Protocol

Diagnosis, evaluation and treatment of Fabry disease in the Netherlands

Version 6, April 2020

Updated by:
M. Langeveld, C.E. Hollak, S. Klein van Loon, S. van der Veen, M. el Sayed, E. Eskes

DISCLAIMER

This protocol describes current treatment of Fabry disease patients at the Amsterdam University Medical Center, location AMC. The AMC 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 20 years. It is not a comprehensive review of Fabry disease.

Content

1. Introduction 3
2. Fabry disease diagnostics 3
3. Initial assessment 7
4. Follow-up assessments 8
5. Supportive care 12
    - Fabry neuropathic pain: chronic 12
    - Fabry neuropathic pain: acute 14
    - Use of neuropathic pain medication and traffic participation 15
    - Albuminuria and renal insufficiency 16
    - Blood pressure and lifestyle 17
    - Preventive measures 18
6. Pregnancy 19
7. Fabry specific treatment 19
    - Enzyme replacement therapy (ERT) 19
    - Future therapies 20
    - Fabry treatment indication committee 20
    - Start of ERT 20
    - Adverse reactions 20
    - Holiday/treatment break 23
8. Fabry and contraception 23
9. References 24

1. *Introduction*

This protocol describes the current standard of care at the AMC regarding the diagnosis, follow-up 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). Has the patient or a family member been seen by a geneticist?
- Specific issues to be addressed in the medical history:
    - Neuropathic pain: 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. Is there evidence of small fiber neuropathy? (see figure 1)[1]. If not, is there an alternative explanation for the pain?
    - 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?
    - Intoxications (smoking, marihuana/other substances, alcohol)
    - Was amiodarone/cordarone or (hydroxyl)chloroquine ever prescribed? When? For how long?

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

Figure 1 Small fiber neuropathy

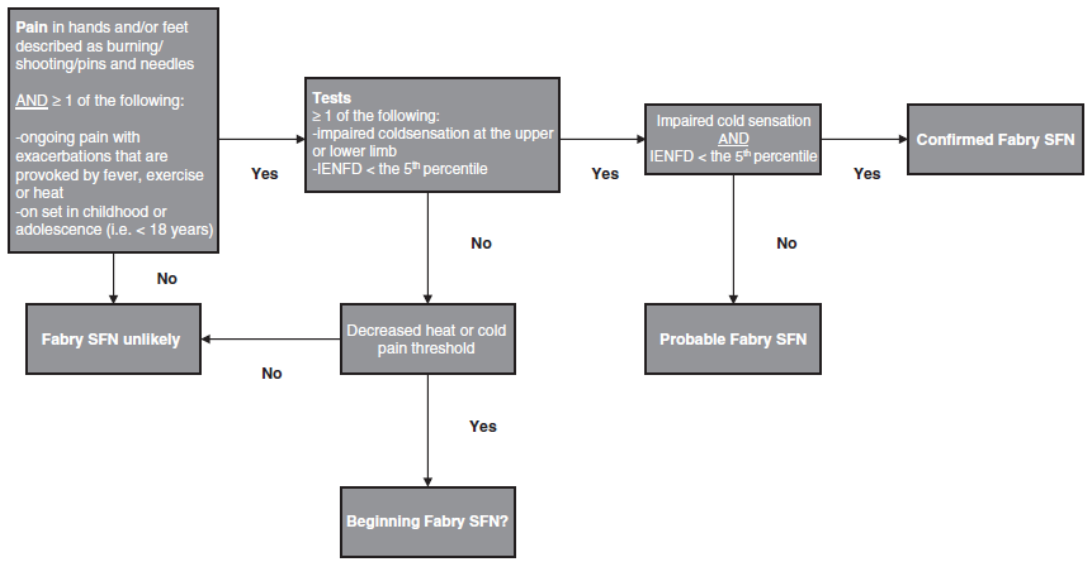


Fig. 2. Flow chart to diagnose Fabry small fiber neuropathy.

