Sticky Staph: A New Story about Mucoidy and Cystic Fibrosis

In 1938, Dorothy Andersen reported her pathological findings on children with cystic fibrosis (CF), describing *Staphylococcus aureus* as the "usual bacteriologic agent" in their respiratory samples (1, 2). These observations convinced Andersen and colleague Paul Di Sant'Agnese to incorporate antistaphylococcal agents into routine CF care, including the early use of aerosolized antibiotics (penicillins) (1). Partly thanks to these and other treatments, the survival age for people with CF (pwCF) increased, with a concurrent decrease in *S. aureus* detection (3). However, this success was eclipsed by a new problem: high infection rates with *Pseudomonas aeruginosa* (3), which was associated with especially poor outcomes. With this ecological shift, the primary concern of CF lung infections transitioned from *S. aureus* to *P. aeruginosa* (3).

Before long, CF labs began to find *P. aeruginosa* colonies covered in a "mucoid" capsule (4), resulting from polysaccharide overproduction (5). Mucoidy represented one of many adaptations that *P. aeruginosa* undergoes during chronic infections (6), reflecting this organism's capacity for diversification in CF airways (7). These evolutionary changes are thought to provide selective advantages; for example, mucoidy may protect against host immunity and antibiotics (8). Most concerning, several adaptations have been linked to poorer clinical outcomes in pwCF (9, 10), including mucoidy (11). Given *P. aeruginosa*'s increased prevalence and association with adverse outcomes, the field largely concentrated on this pathogen until the early 2000s when, perhaps due to antipseudomonal treatments, *S. aureus* reclaimed its status as the most commonly detected conventional pathogen in U.S. and European CF respiratory cultures (Figure 1) (12, 13).

Unlike *P. aeruginosa*, *S. aureus* adaptive mutants have only recently been studied in the CF respiratory context; for example, antibiotic-resistant small colony variants (SCVs) have been found to be common and associated with severe lung disease in CF (14, 15). In 2016, a newly identified adaptive change, mucoidy, was reported in CF *S. aureus* isolates (16). Mucoid *S. aureus* isolates overproduce polysaccharide, similar to *P. aeruginosa*, and form robust biofilms *in vitro* (16, 17), a phenotype hypothesized to protect the pathogen against host defenses (16) and antibiotics (17). Unlike mucoid *P. aeruginosa* and *S. aureus* SCVs, relatively little was known regarding the prevalence, relationships with lung disease, or mechanisms of emergence of CF mucoid *S. aureus*.

In this issue of the *Journal*, Rumpf and colleagues (pp. 854–865) add significantly to this literature by investigating these features of mucoid *S. aureus* in prospective, multicenter studies (cross-sectional and longitudinal) and using laboratory methods that are uncommon in clinical practice (18). For the cross-sectional phase, mostly young adults were recruited from 12 CF centers across Germany and one in Austria. One respiratory sample each was collected from 451 *S. aureus* culture-positive subjects, and 10 cultured colonies of *S. aureus* per sample were screened on mucoidy-indicating media. The authors identified mucoid isolates in 9.1% of subjects, noting that mucoid culture-positive subjects were older than culture-negative subjects. The 3-year longitudinal phase included 35 subjects with (mucoid group) and 36 subjects without (control group) mucoid *S. aureus* detected, sharing similar demographics and treatments between groups. Of note, the mucoid group produced sputum more often than controls, conceivably reflecting worse lung disease but indicating an important potential confounder: Whether sputum is more likely to yield adaptive variants versus other sample types is unknown.

Rumpf and colleagues found average lung function to be nonsignificantly lower in the mucoid group compared with the control group. However, this analysis was complicated by the fact that many subjects were coinfected with *P. aeruginosa*, which has an established relationship with worse lung function (10). Therefore, the authors categorized subjects according to *P. aeruginosa* culture status, finding that, among *P. aeruginosa* culture-negative subjects, the mucoid group had significantly worse lung function than controls. Additionally, as women have more severe CF lung disease, on average than similarly-aged men (19), the investigators repeated their analysis excluding male subjects, and found that female subjects from the mucoid group had significantly worse lung function than controls. The authors concluded that mucoidy is a common *S. aureus* CF adaptation associated with worse lung function in two groups of pwCF: those without *P. aeruginosa* and women.

