Infections in chronic lung diseases 2

Antimicrobial resistance in the respiratory microbiota of people with cystic fibrosis

Laura J Sherrard, Michael M Tunney, J Stuart Elborn

Cystic fibrosis is characterised by chronic polymicrobial infection and inflammation in the airways of patients. Antibiotic treatment regimens, targeting recognised pathogens, have substantially contributed to increased life expectancy of patients with this disease. Although the emergence of antimicrobial resistance and selection of highly antibiotic-resistant bacterial strains is of major concern, the clinical relevance in cystic fibrosis is yet to be defined. Resistance has been identified in recognised cystic fibrosis pathogens and in other bacteria (eg, *Prevotella* and *Streptococcus* spp) detected in the airway microbiota, but their role in the pathophysiology of infection and inflammation in chronic lung disease is unclear. Increased antibiotic resistance in cystic fibrosis might be attributed to a range of complex factors including horizontal gene transfer, hypoxia, and biofilm formation. Strategies to manage antimicrobial resistance consist of new antibiotics or localised delivery of antimicrobial agents, iron sequestration, inhibition of quorum-sensing, and resistome analysis. Determination of the contributions of every bacterial species to lung health or disease in cystic fibrosis might also have an important role in the management of antibiotic resistance.

Lancet 2014; 384: 703–13

This is the second in a Series of two papers about infections in chronic lung diseases

CF and Airways Microbiology Group (L J Sherrard PhD, Prof M M Tunney PhD, Prof J S Elborn MD), **School of Pharmacy** (L J Sherrard, Prof M M Tunney), **and Centre for Infection and Immunity, School of Medicine, Dentistry and Biomedical Sciences** (Prof J S Elborn), **Queen's University Belfast, Belfast, UK**

Correspondence to:
Prof J Stuart Elborn, Centre for Infection and Immunity, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast BT9 7BL, UK.
s.elborn@qub.ac.uk

Introduction

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. This gene encodes an ion channel located on the apical membrane of epithelial cells and is expressed in many cells throughout the body. In the lungs, this ion channel helps to control the volume of airway surface liquid, which affects mucociliary clearance. A defective CFTR in the cystic fibrosis airway surface results in thickened mucus secretions, which cannot be easily cleared. Trapped bacteria colonise the mucus and enables the development and persistence of pulmonary bacterial infection. Various mechanisms link defective *CFTR* gene to the poor clearance of bacteria deposited on the mucus surface, including a reduced volume of airway surface liquid and lower airway surface liquid pH in patients than controls.[1,2]

A small number of bacteria, *Staphylococcus aureus* (including meticillin-resistant *S aureus* [MRSA]), *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Burkholderia cepacia* complex, are recognised as cystic fibrosis respiratory pathogens (figure 1). Additional important opportunistic pathogens, which infect the cystic fibrosis airways, have been described including *Achromobacter xylosoxidans*, *Stenotrophomonas maltophilia*, and non-tuberculous *mycobacterium* (NTM). Isolation of these bacteria has been done on the basis of agar based culture methods in mostly aerobic conditions at 35–37°C.[4] These pathogens have also been associated with pulmonary infection in other respiratory diseases (eg, non-cystic fibrosis bronchiectasis and chronic obstructive pulmonary disease).[5,6] Transient bacterial colonisation of the airways by cystic fibrosis pathogens might be followed by chronic infection, which is related to a progressive decrease in lung function.[7] Patients with cystic fibrosis have intermittent episodes of pulmonary exacerbations, which are associated with an excessive immune response, irreversible tissue damage, and an accelerated decrease in lung function.[8]

Respiratory disease due to chronic bacterial infection is the cause of early morbidity and mortality in a large percentage (85%) of patients with cystic fibrosis.[9] Therefore, the presence of recognised pathogens in cystic fibrosis respiratory secretions is examined by clinical laboratories and targeted by subsequent antibiotic treatment. Antibiotic treatment is initiated at a very young age to manage

Search strategy and selection criteria

We searched PubMed, Medline, and Scopus for literature published in English between Jan 1, 2004, and June 30, 2014. In PubMed and Medline we used the MeSH search terms "cystic fibrosis", "bacterial infections", "drug resistance", "microbial" (two different MeSH terms combined for each search), and the free text terms "diversity", "microbiota", "resistance", "molecular detection", and all of the major cystic fibrosis pathogens stated in this Series paper sequentially in combination with "cystic fibrosis". In Scopus, we searched titles, abstracts, and keywords of articles using the combined terms "cystic fibrosis" with "bacterial infections" and "cystic fibrosis" with "resistance". We manually screened lists of articles by reading the abstracts. Studies were excluded that were not original data, such as reviews, or those that were not related to our topic. Additional relevant articles published within the literature search period and before 2004 were identified through searches of the author's personal archives. We searched UK, US, and European consensus reports to provide details of recommended antibiotic regimens used clinically. We also searched the website http://www.ClinicalTrials.gov with the search term "cystic fibrosis" and intervention "antibiotics" to identify ongoing clinical trials that were related to our paper.

