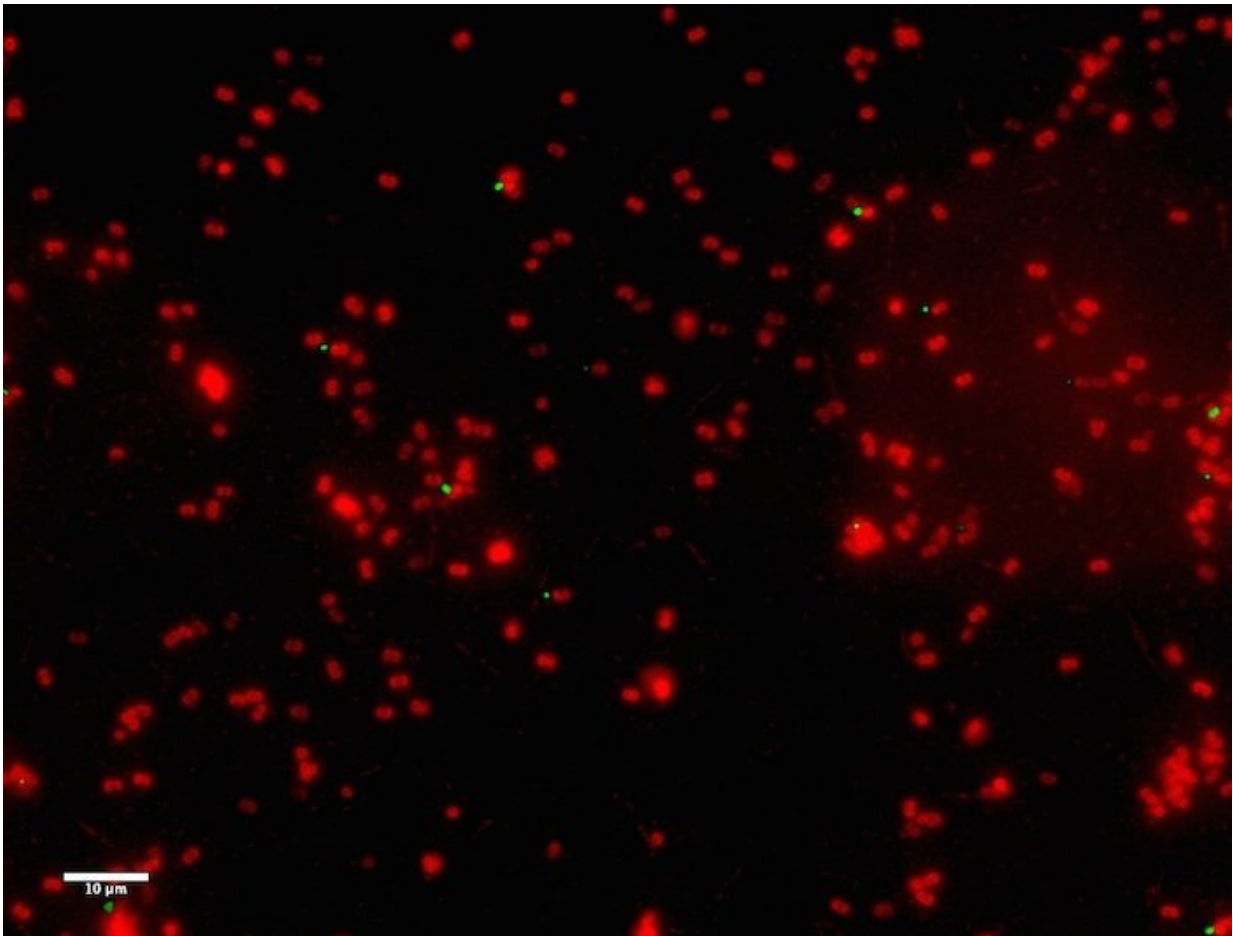


Cystic fibrosis bacterial burden begins during first years of life

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Microscopic image of *Staphylococcus aureus*, a problematic pathogen that infects the airways of children with cystic fibrosis. Credit: University of North Carolina at Chapel Hill School of Medicine

Cystic fibrosis (CF) shortens life by making the lungs prone to repeated bacterial infections and associated inflammation. UNC School of Medicine researchers have now shown for the first time that the lungs' bacterial population changes in the first few years of life as respiratory infections and inflammation set in.

