Canadian Fabry Disease Treatment Guidelines 2018

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Fabry disease is an X-linked lysosomal storage disease characterized by the development of hypertrophic cardiomyopathy, nephropathy with chronic renal failure and stroke. This condition arises from the deficiency of the lysosomal enzyme alpha-galactosidase A with the resultant accumulation of glycosphingolipids in all cells and tissues. This deposition damages and kills cells resulting in premature death and disability, particularly for affected hemizygotes. Treatment for all patients involves control of cardiovascular risk factors and supportive care for issues related to living with a chronic disease; disease specific treatment with enzyme replacement therapy (ERT) or chaperone therapy may have benefit for some individuals. Recombinant human alpha-galactosidase A enzyme is available in two forms, agalsidase-alfa (Replagal™; Shire Inc.) and agalsidase-beta (Fabrazyme®; Sanofi-Genzyme Corporation). Migalastat (Galafold™; Amicus Therapeutics) is the first chaperone therapy for Fabry disease approved in Canada. Clinical guidelines for the use of ERT in Canada were first developed in 2005 by an expert committee based upon the medical literature and this process has been repeated annually since 2007. As new therapies are developed (chaperone therapy, substrate reduction therapy), these will be incorporated into the Canadian Fabry disease treatment guidelines.

These Fabry disease treatment guidelines currently form the basis for disease specific therapy in Canada, specifically in the multicentre Canadian trial of ERT in Fabry Disease, known as the Canadian Fabry Disease Initiative (CFDI). The CFDI has now been transitioned to a national patient registry to continue to track the progress of Canadian patients. These guidelines are intended to apply to all patients with Fabry disease in Canada regardless of gender and age.

Participants in 2019 review

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Dr. Gavin Oudit, although not present at the 2019 meeting, has been involved for multiple previous editions of the guidelines and his work remains as part of the 2018 version.

Disclosures for all participants are included below.

Process

Annual literature review has been conducted since the onset of the CFDI to inform the guideline process; for the 2019 guidelines, available literature on Fabry disease published from January 1 2017 to July 25 2019 was determined by an electronic search of Medline and Pubmed using the search terms Fabry and Fabry disease limited to

abstracts, English language and research articles in humans.   A list of the articles reviewed in 2019 is provided in Appendix 1. Single case reports and review articles were not included in the review unless new information was presented. Standards of evidence were modified from those previously published (Canadian Task Force on the Periodic Health Examination 1979; see Table 2).   Consensus was reached by discussion.

Support

Diagnosis of Fabry disease

The diagnosis of Fabry disease requires the synthesis of clinical, biochemical, molecular and pathologic criteria. Given the challenges with each of these criteria outlined below, it is recommended that a patient have at least 3 of the 4 criteria before making a diagnosis of Fabry disease (van der Tol 2014) although if characteristic pathological findings are present, fewer criteria may be required to point to the correct diagnosis.

a) **Clinical criteria**

i) None of the features of classical Fabry disease are diagnostic in their own right. Some features of Fabry disease (for example, nephropathy, hypertrophic cardiomyopathy, stroke) are very nonspecific with a broad differential diagnosis. Other features of Fabry disease (like cornea verticillata, biopsy-proven angiokeratomas) have a more limited differential diagnosis although there are still conditions other than Fabry disease which can cause these more specific findings (e.g. amiodarone therapy can cause similar corneal changes). For this reason, clinical findings alone cannot be used to confirm the diagnosis of Fabry disease although more weight can be given in the diagnostic process to those findings (corneal verticillata, biopsy proven angiokeratomas) of higher specificity.

b) **Biochemical criteria**

i) Levels of alpha-galactosidase activity measured in whole blood, plasma or leukocytes that are severely decreased or absent (below 5% of mean) are strongly suggestive of Fabry disease in male hemizygotes or female homozygotes. However, higher levels have been reported in many confirmed

cases and are more likely in those patients presenting with a late onset cardiac variant. Females who are Fabry disease heterozygotes may also have enzyme activity levels that are modestly decreased or normal despite other clear manifestations of Fabry disease. The presence of reduced levels of enzyme activity in a related male in a kindred should be considered as strong evidence that Fabry disease is present. Documentation of reduced levels of leukocyte alpha-galactosidase activity is the preferred biochemical marker to use in the evaluation of a patient for possible Fabry disease. In families with variants of unknown significance (VUS), the absence of reduced levels of enzyme activity in a male with the VUS is strong evidence that Fabry disease may not be present.

ii) Biomarkers in urine and plasma such as globotriaosylceramide (Gb3) and sphingosine-globotriaosylceramide (Lyso-Gb3) are often elevated in patients with Fabry disease although the correlation of these biochemical markers with clinical outcomes remain unclear. Conditions other than Fabry disease can cause elevations in urine Gb3 (Schiffmann 2014). Lyso-Gb3 is a more sensitive marker than Gb3 but still may be normal in confirmed cases, especially in women. The presence of elevated biomarkers then can be used as a feature pointing towards Fabry disease but is not diagnostic. The absence of elevated biomarkers does not rule out a diagnosis of Fabry disease particularly in female heterozygotes.

c) **Molecular criteria**

i) Previously reported mutations - There are databases of numerous mutations which have been reported in cases of Fabry disease. However, it is known that there is a high rate of inaccuracy in these databases (Bell 2011). For this reason, the presence of a DNA change that has been reported to cause Fabry disease must be combined with clinical, biochemical and pathological criteria to confirm the diagnosis of Fabry disease

ii) Variants of uncertain significance (VUS) – For DNA changes which have not been previously reported, there are several models which are often used to try and predict pathogenicity but the accuracy of any of these models is limited with most models correctly predicting that a variant is benign or pathogenic in fewer than 80% of the cases (Walters-Sen 2015). Modeling of VUS in cell lines or other systems can be done by some research labs but is not widely available. The presence of a VUS then should not be used as a diagnostic criterion for Fabry disease consistent with current consensus guidelines (Richards 2015). VUS which are not accompanied by an elevation in GB3, lysoGB3, decreased enzyme activity in the diagnostic range, clinical features of

Fabry disease or a known male relative with Fabry disease may not be disease-causing nor benefit from disease-modifying drug therapy. When VUS with these characteristics are identified, further investigations including tissue biopsy should be considered before making a diagnosis of Fabry disease.

