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New insights into the pathogenesis of cystic fibrosis sinusitis

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Abstract

People with cystic fibrosis (CF) sinus disease have developmental sinus abnormalities with airway bacterial infection, inflammation, impaired mucociliary clearance and thick obstructive mucus. The pathophysiology of airway disease in CF is not completely understood, and current treatments in CF sinus disease ameliorate symptoms but do not provide a cure.

This manuscript reviews the history of CF, its manifestations in sinus disease, and the potential impact and relationship of CF on the upper and lower airway. We discuss recent discoveries in the pathophysiology of CF using the CF porcine animal model and exciting treatments that address the primary gene defect that may translate into improved outcomes in CF and non-CF sinusitis in humans.

Keywords

airway biology; electrophysiology; ion transport; gene therapy; CFTR

Introduction

Cystic fibrosis (CF) is a common, lethal genetic disorder in the United States, with 1 in 3,500 babies born with CF and 30,000 people in the US having the disease. Although advances in the clinical care of the CF patient have increased the average lifespan, the most common cause of mortality continues to be airway disease.¹ CF was first named in 1938 by Dorothy Andersen to describe the pathologic changes of the pancreas in children with CF.² The CF phenotype has expanded to multiple organ systems including the intestine, lung, sweat gland, liver, gallbladder, male genital tract, and the paranasal sinus.^{3–6} Although the association between early death and salty sweat was first made in the 18th century,⁷ a severe hot spell in New York in 1948 prompted Kessler's observation that 5 of 10 children admitted for dehydration had CF.⁸ Di Sant'Agnesse tested this association through an elegant set of experiments. He measured the electrolyte composition of sweat by applying occlusive gauze to the skin of subjects in a heated room and discovered that people with CF had increased sweat sodium (Na⁺) and chloride (Cl⁻) levels.⁹ In 1983, Paul Quinton isolated and microperfused the sweat glands from the skin of humans and found that low Cl⁻ transport was the primary defect in CF.¹⁰ Although inheritance patterns in CF suggested an autosomal recessive disorder, it was not until 1989 that a collaborative effort from the labs of Drs. Collins, Riordan, and Tsui identified the *CF transmembrane conductance regulator* (CFTR)

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gene.¹¹ The *CFTR* gene encodes an anion channel expressed on the cell surface that allows the transport of Cl^- and bicarbonate (HCO_3^-). If the channel is analogous to a door, cyclic adenosine monophosphate (cAMP)-agonists open the lock and adenosine triphosphate (ATP) widens the doorway. Mutations in *CFTR* are responsible for CF and can be classified into six different classes: defects in protein production (Class I), processing (Class II), regulation (Class III), conduction (Class IV), reduced number of *CFTR* transcripts (Class V) and accelerated protein turnover (Class VI).^{5,12} The most common CF mutation is the ΔF508 mutation representing a deletion of three nucleotides resulting in absence of phenylalanine at position 508, leading to a misfolded protein that cannot be transported to the cell surface.

The unified airway in CF

As we breathe, air is passed through the conducting upper airway via our sinonasal passages, through the larynx, and enters the lower airway consisting of the trachea, bronchi, and bronchioles. The upper and lower conducting respiratory airway epithelia consist of pseudostratified ciliated epithelia with glandular epithelial cells and submucosal glands that produce mucus that coats the airway and provides a medium for mucociliary clearance. In general, the size of the airway progressively decreases from the sinonasal passage to the small bronchioles, which then progress to the microscopic alveoli that participate in gas exchange (Table 1). The unified airway model suggests that disease processes of the upper airway can influence that of the lower airway, and vice versa.¹³ In CF, loss of *CFTR* in the sinonasal and lower airway epithelia reduces Cl^- and HCO_3^- transport¹⁴ and results in the common end result of airway bacterial infection, inflammation, impaired mucociliary clearance and thick obstructive mucus.

Similar pathogens in upper and lower airway infection: Could the sinus be infecting the lungs in CF?

