Ndds - aminoglycoside as an treatment for treating infection in cystic fibrosis

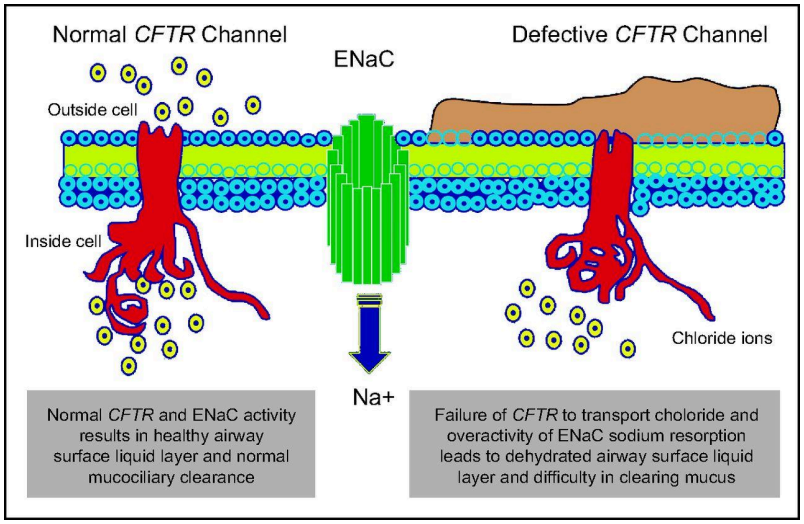
1. About disease and current treatments https://doi.org/10.4187/respcare.06697

Cystic fibrosis (CF) is a genetic disorder inherited in an autosomal recessive pattern, caused by mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene. The CFTR protein plays a key role in forming a chloride channel essential for proper mucus transport. Mutations in this protein impair chloride secretion, disrupt sodium reabsorption, and hinder water transport, leading to thick, concentrated mucus and reduced mucociliary clearance. As a result, the dehydrated mucus promotes infections with a specific range of bacteria, triggering an excessive inflammatory response. This leads to severe bronchiectasis, rather than fibrosis, and ultimately results in respiratory failure.

Patho
Efficient mucociliary clearance is crucial for maintaining respiratory health. The clearance mechanism relies on two hydrogel layers: a mucus layer and a periciliary layer. Proper mucociliary transport depends on adequate hydration of the airway surface liquid. Impairments can occur due to abnormal ciliary movement or changes in mucus composition, making it less responsive to ciliary propulsion. In healthy individuals, the airway epithelium regulates ion and water secretion or absorption, maintaining optimal surface hydration. The higher osmotic pressure in the periciliary layer ensures sufficient hydration, enabling smooth ciliary movement and efficient transport of the mucus layer from the distal airways to the trachea.

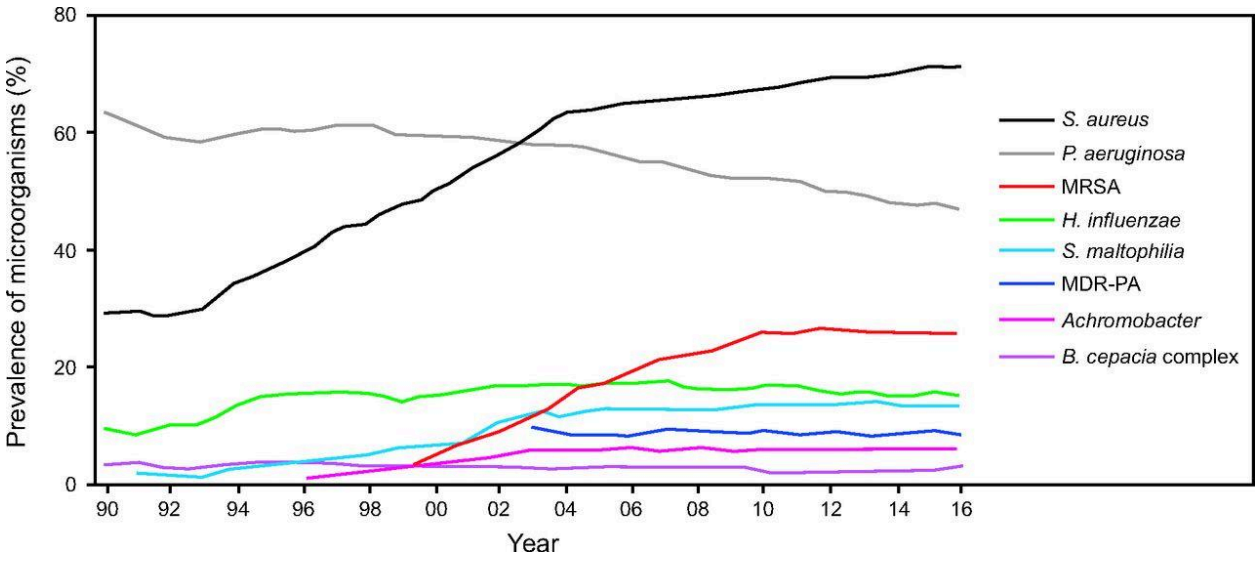
The abnormal mucus concentration in the lungs of patients with cystic fibrosis (CF) stems from a fundamental issue in the transport of ions and water by the airway epithelium. In CF, a defect in chloride and bicarbonate secretion via the CFTR protein, combined with intact sodium absorption, leads to excessive fluid absorption. This imbalance raises osmotic pressure in the mucus layer compared to the periciliary layer, depleting fluid on the airway surface. As a result, the mucus becomes thick, dehydrated, and adheres to airway surfaces, impairing mucus transport.

