UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL
Read more URNCST Journal articles and submit your own today at: https://www.urncst.com

REVIEW OPEN ACCESS

Persistent Bacterial Infections in Cystic Fibrosis Patients: Exploring Lung Pathophysiology and Antibiotic Challenges

Georges Massaad, BHSc Student [1]*, Natalie (Natasha) Tal, BHSc Student [1]

[1] Department of Biochemistry and Biomedical Sciences, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada L8S 4L8

*Corresponding Author: massaadg@mcmaster.ca

Abstract

Introduction: With over 100,000 people affected worldwide, Cystic Fibrosis (CF) is a genetic condition caused by the dysfunction of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein. This defect impacts the cells, tissues, and glands responsible for producing mucus and sweat. Normally, mucus acts as a protective barrier in the airways and the body. In CF, dysfunctional CFTR leads to thick and sticky mucus, clogging airways and impairing organ function. CF was an untreatable disease with high childhood fatality, but scientific advancements have now provided effective treatment options. Persistent bacterial infections significantly impact CF morbidity and mortality, necessitating comprehensive studies to understand these associations. This paper presents a clinician-targeted review investigating bacterial adaptations in CF lungs, their role in treatment-resistant infections, and strategies to mitigate these challenges.

Methods: A review analyzed factors influencing bacterial persistence in CF patients, utilizing sources including PubMed, ScienceDirect, Frontiers, and ATS Journals. Keywords used were CF pathophysiology, bacterial adaptations, treatment resistant, CFTR, antibiotic delivery. Existing research data were compared across different patient groups, antibiotics, and bacteria strains to identify patterns related to antimicrobial resistance, mucus properties, and population age.

Results: Impaired mucociliary clearance and increased mucus viscosity are expected to contribute to bacterial colonization and treatment resistance. Dysfunctional immune responses facilitate persistent infections by impairing immune clearance mechanisms due to chronic neutrophil-dominated inflammation. Bacterial adaptations, particularly antibiotic resistance mechanisms, enable bacteria to evade treatment, perpetuating infections.

Discussion: Bacterial persistence in CF patients is exacerbated by thick mucus and advanced bacterial resistance mechanisms such as biofilm formation and efflux pumps. Early initiation of therapies like Trikafta® significantly improves lung function and reduces infection rates, highlighting the importance of addressing both bacterial adaptations and the CF lung environment. Future research should focus on combination therapies and treatments personalized to genetic profiles.

Conclusion: The study emphasizes the critical interplay between CF lung conditions and bacterial resistance, underscoring the need for innovative therapies. Early intervention with treatments like Trikafta® improves outcomes by enhancing mucus clearance and reducing infection rates. Future research should prioritize combination therapies and personalized approaches to manage chronic infections and improve CF patient quality of life.

Keywords: cystic fibrosis; CFTR; antibiotic resistance; biofilms; mucus clearance; Trikafta®; bacterial adaptations; high-frequency chest wall oscillation

Introduction

Cystic Fibrosis (CF) is a genetic condition affecting over 100,000 people worldwide, caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene [1]. This gene encodes a protein that regulates the movement of salt and water in and out of cells [1]. In healthy patients, the mucus affected by CFTR acts as a protective barrier in the airways and other tissues and helps clear pathogens [1]. In CF patients, dysfunctional CFTR protein leads to the production of thick and sticky mucus, particularly in the lungs and digestive system, resulting in severe respiratory and gastrointestinal complications, such as clogged airways and organ malfunctions, Figure 1 [1-4]. Historically, CF was predominantly a fatal childhood disease [5]. In the early 20th century, children with CF rarely survived past elementary school age [5]. However, significant advancements in the understanding and treatment of CF have dramatically improved patient outcomes. Treatments can improve the quality of life for CF patients by improving lung function, preventing further complications, and improving nutrition status, daily convenience, and overall livelihood [1, 5].

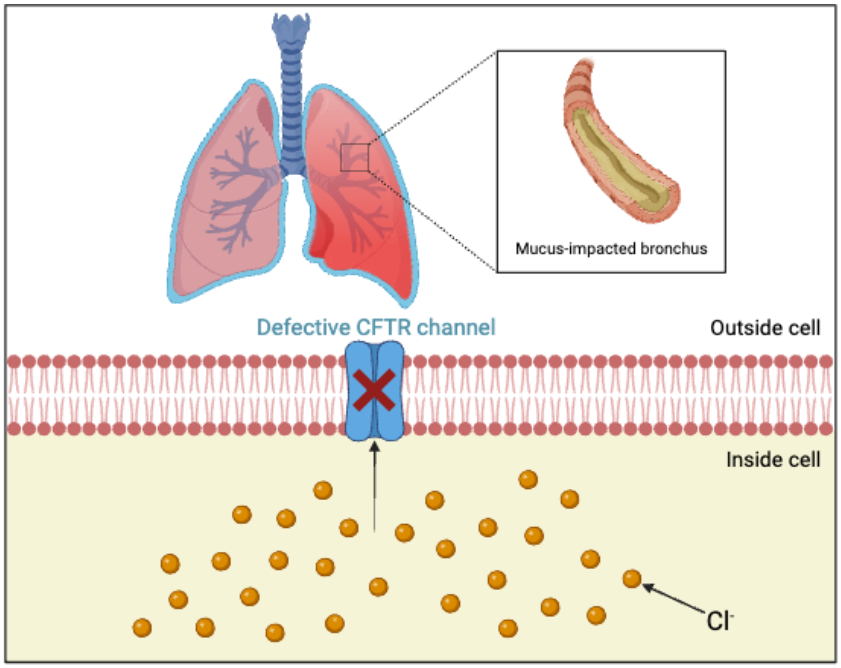

Figure 1. Impact of the dysfunctional CFTR protein in the lungs. The malfunction of CFTR channels disrupts ion balance, leading to thick, sticky mucus that clogs airways. Created with BioRender.com [4].

