A Meta-Study on the Mechanisms Involved in Cystic Fibrosis and Possible Treatments

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Many new avenues of research are looking very promising for the future with new drugs being recently released that focus on the actual cause of Cystic Fibrosis, namely the faulty chloride ion channel in epithelial cells lining the internal organs; however the effectiveness of the currently available medications and drugs is still uncertain. Side effects are also a concern.

This study was made to evaluate the current scientific understanding of the causes of degradation in the lungs and other organs of cystic fibrosis sufferers, and also to find any commonalities in the results of various studies regarding possible treatments that can be utilised to extend the quality and quantity of life of a CF sufferer immediately while we await the development of a cure.
Cystic Fibrosis: A summary of current scientific research

Cystic Fibrosis is the most common lethal genetic disease among persons with northern European ancestry. This genetic disorder results in a faulty chloride ion channel within epithelial cells that line the airways and other organs. These cells are important in creating sweat, digestive juices and mucus. As a result, mucus becomes thick and elastic, thereby providing an ideal environment for bacterial growth and also interfering with normal functions in several organs such as the pancreas. Although there is currently no cure for the disease, it is hoped that one will be found in the near future. New drugs such as Orkambi are starting to be produced that target the actual faulty mechanism within the epithelial cells. Other avenues of study have recently made new progress with gene therapy.

What has new research discovered about cystic fibrosis?
The latest research studies have made breakthroughs in our understanding of how cystic fibrosis actually causes damage. What do we now know?

Why is the mucous thick?
A team led by UC San Francisco professor of medicine John Fahy, MD, has discovered why mucus in the lungs of people with cystic fibrosis (CF) is thick, sticky and difficult to cough up, leaving these patients more vulnerable to lung infection. Fahy and his team found that in CF – contrary to previous belief – inflammation causes new molecular bonds to form within mucus, transforming it from a liquid to an elastic sludge. The researchers found that inflammation causes extra disulfide bonds to form, when mucin polymers are exposed to highly reactive oxygen molecules released by inflammatory cells in a process called oxidative stress. “This qualitative change, driven by oxidation, happens with other natural polymers,” said Fahy. “Think of latex, which starts out as liquid tree sap. When it’s vulcanized – a process of chemical cross-linking – it turns into the solid rubber we use in tires.” They found that mucin polymers become linked together crosswise by newly-forged disulfide bonds. Fahy likened the polymers to logs floating down a river. “The logs can float down the river as long as they are floating independently,” he said. “But if you bolt them together side to side, they will clog the river.” Using confocal microscopy, the scientists learned that CF mucus consists of a dense core of mucin with a layer of DNA wrapped around it, like a thin blanket draped over a solid pillow. Thus, while Pulmozyme makes mucus less stiff by eliminating DNA, NAC succeeds in liquefying it by breaking up the mucin. “We thought Pulmozyme would be more effective than NAC in liquefying the mucus, because CF sputum contains lots of DNA,” said Fahy. “But to our surprise, NAC worked much better.”

The study was reported in the February 25 2015 issue of Science Translational Medicine

What causes the inflammation?
A document available at the following link explains what researchers at Stanford University understand about the cause of inflammation in CF lungs

This is a summary...
CF airways become inflamed when an infection occurs
- The body’s immune response relies on various white blood cells (WBCs) and natural barriers to block any attack any foreign invader.
- CF lung disease is characterized by massive numbers of neutrophils (a type of White Blood Cell) attracted to the lungs all the time.
- Too many uncontrolled neutrophils cause damage and produce oxidative molecules called reactive oxygen species (ROS). ROS are highly unstable and cause damage.
- CF patients have low body stores of GSH, a major anti-oxidant naturally produced in the body.

