CYSTIC FIBROSIS

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- November 2023

To the CHI Original Cystic Fibrosis Clinical Guidance- Issued May 2020

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Abbreviations

ABPA	Allergic Bronchopulmonary Aspergillosis
ACFLD	Advanced Cystic Fibrosis Lung Disease
BGL	Blood Glucose Level
CF	Cystic Fibrosis
CFD/CFRD	Cystic Fibrosis-Related Diabetes
CFTR	Cystic Fibrosis Transmembrane conductance Regulator
CGM	Continuous Glucose Monitoring
CHI	Council of Health Insurance
CKD	Chronic Kidney Disease
ELX	Elexacaftor
ICU	Intensive Care Unit
IDF	Insurance Drug Formulary
IgE	Immunoglobulin E
IRT	Immunoreactivity Trypsinogen Test
IVA	Ivacaftor
LUM	Lumacaftor
NBS	Newborn Screening
NIV	Noninvasive Ventilation
OGTT	Oral Glucose Tolerance Test
PERT	Pancreatic Enzyme Replacement Therapy
RF	Residual Function
SFDA	Saudi Food and Drug Authority
SMBG	Self-Monitoring of Blood Glucose
TEZ	Tezacaftor

Executive Summary

Cystic fibrosis (CF) is a disorder characterized by the malfunction of exocrine glands, affecting various organ systems. However, it primarily leads to persistent respiratory infections, pancreatic enzyme deficiencies, and related complications in individuals who do not receive treatment. CF arises from mutations in the cystic fibrosis gene, responsible for encoding a protein known as the transmembrane conductance regulator (CFTR). CFTR acts as a chloride channel under the regulation of cyclic adenosine monophosphate (cAMP). Mutations in the CFTR gene lead to disruptions in cAMP-controlled chloride transport across epithelial cells lining mucosal surfaces.

Cystic fibrosis stands as the most prevalent and life-threatening inherited condition among the white population. The global occurrence ranges from 1 case per 377 live births in specific regions of England to 1 case per 90,000 live births in the Asian population of Hawaii[1]. A Systematic Review was conducted in 2020 to study the epidemiology of cystic fibrosis in Arab countries. Five of the reviewed articles were from Saudi Arabia. Based on extrapolations made from the reported cases to the population, it was estimated that the incidence of this condition in Saudi Arabian children is approximately 1 in 4,243[2].

When CF was first described in 1938, it was a diagnosis made postmortem on infants who were less than 18 months of age. In the early years following CFTR modulator approval, predicted median survival age for a child born with CF was 40 years. Even before drugs directed at CFTR were available, the quality of life had steadily improved. Oral anti-pseudomonas antibiotics allowed patients to stay out of the hospital more, as did regular immunization against respiratory pathogens. Currently, based on data from 2019, the Cystic Fibrosis Foundation Registry Report from the United States calculated the predicted median survival age of a child born that year with cystic fibrosis to be 48.4 years. Summarized data from the registries of the United Kingdom, Canada, Belgium, Europe, Australia, France, and Ireland show a range of median survival age from 44 to 53 years[3].

The identification of CF relies on recognizable respiratory and gastrointestinal symptoms, family medical history, as well as positive results from sweat tests. The typical age for diagnosing cystic fibrosis is between 6 to 8 months, with most patients receiving their diagnosis in their first year of life. Nevertheless, the age at which diagnosis occurs can differ significantly, as can the way the disease is presented clinically, the severity of symptoms, and the progression rate in affected organs. Clinical symptoms and their presentation can vary based on the patient's age when symptoms first appear[1].

Newborns might exhibit symptoms like meconium ileus or, on rare occasions, other signs such as anasarca. Individuals under the age of one might show respiratory symptoms such as wheezing, coughing, and recurrent respiratory infections,

including pneumonia. In early infancy, gastrointestinal symptoms can manifest as steatorrhea, failure to thrive, or a combination of both. Patients diagnosed during later childhood or in adulthood are more likely to have normal pancreatic function and typically experience chronic productive cough as primary symptoms[1].

Medications used to treat patients with cystic fibrosis may include pancreatic enzyme supplements, multivitamins (particularly fat-soluble vitamins), mucolytics, antibiotics (including inhaled, oral, or parenteral), bronchodilators, anti-inflammatory agents, and CFTR potentiators (e.g., ivacaftor) and correctors (e.g., elexacaftor, lumacaftor, tezacaftor)[1].

Allergic bronchopulmonary aspergillosis (ABPA) is a respiratory condition frequently observed in individuals with asthma or CF. It is characterized by respiratory symptoms due to a hypersensitivity reaction to the allergens produced by the fungus Aspergillus fumigatus[4]. The treatment for this condition will be discussed briefly in this report.

CHI issued Cystic Fibrosis clinical guidance after thorough review of renowned international and national clinical guidelines in May 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Cystic Fibrosis clinical guidance and seeks to offer guidance for the effective management of Cystic Fibrosis. It provides an **update on the Cystic Fibrosis Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being the **addition** of **new guidelines** such as **Cystic Fibrosis Foundation consensus guidelines** for the care of individuals with advanced cystic fibrosis lung disease **(2020)**, **Canadian Clinical Consensus Guideline** for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis **(2022), The UK Cystic Fibrosis Trust Diabetes Working Group:** Management of cystic fibrosis diabetes Consensus Second edition **(November 2022**), **ISPAD Clinical Practice Consensus Guidelines 2022:** Management of cystic fibrosis-related diabetes in children and adolescents, **The Thoracic Society of Australia and New Zealand:** Standards of Care For Cystic Fibrosis **(Australia 2023)**, **2023 Brazilian guidelines for the pharmacological treatment of the pulmonary symptoms of cystic fibrosis**. Official document of the Sociedade Brasileira de Pneumologia e Tisiologia (SBPT, Brazilian Thoracic Association), and Practice Guidelines for the Diagnosis and Management of Aspergillosis: **2016 Update by the Infectious Diseases Society of America**.

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to add **Ursodeoxycholic Acid** in the form of film-coated tablets (500 mg) (newly registered in the SFDA) which was previously registered in the form of capsule (250 mg). Furthermore, there was some changes made to the previously listed drugs: **azithromycin, ciprofloxacin, colistimethate sodium, flucloxacillin, ibuprofen, itraconazole, Pancreatin/dimethicone, prednisolone, prednisolone sodium phosphate, tobramycin, ursodeoxycholic acid and voriconazole** (more details regarding the modifications for these drugs can be found in Section 2.2 – Modifications). Finally, there are no drugs that need to be delisted.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in Cystic Fibrosis therapeutic management.

Below is a table summarizing the major changes based on the different cystic fibrosis guidelines used to issue this report:

Table 1. General Recommendations for the Management of Cystic Fibrosis

Management of Cystic Fibrosis		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Physiotherapy intervention encompasses inhalation therapy, airway clearance, musculoskeletal care, exercise, and the management of any concurrent conditions when appropriate.	Not graded	The Thoracic Society of Australia and New Zealand[5]
The CF Foundation highly suggests the chronic use of dornase alfa and inhaled hypertonic saline as a means to enhance lung function, elevate quality of life, and diminish the occurrence of exacerbations.	Certainty of Net Benefit: High for dornase alfa, moderate for hypertonic saline Estimate of Net Benefit: Moderate for both Recommendation: B for both	2013 American Thoracic Society[6]
Mannitol dry powder for inhalation is recommended for children and adolescents who cannot use dornase alfa and	Not graded	NICE Guideline 2017[7]

hypertonic sodium due to ineligibility, intolerance, or inadequate response.		
The CF Foundation recommends against the routine use of inhaled corticosteroids or the chronic use of oral corticosteroids in patients without asthma or allergic bronchopulmonary aspergillosis.	Certainty of Net Benefit: High for both Estimate of Net Benefit: Zero for inhaled corticosteroids, negative for oral corticosteroids Recommendation: D for both	2013 American Thoracic Society[6]
For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine chronic use of leukotriene modifiers to improve lung function and quality of life or reduce exacerbations.	Certainty of Net Benefit: Low Estimate of Net Benefit: N/A Recommendation: I	2013 American Thoracic Society[6]
The CF Foundation suggests the continuous administration of oral ibuprofen, at a peak plasma concentration ranging from 50 to 100 mg/ml, for individuals aged between 6 and 17 years, with an FEV1 exceeding 60% predicted, in order to decelerate the decline in lung function. (Insufficient to recommend for or against the chronic use of oral ibuprofen in patients 18 years or older).	Certainty of Net Benefit: Moderate for <18 years, Low for ≥ 18 years Estimate of Net Benefit: Moderate for <18 years, N/A for ≥ 18 years Recommendation: B for <18 years, I for ≥ 18 years	2013 American Thoracic Society[6]
In cases of repeated exacerbations of allergic bronchopulmonary aspergillosis or a decrease in forced expiratory volume 1 (FEV1) in individuals with cystic fibrosis, exploring the use of oral itraconazole is suggested as a strategy to reduce dependence on corticosteroids. Incorporating	Weak recommendation; low-quality evidence	IDSA Guidelines (2016)

therapeutic drug monitoring (TDM) is recommended, and if reaching desired therapeutic levels becomes challenging, considering alternative mold-active azole therapy is prudent.		
In the event of a new *P. aeruginosa* infection, treatment should involve a 28-day course of tobramycin solution for inhalation (TIS) and up to three months of combined nebulized colistimethate and oral ciprofloxacin.	Not graded	European Cystic Fibrosis Society (ECFS) Guidelines (2018)[8]
Persistent *P. aeruginosa* infection, when initial treatment fails to eliminate the infection, is addressed through extended use of inhaled tobramycin (alternating months indefinitely), aztreonam, or colistimethate.	Not graded	European Cystic Fibrosis Society (ECFS) Guidelines (2018)[8]
Individuals with cystic fibrosis diagnosed with at least one Class III (gating) or Class IV (conduction) mutation are advised to consider the use of ivacaftor.	Conditional recommendation, very low-quality evidence	2023 Brazilian guidelines[9]
The combination of lumacaftor + ivacaftor is not recommended for individuals with cystic fibrosis carrying the F508del mutation.	Conditional recommendation, very low-quality evidence	2023 Brazilian guidelines[9]
Individuals with cystic fibrosis, either homozygous for F508del or possessing a combination of F508del and a residual function mutation, are encouraged to consider the use of tezacaftor+ivacaftor.	Conditional recommendation, very low-quality evidence	2023 Brazilian guidelines[9]
Administering elexacaftor (ELX)/ tezacaftor (TEZ)/ ivacaftor (IVA) leads to significant clinical	Not graded	Canadian Clinical Consensus Guideline (2022)[10]

improvements for individuals with a single copy of the F508del variant, regardless of the variant present on the other allele.		

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Cystic Fibrosis clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI cystic fibrosis report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

None of the guidelines detailed in the previous CHI report have been updated since March 2020.

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Version	**Updated Version**
European Cystic Fibrosis Society Standards of Care: Best Practice Guidelines (**2018**)	N/A*
American Thoracic Society, Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health (**2013**)	N/A*
NICE Guideline: Cystic Fibrosis – Diagnosis and Management (**2017**)	N/A*

*: No updated version available.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Cystic Fibrosis report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease **(2020)**
Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis **(2022)**
The UK Cystic Fibrosis Trust Diabetes Working Group: Management of cystic fibrosis diabetes Consensus **Second edition (November 2022)**
ISPAD Clinical Practice Consensus Guidelines **2022**: Management of cystic fibrosis-related diabetes in children and adolescents
The Thoracic Society of Australia and New Zealand: Standards of Care for Cystic Fibrosis **(2023)**
Brazilian Thoracic Association Guidelines for the Pharmacological Treatment of the Pulmonary Symptoms of Cystic Fibrosis (**2023**)
Practice Guidelines for the Diagnosis and Management of Aspergillosis: **2016 Update by the Infectious Diseases Society of America**

1.2.1 Cystic Fibrosis Foundation Consensus Guidelines for the Care of Individuals with Advanced Cystic Fibrosis Lung Disease (2020)

The CF Foundation assembled a multidisciplinary expert panel consisting of three workgroups: pulmonary management; management of comorbid conditions; symptom management and psychosocial issues. Topics were excluded if the management considerations did not differ in ACFLD from in the overall CF population or if already addressed in other published guidelines. Recommendations were based on a systematic literature review combined with expert opinion when appropriate[11].

Although there have been advancements in enhancing the quality of life and extending the lifespan of individuals with cystic fibrosis (CF), advanced cystic fibrosis lung disease (ACFLD) continues to be prevalent and remains the leading cause of mortality.

The definition of ACFLD and the additional clinical manifestations associated with worse prognosis and/or disease progression in cystic fibrosis are outlined in table 4:

Table 4. Definition of Advanced Cystic Fibrosis Lung Disease

Definition of advanced cystic fibrosis lung disease (ACFLD)
1. Forced expiratory volume in one second < 40% predicted when stable OR 2. Referred for lung transplantation evaluation OR 3. One or more of the following characteristics: A. Previous intensive care unit admission for respiratory failure B. Hypercarbia ($PaCO_2$ > 50 mmHg on arterial blood gas OR $PvCO_2$ > 56 mmHg on venous blood gas) C. Daytime oxygen requirement at rest (excluding nocturnal use only) D. Pulmonary hypertension (pulmonary artery systolic pressure > 50 mmHg on echocardiogram or evidence of right ventricular dysfunction in the absence of a tricuspid regurgitant jet) E. Severe functional impairment from respiratory disease (New York Heart Association Class IV) F. Six-minute walk test distance < 400 m

The additional clinical manifestations associated with worse prognosis and/or disease progression in cystic fibrosis are outlined in table 5:

Table 5. Additional Clinical Manifestations Associated with Worse Prognosis and/or Disease Progression in Cystic Fibrosis

Additional clinical manifestations associated with worse prognosis and/or disease progression in cystic fibrosis
✓ Frequent pulmonary exacerbations ✓ Rapid rate of decline of forced expiratory volume in one second ✓ Supplemental oxygen requirement with exercise or sleep ✓ Worsening malnutrition despite supplementation ✓ Infection with difficult to manage organisms ✓ Cystic fibrosis-related diabetes ✓ Pneumothorax ✓ Massive hemoptysis (>240 mL) requiring intensive care unit admission or bronchial artery embolization

Care plan in ACFLD

- When individuals with cystic fibrosis (CF) satisfy the criteria for advanced CF liver disease (ACFLD), the CF Foundation suggests regular discussions about advance care planning (ACP) with them and their caregivers. These conversations should encompass topics like prognosis, care goals, recording advance directives, and making decisions related to lung transplantation.
- Palliative care issues are frequently undervalued in cases of lung diseases. Introducing palliative care at an earlier stage of pulmonary disease is linked to increased frequency of advance care planning discussions, decreased healthcare resource utilization, and better symptom management, all without diminishing overall survival.

Recommended screening in individuals with ACFLD

- Screening for indicators of seriousness in ACFLD can pinpoint individuals with an elevated likelihood of experiencing unfavorable consequences, aid in ascertaining when to consider referring them for a lung transplant, and potentially guide the application of particular treatments.
- As per the CF Foundation's guidelines, individuals with ACFLD should undergo assessments for reduced oxygen levels during physical activity and sleep, elevated carbon dioxide levels, and pulmonary hypertension.