Modern therapies, including vibration airway clearance techniques, have extended the median life expectancy for CF patients to over 50 years old [2]. A vital component of CF management is airway clearance to help loosen and remove the thick mucus from the lungs [2]. One effective method is the High-Frequency Chest Wall Oscillation (HFCWO), commonly known as the vest therapy [6]. This technique involves wearing an inflatable vest connected to a machine that rapidly inflates and deflates, creating vibrations that help dislodge mucus from airway walls [6]. The patient then performs huff coughing or other breathing techniques to expel the loosened mucus [6]. Another ground-breaking treatment for CF is Trikafta®, a three-component combination therapy approved by the Food and Drug Administration (FDA) in October 2019, marking a substantial advancement in CF treatment [7]. Despite these advances, persistent bacterial infections in the lungs remain a major challenge, contributing to significant morbidity and mortality [2, 8]. One of the critical issues in managing CF is the persistent bacterial infections that CF patients frequently suffer from [2]. These infections are difficult to eradicate due to the thick mucus that traps bacteria and the development of antibiotic resistance [8]. This creates a cycle of chronic infection and inflammation, further damaging tissue and reducing lung function [8]. Understanding how bacterial adaptations and resistance mechanisms contribute to persistent lung infections in CF patients is crucial. This paper presents a clinician-targeted review that investigates the interplay between the pathophysiological conditions in CF lungs and the mechanisms bacteria use to resist treatment, to identify currently studied potential strategies to combat these infections more effectively.

Methods

This review analyzes existing literature from PubMed, ScienceDirect, Frontiers, and ATS Journals, focusing on CF patients across various demographics. The study evaluates interventions including different antibiotic regimens and advanced therapies like Trikafta® and HFCWO. Data extraction identifies key factors such as antimicrobial resistance, mucus properties, and patient demographics, with statistical analyses conducted to assess associations. Both generic and proprietary drug names are included for clarity. The aim is to understand the interplay between CF pathophysiology, bacterial adaptations, and therapeutic interventions.

Results

The *CFTR* gene codes for the CFTR protein which controls the movement of ions from the inside to the outside of the cell [9]. With CF, the CFTR has mutations, causing improper functioning**,** resulting in a disbalance in sodium and water across membranes [9]. There are over 2000 mutations of the CFTR, which affect the transport, efficacy and produced amount of CFTR protein [9]. There are six main classes of mutations, with the two most common classes being class I and class II. In class I mutations, no CFTR protein is produced, causing major disruptions of the CFTR gene, caused by gene insertions,

deletions and premature stop codons, for example, G542X [43]. In class II mutations, CFTR protein is created but misfolds, keeping it from moving to the cell surface (trafficking defect) [10]. Class II mutations are responsible for around 90% of mutations in CF patients and is usually caused by a deletion of the amino acid phenylalanine at allele 508, called *DF508*. This destabilizes the original conformation of one of the nucleotide binding domains, which in turn, promotes an aggregation-prone structure, leading to the dysfunctional protein [10, 11].

CFTR protein is most often expressed in epithelial cells' apical membrane, found in airway epithelia, paranasal sinuses, pancreas, gut epithelia, and others, with airway epithelia being the location of the most CFTR expression [10]. The protein functions as a cyclic adenosine monophosphate- (cAMP) dependent chloride channel [12]. With the class II mutations, the protein mainly misfolds and does not reach the cell's surface where it is needed, and even if small amounts of protein do reach the intended target, it is highly unstable, causing many defects [11]. Improper functioning of the CFTR protein prevents water and chloride from crossing membranes, making regular mucus thicker due to the lack of water [9]. With the mucus becoming dehydrated, and therefore stickier, it cannot be moved by cilia (small hairlike structures) that line many tissues [13]. This causes the mucus to be difficult to clear and become stuck, leading to CF symptoms, including many lung function issues, and the prevalence of bacterial infections from the uncleared mucus [13]. This can affect the body drastically, not only affecting the lungs, but also the gastrointestinal tract, pancreatic ducts, and others [13].

Bacterial Strains and Antibiotic Use

Chronic bacterial infections in CF patients are particularly challenging due to the unique pathophysiology of CF lungs and the sophisticated resistance mechanisms of the pathogens involved.