There are several studies that have looked at the similarities between bacterial pathogens in the sinus and lung in CF. In early disease, both the sinus and the lungs are infected with common bacteria including *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. In chronic disease, *Pseudomonas aeruginosa* is the major pathogen in both the sinus and the lung.^{15,16} Early aggressive treatment to eradicate *P. aeruginosa* in the lung has been found to be the biggest factor in improving lifespan in CF. Unfortunately, the lungs eventually become recolonized with *P. aeruginosa*, and the bacteria can adapt to become drug-resistant and mucoid, forming biofilms that can be difficult to eradicate. Those who become recolonized with *P. aeruginosa* after eradication therapy often have similar strains as bacteria cultured from the sinus.^{16,17} Researchers have compared the genotypes of *P. aeruginosa* in the sinus and in the lungs of CF patients after lung transplant and found similarities in both genotype and gene expression phenotypes.^{18–20,21} There are various reports of the effect of sinus surgery in reducing CF lung disease, which may be attributed to the lack of a standard criteria for success in CF sinus surgery.^{22–24} These observational findings suggest that the sinus and upper airway can act as a bacterial reservoir and transmit disease to the lower airway. Therefore aggressive eradication of CF infection in the upper airway may improve treatment of lung disease.

Use of a CF porcine model to understand the pathophysiology of CF disease

A major obstacle in the study of CF has been the lack of a suitable animal model that replicates human CF disease. Previous animal models, including the CF knockout mouse,

exhibit gastrointestinal abnormalities but do not spontaneously develop airway disease.²⁵ The expression of a calcium-activated chloride channel (CaCC) may explain the lack of phenotype in CF mice.²⁶ Prospective human studies of infants with CF to investigate the pathogenesis and pathophysiology of disease are difficult to perform due to ethical concerns. We have recently reported a novel, CF porcine knockout model that exhibits altered anion transport in airway epithelia, defective bacterial killing, and spontaneous development of airway disease similar to CF including airway inflammation, remodeling, and infection.²⁷ Here we review recent discoveries from the CF pig model that have shed light on the pathophysiology of CF disease.

CF electrophysiology

The primary defect in CF is due to lack of CFTR anion transport. The main tools for examining ion transport in a cell are electrophysiology studies in humans (*in vivo*), in cultured airway epithelia (*in vitro*), and in freshly dissected tissue (*ex vivo*). If we assume only transcellular transport, we can oversimplify the ion transport of an airway epithelial cell into a sodium–potassium adenosine triphosphatase (Na^+/K^+ -ATPase) pump and channels/transporters on the basolateral side, and the epithelial Na^+ (ENaC) and Cl^- (CFTR) channels on the apical surface. Voltage (V_t) represents the electric potential difference between the apical and basolateral surface of the cell, current (i) the flow of electrical charge through the cell, and conductance (G_t) the ease at which the current flows through the cell via ion channels (Figure 1). We can measure V_t changes in humans *in vivo* by measuring the potential difference between electrodes placed on the nasal epithelium and ground electrode. In 1983, Knowles noted characteristic voltage differences in people with CF: elevated basal V_t levels and an increased V_t change after blocking the ENaC channel with amiloride.²⁸

According to Ohm's law, $V_t = i/G_t$. Therefore two possibilities can account for the increased V_t in CF. Increased Na^+ transport could increase current (i) or lack of CFTR channels could decrease conductance (G_t). In order to distinguish between these two differences, G_t or (i) need to be measured. Measurements in conductance cannot be performed *in vivo*, but are commonly measured in freshly isolated explants or *in vitro* epithelial cultures in Ussing chambers. Electrophysiology studies of CF human *ex vivo* tissue “are confusing and difficult to interpret” according to a review by Geddes.²⁹ Some studies have reported decreased basal G_t and a decrease in G_t after amiloride, suggesting that the V_t changes in CF were due to lack of Cl^- transport.³⁰ Other studies have found the opposite result of increased Na^+ transport and G_t in CF epithelia.³¹ The investigators believed there were several reasons for these discrepancies: impaired function of *ex vivo* tissue due to hypoxia, physical damage of *ex vivo* tissue once mounted in the Ussing chamber, variability in the age and quality of the tissue, and the time to study thereby highlighting the technical difficulties of using *ex vivo* human airway tissue.³¹

