Background

Gaucher disease is an autosomal recessive lysosomal glycosphingolipid storage disorder, resulting from deficiency of the lysosomal enzyme acid β-glucosidase (glucocerebrosidase) [1]. The disease is pan-ethnic and is the most prevalent of the lysosomal storage disorders. It has been classified into three clinical types. Type 1 (non-neuronopathic) occurs in 1 of 450-865 people of Eastern European (Ashkenazi) Jewish descent and in 1 in 200000 non-Ashkenazi Europeans[2]. The overall birth incidence of Gaucher disease (all subtypes) in Australia is 1 in 57,000 [3] and 1.16 in 100,000 in The Netherlands [4]. Men and women are affected equally.

This partial enzyme deficiency, results in the widespread accumulation of glycosphingolipid-laden macrophages (Gaucher cells) throughout the liver, spleen, bone marrow, skeleton and occasionally the lung. In types 2 and 3 pathology also occurs within the brain. Type 1 disease varies in severity partly as a result of varying residual enzyme activity, ranging from mild asymptomatic cases (which may go undiagnosed) to severe, life threatening disease. Onset of clinical features may occur at any age in type 1 disease, whilst type 2 presents in infancy and type 3 typically presenting early in childhood. Early onset in type 1 disease predicts a more aggressive course[5, 6].

Patients with Gaucher disease may present with several clinical manifestations; in particular, an enlarged spleen and associated anaemia or thrombocytopenic bleeding, and enlarged liver with possible evidence of hepatic dysfunction or portal hypertension[2]. Skeletal complications are commonly the presenting feature of the condition, with bone pain, avascular necrosis of the femoral head, or pathological fractures[7, 8]. Occasionally pulmonary, cardiac or renal involvement occurs. Life expectancy varies: the milder forms of type 1 having a normal life expectancy, while untreated severe type 1 disease may lead to death from thrombocytopenic bleeding, asthenia or the complications of splenectomy from the first decade of life[9] [10] [11]. Children with type 2 do not survive beyond 2 to 3 years of age. Patients with type 3 disease may die of progressive neurological deterioration in the second decade, though a few patients with non-progressive neurological features have survived into their fourth decade without specific treatment other than splenectomy.

This lysosomal storage disorder was the first to be treated by enzyme replacement therapy (ERT), based on complementation of lysosomal catalytic activity by intravenous infusion of purified human, and later recombinant, glucocerebrosidase. This treatment is effective, but costly. The cost of treatment imposes a duty on physicians and health-care managers to ensure that it is delivered in an efficient and closely monitored fashion.

This guideline has been written by clinicians of Addenbrooke’s Hospital, Cambridge and The Royal Free Hospital, Hampstead at the invitation of the National Specialist Commissioning Advisory Group of the UK Department of Health. All physicians treating adult Gaucher disease patients in NSCAG-designated centres have been invited to contribute. As Gaucher disease is rare, the data on which this guideline is based are limited. Although many authors have clearly demonstrated the effectiveness of enzyme replacement therapy in open-label studies, no randomised double-blind placebo-controlled trials of ERT have been published. To our knowledge, no formal meta-analysis of studies has been carried out. Optimal dosing remains controversial. The ultimate role of substrate deprivation therapy remains to be determined. Limited data exist on the natural history of untreated Gaucher disease. This guideline draws upon published studies and upon published consensus statements, guidelines and recommendations. It reflects clinical practice in the UK in 2005. It will require ongoing evaluation and revision.
**DIAGNOSIS**

Gaucher disease may be suspected in patients with cytopaenias, visceral enlargement, bone infarction crises and those with a history of previous avascular necrosis such as Perthe’s disease[2]. The diagnosis may be suggested also by the examination of histological material that has been available from bone marrow biopsies, liver biopsies and splenectomy specimens in particular[12].

- **Definitive diagnosis** is made by demonstration of reduced acid β-glucosidase activity in peripheral blood leucocytes or in fibroblasts cultured from skin biopsy samples[13]. Designated laboratories in the UK, capable of this analysis include The Institute Of Child Health, Great Ormond Street Hospital, The Willink Institute, Manchester and the Department of Biochemical Genetics, Addenbrooke’s Hospital, Cambridge. Gaucher disease is associated with a partial deficiency of this activity in of the order of 10 to30% of normal.