The study, published in *PLoS Pathogens*, offers a way to predict the onset of lung disease in [children](#) with CF and suggests a larger role for preventive therapies, such as hypertonic saline.

"Lung symptoms in kids with CF are likely due to an increased burden of bacteria," said study senior author Matthew Wolfgang, Ph.D., associate professor of microbiology and immunology. "This implies there's an opportunity for early intervention that could dramatically increase the quality of life for these kids."

CF affects about 70,000 people globally, and is most common in children of Northern European ethnicity – about one of every 2,500 births. The disease is caused by a dysfunctional version of the CFTR gene that encodes the CFTR protein. In the absence of this protein, mucus becomes dehydrated and thick – a sanctuary for bacteria – leading to repeated infections, [inflammation](#), and eventually structural damage to lungs and upper airway tissues. The life expectancy of CF patients is about 40 years.

Most CF studies have been done in adults and older children, and thus relatively little has been known about how and when inflammation, bacterial infections, and lung damage begin. To shed more light on that question, Wolfgang and colleagues analyzed bacterial DNA in samples of lung-lining fluid gathered from young children as part of an ongoing Australian project called [AREST CF](#).

"It's challenging and rare to get access to such samples," said Wolfgang,

member of the UNC Marsico Lung Institute. "Here in the United States, we don't perform bronchoscopies on children diagnosed with CF if they don't yet have clinical symptoms."

The UNC scientists found that in most of the samples from CF children who were less than a year old, there were little or no signs of bacteria. "If there was no significant evidence of bacteria, there was also no sign of inflammation, and the child generally appeared healthy," Wolfgang said.

In the children between ages one and two, the pattern was different: many samples contained a significant amount of bacterial DNA – from the same bacterial species that normally populate the mouth and throat. These bacteria are not typically regarded as lung pathogens.

"We can't go so far as to say that these kids have active infections, but clearly there's a significant increase in the bacterial burden in their lungs, and we know these bacteria provoke inflammation," Wolfgang said.

In children age three to five, the samples contained increasing evidence of more worrisome bacteria, particularly *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Haemophilus influenzae*, which are commonly found in older CF patients with more severe lung disease. As the bacterial burden worsened, molecular signs of inflammation increased. Also, lung X-ray studies of the children revealed mounting signs of structural lung disease as the bacterial burden increased.

"This tells us lung bacterial infections start much earlier than we had expected in children with CF, and these infections are likely the earliest drivers of structural [lung disease](#)," Wolfgang said.

Many of the bacterial species in the young children with CF, he noted, were "anaerobic" microbes that thrive in conditions of very low oxygen. This finding suggests that the dehydrated, thickened CF lung mucus

creates pockets of low oxygen in lung tissues.

"Therapies aimed at breaking up mucus very early in life might be very beneficial to these kids," Wolfgang said. "These therapies could postpone the increase in bacterial burden, including the shift towards the more pathogenic species."

Doctors already give preventive antibiotics to young children in Australia, Germany, and the UK. However, Wolfgang noted that the children in the AREST CF study, who were treated with antibiotics until the age of two, still showed a clear progression of bacterial burden and inflammation. "It could be that other therapeutic strategies, such as thinning mucus, may be more successful," he said.

Wolfgang and colleagues at the UNC Marsico Lung Institute now hope to do a similar, long-term study analyzing the [lung bacteria](#) of individual children and the changes in these "bacteriomes" over several years. The researchers want to evaluate the effectiveness of an early mucus-thinning intervention, for example hypertonic saline – salt water delivered via inhaler – which is already used to hydrate mucus in older CF patients.

More information: Marianne S. Muhlebach et al. Initial acquisition and succession of the cystic fibrosis lung microbiome is associated with disease progression in infants and preschool children, *PLOS Pathogens* (2018). [DOI: 10.1371/journal.ppat.1006798](https://doi.org/10.1371/journal.ppat.1006798)

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