

Antibiotic Resistance and Fungus

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Today, I'm talking with Dr. David Denning. He's the director of UK's National Aspergillosis Centre in Manchester, UK. Dr. Denning is a physician trained in infectious diseases. We'll be talking about antibiotic resistance and fungal infections. Welcome, Dr. Denning.

[Dr. Denning] Hello. Thank you for offering me the opportunity to speak to you.

[Sarah Gregory] Dr. Denning, would you care to tell us a bit about yourself and what your job entails?

[Dr. Denning] Certainly. I'm an infectious disease physician and I've been looking after patients for over thirty years with many different sorts of infections, including fungal diseases, which is my area of interest and specialty. I manage the UK's National Aspergillosis Centre and we receive about five hundred new patient referrals per year. I'm also a professor at the University of Manchester and do quite a lot of research on different aspects of fungal disease, particularly aspergillosis, including resistance and new diagnostic tests, and I'm also the leader and president of the Global Action Fund for Fungal Infections, which has as its main objective to improve the quality of care and therefore the outcome of patients with fungal diseases across the world.

[Sarah Gregory] So, that's how you ended up writing this article? Was it part of that function, or the being president of that drove your interest in this?

[Dr. Denning] Yes. We're very much committed to improving diagnosis of fungal disease because most patients don't come with a very distinctive clinical picture or syndrome and the tests are very important to pick up a fungal infection, so we register that patients have been treated with antibacterial drugs when actually they've got a fungal disease and that's unhelpful, clearly, because antibacterial drugs, for the most part, have no action against fungal infection.

[Sarah Gregory] Antimicrobial resistance has become, as we all know, a huge problem in recent years. What do you think are some of the causes for this?

[Dr. Denning] Antibacterial resistance is caused by many different things, but one of them, for example, is using antibacterials in food for animals to improve the growth of animals, which is clearly unhelpful if they're antimicrobials that lead to resistance of human pathogens. There's also a lot of pharmaceutical intermediates discharged into waste water and sewage, and the very low concentration of not very active intermediates can lead to resistance occurring in the environment, and also because of inaccurate diagnosis or no diagnosis, for many infections, physicians are not always very precise about giving antibiotics precisely for particular infections and not over treating either the breadth of coverage for an antibiotic or the length of therapy that they give. And on the antifungal side, there's quite a lot of pressure in intensive care units and other sort of high dependency settings in hospitals so that we get more resistant pathogens occurring, and that's a particular problem with *Candida* infections. And also on the antifungal side in the environment, we spray a lot of azole fungicides on crops around the world, and in the Netherlands and other countries this is leading to resistance to *Aspergillus fumigatus*, and that's a

big problem because the azoles are the only class of drugs that we've got that we can give orally to patients with aspergillosis.

[Sarah Gregory] What are some of the fungal complications that are often misdiagnosed?

[Dr. Denning] So, we do see *Candida* infections in intensive care relatively frequently. These patients often very ill; they've often had a bacterial infection already. Some patients have had major surgery on their abdomens and have leaky guts, others had transplants, and others have had multiple complications, such as renal failure, and those patients get counter infections and they're often missed because the blood cultures that we do are only forty percent sensitive, so a large proportion are not diagnosed at all.

We also miss aspergillosis in intensive care and other critical care settings, and also in patients with emphysema or COPD. This is a common problem and a common reason for patients to come into hospital not being able to breathe, and most of the time that's due to a virus or bacterial exacerbation as it's called, but sometimes it's due to *Aspergillus*. And, for example, in Spain and in China the rate of an *Aspergillus* infection which is potentially fatal occurs in between one and four percent of patients with COPD coming to hospitals. We also miss patients with *Pneumocystis* pneumonia in the context of HIV infection, and that's probably quite a big problem in Africa. It's also a problem in high income, well-developed countries like the U.S. because, although some patients have very distinctive features which you can be confident is *Pneumocystis*, many do not and they appear to have an ordinary bacterial pneumonia or some other infection. And we also probably miss fungal asthma a lot in patients treated with steroid antibiotics, when actually they should be treated for fungal asthma with an antifungal drug.

[Sarah Gregory] So fungal asthma is basically asthma that's caused by fungus rather than all the other things that doctors might think are the cause of it. Is that right?

[Dr. Denning] Yes. It's a bigger problem in adults than in children, although it's described in children. And some people are very allergic to fungus, particularly *Aspergillus* which lives in the airways, but also sometimes skin fungi and other brown and black fungi which occur around thunderstorms, and that allergy to the fungus drives the asthma so that the asthma is much worse than it might otherwise be. And the terminology and precise descriptions of different categories are not perfect at the moment, but either patients have fungus living in their lungs which drives asthma and they have exacerbations needing steroids and antibiotics fairly often, whereas actually, if you can eradicate the fungus from the lungs, the exacerbation rate goes way down and the patient's breathing improves and they need much less medication than they needed before.

[Sarah Gregory] Is a course of antifungal medication, how long would that be? Is it an intensive thing that would go on for—like treating TB—for years, or is it something fairly simple?

[Dr. Denning] The typical course of therapy for fungal asthma is a four to eight month course of either itraconazole or one of the newer azoles, such as voriconazole or posaconazole. And most patients who respond to therapy take at least a month before they start to improve and they reach their peak of improvement at typically about four months, although sometimes it takes a little longer. If patients are much, much better, then my practice is often to keep going for much longer periods. If they're only a little bit better, and all they've got significant side effects, then

we tend to stop therapy and they often go into remission and are much better, stay much better for quite long periods of time having stopped therapy, although some patients relapse and become ill again within three or four months of stopping treatment.