The CF pig has enabled us to investigate the changes in V_t , (i) and G_t of airway epithelia *in vivo*, *ex vivo*, and *in vitro* cultures and thereby address controversies in CF electrophysiology. Chen et al. found that similar to *in vivo* studies in humans, CF pigs showed increased amiloride-sensitive V_t and I . However, in contrast to a widely held view, lack of CFTR did not increase transepithelial Na^+ transport or liquid absorption, nor did it reduce periciliary liquid depth. Lack of apical Cl^- conductance caused the change in voltage, not increased Na^+ transport.³² This study identified loss of CFTR anion permeability as the primary transport defect at birth, which could contribute to the development of airway disease in CF.

Decreased HCO_3^- transport and pH in CF impairs innate immunity against bacteria

Although loss of CFTR results in chronic inflammation and infection of human airways, the mechanism of impaired immunity is unknown. One important question in CF has been which appears first: inflammation or infection of the airway? Stoltz et al. found that the airway of newborn CF pigs did not have inflammatory changes, yet bacterial challenges to the airway resulted in impaired killing in CF versus non-CF pigs.²⁷ This finding suggests that CF pigs have a host defense defect against bacteria that results in airway inflammation. In a set of experiments to investigate the pathogenesis of the impaired host defense defect in CF porcine airways, Pezzulo et al. used immobilized bacteria on grids applied to the airway surface *in vivo* and quantified bacterial killing using a live/dead stain. By utilizing this method, they found that CF airway epithelia exhibited a bacteria killing defect independent of mucociliary clearance, phagocyte killing, or inflammation. They hypothesized that the bacteria killing defect was due to impaired HCO_3^- transport resulting in decreased airway surface liquid (ASL) pH in CF airway epithelia. Subsequent studies manipulating the ASL pH confirmed that decreased ASL pH impaired bacteria killing by decreasing the function of antimicrobial proteins in the ASL.³³ These results suggest that increasing ASL pH and antimicrobial activity by HCO_3^- delivery may be an effective strategy in treating airway infection in CF.

The CF pig as a model to test hypotheses in CF sinusitis

There have been several unanswered questions in CF sinusitis. First, does sinus disease precede lung disease in CF? Second, what treatments are effective in CF sinusitis? And third, will early aggressive treatment of CF sinus disease slow progression of lung disease? The pig is a good model to study sinus development and disease, as pigs are born with ethmoid and maxillary sinuses and develop frontal and sphenoid sinuses later in life, similar to humans. Their relatively large size also allows endoscopic visualization and sampling of the sinonasal cavities (Figure 2). We have investigated the phenotype of the CF pigs and found that CF pigs have defective anion transport, newborn CF pigs have sinus hypoplasia, and CF pigs spontaneously develop CF sinus disease similar to that of humans with CF (Figure 3).³⁴

Does sinus disease precede lung disease in CF? We have followed several young children with CF whose first presenting symptom was due to sinonasal disease. These children's sinus CT scans showed severe sinonasal disease, yet their screening lung CT exams in the same period did not identify chronic lung infection (Figure 4). Supporting this hypothesis are studies of children with positive upper airway but negative lower airway cultures in CF.³⁵ This condition may be secondary to anatomical factors where disease occurs in the lumen of the sinus and must be cleared through the narrow ostia, whereas in the lung disease occurs in the small airways and is expelled by the cough mechanism and mucociliary transport through progressively larger airways. There may also be differences in antimicrobial factors, immune defense systems, and ion transport that account for disease in the upper and lower airway. Human studies to investigate the onset of sinus to lung disease in CF are difficult due to the ethical issues of repeated radiologic imaging in young children.^{36,37,38} The CF pig allows us to perform longitudinal studies of endoscopy, bronchoscopy, microbiologic cultures, and radiologic imaging from birth and throughout disease.