Oxygen supplementation and non-invasive ventilation

- The CF Foundation suggests the use of extra oxygen for individuals suffering from ACFLD if they experience a drop in their oxygen levels during physical activity or while sleeping.
- Following the guidelines of the U.S. Center for Medicare and Medicaid Services and most third-party insurance providers, supplementary oxygen should be recommended for those whose oxygen saturation falls to 88% or below during walking or remains below 88% for at least five minutes while asleep.
- The CF Foundation advises contemplating the use of noninvasive ventilation (NIV) during nighttime for individuals with ACFLD who have persistent high levels of carbon dioxide in their blood.
- Nocturnal NIV should be considered in individuals with symptoms consistent with hypercarbia (including dyspnea, fatigue, morning headaches) AND:
    - ✓ $PaCO_2 \geq 55$ mmHg

      OR

- ✓ PaCO2 50–54 mmHg AND nocturnal desaturation

  OR

- ✓ PaCO2 50–54 mmHg AND ≥ two hospitalizations in the preceding year for hypercarbic respiratory failure.

- The CF Foundation suggests that individuals with ACFLD and acute respiratory failure should be evaluated for a trial of high-flow nasal cannula oxygen and/or noninvasive ventilation (NIV).

Pulmonary vasodilator therapy

- The CF Foundation determined that there is not enough evidence to provide a recommendation regarding the utilization of pulmonary vasodilator treatment in individuals with ACFLD and pulmonary hypertension.
- Although Sildenafil seems to be safe in CF and enhances vascular endothelial function without negatively impacting breathing, there is a lack of information on its actual clinical effectiveness. Additional research is required to assess the physiological and clinical impacts of pulmonary vasodilators in ACFLD.

Lung transplantation

- There has been an enhancement in the results of lung transplants, and numerous group studies have shown that individuals with ACFLD experience a better quality of life and increased survival after undergoing a lung transplant.
- The CF Foundation suggests that lung transplantation be considered as a viable treatment choice for individuals with ACFLD, as long as it aligns with their care objectives.

Intensive care unit (ICU) admission

- The CF Foundation advises that individuals with ACFLD and experiencing acute respiratory failure should be evaluated for intensive care unit (ICU) management, irrespective of their transplant status, as long as it aligns with their care objectives.
- Thoughtful conversations between patients, families, and healthcare teams are crucial when contemplating ICU care, especially in cases where lung transplantation is not a viable option.

Invasive mechanical ventilation

- For individuals facing acute respiratory failure in the context of ACFLD and requiring invasive mechanical ventilation, the CF Foundation suggests contemplating an early tracheostomy if the expected duration of mechanical ventilation exceeds 5–7 days and aligns with the individual's care goals.
- The CF Foundation recommends that individuals with ACFLD experiencing refractory respiratory failure, necessitating invasive mechanical ventilation, be considered for an early shift to extracorporeal life support (ECLS) if it aligns with their care objectives.

Antibiotics

- The regular practice for individuals with CF and persistent airway infections involves intermittent use of inhaled antibiotics on a 28-day on/off schedule.
- However, for those with ACFLD, the CF Foundation suggests trying a continuous alternating regimen of inhaled antibiotics based on the specific bacterial pathogens identified in respiratory cultures.
- It is worth noting that certain centers contemplate prolonged or even continuous, intravenous antibiotics for specific individuals with ACFLD who are nearing lung transplantation. However, the risks and benefits of this approach need more thorough investigation.

Microbiological screening

- The CF Foundation suggests that individuals with CF and advancing advanced lung disease should undergo screening for fungal pathogens, in addition to the standard microbiological screening.
- The CF Foundation's guidelines propose regular microbiologic surveillance for bacteria (quarterly) and mycobacteria (yearly), along with annual laboratory evaluations for allergic bronchopulmonary aspergillosis (ABPA).
- Although the role of fungal pathogens other than Aspergillus fumigatus in ABPA is not well understood, organisms like Trichosporon, Scedosporium, and Lomentspora are linked to severe CF exacerbations and potentially unfavorable transplant outcomes.
- For individuals with progressive ACFLD experiencing ongoing deterioration despite optimized standard therapies, an annual sputum culture specifically for fungi is recommended.

Pulmonary rehabilitation

- The CF Foundation suggests that individuals with ACFLD engage in a pulmonary rehabilitation program.
- While there is limited data on pulmonary rehabilitation programs tailored specifically for CF, participating in such programs may prove beneficial, particularly as preparation for lung transplantation, and is mandated by certain transplant programs.

Systemic corticosteroids

- The earlier general CF guidelines advise against the regular and prolonged use of oral corticosteroids for individuals with CF who do not have asthma or allergic bronchopulmonary aspergillosis (ABPA).
- Regarding the use of systemic corticosteroids in individuals with ACFLD, the CF Foundation found insufficient evidence to provide a specific recommendation. An additional consideration highlighted in ECFS guidelines is that, due to concerns about impaired wound healing, many transplant programs stipulate that chronic corticosteroid doses before transplantation should be restricted to less than 15–20 mg per day (equivalent to prednisolone).

Screening for gastroesophageal reflux

- The CF Foundation did not find enough evidence to suggest routine screening for gastroesophageal reflux in individuals with ACFLD.

Enteral tube feeds

- Malnutrition is prevalent in individuals with ACFLD, correlates with poorer outcomes both before and after lung transplantation and may influence the criteria for lung transplant eligibility.
- The CF Foundation suggests employing enteral tube feeds for individuals with ACFLD and malnutrition, following an evaluation of the potential risks and benefits associated with the procedure.
- For individuals experiencing gastroparesis, severe gastroesophageal reflux or difficulties tolerating gastric feed, the consideration of transpyloric feeding (either gastrojejunal or jejunal) is recommended.

Exposure to nephrotoxic and ototoxic agents

- As CF advances, individuals often encounter resistant organisms and undergo more frequent antibiotic treatments, leading to increased cumulative exposure.
- In ACFLD, the significance of ototoxicity and nephrotoxicity related to aminoglycosides and other antibiotics is emphasized, especially since chronic kidney disease (CKD) can influence eligibility and outcomes for lung transplantation.
- It is worth noting that CKD may manifest even if the serum creatinine levels are within the normal range, especially in cases of reduced muscle mass.
- While certain studies may not establish a clear link between antibiotic exposure and renal insufficiency, careful monitoring in individuals with ACFLD is essential, especially when administering intravenous ototoxic or nephrotoxic drugs, considering the antibiotic needs and potential implications for transplantation.

Pregnancy

- In contrast to the general non-CF population, pregnancy in individuals with CF is linked to a heightened risk of perinatal complications. These complications encompass maternal deterioration, preterm labor, low birth weight, Caesarian delivery, respiratory failure, and even death. Most studies indicate elevated risks, particularly in those with ACFLD.
- The CF Foundation suggests that women with ACFLD who are considering pregnancy should thoroughly assess the associated risks through consultations with high-risk obstetric specialists and CF healthcare providers.

Patients taking opioids

- Pain and difficulty breathing are prevalent issues in CF and are associated with unfavorable outcomes.
- When it comes to prescribing opioids for patients with specific needs such as moderate to severe acute or chronic pain, dyspnea in ACFLD, or end-of-life symptoms, concerns about respiratory depression, tolerance, addiction, and potential impacts on transplant eligibility may come into play.
- For individuals with ACFLD who require opioids, the CF Foundation recommends adhering to established guidelines from the Center for Disease Control. This includes thorough monitoring for adverse effects and seeking consultation with pain and/or palliative care specialists as needed.

Anxiety

- For individuals with ACFLD experiencing anxiety, the use of benzodiazepines is recommended for refractory symptoms or for palliating symptoms at the end of life. Consultation with palliative care and a psychiatrist is recommended.

Psychosocial support

- When individuals with CF fulfill the criteria for advanced lung disease and experience alterations in clinical or social circumstances, the CF Foundation suggests organizing a formal care conference. This conference should include caregiver(s) and chosen team members to collaboratively formulate a plan for ongoing psychosocial support.

Transition plan for pediatrics

- For pediatric patients with ACFLD approaching the transition to an adult CF care program, the CF Foundation suggests establishing a formal transition plan. This plan should offer flexibility in terms of timing and coordination for a smooth transfer.

1.2.2 Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis (2022)

This consensus guideline on CFTR modulator therapies was published in 2022 by a working group appointed by Cystic Fibrosis Canada's Healthcare Advisory Council. The main recommendations are summarized below[10]:

General overview

- Since 2012, CFTR modulators have received approval to address the fundamental defect in CF. While not a cure, their goal is to reinstate the functionality of the CFTR protein on the cell surface.
- These modulators are designed to target and correct specific variants of CFTR, exemplifying a personalized approach in precision medicine.
- They are advised as a supplement to current management practices, which traditionally concentrated on addressing the repercussions of the defect. This is because end-organ damage has already taken place, making these downstream treatments likely to remain essential.
- In the past 15 years, substantial research and clinical trials have been conducted to formulate and integrate CFTR modulators into clinical practice.

- The initial commercially available modulator was ivacaftor (IVA; Kalydeco™), exhibiting optimal effectiveness in patients with "gating" variants. Within this subgroup, it proves highly efficacious, restoring CFTR function and yielding clinical advantages such as increased lung function, reduced hospitalizations, improved nutritional status, and real-world evidence indicating enhanced survival rates and a reduced need for lung transplants. In 2021, it gained funding at both the third-party (i.e., private insurance) and provincial levels.
- For patients with two copies of the most prevalent CF variant, F508del (, lumacaftor/ivacaftor (LUM/IVA) and tezacaftor/ivacaftor (TEZ/IVA) have been developed. Studies support the efficacy of LUM/IVA and TEZ/IVA, though not to the extent achieved by IVA in patients with gating variants.
- The introduction of a fourth CFTR modulator introduces a triple combination therapy named elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA). This combination utilizes two correctors, TEZ and ELX, leading to a more effective correction of CFTR function, especially in the F508del variant. Administering ELX/TEZ/IVA results in notable clinical enhancements for individuals with only one copy of the F508del variant, irrespective of the variant present on the other allele. When ELX/TEZ/IVA is integrated into the standard care or substituted for TEZ/IVA in patients with two copies of F508del, substantial improvements in lung function and sweat chloride levels have been observed.

Examples

1. **Ivacaftor (IVA)**
    - IVA is effective in patients with a gating variant (Class III) or conductance variant (R117H 5T or 7T).
    - It is a CFTR potentiator, and its action is to increase the amount of time that the CFTR channel is open, thus improving chloride transport.
    - **Indication:** CF patients with at least one gating variant or R117H
    - **Age:** 4 months or older
2. **Lumacaftor/ivacaftor (LUM/IVA)**
    - LUM is a corrector of the F508del variant, modifying the conformational deformity and allowing the CFTR protein channel to move to its correct position at the cell surface (trafficking).
    - **Indication:** F508del/F508del
    - **Age:** 2 years or older

3. **Tezacaftor/ivacaftor (TEZ/IVA)**
    - Similar to LUM, TEZ is a corrector designed to facilitate proper folding of the defective CFTR protein so it may be transported to the cell surface. It works in combination with IVA, a potentiator of the CFTR protein. TEZ/IVA has comparable efficacy to LUM/IVA, but with fewer drug interactions and fewer reported acute adverse effects.
    - TEZ/IVA has been trialed in patients homozygous for the F508del variant or heterozygous for the F508del variant in combination with other CFTR variants having some residual function (RF).
    - **Indication:** F508del/F508del or F508del in combination with CFTR variants having some RF
    - **Age:** 12 years or older
4. **Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)**
    - This triple therapy builds on the combination of TEZ/IVA by the addition of the next generation corrector, ELX. This compound, when used with TEZ/IVA, substantially increases the amount of CFTR protein and CFTR activity at the cell surface. Clinical trials have shown important benefits in patients with at least one F508del variant.
    - **Indication:** F508del in combination with any other CFTR variant
    - **Age:** 6 years or older

Table 6. Summary of Health Canada-Approved CFTR Modulators and CF Canada Healthcare Advisory Council's Recommended Trial Duration

CFTR Modulator	Indication	Approved Age	Minimum Trial Duration
IVA	Gating (Class III) variant	≥4 months	1 year
	R117H	≥4 months	
LUM/IVA	F508del / F508del	≥2 years	1 year
TEZ/IVA	F508del / F508del	≥12 years	1 year
	F508del / RF variant		
ELX/TEZ/IVA	F508del / Any	≥6 years	1 year

IVA: Ivacaftor, TEZ: Tezacaftor, LUM: Lumacaftor, ELX: Elexacaftor, RF: Residual function

Indications for starting CFTR modulator therapy

The diagnosis of CF requires:

- Clinical symptoms/features or a positive newborn screen **and** either Two disease-causing CFTR variants

  or

  Sweat chloride concentration >60 mmol/L (on 2 occasions if only one CFTR variant known).

To qualify for treatment with CFTR modulator therapy, the following criteria must be met:

1. **Mutation:** F508del/Any CFTR variant or Gating variant/Any CFTR variant or R117H/Any CFTR variant

   The genotype recommendations are derived from Phase 3 clinical trials demonstrating significant clinical advancements with CFTR modulators, and they align with Health Canada's approval.

2. **Age:** Commence CFTR modulators as early as feasibly possible, aiming to slow down disease progression and enhance clinical well-being. Evidence indicates that early initiation can potentially reverse the progression of the disease, including the restoration of pancreatic function.

   There is no supportive data for delaying the introduction of CFTR modulators until substantial clinical symptoms manifest or a decline in lung function is observed.

3. **Lung function:** There should be no set upper limit for lung function, as indicated by FEV1, when determining eligibility, as individuals with mild lung disease in CF can still achieve substantial improvements in respiratory health.

4. **Pancreatic status:** Pancreatic sufficient and insufficient

   The eligibility is not impacted by pancreatic status. While most CF patients have pancreatic insufficiency, there are exceptions. Introducing CFTR modulator therapy early on has the potential to either restore pancreatic function or delay the onset of pancreatic insufficiency. In cases where patients have pancreatic sufficiency, CFTR modulators are likely to help preserve pancreatic function.

Pre-modulator assessment

- If a patient has not undergone a confirmatory sweat test and/or CF genotyping, it is essential to carry out these assessments. The necessary baseline clinical evaluations are outlined in tables 7 and 8.

Table 7. Schedule for Baseline Evaluation and Monitoring of Patients Aged 6 years and Older Who Commence on CFTR Modulators. Adapted from Cystic Fibrosis Canada 2022 Guideline.

Routine Clinic Visits (Clinical Care monitoring): ≥ 6 years of age	**Baseline**	**1 Month visit**	**3 Month visit**	**6 Month visit**	**9 Month visit**	**1 Year visit**
Clinical assessment and review of CFTR genotype, initial sweat test, and past medical history (including decline in FEV1 and frequency of pulmonary exacerbations over past 2 years)	X					
Height, weight, and blood pressure	X	X	X	X	X	X
Blood for CBC, ALT, AST, ALP, GGT, bilirubin, CK, INR	X	X	X	X	X	X
Spirometry/LCI[a,b]	X	X	X	X	X	X
Sputum microbiology[c]	X	X	X	X	X	X
Ophthalmology exam[d]	X			X		X
PHQ-9 and GAD-7 questionnaires[e]	X			X		X
Safety review[f]	X	X	X	X	X	X
Review of prescribed therapy[g]	X		X	X	X	X
Sweat chloride test	X		X			X
CFQ-R: Respiratory Domain	X	X	X	X	X	X
CT imaging of chest	X					X
Fecal elastase	X		X			X
	Standard for CF Clinic visit &/or recommended by product monograph					
	Clinical data needed to support CFTR modulator response					
	May have clinical relevance to CFTR modulator response					

[a] LCI to be measured where available at baseline, 3 months, and 12 months.