- **Confirmative DNA mutational analysis** of the glucocerebrosidase gene should be attempted, as this is often of prognostic use[14]. Of the many mutations that occur in this gene up to 10 are of practical diagnostic value since they are widespread. Many patients show compound heterozygosity for mutant alleles of glucocerebrosidase.

**INITIAL ASSESSMENT AT BASELINE:**

The history of the family pedigree, which may identify others affected by this autosomal recessive condition, is of value. The history should include the occurrence and progression of childhood illnesses and of events such as painful hips or bone crises which may in retrospect be attributable to the disease. Particular note should be made as to whether the patient has undergone surgical procedures to correct squints, has had a splenectomy or orthopaedic interventions. Previous history of bruising, bleeding and the requirements for platelet or red cell transfusions will be of value. Complaints of poor vision, oculomotor difficulties, shortness of breath, recurrent infection, fractures, bone pain, and distension of the abdomen should be sought. Other phenomena to note include frequency of nosebleeds, onset of menarche in women and the nature and duration of menstrual episodes[2].

Clinical examination should pay attention to height, weight, blood pressure and urine analysis. Evidence of corneal opacification should be sought, as well as oculomotor gaze palsies, pingueculae, jaundice, pallor, ecchymoses, purpura and petechiae, spinal deformity, defects of joint movement, the presence of visceromegaly and signs of chronic liver disease.

Neurological assessment to exclude type III (if suspected or if evidence of early onset in childhood or severe phenotype) is recommended and examine for the presence of physical signs of Parkinsonism is warranted..

Genetic counselling: identification of other family members at risk should be performed by experienced and trained clinical staff or by specialist genetic counsellors

Application of a validated health-related quality of life instrument is recommended[13].
Laboratory investigations are listed below

<table>
<thead>
<tr>
<th>Test</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme Activity of Glucocerebrosidase In Leukocytes</td>
<td>Institute of Child Health Willink Institute</td>
</tr>
<tr>
<td>(At baseline only)</td>
<td></td>
</tr>
<tr>
<td>DNA, mutational analysis (at baseline only)</td>
<td>As above plus Addenbrooke’s Royal Free</td>
</tr>
<tr>
<td>Chitotriosidase activity</td>
<td>As above</td>
</tr>
<tr>
<td>PARC/CCL18 (in evaluation)</td>
<td>Addenbrooke’s</td>
</tr>
<tr>
<td>Chitotriosidase DNA Mutational Analysis (recommended)</td>
<td>ICH Willink Royal Free Addenbrooke’s</td>
</tr>
<tr>
<td>Full Blood Count + film</td>
<td>Routine Haematology Laboratories</td>
</tr>
<tr>
<td>Vit B12, folate, ferritin, Urinary and serum lysosome</td>
<td>Routine Clinical Chemistry Laboratories</td>
</tr>
<tr>
<td>(optional)</td>
<td></td>
</tr>
<tr>
<td>Endocrine profile to include PTH + 25-OH Vit D + TFT</td>
<td>Routine Clinical Chemistry Laboratories</td>
</tr>
<tr>
<td>(recommended)</td>
<td></td>
</tr>
<tr>
<td>Biochemistry profile, renal, liver, lipid profiles, serum</td>
<td>Routine Clinical Chemistry Laboratories</td>
</tr>
<tr>
<td>ACE, CRP, TRAP, IGG’s, Serum Protein electrophoresis</td>
<td></td>
</tr>
<tr>
<td>(lipoprotein-a, homocystine LDH - optional)</td>
<td></td>
</tr>
<tr>
<td>Clotting screen to include Factor XI levels and Fibrinogen</td>
<td>Haemostasis lab, must be delivered fresh to the lab for analysis</td>
</tr>
<tr>
<td>Serum Storage for antibody Screening etc</td>
<td>Provision of long-term storage facilities warranted</td>
</tr>
</tbody>
</table>
**DIAGNOSTIC IMAGING:**