[Sarah Gregory] Well, along those same lines, can you give us some details about fungal infections in people with TB?

[Dr. Denning] Patients who have had TB in the lungs are often left with a cavity and when we breath in *Aspergillus* from the air, which we all do every day, in those patients the *Aspergillus* gets into that cavity and can cause a slow, progressive indolent sort of illness with increased coughing, maybe coughing a little blood, restlessness, tiredness, and weight loss. And because the x-ray or the scan looks similar to the TB scan, many times patients are re-treated for TB, when in fact they've got a chronic pulmonary aspergillosis, or an aspergilloma as it's called, if they have a fungal spore. And that's probably a very common problem in countries with a lot of TB, and around the world we think there may be about 1.2 million such patients in different localities, particularly Southeast Asia and Indonesia where TB is so common.

[Sarah Gregory] Are there accurate and accessible tests doctors could and can be using to diagnose pulmonary fungal infections?

[Dr. Denning] The tests for pulmonary fungal infections are straightforward in most cases. So for example, fungal asthma can be diagnosed with a combination of the clinical features of asthma and either skin testing showing an allergy to a fungus, particularly *Aspergillus* or *Alternaria* or *Cladosporium*, or a blood test which is an IgE test showing allergy to those fungi. Chronic pulmonary aspergillosis after TB is pretty easy to diagnose with an *Aspergillus* IgG test, that's an infection antibody test, and that test has been around for many, many years and is quite good, actually, for picking up that infection with about a 95 percent sensitivity and at least 90 percent specificity.

Pneumocystis pneumonias can be difficult, although there's an excellent test with a glucan test in blood which is now available in the U.S, across Europe, and many parts of Asia and China and Japan, for example, but not available in Africa. And if you have not got a glucan test, then a respiratory sample or a molecular test, such as PCR, or looking down the microscope with the microscopy is how the diagnosis can be made, but it does require a really high quality sample to do that.

For a *Pneumocystis* microscopy or glucan test you need a respiratory sample, so it's either sputum or phlegm that patients have coughed up, or an induced sputum, or they need to have a bronchoscopy and wash the lungs out and look on what has been washed out. And *Candida* tests are not perfect, as I mentioned; blood culture is about forty percent sensitive. The glucan test is also good for *Candida*, although it doesn't distinguish *Candida* from *Pneumocystis aspergillosis*, but it's about 80 percent sensitive. And there's a new molecular test made by a small company called T2 that's also pretty good for picking up *Candida* in blood and distinguishing different species, as well. So for the most part, these tests are available but they're not always used in the best or most appropriate fashion by all doctors.

[Sarah Gregory] And why is this? Why aren't they—doctors—testing for fungal infections more often?

[Dr. Denning] I think knowledge about what the alternative diagnoses are is one of the reasons for that. For example, in chronic pulmonary aspergillosis, patients are often re-treated for TB because they've assumed that's what it looks like on the radiology and they haven't thought about *Aspergillus*. The x-ray doctors, or radiologists, don't always report *Aspergillus* as one of the possible causes of the features that they can see—which is something we tried to address with some guidelines published last year—and for fungal asthma, doctors have been used to testing for all IgE, total IgE, but they haven't been doing fungal IgE so often, preferring to test for house dust mite and cats and dog allergy. But of course, there's no anti-house dust mite medicine or anti-cat medicine or anti-dog medicine, but there is anti-fungal medicine. Doing this test for fungal allergy offers a therapeutic opportunity for the patient, which the other things don't always, other than not having a cat or a dog anymore.

[Sarah Gregory] So, do you have suggestions for clinical practitioners?

[Dr. Denning] I think patients who have difficult asthma with recurrent exacerbation should be tested for fungal allergy and then, if they're positive, which many of them will be, then they need to be offered a trial of anti-fungal therapy. Many won't take that or some won't benefit from it, but I think it's something that needs to be offered for them.

There's a drug interaction between itraconazole and inhaled steroids, so there's caution required around the duration of therapy and dealing with that drug interaction. For patients who might have TB but it can't be proven, I think they definitely need to be tested for chronic pulmonary aspergillosis with an antibody test against *Aspergillus*. And on a global scale, we need to enable labs and clinicians in lower income countries to be able to diagnose all of these infections, but also *Pneumocystis pneumonia*, in particular, because that diagnosis is almost impossible to make in children now across the world because the tests are not there and it's very difficult to do a bronchoscopy in a child and get the relevant samples out.

[Sarah Gregory] And, how about the general public? Should patients be requesting tests for fungal disease themselves?

[Dr. Denning] The general public have an important part to play, I think, in improving awareness and quality of care for patients with fungal asthma, as is very common in the U.S. and Europe, Australia, and probably in India and China, as well. And what we're not seeing there is that doctors are actually thinking about fungal asthma and thinking about anti-fungal therapy. So I think patients and their relatives and carers can play a very important role in raising this as a question to their doctors and saying: Do I have fungal asthma? Could I be treated for this? Can you diagnose it for me? And I think, in the future, we're going to have inhaled anti-fungal medicines, as well as the oral medicines, and that's going to offer another opportunity for the patient. But we do need patients and their doctors and carers to think about the diagnosis.

[Sarah Gregory] Thank you, Dr. Denning for talking with me today. Listeners can read the entire February 2017 article, "Delivering on Antimicrobial Resistance Agenda Not Possible without Improving Fungal Diagnostic Capabilities," online at cdc.gov/eid.

I'm Sarah Gregory for *Emerging Infectious Diseases*.

[Announcer] For the most accurate health information, visit www.cdc.gov or call 1-800-CDC-INFO.