Accepted: 7 November 2022

DOI: 10.1111/pedi.13453

ISPAD GUIDELINES

ISPAD WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Management of cystic fibrosis-related diabetes in children and adolescents

Katie Larson Ode[1] | Manfred Ballman[2] | Alberto Battezzati[3] | Amanda Brennan[4] | Christine L. Chan[5] | Shihab Hameed[6,7,8] | Heba M. Ismail[9] | Andrea Kelly[10,11] | Antoinette M. Moran[12] | Remi Rabasa-Lhoret[13] | Nichole A. Saxby[14] | Maria E. Craig[15,16]

[1]University of Iowa Stead Family Children's Hospital, University of Iowa, Iowa City, Iowa, USA

[2]University Medicine Rostock, Rostock, Mecklenburg-Vorpommern, Germany

[3]International Center for the Assessment of Nutritional Status, DeFENS, University of Milan, Milan, Italy

[4]Manchester Adult Cystic Fibrosis Centre, Manchester University NHS Foundation Trust, Manchester, UK

[5]University of Colorado Anschutz Medical Campus, Children's Hospital Colorado, Aurora, Colorado, USA

[6]Sydney Children's Hospital, Randwick and Royal North Shore Hospital, St. Leonards, New South Wales, Australia

[7]School of Clinical Medicine, University of New South Wales, Sydney, New South Wales, Australia

[8]Pediatric Endocrinology, University of Sydney, Camperdown, Australia

[9]Department of Pediatrics, Pediatric Endocrinology, Indiana University School of Medicine, Indianapolis, Indiana, USA

[10]Department of Pediatrics, The University of Pennsylvania, Philadelphia, Pennsylvania, USA

[11]Division of Endocrinology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

[12]Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota, USA

[13]Division of Experiemental Medicine, Montreal Clinical Research institute, Montreal, Canada

[14]Women's and Children's Services, Royal Hobart Hospital, Hobart, Tasmania, Australia

[15]The Children's Hospital at Westmead, University of Sydney, Sydney, New South Wales, Australia

[16]School of Women's and Children's Health, University of NSW, Sydney, New South Wales, Australia

Correspondence
Katie Larson Ode, Pediatric Endocrinology & Diabetes, University of Iowa Stead Family Children's Hospital, 200 Hawkins Dr, BT 2022, Iowa City, Iowa 52242, USA.
Email: katie-larsonode@uiowa.edu

KEYWORDS: adolescents, CFTR modulator, children, cystic fibrosis related diabetes, HEMT therapy

1 | WHAT IS NEW OR DIFFERENT?

- For some people with cystic fibrosis (CF), a new and life-changing era has begun; however, for others, existing disparities have only increased. The lives of persons with CF (PwCF) have been profoundly changed by the advent of highly effective CF transmembrane conductance regulator (CFTR) modulator therapy (HEMT) (elexacaftor/tezacaftor/ivacaftor combination therapy or ivacaftor alone in specific *CFTR* mutations), small molecule compounds that directly correct the basic defect of the CFTR channel and restore channel function.
- Emerging technologies for the management of diabetes including advanced insulin pumps and continuous glucose monitoring (CGM) have improved markedly since the 2018 ISPAD guidelines and will improve care for people with cystic fibrosis-related diabetes (CFRD).

- The guidelines have been updated to recommend insulin pump and CGM therapy for CFRD as appropriate and to address what is known regarding the effect of HEMT therapy on CFRD.
- The screening and therapy sections have been revised and expanded and new sections on hypoglycemia and health related quality of life (HRQoL) have been added.

  Unfortunately, these life-changing and paradigm-shifting medications and technologies, while saving many lives, are dramatically worsening the disparities already affecting PwCF. Disparities will likely come to be a defining feature of the care of PwCF and CFRD going forward due to both HEMT (which cost approximately USD 200,000 per year) and advanced insulin pumps and CGM technology. People of non-northern European descent are more likely to belong to groups that do not respond to HEMT therapy and are less likely to be provided access to advance diabetes technology even when income is equal, creating a worsening double disparity.

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

2.1 | Background/pathophysiology

- CFRD is the most common non-pulmonary comorbidity in CF and increases mortality. **B**
- The pathophysiology of CFRD is unique and complex but is primarily driven by insulin insufficiency and differs from type 1 diabetes (T1D) and type 2 diabetes (T2D). **A**
- The cause of insulin insufficiency in CF is multifactorial and incompletely understood, but exocrine pancreas damage and dysfunction, inflammation, genetic susceptibility, and nutritional state all contribute to beta cell dysfunction. **B**
- CFRD is often clinically silent and clinical decline can occur before diabetes is diagnosed. **C**
- Few individuals with CF have fully normal glucose tolerance (NGT) and even when fasting and 2-h blood glucose levels (BGLs) are normal on an oral glucose tolerance test (OGTT) variable intermittent postprandial hyperglycemia can often be detected by CGM. **B**
- Early CFRD is typically asymptomatic and characterized by normal fasting BGLs. BGLs can vary over time depending on underlying health and medical therapy, but typically worsen with age. **B**
- HEMT does not immediately cure established CFRD; however further data are still needed to determine the long-term effects. **C**

2.2 | Hypoglycemia

- Hypoglycemia is common in CF and can occur even in the absence of CFRD or insulin therapy. **B**
- Post OGTT hypoglycemia is common. **B**
- It is advisable to check for hypoglycemia in PwCF and advice provided to eat at the end of an OGTT. **E**

2.3 | Diagnosis

- Diagnosis of CFRD is made using American Diabetes Association (ADA) criteria during a period of stable baseline health **E**
  - 2-h BGL on OGTT ≥11.1 mmol/L (200 mg/dl)
  - Fasting BGL ≥7.0 mmol/L (126 mg/dl)
    - Fasting BGL ≤7.0 mmol/L (126 mg/dl) does not rule out diabetes in CF
  - HbA1C ≥ 48 mmol/mol (6.5%)
    - HbA1C < 48 mmol/mol (6.5%) does not rule out diabetes in CF
  - Random BGL ≥11.1 mmol/L (200 mg/dl) with classic symptoms of diabetes
- Onset of CFRD is defined as the first time a person with CF meets criteria for CFRD, even if glucose tolerance subsequently improves. **E**
- Diagnosis of diabetes can be made with acute illness (intravenous antibiotics/systemic glucocorticoid therapy) if fasting BG ≥7 nmol/L (126 mg/dl) or 2 h postprandial BG ≥11.1 mmol/L (200 mg/dl) persist for more than 48 h. **E**
- Diagnosis of diabetes can be made in an individual on overnight enteral feedings when mid or post-feeding BG readings are ≥11.1 mmol/L (200 mg/dl) on two separate days. **E**

2.4 | Screening

- HbA1C is not a recommended screening test for CFRD due to its low sensitivity. **C**
- Screening for CFRD should be performed using the 2-h 75 g (1.75 g/kg) OGTT. **B**
- Yearly OGTT should begin at least by age 10 years. **B**
- BGLs should be measured at minimum at fasting and 2 h on OGTT. **B**
- Consideration should be given to utilizing 1-h BGL measurement on OGTT, but there is insufficient evidence to recommend use at this time. **C**
- PwCF who are pancreatic sufficient have a lower risk of CFRD than those who are pancreatic insufficient but still higher than the general population; those with NGT may have OGTT screening every 3–5 years if deemed appropriate by the managing team. **B**
- There is inadequate evidence to recommend other forms of screening at this time. **E**
- Fasting BGL is not recommended for screening for CFRD due to low sensitivity. **B**
- Screening for gestational diabetes is recommended at both 12 to 16 weeks and 24 to 28 weeks gestation in pregnant women without known CFRD, using a 2-h 75 g OGTT with BG measures at 0,1, and 2 h. **E**
- Post-pregnancy screening for CFRD using a 2 h 75 g fasting OGTT is recommended 6 to 12 weeks after the end of pregnancy in women with diabetes first diagnosed during pregnancy.

