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## Cystic Fibrosis: An Ecological Review

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## **Cystic Fibrosis/Respiratory Disease: An Ecological Review**

[Chris Bozer](#)

### **Abstract:**

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This article focuses on the mechanisms of cystic fibrosis and the resulting microbial dysbiosis created through this disease. Through mutations in the CFTR gene, chloride ion proteins become dysfunctional, and mucus secreted in the lungs become thick and heavy, allowing infectious and pathogenic bacteria to thrive. 16s rRNA has been the primary method of sequencing the lung microbiome. Researchers have relied on bronchoscopies to collect proper samples. It can be concluded through current research that chloride ion dysfunction allows for an abnormal lung environment to develop. This abnormal environment allows for chronic infection of the lungs, and the formation of biofilms that would otherwise not be developed. The bacteria that can thrive in this abnormal environment cause a wide range of issues in cystic fibrosis patients, which ultimately leads to early mortality. A greater understanding of the microbiome of cystic fibrosis affected lungs gives a greater insight of the issues that cystic fibrosis presents.

### **Introduction:**

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Cystic fibrosis is an inheritable, autosomal recessive disease that affects nearly 70,000 individuals worldwide. There are over 1,700 different gene mutations (generally point mutations) that have been linked to cystic fibrosis; these mutations lead to complete or partial dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The CFTR protein is responsible for the function of chloride ion channels in the exocrine glands, which are found throughout the human body. Dysfunction of chloride ions channels affects mucus, saliva, tear, and digestive enzyme production by causing less water to be attracted to these substances. This results in these substances becoming thicker and heavier. Issues arising from CFTR dysfunction

generally affect the lungs and pancreas but have been known to also affect other systems such as the upper airways, intestines, liver, and reproductive organs.

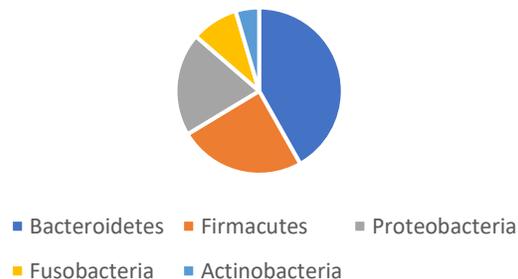
Primary symptoms that can arise from Cystic Fibrosis are chronic pneumonia, fibrosis, chronic rhinosinusitis, male infertility, and more. These symptoms are caused by thickened mucus that becomes trapped inside the lungs and other organ systems. Thickened mucus arises from the lack of chloride ions to attract water, which would generally allow the mucus to be free-flowing and easily expelled. The trapped mucus becomes a harbor for irregular bacterial growth, and an irregular microbiome in the lungs.

It has been found that healthy individuals, unaffected by Cystic Fibrosis or other respiratory diseases have a typical microbiome. The existence of a healthy lung microbiome and understanding of such make-up is important for the comparison of the ecology of Cystic Fibrosis-affected individuals. The healthy lung microbiome is composed of primarily Bacteroidetes and Firmicutes, but additionally has Proteobacteria, Fusobacteria, and Actinobacteria at lower levels.

The lung microbiome is affected by cystic fibrosis through thickened mucus which facilitates lung infections. Bacteria that infect the microbiome of cystic fibrosis individuals disproportionately are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, and *Achromobacter* species. These infections result in the overall shift of the lung microbiome to contain higher percentages of Firmicutes and Proteobacteria.

**A**

### Healthy Lung Microbiome Composition

**B**

### Affected Cystic Fibrosis Microbiome Composition

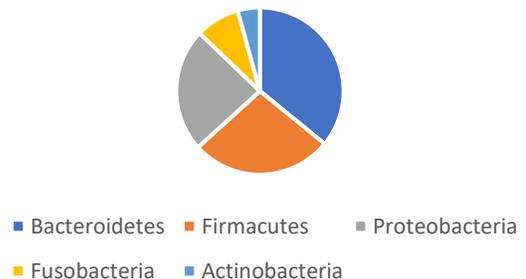


Table 1: Visual representation of the composition of the healthy lung microbiome, and the microbiome of an average cystic fibrosis affected individual. The visual representation is approximations and not based off of exact percentages. Important to note from this table is that there is an increase in the presence of firmicutes and proteobacteria in CF individuals (B) when compared to healthy individuals (A).