[b] If ppFEV1 < 40%, include CPET or 6-minute exercise test at 6 and 12 months.

[c] Samples obtained by sputum or cough swab.

[d] For patients 6 to 18 years of age and then annually until 18 years, to exclude cataracts. May be performed by optometrist.

[e] For patients aged 12 years and older.

[f] Events of special interest: rash, DIOS, pancreatitis, mental health, new organisms isolated in sputum.

[g] Review of all prescribed medication including airway clearance.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transferase; CBC, complete blood count; CFQ-R, Cystic Fibrosis Questionnaire-Revised; CK, creatine kinase; DIOS, distal intestinal obstruction syndrome; GAD-7, General Anxiety Disorder-7; LCI, lung clearance index; PHQ-9, Patient Health Questionnaire-9

Table 8. Schedule for Baseline Evaluation and Monitoring of Patients Under 6 years of Age Who Commence on CFTR Modulators. Adapted from Cystic Fibrosis Canada 2022 Guideline.

Routine Clinic Visits (Clinical Care monitoring): < 6 years of age	Baseline	1 Month visit	3 Month visit	6 Month visit	9 Month visit	1 Year visit
Clinical assessment and review of CFTR genotype, initial sweat test, past medical history (including frequency of pulmonary X exacerbations over past 2 years)	X					
Height, weight, and blood pressure	X	X	X	X	X	X
Blood for CBC, ALT, AST, ALP, GGT, bilirubin, CK, INR	X	X	X	X	X	X
Spirometry/LCI[a]	X	X	X	X	X	X
Sputum microbiology[b]	X	X	X	X	X	X
Ophthalmology exam[c]	X			X		X
Safety review[d]	X	X	X	X	X	X
Review of prescribed therapy[e]	X		X	X	X	X
Sweat chloride test	X		X			X
CFQ-R: Respiratory Domain	X	X	X	X	X	X

Fecal elastase	X		X			X
	Standard for CF Clinic visit &/or recommended by product monograph					
	Clinical data needed to support CFTR modulator response					
	May have clinical relevance to CFTR modulator response					

a LCI to be measured where available at baseline, 3 months**,** and 12 months.

b Samples obtained by sputum or cough swab.

c Done at baseline, 6 months and on annual basis.

d Events of special interest: Rash, DIOS, pancreatitis, mental health, new organisms isolated in sputum.

e Review of all prescribed medication including airway clearance.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transferase; CBC, complete blood count; CBC, complete blood count; CFQ-R, Cystic Fibrosis Questionnaire-Revised; CK, creatine kinase; DIOS, distal intestinal obstruction syndrome; GAD-7, General Anxiety Disorder-7; LCI, lung clearance index; PHQ-9, Patient Health Questionnaire-9

Response to therapy

- Clinical trials evaluating CFTR modulators have documented enhancements in lung function and weight, along with a decrease in pulmonary exacerbations necessitating antibiotics.
- Since CFTR modulators affect CFTR function systemically, they also influence the sweat glands, as evidenced by the chloride concentration in sweat.
- While this may not hold direct clinical significance at the individual level, except for a decreased risk of dehydration or heat stroke, it serves as a biomarker indicating the impact of CFTR modulators.
- Research trials have indicated that the use of modulators is linked to a reduction in sweat chloride levels.
- Key clinical responses to be monitored include:
    1. Improvement in lung function as measured by FEV1 or Lung Clearance Index (LCI) (where available) obtained at a time of clinical stability
    2. Reduction in the number of pulmonary exacerbations
    3. Stabilization in lung function over time (i.e., attenuation of the usual decline in lung function in CF)
    4. Reduction or stabilization of respiratory symptoms
    5. Improvement in nutritional status

6. Improvement in quality-of-life scores
7. Reduction in sweat chloride

Concurrent treatment

- Currently, all patients starting CFTR modulator treatment should adhere to their existing treatments as prescribed by their CF clinic, which may include pancreatic enzymes, mucolytics, inhaled antibiotics, bronchodilators, and anti-inflammatory agents.
- Regular quarterly monitoring, following CF standards of care, should be maintained.
- Ongoing clinical studies will ascertain whether any adjustments in CF care can be safely implemented once patients are undergoing CFTR modulator therapy.

Treatment response

It is expected that responders will have at:

- ✓ **3 months**
  - **a.** Absolute improvement in ppFEV1 of >5%, measured at time of clinical stability or
  - **b.** A decrease in sweat chloride by 20% or 20mmol/L from baseline or
  - **c.** Improvement in respiratory symptoms (as measured by CF Questionnaire-Revised (CFQ-R): Respiratory Domain) by ≥4 points (i.e., the minimum clinically important difference).
- ✓ **12 months**

No treatment-limiting adverse events or medication safety issues, and one or more of:

- **a.** Reduction in pulmonary exacerbations (IV or oral antibiotic treatment) by 20% or
- **b.** Stabilization of lung function rate of decline above baseline or
- **c.** Improvement in nutritional status with normalization of growth and nutrition or
- **d.** Radiological improvement or stability in chest CT scan.

Monitoring

Side effects

Following the introduction of CFTR modulators, it is essential to emphasize safety outcomes and keep a vigilant watch for potential adverse effects.

Table 9. Frequency of Adverse Events Reported in Clinical Trials for CFTR Modulators

Adverse event	IVA	LUM/IVA	TEZ/IVA	ELX/TEZ/IVA
Increase cough, chest tightness		++		+
Drop in FEV1		++		
Elevated blood pressure		+		+
Elevated transaminases	++	++	+	+
Elevated CK	+	+	+	++
Rash	++	++	+	++
Cataracts	+	+	+	+
Neurological symptoms, depression, or anxiety	+	++	+	
Abdominal pain	++	++		+
Nausea and vomiting	+	++	+	
Distal intestinal obstruction syndrome				

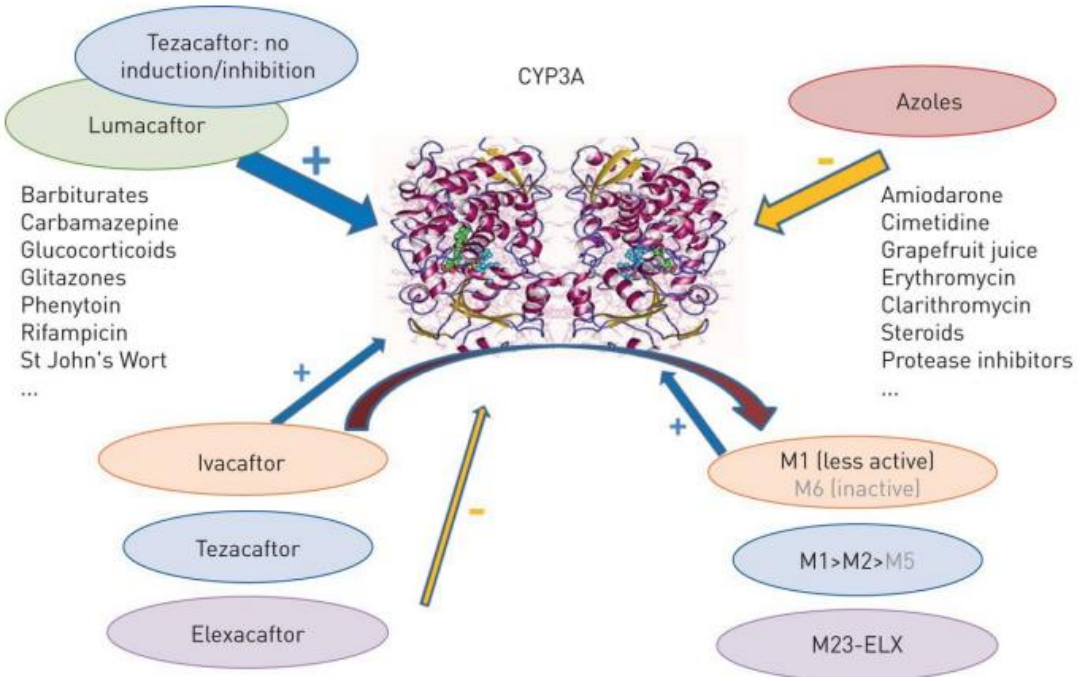
++: Common (>10%)

+: Uncommon

This summary does not capture all reported side effects. Reference should be made to the product monograph for each CFTR modulator.

Drug-drug interactions

- Evaluating potential drug interactions is crucial when initiating or discontinuing medications in individuals undergoing CFTR modulator treatment or switching between different CFTR modulators.
- IVA, TEZ, and ELX are processed by the cytochrome P450 (CYP) enzyme CYP3A. Consequently, potent, and moderate inhibitors (such as azole antifungals) of CYP3A can raise the concentrations of IVA, TEZ, and ELX, whereas inducers (like rifampin) can lower serum levels.
- Recommendations are available for adjusting the dosage of modulators when taken concurrently with moderate or strong CYP3A inhibitors. However, it is advisable to steer clear of simultaneous use with inducers.
- It is noteworthy that not only medications, but also certain foods and herbal products can influence CYP3A activity.
- CFTR modulators, such as IVA and LUM, have been linked to the inhibition or induction of enzymes.
- IVA, along with one of its metabolites, mildly inhibits CYP3A, P-glycoprotein (P-gp), and potentially CYP2C9. Consequently, close monitoring of the international normalized ratio (INR) is advised in individuals on warfarin when initiating or discontinuing an IVA-containing CFTR modulator due to its potential impact on CYP3A and CYP2C9.
- On the other hand, LUM acts as an inducer of CYP3A and UDP-glucuronosyltransferase (UGT) enzymes, potentially accelerating the metabolism of concurrent medications that are substrates of these enzymes (e.g., hormonal contraceptives, azole antifungals, select immunosuppressants, and psychotropic medications). This becomes particularly relevant when transitioning from LUM/IVA to TEZ/IVA or ELX/TEZ/IVA, especially in patients concurrently using medications dependent on CYP3A and/or UGT.
- Upon discontinuation of LUM/IVA and the cessation of enzyme induction, certain medications dependent on these enzymes may require a dose reduction to mitigate the risk of toxicity. Additionally, stopping LUM/IVA may expand the range of suitable therapeutic alternatives, particularly for medications that were previously avoided due to LUM's inductive effects (e.g., hormonal contraceptive options for women).



Blue arrows: induction of the cytochrome; yellow arrow: inhibition of the cytochrome; curved arrow: metabolism of a drug by the cytochrome.

Figure 1. *A Summary of Interactions Between Cystic Fibrosis Transmembrane Regulator Modulators and Other Drugs/Compounds and Cytochrome P450 3A4 (CYP3A). Retrieved from Cystic Fibrosis Canada 2022 Guideline*.

Special considerations for patients receiving IVA, LUM/IVA, or TEZ/IVA

- Research findings indicate that ELX/TEZ/IVA demonstrates superior efficacy compared to TEZ/IVA in individuals with two copies of the F508del mutation.
- Every qualifying patient currently using IVA, LUM/IVA, or TEZ/IVA should be given the chance to shift to the three-drug combination, ELX/TEZ/IVA.

Pregnancy/lactation and CFTR modulators

- CFTR modulators have the potential to enhance fertility in women with CF by improving clinical status and affecting cervical and uterine mucus.
- Therefore, it is crucial for women currently using or planning to start a CFTR modulator to employ reliable contraception to avoid unintended pregnancies.
- Clinical trials of CFTR modulators excluded women not using effective contraception, leading to unknown effects on a developing human fetus.
- Animal studies of the specific drugs IVA, LUM, TEZ, and ELX suggest no impact on organogenesis at typical human doses.
- CFTR modulators traverse the placenta and are present in breast milk.

- It is essential to thoroughly discuss the potential advantages and disadvantages of using CFTR therapy while pregnant and breastfeeding, ideally before conception.
- While real-world experience is limited, case reports/series and an international survey suggest that CFTR modulators are generally well tolerated during pregnancy.
- Discontinuing CFTR modulators has been linked to a substantial decline in clinical status, leading to instances where re-initiation of therapy becomes necessary for pregnant women who had ceased their CFTR modulator during pregnancy.
- Due to the association of CFTR modulators with cataracts in children, it is advisable for infants born to mothers taking CFTR modulators, or those breastfed by them, to undergo ophthalmologic examinations.
- A report from 2021 highlights the potential for newborns with CF born to mothers using CFTR modulators to incorrectly test negative for CF in newborn screens.
- It is recommended to conduct CFTR mutation testing for all infants born to mothers who use a CFTR modulator during their pregnancies.

CF Patients who have received a lung transplantation

- For individuals with CF experiencing end-stage lung disease, a lung transplant is a viable treatment.
- While CFTR modulators are not anticipated to directly enhance lung graft function, they hold the potential to alleviate extrapulmonary manifestations of CF, including chronic rhinosinusitis and gastrointestinal issues.
- It is worth noting that paranasal sinuses could serve as a reservoir for pathogens post-transplantation. Consequently, treating chronic rhinosinusitis with CFTR modulators may help diminish respiratory infectious complications following lung transplantation.
- With the introduction of ELX/TEZ/IVA, there is emerging evidence regarding its use post lung transplant.
- It is anticipated that drug-drug interactions may occur between CFTR modulators and immunosuppressants, particularly calcineurin inhibitors.
- Moreover, the potential for liver injury due to CFTR modulator use could complicate the management of lung transplant recipients who are prescribed antimicrobials and immunosuppressive medications linked to hepatotoxicity.

- The standard recommendations for responding to CFTR modulator therapy initiation may not be applicable to individuals who have undergone a lung transplant. Therefore, it is advised that the initiation of CFTR modulators and subsequent monitoring of a CF patient who has undergone a lung transplant be conducted with the involvement of a CF specialist.

Discontinuation

- In cases where patients experience persistent or recurring clinically significant adverse effects, even after an appropriate dose reduction or cessation, it is advisable to contemplate discontinuing (or reducing the dose of) CFTR modulator therapy, with the option of stopping and re-challenging if deemed appropriate.
- The evaluation of the risk-benefit ratio for discontinuing treatment should be approached individually, taking into account the severity of the adverse event and the potential risks associated with stopping the treatment.
- In instances where patients, as determined by the CF team, do not meet the response criteria for the CFTR modulator or demonstrate non-adherence to it, therapy discontinuation is recommended. This decision should be made when the patient is clinically stable, and any complicating co-morbidities and issues related to non-adherence have been assessed and addressed.