Second, what treatments are effective in treating CF sinus disease? In humans, there is no clear evidence that sinus surgery improves outcomes in CF. Some studies have shown improvement in sinus disease as well as lung disease,^{22,39} while others have shown no

effect.²⁴ Although sinus surgery may improve symptoms of CF sinusitis, the disease invariably recurs evident as chronic bacterial infection and sinus opacification on CT.⁴⁰ Therefore, we are unlikely to implement sinus surgery as a widespread treatment in CF due to the limited evidence of surgery in effectively treating disease. Gene therapy trials in humans directed to the sinus have shown transient gene expression and ion transport changes,⁴¹ but have not changed primary and secondary outcomes of sinonasal disease.⁴² These studies may be confounded by the advanced stage of sinus disease with associated inflammation and infection. We have investigated topical gene therapy to the porcine sinus with the goal of correcting CFTR expression and treating the primary gene defect. The relative symmetry of the sinus allows us to use one animal as its own control, and we have shown that we can selectively transduce sinus epithelial cells in the pig.⁴³ In an *in vitro* model, we can also correct the CFTR defect in CF porcine sinus epithelia, as evidenced by increased anion transport.⁴⁴

One of the biggest advances in CF medical therapy for a select group of patients has been the drug VX-770, also known as Kalydeco or Ivacaftor. VX-770 is the first medical drug that facilitates the opening of defective CFTR channels, and is thereby a “potentiator” of CFTR activity. The use of VX-770 is limited to people with the G551D mutation (Class III mutation), where CFTR protein is present at the cell surface but inactive due to defective regulation of CFTR. The first randomized trial of VX-770 in people with the G551D mutation showed improvements in anion transport measured by nasal electrophysiology and sweat Cl⁻, as well as clinical improvements in lung function.⁴⁵ These promising findings led to U.S. Food and Drug Administration approval of the medication for people with CF and the G551D mutation. Unfortunately, this group represents only 4–5% of people with CF, and the medication is costly and likely needs to be taken long-term.⁴⁶ Regardless, this has been a major medical advance in the treatment of CF, and novel therapies to address more common mutations of CFTR including $\Delta F508$ are being investigated as “correctors” of CFTR. As medical therapies advance to provide options for cure in CF disease, there is a need to quantify the CF sinus phenotype so we can monitor sub-clinical levels of disease with the goal of prevention. Future studies in the CF pig will allow us to investigate if standard interventions including lavage, antibiotics, and surgery, or novel therapies including gene therapy and CFTR potentiators and correctors, can treat CF sinus disease.

Third, will the early aggressive treatment of CF sinus disease slow the progression of lung disease? Early eradication therapy of CF lung disease has been the greatest factor in reducing morbidity in CF, yet eventual recolonization of the lung occurs with bacteria that have adapted to become drug-resistant and form biofilms. If the sinus did act as a bacterial reservoir for lung recolonization, early aggressive therapy to eradicate CF sinus disease could improve outcomes in CF. Because of the paucity of symptoms and early onset of disease, treatment of the CF sinus occurs after chronic inflammatory changes in the sinus epithelia have already developed. The CF pig allows us to test therapies to the airway before the onset of disease in a window of opportunity where treatment may be most effective. We can also investigate if early treatment of CF sinus disease can delay the progression of CF lung disease.

Conclusion

CF is a common, fatal disease involving the airway. There is increasing evidence that CF sinus disease may affect CF lung disease, the most common cause of mortality in CF. We have been limited in treating the symptoms of advanced CF sinus disease with our current therapies. The recent advances of an animal model that replicates CF sinus disease, and novel therapies including gene therapy and potentiators and correctors of CFTR, offer promise to treat the primary gene defect and improve treatment of human CF disease.

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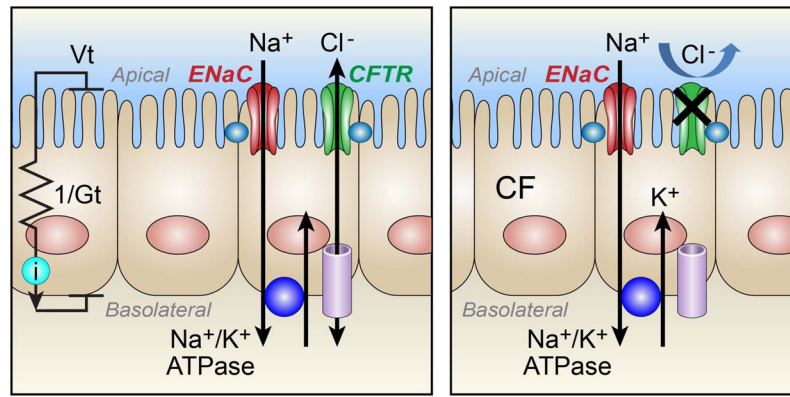


