Protocol

Diagnosis, evaluation and treatment of Fabry disease in the Netherlands

Version 8, June 2026

Updated by:
M. Langeveld, G.M. Alkemade, K. ter Horst, M.M.M.G. Brands, B.C.F. Veldman, I. van den Elzen

DISCLAIMER

This protocol describes current treatment of Fabry disease patients at the Amsterdam University Medical Center, location AMC. The Amsterdam UMC is a designated center of excellence for Fabry disease and has been acknowledged as such by the competent authorities. This protocol reflects current knowledge and is for a large part based on clinical experience that has been gathered in the past 25 years. It is not a comprehensive review of Fabry disease.

Content

1. Introduction 3
2. Fabry disease diagnostics 3
3. Initial assessment 5
4. Follow-up assessments 6
5. Supportive care 11
    - Fabry neuropathic pain: chronic 11
    - Fabry neuropathic pain: acute 13
    - Use of neuropathic pain medication and traffic participation 14
    - Albuminuria and renal insufficiency 15
    - Blood pressure and lifestyle 16
    - Preventive measures 16
6. Pregnancy 18
7. Fabry specific treatment 18
    - Enzyme replacement therapy (ERT) 19
    - Future therapies 19
    - Fabry treatment indication committee 19
    - Start of ERT 19
    - Adverse reactions 20
    - Holiday/treatment break 22
8. Fabry and contraception 22

1. Introduction

This protocol describes the current standard of care at the Amsterdam UMC, regarding the diagnosis, follow-up, counseling and management of Fabry disease.

2. Fabry disease diagnostics

Medical History

- A detailed medical history should be performed, including an extensive family-history and pedigree (family tree) with specific attention for renal disease, cardiac disease, stroke and acroparesthesia
- Specific issues to be addressed in the medical history:
    - Signs and symptoms compatible with arrythmia, heart failure and/or symptomatic renal disease
    - Exercise tolerance, exercise habits
    - Body weight
    - Cardiovascular risk factors
    - Intoxications
    - Pain in hand and feet: when did it start, how it is described, chronic and/or acute, duration of acute attacks, provoking factors, use of analgesics, cold and/or heat intolerance. Do the symptoms fit the diagnosis of acroparesthesia related to small fiber neuropathy (SFN), including reduction of symptoms upon treatment with carbamazepine? If there is doubt about the diagnosis of SFN additional tests (measuring intraepidermal nerve fiber density and/or thermal sensation threshold) to make this diagnosis more likely can be considered
    - Reduced sweat function
    - Hearing problems, vertigo, tinnitus
    - Has ophthalmological examination ever taken place? (and was cornea verticillata described in the report?)
    - Has dermatological examination ever taken place (and were angiokeratoma described in the report?)
    - Were kidney and/or cardiac biopsies ever performed (including electron microscopy examination) and were the findings compatible with Fabry disease?
    - Was amiodarone/cordarone or (hydroxyl)chloroquine ever prescribed? When? For how long?

Extensive physical examination with a specific attention for the presence of angiokeratoma: solitary, clustered, localization (study lips, hand, genital and/or umbilical area).

Assessments:

On clinical suspicion of Fabry disease, perform the following tests:
-genetic analysis (GLA gene sequencing+MLPA)
-enzyme activity analysis (alpha-galactosidase A activity in leucocytes)
-measurement of plasma lysoGb3 concentrations.

In individual cases, for example when the clinical suspicion of Fabry disease is very low but there is a wish for confirmation, measurement of plasma lysoGb3 concentration only can be considered.

In asymptomatic individuals who are evaluated in the context of family (cascade) screening, we typically limit the primary assessment to DNA analysis of the specific familial variant and measurement of plasma LysoGb3 concentration to confirm or rule out the diagnosis of Fabry disease. In children at risk for inheriting a GLA variant associated with classical disease in men, Fabry diagnostics can be considered from age 5 years onwards in boys and age 10 years onwards in girls. For children at risk for inheriting a GLA variant associated with non-classical disease in men, Fabry diagnostics can be considered from age 18 years onwards, after discussion of the pro's and con's with the individual. Exceptions are of course possible, for example if there are complaints that may be related to Fabry disease prior to the age at which diagnostics are generally advised.

Conclusion:
Based on these examination three conclusions are possible:
1. a definitive diagnosis of Fabry disease. The diagnosis is straightforward in patients that found to have a GLA variant known to be associated with a Fabry disease phenotype. The Fabry Working Group Genotype Phenotype Database (http://fabrygenphen.com) can be used to search for genotype-phenotype associations.
2. exclusion of Fabry disease as a cause of the patients' signs/symptoms
3. a possible diagnosis of Fabry disease. In some cases, a definitive diagnosis can only be made after extensive further testing, which may include investigations in family members, imaging of the heart and/or brain and/or tissue analysis (kidney, cardiac biopsies). Of note, in patients with a lysoGb3 lower than the patient range, care should be taken to determine whether the presenting sign and symptoms are related to the GLA variant. Other risk factors should be assessed (e.g. hypertension, smoking, obesity etc.). The GLA variant may be just one of the factors contributing to the phenotype. In some cases, a second genetic variant (e.g. a sarcomere or PLN variant) or a second acquired disorder (e.g. IgA nephropathy) may be the dominant cause of the phenotype. In patients with a low plasma lysoGb3 levels, but severe clinical manifestations, these other potential (genetic) causes should be investigated. This should also be done if the sign or symptom does not follow the pattern expected in Fabry disease.

Classification:
Fabry disease can be classified as:

1. Classical Fabry disease: lysoGb3 > 40 nmol/L and classical symptoms (cornea verticilata, angiokeratoma, childhood onset typical acroparesthesia)
2. Fabry disease: lysoGb3 2,5-40 nmol/L, in male patients this can be classified as non-classical disease. In women this specification is not meaningful since the phenotype is the product of both the genetic variant as well as the pattern of X inactivation and the untreated plasma lysoGb3 is the best predictor of expected disease severity.