<table>
<thead>
<tr>
<th>MODALITY</th>
<th>FREQUENCY</th>
<th>RATIONALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>At baseline and 12 - 18 monthly</td>
<td>Initial assessment, staging and calculation of organ volumes, Visceral Infarction</td>
</tr>
<tr>
<td></td>
<td>Follow up or when clinically</td>
<td>New symptoms suggestive of bone or joint disease</td>
</tr>
<tr>
<td></td>
<td>indicated</td>
<td>Bone marrow fat fraction (preferable, if available)</td>
</tr>
<tr>
<td>DEXA (Dual energy X-ray</td>
<td>Every 2 years (recommended)</td>
<td>Selection of patients at risk of fractures, prior to and at follow up in patients requiring antiresorptive or anabolic bone therapy</td>
</tr>
<tr>
<td>Absorptiometry)</td>
<td></td>
<td>To be discussed</td>
</tr>
<tr>
<td>Plain Radiology</td>
<td>At baseline, every five years</td>
<td>Acute bone crisis, diagnosis of fracture. Pulmonary involvement.</td>
</tr>
<tr>
<td>Skeletal survey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Only if indicated</td>
<td>Organ measurement, gall stones, portal hypertension or chronic liver disease, renal involvement</td>
</tr>
<tr>
<td>Heel Bone Ultrasound</td>
<td></td>
<td>If other sites not accessible to DEXA</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>In selected patients</td>
<td>To confirm or refute the suspicion of pulmonary hypertension or</td>
</tr>
</tbody>
</table>

For patients who suffer from claustrophobia, CT can be considered if MRI is not possible. If MRI necessary (evaluation of bone-marrow involvement) facilities for sedation should be provided.

**FUNCTIONAL STUDIES**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Lung Function Test</td>
<td></td>
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<tr>
<td>Eye movement assessment</td>
<td></td>
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</tbody>
</table>

- Occasionally, although not routinely, diagnostic biopsy may be indicated, typically of the bone marrow or liver to demonstrate Gaucher disease and exclude other haematological malignancies and liver pathology.

**CRITERIA FOR TREATMENT:**

In general, early presentation with clinical features of Gaucher disease signifies a severe phenotype[5, 6]. One aim of intervention in such patients is primary prevention of irreversible bone or liver damage[15]. Similarly, patients identified with genotypes known to be associated with rapid progression are also candidates for early intervention with enzyme replacement therapy.
### Indications for Specific Treatment:

(in the absence of an alternative explanation)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>A steady state haemoglobin value of less than 11g/dl</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>A steady state platelet count less than 100x10⁹/l</td>
</tr>
<tr>
<td>Organ enlargement</td>
<td>Both liver and spleen can be enlarged in Gaucher disease. Mild splenomegaly (less than 10 x normal) is not an indication for treatment but moderate splenomegaly (10-40 x increased size) or severe splenomegaly (&gt; 40 x increased size) indicate the need to treat</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>Prior splenectomy is a marker for disease severity and risk of avascular necrosis</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>Diagnosed by CT scan, pulmonary function tests</td>
</tr>
<tr>
<td>Skeletal involvement</td>
<td>Demonstrable by CT scan, X-Ray or MRI scan should be an indication for treatment if sufficiently severe, especially in children or young adults (Erlenmeyer Flask deformity alone is not currently an indication for specific treatment)</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>For example severe tiredness and lethargy</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Female infertility without alternative explanation may be an indication for treatment</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Particularly if more than 10% body weight is lost over a 1 year period</td>
</tr>
<tr>
<td>Mobility aids</td>
<td>Patients requiring mobility aids such as crutches and wheelchairs to aid mobility for everyday living</td>
</tr>
<tr>
<td>Performance status</td>
<td>Impaired performance status and reduction in quality of life score</td>
</tr>
<tr>
<td>Genotype/phenotype</td>
<td>Patients identified with genotypes known to predict an aggressive phenotype should be considered to receive early intervention, even if symptoms are not yet manifestly severe to prevent irreversible damage, this usually occurs when a symptomatic family member has been identified</td>
</tr>
</tbody>
</table>

### TREATMENT OPTIONS:

1. **Enzyme replacement therapy:** Cerezyme (Imiglucerase) – Analogue of human intracellular glucocerebrosidase, produced by recombinant DNA technology using mammalian cells (CHO cells). It is modified by sequential cleavage of sugars to expose mannose residues, allowing targeting to tissue macrophages, where it catalyses the degradation of glucocerebroside. It is the treatment of choice for Types 1 and 3 Gaucher Disease.