Figure 1. Transcellular ion transport in airway epithelia. Measurements of voltage (V_t), current (i), and conductance (G_t) are drawn in relation to an electric circuit. V_t measures the electric potential difference between the apical and basolateral surface of the cell, i the flow of electrical charge through the cell, and G_t the ease at which the current flows through the cell via ion channels. In this simplified diagram airway epithelia have a sodium–potassium adenosine triphosphatase (Na^+/K^+ -ATPase) pump and channels/transporters on the basolateral side, and the epithelial Na^+ (ENaC) and Cl^- (CFTR) channels on the apical surface (A). In CF epithelia loss of the CFTR channel reduces Cl^- transport with increased basal V_t levels.

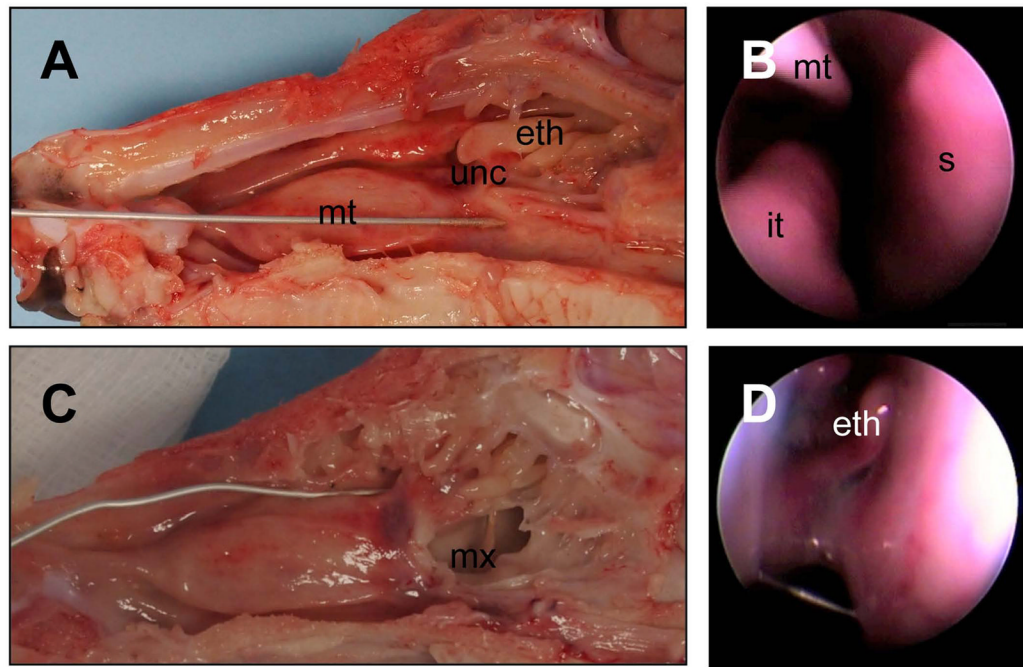


Figure 2. Piglet anatomy. Sagittal split of piglet head. A. Right hemisagittal section : unc = Uncinate process, mt = Middle turbinate, eth = ethmoid sinus. C. Left hemisagittal section with the uncinus process removed and wire into the middle meatus and in the maxillary sinus (mx). The endoscopic view of the anterior (B) nasal passageway showing the septum (s), inferior turbinate (it), and middle turbinate (mt). Further posterior (D) is the ethmoid sinus (eth).