In addition there are individuals with GLA variants and a lysoGb3 level above the reference range (normal values for plasma lysoGb3: ≤0.6 nmol/L), but below 2,5 nmol/L, who are unlikely to develop symptomatic Fabry disease (data available from individuals up to the

eights decade of life). Whether or not the GLA variant contributes to the overall cardiovascular risk in these individuals, especially when other CVD risk factors are present, is not known.

3. Initial assessments

Initial assessments in patients with a definitive diagnosis of FD
(Confirmed diagnosis, evaluation at the outpatient clinic)

Table 2 Initial assessments in patients with a definitive diagnosis of FD
Informed consent
Consent AMC Fabry disease register and biobank (Biobank stofwisselingsziekten) Consent for all medical correspondence to be collected
Clinical chemistry Creatinine, glucose, sodium, potassium, cholesterol (total, LDL and HDL), triglycerides, NT-proBNP, troponin T, TSH, hemoglobin, MCV, leukocytes, thrombocytes, ferritine, (and plasma albumin in case of proteinuria, defined as >500 mg albumin/24 hours in urine) ALAT, ASAT, AF, gGT only if treated with Carbamazepine will be initiated If eGFR<45 ml/min: calcium, phosphate, albumin, PTH, 25-OH-vit D, bicarbonate If eGFR<30 ml/min and or abnormal calcium/phosphate levels: PTH Urine diagnostics (spot sample): creatinine, albumin, UMKR 24-hr urine (on indication): creatinine, sodium, albumin, protein (calculated GFR, UMCR)
Metabolic diagnostics GLA gene analysis including MLPA (if not previously conducted), specific mutation analysis in case of a known familial mutation Alfa-galactosidase A activity in leucocytes Plasma LysoGb3 Antibodies against recombinant enzyme only if initiation of ERT is likely
Discuss with patient the option for Fibroblasts (skin biopsy) for alfa-galactosidase A activity measurement and storage
Biobank plasma and urine samples if consent is given
* If DNA analysis has been performed earlier it is important that a GLA VUS is reclassified based on clinical and biochemical findings
Additional investigations/procedures **

- Referral to ophthalmologist to assess cornea verticillate: this should be considered in patients with novel/unknown GLA variants and/or when there is doubt about the Fabry phenotype. Does not have to be performed in patients with a well-described phenotype and known familial variant.
- Renal ultrasound (length of both kidneys, cysts, renal cell carcinoma?)
- ECG
- Cardiac MRI , including T1 mapping. Hb and Ht in blood needs to be measured in blood on the same day.
- Echocardiography: in addition to routine parameters: assessment of aortic root diameter, LV mass, septal e', lateral e', E/e', TR velocity, PASP en GLS, LAVI, IVSd, PWd and LVEDD.
- Discuss with the patient the option for an MRI of the brain taking into account potential incidental findings (assessments: white matter abnormalities? (stable or progression?) Pulvinar sign? Presence of a (lacunar) infarction? Microbleeds? Fazekas score?), discuss potential incidental findings
- Audiometry in case of complaints of hearing loss
- Discuss family screening and refer patients to clinical geneticist (family members that are obligate mutation carriers can directly be referred to the metabolic specialist)

**** The age at which it is recommended to first perform each of these investigations depends on the a priori risk. See tables 4-7 for age-specific recommendations in relation to Fabry phenotype/familial variant and untreated plasma lyso-Gb3 level.**

Questionnaires (electronically)
- SF36, BPI, CESD

4. Follow-up assessments

Listed below is the routine follow-up schedule. Depending on findings at the outpatient clinic visits, additional examinations may need to be added or the interval between investigations can be shortened or lengthened.

<u>Follow up schedule after starting or switching Fabry specific therapy (all patients)</u>:
- Phone call 3 to 6 months after start (nurse/case manager)
- Outpatient visits: once a year
- Laboratory examinations (see table 3 and 4) and ECG at every visit
- MRI brain: frequency see table 5
- MRI heart: at 24 months after start of treatment, frequency after 24 months of treatment see table 6
- Echocardiography: at 24 months after start of treatment, frequency after 24 months see table 7
- Questionnaires: SF36, BPI, CESD

Follow-up schedule for untreated patients:
Men with classical Fabry disease/all individuals with a plasma lysoGb3 level >40 nmol/L:

- Outpatient visits: once a year
- Laboratory examinations (see table 3 and 4) and ECG at every visit
- MRI brain: frequency see table 5
- MRI heart: frequency see table 6
- Echocardiography: frequency see table 7
- Audiometry: in case of complaints of hearing loss
- Questionnaires (adults): SF36, BPI, CESD

Women and men with Fabry disease with an untreated plasma lysoGb3 between 2.5-40 nmol/L, in the early stages of the disease (might become eligible for Fabry specific therapy)[#]:

- Outpatient visits: once every other year up to age 30, every year after age 30
- Laboratory examinations (see table 3 and 4) and ECG at every visit
- MRI brain: frequency see table 5
- MRI heart: frequency see table 6
- Echocardiography: frequency see table 7
- Audiometry: in case of complaints of hearing loss
- Questionnaires: SF36, BPI, CESD

[#]For patients in whom there are severe disease complications/who have discontinued treatment/who do not require Fabry specific therapy an individual follow-up plan should be made

Individuals with a GLA variant and a plasma lysoGb3 outside of the reference range, but below <2,5 nmol/L:

- Outpatient visits: no outpatient visits up to age 30, after the age of 30 every 5 year, if no clinically relevant disease manifestations have developed discontinuation of follow-up should be discussed, especially at older age
- Laboratory examinations (see table 3 and 4) at every visit
- MRI brain: frequency see table 5
- MRI heart: frequency see table 6
- Echocardiography: frequency see table 7
- Questionnaires: SF36, BPI, CESD (every visit)

Referrals
Patients with significant cardiac involvement should be referred to a cardiologist for follow-up and treatment. In a separate protocol the recommended cardiac follow-up is outlined.