Anti-Oxidants Counteract Inflammation
- When there are not enough antioxidants to protect the cells, reactive oxygen molecules attack healthy cells and break down tissue.
- The 'Master Antioxidant' of the body that recharges all cells and organs is glutathione (GSH).
- GSH is probably the most important cellular defense that allows the body to prevent and fight infections and disease

Glutathione Deficiency in CF
- Normal concentration of GSH in human lung lining fluid is 140x that of plasma.
- GSH in CF Epithelial Lining Fluid (ELF) is low.
- A decrease in GSH content in ELF increases susceptibility of lung to chronic inflammation in CF.
- Blood levels of GSH are low in CF.
- Blood neutrophils are low in GSH in CF.

- Taken orally, NAC is absorbed into the intestinal cells, metabolized into cysteine, then the cells make GSH and secrete it into the blood.
- The liver cells use cysteine to make glutathione (GSH) which is probably the major source of GSH production. GSH is carried by the liver’s major protein, albumin, to tissues and released into the cells.
- Tissues also can take in albumin and break it down into cysteine, and make their own GSH.

Conclusions
- NAC, when taken with other standard CF therapies may slow loss of lung function.
- NAC recipients maintained baseline lung function over 6 months
- Placebo - 4 – 6% decline
- NAC does not appear to affect inflammation in the airways directly.

Potential Mechanisms of Action
• By providing a building block for GSH synthesis, NAC may modulate biological mechanisms involving GSH roles inside cells to maintain homeostasis (balance oxidants with anti-oxidants and decrease oxidative cell stress) 1.
• NAC supplementation, by increasing body stores of GSH2, may modify inflammation2, 3, DNA transcription3, CFTR protein production4, or it may affect tissue fibrosis5.

In another document Doctor Conrad wrote the following about inflammation in CF patients. http://med.stanford.edu/content/dam/sm/cfcenter/documents/facts/LPCH.CF.NL.Spring2015.lores.pdf

For reasons still unclear, in CF, the environment in the airways is strongly pro-inflammatory. After neutrophils have been recruited, neutrophil-derived oxidants are released into the airways, and contribute to ongoing tissue destruction. Oxidants, which include hydrogen peroxide, hypochlorous acid, and other damaging particles called free radicals are released and create a vicious perpetual cycle of tissue destruction.

Oxidative stress is defined as an excessive load of reactive oxygen species (ROS), which cause ongoing or reversible damage in the body. This can occur in individual cells, and in specific body organs, and can affect the health of patients at the whole body level. Antioxidants can chemically react with ROS to quench and thus inactivate these reactive, damaging molecules. Cystic fibrosis is characterized by oxidative stress throughout the body and chronic inflammation in the lungs. Patients with CF are deficient in the body’s major anti-oxidant, glutathione (GSH). This is thought to be due to many reasons, including dietary insufficiency, but being the major anti-oxidant of the body, GSH is highly utilized in areas of oxidative stress and inflammation. GSH serves multiple functions and is utilized by cells to regulate physiological functions such as DNA transcription, RNA translation, and subsequent protein synthesis. It is utilized to regulate protein functions and is vital in regulating dietary absorption of nutrients, storage and availability of essential proteins and fatty acids. Oxidation reactions are essential to fight infection and are generated when neutrophils ingest bacteria to rid the body of pathogens.

Why are CF patients so at risk of infection of the airways?
The following information is from the Meakins-Christie Laboratories, McGill University Heath Centre Research Institute, Montréal, Québec H2X 2P2, Canada http://m.jbc.org/content/285/29/22299.full#ref-5

Pseudomonas aeruginosa infections occur in 70% of the individuals at an early age and contribute to lung destruction and mortality. Moreover, CF patients suffer from exacerbation episodes, which have a profound effect on the patient's quality of life, where P. aeruginosa is the predominant pathogen found (3, 4). Therefore, in CF, the absence of functional CFTR translates somehow into chronic bacterial infection, excessive inflammation, tissue damage, impaired lung function, and eventual death.

