Journal Pre-proof

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PII: S1499-2671(24)00178-3

DOI: https://doi.org/10.1016/j.jcjd.2024.09.001

Reference: JCJD 1799

To appear in: *Canadian Journal of Diabetes*

Received Date: 10 June 2024

Revised Date: 12 August 2024

Accepted Date: 3 September 2024

Please cite this article as: Coriati A, Potter K, Gilmour J, Lam G, Nichols C, Lands L, Doyle M-A, Boudreau V, Alexandre-Heymann L, McKinney M, Sherifali D, Senior P, Rabasa-Lhoret R, on behalf of the Canadian CFRD working group, Cystic Fibrosis Related Diabetes: a first Canadian Clinical Practice guideline, *Canadian Journal of Diabetes* (2024), doi: https://doi.org/10.1016/j.jcjd.2024.09.001.

Cystic Fibrosis Related Diabetes: a first Canadian Clinical Practice guideline

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*** We express our sincere gratitude to the committed patient partners who played a crucial role in shaping and establishing the Canadian CFRD guidelines. Their invaluable insights, experiences, and dedication have significantly influenced the framework of this guideline, ensuring it accurately represents the diverse perspectives and needs of those it aims to serve.**

Dedicated to Dr Mary-Anne Doyle (1972– 2024)

Dr Doyle significantly contributed to these Clinical Practice guidelines

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Key messages for healthcare professionals

- Cystic Fibrosis (CF)-Related Diabetes (CFRD) care requires a coordinated multidisciplinary and interprofessional team with expertise in treating CFRD. The team should ideally include a diabetes specialist, a respirologist, a dietitian, and a nurse. CF healthcare teams can improve their diabetes care expertise by including certified diabetes educators (CDE).

- The expert panel recommends a 2-stage screening process for CFRD starting at age 10, with annual glycated hemoglobin (A1c) as the initial step. Only individuals with A1c between 5.5% and 6.4% will need to undergo a second step with an oral glucose tolerance test (OGTT). This should reduce the number of OGTT per year by 30% or more.

- When CFRD is identified by screening tests, glucose monitoring should be considered by the care team to provide additional information about glucose levels in relation to daily routines (e.g., food consumption) and to identify when to initiate appropriate treatment adjusted to condition.

- For adult individuals with CF who have low nutritional and pulmonary risk, healthcare providers may explore the use of non-insulin medications as an alternative for treating CFRD. This offers people with CFRD a wider range of treatment choices.

- Advanced diabetes technologies, such as continuous glucose monitoring (CGM) devices and insulin pumps, may be helpful for people living with CFRD.

Key messages for people living with CF

- CFRD care should be provided in ways that are most convenient and streamlined as possible for people living with CF. People living with CFRD should have access to physicians and allied health professionals with training in diabetes management and specifically CFRD.

- Annual screening for CFRD should start with a simple (non-fasting) blood test (an A1c). Only people with an A1c between 5.5% and 6.4% will need to do a 2h oral glucose tolerance test (OGTT).

- Adults with CFRD who are interested in knowing if there are diabetes medications that could be used with or in place of insulin should have conversations with their CFRD doctor to understand treatment options available for their specific diabetes and CF needs.

- If CFRD is treated with multiple insulin injections, technological options including glucose sensors (continuous glucose monitoring: CGM) and insulin pumps can be considered.

- If you are taking a CF modulator, your medical team will still monitor and treat CFRD the same way as for people who are not taking these medications. Important research is

ongoing to investigate new screening tools and treatment for CFRD in people living with CF on modulators.

Introduction

Cystic Fibrosis (CF) is an autosomal recessive disease due to dysfunction or absence of the CF transmembrane conductance regulator (CFTR) channel. CF affects more than 4000 Canadians, and has a major effect on the lungs, the gastrointestinal system, quality of life, and lifespan [1]. Innovations in nutrition, physiotherapy, and respiratory medicine have revolutionized CF care and increased life expectancy. The current median survival is 59.9 years [1]. New therapies (highly effective modulators) are expected to further improve lifespan. With age, CF-related diabetes (CFRD) becomes more common, with prevalence rising from 3.6% in children to 58.7% in adults over the age of 35 [1].

CFRD is distinct from both type 1 and type 2 diabetes (T1D and T2D) [2]. CF leads to dysfunction of both the endocrine and exocrine pancreas and CFRD is often associated with pancreatic exocrine insufficiency [3]. Insufficient insulin secretion is the dominant feature underlying CFRD [4] but hyperglycemia may also occur due to insulin resistance from intercurrent illness (e.g., triggered by infection, inflammation, steroid, etc.) [3, 5]. Risk factors for CFRD include age, CFTR mutation type, suboptimal nutritional, diminished lung capacity, persistent inflammation, pregnancy, female sex, frequent lung exacerbations, pancreatic insufficiency, and a familial history of T2D [6]. In addition to risks of microvascular complications, CFRD is associated with increased risk of accelerated lung function and/or weight loss; and reduced linear growth and delayed puberty [3].

There are several areas of uncertainty regarding screening, diagnosis, treatment and management of CFRD that are important for clinicians and people living with CFRD and their families. Indeed, a recent survey highlighted a large heterogeneity for CFRD diagnosis and treatment [7]. At the suggestion of the Canadian CF Foundation, a multidisciplinary panel of clinicians, researchers and patient partners was established to develop evidence based clinical practice guidelines to address these uncertainties. It was recognized that the evidence base would be limited and that some recommendations would be based on consensus, but importantly would be informed by the values and preferences of affected individuals. Here we present a summary of the key recommendations for practitioners. The full guidelines are published online by the CF Foundation (https://www.cysticfibrosis.ca/our-programs/healthcare/guidelines-and-standards-of-care) and some sections are available as supplementary documents.

Methods

The approach used to develop these clinical practice guidelines (CPGs) was modelled and aligned with the processes used by Diabetes Canada [8]. (For detailed methods, see supplementary document (SD), section B). Focus groups were conducted to identify priorities and unmet needs (**figure 1**). A steering committee was established to oversee several working groups. The committee identified 5 key questions (see **SD table 1**) and had final oversight to ensure internal consistency and avoid duplication.

A modified GRADE system was used to indicate the strength of recommendations and the quality of the evidence. The expert panel used the same criteria as Diabetes Canada to assign levels of evidence [8]. Because of a paucity of direct evidence in CFRD, the expert panel chose to make either strong (Best practice) or conditional (Good practice) recommendations where there was evidence from studies in pwCF. Guidance based on clinical consensus or extrapolated from other populations are presented as best or good practice points. Recommendations labelled as “Best

Practice" are strong recommendations with Grade A or B, Level 1 or 2 evidence, while "Good Practice" are conditional recommendations with Grade C, Level 3 or lower (**table 1**).
To incorporate patient preferences and values, all recommendations and practice points were crafted by multidisciplinary working groups which included patient partners. This approach aligns with the recommendations of the GRADE working group [9]. The grading of recommendations and practice points was reviewed independently by two members of the steering committee with experience in CPGs and approved by the steering committee.

All recommendations achieved 100% consensus by the steering committee. Near final drafts were reviewed by a panel of patient partners assembled by CF Canada and by CF respirology and CFRD endocrinologist specialists.

It is important to note that many recommendations in these guidelines are based on expert advice and may be controversial or differ from international guidelines. For instance, the American Clinical Care Guidelines for CFRD (2021) and the European Cystic Fibrosis Society best practice guidelines (2018) both still recommend OGTT as the sole screening method for CFRD [10, 11]. Additionally, they do not endorse the use of glucose-lowering agents other than insulin for glucose management, and they consider that the presence of CFRD should not alter standard CF dietary recommendations. These discrepancies can emerge from recently available data, different evaluation of available data and/or integration of patient partners opinion to reach consensus.

1. Organization of care

Optimal care delivery

Managing CFRD involves a collaborative approach. A coordinated multidisciplinary and interprofessional team including a respirologist, registered nurse, physiotherapist, a dietitian and a diabetes specialist should be available to support, diagnose and treat CFRD. Including certified diabetes educators (CDE) in CF healthcare teams can improve diabetes care.
The diagnosis of CFRD adds significant complexity to the pre-existing high burden of treatment. The delivery of CFRD care should include components of the chronic care model to facilitate self-management and improve quality of care [12]. Quarterly appointments are recommended for individuals living with CFRD and ideally these appointments should coincide with their CF clinic visits. In a survey of individuals with CFRD, lack of clarity in advice about dietary and medical management delivered by healthcare teams was one of the barriers to acceptance of a diagnosis of CFRD [13]. Ongoing diabetes self-management education should be an integral component of care [10]. (For detailed rationale, see SD, section C1)

Transition of care

In Canada, transition to adult CF care usually occurs at 18 years old. Transition of care is the purposeful, planned movement of adolescents and young adults with chronic conditions from pediatric to adult care healthcare systems [14]. This transition period for young adults with chronic health conditions is associated with increased risk of losses to follow up and poorer health outcomes [15]. Effective communication and coordination are required for successful transition

[16, 17]. Hence, the transition planning should begin early (12-16 years old) and should include services that can address transitional care concerns of young adults with CFRD, including lifestyle issues (alcohol, drugs, nutrition, and physical activity), sexual health and reproduction, and support and guidance for issues around ongoing education, employment, and insurance coverage. Health care professionals should offer support and education that promote autonomy, self-management skills, and shared decision making [18, 19]. A transition coordinator or CF coordinator/clinical nurse specialist may help coordinate joint pediatric and adult meetings and ensure that an individualized transition plan is completed and provided to the patient and adult care team [15-18]. A transition coordinator is probably necessary in large CF clinics. Social workers and/or mental health professionals play a crucial role in providing support to people living with CF (pwCF) during the transition period.

Recommendations 1:

1.1. CF clinics should have protocols for CFRD screening and monitoring as part of routine care to ensure prompt diagnosis and treatment of CFRD. (**Best Practice)**

1.2. Interprofessional CF clinics should include healthcare professionals (diabetologist, dietitian and nurse) with CF knowledge and additional diabetes expertise learned by experience or formal training (e.g., certification as a diabetes educator). (**Best Practice)**

1.3. CF clinics individuals benefit from collaboration between local CF and local diabetes clinics to enable consultations in cases of diagnostic or therapeutic uncertainty. Both clinics should work together to establish the best approach for shared care and follow-up, taking into account the specific needs of pwCF and aiming to minimize the frequency of appointments. (**Good Practice)**

1.3.1. Ideally, CFRD care will be provided within the multi-disciplinary CF clinic to streamline patient care and optimize communication between care teams. Alternatively, referral to diabetes clinics with specialized knowledge of CF is encouraged. This approach is not ideal and should be recommended only if a joint clinic is absolutely impossible.

1.3.2. For CFRD management, hybrid multidisciplinary clinics that combine in-person and virtual interactions may be considered to enable reliable access to healthcare expertise and facilitate frequent assessments considering patient preferences and technical abilities.

1.4. Individuals with CFRD (and their families/carers) should receive diabetes education from a certified diabetes educator (CDE) with CF knowledge to facilitate effective self-management. (**Best Practice**) Self-management is a cornerstone of CFRD care and should include:

A. Education about diabetes management: blood glucose monitoring; antihyperglycemic medications including insulin dosing and adjustments; recognition, prevention, and treatment of hypoglycemia (including the use of glucagon for insulin-treated individuals); understanding management of sick days and severe hyperglycemia [10].

B. Due to the risk of hypoglycemia in pwCF using insulin or secretagogues, counselling regarding driving and diabetes should occur as per the Diabetes Canada CPGs [20].

1.5. Processes should be developed to facilitate the complex transition from pediatric to adult care for individuals with CFRD. Collaboration and integration between CF, diabetes, pediatric and adult CF diabetes teams should be planned with a clear pathway and strong support with coordination and communication between the teams. (**Good Practice)**

2. Screening for CFRD

Importance of screening for CFRD

Given that the onset of CFRD is often insidious, screening is recommended to permit early intervention to avoid or reduce the negative consequences of CFRD [21]. (For detailed rationale, see SD, section 2). Annual oral glucose tolerance testing (OGTT) has been recommended but is burdensome for both pwCF and healthcare providers [3, 22]. Consequently, annual OGTT screening rates is low and range between 29 and 48% [23, 24]. High intra-individual variation in OGTT results on follow-up testing (coefficient of variation 25%) [25-27] leads to diagnostic and therapeutic uncertainty.

Simpler screening methods (e.g. glycated hemoglobin (A1C)) were not recommended previously because usual thresholds (A1c > 6.5%) were not sensitive to identify CFRD. Fasting plasma glucose (FPG) is unlikely to be useful as a screening test for CFRD as fasting hyperglycemia is rarely seen at diagnosis of CFRD and emerges later in the course of the disease [28]. However, the use of lower A1c thresholds has emerged as a feasible screening test for CFRD with the potential to reduce the number of required OGTT and increase screening rates [23, 29-31].

We recommend annual A1c as the initial test in a two-step CFRD screening strategy

To reduce the burden of testing, and optimize the identification of clinically important dysglycemia, we recommend a two-step CFRD screening strategy for clinically stable, non-hospitalized ambulatory pwCF (figure 2). Annual A1c is the initial test for all pwCF after the age of 10. Individuals with an A1c value < 5.5% have a very low probability of developing CFRD and in the absence of clinical deterioration, should be rescreened annually. Individuals with an A1c > 6.4% meet criteria of CFRD and should have a confirmatory test (A1c, or OGTT, laboratory-confirmed random glucose ≥11.1 mmol) unless symptoms of hyperglycemia are present, in which case a second test is not required [32]. Individuals with an A1c between 5.5 and 6.4% should undergo OGTT.

