Cystic Fibrosis- Respiratory Care for the Adolescent, Adult, and End-Stage Patient

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Abstract

Cystic fibrosis is a terminal genetic disorder with particularly lethal outcomes among Caucasian populations. While it affects multiple body systems, the respiratory system's involvement in the pathology is the highest cause of morbidity and mortality for cystic fibrosis patients. Therefore, the respiratory therapist's role is critical in cystic fibrosis patients' care and management. Recent advances in the disease's pharmacological, physiotherapeutic, and genetic interventions have significantly increased the lifespan of the typical cystic fibrosis patient. In this regard, while the goals of respiratory therapy for cystic fibrosis are generally consistent throughout the usual patient's lifespan, each life stage presents the respiratory therapist will unique challenges regarding how best to individualize the patient's respiratory care and management. Adolescence and adulthood comprise significant portions of the usual cystic fibrosis patient's life and, therefore, require special focus in the respiratory care process. Accordingly, the current paper presents a respiratory care plan that synthesizes the current research and clinical guidelines to adequately address cystic fibrosis patients' care and management needs during adolescence, adulthood, and the disease's end stage.

Keywords: Cystic fibrosis, CF, respiratory care, respiratory therapy, respiratory care plan, adolescent, adult, palliative care.

Background and Introduction

Cystic fibrosis (CF) pulmonary disease is a genetic condition that causes the dysfunction or absence of the CF transmembrane regulator (CFTR) protein, which under normal physiological performance, helps to maintain a homeostatic balance of water and salt in many of the body's epithelial surfaces. The anatomical regions where CFTR manifests include the lung surface and other respiratory system tissues and organs (Ratjen, 2009). In this regard, a technical description of the CF's pathophysiology, from a respiratory therapy perspective, begins with identifying the CFTR gene mutations responsible for causing the absence of chloride transport across the respiratory system's epithelial cells in the lungs and along the airways (Ratjen, 2009; De Simone et al., 2018). Consequently, the imbalance the genetic condition causes results in highly viscous organ secretions that adversely affect the respiratory system's function by resulting in the production and retention of viscous and thick mucus (DeSimone et al., 2018; Giron et al., 2021; Orenstein 1995). The resulting mucus retention in the lungs precipitates damaging airway inflammation and chronic infection.

CF affects multiple other organ systems, including the pancreas, liver, vas deferens, and sweat glands. It causes a range of adverse health outcomes, such as biliary and pancreatic obstruction associated with the accumulation of viscous mucus in biliary and pancreatic ducts. However, the primary cause of morbidity and mortality among CF patients is the respiratory system's involvement and progressive impairment, principally because of the recurrent respiratory diseases caused by various pathogens among CF patients.

Notably, regarding epidemiology, CF is diagnosed in individuals across all ethnic and racial backgrounds. However, it is the Caucasian population's most lethal genetic disease, with the highest incidence among Caucasians of Australian, European, and North American descent

(Giron et al., 2021, p. 486). Its prevalence in the United States is approximately 1 in 4000 people (De Simone et al., 2018). While CF has no cure, there are multiple evidence-based pharmacological therapies and interventions with demonstrable efficacy, cumulatively known as symptomatic treatments, which, from a respiratory therapy perspective, work to ease the disease's respiratory symptoms, reduce its respiratory complications, and improve the likelihood of survival and the patient's overall quality of life (Giron et al., 2021). In addition, there is also a range of non-pharmacological interventions, particularly related to physiotherapy and physical exercise, which also target the same therapeutic goals as those indicated for the pharmacological interventions highlighted above.

Pharmacological and non-pharmacological CF therapies primarily treat respiratory obstruction, inflammation, infection, and chronic respiratory failure (Kacmarek et al., 2019). Notably, therapeutic advancements have contributed significantly to the increasingly positive prognoses and quality of life improvements for CF patients, including an increase in the estimated average life expectancy at birth from 34 years during the 1990s to approximately 50 years currently (De Simone et al., 2018). However, helping CF patients to successfully and fully achieve the benefits of the available interventions and therapies necessitates effective care planning, particularly in the respiratory therapy and care contexts, given that the respiratory system's involvement is the primary cause of CF-associated morbidity and mortality.

The current paper's primary objective is to develop a comprehensive, effective, and evidence-based respiratory care plan for the CF patient. While CF occurs in patients across various age groups, adolescence and adulthood occupy the most significant proportion of the CF patient's life. They are also the stages where the CF patient typically engages with healthcare services most comprehensively and undertakes extensive self-management (Segal, 2008). CF is

also a terminal disease, implying that end-stage care occupies a critical position in the CF patient's standard care and management (Estrada-Veras & Groninger, 2013). Accordingly, the current thesis and care plan focus on respiratory care for adolescent, adult, and end-stage patients.