Patients who are, based on medical history and brain imaging findings, suspected of having cognitive impairment should be referred for full neuropsychological testing. Patients that score ≥16 on the CESD should be offered depression diagnostics. Patients with severe pain (high scores on the BPI) should, if the pain is not Fabry related, be offered referral for diagnostics into the cause of their complaints and subsequent treatment. Neuropathic Fabry related pain should be treated as outlined in paragraph 5.

Table 3 Laboratory examinations at follow-up outpatient visits
Clinical chemistry: Creatinine, potassium, NT-proBNP, troponin T, (and plasma albumin in case of proteinuria, defined as >500 mg albumin/24 hours in urine) If eGFR<45 ml/min: sodium, calcium, phosphate, albumin, 25-OH-vit D, bicarbonate, Hb, MCV If eGFR<30 ml/min and or abnormal calcium/phosphate levels: PTH If on Carbamazepine: ALAT, ASAT, AF, gGT, hemoglobin, MCV, leukocytes, thrombocytes **Urine diagnostics** In patients with an eGFR >60 ml/min and albuminuria <500 mg/24 hours a random urine sample can be collected, assessing the following parameters: creatinine, albumin (UMCR) In patients with an eGFR <60 ml/min and/or albuminuria >500 mg, 24 hour urine will be collected, assessing the following parameters: creatinine, albumin, protein, sodium (UMCR and calculated GFR) **Metabolic markers/Biobank:** Plasma LysoGb3 **Biobank plasma and urine samples if consent is given**

Table 4 Measurements of anti-drug antibodies against recombinant enzyme		
	Male patients with classical Fabry disease	All other Fabry patient groups
Before start therapy	Yes	Yes
1 year of treatment	Yes	Yes
2 years of treatment	Yes	No
3,5,7,9,11…years of treatment	Only if ADA positive earlier	No
6 months after switch type of Fabry specific therapy	Yes*	Yes*

*Continue biyearly measurements if ADA positive

Table 5 Frequency MRI brain		
Sex, phenotype	**Age in years**	**Scan frequency, every**
Patients with lysoGb3 >2.5 nmol/L	At time of diagnosis (if age > 30 years)	Once
Men, classical phenotype	<20	No scans

(untreated plasma lysoGb3 >40 nmol/L)		
	≥20	4 years
Women and men with an untreated plasma lysoGb3 between 2.5-40 nmol/L	<30	No scans
	≥30	4 years
Individuals with a GLA variant and a plasma lysoGb3 outside of the reference range, but below <2,5 nmol/L	<40	No scans
	≥40	Individual decision, every 5 years can be considered
Before start of Fabry specific therapy	>20 year	Once (if previous MRI was performed more than 2 years before start)
In individual patients the scan interval can be shortened, e.g. in case of (progressive) cognitive complaints, suspicion of CVA		

Table 6 Frequency MRI of the heart		
Sex, phenotype	**Age in years**	**Scan frequency, every**
All patients	At time of diagnosis (if age > 15 years in men with classical disease and age > 20 in all other patients)*	Once
Men, classical phenotype (untreated plasma lysoGb3 >40 nmol/L)	<15	No scans
	>15	3 years
	>50	2 years
Women and men with an untreated plasma lysoGb3 between 2.5-40 nmol/L	<20	No scans
	>20	3 years
	>50	2 years
Individuals with a GLA variant and a plasma lysoGb3 outside of the reference range, but below	<40	No scans

<2,5 nmol/L		
	≥40	Individual decision, every 5 years can be considered
Before start Fabry specific therapy	-	Once
In individual patients there can be an indication to shorten the scan interval, for example: newly detected myocardial fibrosis (which needs to be confirmed on a second scan) or considering starting Fabry specific therapy		

Table 7 Frequency echocardiography		
Sex, phenotype	**Age in years**	**Echocardiography frequency, every**
All patients	At time of diagnosis (if age > 15 years in men with classical disease and age > 20 in all other patients)	Once
Men, classical phenotype (untreated plasma lysoGb3 >40 nmol/L)	>10	At time of start FD specific therapy
	>15	3 yrs
	>50	2 years
Women and men with FD with an untreated plasma lysoGb3 between 2.5-40 nmol/L	<20	No echo
	≥20	3 years
	>50	2 years
Individuals with a GLA variant and a plasma lysoGb3 outside of the reference range, but below <2,5 nmol/L	<40	No echo
Before start Fabry specific therapy	-	Once
In individual patients there can be an indication to shorten the echo interval, for example: complaints compatible with cardiac dysfunction		

5. Additional and supportive care

Supportive care is of importance for quality of life (e.g. pain management). Measures additional to the Fabry specific therapy are critically important for prevention of organ complications (e.g. reduction of proteinuria). Maximum supportive and additional care should be given to each FD patient.

Fabry neuropathic pain (acroparesthesia) - chronic

First it should be established , based on description of the symptoms (see page 3 Medical history) if symptoms fit the diagnosis of acroparesthesia related to small fiber neuropathy (SFN). A positive response to treatment with carbamazepine makes the diagnosis of acroparesthesia more likely. If there is doubt about the diagnosis of SFN additional tests (measuring intraepidermal nerve fiber density and/or thermal sensation threshold) can be considered.

Acroparesthesia require specific pain management. No detailed clinical studies have been performed on which drug works best in Fabry disease. Carbamazepine is the most widely used drug for the management of acroparesthesia and extensive clinical experience indicates that it is highly effective in managing SFN associated pain/acroparesthesia in FD patients, even if used intermittently, e.g. when fever occurs.

Management of chronic acroparesthesia

First choice: Carbamazepine

Start with 100 mg 2 times daily, increase if necessary in steps of 50 mg per dose (first increase 150 mg 2 times daily). Median effective dose appears to be 200 mg 3-4 times daily. Maximum dose: 1200 – 1600 mg per day.