We uncovered that in CFTRΔF508 cells, the extracellular glutathione levels are decreased, leading to a greater sensitivity to reactive oxygen species, providing an explanation for the hyperactivation of the p38 and ERK MAPKs and increased IL-6 synthesis. Taken together, our
study has characterized a mechanism whereby the CFTRΔF508 mutation in airway epithelial cells contributes to increase inflammation of the airways.

CF pathogens activate common signaling pathways in airway epithelial cells, leading to the production of proinflammatory cytokines. Once activated, these pattern recognition receptors trigger a network of intracellular signaling events leading to the production of inflammatory mediators. Patients harboring the CFTRΔF508 mutation lack CFTR expression at the membrane due to misfolding, which leads to the protein being degraded instead of transported to the cell surface (21). In this paper, we describe unexpected findings in CFTRΔF508 cells leading to enhanced IL-6 synthesis in response to P. aeruginosa diffusible material.

The document goes on to describe in full detail the scientific processes used to analyse the mechanism that is triggered by infection of CF cells by P. aeruginosa

Increased IL-6 Synthesis in CFTRΔF508 Cells Is Linked to Pattern Recognition Receptor Activation and Not Cytokine Receptors

IL-6 hypersecretion occurs in response to pattern recognition receptor activation but not following IL-17R activation in CFTRΔF508 AECs. Reactive oxygen species are essential for IL-6 synthesis and prime CFTRΔF508 cells to increased sensitivity to P. aeruginosa filtrates

CFTRΔF508 AEC Decreased Glutathione Levels Prime These Cells to Hyperresponsiveness

P. aeruginosa has been suggested to also signal in AECs through the generation of reactive oxygen species (34). Accordingly, preincubation of both non-CF and CFTRΔF508 AECs with the antioxidant NAC greatly diminished IL-6 synthesis in response to P. aeruginosa filtrates.

Our study not only defined ROS as facilitators of intracellular signaling in CFTRΔF508 cells but also identified them as key intermediates in the response of both non-CF and CF AECs to P. aeruginosa filtrates.

Preincubation of both AEC lines with the antioxidant NAC led to a major reduction of IL-6 synthesis. Because NAC, contrary to extracellular GSH, will act upon both intracellular and extracellular compartments, we believe that the additional inhibition seen in the presence of NAC is the result of intracellular ROS scavenging, leading to inhibition of key intracellular signals necessary to drive IL-6 synthesis in response to P. aeruginosa filtrates.

What does that mean in English?

Essentially, when an infection occurs in a CF patient’s airways, the body releases White Blood Cells to fight the infection. Neutrophils are a particular type of WBC and are found in extremely large numbers in the lung inflammation of CF patients. These Neutrophils release ROS, or Reactive Oxygen Species to destroy sources of infection.

As mentioned earlier, Doctor Conrad from Stanford University summarizes the situation in the Cystic Fibrosis Center News of Spring 2015
After neutrophils have been recruited, neutrophil-derived oxidants are released into the airways, and contribute to ongoing tissue destruction. Oxidants, which include hydrogen peroxide, hypochlorous acid, and other damaging particles called free radicals are released and create a vicious perpetual cycle of tissue destruction.

This process causes Oxidative Stress which is an excessive load of ROS. The body also utilises Antioxidants to balance out and neutralise the effects of the ROS delivered by the neutrophils. Patients with CF are deficient in the body’s major anti-oxidant, glutathione (GSH). This is thought to be due to many reasons, including dietary insufficiency, but being the major anti-oxidant of the body, GSH is highly utilized in areas of oxidative stress and inflammation.

What studies have been done in neutralising these ROS?

A large study was done by Stanford University with 70 recruits over a six month period. 36 patients were orally given NAC N-Acetyl Cisteine (mentioned earlier in other studies) and 34 were given a placebo. The following comments are from Doctor Conrad as published in volume 14 of the Journal of Cystic Fibrosis 2015.

What were the findings?