2. **Ceredase:** No longer licensed for use, however there is a limited residual supply for those patients unable to tolerate Cerezyme for whatever reason. Hospital prescribed only use. The supply is unlikely to continue long term.
3. **Substrate Reduction Therapy**: Zavesca (Miglustat) – Oral daily therapy of 100 mg. tds. Indicated for those patients with mild to moderate Gaucher disease for whom enzyme therapy is not suitable. (Refer to sections below and guidelines in conjunction with EWGGD paper by The Advisory Council To The European Working Group On Gaucher Disease[17]) Hospital prescribed usage only.

4. **Supportive therapy**: Indicated for those patients who decline the above options, (usually elderly patients) and require symptomatic supportive intervention with blood products, bisphosphonate therapy, and/or analgesia.

5. **Monitoring**: Patients identified with a Gaucher disease mutation, who may be asymptomatic, do not require treatment at present, and are monitored for disease progression at which time treatment options will be reviewed.

6. **Bone Marrow Transplantation**: No longer advocated for type 1 patients now that effective ERT and SRT are available. May still be considered under certain circumstances for type 3 patients when a matched, unaffected sibling donor has been identified.

7. **Gene Therapy**: At the research stage.

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**Imiglucerase Treatment – Dosing Regimen**

There is no international consensus on dose of imiglucerase to be administered to adult patients with Gaucher disease. Several groups advocate the high-dose (60U/kg) biweekly infusion regimen, which was the dosing strategy in the original study which lead to licensing[18]. Other groups have advocated a low-dose (1.25-5 U/kg) high-frequency (3 times weekly) regimen[19-21]. The proponents of the low-dose high-frequency regimen have claimed, in support of this regimen, biological plausibility, great cost-savings and efficacy which does not differ from the high-dose regimen. Each of the studies has recruited small numbers of patients and no formal power calculations have been included. No detailed meta-analysis of these studies has been performed, apart from a brief survey by Beutler[22]. The debate between proponents of these dosing regimens has, at times, been controversial[23]. The publication of treatment goals may have, to a certain extent, defused this argument.

The concept of a phased reduction in dose from the initial high dose, once some amelioration of disease features has been achieved, has been proposed [24]Dosing may be individualised to each patient depending on clinical status, disease severity and genotype. Hollak has demonstrated the efficacy of an individualised low-dose regimen, in which dose may be increased or decreased depending on the achievement of certain therapeutic goals[25].

The adult protocol advocates a wide range of dose frequencies (from three times weekly to once every two weeks) and dose quantities (from 10 to 60u/kg body weight per month total). Initial frequency of dosing is usually weekly, with conversion to a biweekly regimen once the condition has stabilised, if the patient chooses this option.

- A dosage guideline for patients under 60 kg. body weight: Commence Imiglucerase (Cerezyme) at 400 i.u per week

- For patients over 60 kg. body weight: Commence Imiglucerase (Cerezyme) 600 – 800 iu. Per week

Initial dose may be higher in patients with severe manifestations or Type 3 disease. The maximum dose recommended by the manufacturer for adults with type 1 disease is 60 units/kg every 2 weeks. Dosage adjustment is based on the response of disease to therapy. Dose may be altered up or down according to the individual patient responses, based on the achievement of therapeutic goals. Dose is also partly determined by the requirement to use whole vials of Cerezyme, which are available as 200U and 400U vials.
SUBSTRATE REDUCTION THERAPY

An orally-available drug, miglustat (Zavesca) has received a limited licence for the treatment of adults with non-neuronopathic Gaucher disease. Licencing was granted on the basis of a non-comparative trial, involving 28 patients with mild/moderated gaucher disease unable or unwilling to receive ERT. At twelve months there was a mean reduction in liver organ volume of 12.15 and in spleen volume of 19%. A mean increase in haemoglobin concentration of 0.26 g/dL and a an increase in platelt count of 8.29 X 10^9/L were observed. Eighteen patients continued to receive miglustat in an extended treatment protocol at the end of which period the mean reduction in liver volume and spleen volume observed were 17.5% and 29.6% respectively, associated with a rise in haemoglobin concentration of 0.95 g/dL and a rise in platelet count of 22.2 X 10^9/L.