Warnings and precautions when prescribing Carbamazepine for acroparesthesia (source Farmacotherapeutisch kompas, check for all warnings and interactions):

-Carbamazepine can alter alertness, for advice regarding traffic participation see below

-Carbamazepine reduces the effectiveness of oral contraceptives. Since Carbamazepine is teratogenic, it cannot be used in pregnancy. For advice on contraception see section 7).

-do not prescribe to patients with an atrioventricular block (without a pacemaker)

-liver biochemistry abnormalities can occur, discuss moderation of alcohol intake and perform liver biochemistry assessments and stop treatment if signs of hepatitis occur

-persistent leukopenia and thrombocytopenia can occur, perform blood count assessments

-carbamazepine causes cytochrome induction, check for interactions with other drugs (eg simvastatin, fluoxetin). When concomitant use of immunomodulatory drugs (post organ transplant), discuss this with pharmacist.

-because of the risk of an acute life-threatening skin reaction, especially in the first months of treatment, there should be awareness for skin symptoms (rash with blister or mucous membrane lesions, discontinue Carbamazepine if this occurs). The risk of Stevens-Johnsons syndrome or toxic epidermal necrolysis is 1-6 per 10.000 users in the Caucasian population, 1-6:1000 in the patients of Han-Chinese or Thai descent. Check the latter patients for HLA-B*1502 (and consider it in other Asian patients, for risk of carriership see Farmacotherapeutisch kompas) and do not prescribe Carbamazepine if positive.

-Carbamazepine can increase ADH levels, check sodium levels in patient that are treated with sodium lowering medication (diuretics) and in older patients, after 2 weeks, during the first 3 months of Carbamazepine treatment and on indication thereafter.
-in case of concomitant hypothyroidism, extra assessment of thyroid hormone levels are necessary since Carbamazepine increases the elimination of thyroid hormone.
-patients with elevated intra-ocular pressure require more stringent evaluation of ocular pressure because of the slight anti-cholinergic effect of carbamazepine .
-reconsider carbamazepine use in the elderly, especially in patients with heart failure. Since acroparesthesia often decrease as patients get older, phasing out of Carbamazepine should be considered in patients that are over 40 and have been symptom free for many years.

Second choice: Amitriptylin. Start with 25 mg at bedtime, if >75 years of age or if the patient is fragile start with 10 mg. If unsatisfactory, increase the dose after 1 week by 10-25 mg every 3-7 days, up to a maximum of 150 mg. If daily dose>75 mg, split in two dosages (e.g. 50 mg two times daily). Median effective dose: 75 mg, analgesic effect is generally reached after 2-4 weeks of treatment.

Relevant warnings and precautions when prescribing Amitriptylin for acroparesthesia (source Farmacotherapeutisch kompas, check for all warnings and interactions):
-do not prescribe in patients with a recent myocardial infarction, arrhythmias, severe conduction disturbances, coronary insufficiency or severe liver function disturbances.
-Amitriptylin can affect alertness, for advice regarding traffic participation see below
-do not prescribe in combinations with drug that alter CYP2D6 activity. CYP-inducers can lower Amitriptylin concentrations and thus effectiveness.
-check full blood count if fever and a sore throat occur within the first 10 weeks of treatment.
-carefully consider use of Amitriptylin in patients with cardiac or vascular conditions (for other conditions in which use of Amitryptylin should be prescribed with care see Farmacotherapeutisch kompas).
-Amitriptylin can cause cardiovascular side effects: arrhythmias (among which QT elongation), hypotension (especially in the context of cardiac disorders). Obtain an ECG prior to treatment initiation, do not prescribe in a patient with (risk of) prolonged QT time. Do not prescribe if risk factors for arrhythmias are present (for details see Farmacotherapeutisch kompas).
-acute glaucoma can occur during use of Amitryptylin in patients with rare ocular conditions (e.g. a shallow anterior chamber of the eye).
-elderly patients are more sensitive to cardiovascular side effects, hypotension and anticholinergic side effects.
-acute discontinuation can cause withdrawal symptoms, Amitriptylin needs to be phased out.

Third choice: If carbamazepine is not successful in amelioration of pain, Gabapentin or Pregabalin can be tried. Since pharmacokinetics of Gabapentin are nonlinear, dosing requires careful titration. Pregabalin has pharmacokinetic advantages to gabapentin as it has linear pharmacokinetics. Consequently, dosing is more straightforward and requires only a twice daily administration. The effectiveness and tolerability of Pregabalin seems to be similar to Gabapentin. Both drugs are fairly well tolerated. Dose-dependent dizziness and

sedation can be reduced by starting with lower dosages and dose titration (for advice regarding traffic participation see below). Although Pregabalin and Gabapentin are widely prescribed and reported to be effective for neuropathic pain in general, little is known about their effect in FD neuropathy.

Gabapentin: Start at 900 mg or 1200 mg/day, increase dose as follows: day 1: 1dd 300 mg or 400 mg, dag 2: 2dd 300 mg or 400 mg; day 3: 3dd 300 mg or 400 mg. Max dose is 3600 mg/day in equal dosages (for further dose escalation see Farmacotherapeutisch kompas). Adjust dosage to kidney function.
Pregabalin: Start at 50 mg 3 times daily or 75 mg twice daily if tolerated. Increase to 300 mg/day after 3-7 days, then by 150 mg/day every 3-7 days if tolerated. Max dose is 600 mg/day in equal dosages. Adjust dosage to kidney function.

Relevant warnings and precautions when prescribing Gabapentin for acroparesthesia (source Farmacotherapeutisch kompas, check for all warnings and interactions):
-Gabapentin can alter alertness, for advice regarding traffic participation see below.
-in case of early signs of hypersensitivity (e.g. fever), investigate whether DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) occurs and discontinue Gabapentin use.
-patients should be checked for suicidal thoughts/behavior during treatment.
-if pancreatitis occurs consider discontinuation of Gabapentin.
-in the elderly and patients with renal, neurological or breathing/airway conditions, risk of respiratory depression seems increased and lowering of the dose may need to be lowered.
-cases of misuse and dependence of Gabapentin have been reported, be careful in patients with a history of substance abuse.