iii) Co-existent disease processes – multiple reports have suggested that GLA mutations can coexist with other mutations causing hypertrophic cardiomyopathy in up to 0.4% of cases (Frustaci 2016 and others). Testing for Fabry disease should be done on all patients with idiopathic hypertrophic cardiomyopathy as part of gene panel screening for genetic causes of this condition. We recommend that patients whose main manifestation of Fabry disease is cardiac hypertrophy undergo comprehensive panel testing to exclude other known diagnoses. If a second diagnosis is present (e.g. a sarcomeric gene mutation), pathologic analysis of a myocardial biopsy may be considered as not all patients with a dual diagnosis may have significant storage material to benefit from ERT or chaperone therapy.

d) Pathologic criteria

i) Characteristic changes suggestive of Fabry disease can be found on biopsies of kidney, heart, skin and other tissues. While a pathologist may be able to identify that storage material is present in tissues, they will not be able to characterize the nature of this accumulated material without doing specific immunohistochemical stains for Gb3, a tool that is not widely available. Also, phenocopies of Fabry disease have been reported where Gb3 storage was documented in tissue (Appelland 2014). Thus, while the finding of characteristic changes in a biopsy is strong evidence for a diagnosis of Fabry disease, it should be combined with at least one other diagnostic feature from the biochemical or molecular categories to confirm the diagnosis). Biopsy of clinically affected tissues can also provide useful prognostic information (such as irreversible changes like the degree of glomerulosclerosis in patients with nephropathy or the degree of fibrosis on a heart biopsy). Biopsy of clinically involved tissue(s) is strongly encouraged in the work up of all patients with Fabry disease. Skin biopsy, while not useful in providing prognostic information, can sometimes help in the diagnostic process (if read by an experienced pathologist) by documenting the presence of glycosphingolipids. This technique, compared with biopsy of internal organs i.e. kidney, is easy to perform and only minimally invasive.

A summary of these diagnostic criteria is provided in Table 1 below.

Table 1. Summary of diagnostic criteria for Fabry disease*

Criterion	Relevant finding	Points towards diagnosis	Comment
Clinical features	Cornea verticillata or biopsy-proven angiokeratomas	Presence of either or both of these will contribute 1 point	Need to exclude other causes
Alpha-galactosidase activity in plasma or leukocytes	Below 5%	1 point	Activity may not be reduced in females but low activity in a male member of the family cohort would contribute towards the diagnosis
Elevated plasma and/or urine biomarkers	Above reference range for lab; lyso-Gb3 is preferred	1 point	Conditions other than Fabry disease can elevate biomarkers
Molecular change	Mutation defined in literature as disease causing	1 point	High rate of error in annotation of mutations in available databases; the presence of a VUS should not be used to contribute towards the diagnosis
Pathologic findings	Presence of typical features of Fabry disease on biopsy of involved tissue	2 points in target organs (kidney, heart) 1 point in other organs (skin)	Should be interpreted by a pathologist with expertise in Fabry disease

Diagnosis of Fabry disease is likely in patients with 3 or more points

*Adapted from Smid BE 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;177:400-8.

Disease specific therapy of Fabry disease

While all patients with Fabry disease may benefit from cardiovascular risk factor reduction strategies and other aspects of general medical care (outlined below), not all patients with Fabry disease will benefit from disease specific therapy. There are currently two forms of disease specific therapy for Fabry disease (ERT and chaperone therapy) and other modalities of treatment including substrate reduction therapy (SRT) are in development (Guerard 2017). Once a diagnosis of Fabry disease is confirmed, there should be a thorough evaluation of whether disease-specific therapy, either ERT or chaperone, is likely to provide clinical benefit. The indication for therapy should precede the decision on which type of therapy should be used. The first decision about any patient with a confirmed diagnosis of Fabry disease is **SHOULD** the patient receive disease specific therapy. In those patients in whom benefit from disease specific therapy can be anticipated, then the next question is **WHICH** therapy should be used. Disease specific therapy should be considered in all patients with documented Fabry disease, of any age and either sex, who meet the criteria outlined below for disease-specific therapy. In all cases, diagnostic accuracy is essential with exclusion of other possible etiologies. The treating physician has the responsibility of ensuring that there is a high likelihood of patient benefit and a low risk of adverse effects of disease specific therapy. A diagnosis of Fabry disease in the absence of clinical evidence of organ involvement is NOT an indication for disease specific therapy. Some manifestations of Fabry disease are not improved by disease specific therapy such as the risk of stroke while others may be improved by this therapy such as the rate of decline of renal function. Thus, disease specific therapy should be considered when there are manifestations for which this therapy is of proven benefit.

Choice of therapy

ERT was the first form of disease specific therapy developed for Fabry disease and is the form of treatment for which the most robust data on the effects of therapy are available. ERT is appropriate for all patients with Fabry disease who have indications for disease specific therapy, regardless of mutation status. Chaperone therapy, by contrast, only works in patients who have mutations which are amenable to binding by the chaperone and thus can only be considered in a subset of patients. In Canada, the only chaperone for Fabry disease currently approved by Health Canada is migalastat. Migalastat has been shown to have favorable effects versus placebo on renal function and left ventricular hypertrophy (Germain 2016) and reduce diarrhea (Schiffmann 2018) in patients with amenable mutations. Patients on long term ERT with amenable mutations switched to migalastat (Hughes 2017) showed stability in renal function and cardiac parameters. However, both of these clinical trials involved patients with very

mild disease manifestations (eGFR 89-94 ml/min/1.73m^2, LVMI 94-97 g/m^2) and did not include patients with high levels of proteinuria (mean albumin/creatinine ratio 13-27 and no patients with nephrotic range proteinuria) which is a known risk factor for adverse cardiovascular and renal events in Fabry disease. These trials are also of short duration (18-24 months). Published data are not yet available on the effects of migalastat in patients with more advanced disease or with duration of therapy beyond 2 years. It should also be noted that switching from ERT to oral therapy with migalastat did not result in an improvement in quality of life indices which remained stable through the switch (Hughes 2017).