We detected a substantial clinical benefit in the outcome of lung function that measures obstruction: the NAC cohort maintained their baseline lung function as measured by the FEV1 (volume) and FEF25–75% (flow) throughout the 24-week period, while 4 to 6 percent declines in these measures occurred in the placebo cohort (Table 2, Fig. 1). We did not expect this result, since 6 months was thought to be too short a period of time to see such an effect in a mall study of this size.

We designed the study to detect any change in inflammatory markers, but instead, our data demonstrate a clinically relevant outcome in pulmonary function even though the study was not powered for the parameter. Our pulmonary function results are clinically meaningful. The CF Foundation Registry reports that, on average, CF patients who have mild to moderate lung dysfunction lose between 2 and 4 percent of lung function per year. In this study the NAC recipients maintained their lung function steady over 6 months.

The mechanism(s) of action of NAC in CF patients remains to be elucidated, though we speculate, based on various studies using NAC on cell cultures, that NAC likely supplies the amino acid cysteine to cells that make GSH synthesis, and that the GSH is then transported to other cells and organs to modulate CF airway disease via downstream biological mechanisms mentioned above that involve cellular regulation, oxidation balance, and cellular regulation.

You can read the article here...

A related study was reported in Europe PubMed Central by Dongyang People's Hospital, Respiratory Medicine, Zhejiang, P.R. China called “Effect of high/low dose N-acetylcysteine on chronic obstructive pulmonary disease: a systematic review and meta-analysis.” (PMID:24378052)

COPD shares many of the same symptoms as CF, although the cause of inflammation is from a different source.

This study was an analysis of data from 11 different previous studies. The purpose was to evaluate the effectiveness of both high and low doses of NAC on persons with Chronic Obstructive Pulmonry Disease (COPD). These are the results of that study...

Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and morbidity worldwide, characterised by persistent airflow limitation, mucus hypersecretion, oxidative stress and airway inflammation. N-acetylcysteine (NAC) have anti-oxidant and anti-inflammatory properties, which have been shown an uncertain benefit in COPD patients.

**CONCLUSION:** Long-term high-dose NAC treatment may lead to a lower rate of exacerbations. But the effect of low-dose NAC treatment remains uncertain. Further researches are needed to confirm this outcome and to clarify its mechanisms.

http://europepmc.org/abstract/MED/24378052

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Experimental Lung Research Volume 41 Issue 5 2015 reports the following study...

**N-acetylcysteine and azithromycin affect the innate immune response in cystic fibrosis bronchial epithelial cells in vitro**

**Background and objective.** We have previously reported that N-acetylcysteine (NAC), ambroxol and azithromycin (AZM) (partially) correct the chloride efflux dysfunction in cystic fibrosis bronchial epithelial (CFBE) cells with the ΔF508 homozygous mutation in vitro.

**Conclusion.** Overall, the results indicate that NAC and AZM not only can correct the chloride efflux dysfunction but also have a weakly strengthening effect on the innate immune system.


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The CFRI Summer 2015 Newsletter quotes the following statement from Dr. John Mark MD...

N-acetylcysteine (NAC) may soon be a standard of care for the antioxidant properties it provides.

The CF Breeze newsletter from the CF Foundation in Minnesota had the following to say: Antioxidants may have a role in the slowing or prevention of CF lung disease. A healthy diet, including fruit and vegetables supplemented by fat-soluble vitamins, can boost the CF patient’s antioxidant protection. In people with CF, however, the digestion does not always guarantee proper nourishment since mucus tends to clog the pancreas. Therefore, researchers are looking for alternative ways to deliver antioxidants to CF patients. One compelling strategy is to supplement the fat-soluble vitamins A, D, E and K. Another strategy is to administer oral N-acetylcysteine, or NAC, which is a building block for the antioxidant glutathione. The CF Foundation is committed to moving new effective antioxidant therapies forward as quickly as possible. The CF Foundation continues to work with physicians and scientists to design and start a double-blind, placebo-controlled clinical trials. http://www.crccs.com/Portals/25/CF%20Newsletters/CF%20Breeze%20April%202015.pdf