How to start CFTR modulators

- Before starting a CFTR modulator, it is advised that patients (and their caregivers) undergo comprehensive education and counseling regarding the therapy, along with understanding all required follow-up and monitoring procedures.
- The suitable modulator dosage, taking into consideration factors such as the patient's age, liver function, and potential drug interactions, should be verified before initiation. This dosage should also be reassessed if any changes occur in these parameters.
- For patients transitioning from one CFTR modulator to ELX/TEZ/IVA, there is no need for titration or cross-tapering.
- The process involves taking the last evening dose of their current modulator and then initiating ELX/TEZ/IVA the next morning, continuing with ELX/TEZ/IVA thereafter.
- However, when transitioning from LUM/IVA, it may take up to 2 weeks for ELX/TEZ/IVA to exhibit its effects.

1.2.3 The UK Cystic Fibrosis Trust Diabetes Working Group – Consensus on the Management of Cystic Fibrosis Diabetes (Second Edition, 2022)

Since the late 1990s the term cystic fibrosis-related diabetes (CFRD) has been used to describe diabetes in people with CF. Prior to this it was referred to as "diabetes of cystic fibrosis" or "cystic fibrosis diabetes mellitus". The guideline committee proposes that a new name is warranted, as the term "related" does not indicate a direct causal relationship between CF and diabetes and this removes emphasis from the significant impact of diabetes on the lives of people with CF. The term cystic fibrosis diabetes (CFD) to stress the direct causal relationship between CF and diabetes is therefore adopted throughout the guideline. These guidelines summarize the current clinical approach to CF diabetes (CFD). The group recognizes that there is a limited evidence base to support some areas of practice[12]. The GRADE approach was adopted to rate the quality of evidence across outcomes and recommendations.

Table 10. Quality of Evidence Based on the GRADE Approach

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

- Cystic fibrosis-related diabetes (CFD) frequently occurs as a complication of CF, contributing to heightened morbidity, increased mortality rates, and a faster decline in lung function.
- The augmented awareness and improved life expectancy in detecting CFD have led to a rise in its prevalence across all age groups.
- CF diabetes, while a distinct form of diabetes, exhibits clinical characteristics shared with both type 1 and type 2 diabetes.
- Its onset is often gradual, with some individuals remaining asymptomatic at the time of diagnosis.

- Alternatively, others may first experience symptoms such as weight loss and a decline in lung function, with reactive hypoglycemia not uncommon.

Screening for CF diabetes

The oral glucose tolerance test (OGTT) or continuous glucose monitoring (CGM) are suitable methods for routine screening for Cystic Fibrosis-Related Diabetes (CFD). Other methods, such as Hemoglobin A1c (HbA1c) and fasting glucose, as discussed below, are not suitable for screening but may provide information to guide management.

Table 11. Pros and Cons of Different Screening Methods

Screening	Pros	Cons
OGTT	• Standardized protocol • Not influenced by diet or activity • Results linked to historical long-term clinical outcome data	• Eight hours fasting is required • Time-consuming • Fluctuation between normal, impaired and diabetic OGTT with clinical status • Requires serial capillary blood glucose (CBG) or CGM to confirm elevations in glucose levels and support diagnosis
CGM	• Detects subtle glucose abnormalities • Detects postprandial hyperglycemia • Correlates well with glucose measured at OGTT • Does not require fasting Measures glucose levels throughout the whole day during normal activity and food intake	• Measures interstitial fluid and not CBG • Time-consuming; need for return of sensors / readers • Can fluctuate with clinical status High cost of sensors and equipment • Absence of clinically validated cut-off levels for commencing treatment

		• Requires concurrent food diary
Fasting glucose	• Single blood sample	• Fasting hyperglycaemia absent in many adults with CFD
HbA1c	• Single blood sample • Abnormal HbA1c should trigger screening for CFD	• No data about cut-off levels Normal HbA1c is often present at the time of diagnosis of CFD

Assessment after screening test

- Additional investigations may be necessary following a screening test to determine the need for treatment.
- When evaluating screening results, the following factors should be taken into account:
    - Screening outcomes may vary with clinical conditions, such as infections and steroid use.
    - An OGTT conducted with only baseline and 120-minute measurements can confirm diabetes based on standard criteria but might overlook significant hyperglycemia. Intermediate samples at 30, 60, and 90 minutes could be beneficial.
    - An OGTT that meets diabetes criteria should be followed by glucose monitoring (using consecutive Capillary Blood Glucose (CBG) measurements or Continuous Glucose Monitoring (CGM)) to identify hyperglycemia before initiating insulin treatment.
    - CGM or serial CBG levels should be considered if there are concerns about clinical status and:
        i. Glucose at 120 minutes during OGTT aligns with an Impaired Glucose Tolerance (IGT) diagnosis.
        ii. Glucose levels during OGTT at 30, 60, or 90 minutes exceed 11.1mmol/L.
    - CGM should be employed for a sufficient duration, and individuals with CF are advised to maintain their usual dietary intake and activity throughout the test.

- If CGM reveals significantly abnormal glucose levels, consideration should be given to whether food intake, activity, or clinical status could have influenced the result, and a repeat test may be warranted.

Criteria to start treatment in CF diabetes and abnormal glucose levels

- Individualized treatment should consider both clinical and nutritional status.
- Any individual meeting diagnostic criteria for Cystic Fibrosis-Related Diabetes (CFD) following investigation should generally receive treatment, unless there are compelling clinical reasons to refrain.
- Early treatment may be contemplated for individuals with concerns about clinical status (e.g., weight loss, declining lung function, increased infection episodes, poor growth in children) if Continuous Glucose Monitoring (CGM) or consecutive Capillary Blood Glucose (CBG) levels confirm subtle glucose abnormalities. However, this alone is insufficient to warrant a CFD diagnosis.
- Individuals with optimal nutritional status and satisfactory lung function might not require treatment for minor glucose handling irregularities, and dietary interventions could be suitable.
- Glucose levels and screening test results can vary with clinical status. In certain clinical scenarios, repeated testing at intervals may be necessary to confirm the need for treatment.
- Treatment considerations can be influenced by factors such as corticosteroid use, enteral feeding, transplant, pulmonary exacerbations, CFTR modulators, and evolving clinical status.

Treatment strategies for CF diabetes

- The treatment objectives encompass:
    1. Prevention of both long-term microvascular and macrovascular complications. Individuals with CFD face risks of diabetes-related complications, and enhanced control of CFD is likely to mitigate this risk, aligning with trends observed in other types of diabetes. This becomes increasingly crucial as individuals with CF experience extended life expectancy through improved care and the utilization of CFTR modulators.
    2. Mitigation of the impact of hyperglycemia on lung function and overall clinical status. This goal is specific to CFD.
    3. Prevention of symptoms associated with hyperglycemia and acute metabolic complications.

4. Reduction of the risk of hypoglycemia. Individuals with CF share similar risks of hypoglycemia and/or loss of hypoglycemia awareness as those with other forms of diabetes.
5. Optimization of nutritional status.

Treatment agents

- Currently, insulin stands as the primary treatment for CFD, and the potential role of other antidiabetic agents is currently under examination.
- Administering a once-daily, long-acting insulin before breakfast might be a suitable approach for addressing glucose abnormalities that do not exhibit a substantial rise after meals.
- For the prevalent glucose abnormality in CFD, namely postprandial hyperglycemia, pre-meal short-acting insulin is frequently employed.
- In cases of fasting hyperglycemia, individuals are likely to benefit from multiple-dose regimens involving both long-acting and short-acting insulin.
- Individuals commencing insulin therapy should undergo education tailored to support the self-management of their diabetes, encompassing Blood Glucose Monitoring (BGM) and insulin injection techniques.
- Those initiating insulin should receive an individualized treatment plan that considers various aspects of their CF care.
- Treatment for all individuals with CFD should aim at alleviating symptoms of hyperglycemia while maintaining adequate nutrition, fostering growth, and preserving respiratory function.
- All individuals with CFD should strive for optimal diabetes control to diminish the likelihood of long-term complications.
- Adjustments to treatment may be necessary during periods of pulmonary exacerbations, corticosteroid therapy, or enteral tube feeding.

Management of reactive hypoglycemia

- Reactive hypoglycemia is a relatively common occurrence in untreated individuals with CF, often manifesting after the consumption of high-refined carbohydrate sources.
- Glucose levels may drop below 4.0 mmol/L, leading to symptomatic hypoglycemia.
- It remains unclear whether reactive hypoglycemia signifies an elevated risk of developing CFD.

- Individuals experiencing symptomatic hypoglycemia after meals might find benefit in dietary adjustments.
- This could involve reducing the intake of refined carbohydrates and incorporating regular meals with complex carbohydrates.
- In cases where hypoglycemia is frequent or problematic, consideration should be given to insulin treatment, which typically resolves the hypoglycemic episodes.

Capillary blood glucose monitoring

- People with CF and CFD should increase the frequency of monitoring their blood glucose in the following situations:
    - Prior to and at the time of solid organ transplantation.
    - When concerns arise regarding a decline in nutritional status.
    - During pulmonary exacerbations.
    - When initiating or adjusting the dose of corticosteroid treatment.
    - Upon the commencement of enteral tube feeding.
    - Throughout pre-conception planning and pregnancy.
    - Following the initiation of CFTR modulator therapy.
- Every hospital admitting individuals with CFD should have a local policy that addresses glucose monitoring, diabetes management, and insulin self-administration.
    - Blood glucose levels should be assessed upon admission for all individuals with CF.
    - If inpatients with CF are started on corticosteroid treatment, blood glucose monitoring is recommended for 48 hours.

Management of children and adolescents with CF diabetes

Glycemic targets in children are the same as for adults; the following should be considered:

- Practical care plans for school should be formulated and incorporated into the child's healthcare plan.
- Diabetes care plays a crucial role in the transition to adult CF and diabetic services.

Adjustment of treatment during infection or corticosteroid treatment

- Glucose levels may increase during infections, and individuals with Normal Glucose Tolerance (NGT) can exhibit glucose levels within the diabetic range during infectious pulmonary exacerbations.
- If already on insulin treatment, insulin doses should be adjusted.
- For those not on insulin, treatment during the episode should be contemplated if elevated glucose levels cause symptoms or are likely to affect clinical status.
- Corticosteroid treatment enhances insulin resistance, and insulin doses may need adjustment during treatment, with a reassessment once steroid doses are reduced.

Dietary/nutritional treatment

- An experienced specialist CF dietitian should provide personalized guidance on an individual's dietary plan.
- Treatment for CFD should be personalized, considering nutritional and clinical status, dietary intake, and psychosocial factors.
- Dietary modification is integral to CFD management to prevent both nutritional decline and overnutrition. The quality and quantity of fat should be adjusted based on age, nutritional and clinical status.
- Encouraging the appropriate use of Pancreatic Enzyme Replacement Therapy (PERT) and regular dosing reviews are essential. If an individual with CFD has a high protein intake (> 75 g) as part of a meal, insulin dosing adjustments may be necessary due to potential delays in postprandial glucose peak.
- Attention should be paid to the timing and quantity of carbohydrate consumption. Avoidance of sources of high refined carbohydrates, such as sugary drinks and sweets, between meals is recommended.
- Maintaining detailed food diaries can be highly beneficial in assessing the impact of different carbohydrate types on an individual's glycemic control.
- Individuals with CFD should receive tailored education about carbohydrates based on their specific needs.
- Consideration should be given to the effects of snacking between meals, oral nutritional supplements, and enteral tube feeds on blood glucose levels.
- Individuals with CF without CFD who start enteral tube feeding should have their glycemic control evaluated.
- People with CFD receiving enteral tube feeding may require adjustments in their insulin dose or type.

- Before commencing treatment, normal weight individuals should undergo a comprehensive assessment. Overweight and obese individuals should receive healthy eating advice and support for weight loss, if clinically appropriate.

CFTR modulator therapy

- In the clinical setting, fluctuations in blood glucose levels have been noted in individuals with CFD undergoing CFTR modulator therapy.
- Consequently, it is crucial to closely monitor blood glucose levels in individuals with CFD receiving CFTR modulator therapy.

Pregnancy

- For women intending to conceive, an OGTT should be conducted if they haven't undergone a normal CFD screening in the preceding six months. (moderate)
- During pregnancy, an OGTT should be performed at both 12–16 weeks and 24–28 weeks gestation, with venous BGM taken at zero, one, and two hours. (moderate)
- Blood glucose levels, measured by Capillary Blood Glucose (CBG), should be assessed at every hospital visit, particularly during infective exacerbations. (moderate)
- For those diagnosed with gestational diabetes, a follow-up OGTT should occur 6–12 weeks after delivery. (moderate)

For more information regarding the short and long-term complications of diabetes, as well as details on antidiabetic drugs, please refer to the individual reports on Diabetes Type 1 and Type 2.

1.2.4 ISPAD Clinical Practice Consensus Guidelines: Management of Cystic Fibrosis-Related Diabetes in Children and Adolescents (2022)

The International Society for Pediatric and Adolescent Diabetes (ISPAD) published in 2022 its updated recommendations on the management of cystic fibrosis-related diabetes in children and adolescents[13]. Levels of evidence have been assigned to evidence-based recommendations where appropriate (table 12).

Table 12. ISPAD Evidence Grading

Level of Evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis
	Compelling nonexperimental evidence, that is, "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford
	Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporate quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies: • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies
	Supportive evidence from a well-conducted case–control study
C	Supportive evidence from poorly controlled or uncontrolled studies: • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports
	Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

Hypoglycemia

- Low blood sugar is frequent in cystic fibrosis (CF) and can manifest even without cystic fibrosis-related diabetes (CFRD) or insulin treatment. (B)
- Post-oral glucose tolerance test (OGTT) hypoglycemia is a prevalent occurrence. (B)
- It is recommended to monitor for hypoglycemia in people with cystic fibrosis (PwCF) and advise them to consume food at the conclusion of an OGTT. (E)

Diagnosis

- Diagnosis of CFRD is made using American Diabetes Association (ADA) criteria during a period of stable baseline health (E)
    - 2-h Blood glucose level (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
- The onset of cystic fibrosis-related diabetes (CFRD) is determined by the first instance when an individual with CF fulfills the criteria for CFRD, even if there is subsequent improvement in glucose tolerance. (E)
- Diabetes diagnosis may occur during acute illness (with intravenous antibiotics/systemic glucocorticoid therapy) if fasting blood glucose is ≥7 nmol/L (126 mg/dl) or if 2-hour postprandial blood glucose is ≥11.1 mmol/L (200 mg/dl) persistently for more than 48 hours. (E)
- In individuals receiving overnight enteral feedings, diabetes diagnosis can be established if mid or post-feeding blood glucose readings are ≥11.1 mmol/L (200 mg/dl) on two separate days. (E)

Screening

- Hemoglobin A1C (HbA1C) is not advised as a screening test for cystic fibrosis-related diabetes (CFRD) because of its limited sensitivity. (C)
- The recommended method for CFRD screening is the 2-hour 75g (1.75 g/kg) oral glucose tolerance test (OGTT). (B)