To determine if a patient has an amenable mutation, clinicians can look up the mutation in a database provided by the manufacturer (http://www.galafoldamenabilitytable.com/hcp/). The definition of an amenable mutation is one that increases activity of alpha galactosidase A in an *in vitro* cell culture system (human embryonic kidney or HEK cells) by 1.2 times the baseline activity with an absolute value for enzyme activity of 3% or greater when compared with wildtype values (Benjamin 2017). Many amenable mutations will increase the absolute values of enzyme activity far above 3% of wild type activity but clinicians should be aware of these thresholds to define a mutation as amenable. Clinicians desiring information about the absolute values of enzyme activity (expressed as % of the wild type) of any given mutation when expressed in the HEK assay in the presence of migalastat may request this information from the manufacturer or consult the supplementary tables published by Benjamin (2017). This HEK assay has been shown to correlate with surrogate markers of disease activity like lyso-Gb3 and kidney Gb3 deposits (Benjamin 2017). However, the tools to define an amenable mutation have already evolved (e.g. in the study by Germain *et al* [2016], 17 of the 67 subjects thought to have amenable mutations using an older technique were not amenable by the newer HEK assay). Oommen et al (2019) have also demonstrated that there may be considerable inter-laboratory variability in the assessment of amenability by the HEK assay. Clinicians need to be aware that the status GLA mutations thought amenable to chaperone therapy with migalastat could possibly change over time if the defining assay changes. The amenability status of a GLA mutation should be re-evaluated in Fabry disease patients whose clinical monitoring parameters deteriorate on migalastat therapy.

Choice of therapy needs to be individualized for each patient in discussion with their physician. ERT is the only therapy appropriate for patients who do not have amenable mutations. For patients who do have amenable mutations in whom ERT or chaperone therapy might be possible, several factors to consider include:

1. Degree of organ involvement – there are no published data on the effects of migalastat in Fabry disease patients with more advanced disease (e.g. chronic kidney disease (CKD) stage 2 or higher, more extensive left ventricular

hypertrophy or nephrotic range proteinuria). The Canadian label indicates that the drug should not be used in patients with eGFR <30 ml/min/1.73m^2. In patients with more advanced disease (but whose eGFR is above 30 ml/min/1.73m^2 in whom migalastat therapy may be considered) newly starting on disease specific therapy, in addition to considering treatment with ERT or migalastat, consideration could be given to a third option such as starting with ERT and then considering "step down" to oral therapy after 3-5 years if the patient has a good response although there are not data at present to evaluate this sequential treatment strategy.

2. Patient compliance – some patients, even with advanced disease manifestations, may prefer to switch to migalastat therapy to avoid further intravenous infusions with the possible issues of difficult intravenous access, antidrug antibodies and infusion-associated reactions. However, switching from ERT (where a nurse supervises the infusions) to migalastat therapy (where the patient has to remember to take the pills every second day) may not be appropriate for patients who have difficulty remembering to take their medications or noncompliance with ERT infusions.

   a. Information on compliance with any form of disease specific therapy should be reviewed on a regular visit (for example by reviewing prescription or infusion records) and the patient should be aware of this review. Patients and physicians should discuss the importance of compliance and agree that the drug will be discontinued for patients who do not meet pre-agreed on thresholds of compliance.

3. Patient age – although oral therapy would be preferable in the treatment of pediatric patients to avoid the need for biweekly venipuncture, migalastat is not licensed in Canada for patients under the age of 18 years. There are also very limited data on the use of migalastat in patients 65 years of age and older although the drug is not specifically contraindicated in this age group.

4. Need for increased surveillance of response to treatment – for patients newly started on any type of disease specific therapy, assessment by their treating physician with relevant investigations including biomarkers is recommended every 3-6 months for the first 5 years of therapy and then annually thereafter if the patient is stable. However, while the available literature on migalastat suggests that it is non-inferior to ERT, this was a short term study (18 months; Hughes 2017). We would recommend that patients who are switched from ERT to migalastat be followed every 6 months for the first 3-5 years of therapy to ensure their clinical parameters are stable. Patients should be advised PRIOR to

starting migalastat that, if their disease parameters deteriorate, a switch to ERT may be recommended by their physician.

    a. In patients being considered for a switch of disease specific therapy from ERT to migalastat or the reverse, it is important to ensure that assessments of their cardiac (EKG, holter monitor, echocardiogram, cardiac MRI) and renal status (24 hour proteinuria, blood pressure, eGFR) as well as biomarkers (plasma and/or urine Gb3, lysoGb3) are up to date prior any treatment switch.

Choice of ERT and dose

Although the standard doses of agalsidase alfa (0.2mg/kg) and agalsidase beta (1.0mg/kg) differ, 5 and 8 year follow up data from the CFDI shows that the overall outcomes of therapy with the two drugs are equivalent (Sirrs 2014; West 2016a) and a recent metanalysis (Pisani 2017) indicated stability of renal and cardiac parameters in patients switched from agalsidase beta to agalsidase alfa during the interval of drug shortages. Longer term data from Arends et al (2018) and the CFDI (Sirrs 2018) show that overall, the two drugs are equivalent in terms of clinical outcomes in most patient groups. However, these more recent data suggest that there may be some advantages of agalsidase beta relative to agalsidase alfa in male Fabry patients with a classic phenotype. The rate of decline in left ventricular mass in the first year of therapy was higher in patients treated with agalsidase beta in a large cohort study but this was only significant in patients with an elevated left ventricular mass at baseline (Arends 2018). While the cohort study from Arends et al (2018) did not show a difference between the two drugs in rate of decline of renal function, 10 year data from the CFDI suggests that there is a trend to a reduced rate of decline of renal function in classical males treated with agalsidase beta rather than agalsidase alfa although the result was not statistically significant (Sirrs 2018). No differences between the two drugs were seen in women or males with nonclassic phenotypes. Antibody responses are more marked in patients treated with agalsidase beta relative to agalsidase alfa (Arends 2018). A cohort analysis by El Dib et al (2017) suggested that there was a benefit of agalsidase beta relative to placebo on renal, cardiac, cerebrovascular outcomes as well as all cause mortality. The confidence intervals for the effects of agalsidase alfa on these outcomes overlapped with the untreated group so that benefit of agalsidase alfa could not be confirmed (El Dib 2017). However, the results of this cohort analysis may be affected by the higher number of classic male patients in the agalsidase beta studies as this is the patient group which is likely to benefit most from treatment on the basis of the data from Arends

et al (2018) and the CFDI (Sirrs 2018). On the basis of these data, agalsidase beta may be considered as the first option in male patients with a classic phenotype who are started on disease specific therapy. Some males with classical phenotypes may prefer agalsidase alfa for other reasons (for example, shorter infusion times) and patient preferences should be considered in choosing a drug. Either drug could be considered for patients with nonclassic phenotypes, women, or older patients in whom total duration of treatment is expected to be less than 10 years and there may be individual patient preferences that lead to the choice of one drug or the other. ERT should be dosed according to the product monograph in most cases. There are circumstances where alternative dosing regimens could be considered (such as the cases where neutralizing antibodies are present in association with poor clinical/biochemical response to ERT [Lenders 2018]) but, at this time, this would constitute off-label use of the drug and should be discussed with experts in the field.