- PwCF who have pulmonary exacerbations requiring IV antibiotics or glucocorticoids should be screened with fasting and 2-h postprandial BGLs for 48 h. **E**
- For PwCF on enteral feeds it is advisable to screen with mid and immediate post-feeding BGLs levels at the time of initiation of enteral feedings. Elevated BGLs detected by self-monitoring of blood glucose (SMBG) or CGM require confirmation at a certified laboratory. **E**
- PwCF without diabetes who are undergoing organ transplantation should be screened preoperatively with 2-h 75 g fasting OGTT if they have not had CFRD screening in the last 6 months. BGLs should be monitored closely in the perioperative period and until hospital discharge. **E**
- Screen for islet autoantibodies in the following scenarios: CFRD diagnosis <10 years of age, presentation in diabetic ketoacidosis (DKA), immediate family history of autoimmunity, or personal history of other autoimmune disease. **E**
- There is inadequate evidence to recommend the use of CGM or other forms of screening to replace OGTT at this time, but additional research is needed. **C**
- OGTT continues to have barriers to full use and additional research to improve CFRD screening is needed. **B**
- There is inadequate evidence at this time to alter CFRD screening based on use of highly effective CFTR modulator therapy. **E**

2.5 | Pregnancy

- Diagnosis of gestational diabetes (GDM) should be made based on the recommendations of the International Association of Diabetes and Pregnancy Study group. New guidelines are anticipated in 2022 and these recommendations should be considered a placeholder until the updated guidelines are released. Diagnosis is based on 0, 1, and 2 h glucose levels with a 75 g OGTT if any one of the following is present: **E**
  - Fasting BGL >/= 5.1 mmol/L (92 mg/dl)
  - BGL1 >/= 10.0 mmol/L (180 mg/dl)
  - BGL2 >/= 8.5 mmol/L (153 mg/dl)
- Women with CF who have GDM, but no history of pre-existing CFRD, are not considered to have CFRD, but should be screened for CFRD 6–12 weeks after the end of pregnancy. **E**

2.6 | Treatment

- PwCF and CFRD (PwCFRD) should ideally be seen quarterly by a specialized multidisciplinary team with expertise in diabetes and CF. **E**
- PwCFRD should receive ongoing diabetes self-management education from diabetes education programs that meet national standards. **E**
- PwCFRD should be treated with insulin therapy. **B**
- Insulin pump therapy should be considered for individuals with CFRD requiring intensive insulin therapy, when accessible and appropriate, including partial closed loop therapies. **C**
- In certain cases (e.g., refusal of insulin therapy in asymptomatic individuals diagnosed by annual screening, but without fasting hyperglycemia) a trial of oral diabetes agents could be considered under close observation. **C**
  - Other oral diabetes drugs like metformin, sitagliptin, empagliflozin are in use in individual cases in single CF centers. However, there remains inadequate information to recommend the use of these diabetes drugs in CF. Further research is needed and ongoing. **E**
- PwCFRD who are on insulin should perform SMBG at least four times a day. For many individuals, more frequent monitoring is necessary. **E**
- Use of CGM in PwCFRD on insulin/anti-hyperglycemic medications is desirable and may be used as an alternative to SMBG. **B**
- PwCFRRD should strive to attain BG goals and time in range on CGM as per the ADA recommendations for all people with diabetes. More or less stringent goals may be indicated for persons early in the disease course or who experience significant or repeated hypoglycemia, and individualization is important. **E**
- HbA1c, as a measure of average glycemia, is recommended quarterly for persons with CFRD to guide insulin therapy decisions. **E**
  - For most PwCFRD the HbA1c treatment goal is ≤7% (53 mmol/mol) to reduce the risk of microvascular complications, bearing in mind that less stringent goals may be indicated for PwCF who experience significant or repeated hypoglycemia, and thus individualization is important. **C**
- Medical nutrition therapy is essential to the management of CFRD as in all forms of diabetes, but should follow CF guidelines for dietary therapy, with individualization based on person-specific weight/BMI goals. **E**
- Evidence-based guidelines for nutritional management of all PwCF are recommended for people with CFRD. **E**
- Nutritional management of diabetes alone without medical therapy is not recommended. **E**
- PwCFRD should be advised to do moderate aerobic exercise for at least 150 minutes per week. **E**

2.7 | Complications

- Education on symptoms, prevention, and treatment of hypoglycemia is recommended for all PwCF and their caregivers. **E**
- PwCFRD on insulin or oral hypoglycemic agents and their caregivers should be provided glucagon therapy and appropriate education. **E**
- PwCFRD should have their blood pressure measured every visit per ADA guidelines. If abnormal blood pressure is discovered, it should be repeated on a separate visit. **E**
- CFRD causes microvascular complications of diabetes including retinopathy, nephropathy and neuropathy. **B**

- Yearly screening for microvascular complications of diabetes is recommended starting at 5 years from diagnosis, or if diagnosis date is unknown, at the onset of fasting hyperglycemia. **E**
- PwCFRD diagnosed with hypertension or microvascular complications should receive standard treatment as recommended by the ADA for all people with diabetes except there should be no restriction of sodium or generalized restriction of protein. Inadequate evidence exists to alter these recommendations for those on HEMT therapy. **E**
- Rates of obesity and overweight are increasing in CF. **C**
- There is inadequate evidence at this time to recommend routine screening for macrovascular complications in people with CFRD and pancreatic insufficiency (PI). **E**
- Yearly lipid screening is recommended in people with CFRD and pancreatic sufficiency (PS). **E**
- Lipid screening is recommended every 5 years in PwCF and PI according to general population guidelines for low-risk individuals. **E**
- The experience of PwCF and their families should be incorporated into designing CFRD management approaches. **E**

3 | INTRODUCTION

Cystic Fibrosis (CF) was the most common fatal single-gene disorder in Caucasians. However, CF is found in non-Caucasians, including people of 100% African descent, and the prevalence of CF varies greatly from country to country and within regions of a single country.[1] It is caused by autosomal recessive mutations in CFTR the gene that encodes the anion channel, CFTR. CF is a multisystem disease characterized by chronic recurrent pulmonary infection and subsequent pulmonary function decline, accompanied by exocrine and endocrine pancreatic failure, gastrointestinal dysfunction, malnutrition, liver disease, and elevated risk for osteoporosis. Death occurs secondary to pulmonary disease. While just 50 years ago affected individuals seldom reached adulthood, steady improvements in care have increased longevity and it is now possible to see PwCF living into their 70s and beyond.