- Annual OGTT screenings should commence no later than the age of 10 years. (B)
- Blood glucose levels (BGLs) should be assessed, at a minimum, in the fasting state and at the 2-hour mark during the OGTT. (B)
- Individuals with cystic fibrosis who maintain sufficient pancreatic function exhibit a reduced risk of cystic fibrosis-related diabetes (CFRD) compared to those with pancreatic insufficiency but still face a higher risk than the general population. For those with normal glucose tolerance (NGT), the managing team may consider OGTT screening every 3–5 years if deemed appropriate, and fasting blood glucose levels (BGL) are not recommended for CFRD screening due to their low sensitivity. (B)
- Pregnant women without known CFRD are advised to undergo gestational diabetes screening at both 12 to 16 weeks and 24 to 28 weeks gestation, utilizing a 2-hour 75g OGTT with blood glucose measures at 0, 1, and 2 hours. (E)
- Post-pregnancy screening for CFRD is recommended using a 2-hour 75g fasting OGTT 6 to 12 weeks after the conclusion of pregnancy in women with diabetes first diagnosed during pregnancy.
- Individuals with CF experiencing pulmonary exacerbations necessitating intravenous (IV) antibiotics or glucocorticoids should undergo screening with fasting and 2-hour postprandial blood glucose levels (BGLs) for a duration of 48 hours. (E)
- For patients with CF reliant on enteral feeds, it is recommended to screen by assessing mid and immediate post-feeding BGL levels at the initiation of enteral feedings. Elevated BGLs identified through self-monitoring of blood glucose (SMBG), or continuous glucose monitoring (CGM) should be confirmed at a certified laboratory. (E)
- Individuals without diabetes who are preparing for organ transplantation and are affiliated with people with CF should undergo preoperative screening using a 2-hour, 75-gram fasting oral glucose tolerance test (OGTT) if they haven't been screened for CFRD (Cystic Fibrosis-Related Diabetes) in the past six months. Blood glucose levels (BGLs) need to be closely monitored during the perioperative period and until the patient is discharged from the hospital. (E)
- It is recommended to screen for islet autoantibodies in specific situations, such as CFRD diagnosis before the age of 10, presentation with diabetic ketoacidosis (DKA), a family history of autoimmunity, or a personal history of other autoimmune diseases. (E)

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)

Treatment

- Individuals with CF and CFRD should ideally have quarterly appointments with a specialized multidisciplinary team possessing expertise in both diabetes and CF. (E)
- Individuals with CF and CFRD should receive continuous education on diabetes self-management through programs that adhere to national standards. (E)
- For the treatment of CFRD, insulin therapy is recommended. (B)
- In cases where intensive insulin therapy is required, especially for individuals with CFRD, the consideration of insulin pump therapy is suggested, provided it is accessible and appropriate, including the potential use of partial closed-loop therapies. (C)
- In specific situations, such as when asymptomatic individuals are diagnosed through annual screening but do not exhibit fasting hyperglycemia and refuse insulin therapy, a trial of oral diabetes agents could be contemplated under close observation. (C)
    - Alternative oral diabetes medications such as metformin, sitagliptin, and empagliflozin are being utilized in isolated instances at individual CF centers. Nevertheless, there is insufficient data to endorse the widespread use of these diabetes drugs in the context of cystic fibrosis. (E)
- Individuals with CFRD who are using insulin are advised to conduct SMBG at least four times daily, with some individuals requiring even more frequent monitoring. (E)

- The use of continuous glucose monitoring (CGM) in patients with CFRD who are on insulin or anti-hyperglycemic medications is encouraged and can serve as an alternative to SMBG. (B)
- For optimal blood glucose (BG) control, patients with CFRD should aim to achieve BG goals and time in range as recommended by the American Diabetes Association (ADA) for all individuals with diabetes. Adjustments to these goals may be necessary for those in the early stages of the disease or those experiencing significant or recurrent hypoglycemia, and customization based on individual needs is crucial. (E)
- To guide decisions regarding insulin therapy, it is recommended that individuals with Cystic Fibrosis-Related Diabetes undergo quarterly measurements of HbA1c, which serves as an indicator of average glycemia. (E)
    - For most individuals with CFRD, the target HbA1c for treatment is set at ≤7% (53 mmol/mol) to minimize the risk of microvascular complications. It's important to note that for those who encounter substantial or recurring hypoglycemia, less strict goals may be considered, underscoring the significance of individualized approaches. (C)
- In the management of Cystic Fibrosis-Related Diabetes (CFRD), medical nutrition therapy is crucial, aligning with the principles applied in all types of diabetes. However, it is advised to adhere to CF guidelines for dietary therapy, with customization tailored to the individual's weight/BMI goals. (E)
- It is advisable to follow evidence-based guidelines for nutritional management applicable to all individuals with CFRD. (E)
- It is not recommended to rely solely on nutritional management without medical therapy for diabetes. (E)
- Individuals with CFRD should receive guidance to engage in moderate aerobic exercise for a minimum of 150 minutes per week. (E)

Complications

- Individuals with CFRD who are using insulin or oral hypoglycemic agents, along with their caregivers, should receive glucagon therapy along with relevant education. (E)
- It is recommended that patients with CFRD have their blood pressure assessed at each visit following the guidelines outlined by the American Diabetes Association (ADA). If any abnormalities in blood pressure are detected, a reevaluation should be conducted during a separate visit. (E)
- Individuals with CFRD who are diagnosed with hypertension or microvascular complications should undergo standard treatment as advised by the

American Diabetes Association (ADA), similar to the recommendations for all individuals with diabetes. It is noteworthy that there shouldn't be a restriction on sodium or a generalized limitation on protein intake. Insufficient evidence is available to warrant alterations to these recommendations for those undergoing hypertonic saline inhalation (HEMT) therapy. (E)

- Annual screening for diabetes-related microvascular complications is advised, commencing five years from the diagnosis. In cases where the diagnosis date is unknown, the screening should begin at the onset of fasting hyperglycemia. (E)
- For individuals with CFRD and pancreatic sufficiency (PS), yearly lipid screening is recommended. (E)
- As for people with CF and pancreatic insufficiency (PI), lipid screening should be conducted every five years, aligning with the general population guidelines for low-risk individuals. (E)

For more information regarding the short and long-term complications of diabetes, as well as details on antidiabetic drugs, please refer to the individual reports on Diabetes Type 1 and Type 2.

1.2.5 Cystic Fibrosis Australia: Standards of Care for Cystic Fibrosis (2023)

Cystic Fibrosis Australia (CFA) is the national body representing all Australians living with cystic fibrosis and the custodian of these Standards of Care. CFA strives for the best outcomes for the cystic fibrosis community through advocacy, increasing access to therapies, supporting research, and improving quality of care and clinical outcomes. These revised Standards of Care will support improved clinical care and highest quality outcomes so that people living with cystic fibrosis can have longer, healthier lives. This revised edition was endorsed by the Thoracic Society of Australia and New Zealand[5].

I. Inpatient care

- CF centers must be equipped with the necessary facilities, personnel, and services to handle all complications associated with CF. They should also have the capability to facilitate prompt access to specialized care within the same hospital or other healthcare facilities as necessary.
- CF centers should provide ward accommodation and facilities designed to meet the specific needs of individuals with CF.
- CF should not share rooms with either CF or non-CF patients. Instead, they should be accommodated in single rooms, following appropriate infection control guidelines.

- CF centers should establish plans and systems for the swift or emergency assessment and admission of CF patients.
- For CF patients that are admitted to the hospital and are not under the direct care of the CF team, there should be prompt communication with the CF center staff to optimize care.
- CF centers should develop protocols for managing all common comorbidities and complications associated with CF.

Admission to hospital and emergency access

- Consult physiotherapy service for treatment and collection of a sputum sample for microbiological culture and sensitivities.
- Consult CF dietitians for prompt assessment to allow timely access to appropriate CF diet in hospital, nutritional and dietary needs assessment and supports including enteral feeds, oral supplements, PERT, and other nutritional medications.
- The plan for each admission should be clearly defined, with indication(s) for the admission, aims, and with therapeutic and patient goals stated and agreed on by the patient/family and team. The treatment plan should be appropriate for the presenting problems and include usual medications, investigations and referrals to specialists as required.
- For most people with CF admitted to hospital, antibiotic treatment should be commenced without delay.
- Antibiotic treatment will depend on usual organisms (usually anti-Pseudomonal) and should follow CF center protocols or guidelines.

Medicines and drug treatment

- Thoroughly inquire about and document each patient's adverse drug reactions, ensuring that records are kept up to date. Review and discuss medication interactions, especially considering CFTR modulators, indications, responses to treatments, and patient preferences with the patient or caregiver.
- When using intravenous (IV) antibiotics, adhere to hospital and CF-center guidelines that offer clear guidance on drug selection, medication doses, and drug level monitoring.
- Discuss the feasibility of self-management or bedside access to medications, such as pancreatic enzyme replacement therapy (PERT), where applicable.

- Provide education and the necessary equipment for nebulized antibiotics and conduct a tolerability test for the initial dose during the inpatient stay.

Physiotherapy – assessment and treatment

- Physiotherapy intervention encompasses inhalation therapy, airway clearance, musculoskeletal care, exercise, and the management of any concurrent conditions when appropriate.
- The treatment plan, including the frequency of sessions, should be customized to meet the individual needs of the patient, taking into account their age and clinical status.
- Physiotherapy devices designed to aid airway clearance, such as bilevel positive airway pressure (BIPAP) and other forms of non-invasive ventilation (NIV), should be accessible. When administering home-based courses of intravenous antibiotics to address pulmonary exacerbations, efforts should be made to incorporate physiotherapy sessions in the home setting as part of a "hospital in the home" program, whenever feasible.

Nutrition and dietetic therapy – assessment and treatment

- The CF dietitian plays a vital role in evaluating and adjusting various aspects of patient care during hospital admission, including PERT, micronutrient status, bowel function, glucose tolerance, CFTR modulator usage, medical progress, and therapy changes. Access to energy-dense foods and oral supplements is essential to supplement the standard hospital diet.
- In selected cases, the use of parenteral nutrition and monitoring of electrolyte, protein, and nutrient balance may be necessary, with an experienced CF dietitian taking the lead.
- Patients with additional complications, such as reduced bone mineral density, may need further dietary support, additional medications, and counseling.

II. Home therapy

- The option of home-based treatment can be considered for managing pulmonary exacerbations in specific individuals with CF.
- The development of protocols for the selection and training of patients (and their caregivers), the administration of treatment, and the monitoring of responses are needed.

- Home therapy services should mirror the essential elements of comprehensive inpatient care, encompassing nursing, physiotherapy, nutritional and psychosocial assessment, and management.
- Factors influencing the decision to offer home-based treatment to individuals include:
    - ✓ The preferences and acceptance of both the CF team and the patient, the complexity of required therapies, the current severity of the disease and the patient's overall health, existing comorbidities, and the patient's social support and available resources.
    - ✓ It is crucial to ensure that local resources are in place to deliver home-based treatment that replicates essential services provided in the inpatient setting, such as nursing, physiotherapy, dietetics, and psychosocial support.
    - ✓ Additionally, the burden of home therapy on patients and caregivers, considering the need for respite or rest, is a significant consideration. This is especially important for individuals with a high care burden, such as parents of young children or caregivers for elderly relatives.
    - ✓ It is emphasized that inpatient bed pressure is not a primary indication for home therapy at CF centers.
- Contraindications to home therapy include:
    1. Ongoing clinical instability necessitating regular monitoring, such as patients experiencing hypoxemia, acute hypercapnia, recent significant hemoptysis, or pneumothorax.
    2. Psychosocial factors, including suboptimal adherence, limited understanding of treatment requirements, and inadequate practical, financial, and/or social support, may diminish the likelihood of successful home therapy.
    3. A history of severe allergic reactions to prescribed drugs that have not been effectively managed through desensitization.
    4. Challenges related to poor venous access.
    5. Antibiotics lacking pharmacological stability when administered through home delivery devices and specific dosing regimens.
- Relative contraindications include:
    1. Challenges related to a remote geographical location or difficulty returning for review.
    2. Very young children.

3. Past unsatisfactory response to home therapy.
4. Involvement in complex therapy that includes multiple antibiotics or other interventions, such as investigations, procedures, assessments, and/or education that necessitate inpatient specialist services.
5. Engagement in complex therapy requiring multiple antibiotics or other interventions, such as investigations, procedures, assessments, and/or education, which demand inpatient specialist services.
6. Patient or caregiver preference for inpatient care.

III. Outpatient care

- All individuals with CF should be able to avail treatment from a multidisciplinary team within specialized CF centers.
- As the current minimum standard, individuals with CF should undergo reviews four times a year by the CF specialist team, with the frequency of individual patient reviews tailored to their clinical progress and needs.
- Respiratory samples need to be collected at least four times annually. In cases where individuals are unable to spontaneously expectorate, oropharyngeal samples and induced sputum should be obtained. For symptomatic patients with a negative culture, consideration should be given to bronchoalveolar lavage.
- An annual review, including relevant tests, should be conducted, and a written report provided to the patient/family and the general practitioner. Goals and plans for the upcoming year should be discussed and agreed upon collaboratively between the CF team and the patient/caregivers.
- It is crucial to implement policies and procedures actively promoting contemporary infection control guidelines to optimize clinical care in the outpatient setting.
- Telehealth facilities should be made available to ensure equitable and enhanced access to multidisciplinary CF healthcare for all patients. The standards of clinical practice using telehealth should be equivalent to the standards of CF care applied in face-to-face settings.

<u>Annual review</u>

- An extensive clinical assessment, known as the annual review, should be conducted on a yearly basis. Alongside the elements covered in routine visits, the annual review visit should involve contributions from all members of the Multidisciplinary Team (MDT) and pertinent subspecialties.

- In addition to a thorough physical examination, investigations, and procedures specific to the annual review should include:
    1. Assessment and overview of respiratory progress and status
        a. Lung function and exercise capacity: Overall spirometry trend and annual decline should be reviewed.
        b. Airway microbiology: Oropharyngeal, sputum or BAL samples should be collected at annual review, as per routine clinic visits.
        c. Airway microbiology: Chest imaging: Annual chest x-ray is recommended and when combined with a scoring system has been shown to predict pulmonary disease progression in children 28, but is less sensitive to early lung disease and structural changes than a chest CT.
        d. Assessment of allergic bronchopulmonary aspergillosis (ABPA) status from around age 5 years. Annual blood tests for total serum IgE, Aspergillus specific RAST test (or skin prick test for Aspergillus) and IgG antibodies are recommended.
        e. A diagnostic sleep study should be performed to diagnose sleep disordered breathing in children and adults, and considered in those with advanced respiratory disease, (FEV1% < 40% predicted and waking SaO2 < 93%).
    2. Assessment of growth and nutritional status:
        a. Assessment of growth trends, pubertal progress, (height, weight, BMI, and head circumference for ≤2years only) and identification of undernutrition and at-risk nutritional status.
        b. Consider assessment of body composition for more detailed information regarding nutritional status including fat-free mass.
        c. Consider measurement of luteinising hormone, follicular stimulating hormone and testosterone or oestradiol in adolescents with pubertal delay, along with bone age assessment.
        d. Blood tests for fat soluble vitamins (A, D, E, and K including retinol binding protein to assist in interpretation), FBC, electrolytes and creatinine, liver function tests and clotting profile (hepatic function), irons studies, calcium levels, and fasting or random blood glucose. Consider celiac serology if growth/nutritional concerns. There is insufficient evidence to

support routine annual testing of selenium or zinc at the present time.

e. Consider measurement of urinary sodium (urinary sodium concentrations< mmol/L) or calculation of fractional urinary sodium (FENa) to detect salt depletion, particularly in children who are failing to thrive, patients with ileostomy/colostomy, and those with symptoms of fatigue and anorexia.

f. Develop a nutritional intervention plan with the patient and family for the coming year and address suboptimal growth or nutritional deficiencies.