The care and management of the target patient populations are more similar than distinct in therapeutic options and other management decisions. For example, all three patient groups have unique but similar physiological characteristics that affect the relevant pharmacological decisions in similar ways, including an increased volume of distribution that necessitates larger dosages of certain medications and faster clearance rates that necessitate shorter periods between dosages or higher frequency across the three CF patient categories (De Simone et al., 2018). However, certain crucial differences require the individualization of the applicable approaches and interventions for each group, including, for example, the higher incidence of anxiety and other physiological disturbances among adolescent CF patients, which makes it more necessary to prioritize psychological intervention in the adolescent CF patients' care and management plans (Ernst et al., 2010). Moreover, the palliative care and types of interventions applicable to the chronic respiratory failure that characterizes CF's end-stage are distinct from the care and management approaches feasible during the condition's earlier phases (Cathcart & Madge, 2020). Accordingly, the care plan herein will not only encompass the respiratory care and management responses to the common attributes of the CF care process that cut across the three patient groups but also highlight and elaborate upon the distinct care aspects individualized to the adolescent, adult, and end-stage patients, respectively, where relevant. The paper commences with a review of CF signs and symptoms and their research-backed etiological explanations before considering various elements of the effective CF respiratory care plan.

Signs and Symptoms

The primary manifestation of the respiratory system's involvement in CF pathology is the lung damage attributable to the associated chronic pulmonary infections and progressive airway disease, accompanied by a demonstrable decline in lung function. Therefore, the primary signs and symptoms to be expected during an adolescent, adult, or end-stage CF patient's clinical presentation should reflect the indicated lung damage and also manifest the principal effects of the implicated CFTR defects on the respiratory system, including the expected highly viscous mucus resulting from the underlying mucociliary escalator's failure and a dehydrated airway surface liquid (Giron et al., 2021; Ratjen, 2009). More specifically, the common respiratory CF signs and symptoms that are consistent with the dynamics indicated above include a persistent cough that generates thick sputum; wheezing; recurrent sinusitis; a stuffy nose or inflamed nasal passages; nasal polyps; pneumothorax; hemoptysis; pulmonary function test results consistent with obstructive airway disease; and hyperinflation of the lung fields observed on chest x-rays (Allan et al., 2021; De Simone et al., 2018; Giron et al., 2021; Maher & Strek, 2019). Other common CF signs consist of recurrent respiratory infections associated with *Pseudomonas aeruginosa* (PA), *Staphylococcus aureus* (SA), and *Haemophilus influenzae* (HI), particularly when there is a history of such infection in the patient's first decade of life (Ratjen, 2009; Orenstein, 1995). In addition, the presentation of acute exacerbations of respiratory chronic bacterial colonization usually features malaise, increased production of green-colored sputum, dyspnea, wheezing, pneumothorax, hemoptysis, and other symptoms of the underlying increase in airway inflammation (Geller & Rubin, 2009). Generally, the common symptoms of respiratory involvement in CF are symptoms of obstruction, inflammation, and infection occurring in the respiratory system.

Notably, although there currently is no scientific consensus on the precise pathophysiological mechanisms that contribute to bacterial lung infections' affinity to CF, multiple extant hypotheses are supported with compelling empirical evidence. For example, some studies suggest that CFTR acts as a PA receptor and mediates the PA intracellular uptake and killing process in the lungs (Ratjen, 2009). Therefore, the CFTR's defects in, or CFTR's absence from, the lung surfaces of CF patients, may explain the higher incidence of PA infections in CF patients compared to normal individuals, given the consequent failure of the PA intracellular uptake and killing process.

Another hypothesis postulated to explain the chronic respiratory infections that typically characterize CF is that the CFTR dysfunctions responsible for the disease's respiratory impact result in the dehydration of airway surface liquid, consequently impairing cilia functioning and mucociliary clearance. This adverse impact results in inhaled bacteria not being efficiently cleared among CF patients (Ratjen, 2009; Giron et al., 2021). However, the core alignment among these competing hypotheses is that the increased CF patient predisposition to bacterial lung infections results from the various pulmonary effects of the underlying CFTR gene mutation and dysfunctions (Ratjen, 2009; Orenstein, 1995). Additionally, repeated respiratory infections cause chronic inflammation by releasing "inflammatory products like elastase by neutrophils" to stimulate mucus breakdown and secretion as an immune response to the infections (Skach, 2002). In this regard, there is also evidence of inflammation dysregulation in CF patients' airways. Respiratory infection and inflammation dynamics generally explain CF's respiratory signs and symptoms.

Respiratory Care Plan

The subsequent discussion details the major elements to be included in a comprehensive respiratory care plan for adolescent, adult, and end-stage CF patients.

Diagnosis

Early CF diagnosis is the cornerstone of effective CF respiratory care and management. Specifically, there is abundant clinical research evidence to support the efficacy of newborn screening for CF and its positive effects on establishing an effective foundation for future management and preventing diagnosis delays hence the incidence and the potential future complications associated with the respiratory system's CF involvement (Smyth et al., 2014; De Simone et al., 2018). The primary methodologies for newborn screening for CF indicated by the latest clinical research and best practice guidelines are sweat conductivity and genetic testing (Savage et al., 2021; De Simone et al., 2018). Genetic testing occurs through the laboratory measurement of immunoreactive trypsinogen (IRT) on a dried blood spot between 24 to 48 hours of age in all newborns (Smyth et al., 2014). Abnormally elevated immunoreactive trypsinogen levels then prompt genotyping to screen for the CFTR mutations characterizing CF's pathophysiology, the "sweat chloride test," which involves "collecting sweat after the transdermal administration of pilocarpine" (Kacmarek et al., 2019; De Simone et al., 2018). The scientific rationale underpinning the IRT and salt tests is that, as part of CF's pathophysiology, infants, adolescents, and adults with CF may have elevated IRT levels and higher chloride levels in their sweat. However, the diagnosis is clear-cut when subsequent genetic testing reveals positive results indicating the anticipated CFTR mutations characterizing CF (De Simone et al., 2018). Therefore, an equivocal or positive IRT screening test followed by CFTR genetic testing and the sweat chloride test cumulatively provide the "gold standard for discriminating between true positive and false positive results in newborns" (De Simone et al., 2018). CF diagnosis

through newborn screening is essential for the respiratory therapy and care approaches feasible during the later adolescent and adulthood life phases of newborn patients diagnosed with CF.