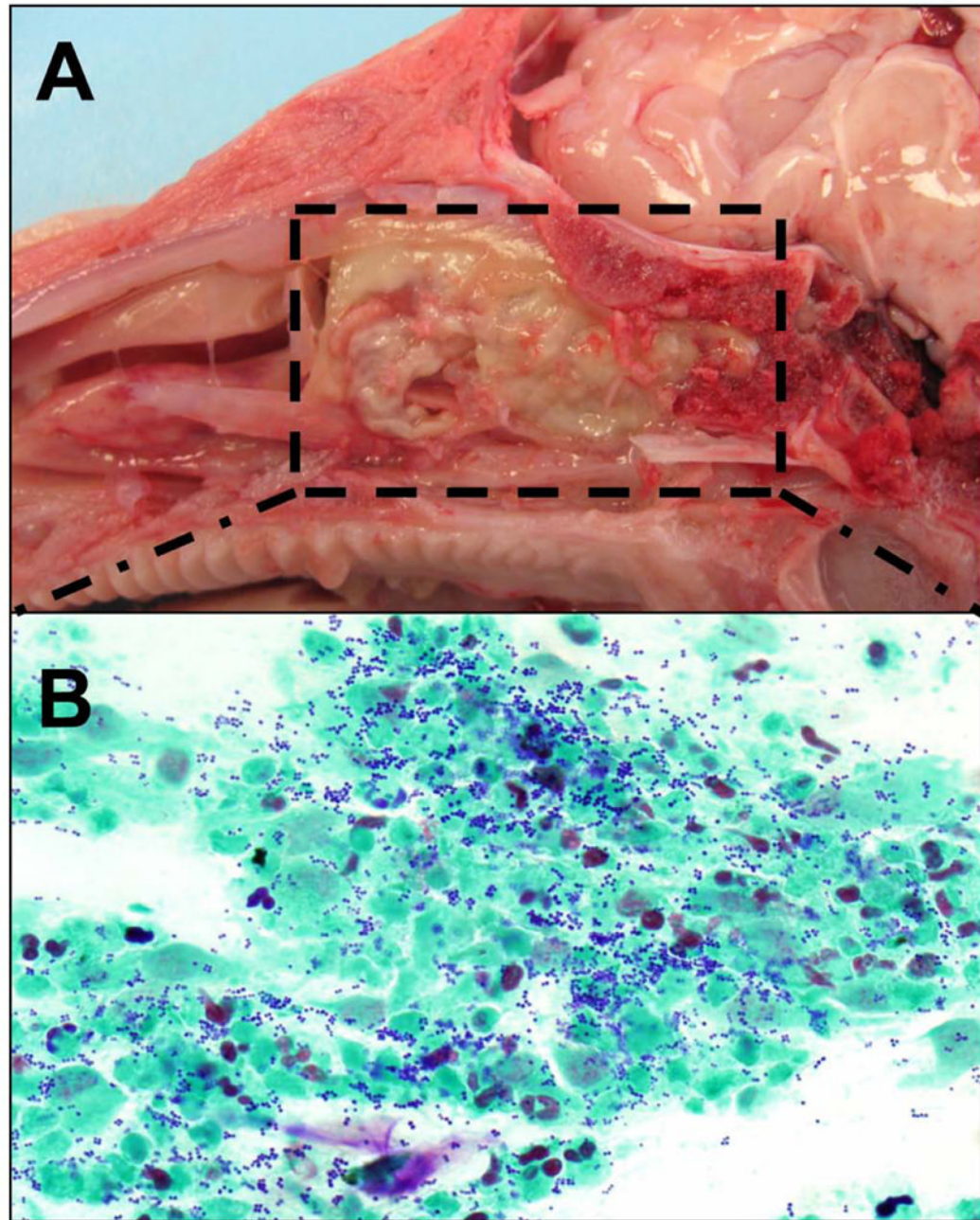


Figure 3. CF piglet with thick mucus occluding the ethmoid and maxillary sinus (A). Histology of the mucus consistent with cellular debris and gram positive cocci consistent with *Staph aureus* (B).