3. Assessment of glucose homeostasis and bone health should be conducted:

    a. Presently, annual oral glucose tolerance testing (OGTT) for patients aged 10 years or older is recommended. Patients diagnosed with CF-related diabetes mellitus (CFRDM) should be referred to endocrinology services (ideally a diabetologist with experience in the management of CFRDM) for surveillance (including 3-monthly HbA1c) and management.

    b. Bone mineral density (BMD) should be assessed annually using DEXA from age 8 years in accordance with clinical practice guidelines.

4. Mental health screening for depression and anxiety should be performed for patients (>12 years) and their carer/parents (all children and adolescents), using standardised and validated tools such as PHQ-9 and GAD-7.

5. Audiology testing and ophthalmology screening should be considered.

6. Sexual and reproductive health matters should be addressed on a yearly basis, approaching the topic in a manner suitable for the individual's age.

7. Examination of medications by the CF pharmacist. During the annual review, a thorough assessment of all medications, including dosage and administration methods, should be conducted to ascertain their appropriateness. This review should also encompass non-prescription medications and complementary therapies. In cases where access to a pharmacist is constrained or unavailable, the CF physician should take on this responsibility.

<u>Health promotion</u>

1. Education

- Imparting disease-specific information about CF and its treatment through health education is a crucial aspect of outpatient care.
- This practice is linked to enhanced self-efficacy, adherence, and improved health outcomes.
- Consistent and age-appropriate education for patients, caregivers, and family members is essential, starting from the time of diagnosis and persisting throughout the individual's life.
- Education should be customized to address the specific needs of patients and their families.

2. Immunization

- All individuals with CF should adhere to the standard Australia immunization schedule.
- For those who are immunocompromised or have undergone a lung transplant, a separate immunization schedule should be discussed with the immunization clinic.
- It is strongly recommended that all patients, including children above 6 months of age, receive the annual influenza vaccine before the onset of winter.
- Family members of children with CF are advised to also obtain the annual influenza vaccine.
- Pneumococcal vaccination is recommended, with an additional dose of Prevenar 13v administered at 6 months, and Pneumovax 23v given at 4 years of age with a second dose at least 5 years later.
- In addition to following the standard adult vaccination schedule, it is recommended that adolescents and adults receive the 23-valent pneumococcal vaccination and boosters.
- Vaccination against SARS-CoV-2 (COVID-19 virus) is currently recommended for all CF patients aged 5 years and above, as well as their families.

3. Avoidance of environmental tobacco smoke and hepatotoxins

- Strategies for minimizing exposure to environmental tobacco smoke (ETS) should be explored, encompassing discussions on vaping and the various vaping fluids available.
- The growing instances of lung injury associated with e-cigarette or vaping product use (EVALI) across the United States are a cause for concern.

- Conversations about smoking or exposure to environmental tobacco smoke should be candidly conducted and actively discouraged.

IV. Diagnosis of cystic fibrosis

- Infants identified through newborn screening should promptly receive attention from experienced medical, nursing, and allied health personnel specializing in cystic fibrosis (CF) within a week of an abnormal newborn screening (NBS) result.
- Infants diagnosed with meconium ileus should have their NBS result prioritized.
- Individuals newly diagnosed with CF should undergo an assessment for respiratory symptoms and signs that may necessitate appropriate respiratory sample collection, antibiotics, and/or the initiation of airway clearance programs.
- Families of individuals recently diagnosed with CF should be provided access to genetic counseling services and psychosocial support services.
- From the time of diagnosis, individuals and their families should have access to current and pertinent educational materials about CF.
- Consideration should be given to salt, electrolyte, and vitamin replacement therapy for individuals at the time of diagnosis, especially those experiencing poor weight gain, evidence of fat malabsorption, and those residing in areas characterized by hot and humid conditions.
- Infants should be evaluated for pancreatic insufficiency, and enzyme therapy should be initiated when indicated.

1.2.6 Brazilian Thoracic Association Guidelines for the Pharmacological Treatment of the Pulmonary Symptoms of Cystic Fibrosis (2023)

The aim of this special article is to carry out a systematic review and meta-analysis of data from the literature involving aspects of the treatment of individuals with CF regarding the use of CFTR modulators and dornase alfa, as well as strategies for the eradication and suppression of pathogens commonly associated with respiratory infections in such individuals. The steps for developing the guidelines followed the model proposed and approved by the Brazilian Thoracic Association, which employs the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[9].

Table 13. Interpretation of the Quality of Evidence Employing the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach

GRADE quality of evidence	Implications	Examples
High (⨁⨁⨁⨁)	Future research is unlikely to change the level of confidence in the estimated effect; we are confident that we can expect a very similar effect in the population for which the recommendation is intended.	Randomized trials without serious limitations Well-executed observational studies with very large effect sizes
Moderate (⨁⨁⨁◯)	Future research is likely to have a major impact on the level of confidence in the estimated effect and could change this estimate.	Randomized trials with serious limitations Well-executed observational studies with large effect sizes
Low (⨁⨁◯◯)	Future research is likely to have a major impact on the level of confidence in the estimated effect and is likely to change that estimate	Randomized trials with very serious limitations Observational studies without special strengths or serious limitations
Very low (⨁◯◯◯)	Any estimate of an effect is very uncertain.	Randomized trials with very serious limitations and inconsistent results Observational studies with serious limitations Nonsystematic clinical observational studies (e.g., case series or case reports)

Table 14. Implications of the GRADE Approach

Target audience	Strong GRADE recommendation		Conditional GRADE recommendation	
	We recommend	We do not recommend	We recommend	We do not recommend

Patients	Most individuals would want the intervention to be indicated, and only a small number would not accept this recommendation.	Most individuals would not want the intervention to be indicated, and only a small number would accept this recommendation.	Most individuals would like the intervention to be indicated, although a considerable number would not accept this recommendation.	Most individuals would not want the intervention to be indicated, although a considerable number would accept this recommendation.
Health professionals	Most patients should receive the recommended intervention.		The professional must recognize that different choices can be appropriate for each patient and should help patients make a decision consistent with their values and preferences.	
Policy makers	The recommendation can be adopted as health policy in most situations.		Substantial debate and stakeholder involvement is required.	

Treatment with ivacaftor

- For individuals diagnosed with CF who have at least one class III (gating) or class IV (conduction) mutation, we recommend considering the use of ivacaftor (conditional recommendation, very low quality of evidence).
- The assessed studies focused exclusively on patients aged 6 years and older, and it is not feasible to extend this recommendation to any younger age category.

Treatment with lumacaftor + ivacaftor

- We do not recommend the use of lumacaftor + ivacaftor for individuals with CF who have the F508del mutation (conditional recommendation, very low quality of evidence).
- The combination of a CFTR corrector and a CFTR potentiator can be advantageous for individuals with the F508del mutation who are homozygous, addressing a subgroup constituting around 45% of those with cystic fibrosis and this particular mutation. However, in the systematic review

conducted, no significant findings were identified regarding critical clinical outcomes.

- It is crucial to highlight that recently approved modulator classes/combinations, including tezacaftor + ivacaftor and the triple combination (elexacaftor + tezacaftor + ivacaftor), have demonstrated improved efficacy and safety profiles in this population.

Treatment with tezacaftor + ivacaftor

- The utilization of tezacaftor + ivacaftor was observed to result in a substantial enhancement in lung function, a decrease in the frequency of exacerbations, and nutritional improvements, all while maintaining a satisfactory safety profile.
- For individuals with CF who are either homozygous for F508del or have a combination of F508del and a residual function mutation, we recommend considering the use of tezacaftor + ivacaftor (conditional recommendation, very low quality of evidence).

***P. aeruginosa* eradication**

- People with CF frequently experience respiratory tract infections, making them more vulnerable to specific microorganisms, notably Pseudomonas aeruginosa.
- Infection with this pathogen is a significant predictor of morbidity and mortality in cystic fibrosis, as well as a leading cause of substantial loss of lung function.
- There is insufficient evidence to either recommend or discourage the use of *Pseudomonas aeruginosa* eradication therapy for individuals with CF.
- While endorsed by various national and international guidelines, additional research is required to ascertain the effectiveness and safety of *Pseudomonas aeruginosa* eradication therapy, particularly in the context of CFTR modulator use.

Treatment with inhaled antimicrobials in patients with CF and chronic *P. aeruginosa* infection

- Through intricate mechanisms, *Pseudomonas aeruginosa* can adapt and persist in the airways of individuals with CF for extended durations.
- Chronic infection in CF is defined as the identification of this pathogen in over 50% of respiratory secretion samples over a 12-month period.

- For individuals with CF exhibiting chronic colonization by *P. aeruginosa*, we recommend the consideration of chronic suppression therapy involving the use of inhaled antibiotics.
- The utilization of inhaled antimicrobials is a common approach to suppress *P. aeruginosa* in individuals with chronic infection, with the goal of mitigating the consequences associated with the presence of the pathogen in the airways.
- Classic options for inhaled drug therapy in this context include colistimethate, tobramycin, and, more recently, aztreonam.

Antimicrobial eradication treatment in CF patients with MRSA colonization of the airways

- Persistent MRSA infection is linked to unfavorable clinical results in individuals with CF. Multiple antimicrobial protocols, incorporating combinations of oral, topical, and inhaled medications, exist for eliminating this pathogen.
- However, for individuals with CF, the current evidence does not provide sufficient grounds to either endorse or discourage the use of MRSA eradication therapy.
- It is plausible that additional research, particularly studies involving larger patient cohorts, may lead to a reassessment of the confidence level associated with this recommendation.

Nebulized dornase alfa for CF patients ≥ 6 years of age

- In individuals with CF, persistent inflammation and infection lead to the continuous release of extracellular DNA from leukocytes into the airways, resulting in its accumulation in lung secretions.
- This process contributes to an escalation in the viscosity and adhesion of mucus.
- For CF patients, we recommend the use of inhaled dornase alfa (conditional recommendation, very low quality of evidence).
- Dornase alfa is an enzyme with the ability to break down the extracellular DNA present in mucus, thereby reducing its viscosity and facilitating improved clearance of secretions.
- The typical administration involves inhalation, with a standard dose of 2.5 mg once daily, and it is recommended to be used in conjunction with other airway clearance techniques.

Antimicrobial eradication treatment in CF patients with airway colonization by *B. cepacia* complex strains

- The *B. cepacia* complex encompasses 22 species, with *B. multivorans* and *B. cenocepacia* being the most prevalent in individuals with CF.
- The clinical presentation varies widely, ranging from chronic, minimally symptomatic infections to severe cases marked by necrotizing pneumonia, respiratory failure, and sepsis, known as cepacia syndrome.
- The *B. cepacia* complex exhibits a distinctive bacterial resistance profile, posing challenges in selecting antibiotic treatments.
- It is often recommended to use a combination of antimicrobial drugs, with preference given to choices guided by antimicrobial susceptibility testing.
- For CF patients, we do not have enough evidence to recommend or not recommend the use of eradication therapy for B. cepacia complex.

1.2.7 Infectious Diseases Society of America Practice Guidelines for the Diagnosis and Management of Aspergillosis (2016 Update)

The practice guidelines for the diagnosis and management of aspergillosis published in 2016 by IDSA covers all types of aspergillus infections[4]. For the purpose of this report, **only allergic bronchopulmonary aspergillosis in patients with cystic fibrosis will be covered**. The GRADE approach was used to rate the quality of evidence and strength of recommendations (tables 13 and 14 above).

- Testing for increased levels of Aspergillus-specific Immunoglobulin E (IgE) and total IgE is advised for confirming the diagnosis and is valuable as a screening measure (strong recommendation; high-quality evidence).
- It is recommended administering oral itraconazole therapy with therapeutic drug monitoring (TDM) for symptomatic asthmatic patients with bronchiectasis or mucoid impaction, even if they are already undergoing oral or inhaled corticosteroid treatment (weak recommendation; low-quality evidence).
- For individuals with cystic fibrosis experiencing recurrent exacerbations or a declining forced expiratory volume 1 (FEV1), we recommend considering oral itraconazole treatment as an approach to reduce the reliance on corticosteroids, along with therapeutic drug monitoring (TDM). If achieving therapeutic levels proves challenging, contemplating alternative mold-active azole therapy is advisable (weak recommendation; low-quality evidence).

Section 2.0 Drug Therapy in Cystic Fibrosis

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details drugs that have been approved by the FDA and/or EMA for the treatment of CF but are not currently registered by the SFDA.

2.1 Additions

No new drugs were registered by the SFDA for the treatment of cystic fibrosis since March 2020.

- However, **Ursodeoxycholic Acid** which was previously registered in the form of capsule (250 mg) is now also available as film-coated tablets (500 mg).

2.2 Modifications

Table 15 lists the modifications to the prescribing edits that were made to the medications listed in the previous CHI report.

Table 15. Prescribing Edits Modifications

Medications	Modifications
Azithromycin	"Prior Authorization (PA)" was removed
Ciprofloxacin	"PA" was removed
Colistimethate sodium	"PA" was removed
Flucloxacillin	"PA" was removed
Ibuprofen	"PA" was removed. Off-label was removed. Limited data available was added.
Itraconazole	"PA" was removed. "MD" was explained in the notes section.
Pancreatin, Dimethicone	"PA" was removed
Prednisolone	"PA" was removed
Prednisolone sodium phosphate	"PA" was removed
Tobramycin	"PA" was removed
Ursodeoxycholic acid	"PA" was removed

Voriconazole	"PA" was removed. "MD" was explained in the notes section.

2.3 Delisting

No medications have been delisted since the previous CHI report.

2.4 Other Drugs

The medications listed in this section have been approved by the FDA and/or EMA for the management of CF but are not currently registered by the SFDA.

2.4.1 Tezacaftor/Ivacaftor

In June 2019, the U.S. Food and Drug Administration extended the indication for tezacaftor/ivacaftor tablets for treatment of pediatric patients ages 6 years and older with cystic fibrosis who have certain genetic mutations. One year earlier (February 12, 2018), FDA approved tezacaftor/ivacaftor to treat patients ages 12 and older who had the same specific genetic mutations[16].

Clinical trials:

- The EVOLVE trial was conducted in CF patients, who have two copies of the F508del mutation. This trial was conducted at 91 sites in the following 12 countries: Canada, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland, and the United Kingdom[17].
- The EXPAND trial was conducted in CF patients, who have the F508del mutation and a second mutation that is predicted to respond to tezacaftor and/or ivacaftor therapy. This trial was conducted at 81 sites in the following 10 countries: Australia, Belgium, Canada, Germany, France, Israel, Italy, Netherlands, and the United Kingdom[17].
- The 3rd trial, published on behalf of the European Cystic Fibrosis Foundation was conducted in CF patients, who have the F508del mutation and a second mutation that is predicted to be unresponsive to tezacaftor and/or ivacaftor therapy. This trial was conducted 38 sites in the following 7 countries: Australia, Austria, Canada, France, Israel, and Spain[17].

1. **EVOLVE Trial: Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del (2017)**[18]

Methods:

- In this phase 3, randomized, double-blind, multicenter, placebo-controlled, parallel-group trial, the aim was to assess the combination therapy with

tezacaftor and ivacaftor in patients 12 years of age or older who had cystic fibrosis and were homozygous for the CFTR Phe508del mutation.

