

# Fatal Fungicide-Associated Triazole-Resistant *Aspergillus fumigatus* Infection, Pennsylvania

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

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Kennedy Bradley, an epidemiology fellow at the Department of Public Health, Philadelphia. We'll be discussing a fatal infection associated with triazole-resistant *Aspergillus fumigatus* in Pennsylvania.

Welcome, Kennedy.

[Kennedy Bradley] Hi, Sarah. Thank you so much for having me today.

[Sarah Gregory] Let's walk through the title of your article, Fatal Fungicide-associated Triazole-Resistant *Aspergillus fumigatus* Infection in Pennsylvania. What is triazole?

[Kennedy Bradley] Triazoles are a class of antifungal agents that are widely used for the prophylaxis and treatment of invasive fungal infection. For example, voriconazole, which is a second-generation triazole, it's a first-line treatment for patients with invasive aspergillosis. Other medical triazoles include fluconazole, itraconazole, and posaconazole. And what's interesting about triazoles is that they are widely used in both clinical and agricultural settings and are highly effective against fungal pathogens of both humans and plants, leading to their widespread use in both settings.

[Sarah Gregory] What is *Aspergillus fumigatus*?

[Kennedy Bradley] *Aspergillus fumigatus* is the most common species of *Aspergillus*, which is a genus of fungi, that are comprised of approximately 180 species of mold. Like other *Aspergillus* species, *Aspergillus fumigatus* is commonly found throughout the environment, particularly in soil, compost, and other decaying plant materials. But it can also be found in household dust, building materials, and in the ambient air. So it goes without saying, you will likely be able to find *Aspergillus* in our home. And unlike other fungi, *Aspergillus fumigatus* is thermal tolerant, meaning that it can grow and thrive in normal and high body temperatures, including during fever response. And it's also the most common species of invasive aspergillosis, which is a life-threatening fungal infection. And while invasive aspergillosis most commonly affects the lungs, it can also spread to other parts of the body.

[Sarah Gregory] Who does it primarily affect?

[Kennedy Bradley] Invasive aspergillosis involving *Aspergillus fumigatus* primarily affects immunocompromised patients. So for example, patients with hematologic malignancies and cell or organ transplant patients, or patients receiving immunosuppressive medication. And it can also affect patients who are critically ill, and we're starting to see some of these cases of invasive *Aspergillus* among patients with severe influenza or COVID-19 infection.

[Sarah Gregory] Finally, a fungicide is?

[Kennedy Bradley] So fungicides are a specific type of pesticide, and they're used to kill or inhibit the growth of fungi and their source. And in agriculture, fungicides have been widely used for centuries to treat plant infection, prevent crop loss, and increase agricultural yield. So for example, in places such as the Midwest and the Southeast, triazole fungicides are widely used

on crops, such as wheat, corn, or soybeans. And in addition to their use in agriculture, fungicides may also be used in nonfood specific settings to control mold and mildew in our homes and commercial property. And they are also used to preserve wood and other materials in the environment.

[Sarah Gregory] What does an agricultural fungicide then have to do with resistance to an anti-fungal medication in a person?

[Kennedy Bradley] That's a great question, Sarah. Recent research in whole-genome sequencing is finding that these resistant *Aspergillus fumigatus* strains found in the environment are closely related to clinical isolates. For example, resistant strains carrying the TR34/L98 mutation (which is essentially just a gene mutation linked to environmental fungicide use) that can cause pan-triazole resistance in patients has also been found in peanut crop debris that had been treated with agricultural triazole fungicides that are similarly structured to medical triazoles. And research is also finding that these isolates are both resistant to fungicides used on plants in the environment and azole medications used in clinical settings. And so, due to the widespread use of triazole fungicides in agriculture, researchers suspect that resistance is developing in the environment due to selection pressure.

[Sarah Gregory] Do we know why fungicides are used so dramatically, as antibiotic use is supposedly waning?