Switching ERT

There is no evidence that one agent should be considered as rescue therapy if there is poor clinical response to the other agent (Goker-Alpan 2015; Tsuboi 2014; Lenders 2015). Data concerning altered dose regimens as a means to affect outcomes are limited with mixed results (Hughes 2013; Schiffmann 2007, Schiffmann 2015). Data from the CFDI suggests that there may be an increased risk of events for the first 6 months after a drug switch (West 2016b) suggesting that optimal management would be to not switch medications if possible. Kramer et al [2017] found that patients switched from AGALB (1 mg/kg) to AGALA (0.2 mg/kg) and then back to AGALB at 1 mg/kg could attenuate but not eliminate the more rapid rate of decline of eGFR (-2.2 ml/min/1.73 m2 in the dual switch group whereas eGFR in those who were not switched was stable) also suggesting that there may be some deleterious effects of the switch itself. Given the lack of data to support alternative dose and dosing and possible risks associated with the switch, considerations of changing drug, dose or dosing are best done in the setting of a formal clinical trial.
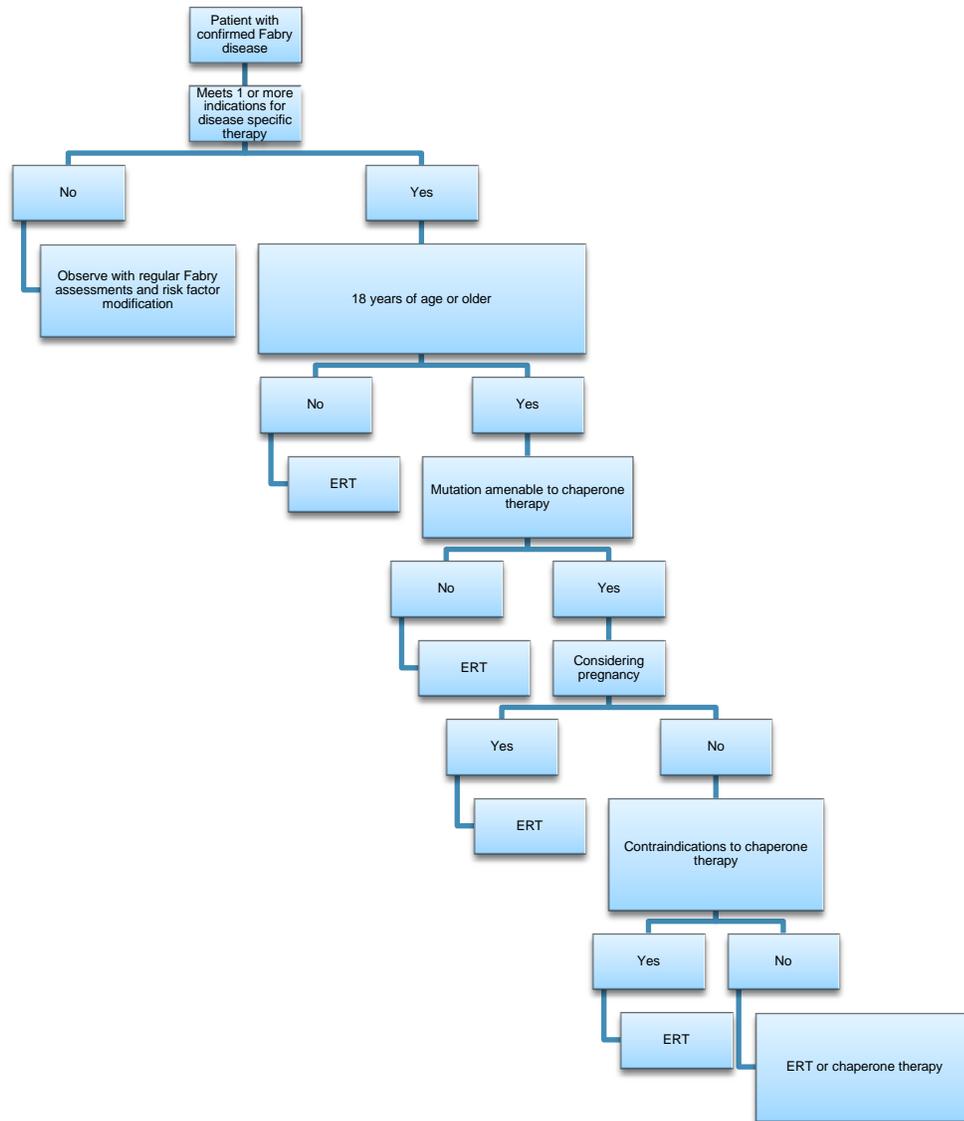
Figure 1. Decision matrix for disease specific therapy in Fabry disease

Potential benefits of disease specific therapy

Based upon current literature, there is evidence of improvement with disease specific therapy with ERT in some aspects of Fabry disease as detailed below:

- Stabilization of Fabry nephropathy with stable proteinuria and glomerular filtration rate (GFR).
- Stabilization of Fabry cardiomyopathy with stable or declining left ventricular mass index (LVMI), LV wall thickness, improvement of PR interval on EKG.
- Improvement in diarrhea, abdominal cramps or pain, nausea, vomiting and heartburn associated with Fabry disease.

Other clinical features of Fabry disease have not yet been shown to respond to disease specific therapy:

- Tachy or brady arrhythmias
- Stroke or TIAs
- Proteinuria
- Depression
- Hearing loss

Potential risks of ERT

- Increased healthcare costs due to costs of drug purchase and drug administration
- Development of infusion reactions to ERT characterized by fever, chills, edema, rash, nausea and dyspnea. Anaphylactic reactions, while rare, are possible.
- Development of anti-agalsidase antibodies; IgG antibodies may be associated with infusion reactions as detailed above, with *in vitro* inactivation of agalsidase or with increased levels of urine and plasma Gb3 as well as plasma lysoGb3 (significance currently unknown); IgE antibodies to agalsidase-beta may be associated with anaphylaxis. IgA and IgM antibodies to agalsidase-alfa have also been identified although the significance of these observations is unknown. Patients who appear to have poor response to ERT either with clinical parameters or with biomarkers such as LysoGb3 should be assessed for the presence of neutralizing antibodies as these may significantly impact patient outcomes on therapy (Lenders 2018).