The usual starting dose is 100mg tds, though this may be reduced in patients with diarrhoea. Undesirable or Adverse effects are as follows:

1. Very Common (>10%): Weight loss, tremor, dizziness, headache, leg cramp, visual disturbance, diarrhoea, flatulence abdominal pain, nausea, constipation, vomiting
2. Common (>1%): Decreased appetite, weight increase, paraesthesiae, peripheral neuropathy, cognitive dysfunction, dyspepsia, abdominal distension.

Two case of peripheral neuropathy were reported after the 12 month follow-up period in the original trial. One case of cognitive decline in a patient in the extension trial was reported, though the association with the drug is not certain.

Weight loss has been observed in approximately 60% of patients with a mean loss of 6-7% of body weight at 12 months with some later increase towards baseline. Gastrointestinal symptoms occur in more than 80%. In most cases these symptoms are mild and remit on treatment, albeit at a lower dose in some cases. The diarrhoea responds to loperamide.

A position paper on the role of this drug in the management of type I Gaucher disease, produced by an advisory council to the European Working Group on Gaucher Disease, has been published[17]. The advisory council makes the following recommendations.

• The preferred treatment for symptomatic Gaucher disease is enzyme replacement.
• Miglustat is indicated in patients naïve to specific treatment, with mild or moderate symptomatic Gaucher disease, who are unwilling or unable to receive ERT for medical or personal reasons.
• Miglustat is also indicated in patients who are unsuitable, unwilling or unable to continue ERT. Examples may include needle phobia, religious reasons, lifestyle and work factors, travelling arrangements.
• Coadministration with ERT may be considered in patients with disabling disease activity despite maximum achievable dosing with ERT.
• Prescription should be restricted to experts in the field of gaucher disease working in dedicated centres
• Choice of ERT or SRT should not be based on financial cost
• Potential adverse events should be discussed with patients prior to treatment.
• Safety monitoring and cooperation with ongoing pharmacovigilance program set up by Actelion Ltd is required
• The safety and efficacy of miglustat in severe Gaucher disease has not been established. For this purpose severe Gaucher disease is defined as HB,9g/dL, Platelet count <50X10^9/L, or evolving bone disease.

GOALS OF TREATMENT

An international consensus on therapeutic goals in the treatment of Gaucher disease[16] has been published. This document includes summary tables which are adapted and appended below.

Table 1 Therapeutic Goals for Anaemia

• Increase haemoglobin levels within 12 to 24 months to
≥11g/dL for women
≥12g/dL for men

• Eliminate blood transfusion dependency
• Reduce fatigue, dyspnoea, angina
• Maintain improved Hb values achieved after the first 12 to 24 months of therapy

Table 2 Therapeutic Goals for Thrombocytopaenia
• All patients: increase platelet counts during the first year of treatment sufficiently to prevent surgical, obstetric and spontaneous bleeding.
• Splenectomised patients: normalisation of platelet count by 1 year of treatment.
• Patients with intact spleen:
  o Moderate baseline thrombocytopaenia (60-120 X 10^9/L): the platelet count should increase by 1.5 to 2-fold by year 1 and approach low-normal levels by year 2.
  o Severe baseline thrombocytopaenia (<60 X 10^9/L): the platelet count should increase by 1.5-fold by year 1 and continue to increase slightly during years 2 to 5 (doubling by year 2), but normalisation is not expected.
  o Avoid splenectomy (may be necessary during life-threatening haemorrhagic events)
  o Maintain stable platelet counts to eliminate risks of bleeding after a maximal response has been achieved.

Table 3. Therapeutic Goals for Hepatomegaly
• Reduce and maintain the liver volume to 1.0 to 1.5 times normal (according to body weight)
• Reduce the liver volume by 20% to 30% within year 1 to 2 and by 30% to 40% by year 3 to 5

Table 4. Therapeutic Goals for Splenomegaly
• Reduce and maintain spleen volume to ≤2 to 8 times normal
• Reduce the spleen volume by 30% to 50% within year 1 and by 50% to 60% by year 2 to 5
• Alleviate symptoms due to splenomegaly: abdominal distension, early satiety, new splenic infarction.
• Eliminate hypersplenism

Table 5 Therapeutic Goals for Skeletal Pathology.
• Lessen or eliminate bone pain within 1 to 2 years
• Prevent bone crises
• Prevent osteonecrosis and subchondral joint collapse
• Improve BMD
  o Adult patients: Increase trabecular BMD by 3 to 5 years