[Kennedy Bradley] So several factors may explain the increase in fungicide use, including increased crop production to meet demands, increases in plant diseases in certain regions, and marketing of fungicides on field crops to farmers such as...for reasons such as plant safety. Fungicides are still commonly used and added to spray paint during insurance applications, which are essentially prophylactic treatments of crops.

[Sarah Gregory] You mentioned *Aspergillus fumigatus* being in homes. How does a person get *Aspergillus fumigatus*?

[Kennedy Bradley] Okay. So *Aspergillus fumigatus* is ubiquitous, so it is found everywhere. And patients can acquire *Aspergillus fumigatus* through inhalation of its spores found in the environment. So it's important to note that most people do breathe in *Aspergillus* spores daily without getting sick.

[Sarah Gregory] Okay, I just want to clarify here. So it's an inhalation thing? It's not eating moldy food or touching mushrooms or anything like that?

[Kennedy Bradley] No. Just inhalation of its spores.

[Sarah Gregory] And how many people do annually get it?

[Kennedy Bradley] *Aspergillus* infections are not reportable in the United States. Therefore, the exact number of cases is difficult to determine. However, it's estimated that invasive aspergillosis accounts for over 14,000 hospitalizations annually.

[Sarah Gregory] That's a lot of people, even though it is a small percentage of the population. What's the annual economic burden of that?

[Kennedy Bradley] So *Aspergillus* infections can pose over 1.2 billion dollars in direct costs on the United States healthcare system annually. However, the true economic burden may be significantly higher, as *Aspergillus* infections are severely underdiagnosed.

[Sarah Gregory] How do people then acquire this triazole-resistant infection?

[Kennedy Bradley] There are two ways that patients can acquire triazole-resistant *Aspergillus fumigatus* infection. The first way is by inhalation of environmental *Aspergillus fumigatus* spores that are already triazole-resistant. I mentioned earlier that data is suggesting an environmental origin of some of these resistant strains that we are seeing due to widespread triazole fungicide use. So in this case, a patient can inhale *Aspergillus* spores in the environment that have acquired a resistance mechanism (such as a TR34 mechanism), and due to selection pressure, acquire a triazole-resistant *Aspergillus fumigatus* infection. And patients can also acquire triazole infections because of exposure to long-term triazole therapy for chronic aspergillosis.

[Sarah Gregory] What's the difference in mortality for people who have a resistant infection versus those who don't?

[Kennedy Bradley] Mortality occurs more commonly in resistant infection. A recent study found that 90-day mortality was 25% higher in patients with resistant aspergillosis versus susceptible aspergillosis. So again, these recent findings further highlight the severity of resistant triazole infections in patients.

[Sarah Gregory] Are these infections a global problem and what's the United States' surveillance like? Is it equal to the rest of the world?

[Kennedy Bradley] Yes. These infections are certainly a global concern. And while the issue of triazole-resistant *Aspergillus* infections may not be as well-defined as bacterial infections that are resistant to certain classes of antibiotics (such as methicillin-resistant *Staphylococcus aureus* or carbapenem-resistant Enterobacterales), we do know that these infections are certainly an emerging threat as more reports of fungal infections are being reported globally. During the last decade alone, Europe and Asia have seen major increases in azole-resistant *Aspergillus fumigatus* infection. And azole-resistance continues to emerge globally. Unfortunately, however, ongoing surveillance for azole-resistant *Aspergillus fumigatus* is lacking, both in the United States and in other countries. So most of the surveillance that's being conducted currently is passive surveillance. However, one of the largest surveillance efforts in Europe through...was in Europe through the Surveillance Collaboration on *Aspergillus* Resistance in Europe. So there are a few countries that perform their surveillance (such as the Netherlands), but not many. However, it's important to note that the Centers for Disease Control and Prevention does provide testing for azole-resistant *Aspergillus fumigatus* through the Antimicrobial Resistance Laboratory Network.

