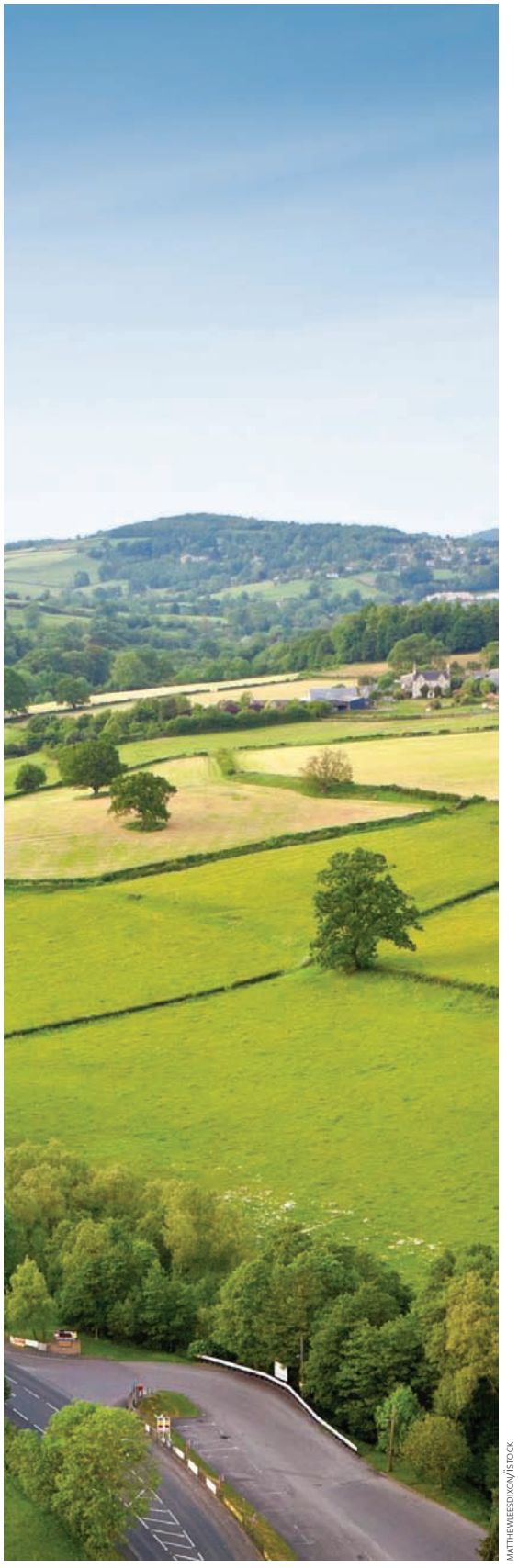

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Cystic fibrosis: A changing landscape

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Abstract: Cystic fibrosis (CF) is an autosomal recessive genetic disorder that causes a lifetime of debilitating and life-threatening complications affecting the lungs and other organ systems. Over 1,700 gene mutations that cause this rare disorder have been identified. This article describes the current treatment landscape for adults with CF, including the 2019 FDA approval of a breakthrough triple-drug combination therapy that may significantly improve the quality of life for an estimated 90% of patients with CF.

Keywords: CF, CFTR gene, CFTR modulators, cystic fibrosis, cystic fibrosis transmembrane conductance regulator gene, genetic disorders, triple-drug combination therapy

THIS ARTICLE is inspired by the journey of a patient born in the early 1990s with cystic fibrosis (CF). This timing of birth allowed the patient to experience the evolution of CF treatment as it has unfolded and achieve early adulthood goals of college, career, and marriage. Nevertheless, although able to live an outwardly normal life, this patient has developed severe pulmonary function loss from fibrotic changes in lung tissue and mucus buildup that obstructs the airways, and complications such as pneumothoraces and pulmonary infections. Consequently, the patient has been unable to engage in many commonplace activities of daily life and can no longer work due to the need for full-time oxygen support. Now homebound, this patient is waiting for a lung transplant due to end-stage respiratory disease.

Thanks to dramatic treatment advances discussed in this article, patients born between 2015 and 2019 have a median life expectancy of 46 years, according to the Cystic Fibrosis Foundation.[1] However, due to a lifetime of CF complications and irreversible damage to the lungs and other organs, patients born in the 1990s have a much shorter life expectancy, about 32 years.