Assessments:
Perform the following tests:
-genetic analysis (GLA gene sequencing)
-enzyme activity analysis (aGal 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 lysoGb3 only can be considered. Of importance, the sensitivity of lysoGb3 is high for classically affected patients, but may overlap with the normal range in non-classical females.[2] In addition, in the lower ranges, the specificity is not entirely known: in patients with Fabry-like symptoms such as heart or kidney disease, no extensive studies have as yet been performed. In other lysosomal storage disorders, which do not clinically resemble Fabry disease, lysoGb3 levels have been reported to be elevated up to the range found in non-classical females.[3]

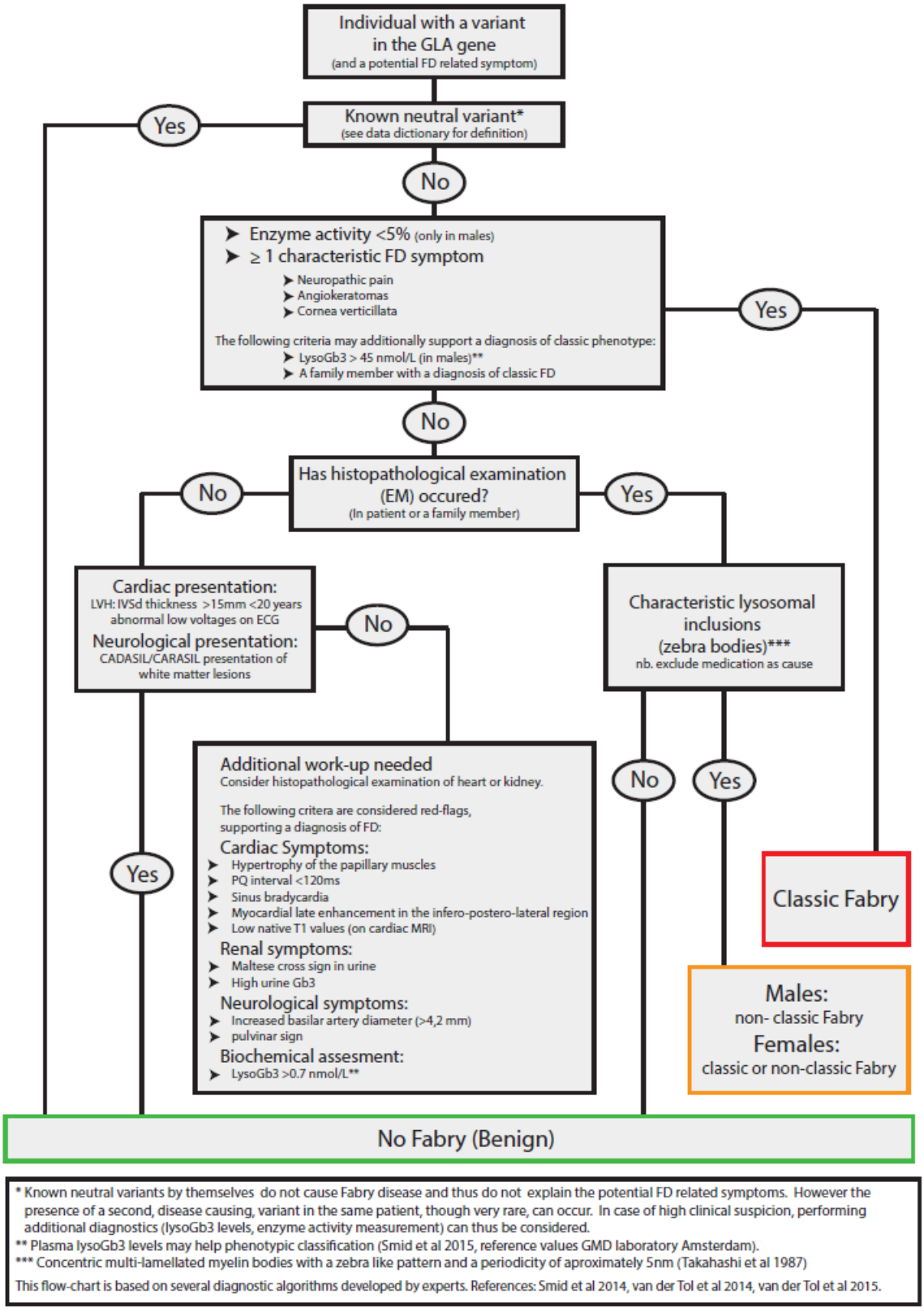
Conclusion:
Based on these examination three conclusions are possible:
1. a definitive diagnosis of Fabry disease (criteria see table 1). The diagnosis is straightforward in patients that found to have a mutation known to be associated with a certain diagnosis of Fabry disease. The Fabry Working Group 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)(see figure 2)