If these options do not result in satisfactory pain reduction, refer the patient to a pain specialist, providing information on Fabry related acroparesthesia. Chronic NSAID use should be carefully considered and is contra-indicated in most Fabry patients given the negative effects on renal and cardiovascular function.

Acute Fabry-related neuropathic pain (acute acroparesthesia)
Acute Fabry neuropathic pain may occur during fever, following exercise, during hot weather or extreme stress. Patients are advised to use paracetamol 3-4 dd 1000 mg (depending on weight) during fever (to reduce body temperature/fever), even if it does not reduce pain. Temporary use of or increase of carbamazepine dose has been reported by several patients to have a good effect, even on the acute pain (anecdotal evidence). Episodes can be difficult to treat. The following scheme can be applied, though patients may respond differently to different drugs.

Table 9 Treatment of acute Fabry related neuropathic pain (acute acroparesthesia)
Step 1: Paracetamol 1000 mg three times daily (every 8 hr) Increase Carbamazepine dose if already on Carbamazepine but not on maximal dose **Step 2:** Patient or treating physician should consult Fabry specialist at the AMC via 020 566 6967,

(internist for inborn errors of metabolism on call). If not on Carbamazepine: start Carbamazepine 3 dd 100 mg (every 8 hr), increase dose if necessary* AND Add Oxycodon 5 mg every 4–6 hours, increase dose till pain control is achieved. (Paracetamol to be continued 1000 mg tid) Assess Pain score every 8 hours. Aim for maximum pain score of 5 or lower.
Step 3 Refer pain specialist

*Consider adding an NSAID for short term use if the patients does not have moderate to severe renal/cardiac disease

Use of neuropathic pain medication and traffic participation

- Carbamazepine: category 2: Slight to moderate influence on driving capacity, comparable with a blood alcohol concentration of 0,5 tot 0,8 g/l (0,5–0,8‰). Advice: Dose up to 200 mg 3 times daily: do not drive the first week after start. If dose is higher than 200 mg 3 times daily: do not drive during the first year of treatment.
- Pregabalin and Gabapentin: category 2: Slight to moderate influence on driving capacity, comparable with a blood alcohol concentration of 0,5 tot 0,8 g/l (0,5–0,8‰).
  Advice: Do not drive the first week after start.
- Amitriptylin: category 3: severe or potential severe influence on driving capacity, comparable to a blood alcohol concentration of >0,8 g/l (>0,8‰).
  Advice: Maximum dose of 75 mg/daily: do not drive the first week. If more 75 mg/day: do not drive . In accordance to Dutch law, driving a car while on 75 mg can only be considered if used consecutively for more than 3 years, after completing an exam in a simulator (CBR).

Albuminuria and renal insufficiency

Source Dutch guideline for treatment of adults with chronic renal insufficiency unless stated otherwise.

All patients with proteinuria or albuminuria should be treated with ACE inhibition (or an AT-2 receptor blocker (ARB) if ACE inhibition is not tolerated). Goal is proteinuria <0.5 g/24 hours for proteinuria and <300 mg/24 hours (or 30 mg/mmol creatinine) for albuminuria. Increase the dose of an ACE-inhibitor if needed and advice salt restriction (<2400 mg sodium or <6 grams of salt intake per day). If tickling cough, as a side effect of the ACE inhibitor treatment, occurs, switch to an ARB. Plasma creatinine and potassium should be checked 1-2 weeks after start or dose increase of an ACEi/ARB in patients with an eGFR ≤60 ml/min/173m^2. Discontinue ACEi/ARB if potassium increases significantly and/or creatinine increases with >25%. Refer to a nephrologist if creatinine increases with >25%.
If albuminuria/proteinuria goal is not reached, add a longacting thiazidelike diuretic (e.g. chloortalidon or indapamide). In patients at risk for electrolyte disturbances check sodium and potassium concentrations 3 to 4 weeks after start of treatment. At start of treatment, discuss the need for discontinuation of ACE/ARB (and in most cases also the thiazide diuretic) in women at the time they wish to become pregnant and in all patients at times of (imminent) dehydration

Choice of ACE inhibitor:
No studies on the outcome of different ACE-inhibitors in Fabry disease have been performed. The choice of ACE inhibition (or angiotensin reception blocker, ARB) is expert opinion only. In general it can be stated that ACE-inhibitors can be titrated more easily and do not have a maximum dose-response. Drugs with a long half-life seem to be preferred (can be taken once daily), such as perindopril of trandolapril, to be taken in the evening preferably (again expert opinion).

Goal: Proteinuria < 0.5 g/24 hours or albuminuria < 300 mg/24 hours (or 30 mg/mmol creatinine)
Step 1: Advice salt restriction in all patients (goal sodium excretion is < 100 mmol/24 hr)
Step 2: Start ACEi (perindopril, start with 2mg once daily, maximum dose 8 mg/day) → if eGFR < 60 ml/min, check plasma creatinine and potassium after 1 to 2 weeks
Step 3: Switch to long-acting ARB (irbesartan 150 mg once daily, maximum dose 300 mg/day or olmesartan 10 mg once daily, maximum dose 40 mg/day) ➔ if eGFR < 60 ml/min, check plasma creatinine and potassium after 1 to 2 weeks Do not combine this with ACE inhibitors
Step 4: **Add SGLT2-inhibitor (dapagliflozine 10 mg once daily)**
➔ **Can be combined with ACEi or ARB**
Step 5: Add thiazide diuretic (can be combined with ACE inhibitors or ARB)

➔ Check sodium and potassium concentrations after 3 to 4 weeks

In pregnancy (or in those who want to become pregnant) stop ACE/ARB. If there is a need for treatment of hypertension refer to a local team to manage hypertension during the pregnancy.

Patients should be referred to a nephrologist once eGFR is below 30 ml/min/1.73m^2.