This algorithm should not be used in individuals who are unwell or hospitalized, who are pregnant, have recently received lung transplant, or with conditions where A1c is not reliable [33]. A1c may be falsely low in CF for a multitude of reasons, including possible reduced red blood cell lifespan from chronic inflammation, solid organ transplantation, hypoxia, anemia and splenic sequestration

in CF-related liver disease [34, 35]. During pregnancy, Diabetes Canada's criteria for gestational diabetes should be used [36].

Recommendations 2:

2.1. All pwCF or their caregivers should receive counseling periodically on 1) risk factors for CFRD, 2) rationale for screening to improve awareness and understanding of this complication, and 3) possible consequences of CFRD. Clinicians should begin counselling prior to the onset of CFRD screening. **(Best Practice)**

2.2. Counseling should include the importance of regular CFRD screening. The impact of CFRD for CF-related outcomes includes increased risk of declining pulmonary function, pulmonary exacerbation, compromised nutritional status, diabetes-related outcomes (e.g. microvascular complications), and in children and adolescents impaired growth and puberty. **(Good Practice)**

2.3. In asymptomatic pwCF, annual screening for CFRD should start by age 10 with an A1c as the initial screening test (see **figure 2**). **(Best Practice)**

2.3.1. In individuals with A1c < 5.5%, A1c measurement should be repeated annually or earlier if clinical concerns.

2.3.2. In individuals with A1c values between 5.5 and 6.4%, oral glucose tolerance testing (OGTT) using 1.75g/kg of glucose up to 75g should be performed (see **figure 2**).

2.3.3. In individuals with A1c > 6.4%, CFRD diagnosis should be confirmed with a second test repeated within 3 months which could be either 1) an A1c or 2) an OGTT.

2.3.4. OGTT may be used as the primary screening method when A1c is considered unreliable.

2.4. In symptomatic individuals or those with suspected CFRD (see **Box 1**), CFRD testing should be expedited using random glucose value and A1c as the initial tests. (**Best Practice**)

2.5. In pwCF experiencing a hospitalized pulmonary exacerbation, receiving systemic corticosteroids, initiating enteral/parenteral nutrition, and/or hospitalized for any other reason, capillary blood glucose monitoring (CBGM) (4x/day, fasting and 2-hours postprandial or mid- and immediate post-feed) should be performed for the first 3 days. Elevated CBGM levels (fasting ≥ 7.0 mmol/L and/or random ≥ 11.1 mmol/L) should be confirmed by at least one venous blood glucose test. **(Good Practice)**

Box 1. Clinical scenarios indicating need for additional or earlier testing for CFRD:

- Symptoms of hyperglycemia: polyuria, polydipsia, blurred vision
- Unexplained
  - Weight loss (or failure of weight gain with BMI < 30^{th} percentile (pediatrics) or < 20 kg/m^2 (adults), despite nutritional intervention.

- Need for initiation of enteral/parental feeding.
- Deterioration in pulmonary function (>2%/year despite clinically appropriate work-up and trials of treatment) and/or frequent pulmonary exacerbations (>2 in 6 months).
- Poor linear growth velocity
- Delayed progression of puberty

· A1c criteria (increased > 0.5% above baseline)
· Before planned pregnancy (Section 5.12), major surgery, and solid organ transplant (Section 5.13)
· During infective pulmonary CF exacerbation (ambulatory or hospitalized) and/or systemic corticosteroid use (intravenous and/or oral).

3. Diagnosis of CFRD

In pwCF, diagnosing CFRD serves a dual purpose: first, to identify those with abnormal blood glucose levels, which may expose them to diabetes-specific health risks, such as microvascular complications. Second, it helps identify pwCF who are at a higher risk of accelerated lung function loss and/or nutritional decline. Previous diagnostic thresholds have been established, however they were based on association with microvascular complications in patients living with T2D [37]. (For further rationale, see SD, section 3)

Recommendations 3:

3.1. The onset of CFRD should be defined as the date a person with CF first meets diagnostic criteria, even if hyperglycemia subsequently abates. (**Best Practice**)

3.2. The diagnostic thresholds for CFRD are:

A. A1c > 6.4%
   or
B. FPG ≥ 7mmol/L
   or
C. 2hr-OGTT or random blood glucose (RBG) ≥ 11.1mmol/L (**figure 2 and SD table 2**)

3.3. In the absence of symptoms of hyperglycemia, a diagnosis of CFRD should be confirmed by a second positive screening test. A single positive test in the presence of symptoms of hyperglycemia is sufficient as a diagnostic test. (**Best Practice**)

3.4. CFRD may also be diagnosed: (**Good Practice**)

A. If hyperglycemia exceeding diagnostic thresholds persists for more than 2 consecutive days during acute illness.
B. In pwCF on stable continuous or bolus enteral feeds, or parenteral nutrition, if RBG exceeds the diagnostic thresholds on 2 consecutive days.

3.5. A diagnosis other than CFRD should be considered in hyperglycemic individuals with clinical features of type 1 or type 2 diabetes.

3.6. Impaired glucose tolerance (IGT) is diagnosed if: FPG < 7mmol/L with a 2hr OGTT 7.8-11mmol/L. IGT is a risk factor for future CFRD and can call for more frequent screening. (**Good Practice**)

3.7. Impaired fasting glucose (IFG) is diagnosed if: FPG 6.1-6.9 mmol/L. Isolated IFG is not a significant risk factor for CFRD. (**Good Practice**)

4. Management of CFRD

Management of CFRD involves many aspects including blood glucose monitoring, medical nutrition therapy and pharmacotherapy to reach glycemic targets. We make recommendations for each of these domains. (For rationale, see SD, section 4)

Recommendations 4:

4.1. Glucose monitoring

4.1.1. Individuals with CFRD should have A1C monitored every 3-6 months to assess adequacy of management. (**Best Practice**)

4.1.2. In individuals with CFRD who are not yet on pharmacological therapy, CBGM (pre- and 1 to 2-hour post-meal) for 3 or 4 days or continuous glucose monitoring (CGM) for 10-14 days may be used every 6 months as an adjunct to A1c monitoring to quantify hyperglycemia exposure and to assess the need for initiation or intensification of healthy behaviour interventions and/or pharmacotherapy. **(Good Practice)**

4.1.3. In individuals with CFRD who are treated with insulin or insulin secretagogues, CBGM (1-4 times per day based on regimen) or CGM is recommended to adjust therapy, as well as to identify and prevent hypoglycemia. (Best Practice)

4.1.4. In individuals with CFRD on intensive insulin therapy, CGM should be considered to achieve recommended glycemic targets while reducing the risk of hypoglycemia. **(Good Practice)**

4.2. Glycemic Targets

4.2.1. In adults and children with CFRD, an A1c ≤ 7% is recommended to reduce the risk of diabetes complications. (**Best Practice**)

4.2.2. Individuals with CFRD should aim for a fasting glucose between 4-7mmol/L, 1 to 2-hour postprandial glucose between 5-10 mmol/L to achieve A1c targets (**table 2**). (**Good Practice)**

4.2.3. Individuals with CFRD wearing CGM should aim for the following CGM targets over a 14-day period to achieve A1c targets (**Good Practice)** unless modified targets are indicated.

A. Time in range (3.9-10mmol/L): > 70%
B. Time below range (<3.9mmol/L): < 4%
C. Sensor usage: > 70% (as close to 100 % as possible)

4.2.4. Modified, less stringent glucose targets may be used if there is frequent hypoglycemia, severe hypoglycemia, or hypoglycemic unawareness. (**Good Practice)**

4.3. Non-pharmacologic therapy

Traditionally, the dietary prescription for CF has been a high-energy, high-fat diet due to increased energy expenditure and decreased nutrient absorption [38]. Improved CF therapies, including pancreatic enzyme replacement and CFTR modulator therapies, have significantly reduced but did not eliminate the need for such diet patterns [39]. (For detailed rationale and complementary recommendations, see **SD, section 4.3)**

4.3.1. In individuals newly diagnosed with CFRD, healthy behaviour interventions are recommended (see **SD, section 4.3 a-k**) to promote both metabolic and respiratory health and to maintain optimal nutrition status, growth, and well-being, while supporting euglycemia. (**Best Practice**)

4.3.2. Pancreatic exocrine function and treatment in case of impairment should be reassessed at the time of diagnosis of CFRD and during follow-up in individuals with CFRD. **(Best Practice)**

4.3.3. In individuals with newly diagnosed CFRD or in those with established CFRD who are not meeting glycemic targets, counseling by a dietitian with expertise in CF and diabetes is recommended to provide personalized nutritional recommendations to optimize glycemic, respiratory, and metabolic outcomes taking into account CF specific needs (**table 3**). (**Good Practice**)

A. For individuals with CFRD <u>above target weight</u>, nutritional recommendations may include modifications in type and quantity of carbohydrates and/or overall calories and/or recommendations about distribution of carbohydrates over the day to help achieve weight and glycemic targets.

B. For individuals with CFRD <u>with weight at target</u>, nutritional recommendations may include modifications in type of carbohydrates and/or recommendations about distribution of carbohydrates over the day to help maintain weight and glycemic targets.

C. For individuals with CFRD who are <u>underweight</u>, nutritional recommendation should follow the CF Foundation guidelines to achieve target weight.

4.3.4. Individuals with CFRD should participate in regular physical activity as recommended for people with CF and may participate in combined exercise programs (aerobic and resistance) to reduce glucose excursions. (**Good Practice**)

4.4. Pharmacological management

Pharmacotherapy should be initiated for individuals with CFRD who are not meeting glycemic targets, despite healthy lifestyle behaviour interventions. Key factors to choose among available

pharmacological options includes glucose profile (degree of hyperglycemia and pattern), impact on weight, complexity (e.g. injections), glucose lowering potency and hypoglycemic risk. With the improvement of nutritional status and the emergence of obesity in some pwCF [40], the aim to achieve optimal glucose control without undesirable weight gain led to consider the use of non-insulin hypoglycemic agents in CFRD management. For further rationale, see **SD, section 4.4.**

4.4.1. In individuals with CFRD who are not meeting glycemic targets (A1c ≤ 7.0%; FPG 4.0-7.0 mmol/L or 2-hours post-meal glucose 5.0-10.0 mmol/L on 50% of measurements over a 4-7 days period) despite healthy behaviour interventions, pharmacotherapy is recommended to achieve glycemic targets within 3-6 months. (**Best Practice**)

4.4.2. In individuals with CFRD who are underweight, have difficulty maintaining body weight and/or experiencing pulmonary decline, insulin is recommended as first-line pharmacotherapy to achieve glycemic targets and contribute to weight maintenance/gain. (**Best Practice**)

4.4.3. In children with CFRD, insulin is recommended as first-line, and only, pharmacotherapy to achieve glycemic targets and support healthy growth. (**Best Practice**)

4.4.4. Individuals with CFRD requiring insulin should be treated with individualized insulin regimens, which may include insulin analogs and technologies (e.g. CGM and/or continuous subcutaneous insulin infusion (CSII)), to achieve glycemic targets while minimizing risks of hypoglycemia. (**Good Practice)**

4.4.5. In some adults with CFRD who prefer alternative options to insulin, non-insulin antihyperglycemic agents may be considered as part of an individualized treatment plan to achieve glycemic targets, optimize body weight, and/or reduce the risk of hypoglycemia. (**Good Practice)**

A. Repaglinide may be used as an alternative to insulin to improve post-prandial glucose levels and A1c.
B. Sulfonylureas, particularly long-acting agents, are NOT recommended because of high risk of hypoglycemia.
C. Metformin and/or dipeptidyl peptidase-IV-inhibitor (DPP-4 inhibitor) might be considered as weight-neutral antihyperglycemic agents with low risk of hypoglycemia.
D. Although not specifically studied in CFRD, glucagon receptor-like-peptide-1 receptor agonists (GLP-1RA) and/or sodium-glucose co-transporter-2 (SGLT2i) may be considered in individuals with CFRD particularly if weight loss would be beneficial or if cardiorenal risk is increased.

4.4.6. In individuals with CFRD who are not achieving glycemic targets despite current pharmacotherapy, treatment should be intensified by one or more of the following strategies, considering the pattern of hyperglycemia, acceptability, cost, and risk of hypoglycemia to reach glycemic targets safely: **(Good Practice)**

A. Initiating basal insulin or bolus insulin
B. Increasing the dose and/or number of bolus insulin injections
C. Increasing the dose of basal insulin

D. Adding bolus insulin to basal insulin or vice versa
E. Transitioning from fixed doses of bolus insulin to a strategy matching insulin dose to carbohydrate intake
F. Consider transition to insulin pump with hybrid closed-loop system (see below)
G. Adding repaglinide (in adults) to basal insulin and vice versa
H. In select adult populations with weight above target and for which the primary goal is glucose control, non-insulin antihyperglycemic agents (including GLP-1RA, SGLT2i, metformin or DPP4I) may be considered.