Table 1 Criteria for a definitive diagnosis of Fabry disease[4,5,6]

Definite diagnosis of FD	
Males	**Females**
GLA mutation + AGAL-A deficiency ≤5% of mean reference value in leukocytes + A or B or C A ≥1 characteristic FD sign/symptom (Fabry neuropathic pain, cornea verticillata or clustered angiokeratoma) B An increase of plasma (lyso) Gb3 (within range of males with definite FD diagnosis)* C A family member with a definite FD diagnosis carrying the same GLA mutation	GLA mutation + Normal or deficient AGAL-A in leukocytes + A or B or C A ≥1 characteristic FD sign/symptom (Fabry neuropathic pain, cornea verticillata or clustered angiokeratoma) B An increase of plasma (lyso)Gb3 (within range of females with definite FD diagnosis)* C A family member with a definite FD diagnosis carrying the same GLA mutation
Uncertain diagnosis of FD in subjects with a non-specific FD sign	
Males/Females	
All patients with a non-specific FD sign, such as LVH (MWTd >12 mm), who do not fulfil the criteria for a definite diagnosis of FD and who have a GLA GVUS For further characterization of these patients see figure 2	

*Plasma lysoGb3 ranges: male patient with classical FD: 45-150, female patients with classical FD: 1.5-41.5, male patients with non-classical FD: 1.3-35.7, female patients with non-classical FD: 0.5-2.0 nmol/L (normal values for plasma lysoGb3: ≤0.6 nmol/L)[2]

Figure 2 Diagnostic flowchart for patients with an uncertain diagnosis of Fabry disease[4,5,6]



* Plasma lysoGb3 ranges: male patient with classical FD: 45-150, female patients with classical FD: 1.5-41.5, male patients with non-classical FD: 1.3-35.7, female patients with non-classical FD: 0.5-2.0 nmol/L (normal values for plasma lysoGb3: ≤0.6 nmol/L)[2]

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 lysosomal disease biobank
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, ALAT, ASAT, AF, gGT (and plasma albumin in case of proteinuria)

If eGFR<45: calcium, phosphate, albumin, PTH, 25-OH-vit D, bicarbonate

24-hr urine: creatinine, sodium, albumin, protein

Metabolic markers/Biobank
DNA (for the biobank)
Urine Gb3
Plasma LysoGb3
Plasma Gb3
Antibodies against recombinant enzyme
Fibroblasts (skin biopsy)

Additional investigations/procedures

- Referral to ophthalmologist to assess cornea verticillata (does not have to performed in patients with non-classical disease with a known familial mutation)
- Renal ultrasound (length of both kidneys, cysts, renal cell carcinoma?)
- ECG
- MRI heart, T1 mapping (if eGFR<15 consider necessity vs risk)[7]
- 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.
- MRI brain (white matter abnormalities? (stable or progression?) Pulvinar sign? Presence of a (lacunar) infarction? Microbleeds?
- Fazekas score)
- Audiometry
- Measured GFR (at start of treatment, in all male patients with classical FD, in other patients only if eGFR may not reflect true

kidney function)
- Discuss family screening and refer patients to clinical geneticist (family members that are obligate mutation carriers can directly be referred to the metabolic specialist)

Questionnaires (electronically)
- FS36, BPI, CESD

4. Follow-up assessments

Listed below are the minimal investigations required. Depending on findings at the outpatient clinic visit, additional examinations may need to be added.

Follow up schedule after starting ERT or switch to a different form of ERT (all patients):

- Outpatient visit at 3 months (after start only, not after switch), 6 months, 12 months, 18 months and 24 months and yearly thereafter
- Full laboratory examinations (see table 3) and ECG every year
- Laboratory examinations at intermittent visits: plasma lysoGb3, antibodies against recombinant enzyme (see table 4) and Biobank samples, creatinine (if eGFR<45: calcium, phosphate, albumin, bicarbonate, PTH), if on Carbamazepine: ALAT, ASAT, AF, gGT, hemoglobin, MCV, leukocytes, thrombocytes, if cardiac involvement NT-proBNP, troponin T.
- MRI brain: at 24 months after start of treatment, frequency after 24 months of treatment see table 5
- MRI heart: at 12 and 24 months after start of treatment, frequency after 24 months of treatment see table 6
- Echocardiography: at 12 and 24 months after start of treatment, frequency after 24 months see table 7
- Questionnaires: FS36, BPI, CESD (every visit)