CF is an autosomal recessive genetic disorder that is most prevalent in White patients.[2] Over 1,700 gene mutations that cause the disorder have been identified.[3] Due to the variety of gene mutations, many people do not realize that they are carriers for this disorder until they have a child diagnosed with CF. The Cystic Fibrosis Foundation reports that over 30,000 people in the US are living with this rare disease, with over 50% being 18 or older.[4]

This article describes the current treatment landscape for adults with CF, including the 2019 FDA approval of a breakthrough triple-drug combination therapy that may significantly improve the quality of life for an estimated 90% of patients with CF.[5]

Pathophysiology and presentation

Patients diagnosed with CF have genetic mutations that affect the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which produces CFTR protein. This protein functions as an ion channel across the membrane of cells that produce mucus, sweat, saliva, tears, and digestive enzymes (*see Pathology of CF*).[6,7]

Normally, the CFTR protein regulates the flow of water and chloride between the intra- and extracellular fluid. Absent or abnormal CFTR protein results in thickened mucus and increased sweat chloride, which impairs normal functioning of the sweat glands, lungs, pancreas, digestive system, and reproductive system. In particular, thickened mucus precipitates fibrotic changes in the lungs and pancreas.[8-10]

In the lungs, thickened mucus supports the establishment of chronic lung infections. Chronic inflammation secondary to infection leads to fibrosis in the lungs and decreases lung function.[8]

In the pancreas, thickened mucus obstructs the ducts and prevents normal pancreatic function, resulting in chronic inflammation, nutritional issues, and eventual fibrosis.[9] Because damage to the pancreas causes insulin deficiency, some patients with CF require administration of insulin.[11]

Impaired transport of sodium, chloride, and bicarbonate creates a viscous exocrine fluid that blocks the proximal pancreatic ducts. Consequently, patients commonly experience steatorrhea, malnutrition, and fat-soluble vitamin deficiencies.[12]

Along with pancreatic manifestations of the disease, patients with CF experience decreased intestinal motility, which leads to small intestine bacterial overgrowth (SIBO), constipation, and anorexia. SIBO can further diminish fat absorption.[12] Malnourishment is a hallmark of CF because patients have difficulty eating and absorbing enough calories and nutrients to maintain their weight.[13]

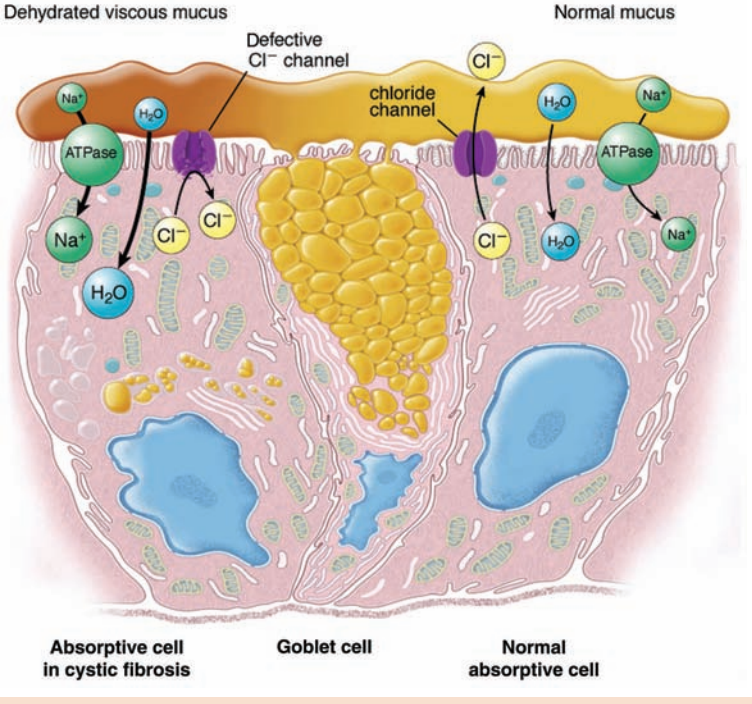
Patients with CF also experience fertility issues. Most males are infertile because of defects in sperm transport.[10] The most common cause of infertility in males is the absence of the vas deferens, which is thought to be caused by the CFTR mutation's impact on embryonic development. In females, reduced fertility is typically attributed to malnutrition and abnormally tenacious cervical mucus. However, although female patients with CF are less fertile than normal healthy women, all females with CF have the potential to become pregnant.[10]

CF is diagnosed based on clinical signs and symptoms consistent with CF in at least one organ system and evidence of CFTR dysfunction, such as elevated sweat chloride or the presence of two disease-causing mutations in the CFTR gene. Clinical signs and symptoms are not required to diagnose infants identified through newborn screening and siblings of patients with CF.[10]

The effects of CF are pervasive in a patient's life and extend well beyond the physical manifestations. CF impacts quality of life due to its effect on mental health, social identity, and professional/family aspirations, as we discuss in more detail below.