4.5. Use of diabetes technologies

4.5.1. In individuals with CFRD using a basal-bolus insulin regimen, CSII may be considered to help achieve glycemic targets and/or reduce the burden of diabetes where training and support to use a pump safely is available. (**Good Practice)**

4.5.2. Individuals with CFRD using CSII should be assessed and followed by diabetes teams with CSII experience. **(Best Practice)**

4.5.3. Automated insulin delivery could provide more efficient (reduced hyperglycemia), safer (reduced hypoglycemia) and simpler (automation) glucose management. (**Good Practice)**

5. Surveillance for diabetes complications and vascular risk

Microvascular complications of diabetes, namely retinopathy, neuropathy and nephropathy, may occur in those with long-standing CFRD [2, 41-45]. Other causes than CFRD should be excluded (e.g. complications related to antibiotics or vitamin deficiency). Most recent reports suggest the emergence of some cardiovascular risk factors (e.g. dyslipidemia) [46]. As life expectancy increases and obesity becomes more prevalent [40, 47], cardiovascular risk might emerge. In persons with CFRD for 5 years or more, healthcare teams may consider following recommendations for screening and treatment according to Diabetes Canada recommendations for T1D [48-50].

Recommendations 5:

5.1. In persons with CFRD, annual monitoring for microvascular complications (albumin:creatinine ratio, dilated eye exam, foot exam with monofilament testing) is recommended, beginning 5 years after diagnosis of CFRD, or sooner if date of diabetes onset is uncertain. Annual monitoring for cardiometabolic risk factors (blood pressure and lipids) is recommended at onset of CFRD diagnosis (**Best Practice**)

6. Management of CFRD in individuals treated with CFTR modulators

Current data from short term studies show that highly effective modulator therapy in established CFRD or pre-diabetes may improve glycemia and reduce insulin requirements but are not consistent. Rapid evolution of this field is awaited. (For rationale, see **SD, section 6.)**

Recommendations 6:

6.1. PwCF receiving modulators should continue with the same screening and monitoring recommendations for CFRD regardless of metabolic response to modulator therapy. (**Good Practice**)

6.2. Individuals with CFRD treated with pharmacotherapy, should increase the frequency of blood glucose monitoring when starting CFTR modulators to detect hypoglycemia and have their A1c checked every three months over the first year to identify opportunities to adjust antihyperglycemic therapy. (**Good Practice**)

7. Pregnancy

Pregnancy is a significant concern in CF for both females with CFRD and those without a history of CFRD, as the latter group is at risk for gestational diabetes (GDM). In the absence of specific studies conducted on the management of diabetes during pregnancy in pwCF, the expert panel recommends that the approaches to GDM in the general population, or pre-gestational diabetes in those with T1D or T2D, be applied to the management of GDM in CF or CFRD during pregnancy [36]. Two CF-specific factors to consider are early screening for GDM during pregnancy and ensuring adequate caloric intake.
(For detailed rationale, see **SD, section 7**).

Recommendations 7:

7.1. Pre-conception counselling

7.1.1. Females of reproductive age with CF should receive pre-conception counseling: (**Best Practice**)

7.1.1.1 In those who do not have CFRD, counseling should address the risks of developing diabetes in pregnancy (gestational diabetes) to ensure timely screening.

7.1.1.2 In those with CFRD prior to pregnancy, counseling should address the importance of optimal glycemic management prior to conception and during pregnancy to optimize maternal and fetal outcomes. An eye exam before pregnancy is also recommended

7.1.2. Females with CF without known CFRD who are planning conception should be screened for CFRD if not already done in the preceding 6 months. **(Best practice)**

7.1.3. Pharmacotherapy should be reviewed and optimized prior to pregnancy. **(Best practice)**

A. First-line therapy consists of diet and physical activity.
B. If glycemic targets are not met, insulin or metformin can then be used.
C. Unsafe medications in pregnancy (e.g. statins, ACE inhibitors) should be discontinued.

D. Consider vitamin supplementation as per Diabetes Canada recommendation [51].

7.2. Screening for, and diagnosis of GDM/CFRD in females with CF

In females with CF who do not have known CFRD, the expert panel recommends that screening for GDM should follow the general approach and glucose thresholds recommended by Diabetes Canada CPGs [36]. However, given that risk of GMD is higher in CF, GDM screening should be performed at an earlier stage than for the general population. To reduce the burden of repeated testing, the single step 75g OGTT can be preferred to the two-step approach initiated with the 50g OGTT.

7.2.1. Pregnant females with CF and no history of CFRD should undergo screening for gestational diabetes using a 75g OGTT according to Diabetes Canada CPG. (**Best Practice**) Screening should be performed:

A. between 12-16 weeks of gestation, or when pregnancy confirmed.
B. and again at 24-28 weeks of gestation if previous test at 12-16 weeks was normal.

7.2.2. GDM is diagnosed if plasma glucose during the 75g OGTT exceeds the following thresholds: (**Best Practice**)

A. fasting ≥ 5.1 mmol/L,
B. 1 hour ≥ 10.0 mmol/L,
C. 2 hours ≥ 8.5 mmol/L

7.2.3. Gestational diabetes or CFRD during pregnancy should ideally be managed by a specialised Diabetes in Pregnancy Clinic with close collaboration between the Diabetes in Pregnancy clinic, obstetric team, and the CF clinic. (**Best Practice**)

7.3. Management of GDM and CFRD during pregnancy

7.3.1. Pregnant females with CF who have GDM or CFRD should not have recommendations to restrict their caloric intake. (**Good Practice**)

7.3.1.1. Individuals who are not gaining weight adequately should be referred for formal nutritional counseling.

7.3.1.2. Moderate carbohydrate intake with low glycemic index foods, targeting a minimum of 175g of carbohydrates in the form of 3 meals and 2 snacks, 1 of which is at bedtime, is recommended for pregnant females with CF and CFRD, GDM or IGT to support appropriate weight gain.

7.3.2. In females with CF who have CFRD, GDM or IGT, the following glucose targets are recommended where they can be achieved safely: (**Best Practice**)

A. preprandial <5.3 mmol/L
B. 1 hour post meal <7.8 mmol/L
C. 2hr post meal < 6.7 mmol/L
D. and A1c < 6.5%
E. If it can be achieved safely, a target A1C ≤6.1% should be sought by the third trimester of pregnancy

7.3.3. Pregnant females with GDM not taking insulin should be asked to perform CBG testing 4 to 6 times daily (fasting and postprandially) for 1 week to assess blood glucose levels and need for pharmacotherapy.

7.3.4. In those who do not require antihyperglycemic medications, capillary blood glucose testing can be reduced to 4 times per day on alternate days. (**Good Practice**)

7.3.5. When glucose targets are not met after two weeks of healthy behaviour interventions, insulin should be started. Insulin dosing should be individualized. Oral agents, such as metformin can be considered as a second-line option for individuals who are unwilling or unable to take or manage insulin. (**Good Practice**)

7.3.6. Pregnant females taking insulin should be asked to perform CBGM at least 4 times per day (fasting and 1 or 2h post meals) or use CGM to achieve glycemic targets and reduce hypoglycemic risk. (**Good Practice**)

7.4. Pulmonary exacerbation or hospitalization for pregnant females with CF

Pulmonary exacerbations are common in females with CFRD or GDM during pregnancy [52]. The use of glucocorticoids is associated with insulin resistance and hyperglycemia. As for all pwCF admitted to hospital, frequent CBG monitoring is recommended for pregnant females with CF.

7.4.1. Pregnant females with CF who have IGT, CFRD, or GDM are advised to increase the frequency of glucose monitoring and maintain regular contact with Diabetes/CF team(s) during pulmonary exacerbations, regardless of whether hospitalization is required.

8. Specific Settings

We make recommendations for screening, diagnosis and management in other specific settings that may be more important for a narrower segment of health care providers, that are provided in supplemental materials. These include recommendations for:

- Diagnosis and management of CFRD during hospitalization (**SD, section 8.1)**
- Detection and management of hyperglycemia with enteral tube feeding (**SD, section 8.2**)
- Solid Organ Transplantation (**SD, section 8.3**)

Summary and Future Directions

Here we have presented the first Canadian comprehensive, evidence-based clinical practice guidelines for the diagnosis and management of CFRD. It was developed using a robust methodology and incorporated the values and preferences of individuals living with CFRD. We hope that these will be widely disseminated and reduce unnecessary variations in care and promote optimal health and wellbeing of pwCF. It is uncertain how more widespread use of CFTR modulators will impact CFRD. Earlier use, prior to dysglycemia may prevent damage to the endocrine pancreas mitigating insulinopenia but may be associated with higher risk of overweight or obesity. New evidence will be incorporated in future revisions.

Figure legends and tables

Figure 1. Key themes identified by Canadian patient partners and patients' families in focus groups. CFRD: cystic fibrosis related diabetes, CFTR: cystic fibrosis transmembrane conductance regulator.

Figure 2. Screening algorithm for stable, non-hospitalized ambulatory patients with no symptoms of hyperglycemia. Glycated hemoglobin: A1c, OGTT: oral glucose tolerance test, FPG: fasting plasma glucose, PG: plasma glucose.

Table 1. Definition of grading for evidence-based recommendations and practice points.

Evidence based Recommendations*		**Meaning for Clinicians and Persons with CF / CFRD**	**Practice Points^**
	Quality and Level of Evidence		
Strong Recommendation	Grade A or B, Level 1 or 2	Robust, strong advice that should apply to (almost) everyone	**Best Practice**
Conditional Recommendation	Grade C, Level 3 or lower	Good advice that would apply to some, but not all patients, depending on multiple factors (time, cost, local resources, clinical situation)	**Good Practice**

* based on evidence from clinical studies involving pwCF

^ based on additional data extrapolated from other populations, clinical expertise, and/or knowledge of pharmacology/physiology

Table 2. Glycemic targets for people living with CFRD

	Optimal glucose targets	**Modified glucose targets***
Fasting/Pre-prandial	4.0-7.0 mmol/L	5.0-10.0 mmol/L
1 to 2-hour post-prandial	5.0-10.0 mmol/L	6.0-12.0 mmol/L
Hypoglycemia	Minimal daytime hypoglycemia only, no nocturnal hypoglycemia	None
Sensor/CGM	Time in range > 70% Time less than 3.9 mmol/L < 4% Coefficient of variation % < 36%	Time in range > 50% Time less than 3.9 mmol/L < 1% Time less than 3.0 mmol/L is none Coefficient of variation % < 36%

	Sensor usage > 70% (using 14 representative day pattern)	Sensor usage > 70% (using 14 representative day pattern)
A1C	≤7.0%	8.0-8.5%

* Modified, less stringent glucose targets may be used if there is frequent hypoglycemia, severe hypoglycemia, or hypoglycemic unawareness.

Table 3. Dietary recommendations

	Body weight at or above target	**Body weight below target**
Calories	**At target weight:** Individualized. **Above target weight:** Consider reduction in total calories	1.2–1.5 times dietary reference intakes (DRIs) for age; individualized based on weight gain and growth.
Carbohydrates	Individualized. Encourage low glycemic index carbohydrates. Limit sugar-sweetened beverages. Consider reducing carbohydrate portion sizes and distributing them equally over the day.	Individualized. Carbohydrates should be monitored to achieve glucose control. Refined carbohydrates can be an important source of energy.
Fats	Consider limiting saturated and trans fat to prevent obesity, dyslipidemia, and potential macrovascular disease risk. Encourage polyunsaturated fats, particularly from fish.	High fat is necessary for weight maintenance. Aim for 35–40% of total calories. Unsaturated fatty acids are favored to avoid potential macrovascular risks.
Protein	15-20% of total energy from protein.	Approximately 1.5–2.0 times the DRIs for age. For chronic kidney disease, consider discussion with HCP with CF knowledge and additional renal expertise by experience or formal training.
Fibre	Individualized. Encourage moderate fiber intake to help with glucose control and to prevent dyslipidemia.	Individualized. Fiber intake may compromise total energy intake.
Artificial Sweeteners	May be used to help with glucose control and/or weight management	Caution that use does not lead to restricted calorie intake.