CFRD is the most common non-pulmonary comorbidity in CF and worsens nutritional status, increases pulmonary function decline, and increases mortality.[2–4] There are important pathophysiologic differences between CFRD, T1D, and T2D which necessitate a unique approach to management of CFRD. PwCF may have CF liver disease and/or chronic and acute inflammation which can drive fluctuating levels of insulin resistance and increase risk for CFRD. Additionally, some PwCF may require high caloric intake and may experience malabsorption, malnutrition, and abnormal gut motility including delayed gastric emptying, all of which complicate the management of diabetes in ways not typical in other populations.

The emergence of HEMT therapy has markedly improved pulmonary function and nutritional status and has dramatically decreased need for hospitalization and lung transplantation in PwCF who are eligible for these therapies. The full effects of these therapies on the natural history, pathogenesis, and future prevalence of CFRD are yet not fully understood. Further information on correctors' impact on CFRD can be found in Section 5.4.

3.1 | Diagnostic criteria for CFRD and abnormal glucose tolerance

The diagnostic criteria for CFRD were updated in 2010 in North America by the CFRD Guidelines Committee in a position statement co-sponsored by the ADA and the Cystic Fibrosis Foundation and endorsed by the Pediatric Endocrine Society.[5] At this time there is inadequate available evidence to support alternative cut offs for CFRD. Therefore, current diagnostic guidelines are identical to those used to diagnose other forms of diabetes, including HbA1c as a diagnostic criterion. Unlike other types of diabetes, however, low or normal HbA1c levels do not exclude the diagnosis of CFRD.[6,7]

Unlike other forms of diabetes, OGTT is the primary method of diagnosis in CF. CFRD is part of a spectrum of progressive glucose tolerance abnormalities defined by a standard OGTT (Table 1). Few individuals with CF have truly NGT when compared to people without CF.[8,9] Even when the fasting and 2-h OGTT glucose levels are normal, elevations in mid-OGTT glucose levels are common, ß-cell function is impaired, and variable, intermittent postprandial hyperglycemia can often be detected at home by CGM.[10–12] Early diabetes is characterized by normal fasting BGLs, but over time fasting hyperglycemia develops. Isolated-impaired fasting glucose (IFG) is sometimes present in PwCF but the significance is unclear.[13,14]

The onset of CFRD is defined as the first time a PwCF meets diagnostic criteria for diabetes, even if glucose tolerance subsequently appears to improve. Microvascular disease and mortality correlate with the duration of diabetes that includes these early years when diabetes appears to wax and wane.[15] This is consistent with a general pattern of progressive deterioration of glucose tolerance as individuals with CF get older.[16] However, the natural history can be variable[17,18] and dependent upon acute changes in pulmonary and infectious status. It is possible that HEMT may alter this course, but at this time there is insufficient evidence to recommend changes in this guideline for those treated with HEMT.

Hyperglycemia is common during pregnancy in women with CF because of the combination of increased insulin resistance and underlying insulin insufficiency.[19] Diagnosis of gestational diabetes should be made based on the recommendations of the International Association of Diabetes and Pregnancy Study group. New guidelines are anticipated in 2022 and the recommendations in this document should be considered to be a placeholder until the updated guidelines are released. Diagnosis is based on 0, 1, and 2 h BG levels with a 75 g OGTT if any one of the following is present: Fasting BG >/-= 5.1 mmol/L (92 mg/dl), or PG1 >/= 10.0 mmol/L (180 mg/dl), or 2 h PG >/= 8.5 mmol/L (153 mg/dl). However, women with CF who have gestational diabetes and who do not meet diagnostic criteria for diabetes before or after pregnancy are not considered to have CFRD.

TABLE 1 Abnormal glucose tolerance categories in CF

Category	FPG	2-h glucose	Notes
Normal (NGT)	<7.0	<7.8	All glucose levels <11.1
Indeterminate (INDET)	<7.0	<7.8	Mid- OGTT glucose >/= 11.1
Impaired (IGT	<7.0	7.8–11.1	
CFRD FH-	<7.0	>/= 11.1	
CFRD FH	>/=7.0		
IFG	6.1–6.9	<7.8	All glucose levels <11.1

Note: Glucose levels reported as mmol/L – multiply by 18 to convert to mg/dl.
Abbreviations: CF, cystic fibrosis; CFRD, cystic fibrosis related diabetes; FH, fasting hyperglycemia; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

In PwCF with pulmonary exacerbations requiring intravenous antibiotics or use of systemic glucocorticoids a diagnosis of CFRD is confirmed when fasting BG ≥126 mg/dl (≥7 mmol/L) or 2-h postprandial BGL ≥200 mg/dl (11.1 mmol/L) are detected and persist for at least 48 h, or with 2 diagnostic BGL values on separate days. In individuals on overnight enteral feedings, CFRD is diagnosed when mid- or post-feeding BG readings are ≥200 mg/dl (11.1 mmol/L) on 2 separate days.

4 | INCIDENCE AND PREVALENCE

People with CF have higher incidence and prevalence of diabetes than any other age matched group. CFRD can occur at any age, including infancy, but prevalence increases markedly with age.

The European Cystic Fibrosis Patient Registry (ECFSPR) data from 2008 to 2015 reported that prevalence increased with increasing age group: < 10 years 0.8%; 10–19 years 9.7%; 20–29 years 24.1%; and ≥ 30 years 32.7%; total prevalence of CFRD was 21.6%. The US Cystic Fibrosis Foundation (CFF) Registry data from 2020 are similar showing ~20% of 20 year olds, 30% of 30 year olds and just under 40% of 40 year olds had a diagnosis of CFRD.[20,21] Unfortunately, both the ECFSPR and the CFF data may underestimate CFRD prevalence. The ECFSPR records insulin use as a proxy for CFRD and not everyone with CFRD is on insulin. The US CFF registry records screening results, but screening rates are consistently <70% teens and < 40% in adults.[21]

Data from Denmark and from the University of Minnesota in the US (UMN) represent the most comprehensive CFRD incidence and prevalence data available.[6,22] These data reveal an age-dependent incidence of 4%–9% per year in Denmark and 2.7 cases per 100 individual years at UMN. UMN also found diabetes in <5% of children under 10 years, 15%–20% of adolescents, 40% of 20–39 years and > 50% of those over 40 years. CFRD is more common with female sex, PI, and severe genotypes, with up to 80% in older people with severe genotypes.[20]

5 | PATHOPHYSIOLOGY OF CFRD

The mechanisms underlying CFRD are complex. Insulin secretion defects are present in essentially all individuals with CF and are at least partly related to collateral damage of islets extending from exocrine tissue destruction. CFRD development is not universal and is likely influenced by multiple other factors including inflammation, genetic susceptibility, and nutritional status. The direct role of the CFTR, the transepithelial chloride and bicarbonate ion channel that is defective in CF, in impaired insulin secretion remains unclear. Clinical, animal, and in vitro studies are positioned to further refine our understanding of CFRD development.

5.1 | Pancreatic pathology

Abnormal CFTR function results in thick viscous secretions and obstructive damage to the exocrine pancreas and progressive fibrosis and fatty infiltration. In pancreata from people with CFRD, this fibrosis and fatty infiltration extends to islets where it disrupts and destroys islet architecture and contributes to endocrine β-, α-, and pancreatic polypeptide-cell loss.[23–25] Most PwCF, with or without CFRD, have lost about half of their islet mass. Data suggests β-cell loss is not simply a by-product of exocrine tissue damage but also a manifestation of reduced β-cell progenitor survival, β-cell proliferation, and perhaps β-cell specification of progenitors.[26] Inflammation may also have a role as islets from individuals with CFRD demonstrate immune cell infiltration[27] but preserved insulin and glucagon secretion during isolated islet perifusion[27] while pancreata from both pediatric and adult individuals with CF with and without CFRD demonstrated enhance interleukin-1β staining alongside relatively preserved β-cell area and higher α-cell area.[28]

β-cell destruction is not related to autoimmune disease in CF, since the frequency of diabetes autoantibodies and human leukocyte antigen types associated with T1D are similar to that of the general population.[29,30] However, individuals have occasionally been found to have both T1D and CF.