Pathology of CF

This illustration depicts how dysfunctional chloride transport alters mucus quality in patients with CF. A defect in the CFTR protein reduces chloride transport into the lumen of a bronchial tube or organ duct. Sodium ion resorption from the luminal surface is then increased, and water moves into the cell along the resulting osmotic gradient. As a result, the mucus layer becomes dehydrated and viscous. The mucociliary escalator has difficulty conveying this thickened mucus out of the respiratory tract and it therefore obstructs the lumen.



Source: Thompson WR, ed. American College of Sports Medicine. *ACSM's Clinical Exercise Physiology.* Philadelphia, PA: Wolters Kluwer; 2019.

Management overview

Conservative treatment of patients with CF typically entails the use of medications to control signs and symptoms. For example, patients with CF follow daily medication regimens to promote airway clearance. Regimens can include the use of metered-dose inhalers and/or ultrasonic nebulizers to locally administer beta-2 adrenergic receptor agonists, which help dilate airways. These regimens can also include the use of inhaled glucocorticoids to decrease lung inflammation. Additionally, aerosolized hypertonic saline can be locally administered to loosen and liquefy inspissated mucus. Dornase alpha, developed specifically for the treatment of CF (as discussed below), can also be used to help with secretion management.[12]

Chest physiotherapy (CPT) is included in conventional treatment regimens to loosen mucus and help transport it out of the lungs and airways. CPT includes the use of postural drainage, percussion, and vibration to promote the transport of mucus out of the lungs. Oscillating devices such as flutter valves and high-frequency chest wall oscillation vests may also be used to help loosen secretions for patients with copious or tenacious sputum.[14,15]

Besides these daily regimens, patients may need antibiotics to treat both acute and chronic pulmonary infections. These antibiotics can be systemic (administered orally or I.V.) or local (aerosolized for delivery to the lungs). Sputum cultures determine the class and route of antibiotic indicated to treat an infection. For example, patients with *Pseudomonas* infections are commonly prescribed aerosolized aminoglycosides, such as tobramycin, or colistin (colistimethate). Severe *Pseudomonas* infections may require the administration of I.V. carbapenems, such as meropenem. Penicillins or cephalosporins can be taken orally or I.V. to treat *Staphylococcus aureus* infections. However, drug resistance may require patients to receive I.V. drugs such as vancomycin for these same infections. Long-term I.V. antibiotic therapy may be needed, requiring patients to self-administer the medication at home via a peripherally inserted central catheter.[16]

Evolution of drug therapy

Over the years, aggressive research on CF has yielded improved treatment modalities as evidenced by the continual increase in life expectancy for patients with CF.[4] Treatment advances between 1993 and 2010 centered on symptom management. The first major breakthrough occurred in 1993 with FDA approval of dornase alfa for inhalation use. Classified as a recombinant deoxyribonuclease I enzyme, it is indicated in conjunction with standard therapies to improve pulmonary function in patients with CF. This drug thins mucus secretions and improves airway clearance. It is administered with an approved jet nebulizer/compressor system and must not be administered simultaneously with any other drug.[17]

Next, the Cystic Fibrosis Foundation advocated for use of newly developed aerosolized antibiotics that would allow localized administration to the lungs to help suppress and contain CF-related lung infections. Aerosolized tobramycin and inhaled aztreonam were approved by the FDA in 1997 and 2010, respectively, for management of *Pseudomonas aeruginosa* infections. Tobramycin is now available in capsule form for use in a dry powder inhaler, providing added convenience for patients.[18]

After the approval of aerosolized tobramycin and aztreonam, pharmaceutical research shifted from symptom management to treatment of the disease at the cellular level with CFTR modulators, which are intended to prevent the thickened mucus and chronic infection/inflammation that lead to such complications as decreased lung function and malnutrition.[19] Drugs in this class improve production, processing, and functioning of the defective CFTR protein. The hope is that patients taking CFTR modulators will not experience advanced disease manifestations that require treatment with insulin therapy or lung transplantation.[20]

Ivacaftor, the first CFTR modulator, was initially approved by the FDA in 2012. It is provided in single-use granule packets for oral administration to pediatric patients age 4 months and older, and as oral tablets (packaged in blister packs) for adults and children age 6 years and older. This drug potentiates the CFTR protein to help facilitate chloride transport.[21]

