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Microbiology of CF

Difficult bacteria, antibiotic resistance and transmissibility in cystic fibrosis

J S Elborn

Three papers published in this issue of *Thorax* add some further twists to our understanding of the microbiology of CF

The link between dysfunction of the CFTR protein and the pathophysiology of lung disease in cystic fibrosis (CF) has recently become clearer. Abnormal sodium and chloride ion transport in respiratory epithelial cells results in depletion of airways surface liquid volume, delayed mucus transport, and impaired bacterial clearance.[1 2] This initiates airways inflammatory responses leading, ultimately, to lung injury in CF. The most important predictors of poor outcome are chronic infection with *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex and reduced forced expiratory volume in 1 second (FEV_1).[3–5]

Pseudomonas aeruginosa

Pulmonary infection in CF is characterised by a narrow spectrum of microorganisms and is dominated in older patients by *P aeruginosa*. This organism and other related Gram-negative bacteria adapt to the conditions found in airways mucus and establish biofilms which allow chronic infection to be established.[6] Recent studies suggest that this microenvironment is relatively hypoxic and this creates a hospitable environment for *P aeruginosa* which, when exposed to low oxygen concentrations, increases alginate formation which assists in the development of micro-colonies within a biofilm.[7] The biofilm protects *P aeruginosa* from host defence, bacterial clearance mechanisms, and antibiotics. In addition, bacterial adherence to mucus is increased in CF which may also contribute to difficulties in clearing it from the airways.[7]

The source of early *P aeruginosa* infection is either the environment or other patients with CF. Aggressive treatment of early infection with this organism can frequently eliminate it for some years but, by the end of the second decade, over 80% of patients with CF have chronic *Pseudomonas aeruginosa* infection.[8 9]

Recent studies have shown that, in some CF centres, clonal spread of *P aeruginosa* can occur.[10 11] This is sometimes associated with a multiply resistant antibiotic profile, although not necessarily so. In general, antibiotic resistance is increasing in the CF population, particularly against the most commonly used antibiotic, ceftazidime. This probably represents antibiotic pressure and the ability of *P aeruginosa* to mutate because of its rather large genome. Antibiotics may select hypermutable strains which can maintain and possibly pass on resistance.[12] A close link between transmissibility, antibiotic resistance, and patient survival has not been unequivocally demonstrated. Transmissibility of resistant strains of *Pseudomonas* is intuitively something that should be avoided. However, further studies are awaited to determine if this has an important clinical outcome for patients with CF.

In addition to *P aeruginosa*, a number of other Gram-negative bacteria have emerged as important potential pathogens in CF lung disease. *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, and *Achromobacter (Alkaligines) xyloxidans* are the most important and, although probably environmental in origin, cause chronic airways infection in patients with CF. These organisms, although phylogenetically unrelated, are usually all multiply resistant to antibiotics.

Burkholderia species

Burkholderia cepacia complex was the first of these organisms to be recognised and is the most pathogenic. A number of epidemics in CF centres have been described. Infection with this group of organisms is associated with an acceleration in the decline in FEV_1 and increased morbidity and reduced survival.[4 13–15] The taxonomy of this genus has recently been fully elucidated and nine groups have been speciated.[16] All these species of *Burkholderia* have been described in patients with CF but the predominant are *B multivorans* and *B cenocepacia*. *B multivorans* is a less common cause of infection than *B cenocepacia*.[17] A number of studies have suggested that *B multivorans* is generally less virulent that *B cenocepacia*. However, *B multivorans* has been associated with ''*cepacia* syndrome'' and epidemic spread.

In a study reported in this issue of *Thorax* from a single centre, patients with *B multivorans* and *B cenocepacia* and *P aeruginosa* were compared.[18] Patients with *B multivorans* had a lower mortality than those infected with *B cenocepacia*. *B multivorans* had a similar clinical impact to chronic infection with *P aeruginosa*. This finding supports studies from other centres. No significant differences in morbidity were found, although others have shown an accelerated decline in FEV_1.[4 19] This study also confirms previous studies which reported mostly unique strains in patients with *B multivorans* infection, suggesting that this organism is usually acquired from the environment rather than by patient to patient transmission. Patients with *B multivorans* should therefore not be exposed to those with *B cenocepacia*, which is strongly associated with patient to patient transmission and is more virulent. This study emphasises the much greater virulence of *B cenocepacia* than *P aeruginosa* and supports the need for careful infection control measures to minimise the risk of cross infection.

