

Aspergillus exposure — a growing problem for cystic fibrosis patients

A recent meeting heard about some of the problems facing patients with cystic fibrosis. Nicola Purcell reports

Aspergillus is a ubiquitous fungus that is becoming a major pathogen in patients with cystic fibrosis, Keith Brownlee, consultant paediatrician at the Leeds regional cystic fibrosis unit, told the meeting. It produces spores between 2µm and 5µm in diameter that, when inhaled, can penetrate the bronchial tree. The average person inhales 200 to 300 spores daily. In patients with medical conditions affecting the lungs this can lead to progressive lung damage.

Allergic bronchopulmonary aspergillosis (ABPA), a complex lung disease, is often seen in these patients, with the incidence in cystic fibrosis patients been reported as being between 0.9 and 15 per cent. Exposure to aspergillus spores leads to an immune response within the lungs, leading to worsening inflammation and mucus plugging, resulting in progressive lung damage. The mainstay of treatment is with oral corticosteroids. However, since long courses of treatment are usually required, patients may experience adverse effects such as diabetes, osteoporosis, growth failure and cataracts.

Some CF centres treat with oral antifungal agents in addition to the steroids. Itraconazole at a dose of 5mg/kg per day is considered the antifungal of choice. Itraconazole capsules are poorly absorbed in CF patients so the liquid preparation is preferred. However its unpleasant taste has led to adherence problems so voriconazole is now being used more often. It is better absorbed but is expensive, costing around £1,000 to £2,000 per month. It is also associated with numerous adverse effects, including visual disturbances and photosensitivity. Dr Brownlee emphasised that pharmacists should monitor patients for adverse effects while on treatment for ABPA.

Adherence and attitude to medication

Amanda Plummer, pharmacy clinical services manager at Sheffield Adult Cystic Fibrosis Centre, discussed a research project she had carried out, looking at adherence and attitudes to medication in adult CF patients at her unit. She found that many patients expressed negative childhood memories regarding medicine-taking, with many using non-adherence as a form of control. Most patients understood the necessity of their medication but there was some concern regarding over-usage, especially with antibiotics, and side effects.

The median number of medicines taken was nine (range: three to 17). Adherence varied with treatments with once-daily tablets having the highest adherence and nebulisers having the lowest. Adherence was found to be low with treatments taken during the day, in public and before food.

She recommended that education and patient involvement play a role in improving adherence. Treatment regimens should be individualised and medication reviews should be carried out addressing patients' views about their treatment.

Renal issues

Christine Etherington, a senior doctor at the Leeds Adult Cystic Fibrosis Unit, talked about the renal issues associated with CF. Nephrotoxic drugs are the commonest cause of renal injury in patients with cystic fibrosis. Aminoglycosides are the main class of drugs associated with renal complications, due to their wide usage to treat pulmonary exacerbation's caused by *Pseudomonas aeruginosa*. The nephrotoxicity manifests clinically as non-oliguric renal failure with a slow rise in serum creatinine. Risk factors include high dose, prolonged therapy, cumulative exposure, dehydration, concurrent nephrotoxic medication (eg, non-steroidal anti-inflammatory drugs) and pre-existing renal disease. She said that pharmacists were important in the therapeutic drug monitoring of aminoglycosides and the prevention of concurrent prescribing of other nephrotoxic agents.

Routine methods are not sensitive enough to detect aminoglycoside renal damage because toxicity is not detected until there is a large reduction in nephron mass. Dr Etherington discussed the use of N-acetyl-b-D-glucosaminidase (NAG), a lysosomal enzyme, as a marker of acute renal tubular injury. In a study that she carried out (*Journal of Cystic Fibrosis* 2007;6:67-73), looking at urinary NAG before, during and after treatment with intravenous antibiotics, she found that there was a three- to five-fold increase in median urinary NAG from day 1 to day 14 of treatment.

In patients who received treatment with tobramycin there was an eight-fold increase in urinary NAG levels compared to that with colistin which showed a two-fold increase. The NAG levels returned to baseline after treatment was stopped in the tobramycin patients but stayed elevated from baseline in the colistin group. She also found a significant correlation between baseline NAG and previous antibiotic exposure.

Atypical mycobacteria

Miles Denton, consultant microbiologist at Leeds Teaching Hospitals, talked about the treatment options for atypical mycobacteria. There has been an increased emergence of CF patients being colonised with atypical bacteria, such as *Mycobacterium abscessus*, *M avium* and *M chelonae*. The increased emergence may be due to better laboratory methods for culturing, growing and identifying the bacteria, an increased awareness of the bacteria or the successful eradication of *Ps aeruginosa*, he said.

Atypical mycobacteria are difficult to treat because of their inherent resistance properties. There is a lack of randomised controlled trials with regards to treatment of these infections. Treatment is often guided by *in vitro* data, anecdotal reports and expert opinion. He emphasised the importance of using three or four drug combinations that have been shown to have better clinical outcomes than two-drug regimens, and that one cannot assume that drugs in the same therapeutic class are equally active.

Lung function often declines once patients are colonised with these pathogens. The decision to treat is based on clinical symptoms and microbiological, radiological and immunological findings. In the future there may be potential for serological tests to aid clinical decision making.

Susceptibility varies widely between the strains of bacteria. Dr Denton stated that macrolides were the most active agents against *M avium*. He recommended the combination of daily oral clarithromycin or azithromycin plus rifampicin and ethambutol for the first-line treatment of *M avium* infection. Intravenous or nebulised amikacin and oral clofazimine can be added as second-line agents. Daily treatment can be reduced to three times weekly once the patient is clinically stable. Treatment must be continued until cultures remain negative for one year, he emphasised.

For rapid growing mycobacteria such as *M abscessus* and *M chelonae*, Dr Denton recommended the use of intravenous amikacin, imipenem and oral clarithromycin for two to four weeks, until there is a clinical response. For maintenance treatment he suggested nebulised amikacin plus oral clarithromycin. Currently there is no evidence or guidance on how long to continue treatment.

Concluding his presentation, Dr Denton stressed the need to update treatment guidelines urgently, particularly with respect to cystic fibrosis.

This meeting of the Cystic Fibrosis Pharmacist Group took place in Leeds on 10 May