Pseudomonas aeruginosa stands out as a major pathogen in CF due to its challenging resistance and biofilm-forming capabilities. Biofilms are structured communities of bacteria encapsulated in a self-produced matrix, which protect the bacteria from both antibiotics and the host immune response [14]. This protection allows *P. aeruginosa* to persist in the lungs, leading to chronic and hard-to-treat infections. The use of β-lactams (e.g., ceftazidime), aminoglycosides (e.g., tobramycin), and fluoroquinolones (e.g., ciprofloxacin) are common in treatment. Inhaled antibiotics, such as tobramycin and colistin, are normally used as they deliver high concentrations of the drug directly to the site of infection, enhancing efficacy while minimizing systemic toxicity [14]. Adjunct therapies, such as DNase enzymes, have shown potential in disrupting biofilms by breaking down extracellular DNA, thereby aiding antibiotic penetration and improving treatment outcome [14].

Another common pathogen in CF is *Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA). *S. aureus* can also form biofilms, although its persistence in CF is less pronounced than *P. aeruginosa* [15]. Treatment strategies for *S. aureus* include β-lactams macrolides (e.g., azithromycin), and fluoroquinolones. In the case of MRSA, more potent antibiotics like vancomycin or linezolid are required [16].

Burkholderia cepacia complex represents another challenging group of pathogens due to their resistance to many antibiotics. *B. cepacian* is particularly problematic because it can lead to a rapid decline in lung function and is associated with poor clinical outcomes. Treatment typically involves combinations of β-lactams, aminoglycosides and fluoroquinolones with therapy being guided by susceptibility testing to ensure effectiveness [17].

The persistent nature of these infections can be attributed to a combination of antimicrobial resistance (AMR) mechanisms and the thick, sticky mucus characteristic of CF lungs. Resistance mechanisms, such as biofilm formation and efflux pumps, prevent antibiotics from reaching their target effectively, while the mucus barrier further complicates drug delivery and bacterial clearance [18]. This synergistic challenge highlights the need for novel therapeutic strategies that can overcome both the physical barriers and the bacterial defense mechanisms in CF. For example, the use of efflux pump inhibitors (EPIs) has been explored to block the expulsion of antibiotics from bacterial cells, thereby enhancing drug retention and efficacy, although further research is needed to confirm their clinical benefits in CF [18].

Therapeutic Approaches

Trikafta®

Trikafta®, a ground-breaking CF therapy, was approved by the FDA in October 2019 for patients aged 12 years and older with at least one F508del mutation in the *CFTR* gene. This mutation affects approximately 90% of the cystic fibrosis population, translating to rougly 27,000 individuals in the United States along, making Trikafta® a potential treatment for the majority of CF patients [7]. Trikafta® consists of three components: elexacaftor, tezacaftor, and ivacaftor. Elexacaftor and tezacaftor function as CFTR correctors, enhancing the amount of CFTR protein at the cell surface, while ivacaftor acts as a potentiator, increasing the protein's functionality by facilitating chloride transport across cell membranes [7, 19]. This combination therapy significantly enhances CFTR protein processing and trafficking to the cell surface and increases chloride ion transport, thereby correcting the osmotic balance and mucus clearance in airways. Clinical trials have demonstrated that Trikafta® can improve lung function, reduce pulmonary exacerbations, and enhance quality of life in CF patients [7, 19]. Percent predicted forced expiratory volume in one second (ppFEV1) is a measurement used to assess lung function, representing the percentage of a person's lung capacity that can be fully exhaled in one second, adjusted for age, sex, height, and

ethnic background [20]. Clinical trials have demonstrated that Trikafta® can increase ppFEV1 by an average of 14% and reduce pulmonary exacerbations by 63%, significantly improving the quality of life for CF patients [21]. The efficacy and safety of Trikafta® were supported by two vital trials. Trial 1 involved CF patients with one copy of the F508del mutation, who were randomly assigned to receive either Trikafta® or a placebo in a double blind study for a 24-week period [7]. Trial 2 included CF patients with two copies of the F508del mutation, comparing Trikafta® to an active control (tezacaftor/ivacaftor) in a double blind study over a 4-week period [7]. Following these studies, a phase 3 extension trial was conducted leading to findings sustained over a 192-week study, reinforcing Trikafta®'s long-term efficacy and safety. Moreover, data from patient registries have corroborated these findings, showing significant improvements in lung function, reduced hospitalizations, and lower rates of infection with common CF pathogens [22].

High-Frequency Chest Wall Oscillation

HFCWO, commonly known as vest therapy, has been a cornerstone in the management of CF since its introduction in the late 1980s [23]. The therapy involves wearing an inflatable vest connected to a machine that rapidly inflates and deflates, creating high-frequency oscillations that generate vibrations throughout the chest wall. These vibrations help to dislodge and mobilize mucus from the bronchial walls, facilitating its movement up the airways where it can be more easily expelled through respiratory maneuvers such as coughing [6]. Studies have shown that regular use of HFCWO significantly enhances mucus clearance, reduces pulmonary exacerbations, and improves lung function. For instance, a randomized controlled trial found that patients using HFCWO experienced a significant improvement in ppFEV1 and a reduction in hospitalizations compared to those using conventional chest physiotherapy. Additionally, long-term studies have demonstrated that consistent use of HFCWO can slow the decline in lung function typically observed in CF patients, thereby extending life expectancy and enhancing quality of life [24].