*Staphylococcus Aureus* is a rod shaped, aerobic firmicute. *S. Aureus* affects children affected by Cystic Fibrosis. It contributes to biofilm formation which becomes antibiotic resistant. *S. Aureus* leads to infections such a pneumonia, and due to biofilm formation, chronic pneumonia is common in almost all CF-affected individuals.

*Pseudomonas aeruginosa* (*P. Aeruginosa*) is an encapsulated, rod shaped, facultative anaerobe. It is classed as a proteobacteria. *P. Aeruginosa* is environmentally acquired by CF- affected individuals and is prevalent in 44.6% of all CF patients. One key factor of this bacterium is that it has flagella which allow it to be more mobile and it uses pili to attach itself to the respiratory tract. This bacterium can also increase the production of biofilm increasing antibiotic resistance.

Once acquired it can lead to chronic infections which accelerates the decline of lung function and often results in early mortality.

The Burkholderia cepacia complex (B.C.C) is a group of 20 different species of gram-negative aerobic bacilli. It is only prevalent in 2.4% of CF-affected individuals, but it is highly virulent and can transfer from individual to individual. B.C.C contain pili that are used to attach to epithelial cells. Attachment will cause epithelial tissue damage through extracellular proteases. B.C.C infection is linked with cepacia syndrome, a condition that is characterized by necrotizing pneumonia and sepsis which results in the lung function decline; this results in near total fatality rates.

Stenotrophomonas Maltophilia (S. Maltophilia) is a gram negative, rod shaped obligate aerobe. It has the ability to form biofilms and develop antimicrobial resistance. Nearly 12-30% of all CF patients are affected by S. Maltophilia through environmental exposure. If chronically infected with S. Maltophilia, patients generally have higher risk of pulmonary exacerbations, and leads patients to be three times as likely to die or require a lung transplant.

Achromobacter Species are gram negative, rod shaped anaerobic proteobacteria. They contain flagella which allow for increased motility. Generally, Achromobacter Species is environmentally acquired but patient-to-patient transmission has been recorded. Less is known about the effects of Achromobacter Species infection, but it is suspected that it doubles the risk of mortality or the need of a lung transplant.

### **Pertinent Research:**

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Cystic Fibrosis as a disease was first recognized as a disease in 1938. Prior to its recognition as a disease, it was coupled with celiac disease. At the time, life expectancy of those with Cystic

Fibrosis was only 6 months and very little was understood about the disease. It wasn't until 1989, 51 years later that the CFTR gene was discovered, propelling CF research forward. Before 1989, not much research was published concerning the disease, however after 1989, research gradually picked up. Today there are thousands of research articles published concerning Cystic Fibrosis. Several different methods of research of have been utilized to study aspects of the healthy lung microbiome and the microbiome of cystic fibrosis-affected individuals.

Prior to modern research, many believed the lungs were sterile and without a microbiome. This was eventually disproven, and it was confirmed that the lung did in fact have a microbiome. To study the healthy lung microbiome, researchers have utilized 16S rRNA sequencing. This has allowed researchers to learn about the bacteria present in the lungs. To collect samples, bronchoscopies were used to allow samples to be collected from the lungs. Initially there was skepticism over the accuracy over such procedures due to possible contamination from the upper-respiratory tract, but repeated research has shown strong evidence of such.

Similar methods have been used in the research of the cystic fibrosis microbiome. Early research relied on culture dependent methods of investigation. In the last 15-20 years however, research has focused more on culture-independent methods which as ultimately allowed for a greater and more specific understanding of what the microbiome looks like in CF-affected individuals. Many of the samples collected from CF-affected individuals has been through sputum samples.

16s rRNA gene sequencing has been and still is the primary method of sequencing of all respiratory studies. Although this continues to be the primary method, other methods have been utilized in an attempt to learn more. 16s OTU samples have been attempted, but they are only effective if sequences are similar to the bacterial species. This has not yet been the case and so 16s rRNA continues to be the primary method.

Current research shows that the overall composition of the microbiome of healthy lungs and CF-affected lungs does not change substantially and only to a small degree. The inability for mucus to attract water molecules causes mucus to become heavier and harder to expel. As a result, mucus remains in the lungs for longer durations of time, and large amounts of mucus builds up over time. The increase of mucus, and the duration of time that mucus remains in the lungs gives rise to an environment that allows for additional bacterial growth that is abnormal when compared to healthy lungs. Hence the reason why sputum samples are frequently used in cystic fibrosis studies.