Key messages

- Complex culture and molecular methods have shown that cystic fibrosis pulmonary infection is polymicrobial, and that the types and abundance of bacteria present in cystic fibrosis respiratory samples differ between individuals and over time
- Emergence of antimicrobial resistance and selection of highly antibiotic-resistant recognised cystic fibrosis pathogens is expected as patients are living longer and ultimately exposed to an increasing number and combination of antibiotics
- Antibiotic resistance has been reported in bacteria belonging to the cystic fibrosis airway microbiota, whose clinical significance is unknown
- The opportunity for horizontal gene transfer between bacteria might be enhanced as the cystic fibrosis pulmonary bacterial community is highly diverse
- Antimicrobial resistance is also affected by an acidic pH and hypoxia in the cystic fibrosis airways, by biofilm formation, and exposure of bacteria to subinhibitory antibiotic concentrations
- Potential future strategies to manage antimicrobial resistance might include the use of antibiotic adjuvants, resistome analysis, and identification of the role of anaerobic bacteria in cystic fibrosis airways infection and resistance

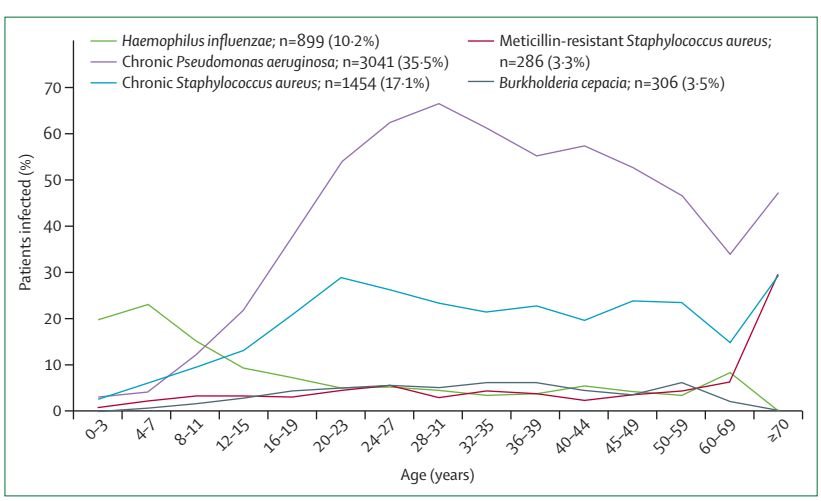

***Figure 1*: Prevalence of recognised pathogens in paediatric and adult patients with cystic fibrosis living in the UK**
Chronic *Staphylococcus aureus* and *Pseudomonas aeruginosa* infection data excludes patients intermittently infected with these pathogens. Reproduced from and with permission of the UK Cystic Fibrosis Trust.[3]

pulmonary infection and slow progression of lung deterioration. Various antimicrobial agents and complex regimens are used for prophylaxis, eradication, treatment of exacerbations, and chronic suppressive therapy.[7,10–13] This Series paper focuses on the emergence of antimicrobial resistance and selection of highly antibiotic-resistant bacterial strains in cystic fibrosis respiratory microbiota, which results from such therapy. We consider why resistance develops and the issues that arise when the present definition of resistance is applied to chronic infection, in which bacteria grow as a biofilm. Although the clinical relevance of antibiotic resistance in cystic fibrosis airways infection remains to be clarified, this Series paper discusses some of the present and future strategies to minimise or overcome antimicrobial resistance.

Cystic fibrosis microbiota

Research during the past 10 years has used complex culture and molecular methods to investigate the types and abundance of bacteria present in cystic fibrosis respiratory samples.[14–26] These studies show that diverse polymicrobial communities exist within the airways of patients with cystic fibrosis with aerobic, facultative, and obligate anaerobes. As a result, the term cystic fibrosis microbiota now describes the intricate array of bacteria detected in pulmonary secretions. The potential role of every individual bacterial species in pulmonary infection, inflammation, and disease progression is uncertain. However, several studies have shown that the combination of species colonising the lungs in cystic fibrosis differs between individuals,[14,20,22,27] with a loss of bacterial diversity associated with increasing age, reduced lung function, and disease progression.[18,19,28] Blainey and colleagues[29] provided additional evidence to support the theory that pulmonary health is correlated with high pulmonary microbial diversity; they recorded greater bacterial diversity in sputum samples from healthy patients than in patients with cystic fibrosis.

Antibiotic regimens used to treat cystic fibrosis lung infections

The median predicted age of survival for patients with cystic fibrosis in the UK is now older than 40 years, whereas 50 years ago, death occurred in the first few years of life.[30] One of the most important interventions that has contributed to increased life expectancy is antibiotic treatment directed against recognised pathogens of cystic fibrosis infecting the airways. Full details of antibiotic regimens used to treat cystic fibrosis lung infections are provided in consensus guidelines developed by the UK, USA, and Europe.[7,10–13]

Although no clinical benefit has been definitively shown with *S aureus* prophylaxis, in the UK, continuous antistaphylococcal treatment (table 1) can be initiated in young children at diagnosis of cystic fibrosis until aged 3 years to reduce the infection incidence with this pathogen.[13] By contrast, this prophylactic treatment is not advocated in the USA because of a scarcity of evidence of its effects and potential to increase the incidence and prevalence of *P aeruginosa* infection.[12]

Infection with cystic fibrosis pathogens is correlated with poor patient outcomes. Eradication of *P aeruginosa* is recommended by all guidelines and is the standard of care for first and subsequent infections.[7,10,12,13] Zemanick and colleagues[31] reported an association between