While the general expectation is that robust newborn screening will reduce the frequency of delayed diagnoses, the current empirical clinical experience and research demonstrate that many CF patients get unequivocal CF diagnoses later in life, typically during adolescence and adulthood. The current epidemiological data indicate, notably, that racial and ethnic minorities have the greatest risk of missed or delayed diagnosis because of multiple precipitating factors, including low suspicion indices by physicians, the low disease prevalence associated with these populations, and rare CFTR gene mutations that today's standard mutation panels do not cover (Kacmarek et al., 2019). Consequently, CF screening and diagnosis during adolescence and adulthood are paramount for effective CF respiratory care and management.

In this regard, the respiratory therapist and other members of the wider CF interdisciplinary team must be aware of the signs and symptoms that typically characterize CF's presentation, as discussed earlier. An essential component of critical knowledge comprises the diagnostic features characterizing CF's clinical presentation, including bronchiectasis, chronic sinusitis, and other symptoms and signs that reflect the respiratory system's involvement in CF's pathophysiology (De Simone et al., 2018). The respiratory therapist must also be aware of other peculiar characteristics of delayed or missed CF diagnosis in the adolescent and adult patient populations and how they manifest during the clinical presentation and upon a comprehensive review of the patient's history (De Simone et al., 2018). Not uncommonly, CF's peculiar diagnostic features at presentation include patients initially diagnosed with asthma but then have repeated respiratory infections, which should alert the care team to the possibility of CF (Kacmarek et al., 2019). More precisely, the two principal diagnostic criteria for CF, according

to the research and guidelines of the Cystic Fibrosis Foundation in the United States (Smyth et al., 2014; Giron et al., 2021; Wilcox et al., 2018, p.2) are:

- "The presence of one or more characteristic clinical features, a history of CF in a sibling, or a positive newborn screening (NBS) test"
- Laboratory evidence of an abnormality in the CFTR gene "(2 disease-causing mutations) or the CFTR protein, elevated sweat chloride, abnormal nasal potential difference test."

The diagnosis criteria above and the diagnostic tests associated with their ascertainment are the same for infants, adolescents, and adults. Therefore, an effective diagnostic procedure relevant to the adolescent and adult patient populations consists of the respiratory therapist's and an entire multidisciplinary team's consideration of the disease's clinical diagnostic features (typical signs, symptoms, and associated features), sweat chloride testing, and genetic testing. The sweat tests confirm the elevated chloride levels in the patient's sweat, while the genetic tests ascertain the anticipated CFTR gene mutations.

Additionally, the respiratory therapist's knowledge and role of CF diagnostics also require knowledge of the complications that sometimes occur during diagnosing of adolescents and adults. Firstly, it is important to be aware of the fact that while sweat testing is the gold standard for discriminating between false positive and true positive results among the infant patient population (De Simone et al., 2018), it can be less reliable in some adolescent- and adult-diagnosed cases whereby the genotyping and clinical presentation demonstrate consistency with a CF diagnosis but the sweat test generates an intermediate or normal, false-negative result (Wilcox et al., 2018). Therefore, an important clinical guideline for the respiratory therapist's involvement in the adult or adolescent CF patient's diagnosis is not to exclude a CF diagnosis based on normal sweat test results alone in the patient cases indicated above, where the clinical

presentation is highly suggestive of CF in contradiction to the sweat chloride result (Wilcox et al., 2018, p.7). Rather, the respiratory therapist should advise the subjection of such patient cases to repeat sweat chloride and extended genetic testing.

As explained, the effective respiratory therapist must also be aware of the probability of the available standard genotyping panels missing some rare CFTR mutations (Wilcox et al., 2018, p.8). Therefore, the respiratory therapist involved in the diagnosis phase of unique patient cases should advise that identifying single or no mutations during the genetic test should not constitute the basis for excluding a diagnosis (Smyth et al., 2014). Rather, "extended/CFTR sequencing is often required to establish a diagnosis," but the extended search's failure to establish two disease-causing CF mutations does not automatically exclude a CF diagnosis (Wilcox et al., 2018). Therefore, respiratory therapists and other healthcare professionals facing challenging diagnoses in the adolescent and adult patient populations where there is compelling evidence to support a CF diagnosis but contradictory genetic test results should consider full gene sequencing based on the patients' relevant, unique genetic characteristics such as Northern European ancestry and descent (Wilcox et al., 2018). Implementing the recommended approach will ensure that the respiratory therapist contributes meaningfully to enhancing the quality and effectiveness of the CF diagnostic process.