Follow-up schedule for untreated patients:

Men with classical Fabry disease
- Outpatient visits: once yearly
- 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: FS36, BPI, CESD (every visit)

Women with classical Fabry disease and men with non-classical Fabry disease
- 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: FS36, BPI, CESD (every visit)

Women with non-classical Fabry disease

- Outpatient visits: up to age 30: no outpatient visits, after the age of 30 every 5 year
- 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: FS36, 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, sodium, NT-proBNP, troponin T, (and plasma albumin in case of proteinuria) If eGFR<45: calcium, phosphate, albumin, PTH, 25-OH-vit D, bicarbonate, Hb, MCV If on Carbamazepine: ALAT, ASAT, AF, gGT, hemoglobin, MCV, leukocytes, thrombocytes 24-hr urine: creatinine, sodium, albumin, protein. **Metabolic markers/Biobank:** Plasma LysoGb3 Antibodies against recombinant enzyme (inhibitory titer): see table 4

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

3 months treatment	Yes	No
6 months treatment	Yes	No
1 years treatment	Yes	Yes
2 years treatment	Yes	No
3,5,7,9,11…years treatment	Only if ADA positive earlier	No
6 months after switch	Yes*	Yes*

*Continue biyearly measurements if ADA positive

Table 5 Frequency MRI brain		
Sex, phenotype	**Age in years**	**Scan frequency, every**
Men, classical	<10	No scans
	10-20	5 years
	20-30	3 years
	≥30	2 years
Men, non-classical	<30	No scans
	≥30	4 years
Women, classical	<30	No scans
	≥30	4 years
Women, non-classical	<40	No scans
	≥40	5 years
At FD diagnosis (if diagnosis in adulthood)	-	Once
Before start ERT	-	Once
ERT = enzyme replacement therapy, FD = Fabry disease, WMLs = white matter lesions. *In individual patients the scan interval can be shortened, e.g. in case of (progressive) cognitive complaints, suspicion of CVA or treatment decisions.*		

Table 6 Frequency MRI of the heart		
Sex, phenotype	**Age in years**	**Scan frequency, every**
Men, classical	<20	No scans
	>20	2 years
Men, non-classical	<20	No scans
	>20	2 years

Women, classical	<20	No scans
	>20	2 years
Women, non-classical	<40	No scans
	≥40	5 years
At FD diagnosis (if diagnosis in adulthood)	-	Once
Before start ERT	-	Once
ERT = enzyme replacement therapy, FD = Fabry disease. *In individual patients there can be an indication to shorten the scan interval, for example: newly detected myocardial fibrosis (needs to be confirmed on a second scan), complaints compatible with cardiac dysfunction, a likely diagnosis of heart failure (with preserved ejection fraction), hospital admittance because of heart failure etc.*		

Table 7 Frequency echocardiography		
Sex, phenotype	**Age in years**	**Echocardiography frequency, every**
Men, classical	>10	2 years
Men, non-classical	<20	No echo
	≥20	2 years
Women, classical	<20	No echo
	≥20	2 years
Women, non-classical	<40	No echo
	≥40	5 years
Specific indications		
At FD diagnosis	-	Once
Before start ERT	-	Once
ERT = enzyme replacement therapy, FD = Fabry disease. *In individual patients there can be an indication to shorten the echo interval, for example: complaints compatible with cardiac dysfunction, a likely diagnosis of heart failure (with preserved ejection fraction), hospital admittance because of heart failure etc.*		

5. Supportive care

Supportive care is of importance for quality of life (e.g. pain management) and prevention of organ complications (e.g. reduction of proteinuria). Maximum supportive care should be given to each FD patient.

Fabry neuropathic pain (acroparesthesia) - chronic

All individuals with pain in hands and/or feet who fulfill the criteria for small fiber neuropathy as reported by Biegstraaten et al[1] should receive specific pain management. No detailed clinical studies have been performed on which drug works best in Fabry disease.[8] Carbamazepine is the most widely used drug for the management of acroparesthesia.

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.[8]

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 acropresthesia. 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[7] 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.

