

Drug resistance fears over killer fungal disease

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(PhysOrg.com) -- Treatments for the most common airborne fungal disease are proving less effective due to increased resistance to the anti-fungal drugs used to combat infections.

Aspergillosis is an incurable disease of the lungs caused by fungal *Aspergillus*. It is treated using compounds called azoles but researchers at The University of Manchester have found that the fungus has been able to mutate making treatment ineffective.

The research, published in the prestigious US journal *Emerging Infectious Diseases*, showed that 13 out of 14 affected [patients](#) recently treated by the team did not respond to therapy and that numerous mutations were responsible.

Lead researcher Professor David Denning, whose clinic is based at the University Hospital of South Manchester, said that most of the fungus strains, or isolates, were completely resistant to all oral antifungals, leading the doctors to resort to long-term intravenous therapy.

"While the very first azole-resistant isolates were identified in the late 1980s in California, the first UK resistant *Aspergillus* wasn't found until 1999 and now we have dozens," said Professor Denning, who is Director of the National Aspergillosis Centre.

"Antifungal resistance rates have been rising since 2004 and stood at 17% in 2007, a trend that has continued into 2008 and 2009. Patients

from all over the UK were found to have resistance, mostly related to long-term treatment of incurable Aspergillus disease."

In 2008, workers in Nijmegen in the Netherlands reported a similar rise in resistance, related to a single resistance mutation, also found in Aspergillus grown from soil. They suggest that extensive azole use in agriculture may be responsible. About one third of all fungicide use in farming is azoles.

Currently, the only class of antifungal that can be used orally for Aspergillus infection and allergy are the azoles, principally itraconazole, voriconazole and posaconazole.

"We also found cross-resistance to voriconazole (65%) and posaconazole (74%) in those isolates we tested that were resistant to itraconazole," said Professor Denning. "The result depends on the particular mutation conferring resistance.

"Patients can be treated with intravenous amphotericin B or caspofungin, but these are not useful when patients leave hospital, or have allergic aspergillosis."

Aspergillosis can take a number of different forms: Chronic pulmonary aspergillosis is a slowly progressive destructive disease of the lung, leading to loss of respiratory function, and general ill health (weight loss, coughing, bringing up blood, shortness of breath). It is almost always caused by Aspergillus fumigatus. Underlying diseases include tuberculosis, atypical tuberculosis, chronic obstructive pulmonary disease (COPD, emphysema), pneumothorax, sarcoidosis, allergic bronchopulmonary aspergillosis, lung cancer treatment. Without adequate treatment about 50% of patients die in 5 years, often by coughing up large quantities of blood. There are estimated to be 500-750 patients nationally with this condition.

Invasive aspergillosis is a life-threatening condition usually of the lungs (85%) in immunosuppressed patients following chemotherapy for leukaemia or cancer, transplantation, AIDS, corticosteroid therapy, and intensive care. Early on, it is clinically silent; later patients develop fever, cough and shortness of breath. It is usually rapidly progressive with ~50% of patients dying in 2 weeks, unless treated. Diagnosis is difficult and requires multiple tests for confidence in the diagnosis. If successfully treated, the patient makes a full recovery in more than 90% of cases. There are estimated to be about 4,000 patients nationally with this condition per year.

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic [fungal disease](#) affecting asthmatics and cystic fibrosis patients. Patients cough up thick plugs of mucus, and are short of breath and tired. Over years, the airways become thickened and wider (bronchiectasis) and multiple bacterial infections are common. It may evolve into CPA. Antifungal treatment has a major impact on quality of life in most patients, particularly in improved breathing and energy levels. Some of these patients also have serious nasal disease. ABPA affects about 1% of adult asthmatics (about 40,000 people) and about 15-25% of adult cystic fibrosis patients (about 300-500 people).

Severe asthmatics may be sensitised (allergic) to multiple fungi, and this disease is called Severe Asthma with Fungal Sensitisation (SAFS). *Aspergillus* is the commonest fungus to which they are sensitized. Those affected have multiple exacerbations of asthma requiring steroids and antibiotics many times a year, being admitted to hospital and generally suffering a poor quality of life. Antifungal therapy helps most of these patients. In the UK there are estimated to be 190,000 to 300,000 affected.

Chronic rhinosinusitis is often caused by fungi, of which [Aspergillus](#) is the most common in the UK (fungal rhinosinusitis). Those affected have

blocked noses, loss of smell, continuous discharge from their nose, recurrent sinus infections and usually nasal polyps. It is a long term condition requiring endoscopic or open surgery, and usually relapses after surgery. Local steroid sprays and treatment of bacterial sinusitis is the main treatment, as antifungal therapy is not always effective (and not convincingly demonstrated to be useful). Chronic rhinosinusitis affects 18% of the UK young adult population (and fungi play a role in 7%), so fungal rhinosinusitis is estimated to affect about 400,000 people in the UK.

Provided by University of Manchester ([news](#) : [web](#))

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