[Sarah Gregory] Kennedy, why did you write this article?

[Kennedy Bradley] We decided to write this article and highlight this particular case in order to raise awareness regarding resistant emerging fungal infections. To our knowledge, this is the first published fatal case of azole-resistant *Aspergillus fumigatus* infection with a mutation linked to environmental use of fungicide in the United States. So again, we know that these infections existed, and we know that resistance is a concern globally. So we wrote this as an opportunity to further fuel conversations regarding fungal infections and hopefully to define the scope of this issue in the United States.

[Sarah Gregory] Tell us about the patient and what happened to him.

[Kennedy Bradley] Sure. So the patient was a 65-year-old male who had a complex medical history. So the patient had previously underwent chimeric antigen receptor T-cell therapy for

*Fatal Fungicide-Associated Triazole-Resistant Aspergillus fumigatus Infection, Pennsylvania*

acute myeloid leukemia, and one month prior to hospital admission, the patient had received a stem cell transplant which was further complicated by cutaneous graft-versus-host disease. And despite topical therapies, the patient was admitted to the hospital due to worsening rashes, fever, and lethargy. And shortly after admission, the patient was transferred to the intensive care unit for wound management and treatment for hypovolemic shock. Following the patient's positive *Aspergillus fumigatus* bronchial culture, clinicians initiated voriconazole therapy for probable invasive aspergillosis. Unfortunately, however, the patient's condition continued to worsen, and the patient's family had decided to focus on comfort care. The patient expired on hospital day 28, and the autopsy determined that that cause of death was sepsis from disseminated *Aspergillus fumigatus* and *Rhizopus* species infection.

[Sarah Gregory] How and where was the susceptibility testing done? Can any lab do it?

[Kennedy Bradley] Unfortunately, most US clinical laboratories do not perform antifungal susceptibility testing. However, as I mentioned earlier, susceptibility testing is available through the CDC's Antibiotic Resistance Laboratory Network. Therefore in this case, the hospital laboratory sent the patient's isolate to the CDC as a part of ongoing passive surveillance which was collaboratively established by the Philadelphia Department of Public Health, the CDC, and the hospital laboratory. So the CDC performed broth microdilution to determine the MICs of itraconazole and voriconazole for the isolate. And for reference, the minimum inhibitory concentration assay (or MIC) is widely used to measure the susceptibility of fungal strains to antifungal agents. And following susceptibility testing, the CDC performed a DNA sequence analysis of the CYP51A gene and determined that the isolate contained the TR34 gene mutation, which has been linked to environmental fungicide use.

[Sarah Gregory] Okay. A person has got this resistant version so they can't get the triazole. Are there alternative treatments?

[Kennedy Bradley] That's a great question. Guidelines for treating these resistant infections are lacking. However, an international panel of experts has published practical recommendations for clinicians pending better quality evidence. Antifungal therapy for patients with these resistant *Aspergillus* infections is complex, and it really depends on the type of mutation involved and the patient's individual situation. But treatment might involve combination therapy such as voriconazole plus echinocandin or liposomal amphotericin B.

[Sarah Gregory] What do you think is the public health importance of your report?

[Kennedy Bradley] So this report really underscores the potential severity of triazole-resistant *Aspergillus fumigatus* infections. With mutations linked to the environment, we use a triazole in immunocompromised patients. As I previously mentioned, invasive aspergillosis is not a reportable condition in the United States, so the scope of azole-resistance is not well-defined. So this report helped to define the scope of azole-resistance in the United States, and this report I hope will highlight the importance of considering the possibility of drug-resistant *Aspergillus fumigatus* infection in clinical settings among patients with invasive aspergillosis who do not improve with first-line therapy.

[Sarah Gregory] What do you think needs to be done to improve understanding of the problem? Better surveillance? Better communication? Other things? All of it?