### **Microbial Ecology Correlation:**

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#### *Population Ecology:*

A good deal of research has been conducted to determine what and how frequent certain bacterium infect the microbiome of CF-affected lungs. Research has used the healthy lung microbiome as a reference to compare levels of dysbiosis. Current studies appear to show a variety of different populations that can exist in CF-affected lungs; however, elements of the healthy lung microbiome populations still exist in a large degree. CF-affected lungs allow for additional biomass to buildup and biofilms to develop; this is caused by the increased amount of mucus, and the inability for mucus to be expelled.

Over the course of a CF-affected individuals' life the population shifts overtime. Earlier in life the population of the lung more closely resembles a healthy lung. Overtime, and because of biofilm formation, the lung's microbial population shifts to contain patches of biofilms and CF-associated microbes. In the event of a lung transplant or death, the CF-affected lung is nearly comprised of CF-affected microbes.

#### *Physiological Ecology:*

The main factor influencing physiological ecology is the increase and build-up of mucus in CF-affect lungs. Mucus provides the proper environment for infectious bacteria to grow and thrive. Bacteria normally present in healthy lungs can still exist normally in the lungs but have to compete more against infectious bacterium. In an attempt to control issues that arise because of the abnormal microbiome, antibiotics are generally administered to target and eliminate certain microbes. In response, many of the harmful bacteria that infects the CF-infected lung begin to form biofilms and become antibiotic resistant.

#### *Community Ecology:*

Communities in CF-affect lungs show similarities with a healthy lung microbiome. The large build-up of mucus creates a perfect environment for infectious bacterium to thrive. Infectious bacteria generally build up where the mucus is present, and elements of the normal healthy lung biome seem to present in other areas of the lungs. Generally once biofilms form, the normal microbiome of the lung participates less.

#### *Ecosystem Ecology:*

The primary difference in the ecosystem of CF-affected lungs is the build-up of mucus. Other than that difference, normal lung conditions are present; the presence of oxygen is one primary component that affects the lung microbiome generally. The presence of mucus in healthy lungs affects the healthy lung microbiome, but to a smaller degree.

#### *Behavioral Ecology:*

Infectious bacteria that primarily affects CF-affected lungs have several commonalities. Many of the bacterium will form biofilms that become antibiotic resistant. This occurs because the environment provide allows these bacteria to thrive and endure. Many bacteria also possess

flagella which allows motility. In addition to these issues, many of the bacterium that affect CF-affected lungs will cause fibrosis, or damage to the lung tissue.

#### *Landscape Ecology:*

A study was conducted on this topic analyzing the difference between CF-affected lungs that were ex-planted and replaced by another lung, and post-mortem lungs that belongs to CF-affected individuals. Results from analysis showed similarities between the spatial distribution of phylum, however, post-mortem lungs had nearly all lung tissue affects by CF-related microbes. Explanted lungs still had healthy lung tissue distributed in patches throughout the lung. The results of the study found that microbial communities in CF-affected lungs tended to be spatially heterogenous, meaning there was uneven distribution of various concentrations of different species throughout the lungs. Maybe this is one reason there is variation between CF-affected individuals.

#### **Future Research/Action:**

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Research on Cystic Fibrosis up until this point has made leaps in that it has significantly increased the lifespan of CF-affected individuals and the general improvement on the quality of life. While current research methods will likely continue and make incremental improvements, there have been several proposals of how to move forward with CF research.

One proposal to further combat the effects of cystic fibrosis is to research pharmacological solutions to circumvent issues presented by cystic fibrosis. Developing a medication that could possibly reduce excess sodium reabsorption and/or improving chloride ion secretion would target the initial problem that is caused by cystic fibrosis. Several hurdles would have to be crossed in order to be successful in such an endeavor. Medications developed would need to undergo

several trials in order to prove efficacy and ensure there are no serious harmful side-effects. These trials can be expensive and require a decent number of willing affected participants. One of the most common gene mutations that causes cystic fibrosis is the  $\Delta F508$  mutation. A second proposal to move forward in cystic fibrosis research is focusing on developing therapies that will help combat defects caused by this mutation. The idea to combat this mutation is to promote skipping premature stop codons that might otherwise cause the CFTR protein to be in a state of dysfunction. Creating therapies in this regard would alleviate the issue of thickened mucus, thus prevented some dysbiosis that is generally created through cystic fibrosis. Gene therapy is a growing field and could also be applied to cystic fibrosis. Another proposal to further cystic fibrosis is to utilize some of these gene therapy techniques to insert healthy and normal copies of the CFTR gene into appropriate cells. The idea behind this proposal is that it would promote healthy CFTR development that in theory would resolve many issues of dysbiosis caused by cystic fibrosis.

