

The new microbiology of cystic fibrosis: it takes a community

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For the past 40 years, the approach to studying infections in the airways of persons with cystic fibrosis (CF) has largely paralleled that taken in the study of other human infectious diseases. A microorganism (the causative agent) recovered in culture from an infected site is studied in isolation using a variety of in vitro and in vivo models intended to approximate some facet of the human infection. Although this strategy has yielded a wealth of information regarding microbial virulence factors and pathogenic mechanisms for many human infections, its limitations, when applied to the chronic, polymicrobial infections that typify CF, are becoming increasingly obvious. We now appreciate that respiratory tract infection in CF most often involves diverse communities of opportunistic bacterial species that are well adapted to the peculiarities of this niche. We have, furthermore, come to understand that species within this community are not merely living unaffected by their microbial neighbours, but rather, are actively engaged with each other. And we are steadily decoding the rules and mechanisms that govern this microbial concert.

Given this expanding understanding of infection in CF, it seems reasonable to shift our attention towards a conceptual framework that considers the airway microbial community as the 'pathogenic unit.' Adoption of this framework leads to several relevant but unanswered questions. How are these communities structured? Are they relatively static or dynamic? Are changes in the community stochastic or canonical? What drives changes in community structure, and how do these changes impact community function and host response? Are there communities that are more or less associated with progression of lung disease? More importantly, to what extent can different communities actually effect the progression of lung disease?

And, in the absence of our ability to 'sterilize' the lower airways (ie, if indeed, either 'natural' or healthy), can we envisage manipulation of communities to favour those that may be kinder to their human host?

The work presented by Stressmann and colleagues¹ adds another piece to this puzzle. This group of investigators has been at the forefront of culture-independent bacterial community profiling for the past decade, having been one of the first to describe the complexity of the bacterial community in CF airways,² and having made several important observations in this area since. This team, led by Professor Kenneth Bruce, now describes the characterisation of bacterial communities in serial sputum samples obtained from 14 CF patients during the course of 1 year. The primary question being addressed pertained to the stability of communities during this period, with particular attention to community response to antibiotic therapy. The authors conclude that while not true in all cases, the microbial communities that chronically infect the airways of CF patients vary little over a year, despite antibiotic perturbation.

A closer look at the data presented in this report provides further insight. The patients included in the study varied widely with respect to their degree of lung disease; the mean per cent predicted forced expiratory volume in one second (%FEV₁) for each patient ranged from 16.5% to 84% during the study period. Predictably, patients with more advanced lung disease experienced, on average, more exacerbations, and received more courses of antibiotics than patients with less lung disease (based on mean %FEV₁). Intuitively, one might have expected that the clinical instability of the former group of patients would have been reflected in less stable bacterial communities in serial sputum samples. It is easy to imagine that exacerbation of respiratory symptoms might result from a change in the bacterial community or, conversely, that symptomatic changes in the host's clinical (and presumably,

inflammatory) state might perturb an otherwise stable resident airway community.

However, the opposite effect was observed. Although the degree of community stability—measured as the dissimilarity in community structures between sequential pairs of samples from individual patients—varied considerably, more change in community structure was observed, on average, in patients with greater lung function and fewer exacerbations. Similar results were recently reported by Zhao *et al*, who examined bacterial communities in serial respiratory samples obtained over the course of 8–9 years from six adult CF patients.³

Further consideration of these unexpected results begins to draw a clearer picture of the ecology of airway infection in the context of advancing lung disease in CF. Similar to previous studies,^{4–6} Stressmann *et al* found an inverse relationship between airway bacterial community diversity and lung disease severity. That is, as %FEV₁ decreases (with progressing lung disease), so too does community diversity. It is not clear whether this decrease in diversity is a driver of lung disease or, conversely, results, in part, from the increasingly intensive antibiotic therapy given to patients as lung disease advances, as suggested by Zhao *et al*.³ Both studies found that the decrease in diversity in patients with advanced lung disease was a reflection of a decrease in the number of species in the community (referred to as community 'richness') and an increase in the relative abundance of *Pseudomonas aeruginosa* (or, in ecological parlance, a decrease in the 'evenness' of species abundance in the community). Thus, we see that as lung disease progresses—as indicated by increasing frequency of exacerbations, decreasing %FEV₁, and, presumably, by increasing antibiotic use—bacterial community richness decreases, as does community evenness, which is marked by an increase in the relative abundance of *P. aeruginosa*.

The findings reported in these studies describe a model in which airway bacterial communities at earlier stages of lung disease are diverse, having the 'bandwidth' to experience changes in their structure in relation to the host's clinical state and therapy. As lung disease progresses, community richness and evenness decrease, and this more constrained community is relatively more stable (ie, less able to be moved by perturbations imposed by the

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host or, presumably, by antimicrobial therapy provided to the host). Additional longitudinal studies are underway to determine if this model holds.

But what does all this mean in terms of advancing our understanding and/or improving our management of CF airways infection? Are diverse, less stable microbial communities 'better' for the host? Does the presence of less diverse, relatively fixed communities signify a 'terminal' microbial state that presages end-stage lung disease? Do these findings suggest that we ought to modify the way we manage CF infection in the earlier or late stages of lung disease?

At this point in time, we simply do not know the answers to these questions. What is clear, however, is that we ought not to readily retreat from the current antimicrobial strategies that have been associated with significant improvements in life expectancy in CF during the past two decades.⁷ But, equally important, we

now have an emerging conceptual framework, the methodological tools, and a budding foundation of knowledge that will enable us to focus on the structure and function of the airway microbial community in CF, rather than (or more likely, in addition to) on select members of that community. This new microbiology will be a critical component of a *systems biology* approach—an approach that considers the complex interplay between community microbes, and between the microbial community and the host—that is needed to take us to the next level in our understanding of airways infection in CF.

Competing interests None.

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