Finally, a confirmed and established CF diagnosis in adolescent and adult patients requires the respiratory therapist and other members of the responsible care team to order a range of follow-up tests to gain further details regarding the disease's dynamics and progression on a patient-to-patient basis. The respiratory therapist should advise the following tests at the initial visit, according to the available clinical guidance and recommendations (Kacmarek et al., 2019; Wilcox et al., 2018): sputum culture, fecal elastase, pulmonary function testing, chest CT scan,

and bloodwork. The respiratory therapist can manage the respiratory care and education of adolescent and adult patients in the ambulatory setting.

Goals of Respiratory Therapy and Care in Adolescent and Adult CF Patients

An effective respiratory care plan for the adolescent, adult, and end-stage patient with a positive CF diagnosis should ideally include the following therapy goals (Wagener & Headley, 2003; Newton, 2009; Geller & Rubin, 2009; Chatburn & Mireles, 2010; Kacmarek et al., 2019; Smyth, 2021):

- Effectively treat obstruction by improving mucociliary clearance, fluidizing respiratory secretions, and loosening and eliminating mucus from the lungs and airways
- Prevent or delay the onset of respiratory infections, eradicate primary infections, and control chronic infections
- Reduce and manage the inflammation associated with chronic respiratory infections through effective anti-inflammatory therapy to avoid lung deterioration
- Prevent and reduce the incidence of pulmonary exacerbations (PEx)s
- Effectively treat non-infectious respiratory complications
- Provide adequate nutrition
- Effectively manage chronic respiratory failure during end-stage CF
- Provide effective palliative care at the disease's end stage.

Pharmacological Therapies and Interventions

Interventions for Treating Obstruction

The pharmacological respiratory care therapies and interventions for treating obstruction as a respiratory CF symptom target improving mucociliary clearance and fluidizing respiratory secretions. They generally include an inhaler, mucolytic agents, and hypertonic substances

(Giron et al., 2021). The two drug classes currently considered the first-line bronchodilator/inhaler treatments for bronchial obstruction and hyper-responsiveness in CF patients are β2-adrenergic receptor agonists and inhaled corticosteroids (ICSs) (Cathcart et al., 2020). ICSs reduce airway inflammation and bronchial hyper-responsiveness, leading to improved airway function (Balfour-Lynn et al., 2019). The most commonly utilized ICSs in CF adolescent and adult patients are fluticasone (a puff containing 100 to 1000 mcg twice daily depending on symptom severity), which comes in an orange inhaler, and budesonide and beclometasone (40 to 80 mcg and a maximum of 320 mcg twice a day), which both come in brown and beige inhalers (Balfour-Lynn et al., 2019; Stahl, 2021). They can also be administered with long-acting agents that help relax the muscles of the airways, such as fluticasone plus salmeterol and formoterol plus budesonide (Stahl, 2021). The common side effects associated with ICSs and reported in CF patients include blood sugar hormone dysregulation, especially in CF patients under itraconazole antibiotic therapy, oral thrush caused by Candida infection, and, more rarely, hoarseness of the voice (Balfour-Lynn et al., 2019). Therefore, a core part of the respiratory therapist's care and management of CF patients undergoing ICS therapy consists of monitoring patients for these potential adverse effects.

Secondly, hypertonic saline (HS) is an inhaled substance with demonstrable efficacy in improving the respiratory symptoms that frequently characterize CF. It increases the airway surface’s hydration and improves mucociliary clearance (Giron et al., 2021). Standard dosages vary in strength and concentration between 6% and 7%, with a typical dosing frequency of twice daily (Stahl, 2021). However, it is associated with multiple side effects, including bronchoconstriction, bronchospasm, cough, and sinusitis (Giron et al., 2021). Accordingly, it is commonly used with a bronchodilator to manage the potential adverse effects.

Thirdly, the common short-acting β2-adrenergic receptor agonist used in adolescent and adult patients' treatment is salbutamol, while its long-acting counterpart is salmeterol. Although no extensive studies currently demonstrate the efficacy of this type of bronchodilator, their use in clinical practice is widespread, and there is substantial empirical evidence (Giron et al., 2021) demonstrating that they are useful in preventing bronchospasm when added to inhaled therapies like antibiotics and hypertonic saline. The recommended Salbutamol adult dosage is 100 mcg in one or two puffs, thrice or four times daily, based on continuous monitoring of the adequacy of the subsequently achieved bronchodilation (Stahl, 2021). On the other hand, the standard dosage of salmeterol is a 50 mcg puff inhaled orally once or twice daily (Stahl, 2021). The common potential adverse effects include chest pain, voice alterations, conjunctivitis, and nasal congestion.

Interventions for Treating Inflammation

Anti-inflammatory therapy also constitutes an important component of CF patients' respiratory care targeted at reducing the progressive loss of lung function that characterizes CF progression. The current clinical guidelines and best practice recommendations advise against the chronic use of inhaled corticosteroids for inflammation treatment. Instead, recommend using other anti-inflammatory medications, particularly non-steroidal anti-inflammatory drugs (NSAIDs) (Giron et al., 2021). Ibuprofen is the most commonly used agent for chronic anti-inflammatory treatment in adolescent and adult patients (De Simone et al., 2018). Its dosing and frequency guidelines are 20-30 mg/kg daily and a maximum of 3200mg daily (Stahl, 2021). While effective in treating the inflammation that characterizes CF, ibuprofen and other NSAID agents are also associated with various potential adverse effects, including abdominal pain, constipation, edema, and prolonged bleeding time.