5.2 | The role of insulin insufficiency

The primary defect in CFRD is insulin insufficiency. Virtually all pancreatic exocrine insufficient individuals, with and without diabetes, show evidence of β-cell dysfunction.[6,31] These insulin secretion

defects are present even in the setting of NGT and manifest as progressive dampening and ultimately complete loss of early-phase insulin secretion (insulin secretion occurring within first 30-min of an OGTT or meal consumption) as glucose tolerance worsens. Fasting insulin secretion is generally preserved.[8,32–35] Insulin secretory defects are found in the earliest years of life[36] and tend to worsen with increasing age.[34] Whether insulin secretory defects also occur in the setting of pancreatic exocrine sufficiency is unclear.[9,37]

5.3 | The role of insulin resistance

In persons without CFRD, insulin sensitivity has generally been reported to be intact; some investigators have found insulin resistance likely related to more severe illness.[38–41] In fact, while most of individuals are insulin sensitive during their baseline state of health, insulin resistance acutely worsens during periods of active infection and may unmask underlying insulin secretion defects and ultimately hyperglycemia.

Individuals with CFRD are modestly insulin resistant, with both decreased peripheral glucose uptake and poor insulin-mediated suppression of hepatic glucose production.[39,40] As with individuals without CFRD, insulin resistance assumes an important role during periods of stress such as acute pulmonary exacerbations and with systemic glucocorticoid therapy, and increases with age.[42]

Additionally, with the advent of HEMT, rates of obesity are increasing[43] which will likely increase insulin resistance in people with CFRD. Please see Section 7.2 for additional details.

5.4 | Genetics of CFRD and HEMT therapy

CFRD is more common in specific (more severe) *CFTR* mutations, leading to speculation of a direct role for *CFTR* in islet function, and hope that HEMT therapy could cure and prevent CFRD.

CFTR RNA may be expressed in a small subpopulation of human islet β-cells,[27,44–46] but immunocytochemistry of human islets did not identify CFTR protein co-expression with insulin-positive, glucagon-positive, or somatostatin-positive cells.[27] Moreover, CFTR modulators and inhibitors did not impact in vitro insulin secretion by human islets.[27] Non-specific inhibition of islet chloride channels by CFTR inhibitors[47] has been suggested to underlie in vitro murine and human islet studies identifying impaired insulin secretion with CFTR inhibition.[48]

CFTR modulators must match the specific *CFTR* mutation and include: ivacaftor (IVA) alone for G551D and other gaiting mutations, lumacaftor/ivacaftor (LUM/IVA), tezacaftor/ivacaftor (TEZ/IVA) and elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for deltaF508 *CFTR* mutation. Only IVA used in gaiting mutations and ELX/TEZ/IVA are highly effective modulators (HEMT) providing a near cure for PwCF. Unfortunately, it has become clear that HEMT does not resolve established CFRD. Studies to this point have shown IVA is associated with small increases in insulin secretion and markers of beta cell function, but not glucose tolerance.[49,50] A registry study utilizing data from both the United States and the United Kingdom demonstrated a slower increase in prevalence in CFRD with IVA,[51] However, these data are tempered as the comparison group had more severe CFTR genotypes (with higher baseline risk for CFRD) than the IVA group. Many more PwCF are eligible for LUM/IVA, however, only a small uncontrolled study found improved glucose tolerance[52] whereas a similar study showed no improvement.[53] There is even less data on the highly effective modulator ELX/TEZ/IVA but what is available is promising and further studies are ongoing.[49,54]

Shared genetics between CF and T2D has been suggested by the increased prevalence of CFRD in monozygotic versus dizygotic twins with CF,[55] increased prevalence of CFRD in individuals with a family history of T2D,[55] and associations with T2D susceptibility loci including *TCF7L2*, *CDKAL1*, *CDKN2A/B*, and *IGF2BP2*.[55–57] Variants in *SLC26A9*, which encodes an anion transporter recently demonstrated to be co-expressed with CFTR in a subset of pancreatic ductal cells,[44] associate with age at CFRD onset[56,57] but are not known to confer increased T2D risk. Differences in genes associated with inflammation such as tumor necrosis factor[32] and Calpain-10 also appear more common in CFRD.[58] These findings may provide insight into the progressive worsening of insulin secretion defects and glucose intolerance and ultimately interventions aimed at preserving β-cell function.

TABLE 2 Symptoms of CFRD

- Unexplained polyuria or polydipsia
- Failure to gain or maintain weight despite nutritional intervention
- Poor growth velocity
- Delayed progression of puberty
- Unexplained chronic decline in pulmonary function

There may be no symptoms.

6 | CLINICAL FEATURES OF CFRD

Onset of CFRD is typically asymptomatic and gradual with the majority of persons experiencing clinical decline prior to obvious symptoms or classic signs of diabetes.[3,59,60] Symptoms may include polyuria, polydipsia, failure to gain or maintain weight, poor growth velocity and unexplained chronic decline in pulmonary function (see Table 2). DKA is rare and should raise concern for the potential of co-occurring T1D. CFRD may first present during situations where insulin resistance is increased, such as acute pulmonary infection or glucocorticoid therapy, or during high carbohydrate food supplementation such as continuous nighttime enteral tube feedings. Unfortunately, diabetes is common in the setting of lung transplantation, where pretransplant individuals are critically ill and insulin resistant, and posttransplant receive diabetogenic medications such as steroids and calcineurin inhibitors.[61–64] In PwCF on HEMT, and/or with increasing age, signs of insulin resistance have been documented, which may contribute to progression toward frank CFRD.[42] The prevalence of CFRD is higher in individuals with CF-related liver disease.[65]

7 | SURVIVAL AND PROGNOSIS

7.1 | Increased mortality in CFRD

Beginning in the 1980s, the diagnosis of CFRD was associated with increased mortality, particularly in women.[2,66–69] Unlike people with T1D and T2D in whom increased mortality is attributable to macrovascular and microvascular disease, people with CFRD almost always die from pulmonary failure. Diabetes has been directly implicated in CF lung function decline because of both the catabolic effects of insulin insufficiency on nutritional status and muscle mass[59,70–72] and the negative impact of chronic hyperglycemia on lung function.[73–76] A 2009 report examining temporal trends in CFRD mortality in a large, well-defined CF population followed longitudinally at one institution found a significant and steady decline in the risk of death associated with CFRD between 1992 and 2008.[22] This substantial improvement in the mortality associated with CFRD was attributed to annual diabetes screening and early institution of insulin therapy. With overall improvements in the health of PwCF, particularly in the large subset treated with highly effective modulator therapy, the relationships of CFRD with increased mortality related to pulmonary failure will require ongoing surveillance to determine if the risk is further ameliorated. Unfortunately, in the only study so far, use of IVA in G551D mutations did not prevent excess lung function decline from CFRD, indicating HEMT therapy alone may not be sufficient to prevent increased morbidity from CFRD.[77]

7.2 | Microvascular and macrovascular complications

Diabetes microvascular complications occur in CFRD. In Denmark, 36% of PwCF with more than 10 years duration of diabetes had retinopathy.[78] In a US series of 285 CFRD individuals, diabetes complications were rare before 10 years duration of diabetes; thereafter, in those with fasting hyperglycemia, 14% had microalbuminuria, 16% retinopathy, 55% neuropathy, 50% gastropathy.[15] In Wales, 42% (18/43) of people with CFRD who underwent retinal scans had evidence of retinopathy ranging in severity from mild to proliferative retinopathy.[79] CFRD requiring insulin therapy for >5 years substantially increased the risk of chronic kidney disease.[80] Therefore, screening for microvascular complications is recommended annually beginning 5 years after the diagnosis of CFRD.

