Expert discusses the antibiotic resistance threat

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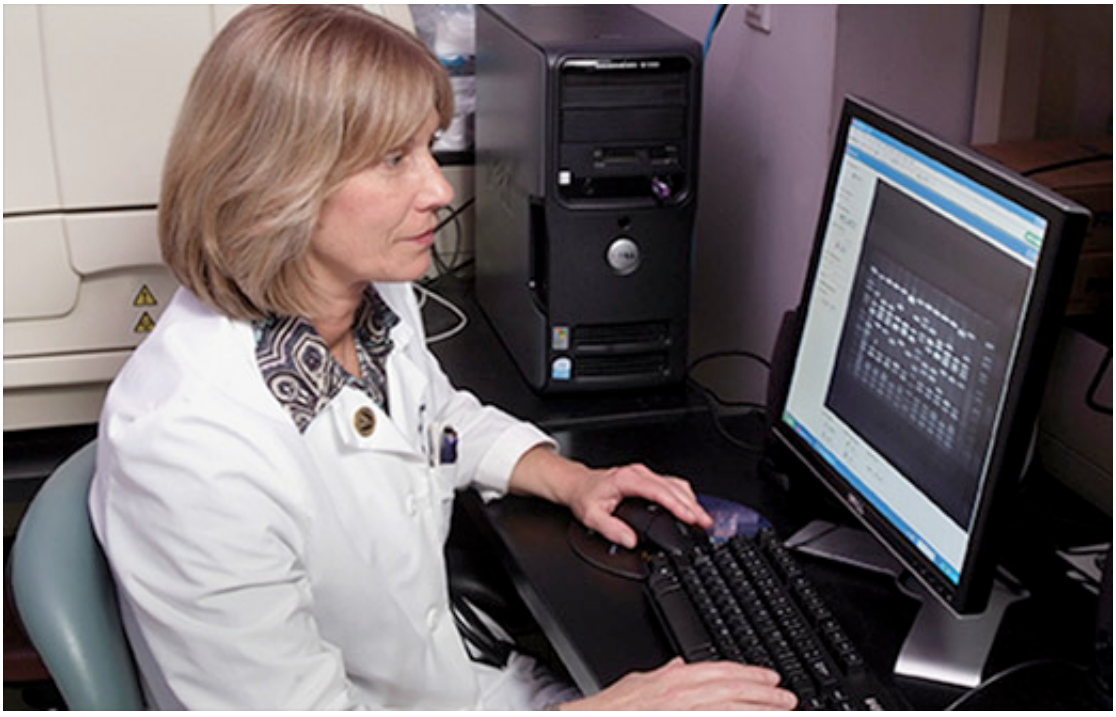

Monica Farley. Credit: Emory University

Monica Farley is principal investigator for the Georgia Emerging Infections Program. She is an Emory professor of medicine in infectious disease, a physician at the Atlanta VA Medical Center, and a faculty researcher at the Emory Antibiotic Resistance Center. Here, she discusses the growing threat of antibiotic resistance.

How does antibiotic resistance change the decisions you make as a doctor?

It's changing the playing field. Isolating bacteria and testing them for antibiotic resistance can sometimes take 24 to 48 hours—too long to wait if someone is sick and needs treatment. We have to make a good guess before we know the results. Twenty years ago, if someone had a suspected staph infection in a cut on their leg, we could assume it would be treatable with cephalosporin or something similar. Now we can't really say that. We have to assume it will be MRSA. It also means we have to treat many more infections with vancomycin, which is now standard for MRSA-type infections. Vancomycin is a compromise, because it doesn't work as fast as the drugs we would have used in the past.

It's the same for pneumonia. If someone develops pneumonia in the hospital, we have to assume it's a bad bug. We can't use the same drug we'd use for someone just coming in from the community. It's also influenced how we treat meningitis. Now we usually need more than one drug, maybe even three.

If the lab tells us we can use one of the older drugs, we will switch back. But we have to assume we're dealing with a resistant infection, unless proven otherwise, in hospital settings. The antibiotics that are left are often the ones we least want to use—ones that are more toxic or harder to tolerate.

Is colistin, which was in the news a lot last year because of emerging resistance, in that category?

That's right. Colistin attracted some attention because it's a drug of last resort. It was often used in the early days of antibiotics but was put on

the shelf for decades because less toxic alternatives were developed. Now we've had to revisit it.

How is antibiotic resistance going to affect medicine?

Around the time I was starting my career (in the 1980s), there was a declaration that infectious disease as a specialty was going to end because we had effective antibiotics. Over the last few decades, everything has flipped and we're seeing the steady emergence of resistance to antibiotics that were once dependable. Common infections that are usually not very serious, like a scrape on the skin that gets infected, can be increasingly resistant and more difficult to treat. Importantly, this extends to more serious infections in the hospital setting, to people who would likely not have survived their infections in the pre-antibiotic era. Bone marrow transplants, solid organ transplants—we would not be able to do these successfully if we did not have effective antibiotics. This phenomenon is threatening the advances we have made in the last 50 years.

What areas of medicine are going to be affected the soonest?

This really affects all areas of medicine. Resistant infections are more likely to be seen in the health care environment. Certainly there are concerns for people who are immunocompromised, such as organ transplant patients or people undergoing chemotherapy for cancer. But it won't be limited to them. It will impact anyone with lots of medical problems. Patients who have experienced a stroke. Patients with long-term catheters in place, or in nursing homes. They tend to have a lot of antibiotic exposure. These are the patients in whom we may see persistent colonization with antibiotic resistant bacteria, leading to recurrent urinary tract infections, for example.