Ivacaftor has been shown to improve lung function, but it is effective in treating only certain CFTR mutations.[21] Initially it was approved for treating one CFTR mutation, but this has been expanded to include nine additional mutations. Ivacaftor monotherapy is still being used to treat the approved mutations, but it is also included in the newer combination CFTR modulators discussed below. Therapy selection depends on the patient's age and genotype.[19]

Drug combinations take the stage

The development of dual therapy drugs was the next step in the treatment of CF on a cellular level. The ivacaftor and lumacaftor combination is administered orally and is provided in single-use granule packs and tablet blister packs.[22] The combination of ivacaftor and tezacaftor is also administered orally.[23]

While lumacaftor and tezacaftor both target the CFTR mutation, they focus on different flaws within the protein than those targeted by ivacaftor. These dual combinations are intended to improve ion transportation.

The combinations of ivacaftor/lumacaftor and ivacaftor/tezacaftor

continued to pave the path from disease management to disease modification. These initial dual combination therapies yielded statistically significant results.[22,23] However, the transition to triple-drug combination therapy was found to have a more dramatic effect on disease modification.[24,25]

In 2019, the FDA approved a triple-drug combination therapy consisting of ivacaftor, tezacaftor, and elexacaftor. It is indicated for adults and pediatric patients age 12 years and older with at least one copy of the F508del mutation. The interaction of these three drugs significantly potentiates their ability to normalize the transport of ions and mitigate manifestations of the disease. Hailed as a milestone in CF management, this triple-drug combination therapy may be an effective treatment for up to 90% of patients with CF.[24,25]

Patients on the triple-drug combination regimen take two orange tablets containing elexacaftor, tezacaftor, and ivacaftor in the morning and one light blue tablet containing only ivacaftor in the evening.[24] Many patients who take triple-drug combination therapy experience fewer CF exacerbations and improved disease management.[24] While dual therapy CFTR modulators have the ability to improve quality of life by decreasing CF exacerbations and their associated infections, triple-drug combination therapy mitigates everyday symptoms and improves the stamina of patients with CF. It has also been shown to significantly improve lung function, decrease CF exacerbations, and decrease sweat chloride in as little as 24 weeks of therapy.[24] Compared with previous CFTR modulators, triple-drug combination therapy provides hope that CF will now be a manageable chronic disease for most patients with CF.[25]

However, keep in mind that the CFTR modulators are mutation-specific. Triple-drug combination therapy is indicated for those with at least one F508del mutation, and about 10% of patients do not have an indicated mutation. These patients are not eligible to receive these pharmacotherapies.[25]

Nurses can disseminate their knowledge of the new CF landscape in professional publications to improve evidence-based care guidelines.

Implications of treatment advances

Children and young adults diagnosed with CF today have the potential to greatly benefit from new drug modalities. The improved ability of CFTR modulators to treat CF gives patients hope for living a productive life well into adulthood. The ability to normalize ion transport may prevent many of the most debilitating complications of CF, such as decreased lung function, diabetes, and gastrointestinal disorders.

Unfortunately, patients with advanced CF may not be able to reap the full benefits of promising therapies such as triple-drug combination therapy because medication cannot reverse damage already done by the CFTR mutation, particularly pulmonary and pancreatic fibrosis. Though the treatment team may add combination therapy to the medication regimens of patients with advanced CF, patients who have irreparable damage will continue to need conventional management such as insulin therapy or lung transplants. Although these medications cannot reverse permanent physiologic damage, clinical judgment calls by the CF team may be made to add these medications to a treatment regimen in an effort to stabilize the patient's CF manifestations.

Conventional treatments can be intimidating for patients. Those with compromised lung function may continue to struggle with severe pain and drug-resistant infections because of the advanced nature of their disease. The uncertainty of conventional treatments such as lung transplants, combined with pain and fatigue secondary to infection, can induce or exacerbate depression for these patients, particularly young adults who want to start a career and/or a family.

Nursing considerations for adult patients

As the life expectancy for patients with CF increases, nurses are taking care of more adults with CF.[26] It is important for nurses to understand the dynamic nature of the disease and the factors that can impair quality of life.

All patients with CF are at risk for depression and decreased motivation for treatment adherence. Their daily treatment regimen entails coordination with CPT and administration of several medications, which can be a daunting challenge. It is estimated that nontransplanted adults with CF take only about 60% of their prescribed medications.[27]

Along with CFTR modulators, patients may take additional medications to manage symptoms—for example, aerosolized hypertonic saline to decrease mucus viscosity and antibiotics delivered by aerosol, oral, or I.V. routes to manage infections.