Classes of Commonly Used Antibiotics and Their Mechanisms

β-lactams

β-lactams, including penicillins (e.g., piperacillin-tazobactam) and cephalosporins (e.g., ceftazidime), are widely used in CF treatment. These antibiotics function by binding to penicillin-binding proteins (PBPs) on the bacterial cell wall, inhibiting the synthesis of peptidoglycan, an essential component of the cell wall [25]. This inhibition leads to cell wall weakening, causing the bacterial cell to lyse and die due to osmotic pressure differences. They are effective against *P. aeruginosa*, a common and persistent pathogen in CF patients [25].

Macrolides

Macrolides, like azithromycin and clarithromycin, inhibit bacterial protein synthesis by binding to the 50S subunit of the bacterial ribosome, preventing the translocation of the peptide chain. This inhibition halts protein synthesis, leading to bacterial cell death [26]. Besides their direct antibacterial activity, macrolides have anti-inflammatory properties that help reduce lung inflammation in CF patients, thereby decreasing the frequency of pulmonary exacerbations and improving lung function [27]. This type of antibiotic can target bacteria such as *P. aeruginosa*.

Aminoglycosides

Aminoglycosides, such as tobramycin work by binding to the 30S subunit of the bacterial ribosome, causing a misreading of messenger ribonucleic acid (mRNA). This misreading results in the production of defective proteins, ultimately leading to bacterial cell death [28]. Aminoglycosides are potent against Gram-negative bacteria, particularly *P. aeruginosa*. The inhaled form of tobramycin is beneficial for CF patients as it delivers high local drug concentrations directly to the lungs while minimizing systemic toxicity [29].

Fluoroquinolones

Fluoroquinolones, such as ciprofloxacin, target bacterial deoxyribonucleic acid (DNA) gyrase and topoisomerase IV. These enzymes are crucial for DNA replication and transcription. By inhibiting these enzymes, fluoroquinolones prevent bacterial DNA from uncoiling and replicating, leading to cell death [30]. These antibiotics are effective against a broad range of bacteria, including *P. aeruginosa* and *S. aureus* [31].

Polymyxins

Polymyxins, particularly colistin, interact with the phospholipids of the bacterial cell membrane, disrupting its structure and increasing its permeability. This disruption leads to leakage of cellular contents and subsequent bacterial cell death [32]. Colistin is used as a last-resort antibiotic for multi-drug resistant *P. aeruginosa* and *Acinetobacter baumannii* infections. Its inhaled form allows for high local concentrations in the lungs with fewer systemic side effects [33].

Discussion

Bacterial Adaptations and AMR

Antimicrobial resistance is the phenomenon where bacteria evolve to survive exposure to antibiotics that would normally kill them or inhibit their growth. AMR complicates the treatment of infections, particularly in chronic conditions like CF. The resistance mechanisms employed by bacteria are varied and sophisticated, allowing them to evade the effects of antibiotics and persist in hostile environments [34].

One key mechanism of antibiotic resistance is the production of enzymes that degrade or modify antibiotics, rendering them ineffective. β-lactamases are enzymes produced by bacteria that hydrolyze the β-lactam ring found in penicillins and cephalosporins, effectively neutralizing these antibiotics [35].

Efflux pumps are another critical resistance mechanism, where bacteria utilize protein pumps embedded in their cell membranes to actively expel antibiotics from their cells. This reduction in intracellular antibiotic concentration helps the bacteria survive even in the presence of antibiotics. Certain experimental therapies, such as EPIs have been developed to block these pumps, allowing antibiotics to accumulate inside the bacterial cell at effective concentrations [18]. Efflux pumps are particularly prevalent in Gram-negative bacteria such as *P. aeruginosa* and *B. cepacia* complex.

Modification of antibiotic targets is another common resistance strategy. Bacteria can alter the structure of key molecules that antibiotics target, such as PBPs in the case of β-lactams, or ribosomal subunits for macrolides and aminoglycosides [36]. These modifications decrease the binding affinity of antibiotics, thereby reducing their efficacy.

Biofilm formation is a significant mechanism of resistance, especially relevant in CF. Biofilms are communities of bacteria that adhere to surfaces and are embedded within a self-produced extracellular matrix [37]. This matrix acts as a barrier to antibiotics and immune cells, making biofilm-associated bacteria much more resistant to treatment. In CF, *P. aeruginosa* is notorious for its ability to form biofilms, contributing to chronic lung infections [37]. Biofilms also facilitate the horizontal transfer of resistance genes among bacterial populations, further enhancing their survival capabilities in subsequent generations of the strain [38]. Additive therapies, such as DNase enzymes, have been explored to degrade extracellular DNA within biofilms, weakening their structure and improving antibiotic penetration [14].

In the context of CF, the thick and sticky mucus in the lungs creates an environment that not only favours bacterial colonization but also promotes the development of antibiotic resistance. The mucus acts as a physical barrier, impeding the penetration of antibiotics to the site of infection [39]. Additionally, the anaerobic conditions within the mucus can reduce the efficacy of certain antibiotics that require oxygen to attain their full capabilities [40]. The dense mucus also provides a conducive environment for biofilm formation, where bacteria can thrive and resist treatment. The persistent nature of these infections can be attributed to a combination of AMR mechanisms and the mucus characteristics of CF. AMR mechanisms, such as biofilm formation and efflux pumps, prevent antibiotics from reaching effective concentrations at the site of infection, while the mucus barrier further complicates drug delivery and bacterial clearance. This synergistic challenge underscores the important of therapies targeting both biofilm integrity and efflux activity, which could enhance antibiotic effectiveness in overcoming these robust bacterial defenses.