*Target weight individualized as per professional/RD evaluation

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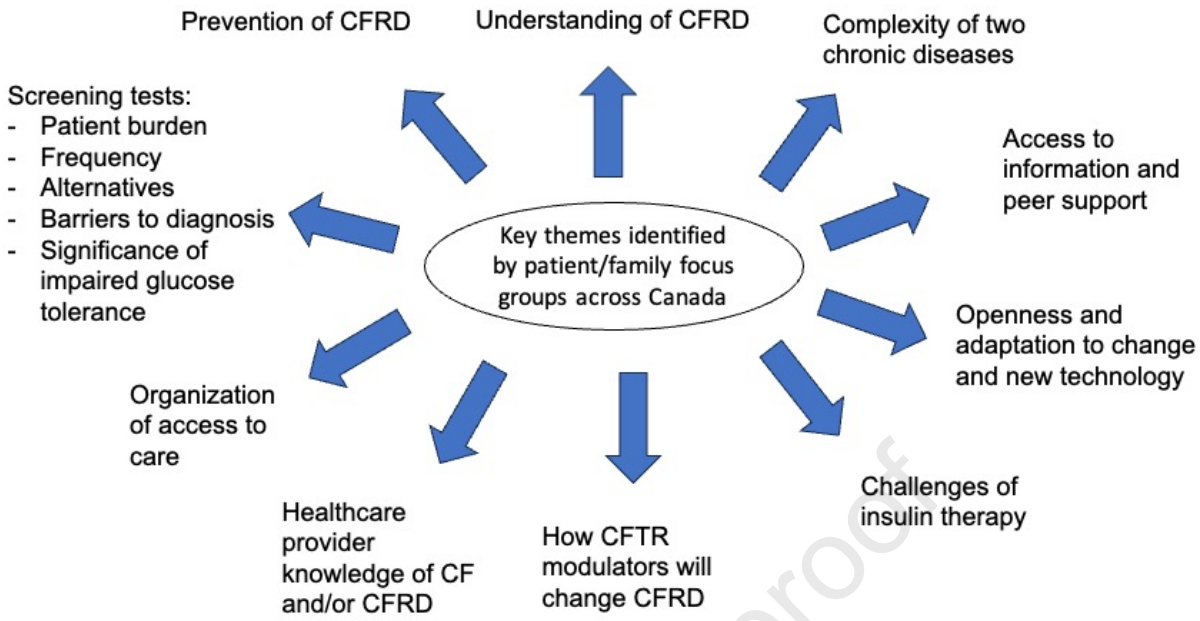
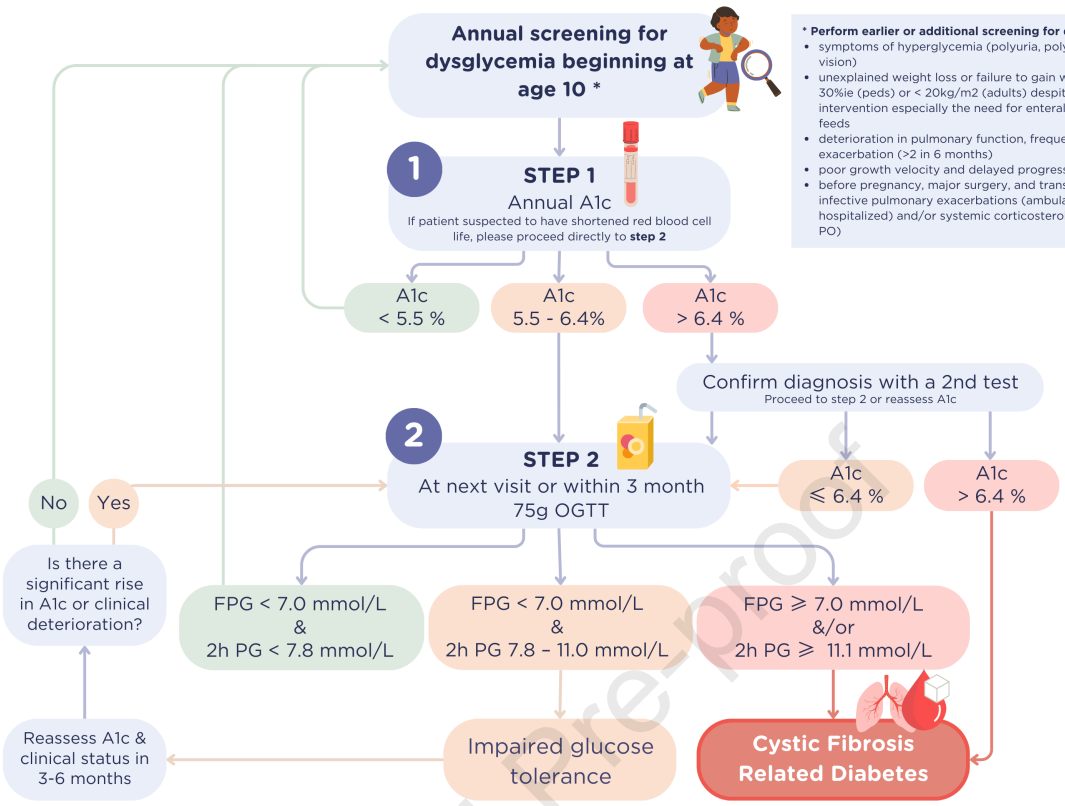




Supplementary document to Cystic Fibrosis Related Diabetes: a first Canadian Clinical Practice guideline

A. Abbreviations

A1c	Glycated hemoglobin
BMI	Body mass index
CBGM	Capillary blood glucose monitoring
CDE	Certified diabetes educator
CF	Cystic Fibrosis
CFRD	CF-related diabetes
CFTR	CF transmembrane regulator
CGM	Continuous glucose monitor
CPG	Clinical practice guideline
CSII	Continuous subcutaneous insulin infusion
DPP4I	Dipeptidyl peptidase-IV-inhibitors
FPG	Fasting plasma glucose
FEV1	Forced expiratory volume in 1 second
GDM	Gestational diabetes mellitus
GLP-1	Glucagon-like peptide-1
GLP-1RA	GLP-1 receptor agonist
HEMT	Highly-effective modulator therapy
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
INDET	Indeterminate glycemia
ISPAD	International society for pediatric and adolescent diabetes
NPH	Neutral protamine hagedorn
NODAT	New onset diabetes after transplant
OGTT	Oral glucose tolerance test
PICO	Population-intervention-comparison-outcome
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
pwCF	People living with CF
RBG	Random blood glucose
SGLT2i	Sodium-glucose co-transporter-2 inhibitor
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus

B. Methods

The approach used to develop these clinical practice guidelines (CPGs) was modelled and aligned with the processes used by Diabetes Canada [1]. Focus groups with patient partners from all over Canada affected by CF and/or CFRD, were conducted in English and French to identify priorities and unmet needs (see **Supplementary Box 1**). Members of the expert panel also undertook a Canadian clinical practice survey of 97 health care professionals caring for adults and children with CF and/or CFRD. This survey identified substantial heterogeneity in screening, treatment, and organization of care for CFRD, which often deviated from existing recommendations [2].

There was substantial overlap between gaps identified in the survey and themes identified in patient partners focus groups. A steering committee was established to oversee several working groups. Each working group included researchers, health care professionals (including medical doctors, registered nurses, and registered dietitians) and patient partners. Adult and pediatric clinicians with expertise in pulmonology, endocrinology, and gastroenterology who provide care to adults and children with CF also participated.

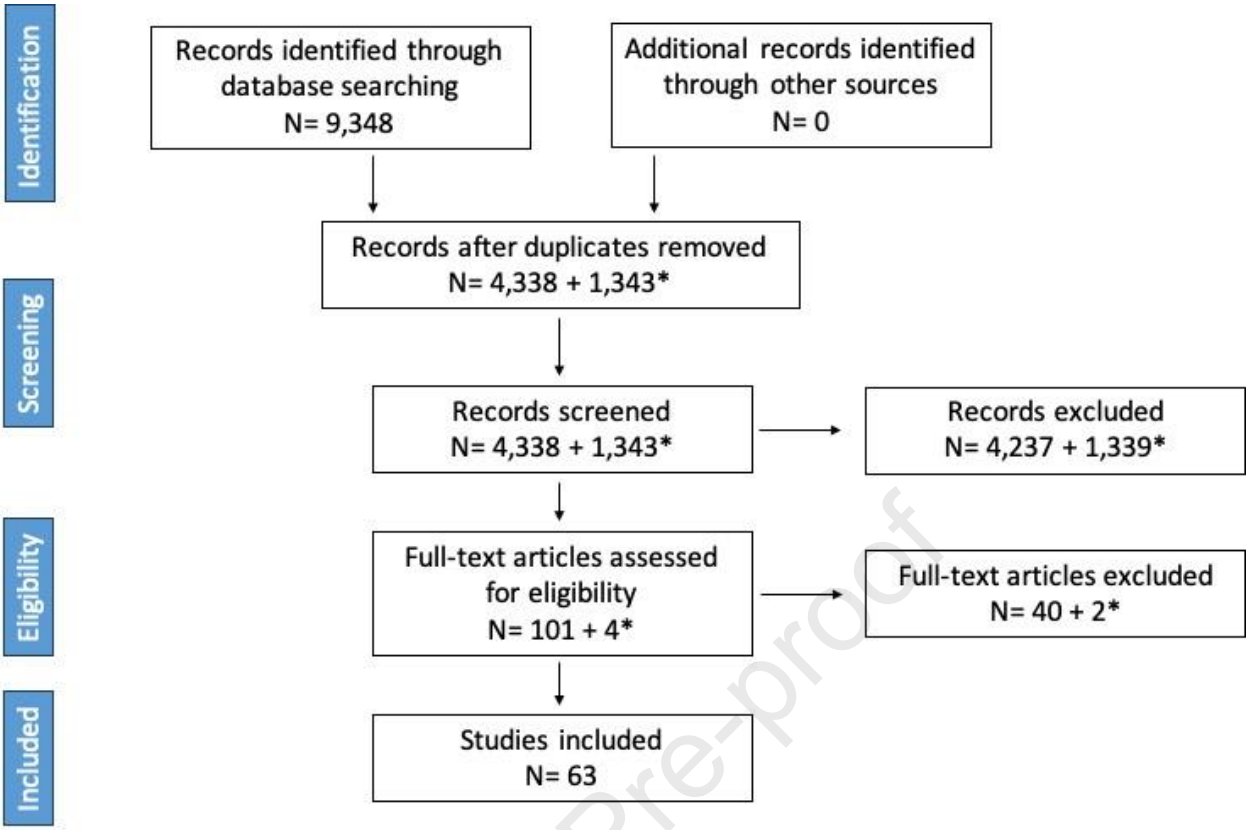
Informed by the national practice survey [2], patient partners focus groups, and a series of online consensus meetings, the steering committee identified 5 key questions and developed Patient-Intervention-Comparison-Outcome (PICO) questions with the working groups (**Supplementary table 1**). From the PICO questions, a search strategy was developed in consultation with a research librarian at McMaster University (McMaster Evidence Review & Synthesis Team) (Appendix 1). MEDLINE, Embase, and Cochrane databases were searched up to October 16, 2021. Search results were deduplicated, and citations uploaded to a secure internet-based platform for screening (DistillerSR, Evidence Partners Inc., Ottawa, Canada). Titles and abstracts were screened in duplicate by two reviewers (MR, DS) from the McMaster Evidence Review & Synthesis Team for eligibility for full-text screening. Full text screening was performed by one of two independent reviewers to identify articles to be included (see **supplementary figure 1**). During the process of literature review and clinical guideline writing (October 2021- August 2023), an additional 2 articles not identified by the initial search were included, corresponding either to new publications or key articles that working groups felt critical to accurately inform or frame the guidelines.

Supplementary Box 1. Priorities and unmet needs identified by patient-partners focus groups:
1) The need for clear education about CFRD (e.g. risk, implications, need for screening),
2) To explore prevention strategies,
3) To simplify screening by reducing annual OGTT burden with better and simpler screening protocols,
4) Optimization of insulin regimens and investigating non-insulin pharmacological options,
5) Access to diabetes technology for glucose monitoring and insulin delivery,
6) Guidance on how CFTR modulator therapy will change current screening and treatment recommendations, and finally
7) Improve caregivers and healthcare professionnals' knowledge of CFRD and to recognize the complexity and challenges of having a dual diagnosis of CF and diabetes (summarized in **Figure 1**, main document).

Supplementary table 1. PICO questions employed in the search strategy.

Question	Population	Intervention/Exposure	Control/Comparison	Outcome(s)
1. How is CFRD defined?	Patients with CFRD (adults ≥18 years and older; children <18 years)	Definition of diagnostic criteria for CFRD (based on glucose data including oral glucose tolerance test, continuous glucose monitoring, fasting glucose and HbA1c; alternate search based on clinical parameters of health in CF other than blood sugars)	CF patients without diabetes	What evidence-based data has been used to define CFRD in an evidence-based manner?

2. How is CFRD diagnosed?	Patients with CFRD (adults ≥18 years and older; children <18 years)	Which other screening tests should be considered?	Current gold standard (oral glucose tolerance test), fasting/random blood glucose, HbA1c, continuous glucose monitoring (CGM)	What are the optimal screening tests and how often should they be done?
3. What are the treatments available?	Patients with CFRD (adults ≥18 years and older; children <18 years)	What are the treatments available for CFRD?	Insulin, glucose lowering medications, exercise, diet (weight reduction)	What are the optimal treatments (models of care in addition to therapeutic and medication treatments) and how are they prescribed?
4. How is diabetes diagnosed and managed during pregnancy (Gestational diabetes in CF)?	Patients with CF who develop gestational diabetes or pregnant patients with pre-existing CFRD	Which screening tests should be considered (and how)?	Pregnant CF patients without gestational diabetes	What are the optimal screening tests, how should they be monitored, and which type of treatment (all types of models of care) is given?
5. How is diabetes diagnosed and managed in post-transplant CF patients?	Solid transplant recipients with CF who develop diabetes	Which screening tests should be considered? How are they treated and managed?	CF solid transplant patients who do not develop diabetes	What are the optimal screening tests, how should they be monitored, and which type of treatment is given?



Supplementary Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram. *An additional database search was carried out to identify eligible studies published between October 2021 and August 2023. Out of the 1,343 records identified and screened, only 4 underwent eligibility assessment, with a final inclusion of just 2 studies.

C. Recommendations: rationale and complementary recommendations

1. Organization of care

Optimal care delivery

The care provided for individuals with CFRD, as well as their family and relatives, should be centered around their specific needs. It should be personalized to reduce the burden of treatment, enhance treatment adherence, and ultimately lead to improved long-term outcomes.