Although generally used as an antibiotic treatment, azithromycin also demonstrates unimpeachable efficacy and significant therapeutic effect in treating inflammation in CF patients. The current research explains azithromycin's observed anti-inflammatory benefits based on the drug's combined "anti-inflammatory and immunomodulatory properties, in addition to the microbiological component" (Giron et al., 2021, p.8). Therefore, 22-30 mg/kg/week is the lowest indicated, demonstrating anti-inflammatory treatment efficacy in adolescent and adult patients according to the current research (Giron et al., 2021). Other potential anti-inflammatory therapy medications in the development pipeline with potential application to the focal patient population's anti-inflammatory treatment include acebilustat, lenabasum, Lau-7b, CB-280, and lonodelestat/ POL 6014.

Interventions for Treating Infection

A defining characteristic of acute and chronic CF in adult and adolescent patients is the pulmonary exacerbations (PEx) often linked to bacterial growth and colonization in the lungs. PEx is a critical event in the CF patient's life primarily because they result in lung function deterioration, with multiple studies demonstrating that lung function does not return to its baseline situation in roughly 25% of all CF patients despite the resolution of the underlying infection through effective antibiotic therapy (Ratjen, 2009; Giron et al., 2021). As explained earlier, PA, SA, and HI are the pathogens demonstrating a high affinity in CF patients based on the findings of robust microbiological research studies (Ratjen, 2009). Therefore, antibiotic therapy is essential in adult and adolescent respiratory care.

Antibiotic therapy is indicated in acute patient cases presenting with symptoms of inflammatory lung diseases and the associated exacerbations. The chronic use of antibiotics is also critical in eliminating infection at the primary stage and delaying the onset of bronchial

infection, thereby reducing the probability and frequency of PEx (Giron et al., 2021). In this regard, most extant microbiological research studies indicate that SA and HI are the pathological agents most frequently implicated in respiratory infections and PEx occurring within the CF pediatric patient population (Ratjen, 2009). On the other hand, PA (*Pseudomonas aeuginosa*) dominates the older patient demographic of adolescents and adults, with the relevant empirical studies finding that "up to 80% of CF patients at age 18 years or older are colonized with PA, which has been associated with progressive and irreversible deterioration of lung infection, with bronchial infection being the most important cause of morbidity and mortality in these patients" (Giron et al., 2021, p.14). The findings inform the extensive respiratory therapeutic efforts to initiate early antibiotic treatment in the first instance of PA isolation, even in asymptomatic patients.

Specifically, the prophylactic use of aztreonam, azithromycin, and tobramycin is recommended in treating PA infection in adolescent and adult CF patients. Inhaled aztreonam and tobramycin facilitate the drugs' local delivery to the lungs, thereby reducing the risk of systemic side effects (De Simone et al., 2018). In acute infection cases and PEx, the recommended aztreonam dosage for adolescent and adult patients is 75mg nebulized thrice daily for 28days, while the indicated dosage and frequency for tobramycin is 300mg inhaled twice daily for 28 days (De Simone et al., 2018; Stahl, 2021). In addition, the oral antibiotic agent of azithromycin, 250 mg, administered for three days weekly (Stahl, 2021) until the targeted therapeutic effect is achieved is also indicated for use in PA infection among CF patients to reduce exacerbations and improve lung function (Giron et al., 2021). However, its estimated effects and benefits are lower than inhaled aztreonam and tobramycin in acute CF cases.

The agents are also indicated for chronic use in adolescent and adult CF patients. Tobramycin administration for chronic use is principally "by nebulization (300mg) or dry powder inhalation (112mg) twice daily for 28 days on and 28 days off" (De Simone et al., 2018). Its administration is also possible via the IM and IV routes at 10 mg/kg/day in four equally divided doses (Stahl, 2021). Similarly, aztreonam for chronic use is administered by nebulization at a dosage and frequency of 75 mg thrice daily for 28 days and then 28 days off (De Simone et al., 2018). The principal potential side effects associated with aztreonam and tobramycin inhalation are cough, nasal congestion, wheezing, pharyngolaryngeal pain, bronchospasm, chest pain, nephrotoxicity, ototoxicity cough, dyspnea, hemoptysis, sinusitis, rhinitis, wheezing, and bronchitis (Estrada-Veras & Groninger, 2013; Maher & Strek, 2019; Giron et al., 2021; Stahl, 2021). Oral azithromycin in CF patients is also associated with potential gastrointestinal adverse effects, including nausea, vomiting, and diarrhea.

Interventions for Treating Chronic Respiratory Failure

In more severe and end-stage CF patients, non-invasive mechanical ventilation and oxygen therapy are often necessary as a bridge support intervention until a pulmonary transplant is possible. Non-invasive ventilation involves delivering positive pressure through a nasal mask, nasal plugs, face mask, or another non-invasive surface rather than through an invasive interface like a tracheotomy or endotracheal tube (Geller & Rubin, 2009). Chronic respiratory failure is also associated with adverse patient events and outcomes supporting the indication of oxygen therapy to maintain adequate tissue oxygenation, including hypoxemia and its manifest symptoms like tachycardia, elevated blood pressure, tachypnea, dyspnea, and hyperventilation; and chronic pulmonary hypertension (Skach, 2002; Wagener & Headley, 2003; Kacmarek et al., 2019). Non-invasive mechanical ventilation and oxygen therapy provide end-stage disease

support or transitional respiratory interventions until the CF patient can receive a pulmonary transplant.