Potential risks of migalastat therapy

- The drug was well tolerated in clinical trials. The most common side effects which occurred more frequently than with placebo were nasopharyngitis and headache. Prescribing physicians are directed to review the product monograph for description of other side effects reported in migalastat treated patients.
- Progression of Fabry disease complications may occur in patients previously stable on ERT if their compliance with migalastat is less than their compliance with ERT.

Indications for disease specific therapy

Indications for disease specific therapy are designed to target patients for such therapies at early stages of disease progression. Although it is attractive to postulate that treatment in asymptomatic stages of the disease (ie. primary prevention) would be more beneficial, the single published study evaluating the use of ERT (agalsidase beta) in the primary prevention setting did not show that this approach was able eradicate accumulation of storage material on biopsy (Ramaswami et al 2019). Although this trial did not evaluate doses as recommended by the product monograph and was

underpowered to detect differences on clinical outcomes such as progressive renal or cardiac disease, these data are the most complete data yet available on treating in the primary prevention setting at this time. Based on these data then, treatment before thereis detectable evidence of end organ involvement cannot be recommended at present. However, it is also important to understand that disease specific therapy will likely be of more benefit in patients in whom irreversible manifestations of Fabry disease (e.g. cardiac fibrosis) have not yet developed. Thus, we recommend that patients who do not meet criteria for disease specific therapy at the time of diagnosis of Fabry disease be followed regularly with full assessment for development of Fabry related organ involvement so that disease specific therapy, if needed, can be introduced at an early phase in the disease.

Renal indications

Renal disease is a common feature of Fabry disease in males but there are numerous case reports where patients with Fabry disease were found to have an alternate treatable cause for renal dysfunction on renal biopsy (Maixnerova 2013 and others). For this reason, all other causes of reduced GFR and proteinuria (including orthostatic proteinuria) need to be excluded. When reduction of GFR is present, the negative effects on GFR by concurrent medications such as ACE inhibitors, angiotensin receptor blockers, diuretics, non-steroidal anti-inflammatory drugs and other agents should be excluded. A nephrology consultation may be needed. Consideration should be given to a renal biopsy if there is any doubt as to the diagnosis. In addition to disease specific therapy, nonspecific measures appropriate for all patients with kidney disease (smoking cessation, control of dyslipidemia and proteinuria, aggressive control of hypertension) are appropriate in patients with Fabry nephropathy. As ERT does not reduce proteinuria to a significant degree, blockade of the renin-angiotensin system is important in all patients with proteinuria with the goal of reducing urine protein excretion below 500 mg/day (Warnock 2015)

Renal Disease Evidence level 1 - Grade B

1 major criterion or 2 minor criteria required

Major criteria:

• Fabry nephropathy with reduced GFR
For GFR < 60 ml/min/1.73m^2 chronic kidney disease (CKD) stages 3-5: at least 2 consistent estimates or measurements of GFR over a minimum of 2 months.

For GFR 60 - 90 ml/min/1.73m^2, CKD stage 2: at least 3 consistent estimates or measurements of GFR over at least 4 months with a GFR slope greater than age-related normal.

For GFR >135 ml/min/1.73m^2: a 15% decrease in GFR or a GFR slope greater than age-related normal as measured by nuclear medicine technique. Estimated GFR is not accurate in this range and thus cannot be used.

Persisting proteinuria of 500 mg/day/1.73m^2 or greater without other cause.

Findings of high risk pathology (glomerular sclerosis, tubulointerstitial atrophy, fibrosis or vascular sclerosis) on renal biopsy are a major criterion in males only (see comments).

Comments:

1. GFR in adults should be estimated (eGFR) by CKD-EPI formula (Levey 2009) and in children by the Counahan-Barrett formula (Counahan 1976). Measured GFR by nuclear medicine technique should be done in adults or children if there is hyperfiltration or inconsistency in renal function. All other methods of estimating GFR such as the MDRD, Cockcroft and Gault formula or old Schwartz formulas or creatinine clearance are less accurate and should not be used (Tondel 2010; Rombach 2010). In particular, these estimates may result in false hyperfiltration readings, especially in children or teenagers. Calculations of GFR in children may be less accurate and, if treatment decisions are to be made using GFR data, clinicians are encouraged to get more accurate measurements of GFR using nuclear techniques.
2. A renal biopsy is not required as a prelude to therapy. However, if the patient has clinical indications for a renal biopsy, renal pathology in men is a major criterion if features known to be of high risk in predicting progressive renal disease (glomerular sclerosis, tubulointerstitial atrophy and fibrosis or vascular sclerosis) are present. A pathologist with extensive expertise in the interpretation of renal biopsies in patients with Fabry disease is required in order to ascertain the prognostic significance of pathological changes in the renal biopsy. Some changes (such as glycolipid deposit volume in podocytes and foot process width in Fabry nephropathy) correlate with age (Najafian 2011) while other features (glomerular sclerosis, tubulointerstitial atrophy and fibrosis or vascular sclerosis) are more effective in predicting the risk of progressive renal disease. While the presence of lamellar bodies characteristic of Fabry disease can occur in podocytes and in all renal cell types, they are not diagnostic of this condition as they can be observed in sphingolipidoses induced by chloroquine and other drugs. Given these difficulties in interpretation, clinicians are strongly encouraged to involve a pathologist with expertise in Fabry disease in renal biopsy interpretation.

Minor criteria:

- Hyperfiltration: There should be at least two (2) consistent measurements of GFR by nuclear medicine techniques at least one month apart when GFR reaches or exceeds 135 ml/min/1.73m^2. Hyperfiltration by eGFR as calculated by any formula is not accurate and thus not acceptable.
- Isolated proteinuria of 300 mg/day/1.73m^2 or greater than normal for age and gender and persistent for at least one year with exclusion of other causes.
- Renal tubular dysfunction. Fanconi syndrome and/or nephrogenic diabetes insipidus confirmed usually with abnormal water deprivation test and resistance to DDAVP.
- Hypertension of at least one year duration.
- Renal pathology in women may be taken into account as a minor criterion if the patient has indications for renal biopsy. If a renal biopsy is done, the presence of glomerular sclerosis, tubulointerstitial atrophy and fibrosis or vascular sclerosis should be considered a minor criterion in women.