Rumpf and colleagues predicted that the mucoid *S. aureus* in this study would exhibit genetic and phenotypic features similar to the mucoid variants in their previous analyses (16). Instead, the investigators found that mucoidy can emerge through as-yet uncharacterized genetic mechanisms, and that mucoidy did not uniformly imply hyperformation of biofilm *in vitro* (whether *in vitro* biofilm formation under their test conditions correlates with lung outcomes remains unknown). These results underscore the need for additional work to define how these adaptive variants emerge and persist, as well as the pressures that drive their selection. The authors discuss the possibility that mucoidy may be a consequence of accumulated antibiotic exposures, which select for SCVs (15). Two of their findings—that SCVs were more common in the mucoid group than in the control group and that SCVs frequently exhibited mucoidy—supports this theory. Host-derived factors may also play a role, such as reactive oxygen species, known to drive *P. aeruginosa* mucoid conversion (20). However, mucoid isolates continued to be observed during modulator treatment, raising questions about the role of airway conditions in the selection and persistence of these adaptive variants.

Despite their multicenter study design, the authors note that sample size limitations warrant validation of their findings. A larger study would also permit a more rigorous investigation of the comparative relationships between mucoid and SCV isolates and disease outcomes, including lung function and pulmonary

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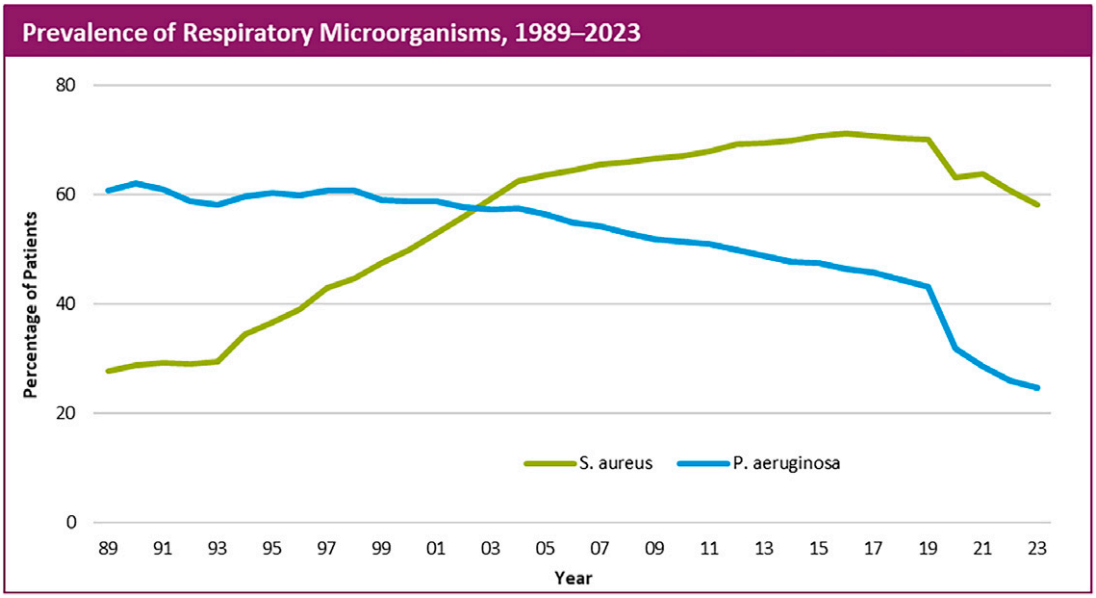

Figure 1. Prevalence of detection of *Pseudomonas aeruginosa* and *Staphylococcus aureus* in respiratory samples from people with cystic fibrosis in the United States as reported to the CF Foundation Patient Registry, demonstrating changes in prevalence of *P. aeruginosa* (blue) and *S. aureus* (green) over 34 years. (Note: The period of 1989–2023 included the widespread availability of elexacaftor–tezacaftor–ivacaftor in the United States, as well as the coronavirus disease pandemic, which affected culture frequency and type.) Adapted by permission from Reference 12 (Elizabeth Cromwell, Ph.D., written communication, February 13, 2025).