CFRD care should include structured clinic visits at regular intervals delivered by the multidisciplinary, collaborative teams [3, 4]. Quarterly appointments are recommended for individuals living with CFRD and ideally these appointments should coincide with their CF clinic visits. When feasible, implementing an embedded model of care, which integrates CF pulmonary and CF endocrinology specialist clinics, is the preferred approach. This model aims to expedite assessments, reduce treatment delays, minimize the frequency of clinic visits and travel for medical care, and enhance communication between different healthcare specialties and disciplines [5]. A hybrid interdisciplinary model (combining in-person and tele-medicine visits) or tele-medicine only can be considered to simplify some follow-ups. CFRD can effectively be addressed with

remote care [6] without compromising CF related clinical outcomes (preserved lung function and BMI) compared with fully in-person clinical care [7]. However, no data is available for diabetes-related clinical outcomes. Importantly, pwCF expressed high satisfaction ratings with telemedicine [8]. The least preferred model of care is separate diabetes clinic visits with in-person follow up. Incorporating the support of social workers and/or mental health professionals can assist pwCF in managing the complexities of their care (e.g., treatment plan adherence) and coping with complications.

Ongoing diabetes self-management education should be an integral component of care [4]. Diabetes education should ideally be provided by a CDE (nurse or dietitian) with knowledge of CF and diabetes. The education provided for CFRD should be well-organized and comprehensive, covering various aspects such as symptoms awareness, blood glucose monitoring, dietary and physical activity recommendations, diabetes treatments, insulin dosing and self-adjustments, handling hypoglycemia (including the use of glucagon), managing sick days, adhering to driving guidelines, and receiving preconception counseling.

2. Screening for CFRD

Importance of screening for CFRD

Screening for CFRD is essential due to its association with unfavourable CF-specific clinical outcomes (increased risk of weight loss, pulmonary exacerbation, pulmonary decline, growth and/or puberty retardation and mortality), as well as microvascular complications [9-12]. A formal CFRD screening strategy results in CFRD being diagnosed on average 8 years earlier with a reduction in the development of the deleterious consequences of hyperglycemia and insulin deficiency (5). Early treatment of CFRD could minimize its possible impact on overall health, nutrition, pulmonary function, hospitalization, and mortality [13]. Indeed, centres with higher rates of CFRD screening report better pulmonary outcomes [14].

The OGTT (1.75 g/kg, up to a max of 75g, of oral glucose) is the currently recommended screening test. OGTT-based CFRD diagnostic criteria are the same as for T2D diagnosis, which were based on its association with retinopathy development. The association of CFRD diagnosis based on OGTT-derived values has been shown to correlate with lung function, vascular complications, and mortality in CF [3, 4, 9, 12, 15]. OGTT should be proposed to a clinically stable pwCF, preferably after a minimum of one month following the completion of treatment for a pulmonary exacerbation.

Though A1c of ≥6.5% has historically been considered an insensitive screening test for individuals with CF and likely underdiagnosed CFRD [16, 17], the use of A1c with lower CF-specific thresholds has emerged as a feasible screening test for CFRD with the potential to reduce the number of required OGTT [18-21]. FPG should not be used as a screening test for CFRD due to its low sensitivity [22]. Generally, fasting hyperglycemia is not observed at the time of CFRD diagnosis and typically emerges later in the course of the disease [23].

Clinical practice surveys have identified the use of other tools to diagnose CFRD: capillary blood glucose monitoring (CBGM, Canadian, 63%; UK, 82%), A1c (Canadian: 43%), and CGM (Canadian: 31%). These approaches are usually used in combination with other tests [2, 24]. Though neither CBGM nor CGM can be used as a primary screen for CFRD, these methodologies

may provide adjunctive information to help confirm a diagnosis and have a clear role in monitoring glucose and/or to decide on treatment initiation in confirmed CFRD.

What is the rationale behind the two-step CFRD screening algorithm starting with an A1c?
North American data has shown that the rate of screening for CFRD according to the recommended annual test is low and, depending on the centre, can range between 29 and 48% [18, 25]. The low screening rate is multifactorial but is largely driven by the burden of testing [26]. The OGTT involves fasting, a minimum 2-hour sitting time commitment, and consuming a large amount of glucose, which may lead to side effects such as nausea. From the healthcare professionals' perspective: planning OGTT, screening for conditions requiring postponement (e.g., pulmonary exacerbation), nurse and material availability, etc. also imply a significant burden [26]. In addition, existing literature has shown high intra-individual variation in OGTT results on follow-up testing (coefficient of variation 25.3% at 2-hours) [27-29], which underscores that OGTT results are subject to poor reproducibility leading to uncertainty in diagnosis and in subsequent therapeutic decision.

The historical concern with using A1c as the primary screening test for CFRD is underdiagnosis [16, 30]. It is important to highlight that this recommendation is not to replace OGTT but rather to use A1c and OGTT together in a stepwise approach. This approach, using an A1c threshold of 5.5%, reduces annual OGTT by 22.7-50.7 % and has high sensitivity (91.8-100%) in both pediatric and adult CF populations [18, 19, 21]. A recent report shows that A1c (> 6.0%) could identify both pwCF at risk of CFRD as well as those at risk of low weight gain [20]. This data highlights the usefulness of A1c for pwCF as well as the need to identify CF-specific thresholds.

This algorithm should not be employed in hospitalized or unwell patients, individuals who have a high likelihood of reduced red blood cell lifespan (i.e. significant anemia, hypoxemia, splenomegaly, etc.), conditions in which an A1c is not reliable (e.g. homozygous hemoglobin variants i.e., HbS or HbC), lung transplantation recipients, or pregnant patients [31]. During pregnancy, the diagnosis of gestational diabetes should rely on Diabetes Canada CPG [32]. During hospitalization, after enteral nutritional support or steroids initiation, healthcare professionals should refer to specific recommendations.

When should screening for abnormal blood glucose levels begin?
Available clinical care guidelines for CFRD have advocated for annual screening by OGTT starting at age 6 (Italian Society for Pediatric Endocrinology and Diabetes) [33] or age 10 (American Diabetes Association and International Society for Pediatric and Adolescent Diabetes (ISPAD)) [3, 4]. Some United Kingdom centres delay screening until 12 years [34]. The recent recommendation to begin testing at 6 years of age was derived from a single study demonstrating that children with abnormal glucose tolerance between 6 and 9 years of age had an 11-fold increased risk of developing CFRD over the subsequent five years; none, however, appeared to have developed CFRD under 9 years of age [35]. The available evidence suggests that few children under 10 years of age will develop CFRD [3]. Therefore, the expert panel recommends screening for dysglycemia to begin at age 10 in asymptomatic children with CF. Signs and symptoms of hyperglycemia (polyuria, polydipsia, nocturia, weight loss) or unexplained decline in pulmonary function in children younger than 10 years should prompt testing to rule out diabetes.

Should other types of diabetes (T1D and T2D) be considered in individuals with CF?
If abnormal blood glucose levels occur in pwCF, conditions other than typical CFRD should also be considered. Multivariate mixed-regression modelling of 837 individuals with CFRD in the German/Austrian Diabetes Patienten Verlaufsdokumentation database identified 8.5% of patients classified as having CFRD also having positive beta cell auto-antibodies, suggesting some pwCF could present with T1D [36]. These patients were diagnosed at an earlier age and had higher insulin needs than antibody-negative patients [36]. A T1D diagnosis significantly influences management decisions and indicates the absolute need for insulin therapy, a higher risk of diabetic ketoacidosis, especially in situations involving insulin omission, sick days, and surgical/hospital procedures.
In addition, with the rising rates of obesity in pwCF [37] including those on CFTR modulators (drugs that partially correct for the CF mutation) [38], a T2D-like phenotype with features of metabolic syndrome-associated conditions (abdominal obesity, hypertension, non-alcoholic fatty liver disease, dyslipidemia, etc.) is becoming more prevalent. These individuals may benefit from non-insulin therapeutic agents for management of dysglycemia. In addition, family history of T2D is associated with a higher and earlier onset of CFRD risk [39, 40].

3. Diagnosis of CFRD

Glucose tolerance can fluctuate in persons living with CF [29], however the onset of CFRD should be defined as the date a pwCF first meets diagnostic criteria, even if hyperglycemia subsequently abates.

A. Diagnostic thresholds for CFRD

In line with the 2018 Diabetes Canada CPG and the 2010 American Diabetes Association CF Guidelines [41], the diagnostic thresholds for CFRD are 1) FPG ≥ 7 mmol/L, 2) 2hr OGTT or random blood glucose (RBG) ≥ 11.1 mmol/L, or 3) A1c > 6.4% [3, 4, 42]. In the presence of classic symptoms of hyperglycemia (polyuria, polydipsia, unexplained weight loss, blurred vision), one test meeting the diagnostic thresholds for diabetes is enough to confirm the diagnosis. In the absence of symptoms, two consecutive diagnostic thresholds should be met.

Supplementary Table 2. Categories of glucose tolerance in individuals with CF

Category of glucose tolerance	Fasting glucose (mmol/L)	2-hour OGTT glucose (mmol/L)
Normal	< 6.1	< 7.8
Impaired fasting glucose (IFG)	6.1-6.9	< 7.8
Impaired glucose tolerance (IGT)	< 6.1	7.8-11.0
CFRD	≥ 7.0	≥ 11.1

In some special circumstances, OGTT and/or A1c are not the recommended method to diagnose CFRD:

- Acute illnesses in CF can be associated with transient insulin resistance and hyperglycemia, especially when systemic corticosteroids are used. The diagnosis of CFRD can be made in those with acute illness if glucose diagnostic thresholds (fasting ≥ 7.0mmol/L or RBG ≥ 11.1 mmol/L) persist for more than 48hrs.
- Patients on bolus or continuous enteral feeds can also be diagnosed with CFRD if they meet the diagnostic thresholds for CFRD on at least two consecutive days. In keeping with the 2010 American Diabetes Association CFRD recommendations, the expert panel recommend glucose screening mid -and immediately post-feed with a diagnostic threshold of 11.1mmol/L on 2 consecutive days.

While CBGM can be used to screen, the diagnosis should ideally be made using a laboratory plasma sample [43]. This stipulation may pose significant logistical concerns in those not admitted to hospital while on enteral feeds, given feeds typically run overnight during out-patient laboratory closures. In addition, many individuals with CFRD have intermittent hyperglycemia during times of acute stress alternating with normoglycemia when clinically well. Patients who receive a CFRD diagnosis during acute illness or enteral feeding screening should undergo repeat testing within 4-8 weeks to confirm the diagnosis.

B. Abnormal blood glucose levels that do not meet criteria for CFRD

Routine screening for children and adult individuals with CFRD can detect higher-than-normal glucose levels, commonly referred to as "prediabetes." As described in **supplementary table 2,** there are three categories of pre-diabetes that have been cited in previous guidelines [4]. Impaired fasting glucose (IFG) may be defined as a FPG between 5.6-6.9 mmol/L (American Diabetes Association) or 6.1-6.9 mmol/L (World Health Organization). Usually, FPG does not tend to be elevated at diagnosis of CFRD, and IFG is not a major predictor for CFRD [44]. IFG might prompt investigation as to whether individuals with CF might have a different type of diabetes mellitus, such as T2D.

Impaired glucose tolerance (IGT) is defined as a blood glucose between 7.8 and 11.0 mmol/L at the 2-hour OGTT timepoint [3, 4, 22, 45]. IGT is a risk factor for CFRD [27, 33], with 14% of adult individuals with CF developing CFRD over 5 years. The majority (54%) who have an OGTT result of IGT, however, will have normalization of glucose levels on subsequent OGTT testing [27, 28] thus establishing a CFRD diagnosis based on one abnormal OGTT result should be made with caution. Still, because IGT is a risk factor for CFRD, individuals with IGT could benefit from undergoing more frequent A1c screening (e.g. every 6 months).

In some centres, an additional 1h-OGTT time-point blood draw is undertaken. Elevated 1-hour OGTT glucose ≥ 11.1 mmol/L with normal fasting and 2h glucose values define a CF-specific glucose tolerance category: indeterminate (INDET) glycemia. In cross sectional studies, INDET pwCF have reduced pulmonary function in some [46] but not all studies [47]. In addition, the evolution of pulmonary function over 4 years does not differ between pwCF with INDET and those with other prediabetes glucose tolerance categories [47]. However, there is an increased risk of developing CFRD for those with combined INDET and IGT [48]. The balance between the burden of this additional OGTT time point and practical implications (e.g., value not always available, unclear clinical benefit) as well as the ability to identify patients at risk of CFRD by

other means (e.g., presence of IGT) led the committee to propose that more research is needed before this value is incorporated into clinical practice. If a pwCF presents with INDET status, more frequent monitoring should be undertaken as proposed for pwCF with IGT.

C. Hypoglycemia detected during OGTT

Hypoglycemia can be detected during OGTT screening for individuals with CF [49-52]. Literature clearly outlines that hypoglycemia during an OGTT is not associated with risk of CFRD. Treatment of hypoglycemia during an OGTT screening should follow Diabetes Canada CPG for the treatment of hypoglycemia in people living with T1D [53].