Comment: The development of progressive renal disease in women is much less common than in men (Sirrs 2014). Therefore, the presence of positive renal pathology for Fabry disease in women is not a hallmark for progression of renal disease making interpretation of the significance of renal biopsy changes much less clear in women than in men. In such cases, review of the biopsy by a center experienced in interpreting renal biopsies in Fabry disease is desirable to aid with interpretation of the findings.

Cardiac Disease Evidence level II-2 - Grade B

2 criteria required

Criteria:

- LV wall thickness >12 mm in males and >11 mm in females

- LV hypertrophy (LVH) by Estes ECG score must be greater than 5

- LV mass index by 2D echo 20% above normal for age

- Increase of LV mass of at least 5 g/m2/year, with three measurements over a minimum of 12 months

- Diastolic filling abnormalities by 2D echocardiogram, Grade 2 or Grade 3 diastolic dysfunction as outlined by ASE and/or the presence of speckle tracking abnormalities

- Abnormal –base to apex circumferential strain gradient

- Increased LA size on 2D echo. In parasternal long axis view (PLAX) >40 mm; Left atrial volume index > 34 ml/m^2

- Cardiac conduction and rhythm abnormalities: AV block, short PR interval, left bundle branch block (LBBB), ventricular or atrial tachyarrhythmias, sinus bradycardia (in the absence of drugs with negative chronotropic activity or other causes)

- Moderate to severe mitral or aortic insufficiency

- Late enhancement of left ventricular wall on cardiac MRI
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- T1 values using a 1.5 Tesla magnet in males below 901 ms and females below 916ms

- Increase of either N-terminal pro-natriuretic brain peptide (NT-proBNP) above the upper limit of normal for age and gender OR an increase of high sensitivity troponin (a surrogate marker of fibrosis) more than 2 times the upper limit of the normal range

Comments:

1. Many of the cardiac manifestations may be influenced by the presence of hypertension. In the event of significant hypertension, adequate control of hypertension for a 12 month period should be considered first.

2. Cardiac MRI provides significant data above that which is obtained by echocardiography and should be considered as an investigation to quantitate cardiac involvement in Fabry patients being considered for disease specific therapy where access to cardiac MRI is available. If cardiac MRI is not available, echocardiography with contrast also can provide additional information on cardiac status beyond that available with conventional echocardiography.

3. Given the development of cardiac fibrosis with late enhancement on cardiac MRI but normal left ventricular (LV) wall thickness (<12 mm) in a significant fraction of Fabry female heterozygotes (Niemann 2011), a lower threshold of LV wall thickness of ≥11 mm is recommended as a criterion for disease specific therapy in this group. As women are now recognized to develop left ventricular fibrosis in the absence of LVH, regular cardiac MRI may be preferred to echocardiogram in some women (Niemann 2011). T1 values (using SASHA protocol) can be low in women prior to the development of either left ventricular hypertrophy or ventricular fibrosis and low T1 values can be one cardiac indication for therapy (Hazari 2018; Nordin 2018). Patients who cannot undergo a contrast MRI to look for fibrosis due to the presence of CKD stage 3 or higher could be screened with high sensitivity troponin levels as these are higher in patients with underlying fibrosis then in patients with no fibrosis (Seydelmann 2016). Consultation with local laboratory to interpret troponin levels (based on local normative data) in the context of renal insufficiency is recommended.

4. The identification of LV diastolic dysfunction by cardiac tissue Doppler imaging is an important feature of Fabry cardiomyopathy as this can be corrected by ERT prior to the development of cardiac fibrosis (Koeppe 2012). Data is lacking at this time on the

effects of chaperone therapy on tissue Doppler imaging in patients. All other causes of these cardiac features need to be excluded. A cardiology consultation may required.

5. Consideration should be given to a left ventricular biopsy if there is any doubt as to the diagnosis. Biopsy may help confirm the diagnosis of Fabry disease in patients in whom the diagnosis is not clear (e.g. those patients where GLA mutation analysis reveals a variant of unknown significance) but the finding of changes on a cardiac biopsy are not an indication for therapy – i.e. cardiac findings on pathology alone are not sufficient indication for treatment

6. Atypical chest pain in the absence of LVH may indicate the presence of small vessel disease and patients should undergo specific investigation including cardiac flow reserve assessment with a PET scan (Chimenti 2008).

7. Patients with Fabry disease are at high risk of cardiovascular brady- and tachyarrhythymias, especially if they have cardiomyopathy and cardiac fibrosis. 24 hour Holter monitoring may not be sufficient to detect all arrhythmias requiring therapy and longer cardiac monitoring (for example, 14 day Holter monitoring, loop recordings) may be indicated for this patient population.   Male patients who have LVH and evidence of fibrosis on cardiac MRI and significant ventricular arrhythmias (complex ectopy, multifocal PVCs, nonsustained ventricular tachycardia [3-30 beats] etc) on monitoring should be considered for implantation of an intracardiac device to reduce the risk of sudden death (Baig 2017, Hanneman 2018).

Neurologic Disease Evidence level III - Grade F

1 major criterion required

• Stroke or TIA documented by a neurologist diagnosed on the basis of clinical features (TIA) and/or CNS imaging criteria consistent with the diagnosis of stroke .

• Sudden onset unilateral hearing loss when other possible causes have been excluded.

• Acute ischemic optic neuropathy when all other possible causes have been excluded

Comments:

1. There is no evidence that disease specific therapy prevents stroke in Fabry disease. However, the presence of serious neurological disease (stroke, TIA, acute hearing loss) often with irreversible CNS damage indicates severe Fabry disease so for this reason, severe neurological events are considered an indication for therapy to try and prevent the development of complications outside the central nervous system. The possible beneficial impact of disease specific therapy in severe Fabry disease warrants consideration of initiating such therapy.

2.   Imaging abnormalities (white matter lesions, vessel dolichoectasia, cerebral microbleeds) on their own are not an indication for enzyme replacement as their clinical significance remains unclear. The prevalence of these lesions is high in adult patients and progression can occur with or without enzyme replacement therapy (Korver et al 2018).