When do you think we're going to be "out of options" for many—or even most—infections?

It's now a rarity to encounter isolates for which there are no effective treatments. But without action, it could happen in the next decade. A report from the British government predicted a potential for 10 million deaths per year by 2050. We're not just going to wait for it to happen—this was a main driver for the creation of Emory's Antibiotic Resistance Center.

What is meant by antibiotic stewardship?

Because development of new antibiotics is slower than we need it to be, we want to preserve the value of antibiotics that are still effective. That means: don't use antibiotics against viral infections. Choose the narrowest spectrum antibiotics—don't expose other organisms to selective pressure if we don't have to. It means the right dosing, and shortening courses of antibiotics from 10, 14, and 21 days down to 5, 7, or 8 days for pneumonias and other common infections. Every day an antibiotic is in use against an organism that causes disease, we have to balance its effects against others that may become resistant. We may have to go beyond antibiotics, to find compounds that stimulate the immune system, or work with standard antibiotics to make organisms susceptible again.

What are some consequences of antibiotic overuse?

Antibiotic use can change the whole microbial flora in the body, sometimes for months or years. The change in intestinal flora can result in colonization and disease caused by C. diff, which is difficult to treat and can be life threatening. We've also seen this with VRE (vancomycin-resistant enterococci), a Gram-positive bacteria that is carried in the gut

and is usually a minor part of flora. When a patient's internal balance is destabilized, VRE can become a major part and can spread to linens or bed rails. This is how antibiotic use in one patient can affect another who is vulnerable.

Why are so many antibiotic-resistant infections seen in hospitals?

It's partly because of the routine use of antibiotics. A recent study of health care associated infections, which the Emerging Infections Program (EIP) was involved in, found that 50% of people in hospitals on any given day were on antibiotics. It didn't matter whether they were in intensive care or not. There's a danger from health care providers going from patient to patient, carrying bacteria on their hands or on items. Jesse Jacob and others at Emory have been looking at this systematically, in collaboration with Georgia Tech. They have a studio mock-up of a hospital room so they can ask: What changes to the environment reduce contamination?

How do clinicians test for antibiotic resistance?

In almost all cases, if a patient is hospitalized and an infection is suspected, we will take a sample from the blood, urine, lungs, or pus from an abscess—wherever the problem is. We get a specimen, we put it on an agar plate, and we're able to grow it out and obtain a single colony. That way we know that it's just one kind of bacteria. Then we subject the bacteria to a panel of different antibiotics. It can be susceptible, intermediate (takes more drug to kill it,) or flat-out resistant. With multiple-drug-resistant organisms, this means not only individual antibiotics, but entire drug families. Unfortunately, most of the standard panels don't include the less common drugs that we have to sometimes use now. If we need to look further, we can do manual testing for

resistance or send the sample to a reference lab, but it takes more time. What's newer are molecular diagnostics. Instead of growing the bacteria on an agar plate, we sequence the DNA. It's either direct from the specimen or we amplify part of the bacterial DNA and get a profile. With whole genome sequencing, we can predict the type of bacteria, and also antibiotic susceptibility, based on the resistance genes. As part of the EIP, all isolates for certain types of infections, such as food-borne infections, are subjected to whole-genome sequencing.

Are DNA-based tests faster?

Theoretically, yes. In the EIP, the sequencing is not done in real time but after the fact. Still, there are some good examples. C. diff and gonorrhea are mostly diagnosed by molecular tests. We can get the results back in three to four hours. Respiratory infections are increasingly being diagnosed by molecular test panels. Similar panels are being developed for intestinal pathogens. They're useful for hard-to-grow organisms like mycoplasma. Ten years from now, molecular diagnostics will be the norm in the clinical microbiology lab. We have to keep up with the technology and the resistance patterns. And, even if you know all the resistance genes, what happens if a new gene emerges? There will always be a component of culture.

Some Emory researchers have found sneaky bacteria that are "heteroresistant"—only part of their population is resistant to an antibiotic, confusing diagnostic tests. Have more examples of this been found?

We're planning to investigate this across all 10 national sites of the EIP. How widespread is it? We want to take a closer look, not only at colistin heteroresistance, which is what Eileen Burd and David Weiss's lab studied, but at other critical antibiotics, such as carbapenems. We've seen similar heteroresistance with Pseudomonas, and it may switch on

and off, further confusing laboratory testing. Much more work needs to be done to understand this phenomenon.

What's next for the Emory Antibiotic Resistance Center?

We'd like to strengthen the connection between clinical and basic researchers. When the clinical lab takes a culture from the patient's throat, urine, or blood, it usually stops there. They report what they found back to the clinic, but we don't learn more about those bacterial isolates. What we are planning to establish is an "investigational clinical microbiology lab," led by Sarah Satola. It will allow us to routinely and serially collect isolates and perform detailed characterization of the mechanisms of resistance, tying that to clinical and demographic information. Did this patient have a stroke? Does he have diabetes? Was there antibiotic exposure? It's very powerful to be able to say that we're seeing this mechanism of resistance in certain populations, or in people who have particular medical problems. Our objective is to tighten the pipeline of communication.

Provided by Emory University