unit.

## Particular or additional monitoring

All standard monitoring including oxygen saturations, ECG (ideally 5 lead) and blood pressure monitoring must be started prior to the induction of anaesthesia. Where possible direct arterial blood pressure monitoring should be placed prior to induction or as soon after if indicated. If cardiac output monitoring through arterial pulse contour analysis is available this can be very helpful [11].

Due to the high risk of peri-operative arrhythmias, full resuscitation equipment should be readily available. It is advisable to attach defibrillator pads to the child before induction of anaesthesia [6,9,11].

## Possible complications

Complications of Pompe disease related to anaesthesia may be divided into cardiac and respiratory complications.

Cardiac complications consist of cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, bradycardias and asystolic arrest.

The pathophysiology behind these arrhythmias is complex. The considerable hypertrophic cardiomyopathy and reduced left ventricular volume result in high left ventricular filling pressures. Good hydration and sufficient preload are essential to ensure an adequate cardiac output. It is also vital for diastolic blood pressure to remain high in order to ensure an appropriate coronary perfusion pressure. Any imbalance to this system, such as might occur during anaesthetic induction, can result in coronary ischaemia [11].

Glycogen accumulation within the heart can also occur in the cardiac conduction system predisposing to abnormal cardiac rhythms. In the presence of coronary ischaemia this can cause ventricular and supraventricular tachycardias which often rapidly progress to fatal cardiac rhythms and death.

In an extensive case series of 139 patients, 6% (9 patients) suffered cardiac arrhythmias on induction. In this series of arrests ventricular fibrillation (VF) occurred on 5 occasions, ventricular tachycardia (VT) on 3 occasions and bradycardia on 3 occasions. 3 patients died as a result of these arrhythmias; ventricular fibrillation being the abnormal rhythm on each occasion [11,6].

Another case involving anaesthesia for a child with Pompe disease describes the development of a Torsade de pointes rhythm on induction. This was successfully converted to VF, and then to sinus rhythm [9].

A final case report reviews two anaesthetics for the same child. In the first induction the child developed bradycardia with 2% halothane. This progressed to asystolic arrest with suxamethonium and atropine. The child was subsequently converted to VF. This then reverted to complete heart block after 3 shocks, and was finally restored to sinus rhythm after isoprenaline and atropine were given [7].

Respiratory insufficiency as a result of the hypotonia and neuromuscular weakness in Pompe disease can become exacerbated by surgery and general anaesthesia, and sensitivity to neuromuscular blocking agents and opioids. Prolonged mechanical ventilation is therefore a risk of surgery for patients with Pompe disease.

In the presence of a high left ventricular end diastolic pressure where fluid resuscitation has been too extensive, it is possible for some cases to develop pulmonary oedema. This will often occur after extubation.

Rhabdomyolysis and hyperkalaemia can occur in patients with Pompe disease as a consequence of using suxamethonium [7].

## Postoperative care

Attentive care of the patient with Pompe disease must continue into the post-operative period. They must be fully monitored with oxygen saturations, ECG and blood pressure in an intensive care or high dependency setting for an appropriate period of time after the surgery. A multimodal approach to pain relief is recommended, with careful use of opioids, which can exacerbate respiratory compromise.

There are no case reports in the literature documenting post-operative deterioration, but from the series of 22 children with Pompe disease at the author's institution one child had a respiratory arrest in the post-operative period requiring intubation and admission to PICU.

## Information about emergency-like situations / Differential diagnostics

In the event of cardiac and/or respiratory compromise or arrest, standard national paediatric resuscitation guidelines should apply to children with Pompe disease.

## Ambulatory anaesthesia

Children with Pompe disease should not be considered for ambulatory anaesthesia.

## Obstetrical anaesthesia

In the past, children with infantile-onset Pompe disease have not survived into adulthood. Current treatment with enzyme replacement therapy has changed the natural history of this disease, and it is yet to be seen if these children will survive to reproductive age and be able to conceive. Adults with late-onset Pompe disease have presented in pregnancy for obstetric management.

A decline in the respiratory function of pregnant patients with Pompe disease has been reported, but there is no obvious associated increase in the rate of caesarean sections [14].

One case report describes a 31year old parturient and describes her two pregnancies which were also complicated by severe preeclampsia. In the first pregnancy she was induced at 27 weeks and had an emergency caesarean section for foetal distress and intrauterine growth retardation. This child did not survive, but the mother had an uncomplicated perioperative course.

Her second pregnancy was again complicated by preeclampsia, which was successfully managed with labetolol. At 37 weeks her preeclampsia deteriorated and she was admitted for blood pressure management that was assisted by direct arterial monitoring. She had a caesarean section using a combined spinal epidural technique and successfully delivered. Her preoperative course was uncomplicated [12].

This paper's authors recommend a routine preoperative assessment of the parturient with an emphasis on a pulmonary function review to test for respiratory compromise. They recommended regional anaesthesia as the technique of choice in the obstetric patient, but stressed that the presence of a scoliosis may complicate the technique. Where general anaesthesia was required they cautioned against the use of suxamethonium because of the

risk of hyperkalaemia in association with the neuromuscular weakness. They also advocated judicious use of non-depolarising muscle relaxants and opioids, which may exacerbate the respiratory weakness [12].

**Literature and internet links**

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