The Journal of Cystic Fibrosis published the following document in September 2014

The effect of short-term, high-dose oral N-acetylcysteine treatment on oxidative stress markers in cystic fibrosis patients with chronic P. aeruginosa infection — A pilot study

Here are some highlights from that study:

Twenty-one CF patients with chronic P. aeruginosa lung infection were included in the study (12 males and 9 females), median age 39 years (range 25–61 years). Chronic P. aeruginosa infection was defined as the persistent presence of P. aeruginosa for at least 6 consecutive months, or less when combined with the presence of two or more P. aeruginosa precipitating antibodies.

**Background:** Patients with cystic fibrosis (CF) and chronic Pseudomonas aeruginosa lung infection have increased oxidative stress as a result of an imbalance between the production of reactive oxygen species caused by inflammation and their inactivation by the impaired antioxidant systems. Supplementation with anti-oxidants is potentially beneficial for CF patients.

**Conclusion:** Treatment with N-acetylcysteine 1200 mg × 2/day for 30 days significantly decreased the level of oxidized vitamin C and increased the level of vitamin C (primary end-points) and a not statistically significant improvement of lung function was observed in this group of patients.

The patients in the intervention group received NAC in a mean dose of 36 mg/kg/day (max 59 mg/kg/day and min 25.8 mg/kg/day). After 4 weeks of NAC treatment, a significant increase in the plasma level of ascorbic acid (AA) (p = 0.037) and decrease in the level of
oxidized ascorbic acid (DHA) \( (p = 0.004) \) compared to baseline were observed, while no significant changes were observed in the control group (Fig. 1 and Table 2).

An improvement compared to baseline in the FEV1 (% predicted) mean (95% CI) +2.11 \((-1.44; 5.66)\) was observed in the NAC treated group while a decrease was observed in the control group mean (95% CI) \((-1.4 (-4.7; 1.9))\), both changes did not reach the level of significance \((p N 0.05)\) (Table 2).

Safety and adverse events profile: One patient stopped treatment with NAC due to stomach pain. No other adverse events were observed.

From early childhood, patients with cystic fibrosis (CF) have recurrent and chronic respiratory tract infections characterized by polymorphonuclear neutrophil (PMN) inflammation. Counts of PMNs in CF airway fluid have been found to be thousands of times higher than normal... which is consistent with neutrophils playing a central role in CF airway destruction. A consequence of the PMN-dominated inflammation is the release of proteases and reactive oxygen species (ROS). The neutrophils continuous interaction with bacterial products and their inability to engulf bacteria embedded in biofilms contribute to this exaggerated ROS production. Subsequently, ROS lose their physiological role in killing pathogens and turn into toxic effectors responsible for damaging the pulmonary epithelium as well as of other components of the lung parenchyma. Importantly, ROS can also modify the antioxidant homeostasis of extracellular fluids and epithelia causing the immune-inflammatory imbalance observed in the CF lung.

The mechanisms by which ROS cause tissue injuries are many, and among them it is important that the role played by ROS attacks on polyunsaturated fatty acids of lipid structures (membranes) and DNA

NAC has been used in our study as an antioxidant agent in a mean dose that was calculated to be 36 mg/kg/day. The optimal dosage as anti-oxidant agent in CF is not known but this dosage is higher than what is usually recommended as mucolytic agent (400–1200 mg/day). Taking into account the benign side-effect profile of NAC, the dosage can probably be safely increased to 50 mg/Kg/day [30].

Based on the data collected in this pilot study, we suggest a treatment period of 6 months with NAC in a dose of 50 mg/kg/day.