There is currently a good understanding of how some elements of dysbiosis affects the human body. One bacterial infection that is frequently associated with cystic fibrosis that is an *Achromobacter* Species. Various studies have shown that *Achromobacter* Species infections occur anywhere from 3-30%, but exact percentages are still unknown. There is general knowledge of what *Achromobacter* Species might do to the dysbiosis of lung microbiome, Additional research into *Achromobacter* Species might provide beneficial insights into better treatments for cystic fibrosis affected individuals.

In addition to these proposals above, I believe that additional research into the lung microbiome in general would be beneficial. Collecting samples from the lungs has presented difficulties in the past and still does currently. It is difficult to properly collect samples without the mouth or

throat interfering with the sample. Additionally, the methods of collecting samples are uncomfortable which discourage people from participating, which then leads to a less representative sample. Because of these difficulties, the lung microbiome is only partially understood, and without a solid foundational understanding of how a healthy lung microbiome exists or functions it is difficult to use as a comparison for lungs in dysbiosis.

Since it is difficult to fully understand the healthy lung microbiome, it is even more difficult to understand how cystic fibrosis. Difficulties that arise from fully understanding the microbiome of cystic fibrosis-affected lungs include all the same difficulties as stated above, but additionally there is an even more limited sample size available.

Due to these difficulties, I believe that additional research needs to be conducted in better sample collection methods for the lung. Doing so would open up to further ecological studies of the lungs that may better represent the standard microbiome of the lungs. When a standard microbiome is established, better understanding can come to diseases such as cystic fibrosis.

## **Conclusion:**

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Cystic fibrosis is a common, life-shortening disease that affects multiple systems in the body. It is caused by a variety of gene mutation, the most common being the  $\Delta F508$  mutation, which results in partial or complete dysfunction of important chloride ion transport proteins; this inhibits proper hydration of mucus in several body organs, but primarily affects the lungs and pancreas. Symptoms of such dysfunction causes chronic pneumonia, fibrosis of lung tissue, in addition to other bacterial infections. While life expectancy for cystic fibrosis-affected individuals has improved over the last century, lifespan is still relatively short, being around 40 years.

The healthy lung microbiome is composed of primary Bacteroidetes and firmicute species, however proteobacteria, fusobacteria, and actinobacteria species still exist but in lower concentrations. Cystic fibrosis affected lungs have very similar microbiomes, but the additional mucus formation along with the mucus being heavier and harder to expel give rise to additional firmicute and proteobacteria populations. Some of the most common infections associated with the dysbiosis created by cystic fibrosis are staphylococcus aureus, pseudomonas aeruginosa, Burkholderia cepacia complex, stenotrophomonas maltophilia, and achromobacter species; all of these bacterial infections pose life-threatening ailments to those affected.

Research into the causes of cystic fibrosis and the effects of cystic fibrosis have been occurring ever since its discovery in 1938. Since that discovery important discoveries into the function and causes of cystic fibrosis have been made including the 1989 discovery of the CFTR gene. These discoveries, along with current and modern research have improved the quality of life and the life expectancy of those affected by cystic fibrosis. Several proposals have been made for the future of cystic fibrosis research with the majority of proposals including some sort of gene therapy.

The primary cause of the issues arising from cystic fibrosis stem from the thickened mucus that creates an abnormal environment allowing pathogenic and infectious bacteria to thrive. Further research should be done to focus on repairing the dysfunction through either gene therapies or pharmacological solutions that would alleviate improper hydration of mucus. Additionally, further research into the general microbiome of the healthy lungs and cystic fibrosis-affected lungs should be conducted to possibly lead to better therapeutics.

**Statement of Responsibility:**

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My group consisted of myself, Makenna Bloxham, Hunter Hassel, Jackson Downey, and Danny Burrola. It is my opinion and impression that the groupwork for the presentation earlier this semester was equally and equitably distributed, and all groups members worked without incident to complete the assignment. Topics for the presentation were distributed as such, Makenna and I were responsible for the introduction, general overview, and conclusion. Jackson and Danny were responsible for presenting on the healthy and affected microbiome. Hunter was responsible for presenting on current research and discoveries.

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