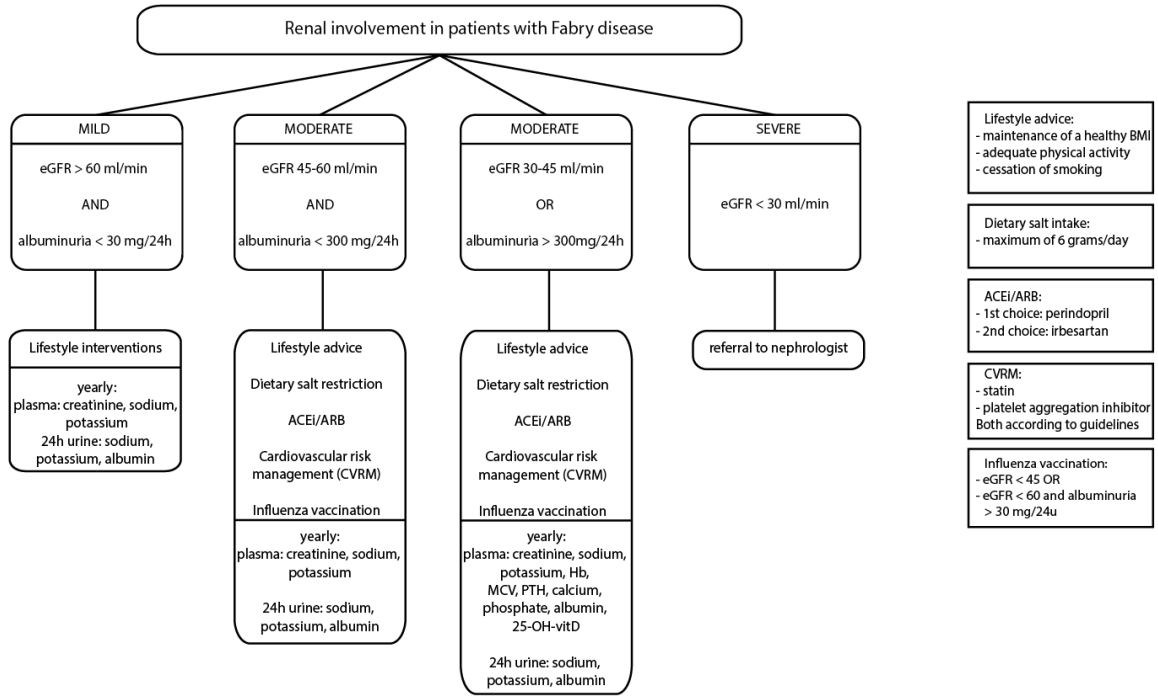
Choice of ACE inhibitor:

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: 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: ARB (irbesartan 150 mg once daily, maximum dose 300 mg/day) ➔ if eGFR < 60 ml/min, check plasma creatinine and potassium after 1 to 2 weeks
Step 4: Add thiazide diuretic ➔ 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/173m^2.



<u>Blood pressure and lifestyle</u>

Male patients with classical Fabry disease rarely have hypertension. If an increased blood pressure is measured at the outpatient clinic, have it repeated at the GP (consider 24 hour bloodpressure 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

Objective 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/173m^2 or eGFR below 60 ml/min/173m^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 will be treated with anti-platelet (without cardiac embolic source) or anti-coagulant therapy (in patients with atrial fibrillation) according to standard practice.[9]

Prescription of anti-platelet drugs for patients with white matter lesions (without TIA/stroke) is not supported by clinical evidence, though routinely advised by many experts. In the case of multiple WML's in a relatively young patient, anti-platelet drugs are recommended (expert opinion). In 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 of medication that increase the risk of a stomach ulcer (e.g. cumarine derivative, DOAC, P2Y12-inhibitor (Clopidogrel, Prasugrel of Ticagrelor), systemic acting glucocorticoïd, SSRI, Venlafaxine, Duloxetine, Trazodon of 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.[9]

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[10], 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, showed a dose-dependent beneficial effect of atorvastatin on kidney function.[11]

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 (classical or non-classical). 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.[12] 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 alfa or beta 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.[13] 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 advanced 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. With all patients, the possibility of treatment discontinuation, if disease stabilization does not occur, is discussed at treatment initiation. As for start of treatment, the possibility of discontinuation is discussed in the indication committee and can only be implemented if consensus is reached.