[Kennedy Bradley] Yes, I think there are many opportunities to improve understanding for guarding fungal infections in general. I think often times when we think about fungal infections,

we think about ringworm, vaginal yeast infections, or maybe even athlete's foot. But the issue with fungal infections that are resistant to currently available antifungal medications are not commonly addressed. Therefore, raising awareness of these infections will help to improve understanding. I think it's also really important to consider the concept of One Health when thinking about resistance. As you know, antifungal resistance is not just a concern to human health, but also to plant health and animal health. We also need more robust laboratory-based surveillance and diagnostic tools for *Aspergillus* infections, including systematic antifungal susceptibility testing. Performing susceptibility testing and detecting resistant strains early can not only help to define the scope of this issue in the US, but also to help to prevent the spread and inform future interventions, if possible. And lastly, we need surveillance—active surveillance. Again, *Aspergillus* infections are severely underdiagnosed. So conducting active surveillance can help us to better understand the true burden of these resistant infections.

[Sarah Gregory] Should clinicians be doing anything differently? You did mention looking for this resistant infection sooner. Anything else?

[Kennedy Bradley] Well, one way clinicians can help to prevent the spread of these resistant infections is by ensuring that they are being good stewards of the medications that we currently have available. Would you believe that there are only three classes of antifungal medications available to treat fungal infections such as invasive aspergillosis?

[Sarah Gregory] No.

[Kennedy Bradley] It goes without saying that it's really important that clinicians are being good stewards in order to preserve the effectiveness of these lifesaving medications and also for any future drugs that may become available. Health systems should also ensure that they're monitoring antifungal usage and appropriateness of prescribing, similarly to what's being done for antibiotics.

[Sarah Gregory] Is there a way for people to protect themselves?

[Kennedy Bradley] So it is difficult to avoid breathing in the spores because the fungus is so common in the environment. However, there may be a few ways to lower the chances of developing a severe *Aspergillus* infection for high-risk patients. So for example, avoiding areas with a lot of dust like construction sites or evacuation sites, which are some of the areas where the fungus tends to thrive, or wear an N95 respirator while visiting these sorts of sites where *Aspergillus* may be more prevalent. High-risk patients should also avoid activities that involve close contact to soil or dust, such as yardwork and gardening, if possible. Or wear protective clothing and gloves while performing activities in handling things such as soil, mulch, and manure—again, all places where *Aspergillus* may be more prevalent.

[Sarah Gregory] Kennedy, tell us about your job.

[Kennedy Bradley] Sure. I'm a CSTE Applied Epidemiology Fellow at the Philadelphia Department of Public Health within the Healthcare-associated Infections and Antimicrobial Resistance Program. My primary subject area is in healthcare-associated infections. However, we also focus on other communicable diseases such as COVID-19. And as a fellow, I've worked on a variety of projects that are designed to address certain public health competencies such as epidemiologic methods. I also collaborate often with other programs within the Division of Disease Control (such as the TB control program, the bioterrorism program) for efforts such as

developing toolkits for healthcare workers, with any program-related work at national conferences, and participating in large scale vaccination clinics.

[Sarah Gregory] And what do you like most about it?

[Kennedy Bradley] So what I like most about being an Applied Epidemiology Fellow is the unique opportunity to apply my previously acquired epidemiologic skills to a wide array of infectious disease-related projects and tasks. I also really appreciate the opportunity to be involved in a part of a variety of public health efforts such as promoting stewardship, participating in onsite infection control assessments, and developing timely educational materials.

[Sarah Gregory] Well, thank you so much for taking the time to talk with me today, Kennedy.

[Kennedy Bradley] Thank you for having me today, Sarah.

[Sarah Gregory] And thanks for joining me out there. You can read the September 2022 article, Fatal Fungicide-Associated Triazole-Resistant *Aspergillus fumigatus* Infection, Pennsylvania, USA, online at [cdc.gov/eid](https://www.cdc.gov/eid).

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

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