Medical News & Perspectives

Infectious Disease Expert Sees Threat From Colistin-Resistant Superbug

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Scientists at the Walter Reed Army Institute of Research (WRAIR) and the Walter Reed National Military Medical Center recently published a troubling finding: *Escherichia coli* carrying a gene conferring resistance to the antibiotic colistin in the urine of a Pennsylvania woman (McGann P et al. *Antimicrob Agents Chemother*. 2016;60[7]:4420-4421). It was the first time the gene, *mcr-1*, had been found in a human bacterial infection in the United States.

Mcr-1 thwarts colistin, a 1950s-era antibiotic called out of retirement to treat multidrug-resistant infections including carbapenem-resistant Enterobacteriaceae. Even more concerning, the gene is carried on a plasmid, a short, circular strand of nonchromosomal DNA that can transfer to other types of bacteria, spreading its potentially lethal resistance.

Scientists reported the discovery of the gene in China just last year (Liu YY et al. *Lancet Infect Dis*. 2016;16[2]:161-168). By then, it was already widespread in *E coli* and *Klebsiella pneumoniae*, two species of Enterobacteriaceae, found in a number of pigs and patients in South China. Enterobacteriaceae is a family of gram-negative bacteria that also includes *Salmonella*, *Shigella*, and *Yersinia pestis* (plague).

The gene has now been detected in livestock, meat, and people on most continents (Skov R, Monnet D. *Euro Surveill*. 2016; 21[9]:1-6). In July, a second case of *E coli* with the *mcr-1* gene was reported in a human patient in New York (Castanheira M et al. *Antimicrob Agents Chemother*. doi:10.1128/AAC.01267-16 [published online July 11, 2016]).

News of the superbug in US patients came as no surprise to Barbara E. Murray, MD, director of the division of infectious diseases at the University of Texas Health Science Center at Houston and an internationally recognized expert on antibiotic resistance. "Once [resistance has] appeared somewhere, you know it's going to appear other places, so it was just a matter of time," said Murray, a past president of the Infectious Diseases Society of America. "I've been working on antibiotic resistance for 30 years, and it always happens [this way]."

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Barbara E. Murray, MD

The emergence of the *mcr-1* gene comes at a time when federal agencies are stepping up surveillance to detect antibiotic resistance, Murray said. The Pennsylvania case was confirmed by the Department of Defense's Multidrug-resistant Organism Repository and Surveillance Network at WRAIR, a program that is being formalized by the "National Action Plan for Combating Antibiotic-Resistant Bacteria," introduced in 2015. In the past few months, the National Antimicrobial Resistance Monitoring System—a joint effort between the US Department of Health and Human Services and the US Department of Agriculture (USDA)—found colistin-resistant *E coli* in 2 pigs from slaughterhouses in South Carolina and Illinois, a USDA spokesperson confirmed.

Recently, Murray spoke with *JAMA* about the challenges posed by *mcr-1* and antibiotic-resistant bugs. The following is an edited version of the interview.

JAMA: What was your initial response to the news that the colistin-resistant gene, *mcr-1*, had been discovered in *E coli* bacteria cultured from a patient in the United States?

DR MURRAY: The Chin[ese] report was the real surprise because [before the report] I didn't know that colistin was being used in animals. The reaction [to the US report] was kind of like the other shoe dropped. We are in these situations where we really don't have anything to treat some patients. It's closing in on us and you can just kind of feel it constricting, constricting, constricting what our options are. And I've been through this before with other resistance cycles and it's very worrisome for patients because you see these examples and it's like, "Well gosh, there's nothing else we can do."

JAMA: Can you tell us a little bit about the *mcr-1* gene? How was it discovered and how does it give rise to antibiotic resistance?

DR MURRAY: It was discovered because they were seeing a lot of colistin resistance [in China] and they knew colistin was being used a lot in animal feeds. They did whole-genome sequencing on the bacterium [samples from pigs] and saw a gene that looked like it might be involved in modifying lipid A. Lipid A is a component of the outer membrane of gram-negative bacteria and is the target for the drug colistin.

JAMA: So why is the colistin-resistant gene so concerning to infectious disease experts?

DR MURRAY: Colistin has become the last go-to antibiotic for some of our multidrug-resistant bacteria. Colistin's been around for at least 50 years, [but] it wasn't used very much because it was toxic and other [less toxic] agents were developed. What's happening [now] is [that] we have these infections where the bacterium is resistant to almost everything, and we've gone back and started using colistin. When you're left with only one drug and now you see resistance developing to it, it's very concerning.