Choice of drug is up to the treating physician and the patient. Given a more robust reduction of the biomarker plasma lysoGb3 and a potential better effect on cardiac hypertrophy and complication rate in agalsidase-beta versus agalsidase-alfa treated patients[14,15], in most patients agalsidase-beta will be prescribed. In individual cases agalsidase-alfa may be

preferred, given the shorter infusion time and a lower rate of infusion related reactions and formation of anti-drug antibodies (which may be dose related).[14,16,17]

Future therapies

Several new therapies for Fabry disease (e.g. chaperone therapy, new forms of ERT, substrate inhibition and, further down the line, gene and RNA based therapies) will become available in the coming years.[18] Decisions on initiation of or switch to these new drugs go through the Fabry indication committee. Currently none of them are available in the Netherlands. 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.[19]

Fabry treatment indication committee

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

- Prof. Dr Carla Hollak, internist, consultant inherited metabolic disorders
- Dr Mirjam Langeveld, internist, consultant inherited metabolic disorders
- Dr Barbara Sjouke, fellow endocrinology and metabolic disorders
- Prof. Dr Frits Wijburg, pediatrician, metabolic diseases
- Dr Marion Brandts, pediatric fellow metabolic diseases

Other members:

- Dr Matthijs Boekholdt, cardiologist
- Dr Pieter Postema, cardiologist
- Dr Liffert Vogt, internist-nephrologist
- Dr Lily Jakulj, internist-nephrologist
- Dr Astrid Plomp, clinical geneticist
- Dr Jonathan Coutinho, neurologist

Start of enzyme replacement therapy

Treatment can safely be given at home after start of therapy in the hospital.[20] Male patients with classical disease have the greatest risk of infusion related reaction and should receive the first 14 infusions in the hospital. Infusion time is gradually shortened during these infusions. Male patients with non-classical disease will receive 6 infusions and female patients 1 infusion in the hospital. In these patients, infusion time is fixed. All male patients will be prescribed emergency medication (10 mg Cetirizine and 5 mg dexamethason) to be kept at home and taken (after consultation with the treating physician) if a reaction occurs. Patients can choose to administer the medication themselves or have a home care nurse administering the medication. For male patients with classical disease, the nurse needs to be present during the first year of treatment.

Infusion duration and preparation requirements are described in the local enzyme replacement therapy protocol (Amsterdam UMC, Kwadraet).