Mechanisms of Bacterial Trapping in CF Mucus

CF mucus is primarily composed of dehydrated and highly viscous glycoproteins, which significantly differ from the thinner mucus found in healthy individuals.

Hydration and Mucus Composition

The CFTR protein, which is defective in CF patients, regulated the transport of chloride ions across epithelial cells. When CFTR is non-functional, chloride ions, along with sodium and water, are not transported effectively, leading to dehydration of the mucus layer. This dehydration results in thickened mucus that is difficult to clear from the airways [40, 41]

Bacterial Colonization

Bacteria such as *P. aeruginosa*, *S. aureus*, and *B. cepacia complex* readily colonize the CF mucus. These bacteria have evolved mechanisms to adhere to the mucus and evade host defenses. For instance, *P. aeruginosa*, produces alginate, an exopolysaccharide that enhances its adhesion, and biofilm formation in the mucus [41].

Avoiding Colonization

Avoiding bacterial colonization in CF patients is challenging due to the inherent nature of the mucus and the persistent exposure to pathogens. Strategies to mitigate colonization include maintaining optimal hydration levels to reduce mucus viscosity and enhance clearance. Nebulized hypertonic saline and DNAse are used to hydrate the mucus and break down DNA in the mucus, respectively, making it less sticky and easier to clear [42]. However, these measures often only temporarily reduce bacterial load, and complete eradication is difficult [29]. Therefore, ongoing research is focused on developing novel therapies that target both the mucus properties and bacterial biofilms to more effectively manage infections in CF patients [43]. Early initiation of Trikafta® therapy has been shown to significantly reduce the time and likelihood of bacterial colonization in CF patients. By improving the function of the CFTR protein and enhancing mucus clearance from an early age, Trikafta® helps maintain a healthier lung environment, thereby decreasing the risk of chronic bacterial infections and improving long-term health outcomes [44].

Future Possible Combination of Therapies

The future progression of medicine may look to combine successful known methods to produce a superior, or at least alternative option. For example, with the success seen in CF patients with the usage of Trikafta®, scientists might investigate where antibiotics may or may not fit into

the treatment plan. Some studies have found that the use of Trikafta® in CF patients has decreased the usage of antibiotics, and infections overall [45]. This may be because of the increased function of the antibiotics due to Trikafta®, but more research is needed in order to confirm this theory. Trikafta® simulations suggest that the usage of an antibiotic such as erythromycin, may increase the exposure of Trikafta®, when looking at drug-drug interactions, suggesting a potential increase in function of Trikafta® [46]. However, with Trikafta® being a recently introduced drug, there is a lack of information and studies with these therapy combinations long-term. Therefore, more research is needed in this area to improve knowledge surrounding this topic, and its potential effects. There are also additional factors to consider when working with the combination of drugs. One major factor is which CF mutation each patient has, which would largely change the treatment plan. Trikafta® is currently eligible for patients with at least one copy of *ΔF508*, the most common CF mutation [47]. However, rare mutations are left out from eligibility of access to this drug, prompting for new research.

The Emergency of Antibiotic Resistance and the Promise of Phage Therapy

The alarming rise in antibiotic resistance is a significant challenge, particularly for treating chronic infections such as those seen in CF. Overuse and misuse of antibiotics have accelerate the evolution of resistant bacteria, rendering many conventional treatments infective [31]. This situation is exacerbated in CF due to the persistent and resistant nature of pathogens previously mentioned. According to the World Health Organization (WHO), antibiotic resistance is one of the most pressing global health threats today [48]. In response to this crisis, phage therapy has emerged as a promising alternative to traditional antibiotics. Bacteriophages (phages) are viruses that specifically target and kill bacteria [49]. They work by attaching to bacterial cells, injecting their genetic material, and using the bacterial machinery to replicate, eventually causing bacterial cell lysis. Phages are highly specific, reducing the impact on beneficial microbiota, and can evolve alongside bacteria, potentially overcoming resistance mechanisms that render antibiotics ineffective [49]. Moreover, some phages can penetrate biofilms, making them particularly useful in treating biofilm-related CF infections, by disrupting the biofilm matrix and directly attacking the embedded bacteria [50]. Despite these advantages, phage therapy faces challenges, including regulatory hurdles and the potential for bacteria to develop resistance to phages. Nonetheless, its potential for treating multi-drug resistant infections offers a hopeful outlook for future CF therapies [50].

Conclusions

In conclusion, cystic fibrosis is a serious disease that effects the lives of tens of thousands of people worldwide [51]. The severe symptoms of the disease, coupled with the added effects from the frequent additional infections from uncleared and lingering bacteria make this disease very devastating, and in need of treating. There are therapies that contribute to the treatment plans used today, including antibiotics, CFTR modulator drugs, vibration therapy, among others. However, despite these advancements, further research is needed to combat issues including, but not limited to, antimicrobial resistance, rare mutations, access equality and distribution, in order to improve the lives of those with this disease. To further improve the treatment of CF, more research is quintessential. Researchers and physicians may inquire to combine current therapies together to improve the current treatment. Any option would require significant research and time but may just bring life-changing advancements to treating cystic fibrosis.