Since it has been shown that inflammation in CF patients starts as early as infancy [45–47], clinical trials aiming at correcting the oxidant/antioxidant imbalance in young children, especially in countries with newborn screening, could be considered.

http://www.cpnc.dk/NAC%20paper_JCF.pdf
Liposomal N-acetylcysteine Modulates the Pathogenesis of P. aeruginosa Isolated from the Lungs of Cystic Fibrosis Patient

We evaluated the antimicrobial activity of the free and liposomal NAC (F-NAC; L-NAC) against Pseudomonas aeruginosa...

L-NAC provided 75% protection against biofilm formation, 90% reduction in the formed biofilms, and a 46% eradication effect on bacterial community within biofilms compared to treated biofilm with PBS (P<0.001). Finally, L-NAC at 2500 mg/L was safe to A549 cells, reduced bacterial adhesion by 15% compared to control (P<0.001). These data indicate that L-NAC formulation is more effective than F-NAC against P. aeruginosa and has the potential to improve therapeutic outcomes in CF patient.


A study published in BioMed Central back in 2010 May 12 commented the following

N-acetylcysteine inhibit biofilms produced by Pseudomonas aeruginosa

In this study, we investigated the inhibitory effects of N-acetylcysteine (NAC) on biofilms produced by *P. aeruginosa*.

Conclusions

NAC has anti-bacterial properties against *P. aeruginosa* and may detach *P. aeruginosa* biofilms. Use of NAC may be a new strategy for the treatment of biofilm-associated chronic respiratory infections due to *P. aeruginosa*, although it would be appropriate to conduct clinical studies to confirm this.

Due to its ability to produce a biofilm, *P. aeruginosa* is responsible for some chronic pulmonary infections, such as those in cystic fibrosis (CF), bronchiectasis and chronic obstructive pulmonary disease (COPD).

*P. aeruginosa* eventually causes infections in most patients with CF, and once a chronic infection is established, eradication of *P. aeruginosa* strains is nearly impossible.

Our results showed that NAC dispersed the biofilms formed by *P. aeruginosa*

Our research showed that the amounts of EPS produced by *P. aeruginosa* strains were also significantly inhibited by 0.5 and 1 mg/ml of NAC. Taking into account the results given
above, NAC may be a potent agent for treating *P. aeruginosa* biofilms associated infections, and can be used in combination with ciprofloxacin.

Stafanger studied the effect of peroral NAC in patients with cystic fibrosis and chronic pulmonary *P. aeruginosa* infection, a significant improvement of the spirometric values was proved after NAC treatment in the patients with peak expiratory flow rate below or equal to 70% of predicted normal values. Stey reviewed the publications on the effect of oral NAC in chronic bronchitis, eleven randomized controlled NAC trials were analysed (a total of 2,011 patients), concluded that oral NAC reduced the risk of exacerbation and improved symptoms in patients with chronic bronchitis compared with placebo.

In conclusion, our results suggest that NAC has anti-bacterial properties against *P. aeruginosa* and may detach *P. aeruginosa* biofilms. It may be a new strategy for the treatment of biofilm-associated chronic respiratory infections, although it would be appropriate to conduct in vivo animal models and clinical studies to confirm this.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882372/

**Cell Biology International published the article “The effect of N-acetylcysteine on chloride efflux from airway epithelial cells” on January 2 2013**

This study indicated that the actual defect in the Cloride Ion channel can be affected through the administration of NAC. It says:

The effect of NAC on Cl\(^-\) transport was measured by Cl\(^-\) efflux measurements and by X-ray microanalysis. Cl\(^-\) efflux from CFBE cells was stimulated by NAC in a dose-dependent manner, with 10 mM NAC causing a significant increase in Cl\(^-\) efflux with nearly 80% in CFBE cells. The intracellular Cl\(^-\) concentration in CFBE cells was significantly decreased up to 60% after 4 h treatment with 10 mM NAC.
Summary:

The environment in the airways is strongly pro-inflammatory in CF cells. Particularly with the CFTRΔF508 mutation the cells are hypersensitive to pathogens such as P. aeruginosa.