- Participants were randomly divided in a 1:1 ratio to receive either a daily dose of 100 mg of tezacaftor and twice-daily doses of 150 mg of ivacaftor or a corresponding placebo for a duration of 24 weeks.
- The primary end point was the absolute change in the percentage of the predicted forced expiratory volume in 1 second (FEV1) through week 24 (calculated in percentage points); relative change in the percentage of the predicted FEV1 through week 24 (calculated as a percentage) was a key secondary end point.

Results:

- The mean FEV1 at baseline was 60.0% of the predicted value.
- The effects on the absolute and relative changes in the percentage of the predicted FEV1 in favor of tezacaftor–ivacaftor over placebo were 4.0 percentage points and 6.8%, respectively (P<0.001 for both comparisons).
- The rate of pulmonary exacerbation was 35% lower in the tezacaftor–ivacaftor group than in the placebo group (P=0.005). The incidence of adverse events was similar in the two groups.

Conclusions:

- The combination of tezacaftor and ivacaftor demonstrated effectiveness and safety in individuals aged 12 years and older with cystic fibrosis who were homozygous for the CFTR Phe508del mutation.

2. EXPAND Trial: Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis (2017)[19]

Methods:

- A randomized, double-blind, placebo-controlled, phase 3, crossover trial was conducted to examine the efficacy and safety of ivacaftor alone or in combination with tezacaftor, a CFTR corrector, in 248 patients 12 years of age or older who had cystic fibrosis and were heterozygous for the Phe508del mutation and a CFTR mutation associated with residual CFTR function.
- Participants were randomly allocated to one of six sequences, each consisting of two 8-week intervention periods separated by an 8-week washout phase. During these intervals, they were administered tezacaftor–ivacaftor, ivacaftor monotherapy, or a placebo.
- The primary end point was the absolute change in the percentage of predicted forced expiratory volume in 1 second (FEV1) from the baseline value

to the average of the week 4 and week 8 measurements in each intervention period.

Results:

- The least-squares mean difference versus placebo with respect to the absolute change in the percentage of predicted FEV1 was 6.8 percentage points for tezacaftor–ivacaftor and 4.7 percentage points for ivacaftor alone (P<0.001 for both comparisons).
- Scores on the respiratory domain of the Cystic Fibrosis Questionnaire–Revised, a quality-of-life measure, also significantly favored the active-treatment groups.
- The incidence of adverse events was similar across intervention groups; most events were mild or moderate in severity, with no discontinuations of the trial regimen due to adverse events for tezacaftor–ivacaftor and few for ivacaftor alone (1% of patients) and placebo (<1%).

Conclusions:

- Treatment with CFTR modulators, whether it be tezacaftor–ivacaftor or ivacaftor alone, proved to be effective in individuals with cystic fibrosis who had a combination of the Phe508del deletion and a residual-function mutation in the CFTR gene.

3. **Tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for minimal function CFTR mutations (2020), Published on Behalf of the European Cystic Fibrosis Society**[20]

Methods:

- This randomized, double-blind, placebo-controlled Phase 3 study evaluated the efficacy, safety, tolerability, and pharmacokinetics (PK) of tezacaftor/ivacaftor in participants ≥12 years of age heterozygous for the F508del-CFTR mutation and a minimal function mutation (F/MF), which produces no CFTR protein or a protein unresponsive to tezacaftor/ivacaftor in vitro.

Results:

- The study did not show a significant enhancement in ppFEV1 or any of the primary secondary outcomes with tezacaftor/ivacaftor, leading to the termination of the study due to its lack of efficacy.
- The safety profile and pharmacokinetic parameters of tezacaftor/ivacaftor were consistent with those documented in earlier studies involving participants aged 12 years and older with cystic fibrosis.

Conclusions:

- Tezacaftor/ivacaftor did not exhibit a clinically significant advantage in individuals with F/MF genotypes. However, it was generally safe and well-tolerated, aligning with the safety profile observed in previous Phase 3 studies.

Dosing:

- **Adults, Adolescents, Children ≥6 years to <12 years weighing ≥30 kg and Children ≥12 years: Cystic fibrosis: Oral:** Tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg in the evening, ~12 hours apart[21].
- **Children ≥6 years to <12 years weighing <30 kg: Cystic fibrosis: Oral:** Tezacaftor 50 mg/ivacaftor 75 mg (1 tablet) in the morning and ivacaftor 75 mg in the evening, approximately 12 hours apart[21].

Most common side effects: Headache, nausea, dizziness and paranasal sinus congestion[21].

Warnings/Precautions

- Cataracts
- CNS effects
- Hepatic effects: May increase hepatic transaminases.
- Hypersensitivity reactions: Hypersensitivity reactions, including anaphylaxis, have been reported with tezacaftor/ivacaftor use.
- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment recommended in patients with moderate to severe (Child-Pugh class B or C) impairment.
- Renal impairment: Use with caution in patients with severe impairment (CrCl ≤ 30 mL/minute) or ESRD[21]

Contraindications:

- There are no contraindications listed in the US manufacturer's labeling.
- Canadian labeling: Hypersensitivity to ivacaftor, tezacaftor, or any component of the formulation[21].

2.4.2 Elexacaftor/Tezacaftor/Ivacaftor

On October 21, 2019, The U.S. Food and Drug Administration has granted approval for elexacaftor/ivacaftor/tezacaftor, marking the first triple combination therapy for individuals with the most prevalent cystic fibrosis mutation. The elexacaftor/ivacaftor/tezacaftor combination is authorized for use in patients aged 12 years and older who have cystic fibrosis and possess at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, a mutation estimated to be present in 90% of the cystic fibrosis population[22].

On April 26, 2023, Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) disclosed that the U.S. Food and Drug Administration (FDA) has given approval for an extended application of elexacaftor/tezacaftor/ivacaftor to encompass children aged 2 through 5 years with cystic fibrosis (CF). This includes those who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or a mutation in the CFTR gene that shows responsiveness to TRIKAFTA® based on in vitro data. Previously, the FDA had sanctioned triple therapy elexacaftor/ivacaftor/tezacaftor for use in individuals with CF aged 6 years and older who have at least one F508del mutation or a mutation in the CFTR gene that responds to TRIKAFTA® based on in vitro data[23].

Internationally, triple therapy elexacaftor/ivacaftor/tezacaftor is authorized for use in cystic fibrosis (CF) patients aged 6 and above with specific mutations. This approval applies to regions such as Canada, the European Union, the U.K., Switzerland, and Australia[24].

Vertex is presently anticipating regulatory decisions in the European Union and the United Kingdom for the approval of the medication for children between the ages of 2 and 5[24].

Clinical trials:

The efficacy of elexacaftor/ivacaftor/tezacaftor in patients with CF aged 12 years and older was evaluated in two double-blind, controlled trials.

1. **Trial 1 (VX17-445-102): Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele (2020)**[25]

Methods:

- A phase 3, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of elexacaftor–tezacaftor–ivacaftor in patients 12 years of age or older with cystic fibrosis with Phe508del–minimal function genotypes.

- Patients were randomly assigned to receive elexacaftor–tezacaftor–ivacaftor or placebo for 24 weeks.
- The primary end point was absolute change from baseline in percentage of predicted forced expiratory volume in 1 second (FEV1) at week 4.

Results:

- Elexacaftor–tezacaftor–ivacaftor, relative to placebo, resulted in a percentage of predicted FEV1 that was 13.8 points higher at 4 weeks and 14.3 points higher through 24 weeks, a rate of pulmonary exacerbations that was 63% lower, a respiratory domain score on the Cystic Fibrosis Questionnaire–Revised (range, 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory symptoms; minimum clinically important difference, 4 points) that was 20.2 points higher, and a sweat chloride concentration that was 41.8 mmol per liter lower ($P<0.001$ for all comparisons).
- Elexacaftor–tezacaftor–ivacaftor was generally safe and had an acceptable side-effect profile. Most patients had adverse events that were mild or moderate.

Conclusions:

- In individuals with cystic fibrosis who possess Phe508del–minimal function genotypes and have not experienced effectiveness with previous CFTR modulator regimens, elexacaftor–tezacaftor–ivacaftor demonstrated effectiveness.

2. **Trial 2 (VX17-445-103): Efficacy and safety of the elexacaftor/tezacaftor/ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial (2020)**[26]

Methods:

- A phase 3, multicenter, randomized, double-blind, active-controlled trial evaluated ELX in triple combination with TEZ/IVA (ELX/TEZ/IVA) in individuals with cystic fibrosis who were homozygous for F508del.
- Eligible participants were aged 12 years and older, had stable disease, and a percent predicted forced expiratory volume in 1 second (ppFEV1) ranging from 40 to 90, inclusive.
- Following a four-week TEZ/IVA run-in period, participants were randomly assigned in a 1:1 ratio to receive either four weeks of ELX/TEZ/IVA or TEZ/IVA alone.
- The primary endpoint was the absolute change from baseline (measured at the end of the TEZ/IVA run-in) in ppFEV1 at week 4.

- Key secondary endpoints included the absolute change in sweat chloride and the CF Questionnaire–Revised respiratory domain (CFQ-R RD) score.

Results:

- The ELX/TEZ/IVA group had improvements in ppFEV1 (10·0 percentage points, 95% CI 7·4 to 12·6, p<0·0001), sweat chloride concentration (−45·1 mmol/L, 95% CI −50·1 to −40·1, p<0·0001), and CFQ-R RD score (17·4 points, 95% CI 11·8 to 23·0, p<0·0001) compared with the TEZ/IVA group. ELX/TEZ/IVA was well tolerated, with no discontinuations.
- Most adverse events were mild or moderate; serious adverse events occurred in 4% (n=2) of participants receiving ELX/TEZ/IVA and 2% (n=1) receiving TEZ/IVA.

Conclusions:

- ELX/TEZ/IVA delivered substantial clinical advantages compared to TEZ/IVA alone, exhibiting a favorable safety profile. This suggests the potential for transformative enhancements in the lives of individuals with cystic fibrosis who are homozygous for F508del.

The label expansion was supported by data from a Phase 3 clinical trial (NCT04537793) in children ages 2 to 5 with at least one F508del mutation in CFTR.

3. **Trial (NCT04537793): Phase 3 Open-Label Clinical Trial of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged 2-5 Years with Cystic Fibrosis and at Least One F508del Allele (2023)**[27]

Objectives:

- To assess the safety, pharmacokinetics, pharmacodynamics, and efficacy of ELX/TEZ/IVA in children with CF aged 2-5 years.

Methods:

- In this phase 3, open-label, two-part study (parts A and B), children weighing <14 kg (on Day 1) received ELX 80 mg once daily (qd), TEZ 40 mg qd, and IVA 60 mg each morning and 59.5 mg each evening; children weighing ⩾14 kg received ELX 100 mg qd, TEZ 50 mg qd, and IVA 75 mg every 12 hours.

Measurements:

- The primary endpoints for part A (15-d treatment period) were pharmacokinetics and safety and tolerability.

- For part B (24-wk treatment period), the primary endpoint was safety and tolerability.
- Secondary endpoints included pharmacokinetics and absolute changes from baseline in sweat chloride concentration and lung clearance index$_{2.5}$ (LCI$_{2.5}$, defined as the number of lung turnovers required to reduce the end tidal N_2 concentration to 2.5% of its starting value) through Week 24.

Main results:

- Analysis of pharmacokinetic data from 18 children enrolled in part A confirmed the appropriateness of the part B dosing regimen. In part B, 75 children (F508del/minimal function genotypes, n = 52; F508del/F508del genotype, n = 23) were enrolled and dosed.
- Seventy-four children (98.7%) had adverse events, which were all mild (62.7%) or moderate (36.0%) in severity.

Conclusions:

- In this open-label investigation involving children aged 2-5 years, the administration of ELX/TEZ/IVA was generally safe and well-tolerated. The safety profile aligns with that observed in older age groups, and the treatment resulted in significant and clinically meaningful reductions in sweat chloride concentration and LCI2.5.

Dosing:

Cystic fibrosis

- **Adults: Oral:** 2 tablets (each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg per tablet) in the morning and one ivacaftor 150 mg tablet in the evening, approximately 12 hours apart[28].
- **Children ≥ 2 to < 6 years:** Oral granules:
    1. Weight <14 kg: Elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg per packet and ivacaftor 59.5 mg per packet: Oral: 1 packet (total dose of elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg) in the morning and one ivacaftor 59.5 mg packet in the evening approximately 12 hours apart[28].
    2. Weight ≥14 kg: Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg per packet and ivacaftor 75 mg packet: Oral: 1 packet (total dose of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) in the morning and one ivacaftor 75 mg packet in the evening approximately 12 hours apart[28].
- **Children ≥ 6 to < 12 years: Oral tablets:**

1. Weight < 30 kg: Elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg per tablet and ivacaftor 75 mg per tablet: Oral: 2 tablets (total dose of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) in the morning and one ivacaftor 75 mg tablet in the evening, approximately 12 hours apart[28].
2. Weight ≥30 kg: Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg per tablet and ivacaftor 150 mg per tablet: Oral: 2 tablets (total dose of elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg) in the morning and one ivacaftor 150 mg tablet in the evening, approximately 12 hours apart[28].

- **Children ≥ 12 years and Adolescents:** Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg per tablet and ivacaftor 150 mg per tablet: Oral: 2 tablets (total dose of elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg) in the morning and one ivacaftor 150 mg tablet in the evening, approximately 12 hours apart[28].

Most common side effects: Abdominal pain, diarrhea, increased indirect serum bilirubin, increased serum transaminases, increased serum aspartate aminotransferase, headache, upper respiratory tract infection.

Warnings/Precautions:

- Cataracts
- Hepatic effects (liver failure, increased LFTs)
- Hypersensitivity reactions

Contraindications:

- There are no contraindications listed in the manufacturer's US labeling.
- Canadian labeling: Hypersensitivity to elexacaftor, tezacaftor, ivacaftor, or any component of the formulation.

Section 3.0 Key Recommendations Synthesis

- Physiotherapy intervention is recommended, and it includes inhalation therapy, airway clearance, musculoskeletal care and exercise[5].
- The CF Foundation highly suggests the chronic use of dornase alfa and inhaled hypertonic saline as a means to enhance lung function, elevate

quality of life, and diminish the occurrence of exacerbations. (Certainty of Net Benefit: High for dornase alfa, moderate for hypertonic saline, Estimate of Net Benefit: Moderate for both, Recommendation: B for both)[6].

