



Responding to an 'Unprecedented' Outbreak

COOLER

Last September, as evidence mounted that a batch of steroids contaminated with a potentially fatal black mold had been injected into thousands of patients across the country, the CDC tapped infectious diseases specialist Carol A. Kauffman, M.D., to be part of an expert panel tasked with figuring out how best to respond. Chief of Infectious Diseases at the VA Ann Arbor Healthcare System and professor of internal medicine at the U-M, Kauffman helped establish guidance for clinicians and co-authored a commentary about the outbreak for the *New England Journal of Medicine*. ➔

Q: How were you involved with the outbreak?

A: On October 1, we had the first conference call involving six of us whom the Centers for Disease Control and Prevention had asked for help. I study fungal infections for a living and so did the others on the call.

At that time we thought we were dealing with a meningitis outbreak involving *Aspergillus fumigatus* — because the first case, which was reported from Tennessee in late September, was *Aspergillus*. In the end, however, that fungus only showed up in that one case. It's still a mystery how that happened.

But by then we already knew that all the contaminated material came from one place, the New England Compounding Center, and the CDC had already started alerting state health departments, who in turn alerted pain clinics to stop using the drugs.

It became clear before too long that Ann Arbor was going to be a hotbed for infections. As the number of cases mounted, several of us from the U-M and VA Infectious Diseases Division helped out by seeing patients at Saint Joseph Mercy Hospital, which treated the vast majority of Michigan patients.

They set up special clinics, organized a system for screening people to detect early infection, and brought in a portable MRI machine.

They did a tremendous job. There was one day when their emergency department did more than 60 spinal taps and at one point there were more than 75 patients hospitalized.

Q: Why did the NEJM article call the outbreak 'unprecedented'?

A: Out of 14,000 people who received the injections, there have been 745 cases across 20 states resulting in 58 deaths. More than a third — 264 cases — were in Michigan.* This has become the largest health-care-associated outbreak ever in the U.S. The last similar outbreak happened a decade ago, when five people were infected by contaminated steroids from a South Carolina compounding pharmacy, leading to one death.

Q: Why is treating fungal infections so difficult?

A: Fungi are eukaryotes, like we are. They have cell membranes, mitochondria and endoplasmic reticulum, just like we do. Bacteria are much simpler. It's easier to kill bacteria and not hurt the person carrying it because the two organisms are so different. But the drugs that work against fungi have negative side effects on our own cells.

Q: What about the fungus involved in the outbreak, *Exserohilum rostratum*?

A: It's a brown-black fungus. There are a lot of molds that have melanin in

them — just like the pigment we have in our skin — and melanin is a virulence factor. *Exserohilum* is a plant pathogen. It's happy as can be infecting plants. But, obviously, it has the potential in the right circumstances — like being injected into the body with a huge dose of steroids — to grow in humans. There are only a few previous case reports of people who have had widely disseminated infections, and they were all immunosuppressed.

Q: What symptoms does it cause?

A: The first cases that were seen — and in some places the only kind of cases that they saw — were meningitis, a very serious infection of the membrane around the brain and spinal cord. Patients have terrible headaches, maybe some visual symptoms, sometimes seizures and neck pain. So the initial wave was meningitis. And then later, some of these patients started complaining of back pain where they had their injection. When MRI scans were done, it was found that they had abscesses at these sites caused by the *Exserohilum*.

And the more they looked, the more they found. Some of the patients

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didn't have any symptoms, but when an MRI was performed, infections were found at the injection site. St. Joe set up a program to image everybody who had received the contaminated drug because it was clear that one of our local pain clinics had received some of the most heavily contaminated vials of steroid.

Q: How have patients and their families been affected?

A: In the clinic, I probably spend three-quarters of my time dealing with side effects of the drugs and a quarter of the time dealing with patients' pain.

There are two drugs that we use. The first is amphotericin B, which has to be given by IV. It's pretty toxic, but is effective against many fungi. Patients who get the drug frequently have fevers, chills, nausea and vomiting, and they can also have problems with their electrolytes and kidney

function. It is given every day, so it requires a long hospitalization.

The other drug is voriconazole, which patients can continue to take after they leave the hospital. We knew that it had some side effects, but we have seen a far greater number than expected.

One major problem is that patients complain of visual symptoms: bright lights, wavy lines. At higher doses, visual hallucinations are common. In addition, a lot of people just say, "My brain is foggy, I can't make decisions, I can't drive a car." Some of them will have that feeling for an hour, some for six hours, some all day long. I've seen executives who say, "I get up in the morning early and get all of my business done before 10 o'clock, when I take my vori. After that I can't make major decisions." I just saw somebody whose husband lost his job because he has to be home taking care of the kids, driving his wife to various

appointments, or doing housework because she is so ill.

Not to mention the fact that both of the drugs cost a huge amount of money. The amphotericin B is upwards of \$500 a day. And that's every day for weeks. Voriconazole costs as much as \$2,000 a month. A lot of insurance companies do not pay for drugs taken in the outpatient setting. Pfizer does have a compassionate program through which it provides voriconazole for patients whose medications are not covered by insurance.

Q: How long do treatments last?

A: The minimum is about three months, but many patients will need at least six months of therapy. If they have invasion of bone, it might be a year.

Q: What lessons has the outbreak taught us?

A: On a national level, I think we learned that compounding pharmacies should be regulated by the federal government, not by the states. The FDA needs to have oversight. On a local level, we have learned how many resources are needed to effectively respond to an emergent infectious disease, and we will hone our organizational skills in case something similar happens again. On a personal level, we all have learned what a devastating disease this is and have come to realize that we are far from finished with this saga. **[M]**

Interview by Ian Demsky

**Figures current as of June 10, 2013.*