At the current time, case reports of established cardiovascular disease remain rare.[81–83] Overweight/obesity are increasingly prevalent in adults with CF.[84,85] Blood pressure increases with increasing age in CF.[86] In a US cohort of 484 adults with CF, the prevalence of hypertension was 17% in normal weight CF adults increasing to 31% in overweight adults.[84] Studies of vascular distensibility suggest subtle changes, traditionally recognized as precursors to cardiovascular complications in non-CF populations, may be present in CF.[87,88] Prior to the introduction of HEMT, cholesterol has been generally low in CF.[89–92] Although a recent study of 256 Canadian adults with CF found hyperlipidemia in a small percentage, it was not associated with CFRD or hyperglycemia.[42] A separate large Canadian study found weight gain was associated with better pulmonary function but increased insulin resistance and dyslipidaemia.[93] Similar findings have also been seen in smaller studies in US adults.[94] With the changing demographics, nutritional status, and overall health of people with CF, cardiovascular disease risk in CF may need to be reconsidered.

7.3 | Increased morbidity in the prediabetes state

Several studies have shown an insidious decline in clinical status in the years before the diagnosis of CFRD, during the insulin-insufficient, prediabetic state.[3,38,59,60,66] In a prospective study, the decline in pulmonary function over 4 years was least in individuals with NGT, greater in persons with IGT, and greatest in PwCF with untreated early diabetes.[3] In this study and others,[34] pulmonary deterioration correlated with the severity of insulin insufficiency. More contemporary data from the US CF Registry (2008–2015) identifying greater declines in pulmonary function in the 2 years prior to CFRD diagnosis in CF Centers with lower screening rates[95] continue to suggest delayed diagnoses contributes to worse outcomes. Recently, isolated elevations in the 1-h OGTT glucose and higher glucose excursions identified with CGM were weakly related to pulmonary function.[96,97]

Because protein catabolism, malnutrition, and death are associated in CF and because insulin is a potent anabolic hormone, insulin insufficiency has been considered of greater consequence in CF than the traditional metabolic impact of hyperglycemia. The catabolic effect of insulin insufficiency may be most important in growing children.[98–100] With the emergence of overweight/obesity[84,101] and better overall health in people with CF, particularly with HEMT,[102] insulin insufficiency may pose less of a threat to nutritional status and pulmonary function.

8 | HYPOGLYCEMIA

As in other forms of diabetes, hypoglycemia can be a complication of CFRD treatment. Spontaneous hypoglycemia is also experienced by PwCF who do not have diabetes and are not on glucose-lowering therapies. Hypoglycemia is usually described as reactive, occurring during or after an OGTT (with a prevalence ranging from 7% to 60%),[34,103,104] as well as during the post-prandial state and in the fasting state of PwCF with suboptimal clinical status.[34] Hypoglycemia in these contexts in CF is generally self-limited and is rarely symptomatic even when BGLs are severely reduced, which raises concerns of under recognition and potential hypoglycemia unawareness.[105,106]

Multiple mechanisms may lead to hypoglycemia in CF. Studies have shown that the glucagon counterregulatory response is impaired and only in part compensated by an intact or attenuated catecholamine response.[8,104,105] The timing of insulin secretion is generally delayed, leading to inappropriately high insulin secretion during the descending phase of BGLs of a glucose challenge.[8,104] Furthermore,

PwCF with more severe insulin secretory defects may be at higher risk of hypoglycemia.[105]

As with all individuals on insulin therapy, hypoglycemia is a risk that PwCFRD and their families must know how to anticipate, prevent, and treat. In a few individuals with CFRD, therapy with modulators has dramatically improved their glycemic management leading to ongoing recurrent hypoglycemic events off insulin therapy.[107] This phenomenon will need ongoing research.

For PwCF, hypoglycemia may be a concern also in the absence of diabetes and related therapy. Therefore, PwCF should be queried for symptoms of post-prandial hypoglycemia. After the conclusion of an OGTT their BGLs should be monitored, and they should be advised to eat following the test. Interestingly, those who experienced hypoglycemia during OGTT appear to have lower rates of progression to IGT and CFRD[108,109] However, the potential risks of repeated hypoglycemia and hypoglycemia unawareness are presently unknown in these individuals.

9 | SCREENING FOR CFRD

Because CFRD can be associated with an increased risk of clinical decline (e.g., accelerated weight and/or lung function loss) but often may be clinically silent,[3,59,60,66,110] routine screening is important.[95] The standard OGTT (after an 8 h fast, 1.75 g/kg body weight oral glucose up to a maximum of 75 g, 2 h test) is at present the recommended screening test. Screening is recommended annually starting at age 10 years, and it is also recommended in situations where individuals are at higher risk for hyperglycemia (e.g., steroid initiation, pregnancy, enteral or parenteral nutrition support, etc.)

9.1 | Oral glucose tolerance test

The North American CFRD Guidelines Committee determined that the OGTT is the screening test of choice for CFRD.[5] This recommendation is based on: (1) the poor performance of other tests in CF relative to the OGTT (e.g., fasting BGL, A1c); (2) the availability of long-term prognostic data linking OGTT results to relevant clinical outcomes such as an increased risk of weight and/or lung function decline[3,6,30]; (3) improvements in nutritional status and pulmonary function observed with insulin therapy[111–113]; and (4) the importance of diagnosing CFRD early to reduce the risk of CF-specific outcomes as well as diabetes-related microvascular complications (e.g., retinopathy).[15,114]

A diagnosis of CFRD is based on elevated fasting and/or 2-h BGLs. These values also serve to identify prediabetes categories: IFG, IGT, and indeterminate glycemia (see Table 1). These prediabetes categories are associated with increased risk of developing CFRD[115] and may also identify individuals at higher risk for weight and lung function decline.[3,6,116,117]

It is recommended that OGTT screening begin by at least 10 years of age. While overt diabetes is rare before 10 years of age, 42% to 78% of children with CF ages 9 years and under are reported to have abnormal glucose tolerance.[118,119] A retrospective study at one North American CF center found that in children ages 6 to 9 years, IGT or indeterminate glycemia each predicted a high risk of progression to diabetes in the early adolescent years.[118] For this reason, some centers and associations choose to begin screening at 6 years of age.[120]