In this regard, the following conditions indicate pulmonary transplant as an intervention for treating chronic respiratory failure (Giron et al., 2021):

- A forced expiratory volume in 1 second (FEV1) that is persistently below the normal values or rapid FEV1 drop despite optimal treatment
- A six-minute walk test of fewer than 400 meters
- Pulmonary hypertension without hypoxic exacerbation
- Clinical impairment co-occurring with an increased PEx frequency associated with respiratory failure and requiring non-invasive ventilation.
- Increased antibiotic resistance
- Relapsing pneumothorax

However, multiple absolute and general factors can contraindicate a pulmonary transplant. Infection by multi-resistant pathogens is an important contraindication against pulmonary transplantation relevant to end-stage CF patients' respiratory care (Giron et al., 2021). However, most of the remaining contraindications are general for any disease. For patients on the lung transplant list, the focus of the appropriate end-stage respiratory care on keeping the patient as well as possible until a potential donor organ is found justifies more aggressive interventions like non-invasive ventilation, invasive mechanical ventilation, enteral feeding, intensive care, and indwelling catheters (Kacmarek et al., 2019). Effective palliative care is paramount for terminal CF patients not anticipating lung transplantation.

Palliative Care Interventions

CF's terminal phase still requires oxygen therapy, nebulized medication, and the non-pharmacological intervention of physiotherapy. The primary symptoms requiring medical management in CF's terminal phases are dyspnea, anxiety, nausea, pain, and confusion (Cathcart et al., 2020). A typical presentation in patients in the terminal phase is breathlessness, which causes distress. Non-mechanical ventilation and the use of antidepressants and benzodiazepines are indicated in these instances (Estrada-Veras & Groninger, 2013). In this regard, morphine and its derivatives are indicated for the terminal dyspnea that characterizes end-stage CF (Cathcart et al., 2020). They can be administered via multiple routes based on the patient's specific needs, including transdermal, oral, intravenous, and sublingual modalities (Cathcart et al., 2020). Morphine can also be occasionally nebulized, although the drug absorption effectiveness varies from patient to patient (Cathcart et al., 2020). The current research shows that IV morphine of less than 5 mg hourly controls dyspnea in most terminal CF patients (Cathcart et al., 2020). The use of opiate medications combined with antidepressants, benzodiazepines, antiemetics, and anxiolytics, adjusted to the patient's needs, can also significantly enhance pain control in the palliative care dispensed during the CF's end-stage (Estrada-Veras & Groninger, 2013). Effective palliative sedation is also crucial during end-stage CF and is achievable through the monitored use of medications to relieve unendurable and refractory symptoms (Cathcart et al., 2020). It involves inducing various degrees of unconsciousness to control the patient's suffering. Notably, planning for the spiritual, social, and psychological support of the patient and their family is mandatory before initiating palliative therapy (Estrada-Veras & Groninger, 2013). It is particularly important to provide effective counseling to ensure that the patient and their loved ones understand that the rationale of palliative therapy is to help with symptoms like breathlessness and clear lung secretions rather than prolonging the dying process.

Non-Pharmacological Therapies and Interventions

The two primary non-pharmacological interventions utilized in CF respiratory care are physiotherapy and physical exercise. The principal goal of the different respiratory physiotherapy techniques used in managing adult and adolescent respiratory patients is to maintain the airway free of secretions (Chatburn & Mireles-Cabodevila, 2010). Therefore, the rationale underpinning the indicated physiotherapy interventions is the correlation between the elevated risk of an exacerbating infection-inflammation cycle and the secretions' accumulation in the respiratory system (Giron et al., 2021). Specifically, the main physiotherapy intervention or technique for CF adult and adolescent patients consists of airway clearance therapy (ACT), which consists of various related techniques (Newton, 2009; Giron, 2021). The range of ACT techniques with demonstrable, evidence-based effectiveness encompasses "active cycle of breathing technique (ACBT), positive expiration pressure (PEP), oscillating devices, postural drainage, and autogenic drainage" (Giron et al., 2021, p.3). ACBT is the ACT technique comprising thoracic expansion exercises, breath control, and forced expirations. The technique's goals are to achieve airway relaxation, to get air behind the mucus, and to clear and expel mucus out of the lungs (De Simone et al., 2018). Giron et al. (2021) are a comprehensive systematic review of the current pharmacological and non-pharmacological CF interventions to establish that ACBT effectively eliminates respiratory secretions.

The definition of PEP (positive expiration pressure) is "breathing against a PEP of 10-20cm" water utilizing a mouthpiece or mask (Giron et al., 2021, p.3). However, PEP's principal goal as an ACT physiotherapy technique is to open the airways (De Simone et al., 2018). In this regard, a common PEP innovation or variant is the oscillating PEP, which involves loosening secretions by combining PEP with airflow oscillation.

Oscillating devices also constitute a technical type of ACT. The physiotherapy devices operate primarily by causing vibrations that stimulate the loosening and elimination of respiratory secretions to address the pulmonary obstruction that typifies CF (De Simone et al., 2018). For example, the high-frequency chest wall oscillation machine vibrates the chest, thereby thinning and loosening mucus (De Simone et al., 2018). Other notable oscillating devices include the "Flutter, Acapella, Cornet, Quake, Aerobika, intrapulmonary percussive ventilation, VibraLung, and Metaneb" (De Simone et al., 2021, p.3). While each device has a unique operating mechanism, their fundamental underpinning rationale is similar in that it involves the application of vibration to resolve pulmonary obstruction in CF patients.