3.   Anti-platelet treatment with ASA and other drugs e.g. clopidogrel, should be the mainstay of treatment in patients who have experienced stroke unless contraindicated. Aggressive control of vascular risk factors should be implemented in all patients. ASA for the primary prevention of stroke is not recommended at this time.

4. Drugs that are associated with an increased risk of stroke (such as hormonal forms of contraception) may theoretically increase the risk of stroke in Fabry patients. This possibility should be considered when selecting a method of birth control.

5. Cardioembolic causes of stroke are more likely to be identified with longer duration of recording of cardiac rhythm, which should influence decisions as to appropriate investigations in Fabry patients with a new stroke (e.g. holter monitor for 2+ weeks, loop recorder, Reveal device etc.). Low ejection fraction and atrial fibrillation are independent risk factors for cardioembolic stroke. Consultation with cardiologists and/or stroke neurologists regarding anticoagulation should be sought in patients with these risk factors.

Neuropathic Pain Evidence level I - Grade E

Pain is **NOT** considered an isolated indication for disease specific therapy in most patients.

If pain is the only indication for consideration of disease specific therapy, then consideration for a one year trial of disease specific therapy could be given as long as all of the following criteria are met:

a. Prespecified outcomes as to what would constitute a positive effect of disease specific therapy for this symptom are agreed to prior to the trial by the treating physician and the patient. Such outcomes may include tangible benefits such as:

     1. Significant reduction in the need for analgesics

     2. Significant reduction in time lost from work or school due to pain

     3. Significant reduction in the frequency of pain crises requiring hospital admission etc.

b. Other outcomes may be appropriate treatment targets in some patients and can be determined prior to a trial of therapy on a patient by patient basis. Improvements in validated pain scoring materials can be included as secondary outcomes but should not replace more tangible outcomes

c. Adequate data are to be collected prior to the start of the disease specific therapy trial to establish a baseline – e.g. a review of use of prescription medication and time lost from work or school

d. Agreement is obtained from the patient and documented in the health record that disease specific therapy will be stopped if the prespecified outcomes are not met and no other indications for disease specific therapy are present.

Comments:

1. Short term controlled clinical trials show conflicting data on the efficacy of ERT for pain (Eng 2001; Schiffman 2001) and effects that have been seen are present within 6-12 months although data are conflicting on this point. Thus, a one year trial should be adequate to assess an effect on pain. There is a paucity of controlled clinical trial data documenting the long term efficacy of ERT on pain in patients with Fabry disease. Analysis of controlled data that do exist do not support a durable effect of ERT on pain in patients with Fabry disease (Wyatt 2012; Alegra 2012; El Dib 2016)

2. Switching from ERT to chaperone therapy with migalastat did not result in any changes in patient reported pain (Hughes 2017) so ongoing pain in ERT treated patients is not a reason to consider switching modalities of therapy.

3. All other strategies should be considered as treatments of choice for pain in patients with Fabry disease. These should include physical strategies (avoidance of pain triggers such as temperature extremes etc.), supportive care (management of associated anxiety, depression, and sleep disturbance), and pharmacological strategies (anticonvulsants, NSAIDs in patients with normal renal function, analgesics). Referral to a specialist in the management of chronic pain may be needed.

4. While opiate analgesics may play a role in the treatment of severe acute Fabry neuropathic pain crises in the emergency room, such agents **should be avoided** where possible in the management of chronic pain in Fabry patients as in patients with other types of non-cancer pain. Recent guidelines on the use of opiates in patients with non-cancer pain have been published (Busse 2017) and are a useful reference for clinicians treating such patients.

5. Pain is a major predictor of quality of life in patients with Fabry disease. However, disease specific therapy with ERT did not demonstrate an impact on self-reported

quality of life in a large cohort of patients with Fabry disease from two expert centers (Arends 2018). Physicians should be aware of the large impact of pain on self-reported quality of life to ensure optimal use of available resources in patients with pain as a symptom of Fabry disease.

6. Although neuropathic pain is the most well known feature of Fabry disease, men and women with Fabry disease who are below the age of 50 also have an increased prevalence of joint pain relative to age-matched controls (Ivleva 2017) and would require different types of treatment relative to neuropathic pain. Clinical evaluation as to the source of the pain is needed to ensure appropriate targeted therapy.

Gastrointestinal Disease Evidence level II-3 - Grade B.

- Significant gastrointestinal symptoms unresponsive to other measures for at least six months or associated with poor growth or significant reduction in quality of life.

Comment:
There is a high prevalence of positive tests for H. pylori and bacterial overgrowth in Fabry patients when compared with controls populations and these patients are more symptomatic than those without overgrowth and respond to targeted therapy. (Franceschi 2015). Patients with prominent GI symptoms should be screened for these complications and have a trial of therapy if appropriate before considering enzyme replacement therapy as a treatment for GI symptoms.

Treatment initiation in patients above the age of 65 years of age
Age per se is not a contraindication to disease specific therapy. However, there are no studies systematically evaluating the benefits of ERT or chaperone initiation in patients ages 65 and older. Data from international registries (Lidove 2016) show that the non-classic cardiac phenotype of Fabry disease dominates in this age group and that other manifestations of Fabry disease which are responsive to disease specific therapy such as renal events are uncommon. It may be difficult to distinguish Fabry related cardiac events from those related to normal aging processes in patients of this age group. As the benefits of disease specific therapy on progressive cardiac enlargement related to Fabry disease are seen over decades of disease progression, patients in this age group with asymptomatic mild to moderate LVH who are started on such treatment may not always be expected to get benefit from it although patients with other Fabry related symptoms (such as microvascular angina) may benefit from a trial of disease specific therapy. Supportive care including cardiovascular risk factor modification is likely of even more benefit in the older age group and should therefore be a primary focus of Fabry-related care.

Contraindications to disease specific therapy Evidence level II-I - Grade E

Disease specific therapy is not recommended in the presence of the following:

- Pregnancy and lactation. Pregnancy is a relative contraindication to ERT but patients on migalastat therapy should be advised to stop the chaperone therapy prior to conception and remain off it while breastfeeding and to use adequate contraception while taking migalastat therapy. Patients in whom disease specific therapy is medically advisable during pregnancy should be treated with ERT rather than migalastat therapy. A number of successful pregnancies have been reported in Fabry women receiving both forms of ERT (Kalkum et al 2009; Germain et al 2010 and others).
- Severe disease or concomitant medical condition in which death is expected within a year (absolute contraindication)
- Presence of a severe co-morbid condition such that ERT for Fabry disease is unlikely to significantly improve quality of life (absolute contraindication)
- Other conditions in which the benefit to risk ratio for ERT use is not favourable (absolute contraindication)
- Presence of IgE antibody to ERT; this may be associated with anaphylaxis (absolute contraindication)

Withdrawal of disease specific therapy Evidence level II-2 - Grade E

Consideration should be given to discontinuation of disease specific therapy if there is evidence that the patient is not responding to treatment after a reasonable period of observation, of at least a year.