Blood pressure and lifestyle

If an increased blood pressure is measured at the outpatient clinic, have it repeated at the GP (consider 24 hour blood pressure monitoring) before start of treatment. Aim for normal blood pressure <140/90 mmHg in all patients and <130/80 mmHg in patients with an eGFR below 60 ml/min/1.73m^2.

Obesity and exercise
Treatment of obesity should be discussed. Find possibilities for weight reduction, which may be a challenge because of cardiac involvement or occurrence of acroparesthesia with exercise. Swimming is a good exercise for classical disease patients with acroparesthesia. Exercise should be encouraged in all Fabry patients given its positive influence on especially cardiac function.

Smoking
Actively and repetitively advice to stop smoking. Refer to GP for smoking cessation programs.

Alcohol
Discuss alcohol intake and its negative influence on cardiac function. Particularly relevant is the role of alcohol use in triggering atrial fibrillation.

Sodium-excretion
Target for sodium excretion is < 100 mmol/24 hr. ACEi/ARB effect is greater when patients are salt restricted. Refer to information on the Nierstiching website for practical advices (https://www.nierstichting.nl/nierschade-voorkomen/zoutbewust-eten/).

Influenza vaccination
Influenza vaccination is advised for all patients with an eGFR below 45 ml/min/1.73m^2 or eGFR below 60 ml/min/1.73m^2 and microalbuminuria >30 mg/24 hours, for patients with severe acroparesthesia, post renal transplant and in patients with a compromised cardiac function.

Preventive measures

Anti-platelet therapy and anti-coagulation

All patients who suffered a cerebral stroke or TIA should be referred to a neurologist and should receive secondary prophylaxis with anti-platelet (without cardiac embolic source) or anti-coagulant therapy (in patients with atrial fibrillation) according to standard practice.

Primary prophylaxis of TIA/stroke in patients with Fabry disease by prescription of anti-platelet drugs is **not** supported by clinical evidence. Lifestyle measures and cardiovascular risk factor control are the foundational therapy of primary prophylaxis.

Prescription of anti-platelet drugs for patients with white matter lesions (without TIA/stroke) is also not supported by clinical evidence, although this was often advised by experts in the past. On the basis of a recent Delphi procedure involving 27 Fabry specialists from around the world, the consensus is that anti-platelet drugs are **not** recommended for most patients with white matter lesions in the absence of TIA/stroke or another form of atherosclerotic arterial disease. Lifestyle measures and cardiovascular risk factor control remain the foundational therapy of primary prophylaxis. Given the limited available evidence, the panel acknowledged that there is room for individual considerations and that anti-platelet prophylaxis may be considered in cases with rapidly progressive white matter lesions or extensive white matter lesions in association with neurocognitive symptoms/executive dysfunction.

When prescribing antiplatels to individuals over 80 years of age, a proton pump inhibitor should be added. This is also advised in patients over 70 years old who use other medication that increases the risk of a stomach ulcer (e.g. systemic acting glucocorticoïd, SSRI, Venlafaxine, Duloxetine, Trazodon or Spironolactone) and in patients over 60 years of age with an stomach ulcer or complications of a stomach ulcer in the past. Pantoprazol is preferred to Omeprazol or Esomeprazol in patients that use Clopidogrel.

If there is a clear indication, acetylsalicylic acid can be continued during pregnancy. Unless there is a strict indication for continuation, acetylsalicylic acid needs to be stopped in the third trimester until (after) delivery. If continued, an additional blood loss of 50 ml during or after delivery is expected. Continuation should be discussed with the patient and the obstetrician.

Cholesterol-lowering drugs

As part of secondary prevention statins are often prescribed. The effect of statin treatment (or other lipid lowering drugs) in Fabry disease has not been shown and its use as primary prevention of cerebral and cardiac Fabry complications remains a matter of debate. In each patient, a lipid profile should be determined at least once. If dyslipidemia is present (use age corrected cut off values: http://www.jojogenetics.nl/wp/tools/referentiewaarden/), strongly consider life style measures first and cholesterol/lipid lowering second. The CVD risk threshold for starting cholesterol/lipid lowering drugs may be lower in Fabry disease patients compared to the general population, given the double risk of the Fabry disease and dyslipidemia, though no evidence based advises can be given at this point in time. Regarding the type of statin, one might consider prescribing a more potent statin (ie. atorvastatin, rosuvastatin), as these have shown reductions in plasma LDL-C as well as triglyceride levels in patients with combined dyslipidemia. Moreover, a post-hoc analysis of 6 double-blind RCT's in non-Fabry patients at risk for or with cardiovascular disease and a meta-analysis of

RCT's in adults, showed a dose-dependent beneficial effect of atorvastatin on kidney function.

6. Pregnancy

Inheritance pattern and possible reproductive choices should be discussed with all patients that (may in the future) wish to start or expand a/their family. In case of an active pregnancy wish, patients should be referred to clinical geneticist to discuss options. An exception regarding referral can be considered for patients with non-classical FD, in which case organ involvement can be limited and occur late in life. These choices should be tailored individually. Given the complexity of the topic, referral to an experienced clinical genetics team is advised. Broadly speaking there are four options: 1. Pregnancy without knowledge whether or not the child is affected, in this case a plan should be made for timing of Fabry disease diagnostics in the child (depends on sex and type of disease in the family). 2. Decision not to have biological children. 3. Conception with prenatal diagnostics and a decision on termination of the pregnancy in case of an affected child. 4. Pre-implantation genetic diagnostics with transfer of an unaffected embryo. Option 2-4 are especially relevant for classical Fabry disease, as non-classical Fabry disease can have an asymptomatic course for many decades.

Medication use should be re-evaluated before discontinuation of birth control (see relevant sections above). Fabry disease does not seem to result in a higher risk of pregnancy complications, though (pre-) eclampsia has been described in individual cases. Patients with proteinuria that discontinued there ACEi/ARB should be carefully monitored throughout pregnancy. Patients developing hypertension and/or (pre)eclampsia should be treated according to local protocols.