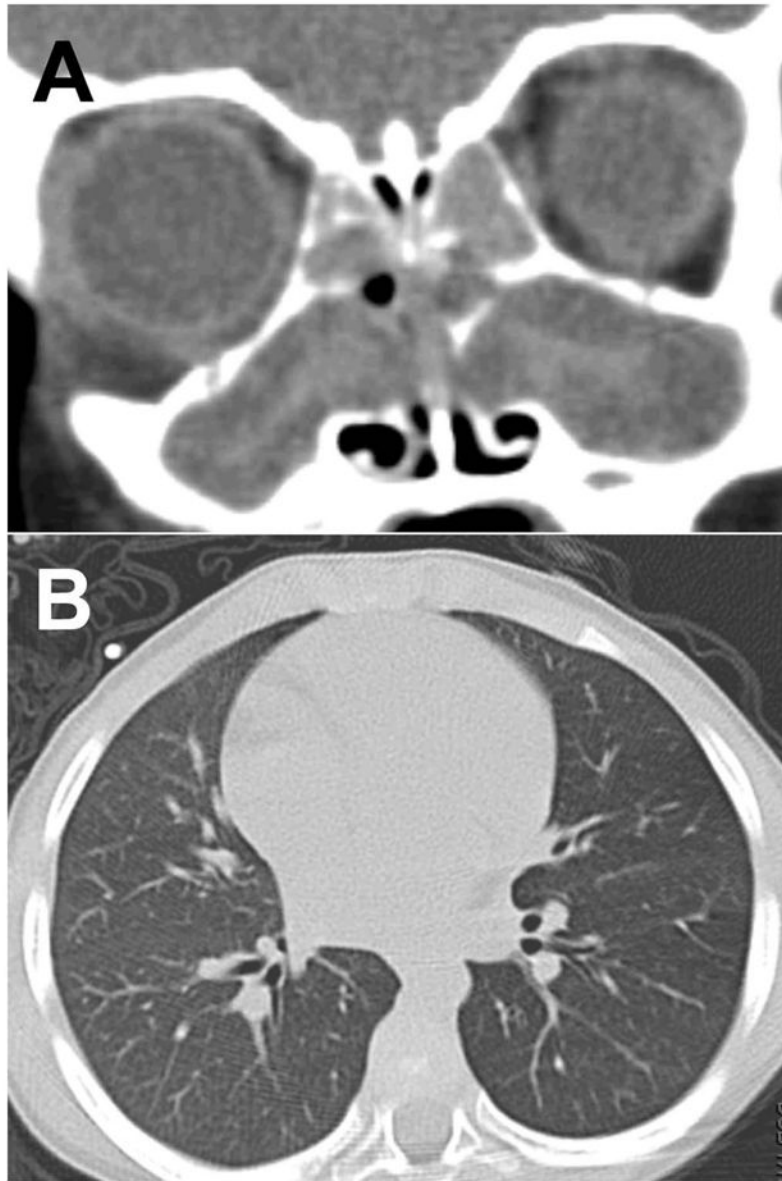


Figure 4. Sinus disease without lung disease in a child with CF. Sinus CT scan taken at 4 years of age consistent with chronic sinusitis with thick hyperdense mucus completely occluding the ethmoid and maxillary sinus (A). Lung CT scan taken at the same time without radiologically apparent lung disease (B).

Table 1

Characteristics of the upper and lower airway

Airway	Function	Cell types	Diameter (mm)
Nasal/Turbinates	Humidification, temperature regulation, filtration, mucociliary clearance	Pseudostratified columnar ciliary epithelia	10
Sinus	Pneumatized airway lumen in the skull, immunologic defense, patterned mucociliary clearance to ostial openings	Pseudostratified columnar ciliary epithelia	Ostial diameter = 2
Olfactory	Specialized neuro-epithelia to detect odor	Olfactory cells, supporting cells, basal cells, brush cells	
Trachea	Cartilaginous tube that connects the upper airway to the pulmonary system	Pseudostratified columnar ciliary epithelia	18
Bronchi	Division of the trachea that conducts air in to the lungs	Pseudostratified columnar ciliary epithelia	5–12
Bronchioles	Division of the bronchi that conducts air to the alveoli	Pseudostratified columnar ciliary epithelia, Clara cells	0.5–3.5
Alveoli	Site of gas exchange, terminal division of respiratory tree	Type 1 and 2 alveolar cells	0.4