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Anaerobic bacteria in cystic fibrosis: pathogens or harmless commensals?

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The application of molecular non-culture-based techniques designed for characterising bacterial communities, such as 16S rRNA gene profiling by terminal restriction fragment length polymorphisms (T-RFLPs) or pyrosequencing, has provided new insights into the microbiology of cystic fibrosis (CF) lung disease.^{1–3} Studies have revealed that rather than being dominated by a single or small numbers of microorganisms, the CF lung is populated by a much more diverse polymicrobial community, including facultative anaerobic bacterial species. Analyses of CF airway samples by strict anoxic culture and culture-independent molecular methods have demonstrated that the anaerobic species can be repeatedly isolated, suggesting that their presence is persistent rather than transient, and are present in numbers comparable with those of the typical aerobic bacterial pathogens.^{1–9} The anaerobes present often represent those that usually colonise the oropharynx. The relative abundance of anaerobes in samples, and differences in composition of anaerobic species between mouthwash specimens and sputum samples, suggests that they are not oral contaminants but do truly originate from the lower respiratory tract.^{5–9–10} That anaerobes are present in the CF lung is

perhaps not surprising. There is a steep oxygen gradient within the CF airway, with regions of hypoxia within mucus plugs. During chronic infection, the major CF pathogen, *Pseudomonas aeruginosa*, adapts to these conditions by increasing alginate production, forming biofilms and changing to an anaerobic metabolism.¹¹ Regions of anoxia in a warm, humid, nutrient-rich environment combined with a defective mucociliary clearance mechanism may allow obligate anaerobic bacteria to colonise or infect the CF lung. Although there is compelling evidence that obligate anaerobic species are part of a complex microbial ecosystem in the CF lung, their role in the pathophysiology of CF lung disease remains unclear.

Current practice in routine CF diagnostic microbiology is to use conventional bacterial culture, including use of selective media, to identify and characterise those bacterial species that are generally considered as having a clinically significant role in CF lung disease. The findings guide infection control practices and antibiotic treatment, including the attempted eradication of early infection with species thought to be key pathogens, use of maintenance antibiotic treatment for chronic infection and management of acute exacerbations. The treatment of acute exacerbations in CF is aimed at resolution of symptoms and restoring objective measures of clinical status back to baseline for the patient, rather than clearance of the infection. However, for

patients with chronic infection there is often little correlation between results of conventional antibiotic susceptibility testing and treatment outcome.¹² Could the action of intravenous antibiotics on the anaerobic species present explain why some patients have a beneficial response to antibiotic regimens to which the dominant aerobic pathogen appears resistant in vitro?

In this issue of *Thorax* (see page 579), Tunney and colleagues report the effect of intravenous antibiotic treatment for acute infective exacerbations on the bacterial composition in adults with CF.¹³ The exacerbations were treated with intravenous antibiotics directed against the main aerobic bacterial pathogen harboured by the individual patient as identified by conventional culture. Treatment resulted in an improvement in clinical status for all patients. There was a small fall in numbers of both aerobic and anaerobic bacterial species with intravenous antibiotic therapy, with a greater relative fall in numbers of aerobes, but the overall the composition of anaerobes and aerobes was little altered. Worlitzsch and colleagues also demonstrated an improvement in lung function in patients with CF following treatment with intravenous antibiotics, but without a reduction in the numbers of obligate anaerobes.⁶ The greater relative fall in aerobic bacteria is perhaps not surprising since the antibiotic regimens used were selected by anticipated activity against the main aerobic pathogens. The lack of a significant fall in numbers of obligate anaerobic bacteria with intravenous antibiotics despite demonstrable improvements in clinical outcome for the patients may suggest that these organisms have little role in acute exacerbations of CF; however, this would be a premature conclusion. Multiple anaerobic species are often isolated in CF respiratory samples, and the conditions used for culture can have a significant

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bearing on the result. In one study, several different media were required to recover all *Prevotella* species isolates in CF respiratory samples,⁸ highlighting some of the challenges faced in determining changes in the quantities and composition of anaerobes in CF sputum. The mechanisms of action of antibiotics in chronic CF infections are complex and not always fully understood. It is recognised that numbers of aerobes and facultative anaerobes do not always decline despite some patients clinically responding to treatment.

It is possible that if obligate anaerobes are pathogenic in CF, then pathogenicity may apply to specific species rather than to all anaerobic bacteria. There are preliminary in vitro data that may support a potential pathogenic role for some anaerobic organisms in CF. *Prevotella* species are commonly detected in CF respiratory secretions^{5,8} and are able to produce β -lactamases and an autoinducer molecule.⁸ The majority of patients with CF, as opposed to healthy controls, have antibodies against antigens of *Prevotella intermedia*,⁹ providing evidence of a host response to the organism. Furthermore, culture supernatant from *P intermedia* has been shown to be inflammatory and cytotoxic to airway cells when cell numbers were $>10^9$ the concentration of organisms.⁹

Even if the anaerobic bacteria themselves are not directly pathogenic, could they influence the behaviour of other species, by either stimulating or inhibiting pathogenic activity? Bacterial activity, including the production of virulence factors, can be influenced by interactions both within and between species through quorum-sensing concentration-dependent signalling molecules and concentration-independent signalling systems. One study showed that anaerobes of the oropharyngeal flora could enhance the pathogenicity of *Paeruginosa* in an agar bead model of chronic lung infection in rats¹⁴ and modulate *P aeruginosa* gene expression, including those coding for pathogenicity factors.

The question as to whether obligate anaerobic bacteria play an integral part in the pathophysiological process that drives the progressive lung damage that afflicts patients with CF, or are merely simple bystanders, is still at present unanswered. Undertaking studies to selectively target anaerobes with particular antibiotics will be challenging, as in vitro susceptibility

testing of both Gram-positive and Gram-negative anaerobes demonstrates that isolates from patients with CF are often resistant to many antibiotics that are usually recognised as having activity against anaerobic species, including ampicillin, metronidazole, clindamycin and, to a lesser degree, Tazobactam/piperacillin.^{5,6} Meropenem is the only antibiotic with consistent in vitro activity against CF anaerobic bacterial isolates, but it also has activity against the dominant aerobic CF bacterial species.

Are the episodes of exacerbation and progressive lung damage in CF the responsibility of individual organisms or sets of species, or the entire polymicrobial community, including bacterial and possibly fungal and viral species? If the progression of disease is orchestrated by the microbial community, are there major and minor players, and how do changes in composition of species throughout the lifetime of a patient influence their response to treatment? Intriguingly the diversity of organisms initially increases but then progressively decreases in severe CF lung disease.¹⁵ Further advances in molecular profiling technology are likely to allow greater insights into the composition and dynamics of all members of the microbial community within CF lungs. The future application of such techniques, coupled with careful evaluation of the clinical status of patients and outcomes of treatment, may allow a greater understanding of the microbiological determinants, including the roles of anaerobic bacterial species, that influence the pathogenesis of CF lung disease, and in turn provide an insight into why antibiotic regimens succeed or fail. At present, we are not at the stage when we should consider changing therapeutic regimens to ensure activity against anaerobes in addition to the main aerobic pathogens, but should continue to rely on the current treatment strategies that have delivered steady improvements in clinical outcomes and life expectancy for this group of patients.¹⁶

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