Additionally, the postural drainage ACT technique leverages gravity in draining respiratory secretions. It previously involved a head-down position. Multiple research studies subsequently demonstrated a gastroesophageal reflux side effect, prompting the intervention's replacement by a modified postural drainage technique without the head-down position (Newton, 2009). Its autogenic drainage counterpart utilizes controlled breathing to maximize airflow (Giron et al., 2021, p.5). Broadly, the shared goal of postural and autogenic drainage is to loosen, clear, and move mucus out of the lungs. The general assumption is that ACT treatment should be performed on and by all CF patients, given the current absence of evidence indicating the relative superiority of any ACT technique (Newton, 2009). However, patient preferences regarding specific physiotherapy modalities are instructive in selecting the most appropriate intervention.

Physical exercise is also an important component of CF patients' respiratory care. In this regard, two distinct physical exercise types are appropriate for adult and adolescent patients: anaerobic and aerobic exercise, with extended endurance and strength effects when working with large muscle groups (Giron et al., 2021). More precisely, aerobic physical exercise interventions

entail continuous moderate or low-intensity activity, such as cycling, jogging, walking, or swimming. Conversely, anaerobic physical training comprises high-intensity and short-duration activities such as weight and resistance exercises. The current research demonstrates the benefits of both anaerobic and aerobic exercise for CF patients' outcomes, including the enhanced strength, maximum exercise capacity, and overall quality of life associated with aerobic training (Giron et al., 2021); and the optimized lactate levels, fat-free mass, and maximum power associated with anaerobic exercise (De Simone et al., 2018). Generally, the cumulative benefits of physical exercise as a non-pharmacological intervention for CF patients include enhanced maintenance of lung function through improved respiratory secretion drainage and increased respiratory muscle training hence performance (De Simone et al., 2018).

Furthermore, physical exercise can also be beneficial secondarily through the improved outcomes associated with osteoporosis and diabetes co-occurring with CF (Giron et al., 2021), in addition to reducing depression and anxiety, particularly in adolescent CF patients (Ernst et al., 2010). Notably, the available research demonstrates that a twelve-month structured aerobic exercise program with a frequency of cardiovascular sessions of ideally 60 minutes between 3 to 5 times weekly is necessary to achieve the anticipated therapeutic benefits (Giron et al., 2021, p.5). Additionally, the strength improvements achievable through various anaerobic exercises require approximately 8 weeks, with strength sessions conducted ideally two days weekly on non-consecutive days (Giron et al., 2021, p.5). These considerations highlight the need for the respiratory therapist to adopt a structured approach to including physical exercise as a therapeutic intervention in the respiratory care plan for adolescent and adult CF patients.

Nutritional Interventions

CF patients have unique nutritional needs throughout their lifespans. Notable, the rationale for including nutritional interventions in the CF adult and adolescent patient's respiratory care plan is that the CFTR gene mutations, the frequent chronic infections' metabolic consequences, and the added breathing effort necessitate enhanced nutritional intake (De Simone et al., 2018). Notably, the available research indicates a demonstrable and significant association between patients' survival and pulmonary function, on the one hand, and normal weight ranges on the other, thereby highlighting the importance of including achieving effective nutritional balance as a therapy goal for the effective respiratory care plan (Giron et al., 2021). The key considerations for effective nutritional therapy for the focal patient population include, firstly, maintaining a high-calorie diet to achieve the CF patients' requisite high energy intake of approximately between 110% TO 200% of the general healthy population's requirement (Skach, 2002; Giron et al., 2021). Secondly, the effective care plan's provisions for nutritional therapy should also include considerations regarding monitoring the CF patients for evidence of vitamin deficiency and the interventions and approaches required to treat them accordingly to avoid adverse outcomes like oxidative stress through vitamin C supplementation (Smyth et al., 2014). More specifically, the current vitamin supplementation guidelines (Smyth et al., 2014) include 500 to 1000 IU/d vitamin A; adequate sun exposure and 400 to 800 IU/d vitamin D; 400 to 800 IU/d vitamin E; and 2.5 mg to 5 mg of vitamin K weekly. The supplementation interventions respond to the high risk of deficiency and the higher incidence of related adverse outcomes among all CF patients, including adults and adolescents.