7. Fabry disease specific therapies

<u>Enzyme replacement therapy</u>
Initiation of treatment with agalsidase- beta or pegunigalsidase-alfa can be considered when treatment criteria are met, which have been published in an international guideline for the initiation and cessation of enzyme replacement therapy in Fabry disease. Individual deviations from the criteria are possible, if deemed necessary by the indication committee. All cases are discussed in the Fabry treatment indication committee and treatment can only be initiated after approval of this committee. In patients with progressive disease, but that still meet treatment criteria, there is the possibility of a treatment trial of fixed duration. In these cases, a clear definition of disease progression will be made and if this definition is met, treatment will be discontinued. The possibility of treatment discontinuation, if disease stabilization does not occur, is always discussed at treatment initiation.

Choice of drug is up to the treating physician and the patient. Agalsidase-beta (1 mg/kg/eow) and pegunigalsidase-alfa (1 mg/kg/eow) seem to have a comparable effect on renal function, but long term effects, especially the effect on cardiac disease needs to be determined and compared between the two drugs. Pegunigalsidase can also be prescribed in a dose of 2 mg/kg/every 4 weeks, published studies suggest stable disease after switching to

this regime from a different form of enzyme replacement therapy, though these observations need to be confirmed in more comparable patient groups.

Future therapies

Several new therapies for Fabry disease such as substrate inhibition and, further down the line, gene and RNA based therapies, are currently under investigation. Decisions on initiation of or switch to these new drugs, once they become clinically available, go through the Fabry indication committee.

Chaperone therapy (Migalastat, Galafold®) is EMA approved, but the Dutch ministry of health has decided against reimbursement given the lack of robust evidence on its therapeutic effectiveness.

Fabry treatment indication committee

Members that are part of SPHINX (the Amsterdam Lysosome Center):

-
- Prof. Dr Mirjam Langeveld, internist, consultant inherited metabolic disorders
- Prof. Dr Carla Hollak, internist, consultant inherited metabolic disorders
- Dr G. Alkemade, internist, consultant inherited metabolic disorders
- Dr K. ter Horst, internist, consultant inherited metabolic disorders
- Dr Marion Brands, pediatrician, consultant inherited metabolic disorders
- Dr L. van Dussen, post-doctoral research fellow
- I. van den Elzen, case-manager
- O. el Haddadi, nurse

Other members:

- Dr Lourens Robbers, cardiologist
- Dr Pieter Postema, cardiologist
- Dr Liffert Vogt, internist-nephrologist
- Dr Roos Marsman, internist-nephrologist
- Dr Astrid Plomp, clinical geneticist
- Dr Marie van Dijk, laboratory specialist inherited metabolic diseases

Start of enzyme replacement therapy

Treatment can safely be given at home after start of therapy in the hospital. In male patients with classical there is a high risk for the development of anti-drug antibodies against the recombinant enzyme and infusion reactions. In these patients a specific protocol for starting ERT is followed, in which treatment is started with very low dose of enzyme (0,1 mg/kg) which is gradually increased and administered every week, with the goal of inhibiting/lowering antibody formation and reducing infusion related reactions. The full dose, with regular infusion time, is reached after 49 weeks (for details see *Verpleegkundig protocol Enzym vervangende therapie (ERT) bij mannen met klassieke ziekte van Fabry*).

For all other FD patients a personalized approach, depending on the estimated risk of infusion reactions, should be followed. In general, female and male patients with non-classical FD can start ERT at home, provided emergency medication is available. There is a separate protocol for treatment initation with Pegunigalsidase-alfa, since there seems to be a risk for a different type of IgE mediated infusion reaction (on top of the known inhibiting

IgG ADA associated infusion reaction risk) that is not limited to male patients (*Verpleegkundig protocol Behandeling ziekte van Fabry met Pegunigalsidase-alfa*)

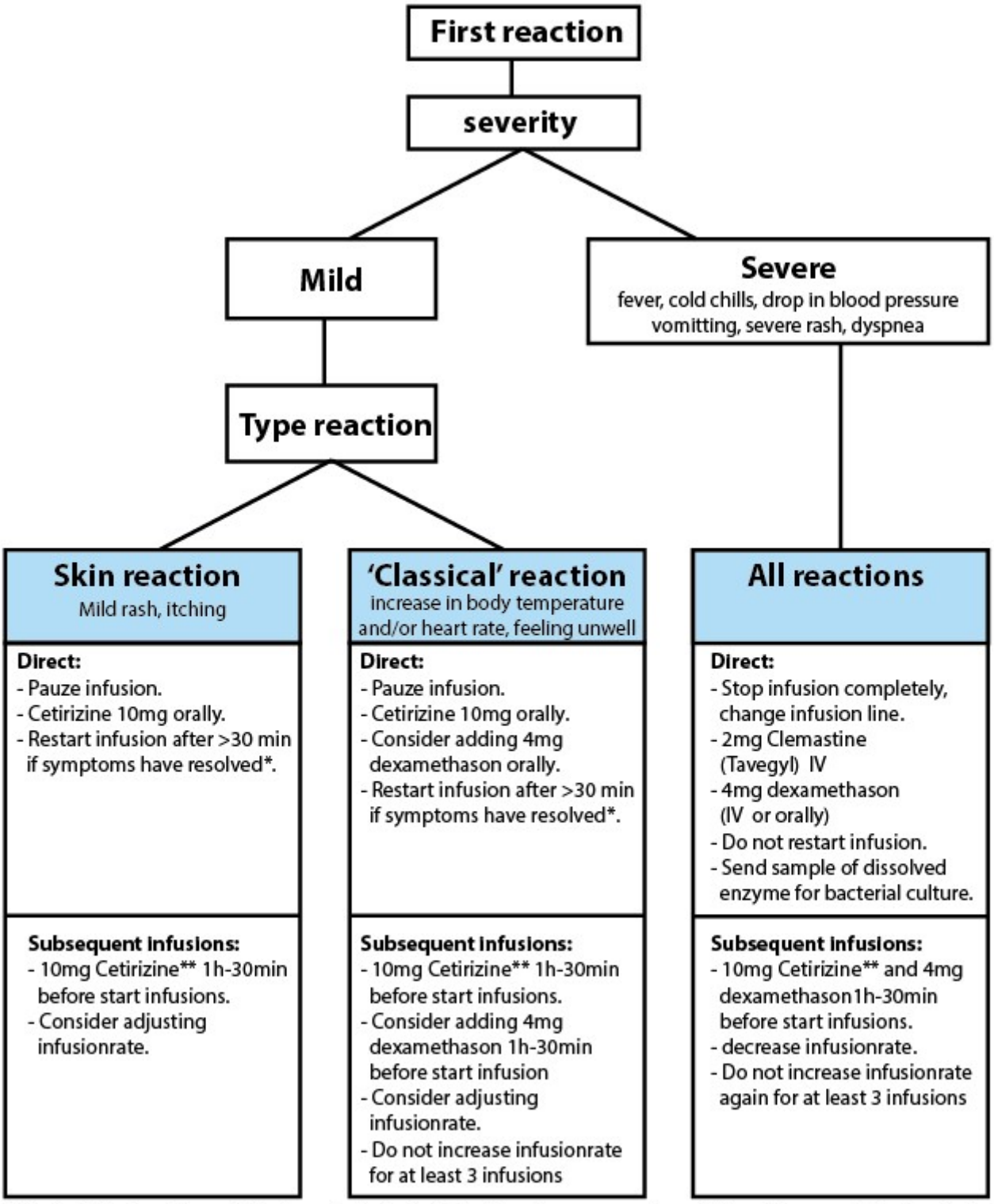
All patients will be prescribed emergency medication (10 mg Cetirizine and 4 mg dexamethason) to be kept at home and taken (after consultation with the treating physician) if an infusion related reaction occurs.Infusion duration, requirements for administration by the patient or family memeber and preparation requirements are described in the local enzyme replacement therapy protocol (Amsterdam UMC, Kwadraet).