4. Management of CFRD

4.1. Blood Glucose Monitoring in CFRD

Individuals with diagnosed CFRD should have A1C monitored every 3-6 months to assess general adequacy of management. CBGM is an important tool for awareness of glucose control and to guide lifestyle and/or pharmacological decisions. For individuals with CFRD who are under lifestyle management only, their glycemic patterns can be evaluated using CBGM from a selection of representative days at home. This may involve a combination of fasting glucose and post-meal (1 to 2h) measurements for 3 or 4 days [54]. Alternatively, CGM can be utilized for 10-14 days, to quantify hyperglycemia and determine if there is a requirement for initiating or intensifying healthy behavior interventions and/or pharmacotherapy. In individuals with CFRD treated with insulin or insulin secretagogues (e.g. repaglinide), glucose monitoring is essential to prevent, detect and treat hypoglycemic events. For patients using insulin secretagogues or basal insulin, once-daily CBGM is likely adequate, with additional testing recommended when hypoglycemia symptoms are present. Individuals with CFRD on multiple daily insulin injection regimens should perform CBGM at least 3 times per day. In these patients, CGM monitoring is an acceptable alternative to CBGM to achieve glycemic targets while reducing the risk of hypoglycemia [55].

In the case of hypoglycemic events or hypoglycemia unawareness in pharmacologically treated CFRD [56-58], increased frequency of CBGM or the use of CGM with alarms is recommended. The increased costs of intermittently scanned or real-time CGM and patients' preference should be considered when determining the benefit versus burden of use in individual patients. It is recommended that access and reimbursement for glucose monitoring should be based on clinical situation rather than type of diabetes.

4.2. Glycemic Targets in CFRD

In the absence of specific evidence in individuals with CFRD, glycemic targets recommended for T1D and T2D can be applied to CFRD to reduce the risk of microvascular complications. Diabetes Canada recommends an A1c target of ≤ 7.0% for most adults with type 1 or type 2 diabetes, although lower A1c targets (< 6.5% if it can be achieved safely without increased risk of hypoglycemia) further reduce the risk of chronic kidney disease and retinopathy [59]. Less stringent targets (7.0 – 8.5%) are recommended for frail or functionally dependent individuals using hypoglycemia-inducing agents or with a history of severe hypoglycemia or impaired hypoglycemia awareness [59]. Diabetes Canada recommends an A1c target < 7.5% for children with T1D (92) and ≤ 7.0% for children with T2D [60] while ISPAD recommends a target of ≤

7.0% for all children with diabetes [61]. The expert panel recommended HbA1c target ≤ 7.0% for children with CFRD where it can be achieved safely.

To achieve A1c targets, both Diabetes Canada and ISPAD have made recommendations for fasting and post-prandial CBGM targets (and time in range for individuals using CGM with diabetes), and these have been applied to people with CFRD due to current lack of evidence regarding specific glycemic targets in this population (summarized in **table 2, main document**) [59]. Individualization of glycemic targets is important and should be considered for all pwCF.
It is important to highlight that the positive impact of achieving recommended glucose targets, while established for lowering microvascular complications risk, remain uncertain for pulmonary and/or nutritional health. Because A1c could underestimate overall glucose control in persons with CF, careful attention should be made towards trends over time.

4.3. Non-pharmacologic therapy

Nutrition is fundamentally important to preserve pulmonary function and improve clinical outcomes and survival in CF [62-64]. Nutrition and physical activity are also integral components of diabetes management. However, in the case of CFRD, there is a paucity of literature to guide lifestyle and dietary recommendations for prevention (e.g. CF-IGT) or for management. Thus, education for individuals with CF-IGT/CFRD should focus on achieving adequate amounts of energy and nutrient intake while contributing to self-management of glucose control. Lifestyle goals (quantitative and qualitative nutritional intake) and recommendations therefore must be individualized (e.g. personal preferences, physical activity, comorbid conditions, etc.) and established together with the multidisciplinary CF team to achieve positive outcomes [3, 65].

Traditionally, the dietary prescription for CF has been a high-energy, high-fat diet due to increased energy expenditure and decreased nutrient absorption [65]. Improved CF therapies, including pancreatic enzyme replacement therapy to address exocrine pancreatic deficiency (affecting approximately 85% of pwCF) and the implementation of CFTR modulator therapies, have significantly reduced but did not eliminate the need for such diet patterns and enhanced the overall well-being and quality of life for individuals with CF [66]. Consequently, there is now an emerging trend of obesity in a subset of pwCF [67-72]. As pwCF live longer, a less calorie-dense nutritional intake is encouraged to improve overall health [68].
Ensuring appropriate pancreatic enzyme replacement therapy, if needed, is essential. Therefore, pancreatic exocrine function and pancreatic insufficiency treatment should be evaluated both at the time of CFRD diagnosis and during follow-up in individuals with CFRD.

The expert panel recommend providing an age-appropriate, healthy diet that emphasizes a healthy relationship with food, nutrient-dense foods, personal and cultural preferences, associated with positive health outcomes in the general population. The optimal diet includes vegetables, fruits, whole grains, lean meat and poultry, fish, eggs, beans, nuts and seeds, dairy products, and healthy fats [65, 68]. It is reasonable to advise supplementation with energy and/or protein dense food, oral or enteral supplements, as needed to achieve or maintain normal growth in children or BMI status in adults [73] (**table 3**, main document). For those with newly diagnosed CFRD or in those with established CFRD who are not meeting glycemic targets, individual counseling by a registered dietitian with proficiency in both CF and diabetes is recommended to personalize nutrition recommendations in optimizing glycemic, respiratory, and metabolic parameters.

Providing ongoing diabetes self-management education from diabetes education programs that meet national standards for Diabetes Self-Management Education is recommended [41].

a. Energy

Energy needs should be individualized based on growth, weight history, nutritional status, medications, physical activity, and disease severity. An ideal dietary regimen should provide appropriate energy to achieve and/or maintain a healthy body weight, to support growth in children and needs during pregnancy and lactation. Energy supply should derive from the carbohydrate, protein, and fat content of foods. The current recommended caloric intake for both individuals with CF and individuals with CFRD is 110-200% that of the general population [74]. Energy needs vary greatly between individuals with CF depending on degree of malnutrition, malabsorption, lung function, inflammation, exacerbations and more recently according to the response of highly effective modulator therapy (HEMT) [75]. The diagnosis of prediabetes or CFRD do not impact these recommendations. With the emergence of obesity in CF [76] if body weight is above the target, it can be appropriate to consider caloric restriction with close supervision of pulmonary and metabolic impact of this approach.

b. Macronutrients

With the changing landscape of nutrition in CF, there is no single ideal recommendation for macronutrient distribution for the management of diabetes. Individuals with CF may have a special dietary regimen that can be high in fat and carbohydrate. Evidence also showed the need for increased protein intake to maintain lean body mass and improve long term outcomes [63]. Alternatively, for individuals with CF-IGT or CFRD with weight at or above target, nutritional recommendations may include restrictions in quality and quantity of carbohydrates to help achieve glycemic targets.

c. Carbohydrate

Carbohydrates contain many important nutrients and are the main source of energy for the body. For individuals with CFRD with body weight at and above target, consumption of low glycemic index carbohydrates should be encouraged. Intake of food and beverages with high added-sugar content and without other nutrients (such as fat, protein, and/or fiber) to counter rapid increase in blood glucose should be discouraged [3]. For underweight individuals with CF or those with difficulty maintaining target weight and/or deteriorating pulmonary function, refined carbohydrates can be an important source of energy. In this respect, consumption of sweetened foods with nutritive value such as baked goods containing fat, protein, fiber and/or micronutrients, candy or chocolate with nuts and seeds, or desserts with fruits and/or nuts is suggested [77]. Recommendations about distribution of carbohydrates over the day rather than concentrated in 1 or 2 large meals could help to achieve glycemic targets.

d. Fat

Despite the lack of evidence in the CF population, dyslipidemia is known to be associated with higher risk of cardiovascular morbidities and mortality [78]. The expert consensus committee recommended the promotion of monounsaturated and polyunsaturated fats and limiting saturated and trans fats to prevent obesity, dyslipidemia, and potential cardiovascular disease risks. There is

no restriction on the type of fat for underweight/deteriorating individuals with CF with decreased appetite and limited intake especially during episodes of illness and exacerbations, as high fat is necessary for weight maintenance and repletion.

e. Protein

To support the need for increased protein intake to maintain lean body mass and improve long term outcomes [63], approximately 1.5–2.0 times the daily recommended intake per age is suggested for pwCF who are below their target weight. For pwCF dealing with chronic kidney disease, consider consulting a HCP who possesses expertise in both CF and renal conditions, either through practical experience or formal training [4].

f. Dietary fibre

Fibre intake that is too high may exacerbate gastrointestinal symptoms in some individuals with CF while fiber intake that is too low may increase risk of constipation [79, 80]. Fibre intake, up to the recommended intake for the general population, should be adjusted according to an individual's unique needs, considering gastrointestinal symptoms and individual tolerance, past responses to fiber intake, dietary patterns, and preferences [80, 81]. A recent small pilot study was unable to replicate in pwCF the demonstrated benefits of acute fibre supplementation on postprandial glucose excursion already demonstrated in T2D [82].

g. Non-nutritive sweeteners

Sugar substitutes are regulated in Canada as food additives. They include high-intensity sweeteners and sugar alcohols. Along with other nutritional measures, sweeteners may be used to help with glucose control and/or weight management for individuals with CF with a body weight that is above target. Caution is advised regarding use of sugar substitutes that may lead to restricted caloric intake for individuals with CF who are underweight or having difficulty maintaining target weight and/or with deteriorating pulmonary function.

h. Alcohol

The recommendations concerning alcohol consumption in the general population [83] and for those with other forms of diabetes, should apply [41].

i. Vitamin supplementation

While some cross-sectional studies reported association between low vitamin D and higher risk of CFRD, recent data suggest that correction of this deficit is not associated with improved glucose tolerance [84, 85]. Vitamin supplementation should follow the CF Foundation recommendations for individuals with CF [86].

j. Physical activity

The current Canadian 24-Hour Movement & Activity Guidelines recommendation for children and youth is at least 60 minutes per day of moderate to vigorous physical activity involving a

variety of aerobic activities [87]. For adults, including seniors, at least 150 minutes of moderate to vigorous physical activity per week is recommended [88]. One small study (n =17) investigating the impact of a 12-weeks combined aerobic and resistance training program in individuals with CF with dysglycemia showed reduced glucose area under the curve and improved insulin sensitivity but only included 2 participants with CFRD [89]. Along with healthy eating, physical activity is an important part of healthy lifestyle at every age. General recommendations promoting physical activity in pwCF (to promote pulmonary function and bone health) may have additional benefits for those with at risk of or with CFRD because of an expected effect to improve insulin sensitivity and/or glucose disposal.

k. Mental health and chronic disease distress

Clinicians should recognize the burden of a diagnosis and the management of CFRD and the potential for anxiety, depression, chronic disease-associated distress, and other mental health conditions [90-92]. Optimal well-being for individuals with CFRD improves quality of life and increase adherence to management recommendations. Recognition of mental burden and chronic disease-associated distress and support are strongly recommended in this population.

4.4. Pharmacological management

a. Insulin therapy

Insulin is the first line therapeutic intervention in most individuals with CFRD given its impact on glucose control along with positive anabolic effects on weight and pulmonary function (forced expiratory volume in 1 second, FEV_1), as well as linear growth in the pediatric population [56, 93-97]. The expert panel recognizes that practice variation exists for the type of insulin regimen used and starting dose. Co-existing clinical factors are major drivers of the varied approach and include both physical and psychological considerations, such as ability to perform multiple daily dose injections, frequent snacking, systemic glucocorticoid use, pattern of hyperglycemia (e.g. post-meal with or without fasting hyperglycemia, physical activity, psychological context, hypoglycemic episodes or hypoglycemia unawareness, etc.). Cost and access for insulin and technology (e.g. CGM & CSII) also largely influence insulin regimen choice.

Because of the specific glucose pattern observed in pwCF in which postprandial glucose excursion mostly dominates with far less frequent increased fasting glucose (usually occurring later during the course of the disease), the use of prandial insulin only without basal insulin can be an appropriate therapeutic regimen [94, 98]. Indeed, when compared to persons living with T1D, individuals with CFRD usually require a higher insulin proportion coming from boluses with overall lower daily insulin doses (units/kg/day) [99, 100]. A retrospective study conducted at the University of Minnesota demonstrated similar insulin requirements between youth and adults with CFRD [101].

Efficacy of prandial bolus insulin has been compared with repaglinide, an insulin secretagogue. Repaglinide is a meglitinide that improves endogenous insulin release by pancreatic beta-cell depolarization [94]. It is an oral agent with short half-life requiring an intake just before each meal and the dose can be adjusted between 0.5 and 4mg per meal [102]. Its pharmacokinetic matches

the postprandial glucose excursion observed in IGT or CFRD but like insulin, it can cause hypoglycemia [94]. Only one randomized controlled trial [94] and one randomized, open-label trial [98] are available about this medication. The randomized control trial was a three-arm trial comparing bolus of rapid-acting insulin aspart, repaglinide, or oral placebo at each meal in 81 adult individuals with CF (61 with CFRD and 20 with IGT, all without fasting hyperglycemia) who presented a decline in BMI in the preceding year [94]. The study concluded that while insulin stabilized BMI, repaglinide only improved BMI initially (at 6 months) but not at one year. Among the subgroup of patients with IGT, neither insulin nor repaglinide affected the rate of BMI decline. Though this study has been widely cited and used in guidelines to suggest superiority of insulin over repaglinide, extrapolation of study results should be done cautiously given its low power and that, despite randomization, there were noticeable baseline BMI differences between the placebo and treatment groups. A more recent, multicentre, randomized, open label study, demonstrated that bolus regular insulin and repaglinide were equally efficacious and safe at 24 months in terms of glucose control, respiratory function, maintaining BMI, and risk of hypoglycemia [98]. This second randomized trial is, however, missing a placebo control arm, which limits the ability to identify the possible benefits of both interventions. Overall hypoglycemic risk was low and neither trial showed a difference in hypoglycemia risk between bolus insulin and repaglinide [94, 98].