exacerbations. Moreover, the prevalence and associations of mucoid *S. aureus* reported by Rumpf and colleagues raise questions regarding current clinical laboratory methodology: Should laboratories adopt methods, including screening more cultured colonies, to detect *S. aureus* adaptive variants? If so, how many colonies are ideal? Although the 10 *S. aureus* colonies that Rumpf and colleagues analyzed per culture are beyond usual practice, this number may still insufficiently reflect the phenotypic diversity of any infection in CF airways. There is also the issue of causality: Whether adaptive variants, such as mucoid *S. aureus,* cause worse CF lung disease or simply identify people with lower lung function (i.e., older, receiving more antibiotics) cannot be established by observational studies. It is interesting to note that one study reported that detection of mucoid isolates of *Burkholderia* species was associated with better, not worse, CF outcomes, arguing against a universally detrimental role of mucoidy in CF (21). These points highlight the importance of studying *S. aureus* adaptations further, especially as the prevalence of *S. aureus* in CF cultures has increased.

With a rigorously designed study, Rumpf and colleagues demonstrate the importance of mucoidy in yet another CF respiratory pathogen, *S. aureus*. It is tempting to consider the similarities between adaptation by *S. aureus*, a Gram-positive human commensal, and *P. aeruginosa*, a Gram-negative environmental bacterium, each known to infect CF airways since Andersen's seminal work. ■

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Exacerbating the Problem: Chronic Obstructive Pulmonary Disease and Atrial Fibrillation

The link between chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) is well established. One fourth of patients with COPD will die not from their respiratory disease, but from CVD (1). People with COPD carry higher risks of developing ischemic heart disease, stroke, heart failure, and arrythmias (2). Coronary artery disease is extremely common in COPD, present in 88% of a U.K. community COPD cohort, with almost 30% having severe obstructive lesions (3). The risk of cardiovascular events is also increased in the postexacerbation period, especially in the first 7 days (4, 5), and remains increased for as long as 1 year after the exacerbation (4). The reasons for this association are likely multifactorial, including inflammation, hypercoagulability, hypoxia, hyperinflation, and increased sympathetic tone.

The risk of atrial fibrillation (AF) is also likely increased after an acute exacerbation of COPD (AECOPD). The rate of AF-related emergency department visits increases significantly in the first 30 days after an exacerbation before decreasing to baseline levels by 90 days (6). A population study in The Netherlands found that one third of patients with COPD who experienced AF during follow-up did so in the 8-week period after an exacerbation (7).

AF is common, with an increasing global prevalence. It is associated with significant morbidity and increased mortality and has worse outcomes when comorbid with COPD (8). The true burden of AF in COPD is not fully recognized, and there is an evidence gap in the optimal strategies for identifying and managing AF to improve long-term outcomes in COPD.

In this issue of the *Journal*, MacDonald and colleagues (pp. 868–870), with a unique use of subcutaneous implantable cardiac monitoring, investigate whether acute exacerbations of COPD are periods of increased AF risk (9). They included patients at high risk for AECOPD, and, among the 40 patients included in the analysis, 30 had at least one exacerbation within the maximum follow-up period of 2 years. The study provides insight into the burden of AF in this patient group, describes the time course of AF burden during an AECOPD, and, importantly, highlights a subset of patients who are most at risk of AF recurrence after an exacerbation.

One fourth of the patients with COPD, who had no history of AF, had periods of AF during continuous monitoring. Without an incident rate, it is difficult to compare this versus other studies in COPD, but it is similar to cardiac populations with pacemakers and implantable defibrillators (10) and those at high risk of stroke (11). However, it remains that the undiagnosed burden of AF in the COPD population with frequent exacerbations is high. Asymptomatic AF episodes detected via implantable devices (i.e., subclinical AF) have

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