9.2 | Prediabetes categories: IFG, IGT, and mid-OGTT glucose elevations

The North American CFRD Consensus Conference in 2009 defined glucose tolerance in individuals with a 1 h BG (BG1) > 11.1 mmol/L (200 mg/dl) as indeterminate (INDET) glycemia. There is some evidence that mid-OGTT glucose elevations may be predictive of CFRD[16,93,115,121–123] and pulmonary function and weight decline.[124–127] Thus, consideration should be given to measuring intermediate glucose levels during the 2-h test.[115,124,125] In a large study of more than 1000 German and Austrian PwCF over 10 years of age, IFG, IGT, and INDET were all predictors of future CFRD.[115] Similarly, a US pediatric study found that youth with a INDET were 10 times more likely to develop CFRD over the subsequent 5 years.[123] The combined presence of both IGT and INDET also appears to identify a unique group at higher risk for CFRD.[115,128]

Lower BGL1 thresholds of >8.6 mmol/L (155 mg/dl) and even > 8 mmol/L (>140 mg/dL) have been proposed to identify those with greater ß-cell dysfunction, risk of CFRD, and clinical decline.[16,123,124,129] However, these associations have not been consistently demonstrated across studies.[123,129–131] At least one recent publication suggests that such associations may be less evident for adults with CF in the context of modern CF-treatments,[130] and additional research is necessary before these measures can be used to guide clinical interventions.

Adherence to screening recommendations for an annual OGTT also continues to be a challenge across CF centers, with fewer than 50% of eligible adults with CF undergoing routine screening at adult centers in North America.[21,132] This could have adverse consequences as individuals followed in centers with low screening rates have faster rates of pulmonary decline prior to CFRD diagnosis.[95] Barriers to screening include fasting and multiple sampling times, as well as lack of understanding surrounding the implications of testing. Furthermore, given the variability of OGTTs, particularly in this population,[17] repeat testing is recommended to confirm a diagnosis of CFRD.[5,13] The resultant burden of testing has led to attempts to shorten this test with intermediate OGTT glucose measurements.[133] Others have proposed to reduce the number of required OGTTs with a stepwise approach using either HbA1c,[134] random BGL,[135] or a first step 1 h glucose challenge test[136] or other intermediate OGTT BGs.[93] However, larger prospective studies are needed before these can be recommended, particularly in the highly effective modulator era, in order to inform evidence-based recommendations.

9.3 | HbA1c for screening and diagnosis

HbA1c is unreliable in the diagnosis of CFRD because it has low sensitivity for identifying CFRD detected by OGTT[6,11,137,138] and poor

ability to differentiate among different glucose tolerance categories.[139] When using ADA criteria for diagnosing diabetes with an HbA1c cut point of 48 mmol/mol (6.5%), many individuals with early CFRD defined by OGTT will be missed.[110,140] Historically, HbA1c has been thought to underestimate glycemia in CF, and this has been postulated to be due to increased red blood cell turnover related to chronic inflammation.[141] More recent reports from youth and adults with CF suggest that HbA1c has a similar relationship to mean glucose as described in other populations with diabetes.[7,142] As a measure of average glycemia over the preceding 2–3 months, HbA1c rises when average BGLs increase, but this test may miss individuals with normal fasting and average glucose concentrations but who have postprandial glucose excursions that are better captured by an OGTT. Thus, an elevated HbA1c is evidence of hyperglycemia, but a normal HbA1c does not exclude it.

Increasingly, studies are investigating alternate, lower HbA1c thresholds that may aid CFRD screening. In retrospective studies from pediatric and adult individuals with CF, an HbA1c value below 5.5% to 5.8% (37–40 mmol/mol) was associated with a low risk of developing CFRD.[132,137,143,144] A stepwise approach using HbA1c as a first line screening tool, for example, could reduce the number of required OGTTs.[134] However, variability in HbA1c assays still exist and additional studies are needed to validate a specific HbA1c cutpoint that would decrease the burden of OGTTs without missing cases of CFRD.

Other measures of average glycemia, including fructosamine, 1,5-anhydroglucitol, and glycated albumin, have been investigated in small studies in the CF population, but thresholds have not been identified that outperform HbA1c or OGTTs at identifying those at risk for CFRD.[137,145]

9.4 | Random and fasting BGLs, or SMBG for CFRD diagnosis

Normal fasting or random BGLs do not exclude a diagnosis of CFRD, as nearly two-thirds of individuals with de novo CFRD do not have fasting hyperglycemia.[22] However, in some high-risk situations such as hospital admissions for pulmonary exacerbations or need for intravenous antibiotics or initiation of gastrostomy feedings, it is practical to perform initial prescreening with bedside glucose checks or home monitoring with SMBG (see Special circumstances Section 9.6). SMBG is not sufficiently accurate to make a diagnosis of CFRD, and subsequent laboratory screening must occur in individuals identified as high-risk by SMBG.

9.5 | Continuous glucose monitoring

CGM has been validated in people with CF and is generally accepted to be useful for glucose monitoring in individuals with insulin-treated CFRD, where it can help guide safe and effective insulin therapy.[12] Its role in PwCF who do not have diabetes and/or to establish a diagnosis of CFRD is less clear. Glucose abnormalities captured by CGM are common in CF, including in very young children[96,146]; however, there are as yet neither established criteria using CGM for screening nor diagnosing diabetes.[121,142] Retrospective and cross-sectional single-center studies have associated glucose abnormalities on CGM with ß-cell dysfunction on OGTT,[121] weight decline,[125] lower lung function,[96,147] and elevated inflammatory markers.[148] However, evidence from larger multi-center studies are lacking to support the benefits of treating intermittent elevations in blood glucose concentrations prior to a diagnosis of diabetes. For now, CGM should be considered a useful tool for insulin dosage adjustment and to alert individuals to hypoglycemia, however, additional studies are needed before CGM criteria can be used for screening or diagnosis of CFRD or for identifying individuals at higher risk of pulmonary function and weight decline.

9.6 | Situations associated with an increased risk for new onset CFRD

Gestational diabetes can develop earlier in pregnancy in PwCF compared to those at risk for T2DM with prevalence rates ranging from 11% to 36%.[19,149,150] OGTT screening for preexisting diabetes should be done before or immediately after the onset of pregnancy, and screening for gestational diabetes is recommended at the end of both the first and second trimesters.[5]

Additional high-risk situations in which increased glucose monitoring (by SMBG and/or CGM) is recommended include pulmonary exacerbations requiring hospital admissions for intravenous antibiotics, initiation of gastrostomy tube feedings, use of systemic glucocorticoids, and organ transplantation. Recommendations are to monitor fasting and 2-h post-prandial glucose levels for the first 48 h of hospitalization. A diagnosis of CFRD is confirmed when fasting BG ≥126 mg/dl (≥7 mmol/L) or 2-h postprandial BG ≥200 mg/dl (11.1 mmol/L) are detected and persist for at least 48 h, with 2 or more elevated BGL values. PwCF on enteral feeds should be screened with mid- and immediate post-feeding BGLs at the time of initiation of gastrostomy tube feedings and then monthly. CFRD is diagnosed when mid- or post-feeding BGLs are ≥200 mg/dl (11.1 mmol/L) on 2 separate days. Given the importance of maintaining glucose values in target range for transplant outcomes, CFRD screening with an OGTT is recommended in the 6 months prior to transplant.[5] Post-transplant, immediate close bedside BGL monitoring is important, particularly given the increased risk of diabetes with glucocorticoids and other immunosuppressive agents.[151,152] It is recommended to verify elevations captured by SMBG with plasma glucose measurements.