Additionally, increased secretion of mucin (the main component of mucus) is indicated by the presence of mucus plaques and plugs, which become the primary sites of chronic infection rather than the airway epithelial cells themselves. CF lung disease is often marked by airflow obstruction and recurring bacterial infections. These infections trigger an exaggerated and ineffective inflammatory response, characterized by high levels of neutrophil elastase, which further increases the stickiness of mucus



Bacterial infection-

The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) has increased to 25% in recent years. Its transmission is well understood, as MRSA is common in the general population and can survive on surfaces, making it more easily spread between patients.



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Antibiotic eradication therapy (AET) for *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients has shown significant benefits, with high eradication rates and prolonged periods of pathogen-free airways. Various AET regimens, including inhaled tobramycin and colistin, with or without oral ciprofloxacin, have been widely used and documented as effective. The ELITE and EPIC trials demonstrated that a 28-day inhalation of tobramycin (TIS) effectively eradicated *P.*

aeruginosa in many patients, with some remaining infection-free for up to 27 months. However, no single treatment regimen has been proven superior, and clinicians are advised to choose the most convenient option based on patient needs. Safety concerns, especially in young patients, are minimal with TIS. While ongoing studies aim to provide clearer guidance, a 28-day TIS regimen is currently a recommended approach for *P. aeruginosa* eradication, though optimal treatment protocols are still undetermined due to limited comparative research.

Limitation of ate

AET for *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients shows an average eradication rate of 81.2%, but it can fail due to several factors. Patient adherence is crucial, and timing may play a role, as treatment is most effective within 12 weeks of detection. Once the infection becomes chronic, bacterial resistance, host factors, and airway obstruction reduce the effectiveness of antibiotics. Additionally, re-infection from areas like the sinonasal cavities may occur, and negative cultures don't always indicate true eradication. Serological tests may help identify patients at higher risk of re-infection. These challenges explain why AET is not always successful.

Tobramycin, an aminoglycoside antibiotic, has long been used as an aerosol therapy for cystic fibrosis (CF) and was the first aerosol antibiotic approved for this purpose. It is included in CF treatment guidelines to manage *Pseudomonas aeruginosa* infections, improving lung function and preventing exacerbations. The standard dose is 300 mg nebulized twice daily every other month, and it is widely available

An alternative nebulized formulation, Bramitob® (Chiesi), offers a higher concentration (75 mg/mL) to reduce nebulization time, with the same dosage of 300 mg nebulized twice daily every other month. In clinical trials, Bramitob® significantly improved lung function and was well tolerated, though it is currently available only in Europe.

Tobramycin is also available as a dry powder (TOBI® Podhaler®, TIP™, Novartis) for CF management. The TIP capsules, designed for use with the T-326 dry powder inhaler, have a similar pharmacokinetic profile to the nebulized formulation. Clinical trials, including the EAGER and EVOLVE studies, showed that TOBI Podhaler® is as effective and well-tolerated as nebulized tobramycin, with improved FEV1 compared to placebo. The recommended dose is 112 mg (four 28 mg capsules) inhaled twice daily in alternating 28-day treatment cycles. TIP is available in some European countries, South America, and Canada.

Medication development

i)A combination antibiotic of fosfomycin and tobramycin, known as fosfomycin/tobramycin (FTI), is under development for managing chronic bacterial infections in cystic fibrosis (CF) patients. A Phase II study (NCT00794586) has assessed the safety and efficacy of two dosing regimens of FTI following a 28-day course of AZLI in CF patients with *Pseudomonas aeruginosa* lung infections.

ii)Liposomes are biodegradable vesicles made of phospholipid layers that can shield polycationic antibiotics like aminoglycosides from inactivation by sputum components such as mucins or DNA. Liposomal amikacin for inhalation (Arikace®, INSMED) uses neutral-charge liposomes to enhance the delivery of the aminoglycoside into mucus plugs and *Pseudomonas aeruginosa* biofilms. Clinical studies with Arikace, administered via the eFlow® nebulizer, demonstrated a sustained release of amikacin in the lungs of cystic fibrosis (CF) patients. Phase Ib studies involving 24 CF patients showed that 500 mg of Arikace once daily for 14 days was effective. Phase II trials found that a daily dose of 560 mg for 28 days, followed by a 28-day break, significantly improved lung function and reduced *Pseudomonas aeruginosa* density compared to placebo. Patients on Arikace also experienced greater improvement in respiratory symptoms and tolerated the treatment well.