Adverse reactions

Adverse reaction to enzyme replacement therapy occur almost solely in male patients. There is a relation with the development of anti-drug antibodies, but not all patients with antibodies develop adverse (or infusion-related) reactions. There seem to be two types of reactions: one with a predominantly dermal reaction (hives) and one with generalized symptoms (feeling unwell and restless, nausea (sometimes with vomiting) and subsequently chills and fever). Fever can trigger neuropathic pain. The generalized reaction typically occurs 45-60 minutes after start of an infusion, but can occur earlier with repeated infusions. The skin reaction also usually occurs during infusion. If an infusion related reaction has occurred, the ADA titer has to be measured (not directly after infusion because the antibodies can then be saturated). If a patient reports a typical infusion reaction at home, it is recommended to have the next infusion in a hospital for observation. In case of an infusion related reaction follow the algorithm in **figure 4.**

Infusion associated reactions can be ameliorated (or prevented) with 10 mg Cetirizine and 4 mg dexamethason orally pre-infusion, taken between 60 to 30 minutes before each infusion. In addition, the infusion time should be lengthened. Patients should be treated with Dexamethason for 3-6 months, subsequently Dexamethason dose reduction be tried. An example scheme is 4-4-3-3-2-2-1-1 mg, per infusion. If this is successful, cessation of the cetirizine and subsequently shorting of infusion time can be tried, though recurrence of infusion reactions can occur. In patients with recent infusion reactions that are able to return to home care, a home care nurse should be present for the entire duration of the infusion for at least the first six months.

Figure 4 Management of infusion related reactions



* Restart infusion at lower infusion rate (last rate that **did not** cause symptoms). Do not increase infusionrate further.
** If eGFR <50 check instructions for adjusted dosing.

NB: Advise patients not to drive motorized vehicles when cetirizine or clemastine is administered.

Holiday / treatment break

Administration of enzyme replacement therapy outside the Netherlands is not possible under supervision of the treatment team at the Amsterdam UMC. A treatment break of several weeks does not affect treatment outcome. If a patient is planning a prolonged stay abroad and needs to continue treatment the care should be delegated to a local treatment team.

8. Contraception and Fabry disease

Contraception and combined use of pain medication (Carbamazepin, Gabapentin, Pregabalin):

- Short term use of carbamazepine and use of oral contraceptive: use additional non-hormonal contraceptives (eg condoms), at least until 4 weeks after cessation of medication.

- Long term use of Carbamazepin: options: use of non-hormonal contraceptives, use of an IUD (copper or prostagen containing), use of medroxyprogesterone intramuscular (Depo-Provera, dose interval should be shortened to once every 10 weeks instead of once every 12 weeks), sterilisation. Given the side effect profile of medroxyprogesterone and the generally lower effectiveness in preventing pregnancy of non-hormonal contraceptives (also in the light of the teratogenicity of Carbamazepine) use of an IUD is preferable. It is advised not to use carbamazepine in combination with transdermal patches, vaginal ring and prostagen only taken orally.

-2^{e} generation anti-epileptics and contraception: second generation anti-epileptics like gabapentin, and pregabalin can be prescribed safely in conjunction with oral contraceptives in their normal dosages.

Contraception and the risk of thrombo-embolic events

In general, ethinylestradiol/levonorgestrel (Microgynon) and medroxyprogesteron (Depo-Provera) are contra-indicated when a thrombotic event has occurred (such as a stroke or myocardial infarction). Etonorgestrel (Implanon) and levonorgestrel (Mirena) are only contra-indicated if there is an active thrombo-embolic event. The Canadian Fabry Disease Treatment Guidelines mentions that drugs that increase the risk for a thrombosis/TIA/CVA, such as contraceptives, may theoretically additionally increase the risk of TIA/CVA in females with Fabry disease. It is suggested to take this into account when prescribing contraceptives. There is no literature available on contraceptives and Fabry disease.