Pattern recognition receptors trigger a network of intracellular signaling events through enhanced IL-6 synthesis which results in excessive white blood cells (neutrophils) being sent to the infection site. Neutrophils release Reactive Oxygen Species (ROS) to kill the infection. Normally the body produces the antioxidant called glutathione to balance and neutralise the ROS when their job is done.

CF cells are low in the master antioxidant glutathione (GSH). When there are not enough antioxidants to balance out the oxidants (ROS) and protect the cells, reactive oxygen molecules attack healthy cells and break down tissue.

Polymers in mucus are exposed to the highly reactive oxygen molecules released by inflammatory cells in a process called oxidative stress. Oxidative stress causes a vulcanising type effect that cross-links the polymers turning the mucus into an elastic sticky compound which is an ideal environment for the continued reproduction of the pathogen.

The damage to the tissue caused by the ROS leads to further inflammation, which in turn causes the release of more neutrophils to the area. After neutrophils have been recruited, neutrophil-derived oxidants are again released into the airways, and contribute to ongoing tissue destruction. Oxidants, which include hydrogen peroxide, hypochlorous acid, and other damaging particles called free radicals are released and create a vicious perpetual cycle of tissue destruction.

The continual cycle of infection, inflammation and tissue destruction results in a reduction in lung capacity between 2% to 4% per year.

This can result in a reduction in lung capacity of 40% to 80% by the time a CF patient reaches 20 years of age.

What is NAC and why is it not used more in the treatment of Cystic Fibrosis?

NAC is a slightly modified version of the sulfur-containing amino acid cysteine.

NAC has been used in conventional medicine for more than 30 years, primarily as a mucolytic (mucous-thinner) inhaled to manage conditions such as cystic fibrosis, in which mucous is abnormally thick and tenacious. There is little in the scientific literature to support its use as an inhalant, however NAC is still administered in this form by some pulmonary specialists.
I do NOT encourage nebulization of the N-acetylcysteine liquid, as reactive oxygen, reactive sulfur species are then introduced into already inflamed airways, adding fuel to the fire, so to speak.

However, when taken internally, NAC replenishes intracellular levels of the natural antioxidant glutathione (GSH), helping to restore cells’ ability to fight damage from reactive oxygen species (ROS).

NAC also has anti-bacterial properties which have an additive effect when used with antibiotics. This has been shown to reduce the risk of exacerbation and has improved symptoms in patients.

NAC taken orally has been shown in multiple clinical trials to help CF patients maintain lung capacity over an extended period. A dosage of 50 mg per kg of body weight per day has been suggested.

NAC has proven extremely safe even in large doses over the past four decades. Mild stomach discomfort has been reported in rare cases. Doses as high as 3000mg per day have been proven to be safe over periods of 12 months.

NAC is listed by the World Health Organisation as an essential medicine.

Some claims have been made that NAC loses its antioxidant properties during storage due to exposure to oxygen in the atmosphere. Effervescent tablets are available from some suppliers that are prepared under strict environmental conditions and sealed in foil which avoids any deterioration.

The effervescent tablets are also free of any undesirable odour and have a pleasant taste. They are generally available in 600mg tablets.

**Does NAC interact with other medications?**

NAC can improve the efficiency of immunosuppressants, nitroglycerin and some skin antifungals so you would check with a doctor if you were on those. It also improves the effectiveness of antibiotics but that is all positive. It can also raise blood sugar so would need monitoring if you are a diabetic. Activated charcoal can negate the effectiveness of NAC. It is generally considered very safe. You can Google N-Acetyl Cysteine and see for yourself.

**What Dosage?**

Most of the trials showed dosage between 34mg and 50mg per kg of body weight three times a day were considered a high enough dose to be effective.