As shown in other forms of diabetes, long-acting basal insulin analog (e.g. Glargine U100) provide comparable glucose control compared to Neutral Protamine Hagedorn (NPH) insulin but with lower hypoglycemic risk [57]. Some small, mostly uncontrolled studies suggest that for anabolic goals (BMI and/or FEV_1), a single daily long-acting basal insulin might provide comparable benefit to the one observed in older studies using prandial insulin [95, 97, 103, 104].

Diagnosis and treatment of hypoglycemia should be aligned with Diabetes Canada recommendation [41].

b. Non-insulin agents

As mentioned above, most existing literature examines the use of repaglinide, an insulin secretagogue that still exposes to risk of iatrogenic hypoglycemia. However, in recent years, the development of incretin therapies (glucagon receptor-like-peptide-1 receptor agonists [GLP-1-RA]) and dipeptidyl peptidase-IV-inhibitors [DPP-4-I]) and sodium-glucose co-transporter-2 (SGLT-2) inhibitors offer new options without hypoglycemic risk, with possible weight loss and with some demonstrated cardiorenal benefits demonstrated for patients living with T2D [105]. The safety and efficacy of these medications in individuals with CFRD has yet to be established.

Incretin-based therapies use a synthetic GLP-1 agonist or inhibit the breakdown of endogenous GLP-1 (DPP-4-I) to stimulate insulin secretion in a glucose-dependent manner [106]. These therapies minimize the risk of hypoglycemia. GLP-1 agonists also promote weight loss via centrally mediated promotion of satiety. Most GLP-1 agonists have cardiovascular benefits, while DPP-4 inhibitors have established cardiovascular safety for patients living with T2D [106]. Two studies suggested benefit of GLP-1 RA therapies in the management of postprandial hyperglycemia in individuals with CF [107, 108]. As for DPP-4-I, a 6 month double-blind trial of sitagliptin (100 mg daily) compared to matched placebo showed no effect on postprandial hyperglycemia [109], while a small uncontrolled report showed a higher time in range after treatment by sitagliptin [110]. The main side-effect of GLP-1 agonists is gastrointestinal intolerance (e.g. nausea), but experience in people living with T2D shows that starting at low dose

with slow upward titration significantly reduces this side effect. In pwCF, two specific additional side-effects can raise concerns and/or need to be monitored. Incretin-based therapies are associated with a very small but measurable risk of acute pancreatitis in pancreatic sufficient people living with diabetes [111, 112]. In pwCF, data is very scarce, with some small studies with DPP-4-I reporting no side effect [113] and one case report showing no effect on pancreatic enzymes concentration after Semaglutide administration [114]. Therefore, GLP1-agonists use should be prohibited in case of history of pancreatitis. Furthermore, GLP-1 agonists promote weight loss and thus should not be considered in pwCF at/or below target weight [76, 115, 116].

SGLT-2 inhibitors decrease glucose reabsorption in the renal proximal tubule, thus lowering blood glucose in an insulin-independent manner [106]. In persons living with T2D, this translates into a glucose lowering effect, some weight loss, improved blood pressure, and cardiorenal benefits. The most frequent side effects are genital mycotic infections. SGLT-2 inhibitors should be suspended during sick days, a situation requiring specific training for individuals. This last point is of major importance in the context of CF (e.g., at the time of exacerbation). At this stage, there is no data on the efficacy and safety of use of SGLT-2 inhibitors in individuals with CFRD. If a concomitant diagnosis of T1D is suspected, the usage of SGLT2i should be avoided because of the risk of life threating euglycemic ketoacidosis.

Metformin mainly reduces hepatic glucose production. Its safety and efficacy are well established in persons living with T2D, in which it is usually the 1st line of pharmaceutical treatment. Its main side effect is gastrointestinal intolerance, usually minimized by starting at low dose, slowly titrating, and taking the medication with meals. Main concerns are related to accumulation risk in case of renal insufficiency and increased risk of extremely rare lactic acidosis.

Alpha-glucosidase inhibitors delay carbohydrate absorption with a modest impact on glucose values in people living with T2D and frequent gastrointestinal intolerance.

Pioglitazone is an insulin sensitizer drug that raised concerns about bone health (increased risk of bone fractures) with long-term use, as well as some potential cardiovascular negative outcomes (e.g. heart failure), preventing it from being used in pwCF with CFRD [41].

After a review of the existing literature, the committee recommends the use of oral repaglinide in adult patients with 1) predominantly post-prandial glycemic excursions with no significant weight loss, pulmonary decline, or recent pulmonary exacerbation, 2) factors limiting use of insulin therapy (e.g. fear). The aim is to reduce treatment burden with a goal of increasing adherence. There is a potential drug interaction between repaglinide and HEMT suggesting it is useful to monitor blood glucose or choose alternate therapeutic options in patients using HEMT. In addition, co-prescription might lead to hepatotoxicity, thus monitoring liver enzyme is recommended. The clinical relevance of these potential interactions remains to be established.

There is no clear evidence in CFRD for the use of other anti-hyperglycemic medications used in T2D, but these may be considered in adults at the discretion of experienced practitioners under close supervision. DPP-4-I might be considered as an alternative to repaglinide to reduce hypoglycemic risk [117]. The committee recommends the use of GLP-1 agonists (liraglutide, dulaglutide and semaglutide) and/or SGLT2i (empagliflozin, canagliflozin or dapagliflozin), in adults with CFRD and overweight/obesity and/or if pwCF may benefit from cardio-renal

protection established in patients living with T2D. The use of these medications needs to be part of an individualized treatment plan to achieve glycemic targets by experienced practitioners.

Due to the limited available literature in the pediatric population and of the importance of supporting healthy growth, insulin is the only recommended therapeutic agent in children with CFRD.

4.5. Advanced Insulin Delivery Technologies

The addition of CGM and sensor-augmented CSIIs has significantly improved management of T1D in recent years [118, 119]. A few studies highlighted the low usage of CSII and sensor-augmented CSIIs therapy in individuals with CFRD but also confirmed safety and efficacy in this population [120-122]. Automated insulin delivery (also called hybrid closed-loop or artificial pancreas) can be achieved using a combination of CSII, CGM, and an algorithm adjusting dynamically insulin delivery according to interstitial glucose trends. Automated insulin delivery improves glucose control with improved efficacy (less hyperglycemia), improved safety (less hypoglycemia), and treatment burden with automation [123]. Sherwood et al. recently demonstrated the feasibility of using a dual hormone (insulin and glucagon) automated insulin delivery in a randomized control study with 20 individuals with CFRD [124, 125]. Given the burden of disease in individuals with CFRD (e.g. large variability of insulin needs, frequent intercurrent illness with sick days), the use of automated insulin delivery might improve both clinical outcomes and quality of life, but larger studies are needed for validation of this technology in individuals with CFRD. Optimal initiation and use of diabetes technologies might need a referral and concomitant follow-up with a diabetes team having specific expertise [41].

5. Surveillance for diabetes complications and vascular risk

See main document for recommendations.

6. Management of CFRD in individuals treated with CFTR modulators

Over the last 20 years, a concerted effort was placed on identifying novel compounds that can modulate specific classes of protein defects that result from CFTR mutations. These compounds are collectively termed CFTR modulators [16]. Medications that directly target the cause of CF and have a significant impact on key CF outcomes are referred to as HEMT. The first-generation modulator is ivacaftor (Kalydeco™), a potentiator of CFTR channel gating and function. The next generation of modulators include lumacaftor-ivacaftor (Orkambi™) and tezacaftor-ivacaftor (Symdeco™), which are combined correctors of protein misfolding in conjunction with potentiators. In Canada, the most recent HEMT is the third generation of modulators known as elexacaftor-tezacaftor-ivacaftor (Trikafta™). Elexacaftor-tezacaftor-ivacaftor is indicated to treat people with CF who have at least one copy of the F508del mutation (irrespective of their second mutation) [126]. The phase III trials demonstrating efficacy of these drugs focused on pulmonary outcomes as the primary endpoints. As such, there is a paucity of data on how the trajectory of the continuum of CF blood glucose abnormality will be impacted by modulator use.

Preliminary evidence indicates that HEMT may have a beneficial effect on glucose control in individuals with established CFRD. New initiation of ivacaftor therapy has been associated with improvements in glucose control and reduction of insulin dose requirements in individuals with CFRD [127-129]. Although studies currently have a limited number of participants per study, the effect of lumacaftor-ivacaftor or elexacaftor-tezacaftor-ivacaftor on glucose control has been inconsistently demonstrated, showing some improvement in certain cases (no improvement: [130, 131]; some improvement: [127, 129]). In one of the largest observational studies to date, Petersen and colleagues found that elexacaftor-tezacaftor-ivacaftor improved RBG and A1c measurements in those with IGT but not CFRD [38].

There is a paucity of evidence on how modulators might impact the risk of developing CFRD in individuals with CF without known glucose abnormalities. There are conflicting reports with regards to changes in glucose tolerance after starting HEMT. Three studies failed to identify changes in glucose tolerance after starting lumacaftor-ivacaftor [130, 132, 133], but the most extensive and reliable observational, prospective multicenter study revealed that half of the patients with abnormal glucose tolerance could be reclassified as normal glucose tolerance one year after commencing lumacaftor-ivacaftor treatment [129]. With regards to elexacaftor-tezacaftor-ivacaftor, there is emerging pilot data to suggest some with abnormal glucose tolerance may experience enough improvement in glucose tolerance to be reclassified as normal glucose tolerance after just 4-6 weeks of elexacaftor-tezacaftor-ivacaftor therapy [134]. Finally, in retrospective examinations of the United Kingdom and United States registries, individuals on ivacaftor therapy showed a lower prevalence of CFRD compared to the untreated cohort with a similar genotype over time [135, 136]. A recent systematic review suggested that HEMT therapy is associated with improved glucose regulation for at least some patients with the F508del mutation [137].

Therefore, though short-term studies indicate certain metabolic improvements with HEMT, especially in individuals with IGT or newly diagnosed CFRD, it remains uncertain if this will be the case for those with established CFRD or if these improvements will be sustained in the long term. Additionally, it is unclear whether the enhanced nutrition and increased lifespan associated with HEMT will lead to a shift in the phenotype of CFRD or the emergence of T2D in CF. In individuals with CF rapidly gaining weight with HEMT it might be necessary to reassess energy needs and nutritional counseling. It is advisable to monitor glycemia in CFRD after initiating HEMT to assess if a reduction in glucose-lowering therapy is needed. However, the expert panel do not recommend using OGTT testing to identify diabetes remission in clinical practice.

Some drugs frequently prescribed in people with CFRD are metabolized by the same route as HEMT thus leading to potential interactions increasing the risk of getting higher plasma concentrations at potentially supraphysiological doses. This drug list includes repaglinide, glimepiride, gliclazide and most statins.

7. Pregnancy

Gestational diabetes is a diabetes diagnosed for the first-time during pregnancy, it can develop early in pregnancy due to reduced insulin secretory capacity. In the general population and in other forms of diabetes, hyperglycemia during early pregnancy is linked to an increased risk of fetal malformations. Later in pregnancy, hyperglycemia is associated with higher risks of pre-

eclampsia, stillbirth, increased birth weight, macrosomia, shoulder dystocia, the need for operative deliveries, neonatal hypoglycemia, and neonatal intensive care unit admissions [32, 138]. Limited detailed information is available on maternal and fetal outcomes in women with CFRD during pregnancy and those with GDM and their infants. In two recent studies, females with CFRD had higher rates of caesarean-sections compared to those with CF without diabetes, with no differences in other examined adverse outcomes [139, 140]. Hospital admission for CF exacerbations is common during pregnancy in those with CFRD or GDM (75-87.5%) [140].

7.1. Pre-conception counselling
See main document for further detail.

7.2. Screening for, and diagnosis of GDM/CFRD in females with CF
See main document for further detail.

7.3. Management of GDM and CFRD during pregnancy

Overall, the recommendations are consistent with those of Diabetes Canada CPG. Historically, unlike patients with GDM in the general population, women with CF were not advised to restrict carbohydrate intake to attain sufficient weight gain during pregnancy. Moderate carbohydrate intake with low glycemic index foods aiming for sufficient carbohydrate intake is recommended, spread over 3 meals and 2 snacks (including one at bedtime) throughout the day. Simple sugars should be consumed only at mealtimes. With improvement of nutritional status and in case of adequate weight gain, some restrictions to carbohydrate intake can be considered. Physical activity interventions should be encouraged, except in the presence of obstetrical contraindications. Currently, there are no studies investigating the safety and efficacy of these dietary modifications in females with CF and GDM. Additionally, there is a lack of clarity regarding the type, duration, or intensity of physical activity that should be recommended for this population. When needed, the preferred pharmacological treatment is insulin which requires training for initiation, management and prevention of hypoglycemic risk [41]. The risk of hypoglycemia is increased during labour and early post-partum.