In another paper published in this issue of *Thorax*, Coenye and colleagues describe a clonal strain of *B cenocepacia* not previously identified in Europe.[20] Over the past few years it has become clear that *B cenocepacia* is made up of clonal subspecies and there may be differences in virulence and transmissibility between clones. The most common subspecies in the UK is the ET12 group (Electrophoresis Type 12), first described in Edinburgh and associated with most of the severe epidemics in the

UK and Canada. This strain is very virulent and is associated with ''*cepacia* syndrome''. A new strain, PHDC, has now been described and has affected patients in a number of centres around Europe. No clinical data are yet available with regard to its virulence in patients from whom this organism has been isolated, but it is of considerable concern that there is evidence of clonal spread between continents. The majority of samples were from patients with CF but one was from a urine sample from 1964. This is an unusual finding which is unexplained. Further studies will be required to determine the clinical relevance of this and possibly other clonal strains of *B cepacia* complex organisms. It is possible that a number of other clonal variants of *B cenocepacia* and other species are present in CF clinics and that there may be differences in the clinical impact of these clones.

This new finding emphasises the need for careful microbiological surveillance of patients with CF. Phenotypic identification of *B cepacia* is difficult. It is almost always pan-resistant to commonly used antipseudomonal antibiotics and this cannot be used for typing purposes. There are now specific phenotypic tests for identifying *B cepacia* complex species, but these are not helpful in identifying clonal subgroups such as ET12 or PHDC which require diagnosis at a molecular level using various DNA typing methods. It is very important that all CF centres should have access to such surveillance. This is available from two laboratories in the UK and reference laboratories in the US and in Europe.

Stenotrophomonas maltophilia

In a third paper published in this issue of *Thorax*, Goss *et al* provide further data on the virulence of *Stenotrophomonas maltophilia*.[21] This organism is multiply resistant but, in contrast to *B cepacia* complex, it appears to have a comparatively benign effect on the CF lung. This is the second study of *S maltophilia* published by this group from the North American database and reports morbidity on a large cohort of people infected with the organism. The previous study showed that *S maltophilia* infection is not associated with an increase in short term mortality.[22] Their data do not tell us whether this organism is transmissible, although this seems in general to be unlikely. However, one centre is reported to have a case rate of 38% which raises the possibility of cross infection in some situations. Their data suggest that the organism, although multiply resistant to antibiotics, is not associated with an acceleration in the decline in FEV_1. Those with *S maltophilia* infection had a lower starting FEV_1 before infection, suggesting that poorer lung function predisposes to acquisition of this organism. The majority (66%) were co-infected with *P aeruginosa*, but it is not clear if this was of any clinical significance.

Significance of these findings

The microbiology of CF can be very confusing. The nomenclature is complex and organisms change their names, and there are few generalisations that can be made across the different species. The studies published in this issue of *Thorax* add some further twists. A hierarchy of virulence of Gram-negative organisms is emerging. *S maltophilia* seems to be the most benign followed by *P aeruginosa*. *B multivorans* is similar to *P aeruginosa* but *B cenocepacia* is the most virulent by a significant degree. There may be important differences in the virulence of subspecies of *B cenocepacia* but this requires further epidemiological study. It is not yet clear how other organisms which cause chronic infection in CF such as *A xyloxidans* or *Pandorea* species fit into this hierarchy.

These organisms are generally multiply antibiotic resistant, but this by itself does not imply transmissibility or virulence. There must be other virulence factors associated with specific organisms or possibly host-bacteria interactions which ultimately result in lung injury. These studies further emphasise the importance of surveillance of patients with CF to determine their airway microbiology. Careful infection control policies are required to prevent acquisition of the more problematic organisms such as *B cenocepacia*. These should be tailored to the epidemiology of the individual centre and based on accurate identification and typing of the bacteria. There is a need for further understanding of how infection and inflammation result in airway damage, hopefully to find ways of circumventing the lung damage which ultimately leads to early death in individuals with CF.

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