Ongoing Monitoring

Various components of the proposed care plan, such as the potential adverse effects associated with the recommended pharmacological and non-pharmacological interventions and

the nutritional risks inherent in the adult and adolescent CF patient profile, indicate the necessity of continuous monitoring as a cornerstone of the effective respiratory care plan for the target patient populations. Regarding clinical monitoring, all CF patients should be monitored for the clinical symptoms and signs of respiratory compromise (Wagener & Headley, 2003). Signs and symptoms such as persistent cough, chronic throat clearing, crackles on chest examination, reduced exercise tolerance, sputum appearance and production, wheezing, hemoptysis, and reduced sleep quality should be treated as pathologies implicated in the CF's pathophysiology and as indicators of potential exacerbations that require further investigation and possibly therapy directed toward resolving infection and airway obstruction (Davies & Alton, 2009; Chatburn & Mireles-Cabodevila, 2010; Kacmarek et al., 2019). Respiratory therapists should also follow the CF patients' clinical status through continuous pulmonary function monitoring using spirometry, respiratory rate, and pulse oximetry (Kacmarek et al., 2019). Spirometry has demonstrable clinical effectiveness in monitoring CF patients' health status. Using pulse and respiratory oximetry to detect early signs of worsening respiratory function can further augment spirometry's effectiveness, particularly when implemented in measuring oxygenation during sleep among adolescent and adult patients with acute respiratory deterioration or following the presentation of pulmonary hypertension signs during the end-stage phase of chronic respiratory failure (Wagener & Headley, 2003, P. 236). Lung volume measurements are also essential upon positive spirometric evidence of restrictive changes (Kacmarek et al., 2019).

Additionally, radiographic monitoring complements pulmonary function testing's detection of airway functional abnormalities by detecting structural changes as they occur throughout the CF patient's lifespan (Davies & Alton, 2009). Finally, as explained in the plan's previous section, it is essential for the respiratory therapist to also contribute to the continuous

monitoring of the patient's nutritional adequacy to maintain alertness for evidence deficiency and to make nutritional assessments and treatment recommendations accordingly (Wagener & Headley, 2009). Therefore, the respiratory care plan should also include body-mass-index assessments and the monitoring of dietary intake, essential acid, micronutrient status, pulmonary status, and overall quality of life to help enhance clarity regarding the indicated supplements the other relevant nutritional interventions.

Interdisciplinary Care Considerations

As explained, CF in adolescence and adulthood is associated with multiple intersecting physical and psychological challenges for patients and their caregivers. Consequently, a multidisciplinary approach is essential in establishing a care team with the expertise necessary to provide effective physical and psychosocial care to meet these diverse challenges while providing the patient and their family with the necessary support (Wilcox et al., 2018). The model of an effective multidisciplinary care team should include the roles of all the clinical and non-clinical professionals involved in the patient's care process, ranging from the clinical clerical support and the medical director to the physicians, nurses, and respiratory therapist (Wilcox et al., 2018). From the clinical perspective, the physician’s primary roles in the interdisciplinary care team are to evaluate the patient’s functional status at each clinic, to apply the applicable disease management knowledge to interpreting results and planning care, use effective interpersonal communication skills to facilitate patient education as the disease progresses and to collaborate with the multidisciplinary CF team to undertake comprehensive patient status reviews and plan care periodically (Kacmarek et al., 2019). Additionally, the dietician provides specialized nutrition therapy and care planning to optimize the patient’s nutritional status; the physiotherapist works collaboratively with the patient and family to develop, implement, and

continuously modify the appropriate treatment plan; the social worker undertakes clinical reviews to inform the patient's psychosocial support; and the pharmacist provides patient-focused pharmaceutical care (Savage et al., 2021; Wilcox et al., 2018; Kacmarek et al., 2019). The nurse practitioner, nurses, and nurse assistants work directly with the patient and the family to provide education, advocacy, and psychosocial support while developing and implementing the appropriate care plans in collaboration with the patient and family (Wilcox et al., 2018). Together with the social worker and the psychologist, who helps address the patient's and their family's mental health needs when dealing with the challenges associated with CF, the nurse also serves as the primary patient/family educator by teaching patients and families about various aspects of CF using their evidence-based knowledge of the disease. Finally, the effective respiratory care plan should also account for how the respiratory therapist performs the following roles collaboratively within the multidisciplinary CF team (Wilcox et al., 2018):

- Assist in caring for the CF patient's respiratory needs
- Provide the knowledge and experience input regarding the pulmonary tests and issues related to CF
- Recognize the warning signs of a decline in the patient's lung function and alert the team
- Perform all tests and procedures to establish lung function measurements at each clinic visit
- Produce longitudinal studies of the CF patients' status.

Conclusion

This respiratory care plan first demonstrates the importance of the respiratory therapist's knowledge of CF's pathophysiology and how it provides the basis and rationale for the relevant diagnostic tests and therapies, and interventions. Specifically, the plan reveals that the effective

diagnosis of adolescent and adult patients for CF considers the disease's clinical characteristics and typical clinical presentation required to justify the sweat chloride and the genetic tests necessary to ascertain a CF diagnosis and rule out the potential differential diagnoses. Notably, the care plan highlights the patient cases and challenging diagnoses that require additional considerations for extended and full panel genetic testing, particularly the adolescent and adult patient cases necessitating extended or full panel genetic diagnoses. The plan also comprehensively details the appropriate pharmacological interventions for treating respiratory obstruction, inflammation, infection, and chronic respiratory failure and providing adequate palliative care during CF's terminal stage. The non-pharmacological interventions explored include various ACT physiotherapy techniques and physical exercise. Nutritional therapy also emerged as a focal point in the respiratory plan. The plan concluded with a detailed examination of the appropriate considerations for continuous monitoring and multidisciplinary care and the respiratory therapist's role in the multidisciplinary care team. Overall, implementing the guidelines and recommendations synthesized herein will result in a respiratory care plan that effectively meets the goals of respiratory therapy for adolescent, adult, and end-stage CF patients, as anticipated at the outset of this paper.

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