List of Abbreviations

AMR: antimicrobial resistance
cAMP: cyclic adenosine monophosphate
CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
DNA: deoxyribonucleic acid
FDA: food and drug administration
HFCWO: high-frequency chest wall oscillation
MRSA: methicillin-resistant staphylococcus aureus
PBPs: penicillin-binding proteins
ppFEV1: percent predicted forced expiratory volume in one second

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Approval and/or Participant Consent

As this study is a review of existing literature, no ethics approval was required.

Authors' Contributions

GM: Made equal contributions to the conception and design of the study, collected and analyzed data, drafted significant portions of the manuscript, and critically revised it for important intellectual content. Gave final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
NT: Made equal contributions to the conception and design of the study, collected and analyzed data, drafted significant portions of the manuscript, and critically revised it for important intellectual content. Gave final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements
We would like to extend our deepest gratitude to our mentor, Montserrat Mora Ochomogo, for her exceptional guidance and steadfast support throughout the course of this investigation.

Funding
This paper was not funded.

References

[1] National Institute of Health: National Heart, Lung and Blood Institute. Cystic Fibrosis - What Is Cystic Fibrosis? [Internet]. National Heart, Lung, and Blood Institute, National of Health. [cited 2024 Jun 1]. Available from: https://www.nhlbi.nih.gov/health/cystic-fibrosis

[2] Cystic Fibrosis Foundation. CF Foundation Estimates Increase in CF Population [Internet]. Cystic Fibrosis Foundation. [cited 2024 Jun 1]. Available from: https://www.cff.org/news/2022-07/cf-foundation-estimates-increase-cf-population

[3] Mayo Clinic. Cystic fibrosis - Symptoms and causes [Internet]. Mayo Clinic. [cited 2024 Jun 1]. Available from: https://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/symptoms-causes/syc-20353700

[4] Biorender [Internet]. BioRender. [cited 2024 Jul 27]. Available from: https://app.biorender.com/biorender-templates/figures

[5] De Boeck K. Cystic fibrosis in the year 2020: A disease with a new face. Acta Paediatrica. 2020;109 (5):893–9. https://doi.org/10.1111/apa.15155

[6] Cystic Fibrosis Foundation. High-Frequency Chest Wall Oscillation (the Vest) [Internet]. Cystic Fibrosis Foundation. [cited 2024 Jun 1]. Available from: https://www.cff.org/managing-cf/high-frequency-chest-wall-oscillation-vest

[7] Commissioner of the. FDA. FDA approves new breakthrough therapy for cystic fibrosis [Internet]. FDA. [cited 2024 Jun 18]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis

[8] Cystic Fibrosis Foundation. About Cystic Fibrosis [Internet]. Cystic Fibrosis Foundation. [cited 2024 Jun 1]. Available from: https://www.cff.org/intro-cf/about-cystic-fibrosis

[9] National Heart, Lung and Blood Institute: Cystic Fibrosis - Causes [Internet]. National Institute of Health. [cited 2024 Jun 20]. Available from: https://www.nhlbi.nih.gov/health/cystic-fibrosis/causes

[10] Zaher A, ElSaygh J, Elsori D, ElSaygh H, Sanni A. A Review of Trikafta: Triple Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulator Therapy. Cureus. 2021 Jul;13(7):e16144. https://doi.org/10.7759/cureus.16144

[11] Wang Y, Wrennall JA, Cai Z, Li H, Sheppard DN. Understanding how cystic fibrosis mutations disrupt CFTR function: from single molecules to animal models. The International Journal of Biochemistry & Cell Biology. 2014 Jul;52:47–57. https://doi.org/10.1016/j.biocel.2014.04.001

[12] Rowntree RK, Harris A. The Phenotypic Consequences of CFTR Mutations. Annals of Human Genetics. 2003;67(5):471–85. https://doi.org/10.1046/j.1469-1809.2003.00028.x

[13] Morrison CB, Markovetz MR, Ehre C. Mucus, Mucins and Cystic Fibrosis. 2019 Nov;54(Suppl 3):S84–96. https://doi.org/10.1002/ppul.24530

[14] Yin R, Cheng J, Wang J, Li P, Lin J. Treatment of Pseudomonas aeruginosa infectious biofilms: Challenges and strategies. 2022 Aug;13. https://doi.org/10.3389/fmicb.2022.955286

[15] Rumpf C, Lange J, Schwartbeck B, Kahl BC. Staphylococcus aureus and Cystic Fibrosis—A Close Relationship. What Can We Learn from Sequencing Studies? Pathogens. 2021 Sep 13;10(9):1177. https://doi.org/10.3390/pathogens10091177

[16] Xu X, Zhang X, Zhang G, Abbasi Tadi D. Prevalence of antibiotic resistance of Staphylococcus aureus in cystic fibrosis infection: a systematic review and meta-analysis. Journal of Global Antimicrobial Resistance. 2024 Mar 1;36:419–25. https://doi.org/10.1016/j.jgar.2023.05.006