Table 6 (not relevant to adult patients)

Table 7. Therapeutic Goals for Pulmonary Involvement
• Reverse hepatopulmonary syndrome and dependency on oxygen
• Ameliorate pulmonary hypertension (ERT plus adjuvant therapies)
• Improve function status and quality of life
• Prevent rapid deterioration of pulmonary disease and sudden death
• Prevent pulmonary disease by timely initiation of ERT and avoidance of splenectomy

Table 8 Therapeutic Goals for Functional Health and Well-being
• Improve or restore physical function for carrying out normal daily activities and fulfilling functional roles
• Improve scores from baseline of a validated quality of life instrument with 2 to 3 years or less depending on disease burden.
ADMINISTRATION OF IMIGLUCERASE:

To be administered as an intravenous infusion in 100 ml. Sodium chloride 0.9% over 1 – 2 hrs. Higher total doses may be added to 250 ml. Sodium chloride and administered over the same time of 1 – 2 hours. The infusion must not be given in less than 60 minutes.

Doses are prescribed in vial size of 200/400 iu only, only complete vials may be used, this being a very costly enzyme, under no circumstances should enzyme be discarded. Doses should be adjusted to vial size prescribing, variable dose can be alternated each infusion to round the dose up.

Patients are offered the choice of receiving hospital-based infusions, home therapy or local clinic treatment depending on which option is preferred. The majority of patients opt for home therapy and are trained by the clinical nurse specialists. Supervision and continued training is consolidated by the home care team until the patients or carers are assessed to be fully competent in self administration of the enzyme. An on-call service is available via the home care nursing service should patients have problems infusing themselves.

The first several infusions of Cerezyme are administered in one of the NSCAG-designated centres to ensure that they are tolerated without adverse event. The therapy is generally very well tolerated, hypersensitivity to the treatment is very unusual and patients are able to switch to home therapy soon after therapy is initiated, with the appropriate support provided by the home care team.

As outlined by NSCAG, prescriptions for the treatment are issued only by the designated centres.

ADVERSE EFFECTS OF IMIGLUCERASE:

Adverse effects of Cerezyme are very rare but include the following:

<table>
<thead>
<tr>
<th>Pruritus</th>
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</thead>
<tbody>
<tr>
<td>Pain, swelling or sterile abscess at injection site</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>Nausea, vomiting diarrhoea and abdominal pain</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Anaphylaxis</td>
</tr>
</tbody>
</table>

Management of reactions can usually be achieved by slowing the infusion rate. Occasionally pre-medication with steroid and antihistamine given orally or IV together with 1G. oral Paracetamol is required
Antibody formation to Cerezyme frequently (13% of patients)occurs within the first year of treatment, however, in general, antibodies are non-neutralizing and do not affect the efficacy of the enzyme. Immunological tolerance commonly develops upon continued infusion of the enzyme preparation[26] (63% tolerized by 12 months and 93% tolerized by 30 months of treatment) In the event of a serious reaction, blood should be sampled for antibody status, which service is provided by Genzyme. Adverse event forms should be submitted to Genzyme Corporation.

FOLLOW UP ASSESSMENT:

Every 3 months until stable then 6 monthly.
Clinical evaluation of haematological, visceral, skeletal and, where appropriate, neurologic disease and application of a validated health-related quality of life instrument are recommended.
Blood tests - same as at baseline, except for DNA and enzyme activity. PTH, 25 OH & Vit D repeated annually unless abnormal. Factor XI does not need repeating unless abnormal.

**ASPLENIC PATIENTS:**

Asplenic Gaucher disease patients are at increased risk of osteonecrosis [27], though a causal relationship has been disputed[28] Monitoring therapy by serial measurement of haemoglobin, platelet count are usually unhelpful. Spleen size clearly cannot be used to monitor response to treatment. Thus particular attention should be paid to systemic and bony symptoms and to biomarkers of disease in order to prevent episodes of bone infarction. Asplenic patients are also at increased risk of pulmonary hypertension. Clinicians should maintain a high index of suspicion for this complication.