9.7 | Additional scenarios

Pancreatic sufficient CF

Individuals with PS are at lower risk for development of CFRD than those with PI.[153] The presence of exocrine defects have been shown to increase risk for insulin secretory defects[8,37] and therefore

TABLE 3 Dietary recommendations for CFRD[a]

Calories	Standard requirements are 120%–150% of normal caloric intake for age and gender to prevent underweight[a]
Fat	40% of total energy
Total carbohydrate	45%–50% total energy
Protein	200% of reference intake for a non-CF individual
Salt	Increased requirement: unrestricted intake

Note: See ISPAD 2022 Consensus Guidelines Chapter 10 on Nutritional Management in Children and Adolescents with Diabetes.
Abbreviations: CF, cystic fibrosis; CFRD, cystic fibrosis related diabetes; HEMT, highly effective CFTR modulator therapy.
[a]This recommendation may change in individuals on HEMT given increasing overweight in that population.

CFRD. Given this low risk, particularly with a normal 2-h glucose, it would be reasonable for PS individuals with normal glucose tolerance to reduce frequency of OGTT screening to every 3–5 years.

Evaluation for Type 1 Diabetes

Individuals with CF can also develop T1D with a similar risk as seen in the general population.[154] Therefore, screening for T1D with islet autoantibodies is recommended in scenarios where individuals may present with risk factors for T1D, including: new onset diabetes <10 years of age, co-existence of autoimmune diseases or family history of autoimmunity in first degree relatives, higher insulin needs at onset,[155] development of DKA, or presence of ketones.

Future of CFRD screening and impact of CFTR modulators

The effects of CFTR modulator therapy on the incidence and prevalence of CFRD remain uncertain. Registry studies from the United Kingdom and United States 5 years after the introduction of ivacaftor have suggested a lower prevalence of CFRD relative to those untreated with CFTR modulators.[51] However, CFTR modulators are also increasing weight and BMI,[102] which may also increase risk for insulin resistance. With the recent introduction of triple-combination-therapy CFTR modulators to the wider CF population, prospective studies are needed to determine the longer-term implications on the epidemiology of CFRD.

10 | TREATMENT OF CFRD

10.1 | Medical nutritional therapy

The dietary recommendations for persons with CFRD are very different from those for persons with T1D or T2D (Table 3), both because their needs are very different, and because they are at low risk for cardiovascular disease.[156] PwCF, including those with CFRD, require a high-calorie, high-salt, and high-fat diet. Caloric restriction is almost never appropriate (although it may be considered in older individuals with milder CF mutations who are overweight, and in the currently uncommon, but emerging, group of PwCF who are obese). For individuals on multiple-daily injections or insulin pump therapy, carbohydrate counting is useful for determining the premeal insulin dose. Sugar-sweetened beverages are generally discouraged. Although some people with CFRD do utilize this,[157] nutritional management alone (without insulin/medical treatment) is not recommended.

10.2 | Insulin therapy

Insulin insufficiency is the primary pathologic feature of CFRD, and therefore insulin replacement is the recommended medical treatment.[5]

Insulin therapy stabilizes lung function and improves nutritional status in persons with CFRD.[22,158] The general principles of insulin therapy are presented in Table 4. When these individuals are in their baseline state of health, insulin requirements tend to be modest because of the persistence of endogenous insulin secretion (average insulin dose of <0.5–0.8 units/kg/d in both adolescents and adults).[114,159] When insulin secretion declines, they may eventually develop fasting hyperglycemia, and are generally treated with basal-bolus therapy with an insulin pump or with a combination of long-acting basal insulin and rapid-acting insulin. In persons with CFRD without fasting hyperglycemia, premeal rapid-acting insulin was demonstrated in the CFRDT trial to reverse chronic weight loss and is now considered standard care.[22] Some young people (especially those that consume modest amounts of carbohydrates multiple times during the day) may be successfully treated with basal insulin therapy alone.

Advanced diabetes technology

Insulin pumps provide continuous subcutaneous infusion of rapid- or short-acting insulin. They can be utilized without CGM or combined with CGM either in an open loop (the individual enters the glucose values into the pump), partial closed loop (a pump algorithm increases and decreases insulin autonomously in some circumstances) or hybrid closed loop (the algorithm nearly fully controls insulin dosage with minimal user input). These devices have revolutionized care for children, youth, and adults with T1D. For further details see the ISPAD 2022 Consensus Guideline Chapter 16 on Diabetes Technologies: Insulin Delivery.

Insulin pump therapy without CGM has been associated with improved glycemic management and lean body mass in small studies, mostly secondary to better coverage of meals and snacks in people with CFRD.[160] A small study of teens and adults with CFRD found that transition from open loop with CGM to partial closed loop was associated with increase percent time in target range without increase in hypoglycemia.[49] In a pilot study investigating a closed loop device in 3 individuals with CFRD there were non-significant improvement in mean glucose (likely due to small size) but significant improvements in treatment satisfaction and decreased treatment burden.[161] However, there is a study in progress to further evaluate the use of closed loop insulin pump therapy (clinicaltrials.gov/ct2/show/NCT03258853). While there is not the degree of evidence for use of these devices in CFRD as there is in T1D, the existing data indicate that there is likely real benefit to utilization of advanced diabetes technology where available.

Lower cost regimens

Combined Neutral protamine Hagedorn (NPH) and regular insulin regimens have been used with success in CFRD. The major disadvantage is that NPH regular regimens are inflexible which is problematic for

TABLE 4 Principles of insulin therapy in CFRD

General principles	• CFRD persons typically require 0.5 to 0.8 units insulin per kg body weight per day when they are in their usual state of health. Much more may be required during stress, illness, times of systemic glucocorticoid use, or puberty. • Because of the catabolic effects of insulin insufficiency, the goal is to give the person as much insulin as can be safely tolerated without hypoglycemia. • Choose the insulin regimen that best fits the individual's lifestyle and meets the needs of their CF management.
Basal insulin	• Generally, the goal is about 0.25 U per kg body weight per 24 h; start at half this and adjust upward based on fasting glucose levels.
Meal coverage	• A common starting dose is 0.5 to 1 U rapid-acting insulin for every 15 g of carbohydrate consumed. Insulin pens or syringes that deliver half units may be needed. • The dose is adjusted by increments of 0.5 U per 15 g carbohydrate to achieve 2-h postprandial BGL goals. • For very young people or those who are unsure of what they will eat due to nausea or gastroparesis, the dose may need to be given right after the meal (although before is always better, if possible, in order to reduce hyperglycemia following the meal). • Persons with CFRD without fasting hyperglycemia may be managed with premeal insulin alone, or with basal alone, or both (depending on individual factors, including eating habits)
Correction dose (sensitivity)	• Premeal correction is usually started at 0.5 to 1 U rapid-acting insulin for every 2.8 mmol/L (50 mg/dl) above 8.3 mmol/L (150 mg/dl) and adjusted as needed.
Coverage of overnight drip feeding	• Overnight enteral (drip) feeds: 8-h feeds can be treated with a combination of a single dose of regular/soluble insulin (or rapid-acting/analog insulin) plus the intermediate insulin Neutral Protamine Hagedorn (NPH) or Detemir. The regular insulin covers the first half and the NPH the second half of the feeding; 12 h feeds can be covered with insulin detemir. • Starting dose: calculate the total grams carbohydrate in the feeding, determine a total insulin dose based on the insulin to carbohydrate ratio (typically 0.5–1 units per 15 g) and deliver half of this as regular and half as NPH insulin for an 8 h feed or 100% of the dose as detemir for a 12 h feed. • BGLs 4 h into the feeding are used to adjust the regular insulin dose and those at the end of the feeding to adjust the NPH insulin dose. If using detemir, BGL at the end of the feed is used to adjust insulin dosing. Occasionally a little rapid-acting insulin is also needed at the beginning for correction. • Think of this as a "long meal." It does not replace basal insulin, and individuals should only take this insulin when they have the overnight feeding.
Limited care in a resource-poor setting	• When analog insulin is not available, NPH (isophane) insulin and regular/soluble insulin can be used to treat CFRD, but care needs to be taken to avoid late postprandial hypoglycemia. One possible regimen is NPH insulin at bedtime, and regular insulin with breakfast, lunch, and supper, in an individual who is eating three meals and three snacks a day. • When using and NPH/regular insulin for MDI 2/3 of the total daily dose (TDD) is given in the morning, with 2/3 of that being NPH and 1/3 regular insulin. The other 1/3 of the TDD is administered in the evening, half as NPH and half as regular. TDD is calculated as listed in general principles above. NPH lasts for 8 h and has a marked peak at 4 h. Therefore, an individual who is treated with NPH must eat lunch and must eat an appropriate bedtime snack, or they are at significant risk for severe hypoglycemia. • There is often limited availability of BG monitoring test strips in resource-poor settings. The goal is to test as often as possible, varying the time from fasting to 2 h postprandial readings, to try to get a representative sample of how well the insulin doses are working.