8. Specific Settings

8.1. Diagnosis and management of CFRD during hospitalization

Inpatient detection and management of hyperglycemia are often overlooked in the CFRD literature, despite its frequent occurrence. Hyperglycemia in the inpatient setting can happen due to limited insulin secretion capacity and insulin resistance triggered by factors like pulmonary exacerbations, inflammation, stress, and steroids [141]. Risk factors for hyperglycemia during hospital stays include steroid treatment, irregular food intake, and enteral feeding [142]. Additionally, hyperglycemia is associated with slower recovery of FEV1, emphasizing the importance of appropriate management [143]. Insulin is typically the most effective treatment for hyperglycemia in the hospital [144]. A proactive approach using scheduled basal, bolus, and correction insulin is preferred, discouraging the use of correction-only insulin (sliding scale) for elevated blood glucose levels [144]. For steroid-induced hyperglycemia, NPH insulin can be considered for administration concomitantly with steroid medications [142]. For noncritically ill hospitalized individuals with CF and diabetes, pre-prandial blood glucose targets should be 5.0 to 10.0 mmol/L if safely achievable [144]. For critically ill hospitalized individuals with CF with or without CFRD, blood glucose levels should be maintained between 6.0 and 10.0 mmol/L [144]. Hypoglycemia is a significant obstacle to achieving targeted glucose control in the hospital,

warranting the development of specific protocols by healthcare teams for its prevention, assessment, and treatment [144].

Recommendations 8.1:

For individuals with CFRD who are admitted to hospital, diabetes management should be tailored to the unique needs of CFRD to promote optimal glycemia and nutrition. (**Good Practice**). This approach may deviate from that used for the general diabetes population. In general, it is recommended to:

8.1.1. Continue pre-hospital insulin regimens or oral antihyperglycemic medications provided that dietary intake and glucose control are stable and there are no specific contraindications for oral agents (e.g. reduced glomerular filtration rate with metformin).

8.1.2. Continue their usual CF diet or initiate nutrition support to meet nutritional needs. Calorie-restricted diets are not recommended in this population, particularly during hospitalization.

8.1.3. Monitor capillary blood glucose levels 4 times daily for 3 days to identify hyperglycemia and to facilitate adjustment of insulin doses in a setting where insulin requirements may change rapidly. After 3 days, the need for and frequency of CBGM should be reassessed and individualized.

8.1.4. Insulin dose requirements in the hospital may increase due to illness and insulin doses may need to be adjusted. As an individual with CF's health improves, the insulin dose may need to be reduced or discontinued to avoid hypoglycemia.

8.1.5. Hospitalized individuals with CFRD at risk of hypoglycemia should always have easy access to an appropriate source of glucose (oral or intravenous) and/or glucagon at all times, particularly when fasting or during diagnostic procedures. (**Good Practice)**

8.1.6. Avoidance of hypoglycemia is strongly recommended for all individuals with CFRD who are admitted to hospital.

8.1.7. For the majority of hospitalized individuals with CFRD, blood glucose targets during hospitalization should be between 5.0-10.0 mmol/L, provided that these targets can be achieved safely without hypoglycemia. (**Good Practice**)

8.1.8. Individuals with CF or CFRD with persistent hyperglycemia for more than 2 consecutive days during hospitalization should be started on basal and/or bolus insulin to achieve glycemic targets. (**Good Practice)**

8.1.9. When bolus insulin is used, it should be given proactively at the start of the meal to account for meal-time carbohydrates in addition to correction dose for pre-meal hyperglycemia. Reactive insulin dosing strategies (commonly referred to as a sliding scale) are not recommended.

8.1.10. For hospitalized individuals who experience glucocorticoid-induced hyperglycemia, NPH insulin, given at the same time as the steroid medication, may be added to the existing insulin regimen (e.g. basal/bolus) to improve glucose control. (**Good Practice**)

8.1.11. Longer-acting basal insulin analogs may be considered when longer-acting glucocorticoids (e.g. twice daily methylprednisolone, dexamethasone) are used.

8.1.12. Hospitalized individuals with CFRD who are clinically stable should be encouraged to self-manage their diabetes in the hospital, where appropriate, in collaboration with

the healthcare team and in accordance with hospital policies. (**Good Practice**) This may include:

A. Continuing use of insulin pumps while in hospital
B. Use of CGM as an alternative/adjunct to bedside CBGM. This can be considered where allowed by hospital policies and when there are no contra-indications (e.g. significant edema). Limitations of CGM for inpatient management (e.g. possible reduced accuracy, increased lag-time, etc.) should be considered if used to make therapeutic decisions.

8.2. Detection and management of hyperglycemia with enteral tube feeding

Enteral tube feeding is commonly employed in CF when oral intake is inadequate to meet nutritional requirements [3, 4]. Close monitoring of blood glucose levels is necessary when initiating enteral tube feeding since individuals with CF using this method face a 2-fold higher risk of developing hyperglycemia [145, 146]. Insulin is the preferred treatment for hyperglycemia in individuals with CFRD on enteral feeds. Different insulin types are used to cover enteral tube feeding depending on the feed type and duration. For nocturnal feeds lasting 8-to-12 hours, a combination of regular insulin and NPH insulin is often used [147]. The regular insulin covers the first half of the feeding with a peak of 2-3 hours, while the NPH covers the second half with a peak of 5-8 hours. Daytime bolus feeds should be treated with insulin as meals, using rapid- or short-acting insulin with a dose calculated using the insulin-to-carbohydrate ratio when available. In cases where optimal glucose control cannot be achieved with multiple insulin injections, CSII may be considered to better titrate insulin dosing during tube feeds. Practical education about enteral tube feeding and potential issues, including the risk of hypoglycemia due to suspended feeds, feeding pump failure, or vomiting, is crucial for individuals with CF and their caregivers [34].

Recommendations 8.2:

8.2.1. In individuals with CF or CFRD starting or changing enteral tube feeds, capillary blood glucose levels should be monitored pre- and post-feed and at least once during a feed (mid-way) for a minimum of 3 consecutive days to assess the effects of enteral tube feeding on glycaemia. (**Good Practice)**

8.2.2. In individuals with CFRD receiving enteral tube feeding, with evidence of hyperglycemia, insulin therapy is recommended to prevent prolonged hyperglycemia. Consultation with a diabetes specialist may be considered to assist in choice and timing of insulin preparations. (**Good Practice)**

8.3. Solid organ transplantation

The most common solid organ transplantation in individuals with CF is lung transplantation for end-stage lung disease. In Canada, around 40-50 individuals with CF undergo lung transplantation each year, with a median survival of 10.7 years [148]. However, with the introduction of CFTR modulator therapy, the frequency of lung transplantation for the CF population is expected to

decrease in the coming years. Besides lung transplantation, other organs like the liver, kidney, pancreas, or isolated pancreatic islets can also be transplanted in individuals with CF. In some cases, islets or pancreas transplant may be considered as a treatment for CFRD, especially in individuals who have already undergone, or are undergoing, solid organ transplantation and are on chronic systemic immunosuppression. While these guideline recommendations primarily apply to lung or liver transplant recipients, they may also be considered for other types of organ transplants.

8.3.1. Screening for CFRD and new-onset diabetes after transplant (NODAT)

CFRD can be found in approximately 30-50% of individuals with CF who are awaiting a solid organ transplant [149, 150]. Furthermore, new-onset diabetes after transplant (NODAT), also known as post-transplant diabetes mellitus, may arise in 25-50% of those who did not have CFRD before the transplantation [151, 152]. NODAT may be transient (hyperglycemia following transplantation that resolves within 3 months) or sustained [153]. Factors associated with the development of NODAT include post-surgical inflammation and/or diabetogenic immunosuppressive medications such as corticosteroids, especially with high doses in first months after transplantation, tacrolimus, and sirolimus [153]. The development of NODAT is attributed to reduced insulin secretion in the presence of increased insulin resistance [153]. The glucose thresholds used to define NODAT are the same as those used for CFRD.

While the risk of NODAT is highest in the peri-transplant period, there is still a risk of developing diabetes (NODAT or CFRD) later [151, 152, 154]. For stable patients, screening should begin with daily CBGM during the initial 6 weeks after discharge. Subsequently, an OGTT should be conducted 3-6 months after transplantation [155, 156]. OGTT should be considered earlier if A1c > 6.4%, FPG ≥7 mmol/L, glucose ≥11.1 mmol/L during or after enteral feeds, and post-prandial glucose ≥ 11.1 mmol/L on stable corticosteroid regimen on more than one occasion on two separate days. For screening, there is some evidence that glycated hemoglobin and/or afternoon glucose are more sensitive than FPG [157]. After this initial 3 to 6 months following transplantation, screening should be undertaken as generally recommended (**figure 2**).

Recommendations 8.3:

8.3.1.1. Individuals with CF undergoing evaluation for organ transplantation should be screened for CFRD according to screening general recommendation (section 5.2). (**Best Practice**)

8.3.1.2. Individuals with CF who are hospitalized prior to transplantation, during the peri-transplant period, or admitted to treat solid organ rejection, should have CBG levels monitored 4 times daily for 3 days according to recommendations for Diagnosis and management of CFRD during hospitalization (section 5.9). (**Good Practice**)

8.3.1.3. Following solid organ transplant, individuals without CFRD should be monitored to identify NODAT: **(Good Practice)**

A. Perform CBGM at least once a day 1 to 2 h after meals for the first 6 weeks following discharge from hospital. CBGM values ≥ 11.1 mmol/L on more than 2 days per week should prompt formal assessment for diabetes.
B. OGTT should be performed at 3-6 months following transplantation. If NODAT is not identified, regular screening for CFRD should resume.

8.3.2. Management of hyperglycemia and NODAT after solid organ transplant

The suggested recommendations for CF align with those put forth for NODAT and other endocrine issues [158-160]. There is no apparent increase in the risk of post-transplant mortality in individuals with pre-existing CFRD following solid organ transplantation [161]. NODAT, however, is a significant risk factor for mortality in lung transplant recipients [162]. Maintaining good glucose control after transplantation is associated with a reduced incidence of infections and lower graft rejection rates [152]. Individuals with pre-existing CFRD commonly experience hyperglycemia after transplantation and typically require intensified treatment.

During the peri-transplant period, prednisone is the most commonly used corticosteroid in the immunosuppressive regimen, given as either a single morning dose or twice daily dosing. Prednisone-induced hyperglycemia peaks within a few hours after taking the medication. To optimally manage this hyperglycemia, intermediate-acting NPH insulin is administered with prednisone, with the NPH peak occurring 4-10 hours after injection [160]. The target glucose level for therapy during this early post-graft corticosteroid-intense period is 6-10 mmol/L, with an acceptable range of 6-12 mmol/L [163]. After the first 3 months following transplantation, a transition to basal long-acting insulin with or without bolus insulin can be considered based on the insulin dosing recommendations mentioned above for individuals with CFRD.

Limited research is available on non-insulin therapies, resulting in a lack of sufficient evidence to make specific recommendations on the choice of antihyperglycemic therapy. As emphasized by Diabetes Canada CPG, several factors should be taken into account when selecting glucose-lowering therapies [105]. The two primary considerations are weight and the risk of hypoglycemia. Considering that steroids can lead to significant weight gain, for individuals without undernutrition concerns, antihyperglycemic agents that do not promote weight gain are typically preferred. **Supplementary Table 3** summarizes certain aspects related to the choice of treatment [41, 164]. In addition, some immunosuppressive drugs can reduce metabolism of some diabetes drugs (e.g. Repaglinide with possible increased hypoglycemic risk) thus gradual titration is recommended. Conversely there is no evidence that diabetes drug interacts with immunosuppressive drug absorption and metabolism [165].

Supplementary Table 3. Choice of non-insulin therapies.

Non-insulin drug Class	Impact on weight	Hypoglycemic risk	Specificities related to NODAT
Biguanides	Modest reduction	No	Adjust to kidney and hepatic function
Dipeptidyl peptidase (DPP)-4 inhibitors	Neutral	No	Possible increased exposure due to immunosuppressive drugs
Sodium-glucose cotransporter-2 (SGLT2)	Reduction	No	Consider reduced hypoglycemic effect with reduced kidney function, the risks of genitourinary infection and education about sick day management
Glucagon-like polypeptide (GLP)-1 receptor agonist	Reduction	No	Slow titration to reduce the risk of gastro-intestinal side effects

Insulin secretagogues	Increase	Yes	Not recommended to manage NODAT (178) because of concerns about durability, hypoglycemia, weight gain. Possible increased exposure due to immunosuppressive drugs

8.3.2.1. Individuals with acute hyperglycemia post-transplant should be treated with basal and/or bolus insulin targeting capillary blood glucose levels between 6 and 12 mmol/L to reduce the risk of rejection and infection. **(Good Practice)**

A. Insulin withdrawal attempt, with intensive glucose monitoring, may be considered in individuals with stable weight and lung function and with low insulin requirements (e.g. < 20 units per day). Either insulin or non-insulin antihyperglycemic agents may be considered if capillary blood glucose, CGM, and/or A1c values are above target.
B. Individuals with remission of NODAT who have discontinued insulin should undergo CFRD screening three months after withdrawal of insulin. (**Good Practice**)

8.3.2.2. Solid organ transplant recipients with NODAT should follow the same general recommendations for blood glucose monitoring, glycemic targets and non-pharmacologic management as individuals with CFRD (section 4). (**Good Practice**)

8.3.2.3. Solid organ transplant recipients with NODAT who require pharmacotherapy to reach glycemic targets should follow Diabetes Canada CPG [41]. The relative importance of avoiding weight gain after transplant as well as reducing hypoglycemic risk should be considered when non-insulin antihyperglycemic agents and/or insulin are selected for individuals with CF and NODAT. (**Good Practice**)

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