One of the principal complications of the asplenic state is overwhelming sepsis, principally as a result of infection with gram-positive encapsulated organisms[9]. Ensure that patients who have undergone splenectomy have received the following immunisation preparations:

- Haemophilus influenzae type b (Hib)
- Pneumovax: Repeated every 5-10 years.
- Meningococcal vaccine
- Yearly Influenza immunisation

Long-term regular antibiotic prophylaxis with Penicillin V 250mg BD or Erythromycin 250 mg BD, if allergic to penicillin, is mandated.

Patients should carry the standard medical information card: “I have no functioning spleen” (Department of Health LA4/002), together with the green information sheet. Patients should be warned that they are at increased risk of sepsis.

**ADJUVANT THERAPY**

Patients with osteoporotic skeletal disease and particularly those with chronic bone pain may benefit from bisphosphonate therapy either orally (which can be prescribed by their general practitioner) or intravenously. using Pamidronate or Zoledronate. Patients may attend on a regular basis to receive the infusions. Neither pamidronate, nor zoledronate, potent bisphosphonates used in the treatment of Paget's disease and bone disease of malignancy, have specific licences for use in Gaucher disease or in post-menopausal osteoporosis. Thus the use of these products for this indication requires ongoing evaluation.

**SURGICAL MANAGEMENT**

Orthopaedic surgical intervention is commonly required to restore function and correct deformity. Subchondral bone collapse as a result of avascular necrosis leads to pain and loss of function and may require joint replacement, most commonly of the hip joint, but also of the knee and shoulder [29]. Given that joint replacement is often carried out at a young age, there is frequent requirement for complex revision surgery. Gallstone disease is also more prevalent in Gaucher disease [30, 31].

Medical management of Gaucher disease patients in the perioperative period must take account of (1) the risk of infection in the asplenic patient, (2) the risk of bleeding associated with thrombocytopenia, platelet function defects, and coagulopathies associated with the condition.[3]
STANDARDS OF SERVICE DELIVERY
The appropriate standards for delivery of the service are set out in the Service Standards Document produced by NSCAG and agreed with the treating centres (appended).

HOMECARE SERVICE
For those patients who choose home therapy, each centre will contract with a homecare provider according to its host Trust’s Home Care policy, in accordance with standards of confidentiality, clinical practice and fair trading.

SHARED CARE PROTOCOL
Because many patients travel from far afield to the Gaucher centre and because it is important to have the support of an informed local physician in the case of clinical emergency, the service supports the use of shared-care arrangements with physicians based closer to the patient’s home. The principles and responsibilities of the shared care arrangements between Trusts are outlined in Shared Care policy documents (an example from Addenbrooke’s NHS Trust is appended).

INDICATIONS FOR CESSION OF SPECIFIC TREATMENT
Specific treatment may be withdrawn, following careful discussion with the patient and the multi-disciplinary team, under the following circumstances:
1. Intolerable and unavoidable adverse effects.
2. Intercurrent illness, where either long-term quality of life or expected survival is such that the patient will gain no significant benefit from specific treatment for Gaucher disease.
3. Lack of responsiveness to treatment, having made all appropriate dose adjustments and measures to improve effectiveness of treatment. This applies in the unlikely event of complete resistance to treatment and to irreversible progression of individual aspects of Gaucher disease (most likely neurological) whereby the patient’s quality of life is very poor and where there is little or no prospect of response to treatment.
4. At the request of the patient, or properly allocated guardian acting in the patient’s best interests, if the patient is properly deemed not competent.
5. If the circumstances of the patient’s lifestyle are such that sufficient compliance with treatment is not possible. Such cases might include intravenous drug abuse associated with a peripatetic lifestyle.
6. If the health and well-being of medical and/or nursing staff are placed under significant threat as a result of the actions or lifestyle of the patient.
7. Emigration of the patient outside the jurisdiction of the UK, when administration and funding of the treatment becomes the responsibility of Health Services in the new country of residence / domicile.

INTERACTION BETWEEN CENTRES
All centres will undertake to give the patient the opportunity of a second medical opinion if requested. All centres will inform patients of their right to seek advice from another centre and from the Gaucher’s Association.
Adult treatment centres will undertake to refer patients in the paediatric age-group to a paediatric centre of the patient’s and parents’ choice. Paediatric centres will undertake to refer patients to the adult centre of their choice on reaching the age of 16-18. Adult and paediatric centres undertake to ensure as much as possible a seamless transfer of care.
LIST OF SPECIALIST STAFF IN DESIGNATED CENTRES