A leading research doctor recommended to me that a dosage of 900mg taken three times a day would be appropriate for an adult.
It has proven safe in much higher doses over extended periods without any real contraindications

This document was compiled with the express purpose of highlighting some of the recent studies into CF by scientific research organisations. This document is not provided for the purpose of providing medical advice. Please do your own research or seek medical advice before making any decisions. Be advised that many doctors are not aware of the benefits of NAC.

Where Can I Buy NAC?

It is not the purpose of this document to promote any particular brand or distributor of NAC. It is however important to only purchase good quality foil sealed effervescent tablets for best results. If you have difficulty sourcing this yourself, or you have other questions, you can contact the author David White at the following email address...

david@advancedrobotic.com
About the author

The author of this document assigns all credit to the respective scientific publications and research scientists as listed in the body of this study and the web links at the end of the article. He takes no credit for the information presented here but hopes that it will assist non-medical persons in the understanding of current scientific research into the disease.

David White has a granddaughter that suffers from the CFTRΔF508 mutation and is therefore highly motivated to research any possible therapies that can minimise her symptoms.

He is a Research & Development Engineer in the field of Industrial Robotics and specialises in mechanical, electronic and software engineering with over 30 years of experience in developing control systems.

His experience is extensive in feedback loop systems in mechanical devices that mimic organic processes. It is the apparent feedback loop present within the immune system of Cystic Fibrosis that struck him as almost identical to a poorly tuned Proportional/Derivative loop in a servomotor controller. The PD algorithm is designed to maintain a desired status quo such as position or torque. If any single parameter is out of adjustment it may cause a runaway situation that results in wild oscillations and possible mechanical damage.

It is this very same effect that appears to cause the inflammatory reaction and thickened mucous within the tissues of the lungs in CF patients.

In a PID loop, the P stands for Proportional Gain. It is this parameter that causes the reactionary effect of a disturbance. The algorithm responds proportionally to any error in position or torque by producing an opposing force. In CF this is likened to the inflammatory reaction to infection through the release of Neutrophils and the resulting ROS.

The D parameter stands for Derivative Gain. This parameter is responsible for dampening the effects of the P. Gain as the desired target is approached. Without enough derivative gain the result is an overshoot of the target. The results of this can be wild oscillations resulting in damage. In CF, it is the low levels of the antioxidants, primarily glutathione, that fails to dampen the effect of the ROS before cells are damaged and the mucin becomes cross-linked into a polymer resin, thereby providing a further ideal habitat for pathogens to multiply.

Due to the aggressively “Proportional” effects of the strongly pro-inflammatory CF cells, it seems obvious that it is vital to increase the “Derivative” or dampening capability of antioxidant glutathione through increasing its levels in the epithelial cells. While it is nearly impossible to absorb glutathione by ingestion, it is possible to increase the levels through oral or intravenous administration of N-Acetyl Cisteine which is converted to glutathione by...
the liver, and distributed by the liver’s major protein, albumin, to tissues and released into the cells.

References:

Following are a list of links to reference works used in this document as well as some other interesting articles.

http://www.cpnc.dk/NAC%20paper_JCF.pdf
http://www.hindawi.com/journals/jpath/2015/S40271/
http://www.druglib.com/druginfo/mucomyst/
http://m.jbc.org/content/285/29/22299.full
http://europepmc.org/articles/pmc4619981
http://europepmc.org/articles/pmc4619981#B156
http://europepmc.org/abstract/MED/25228446
http://europepmc.org/articles/PMC4245155/
http://europepmc.org/abstract/MED/24378052
http://www.crccs.com/Portals/25/CF%20Newsletters/CF%20Breeze%20April%202015.pdf
http://lungdiseasenews.com/2015/03/06/researchers-reveal-molecular-mechanism-behind-thick-mucus-production-in-cystic-fibrosis-patients/
http://onlinelibrary.wiley.com/doi/10.1042/CBI20090007/abstract;jsessionid=B3EE060AC0CBE4DCB1568EAC3723114CEE70.f04t04?userIsAuthenticated=false&deniedAccessCustomisedMessage=