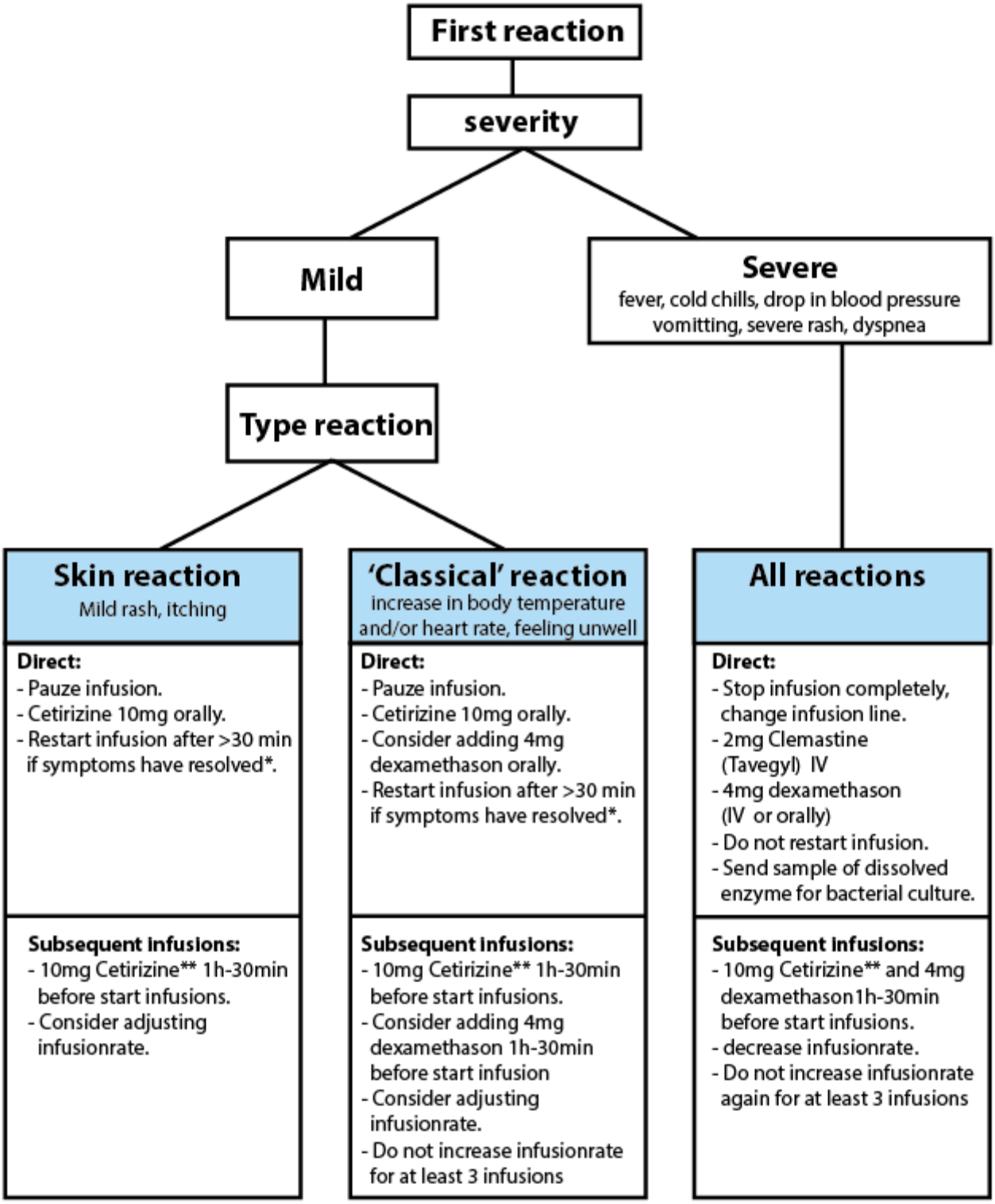
Adverse reactions

Adverse reaction to enzyme replacement therapy occur almost solely in male patients. There is a relation with the development of anti-drug antibodies of antibodies, but not all patients with antibodies develop adverse (or infusion-related) reactions.[20] 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 befor 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.

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

Patients can request a treatment breaks or prefer to continue treatment whilst on holiday. It is possible to continue ERT on holiday, but proper care of medication (transport and storage of agalsidase and infusion sets) is the responsibility of the patient. A treatment break of several weeks does not affect treatment outcome.

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.[21] There is no literature available on contraceptives and Fabry disease.