The timing of these medications in conjunction with CPT that help expel mucus are burdensome and can consume the patient's entire day, leaving minimal time and energy for work, hobbies, or socializing with family members. Nonadherence to medication regimens can further exacerbate breathing difficulties and nutritional issues. This sets up a snowball effect, leaving patients feeling weak and depressed.

Patients with CF may struggle with proper nutrition because they lack the energy to eat. Patients are encouraged to eat frequent small, high-calorie, high-fat meals to maintain their nutritional status and weight. In addition, patients prescribed ivacaftor should take doses with fat-containing food to increase drug exposure.[22-24]

Maintaining a schedule of frequent meals can feel like one more burden to patients, particularly when they are experiencing a CF exacerbation. Consequently, patients in this situation may elect to sleep and conserve energy rather than eat. This choice will further deplete the patient's energy and raise the risk of inactivity, skipping medications, and depression. All of these factors can lead to fears of future infections and hospitalizations that can fuel feelings of hopelessness. Nurses need to screen patients for depression and share the screening results with the interprofessional team so patients can receive appropriate counseling and other support services.

While treatment advances have raised expectations for improved quality of life for most younger patients, those who do not have mutations that respond to CFTR modulator therapy and those with advanced lung disease may feel left out and struggle to cope as they grieve for the life they may not have. It is especially important to screen these patients for anxiety, depression, and suicidal ideation and share findings with the interprofessional team. Counseling and other mental health resources can help patients develop effective strategies that will enable them to better cope with hospitalizations and manage daily life struggles once they are discharged home.

Supporting families

Nurses are in a key position to support patients' spouses or significant others through the emotional turmoil associated with ongoing management of CF. Like patients with CF, family members may also grieve losses associated with decreased functional ability, decreased lifespan, or the inability to have children. Responsibilities of running the household, providing an income, and serving as a support and care provider to the partner may impact the mental and physical health of spouses or significant others. As part of the interprofessional team, nurses can advocate for spouses or significant others to help them utilize community support services such as counseling and/or support groups. If support groups are not available in the community, nurses can encourage the spouse or significant other to reach out to other CF patient partners through venues such as social media.

The CF population celebrates that more people are successfully planning and executing career and lifetime goals. However, symptoms and infections associated with advanced lung disease can impair a young adult's ability to work and advance a career. Nurses caring for these patients in an acute care setting can help them vent their feelings and refer them to resources such as Compass. Offered through the Cystic Fibrosis Foundation, Compass provides personalized help to patients on a range of topics, such as insurance, financial, and legal issues. For example, Compass could help a patient who is no longer able to work apply for disability benefits.[28]

People diagnosed with CF who can fully benefit from triple-drug combination therapy may have the ability to achieve developmental milestones associated with adulthood and feel comfortable planning for a future with children. The nurse can play a vital role in helping them understand the importance of reproductive counseling, which can help CF couples identify if they can have children naturally. This counseling also supports CF couples with decision-making related to topics such as reproductive technologies, surrogacy, third-party reproduction, and adoption. The nurse can also help the couple determine if genetic counseling coincides with their value system and if it would benefit their family planning process.

Finally, nurses are in a key position to help shape CF treatment in the future. The long-term effects of CFTR modulator therapy are not known. Nursing assessments can help identify unforeseen comorbidities in this patient population that may be related to increased life expectancy resultant from CFTR modulator therapy. As patients are living longer and experiencing better outcomes, they may develop conditions that were not previously associated with the CF disease process. For instance, patients are typically underweight due to malnourishment related to the gastrointestinal manifestations of the disease. These patients were historically encouraged to have a high-fat, high-calorie diet to maintain a normal weight and body composition. Now, with the advent of triple-drug combination therapy, patients with CF may become obese because the drug therapy corrects the malabsorption issues associated with CF. The ability to assess, identify, and trend these unforeseen comorbidities will provide vital evidence in developing best practices in the treatment of patients with CF.

Living longer and better

Awareness of CF and disease burden is important for nurses so they can provide holistic care to all patients

with CF. Nurses can also disseminate their knowledge of the new CF disease landscape in professional publications that will in turn help improve the evidence-based care guidelines for patients with CF.

The authors of this article would like to thank all the members of the interprofessional CF care teams for their dedication and support of patients with CF. The health professionals in these teams go beyond collaboration; they have an alliance to holistically support patients in dealing with the disease manifestations. The CF care teams truly advocate for these patients by helping them live the best spiritual, mental, and physical life possible. ■

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The authors and planners have disclosed no potential conflicts of interest, financial or otherwise.

DOI-10.1097/01.NURSE.0000751344.57701.75