[17] Gutiérrez Santana JC, Coria Jiménez VR. Burkholderia cepacia complex in cystic fibrosis: critical gaps in diagnosis and therapy. Annals of Medicine. 2024 Dec 31;56(1):2307503. https://doi.org/10.1080/07853890.2024.2307503

[18] Lorusso AB, Carrara JA, Barroso CDN, Tuon FF, Faoro H. Role of Efflux Pumps on Antimicrobial Resistance in Pseudomonas aeruginosa. International Journal of Molecular Sciences 2022 Dec 13;23(24): 15779. https://doi.org/10.3390/ijms232415779

[19] Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. The New England Journal of Medicine. 2019 Oct 31;381(19):1809–19. https://doi.org/10.1056/nejmoa1908639

[20] Reamer C, O'Malley C, Nufer J, Savant A. Improved outcomes in cystic fibrosis using modified Re-Education of Airway Clearance Technique (REACT) programme. BMJ Open Quality. 2020 Jul 1;9(3):e000890. http://dx.doi.org/10.1136/bmjoq-2019-000890

[21] Ng C, Nadig T, Smyth A, Flume P. Current opinion in pulmonary medicine – Treatment of pulmonary exacerbations in cystic fibrosis. Current Opinion in Pulmonary Medicine. 2020 Nov;26(6):679–84. https://doi.org/10.1097/mcp.0000000000000730

[22] Wainwright C, McColley SA, McNally P, Powers M, Ratjen F, Rayment JH, et al. Long-Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged ⩾6 Years with Cystic Fibrosis and at Least One F508del Allele: A Phase 3, Open-Label Clinical Trial. American Journal of Respiratory and Critical Care Medicine. 2023 Jul;208(1):68–78. https://doi.org/10.1164/rccm.202301-0021oc

[23] Leemans G, Belmans D, Van Holsbeke C, Becker B, Vissers D, Ides K, et al. The effectiveness of a mobile high-frequency chest wall oscillation (HFCWO) device for airway clearance. Pediatric Pulmonology. 2020 Aug; 55(8):1984–92. https://doi.org/10.1002/ppul.24784

[24] Lange DJ, Lechtzin N, Davey C, David W, Heiman-Patterson T, Gelinas D, et al. High-frequency chest wall oscillation in ALS. Neurology. 2006 Sep 26;67 (6):991–7. https://doi.org/10.1212/01.wnl.0000237439.78935.46

[25] Bush K, Bradford PA. β-Lactams and β-Lactamase Inhibitors: An Overview. Cold Spring Harbor Perspectives in Medicine. 2016 Aug;6(8):a025247. https://doi.org/10.1101/cshperspect.a025247

[26] Vázquez-Laslop N, Mankin AS. How Macrolide Antibiotics Work. Trends Biochem Sciences. 2018 Sep;43(9):668–84. https://doi.org/10.1016/j.tibs.2018.06.011

[27] Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, et al. Azithromycin in Patients With Cystic Fibrosis Chronically Infected With Pseudomonas aeruginosaA Randomized Controlled Trial. The Journal of the American Medical Association. 2003 Oct 1;290(13):1749–56. https://doi.org/10.1001/jama.290.13.1749

[28] Krause KM, Serio AW, Kane TR, Connolly LE. Aminoglycosides: An Overview. Cold Spring Harbor Perspectives in Medicine. 2016 Jun;6(6):a027029. https://doi.org/10.1101/cshperspect.a027029

[29] Gibson RL, Burns JL, Ramsey BW. Pathophysiology and Management of Pulmonary Infections in Cystic Fibrosis. American Journal of Respiratory and Critical Care Medicine. 2003 Oct 15;168(8):918–51. https://doi.org/10.1164/rccm.200304-505so

[30] Paton JH, Reeves DS. Fluoroquinolone antibiotics. Microbiology, pharmacokinetics and clinical use. Drugs. 1988 Aug;36(2):193–228. https://doi.org/10.2165/00003495-198836020-00004

[31] Høiby N, Bjarnsholt T, Givskov M, Molin S, Ciofu O. Antibiotic resistance of bacterial biofilms. International Journal of Antimicrobial Agents. 2010 Apr 1;35(4):322–32. https://doi.org/10.1016/j.ijantimicag.2009.12.011

[32] Ayoub Moubareck C. Polymyxins and Bacterial Membranes: A Review of Antibacterial Activity and Mechanisms of Resistance. Membranes (Basel). 2020 Aug 8;10(8):181. https://doi.org/10.3390/membranes10080181

[33] Mondal AH, Khare K, Saxena P, Debnath P, Mukhopadhyay K, Yadav D. A Review on Colistin Resistance: An Antibiotic of Last Resort. Microorganisms. 2024 Apr;12(4):772. https://doi.org/10.3390/microorganisms12040772

[34] Habboush Y, Guzman N. Antibiotic Resistance. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. [cited 2024 June 20]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK513277/

[35] Tooke CL, Hinchliffe P, Bragginton EC, Colenso CK, Hirvonen VHA, Takebayashi Y, et al. β-Lactamases and β-Lactamase Inhibitors in the 21st Century. Journal of Molecular Biology. 2019 Aug 23;431(18):3472–500. https://doi.org/10.1016/j.jmb.2019.04.002