The [Pennsylvania] patient sounded like a healthy person [who] was not in the hospital, and there were still options for therapy. But the sicker the patient, the more likely [he or she] is to have these multidrug-resistant bacteria. Organ transplant patients, bone marrow transplant patients, and very sick ICU [Intensive Care Unit] patients [who] have been in the hospital a long time and keep getting recurrent infections—you treat them first with a simpler drug and then you move it up to the extended-spectrum β-lactamases. And then something infects them and it's resistant. You move to the carbapenems and then resistance develops. It's this sequential development of this resistance that we often see. And you're left with colistin being the only therapeutic option.

JAMA: And there's some concern that the gene could be transferred to other types of bacteria? How could that occur—and what would the worst-case scenario be?

DR MURRAY: Absolutely. There are certain plasmids that can transfer from bacterium to bacterium. Some of them can transfer widely, to whole different species and genre of bacteria. We call this conjugation or bacterial mating because it's spreading DNA. *E coli* can frequently genetically communicate with all sorts of other bacteria like *Salmonella*, *Shigella*—those are diarrhea germs—and other kinds of bacteria that cause infections in hospitals, like *Klebsiella*, *Enterobacter*. These plasmid-mediated things can spread like wildfire, and they can spread from species to species, to all of the moderately related types of bacteria. Then they have their own resistances, which just makes the problem exponentially worse.

JAMA: Physicians often say they feel pressured by patients to dole out antibiotics. What would you say to them?

DR MURRAY: I think that's tough. The big pressure in an outpatient setting is for respiratory infections—colds, sore throats, and sinusitis—and the vast majority of those are viral. I think we just have to tell patients that this is a virus. And it's not good for you or the world to put you on antibiotics for a viral infection against which antibiotics don't work.

JAMA: Would restricting colistin use in agriculture help?

DR MURRAY: Absolutely. China is one of the world's highest users of colistin in agriculture. In France, 90% of farms in the pig industry report using colistin during the postweaning period. Belgium, Spain, Austria, Sweden, Germany, Vietnam, the Netherlands. It's used all over the world in animal food. I was really surprised to read that it was in products going to animals in the European Union because they had banned a lot of antibiotic use already in animals because of their prior experience with vancomycin-resistant enterococci.

I think people thought colistin was kind of a dead drug for humans because it had been supplanted by a whole bunch of different ones and therefore wasn't going to be used in man. So my guess is that it was thought to be okay to use in animal feeds because it was not going to conflict, not realizing that in the next 20 years we were going to need it in humans as well.

Like *Salmonella* with your chickens, you could come in contact with these bacteria on the meat products and then ingest them. If it's in animals, it's going to get on animal meat because there's no way they can butcher animals and not have them contaminated to some extent with what's in their intestinal tract. We could consume the bacteria that has the resistance genes. And it could either just lie dormant in us or it could spread to other bacteria.

JAMA: There's been a lot of public attention around antibiotic resistance for many years now. What are the biggest barriers you've encountered to curbing antibiotic resistance?

DR MURRAY: There are efforts being made to decrease the use of antibiotics, to decrease the spread of resistance once it occurs, and to stimulate the industry to make new antibiotics, but it's a very tough problem.

There have been campaigns in the community, particularly among pediatricians, to try not to use antibiotics when not needed. And in hospitals, the goal of the antibiotic stewardship program is to try to reduce unnecessary use of antibiotics. But when you're dealing with a very sick patient in the hospital, you're not thinking of the public health implications, you're just thinking of that patient. As clinicians, we tend to just keep changing antibiotics and adding new antibiotics. And I can't say that's wrong. But at the same time, it does drive the selective pressure for resistance.

The other aspect is how quickly resistance spreads. There was a study a while back that if every ICU nurse washed her hands every time it was indicated, she would spend something like 22 minutes on the hour washing hands. The medical system just will not take that. It's very difficult to keep things from spreading in the hospital, and that's where the real danger is. In the hospital setting, the bacteria that may acquire the *mcr-1* gene may already be resistant to everything else.

Finally, major pharma has gotten out of the antimicrobial industry because they don't make money from it.

JAMA: The federal government is addressing the issue with initiatives including an executive order, a national strategy, and the "National Action Plan for Combating Antibiotic-Resistant Bacteria" (http://1.usa.gov/28NYmNM). Have we seen any tangible results of these initiatives?

DR MURRAY: It's quite early. There's certainly some increased funding for surveillance and I think that will trickle down to increased funding for investigator-initiated studies. The Generating Antibiotics Incentives Now (GAIN) Act is prolonging the patent life on certain antibiotics. The FDA [US Food and Drug Administration] now has a rapid pathway for agents that fill an unmet need. The FDA has also gotten the signal that when it's a crisis situation, [it] may need to consider approving agents with smaller studies. Because you don't have hundreds and hundreds of patients out there—thank goodness—[who] are infected with these multidrug-resistant organisms. ■