Abbreviations: CF, cystic fibrosis; CFRD cystic fibrosis related diabetes; NPH, neutral protamine hagedorn insulin.

PwCF who commonly have variable appetites. There has been one small study done in PwCFRD comparing a single dose of NPH to a single dose of glargine insulin in a crossover study in 19 subjects which found greater weight gain and reduction in fasting BG levels with glargine.[162] It is important to maintain adequate nutrition support even when unable to access diabetes specific treatments, and diet should not be restricted in an attempt to treat hyperglycemia. CF-specific nutritional guidelines should be followed as much as possible, although it is reasonable to limit high simple sugar foods with low nutritional value.

10.3 | Non-insulin treatments

Guidelines have not yet recommended oral diabetes agents for the treatment of CFRD. This is not only due to the importance of insulin in CFRD but also inadequate data to recommend the use of other diabetes therapeutics,[163] and concerns regarding side effects. New data may support use of non-insulin medications in well-defined circumstances.[164,165] However, there are only a limited number of studies in the area to guide clinical practice.

The CFRDT trial[22] randomized adult PwCF with IGT or CFRD without fasting hyperglycemia to multiple daily injections of pre-meal insulin aspart, the oral insulin secretagogue repaglinide, or oral placebo. BMI remained suboptimal in the placebo arm, temporarily increased in the repaglinide arm, and showed sustained increase in the insulin arm. Somewhat conversely, results of a more recent multicenter European study[164] (comparing multiple daily injections of regular insulin and repaglinide in both children and adults with CF) found no difference in HbA1c, BMI, lung function, or adverse events after 2 years.[164] These results should be interpreted with caution.[166] In

both RCTs[111,164] the drop-out rate was high (around 20% at 12 months), the insulin dose was not reported[111] or variable[164] and outcomes of the insulin-treated arms may have been adversely affected by inadequate dosing and suboptimal usage of insulin. A recent Cochrane review concluded that there was not yet conclusive evidence that any agent has a distinct advantage over another therapy in CFRD at present.[165]

However, there are plausible theoretical concerns with non-insulin therapies. It is possible that insulin secretagogues could accelerate the loss of ß-cells if they are already under stress.[167] Agents that reduce insulin resistance are unlikely to be effective in CFRD, because insulin resistance is not the primary etiology of CFRD, although this could potentially change if obesity rates continue to increase with HEMT therapy. Furthermore, currently available insulin sensitizers might be particularly unacceptable in the CF population, due to gastrointestinal side effects (metformin) and osteoporosis (thiazolidinediones), for which PwCF are already at increased risk. There are ongoing studies (NCT01851694) of incretin mimetic agents such as the glucagon-like peptide-1 (GLP-1) agonists or the dipeptidyl peptidase-4 (dpp-4) inhibitors, and small studies show GLP-1 agonists increased insulin secretion in PwCF with glucose intolerance.[168] However, an RCT on the effect of Sitagliptin (a DPP-IV inhibitor) on islet function in pancreatic insufficient PwCF with abnormal glucose tolerance found no improvement in meal-related glucose excursion or insulin response.[169]

10.4 | Treatment of PwCF with abnormal glucose tolerance

Small, uncontrolled studies suggest that individuals with IGT might benefit from insulin therapy.[158,170–172] However, there are no definitive data on the benefits of insulin therapy for PwCF without a diagnosis of diabetes. This has been identified as a high-priority research question,[5] and two large studies in the United States and Australia ("CF-IDEA Trial" clinicaltrials.gov: NCT01100892 and "The Impact of Insulin Therapy on Protein Turnover in Pre-Diabetic Cystic Fibrosis Patients" clinicaltrials.gov: NCT02496780) are in progress to address this issue (Data S1).

There are also small, uncontrolled studies/case reports reporting the effect of the oral insulin secretagogue tolbutamide in CF children with normal glucose tolerance[173] showing improved glucose homeostasis, linear growth and lean body mass, and the sulfonylurea glipizide,[174] showed improved A1C and reduced urinary glucose but no change in BMI.

11 | QUALITY OF LIFE AND PERSPECTIVE OF PEOPLE WITH CF

A diagnosis of CFRD complicates the medical management of an already complex condition by increasing treatment demands, and for individuals with markedly improved lung function due to HEMT may become their primary chronic illness to manage.

The literature reports inconsistent effects of CFRD on HRQoL. A study by Tierney et al (2008) found no difference in HRQoL due to hypoglycemia in CFRD compared to T1D despite similar rates of hypoglycemia.[175] Similarly Havermans et al.[176] found no association between CFRD and treatment burden and Dill et al. found CFRD not to be a significant predictor of HRQoL.[177] Conversely, Kwong et al. identified a significant negative association between different glycemic patterns and treatment burden, with worsening glycemia being associated with increased treatment burden.[178] Additionally, Abbott et al.[179] followed 234 participants aged 14–48 years over a 12-year period and found that a CFRD diagnosis was important for more than half of the HRQoL domains. Additional large-scale longitudinal studies are needed to further assess the added effect of a second chronic disease on mental health in these individuals and the burden of management and quality of life. Nonetheless, providers should remain cognizant of potential negative effects of the diagnosis on the overall well-being of individuals with CFRD.

AUTHOR CONTRIBUTIONS

All authors reviewed and summarized literature regarding CFRD and drafted one or more sections of the manuscript. All authors reviewed and edited the manuscript drafts. KLO coordinated revisions of the manuscript based on input form the co-authors and reviewers.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this article.

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How to cite this article: Ode KL, Ballman M, Battezzati A, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Management of cystic fibrosis-related diabetes in children and adolescents. *Pediatr Diabetes*. 2022;23(8):1212-1228. doi:10.1111/pedi.13453