[36] Blair JMA, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJV. Molecular mechanisms of antibiotic resistance. Nature Reviews Microbioly. 2015 Jan;13 (1):42–51. https://doi.org/10.1038/nrmicro3380

[37] Martin I, Waters V, Grasemann H. Approaches to Targeting Bacterial Biofilms in Cystic Fibrosis Airways. International Journal of Molecular Sciences. 2021 Feb 22;22(4):2155. https://doi.org/10.3390/ijms22042155

[38] Michaelis C, Grohmann E. Horizontal Gene Transfer of Antibiotic Resistance Genes in Biofilms. Antibiotics (Basel). 2023 Feb 4;12(2):328. https://doi.org/10.3390/antibiotics12020328

[39] Perikleous EP, Gkentzi D, Bertzouanis A, Paraskakis E, Sovtic A, Fouzas S. Antibiotic Resistance in Patients with Cystic Fibrosis: Past, Present, and Future. Antibiotics (Basel). 2023 Jan 20;12(2):217. https://doi.org/10.3390/antibiotics12020217

[40] Kim D, Bhat A, Kim SK, Lee S, Ryu CM. Small RNA-modulated anaerobic respiration allows bacteria to survive under antibiotic stress conditions. Frontiers in Cellular and Infection Microbiology. 2024 Mar 13;14. https://doi.org/10.3389/fcimb.2024.1287557

[41] Ryder C, Byrd M, Wozniak DJ. Role of polysaccharides in Pseudomonas aeruginosa biofilm development. Current Opinion in Microbiology. 2007 Dec;10(6):644–8. https://doi.org/10.1016/j.mib.2007.09.010

[42] Elkins Mark R., Robinson Michael, Rose Barbara R., Harbour Colin, Moriarty Carmel P., Marks Guy B., et al. A Controlled Trial of Long-Term Inhaled Hypertonic Saline in Patients with Cystic Fibrosis. New England Journal of Medicine. 2006;354(3):229–40. https://doi.org/10.1056/nejmoa043900

[43] Ratjen F, Bell SC, Rowe SM, Goss CH, Quittner AL, Bush A. Cystic fibrosis. Nature Reviews Disease Primers. 2015 May 14;1:15010. https://doi.org/10.1038/nrdp.2015.10

[44] Mall MA, Graeber SY, Stahl M, Zhou-Suckow Z. Early cystic fibrosis lung disease: Role of airway surface dehydration and lessons from preventive rehydration therapies in mice. The International Journal of Biochemistry & Cell Biology. 2014 Jul 1;52:174–9. https://doi.org/10.1016/j.biocel.2014.02.006

[45] Miller AC, Harris LM, Cavanaugh JE, Abou Alaiwa M, Stoltz DA, Hornick DB, et al. The Rapid Reduction of Infection-Related Visits and Antibiotic Use Among People With Cystic Fibrosis After Starting Elexacaftor-Tezacaftor-Ivacaftor. Clinical Infectious Diseases. 2022 Oct 1;75(7):1115–22. https://doi.org/10.1093/cid/ciac117

[46] TRIKAFTA®. Drug Interactions with TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) [Internet]. TRIKAFTA®. [cited 2024 Jul 12]. Available from: https://www.trikaftahcp.com/drug-interactions

[47] TRIKAFTA®. Who Is TRIKAFTA® For? [Internet]. TRIKAFTA®. [cited 2024 Jul 12]. Available from: https://www.trikafta.com/who-trikafta-is-for

[48] World Health Organization. Antimicrobial resistance [Internet]. WHO. [cited 2024 Jul 11]. Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance

[49] Ghannad MS, Mohammadi A. Bacteriophage: Time to Re-Evaluate the Potential of Phage Therapy as a Promising Agent to Control Multidrug-Resistant Bacteria. Iranian Journal of Basic Medical Sciences. 2012 Apr;15(2):693. https://pmc.ncbi.nlm.nih.gov/articles/PMC3586887/

[50] Kortright KE, Chan BK, Koff JL, Turner PE. Phage Therapy: A Renewed Approach to Combat Antibiotic-Resistant Bacteria. Cell Host & Microbe. 2019 Feb 13;25(2):219–32. https://doi.org/10.1016/j.chom.2019.01.014

[51] Lloyd EC, Cogen JD, Maples H, Bell SC, Saiman L. Antimicrobial Stewardship in Cystic Fibrosis. Journal of the Pediatric Infectious Diseases Society. 2022 Sep 1;11(Supplement_2):S53–61. https://doi.org/10.1093/jpids/piac071

Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Montserrat Mora Ochomogo, Arthur Tung
Article Dates: Received Jul 28 24; Accepted Nov 18 24; Published Jan 30 25

Citation
Please cite this article as follows:
Massaad G, Tal N. Persistent bacterial infections in cystic fibrosis patients: Exploring lung pathophysiology and antibiotic challenges. URNCST Journal. 2025 Jan 30: 9(1). https://urncst.com/index.php/urncst/article/view/711
DOI Link: https://doi.org/10.26685/urncst.711