The treating physician should discuss withdrawal of disease specific therapy with the Fabry disease patient under the following circumstances:

- Patient request.

- Life expectancy less than one year due to severe comorbid illness or due to severe Fabry disease with end stage heart failure if not a candidate for heart transplantation.

- Permanent severe neurocognitive decline of any cause.

- Severe reduction in quality of life and functional status despite disease specific therapy.

- Persistent life threatening or severe infusion associated reactions that do not respond to prophylaxis e.g. anaphylaxis.

- Persisting IgE antibody against agalsidase.

- Lack of response to disease specific therapy in standard dose given for a minimum of 1 year when the sole indication for disease specific therapy is neuropathic pain.

- Lack of response to disease specific therapy in standard dose given for a minimum of 1 year when the sole indication for disease specific therapy is the presence of severe gastrointestinal symptoms.

- Lack of response to disease specific therapy of organ involvement that initially mandated treatment start. In such patients, ongoing cardiovascular risk factor modification may still be indicated and such patients should continue to be followed as data on the history of patients in whom disease specific therapy is stopped because of lack of response is urgently needed

- Poor patient adherence to disease specific therapy,

    - This will be defined differently in different jurisdictions and should be a topic of discussion between the patient and their physician prior to starting disease specific therapy

- In addition to these specific situations in which withdrawal of therapy should be considered, the issue of patient age also needs to be considered. Patients with mild disease manifestations (particularly females with the non-classic phenotype) who are over the age of 80 may not be receiving any benefit of the therapy in terms of prolongation of life or prevention of Fabry-related complications but may still be having the impact of the need for regular infusions on quality of life. In such patients, discussion should be held between the patient and treating physicians as to what, if any, benefits could be accrued from continuation with treatment.

Non-disease specific therapy for patients with Fabry disease

A comprehensive list of the morbidities seen in patients with Fabry disease and the therapeutic goals for therapy with an emphasis on non-disease specific therapy has been published (Wanner et al 2018).

Screening for risk factors for cardiovascular and cerebrovascular disease

- Diabetes mellitus
- Hypertension
- Hyperlipidemia
- Smoking
- Positive family history of cardiovascular or cerebrovascular disease
- Sedentary life style
- Microalbuminuria
- Chronic kidney disease

These risk factors should be sought out in all patients with Fabry disease and aggressive treatment provided to reduce these influences recognizing that they will promote atherosclerotic vascular disease that would be superimposed on the vascular damage of Fabry disease. Guidelines for the management of blood pressure, lipids, and glycemic control as well as those for the use of anti-platelet agents at high vascular risk should be followed in all adult patients without contraindications.

Management of atrial fibrillation

Patients with Fabry disease who have been diagnosed with atrial fibrillation (either paroxysmal bursts of atrial fibrillation which are sustained for 6 seconds or longer or chronic atrial fibrillation) should be anticoagulated. This is not a patient population in whom the CHADS scoring system should be applied as this scoring system is for patients who do not have underlying heart disease. As almost all adults with Fabry disease will have evidence of infiltration on cardiac T1 imaging, they are considered to have structural heart disease and therefore should be anticoagulated if atrial fibrillation is identified (Yogasundaram 2017). A 2018 paper suggests that Fabry disease was associated with stroke risk similar to lowering the threshold for anticoagulation of the CHA2DS2-VASc score (Liu 2018) consistent with this recommendation.

Management of Hypertension

Hypertension should be diagnosed and promptly treated; treatment values should be directed towards SPRINT target values (Yogasundaram 2017; Kramer 2015; Putko 2015). Blood pressure control is essential to minimize renal and cardiac damage in patients with Fabry disease. Agents that block the renin-angiotensin system (ACE inhibitors, angiotensin-receptor blockers) are considered the first line of therapy.

ASA therapy

Although patients with Fabry disease are at high risk for heart disease and stroke, the physiology of these events in Fabry disease differ from those in the general population. Large vessel coronary artery disease is not increased in patients with Fabry disease. Recent trials suggest that ASA in the general population is useful in the secondary prevention of large vessel coronary artery disease and stroke/TIA but is not of benefit in the primary prevention of these disorders (Rabar 2019). As the chronic use of ASA is associated with an increased risk of bleeding, ASA therapy is not indicated as a primary prevention tool. Indications for ASA then in the Fabry disease population in the secondary prevention setting are similar to those in the general population (Rabar 2019). Some patients with Fabry disease may have altered levels of von Willebrand factor and other thrombophilic disorders (DeGraba 2001; Kang 2019; Koca 2019) and,

in these patients, anti-platelet agents in the primary prevention setting could be considered on a case by case basis.

Depression and anxiety

Depression and anxiety are common in patients with Fabry disease (Ali 2017 and others). Screening with commonly used tools (such as the validated depression and anxiety indices) may help identify patients who would benefit from counseling and/or medical therapy for these symptoms.

Table 2. Levels of evidence and strength of recommendations

Level of Evidence	Description
I	Evidence obtained from at least one properly randomized trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-controlled analytical studies, preferably from more than one centre or research group.
II-3	Evidence obtained from comparisons between times and places, with or without the intervention. Dramatic results in uncontrolled experiments could also be included in this category.
III	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.
Grade	**Description**
A	There is good evidence to recommend the clinical preventive action
B	There is fair evidence to recommend the clinical preventive action
C	The existing evidence is conflicting and does not allow a recommendation to be made for or against use of the clinical preventive action: however, other factors may influence decision-making.
D	There is fair evidence to recommend against the clinical preventive action.
E	There is good evidence to recommend against the clinical preventive action.
F	There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision making

Table adapted from Canadian Task Force on the Periodic Health Examination. The periodic health examination. CMAJ 1979;121:1193-254.

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Appendix 1. Literature reviewed for 2019 version of CFDI guidelines

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