- The CF Foundation recommends against the routine use of inhaled corticosteroids or the chronic use of oral corticosteroids in patients without asthma or allergic bronchopulmonary aspergillosis. (Certainty of Net Benefit: High for both, Estimate of Net Benefit: Zero for inhaled corticosteroids, negative for oral corticosteroids, Recommendation: D for both)[6].
- For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine chronic use of leukotriene modifiers to improve lung function and quality of life or reduce exacerbations. Certainty of Net Benefit: Low, Estimate of Net Benefit: N/A, Recommendation: I)[6].
- The CF Foundation recommends the chronic use of oral ibuprofen, (at a peak plasma concentration of 50–100 mg/ml) between 6 and 17 years of age, with an FEV1 > 60% predicted to slow the loss of lung function. (insufficient to recommend for or against the chronic use of oral ibuprofen in patients 18 years or older). (Certainty of Net Benefit: Moderate for <18 years, Low for ≥ 18 years, Estimate of Net Benefit: Moderate for <18 years, N/A for ≥ 18 years, Recommendation: B for <18 years, I for ≥ 18 years).
- Mannitol dry powder for inhalation is recommended for children and adolescents unable to utilize dornase alfa and hypertonic sodium, either due to ineligibility, intolerance, or insufficient response[7, 8].
- In cases where individuals with cystic fibrosis face repeated exacerbations of allergic bronchopulmonary aspergillosis or a decrease in forced expiratory volume 1 (FEV1), we suggest exploring the use of oral itraconazole as a strategy to decrease dependence on corticosteroids. Additionally, incorporating therapeutic drug monitoring (TDM) is recommended. If reaching the desired therapeutic levels becomes challenging, considering alternative mold-active azole therapy is a prudent option (weak recommendation; low-quality evidence)[4].
- In the case of a new *P. aeruginosa* infection, treatment should involve a 28-day course of tobramycin solution for inhalation (TIS) and up to three months of combined nebulized colistimethate and oral ciprofloxacin[8].
- Persistent *P. aeruginosa* infection (when initial treatment fails to eliminate the infection) is addressed through extended use of inhaled tobramycin (alternating months indefinitely), aztreonam, or colistimethate[1].

- Azithromycin is employed for its dual impact on both infection and inflammation in cases of chronic *P. aeruginosa* infection[8].
- Flucloxacillin is employed as a preventive measure against respiratory Staphylococcus aureus infection in children diagnosed with cystic fibrosis, starting from the initial diagnosis up to the age of 3, with the option of extending it until the age of 6[7].
- The regular use of antibiotics to control chronic MRSA in individuals with stable pulmonary conditions is not advised. Patients with new MRSA infections or those experiencing pulmonary exacerbations due to chronic MRSA are encouraged to consult with a microbiology specialist for guidance[7].
- The preventive utilization of oral antistaphylococcal antibiotics for the purpose of enhancing lung function, improving quality of life, or reducing exacerbations is discouraged[6].
- Individuals with cystic fibrosis, diagnosed with at least one class III (gating) or class IV (conduction) mutation, are advised to contemplate the utilization of ivacaftor (conditional recommendation, very low quality of evidence)[9].
- The combination of lumacaftor + ivacaftor is not advised for individuals with cystic fibrosis carrying the F508del mutation (conditional recommendation, very low quality of evidence)[9].
- Individuals with cystic fibrosis, either homozygous for F508del or possessing a combination of F508del and a residual function mutation, are encouraged to contemplate the utilization of tezacaftor+ivacaftor (conditional recommendation, very low quality of evidence)[9].
- Administering elexacaftor (ELX)/ tezacaftor (TEZ)/ ivacaftor (IVA) leads to significant clinical improvements for individuals with a single copy of the F508del variant, regardless of the variant present on the other allele[10].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Cystic Fibrosis report** and aims to provide recommendations to aid in the management of Cystic Fibrosis. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Cystic Fibrosis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Cystic Fibrosis Scope

2020	Changes	2023	Rationale
Section 1.0 Cystic Fibrosis Clinical Guidelines			
European Cystic Fibrosis Society Standards of Care: Best Practice guidelines 2018	N/A		
2013 American Thoracic Society, Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health	N/A		
Cystic fibrosis: diagnosis and management NICE guideline Published: 25 October 2017	N/A		
	Missing	Cystic Fibrosis Foundation consensus guidelines for the care of individuals	• Definition of advanced cystic fibrosis lung disease • Additional clinical manifestations associated with worse prognosis and/or disease progression in cystic fibrosis • Care plan in ACFLD

		with advanced cystic fibrosis lung disease (2020)[11]	• Recommended Screening in Individuals with ACFLD • Oxygen supplementation and non-invasive ventilation • Pulmonary vasodilator therapy • Lung transplantation • Intensive care unit (ICU) admission • Invasive mechanical ventilation • Antibiotics • Microbiological screening • Pulmonary rehabilitation • Systemic corticosteroids • Screening for gastroesophageal reflux • Enteral tube feeds • Exposure to nephrotoxic and ototoxic agents • Pregnancy • Patients taking opioids • Anxiety • Psychosocial support • Transition plan for pediatrics
	Missing	Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for	**CFTR Modulator treatments** **A. General overview** **B. Examples:** Ivacaftor (IVA; Kalydeco™), Lumacaftor/ivacaftor (LUM/IVA; Orkambi™), Tezacaftor/ivacaftor (TEZ/IVA; Symdeko™), Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA; Trikafta™) **C. Indications for starting CFTR modulator therapy:** Mutation, Age, Lung function, Pancreatic status

		Patients with Cystic Fibrosis (2022)[10]	**D. Pre-modulator assessment** **E. Response to therapy** **F. Concurrent treatment** **G. Treatment response** **H. Monitoring:** Side effects, DDIs **I. Special considerations for patients receiving IVA, LUM/IVA, or TEZ/IVA** **J. Pregnancy/lactation and CFTR modulators** **K. CF Patients who have received a lung transplantation** **L. Discontinuation** **M. How to start CFTR modulators**
	Missing	The UK Cystic Fibrosis Trust Diabetes Working Group: Management of cystic fibrosis diabetes (Consensus) Second edition (November 2022)[12]	- **Introduction** - **Screening for CF diabetes** - **Assessment after screening test** - **Criteria to start treatment in CF diabetes and abnormal glucose levels** - **Treatment strategies for CF diabetes** - **Treatment agents** - **Management of reactive hypoglycemia** - **Capillary blood glucose monitoring** - **Management of children and adolescents with CF diabetes** - **Adjustment of treatment during infection or corticosteroid treatment** - **Dietary/nutritional treatment** - **CFTR modulator therapy**

			- **Pregnancy**
	Missing	ISPAD Clinical Practice Consensus Guidelines 2022: Management of cystic fibrosis-related diabetes in children and adolescents.[13]	- **Hypoglycemia** - **Diagnosis** - **Screening** - **Pregnancy** - **Treatment** - **Complications**
	Missing	Thoracic Society of Australia and New Zealand: Standards of Care For Cystic Fibrosis (Australia 2023)[5]	**Inpatient care** **1- Admission to Hospital and Emergency Access** **2- Medicines and Drug Treatment** **3- Physiotherapy - Assessment and Treatment** **4- Nutrition and Dietetic Therapy - Assessment and Treatment** **Home therapy** **Outpatient care** **Diagnosis of Cystic Fibrosis**
	Missing	2023 Brazilian guidelines for the pharmacological treatment of the pulmonary symptoms of cystic fibrosis. Official document of the Sociedade	**Treatment with ivacaftor** • For individuals diagnosed with cystic fibrosis who have at least one class III (gating) or class IV (conduction) mutation, we recommend considering the use of ivacaftor (conditional recommendation, very low quality of evidence). **Treatment with lumacaftor + ivacaftor** • We do not recommend the use of lumacaftor + ivacaftor for individuals with cystic fibrosis who have

		Brasileira de Pneumologia e Tisiologia (SBPT, Brazilian Thoracic Association)[9]	the F508del mutation (conditional recommendation, very low quality of evidence). **Treatment with tezacaftor + ivacaftor** • For individuals with cystic fibrosis who are either homozygous for F508del or have a combination of F508del and a residual function mutation, we recommend considering the use of tezacaftor+ivacaftor (conditional recommendation, very low quality of evidence). **P. Aeruginosa eradication** • While endorsed by various national and international guidelines, additional research is required to ascertain the effectiveness and safety of Pseudomonas aeruginosa eradication therapy, particularly in the context of CFTR modulator use. **Treatment with inhaled antimicrobials in patients with CF and chronic P. aeruginosa infection** • For individuals with cystic fibrosis exhibiting chronic colonization by P. aeruginosa, we recommend the consideration of chronic suppression therapy involving the use of inhaled antibiotics. **Antimicrobial eradication treatment in CF patients with MRSA colonization of the airways** • However, for individuals with cystic fibrosis, the current evidence does not provide sufficient grounds to either endorse or discourage the use of MRSA eradication therapy. **Nebulized dornase alfa for CF patients ≥ 6 years of age**

			• For cystic fibrosis patients, we recommend the use of inhaled dornase alfa (conditional recommendation, very low quality of evidence). **Antimicrobial eradication treatment in CF patients with airway colonization by B. cepacia complex strains** • For CF patients, we do not have enough evidence to recommend or not recommend the use of eradication therapy for B. cepacia complex.
	Missing	Practice guidelines for the diagnosis and management of aspergillosis published in 2016 by IDSA covers all types of aspergillus infections[4]	• Testing for increased levels of Aspergillus-specific Immunoglobulin E (IgE) and total IgE is advised for confirming the diagnosis and is valuable as a screening measure (strong recommendation; high-quality evidence). • It is recommended administering oral itraconazole therapy with therapeutic drug monitoring (TDM) for symptomatic asthmatic patients with bronchiectasis or mucoid impaction, even if they are already undergoing oral or inhaled corticosteroid treatment (weak recommendation; low-quality evidence). • For individuals with cystic fibrosis experiencing recurrent exacerbations or a declining forced expiratory volume 1 (FEV1), we recommend considering oral itraconazole treatment as an approach to reduce the reliance on corticosteroids, along with therapeutic drug monitoring (TDM). If achieving therapeutic levels proves challenging, contemplating alternative mold-active azole therapy is advisable (weak recommendation; low-quality evidence).

Appendix C. MeSH Terms PubMed

C.1 Pubmed Search for Cystic Fibrosis

The following is the result of the PubMed search conducted for cystic fibrosis guideline search:

Query	Filters	Search Details	Results
((((((((((Cystic Fibrosis[MeSH Terms]) OR (Fibrosis, Cystic[Title/Abstract])) OR (Mucoviscidosis[Title/Abstract])) OR (Pulmonary Cystic Fibrosis[Title/Abstract])) OR (Cystic Fibrosis, Pulmonary[Title/Abstract])) OR (Pancreatic Cystic Fibrosis[Title/Abstract])) OR (Cystic Fibrosis, Pancreatic[Title/Abstract])) OR (Fibrocystic Disease of Pancreas[Title/Abstract])) OR (Pancreas Fibrocystic Disease[Title/Abstract])) OR (Pancreas Fibrocystic Diseases[Title/Abstract])) OR (Cystic Fibrosis of Pancreas[Title/Abstract])	Guideline, in the last 5 years	("cystic fibrosis"[MeSH Terms] OR "fibrosis cystic"[Title/Abstract] OR "Mucoviscidosis"[Title/Abstract] OR "pulmonary cystic fibrosis"[Title/Abstract] OR "cystic fibrosis pulmonary"[Title/Abstract] OR "pancreatic cystic fibrosis"[Title/Abstract] OR "cystic fibrosis pancreatic"[Title/Abstract] OR "fibrocystic disease of pancreas"[Title/Abstract] OR "pancreas fibrocystic disease"[Title/Abstract] OR (("pancrea"[All Fields] OR "Pancreas"[MeSH Terms] OR "Pancreas"[All Fields]) AND "fibrocystic diseases"[Title/Abstract]) OR "cystic fibrosis of pancreas"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	9

Appendix D. Treatment Algorithm for Cystic Fibrosis

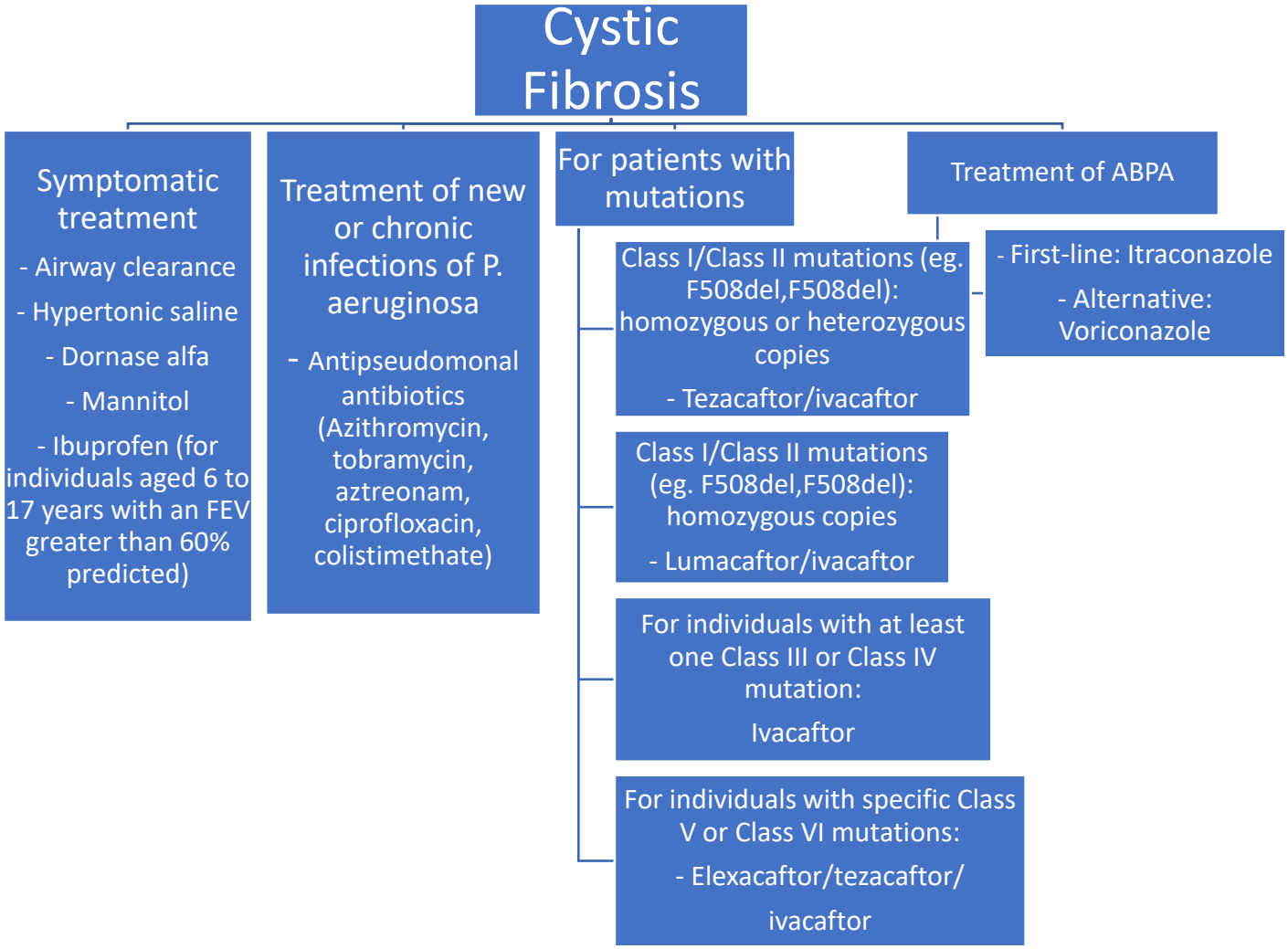

Figure 2. *Treatment Algorithm for the Management of Cystic Fibrosis*[4,6–11,14]