9. References

1. Biegstraaten M, Hollak CE, Bakkers M, Faber CG, Aerts JM, van Schaik IN. Small fiber neuropathy in Fabry disease. Mol Genet Metab. 2012 Jun;106(2):135-41. doi: 10.1016/j.ymgme.2012.03.010.
2. Smid BE, van der Tol L, Biegstraaten M, Linthorst GE, Hollak CE, Poorthuis BJ. Plasma globotriaosylsphingosine in relation to phenotypes of Fabry disease. J Med Genet. 2015 Apr;52(4):262-8. doi: 10.1136/jmedgenet-2014-102872.
3. Voorink-Moret M, Goorden SMI, van Kuilenburg ABP, Wijburg FA, Ghauharali-van der Vlugt JMM, Beers-Stet FS, et al. Rapid screening for lipid storage disorders using biochemical markers. Expert center data and review of the literature. Mol Genet Metab. 2018 Feb;123(2):76-84. doi: 10.1016/j.ymgme.2017.12.431.
4. Smid BE, van der Tol L, Cecchi F, Elliott PM, Hughes DA, Linthorst GE, et al. Uncertain diagnosis of Fabry disease: consensus recommendation on diagnosis in adults with left ventricular hypertrophy and genetic variants of unknown significance. Int J Cardiol. 2014 Dec 15;177(2):400-8. doi: 10.1016/j.ijcard.2014.09.001.
5. Smid BE, Hollak CE, Poorthuis BJ, van den Bergh Weerman MA, Florquin S, et al. Diagnostic dilemmas in Fabry disease: a case series study on GLA mutations of unknown clinical significance. Clin Genet. 2015 Aug;88(2):161-6. doi: 10.1111/cge.12449.
6. van der Tol L, Smid BE, Poorthuis BJ, Biegstraaten M, Deprez RH, Linthorst GE, et al. A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance. J Med Genet. 2014 Jan;51(1):1-9. doi: 10.1136/jmedgenet-2013-101857.
7. https://richtlijnendatabase.nl/richtlijn/chronische_nierschade_cns/startpagina_-_chronische_nierschade_cns.html
8. Schuller Y, Linthorst GE, Hollak CE, Van Schaik IN, Biegstraaten M. Pain management strategies for neuropathic pain in Fabry disease--a systematic review. BMC Neurol. 2016 Feb 24;16:25. doi: 10.1186/s12883-016-0549-8. Review. Erratum in: BMC Neurol. 2016;16:67. PubMed PMID: 26911544
9.https://richtlijnendatabase.nl/richtlijn/herseninfarct_en_hersenbloeding/secundaire_preventie_na_tia_of_herseninfarct/plaatjesaggregatieremmers_na_tia_of_herseninfarct.html.
10. François Mach, Colin Baigent, Alberico L Catapano, Konstantinos C Koskinas, Manuela Casula, Lina Badimon, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), European Heart Journal, Volume 41, Issue 1, 1 January 2020, Pages 111–188, https://doi.org/10.1093.
11. Vogt L, Bangalore S, Fayyad R, Melamed S, Hovingh GK, DeMicco DA,et al. Atorvastatin Has a Dose-Dependent Beneficial Effect on Kidney Function and Associated Cardiovascular Outcomes: Post Hoc Analysis of 6 Double-Blind Randomized Controlled Trials. J Am Heart Assoc. 2019 May 7;8(9):e010827. doi: 10.1161/JAHA.118.010827.
12. Madsen CV, Christensen EI, Nielsen R, Mogensen H, Rasmussen ÅK, Feldt-Rasmussen U. Enzyme Replacement Therapy During Pregnancy in Fabry Patients: Review of Published Cases of Live Births and a New Case of a Severely Affected Female with Fabry Disease and Pre-eclampsia Complicating Pregnancy. JIMD Rep. 2019;44:93-101. doi: 10.1007/8904_2018_129.

13. Biegstraaten M, Arngrímsson R, Barbey F, Boks L, Cecchi F, Deegan PB, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. Orphanet J Rare Dis. 2015 Mar 27;10:36. doi: 10.1186/s13023-015-0253-6.
14. Arends M, Biegstraaten M, Wanner C, Sirrs S, Mehta A, Elliott PM,et al. Agalsidase alfa versus agalsidase beta for the treatment of Fabry disease: an international cohort study. J Med Genet. 2018 May;55(5):351-358. doi: 0.1136/jmedgenet-2017-104863.
15. El Dib RP, Nascimento P, Pastores GM. Enzyme replacement therapy for Anderson-Fabry disease. Cochrane Database Syst Rev. 2013 Feb 28;(2):CD006663. doi: 10.1002/14651858.CD006663.pub3.
16. Lenders M, Canaan-Kühl S, Krämer J, Duning T, Reiermann S, Sommer C, et al. Patients with Fabry Disease after Enzyme Replacement Therapy Dose Reduction and Switch-2-Year Follow-Up. J Am Soc Nephrol. 2016 Mar;27(3):952-62. doi: 10.1681/ASN.2015030337.
17. van der Veen SJ, van Kuilenburg ABP, Hollak CEM, Kaijen PHP, Voorberg J, Langeveld M. Antibodies against recombinant alpha-galactosidase A in Fabry disease: subclass analysis and impact on response to treatment. Mol Genet Metab. 2019 Feb;126(2):162-168. doi: 10.1016/j.ymgme.2018.11.008.
18. van der Veen SJ, Hollak CEM, van Kuilenburg ABP, Langeveld M. Developments in the treatment of Fabry disease. J Inherit Metab Dis. 2020 Feb 21. doi: 10.1002/jimd.12228.
19. https://www.zorginstituutnederland.nl/publicaties/adviezen/2017/04/25/migalastat-gvs-advies
20. Smid BE, Hoogendijk SL, Wijburg FA, Hollak CE, Linthorst GE. A revised home treatment algorithm for Fabry disease: influence of antibody formation. Mol Genet Metab. 2013 Feb;108(2):132-7. doi: 10.1016/j.ymgme.2012.12.005.
21. ref http://garrod.ca/wp-content/uploads/2019/04/Canadian-Fabry-Treatment-Guidelines-2018-final.pdf