Carbapenem resistance: advice from the frontline

Ann Griswold

August 2015—The problem of carbapenem resistance first made its way to Detroit's Henry Ford Hospital in 2007, when a multidrug-resistant organism appeared in a sputum sample from the intensive care unit. Within weeks, several other cases emerged.

"At that time, we had a brand-new physician in charge of infection control. So I contacted him and was sort of like, 'Houston, I think we have a problem,'" recalls Eileen Burd, PhD, D(ABMM), Henry Ford's clinical microbiology laboratory director at the time. "And he said, 'Yes, I think we do.'"

"Just trying to get it contained was a major challenge," says Dr. Burd, who soon after the outbreak left Detroit for Atlanta, where she is now director of clinical microbiology at Emory University Hospital and associate professor, Emory University School of Medicine.

Henry Ford wasn't alone with its cluster of difficult cases. That year, the National Healthcare Safety Network reported new findings in a disturbing trend: Nearly four percent of Escherichia coli isolates and 10.8 percent of Klebsiella pneumoniae isolates from device-associated infections were carbapenem resistant.

Some warned it was only a matter of time before plasmid-borne carbapenemases would appear in other health-care–associated pathogens.

By many accounts, that time has come.

Carbapenem-resistant Enterobacteriaceae (CRE) now pose a serious threat to hospitalized patients in the United States and around the world, and the Centers for Disease Control and Prevention is monitoring the emergence of carbapenemases in superbugs such as Pseudomonas aeruginosa.

As of January of this year, all states except Idaho and Maine had reported to the CDC Klebsiella pneumoniae carbapenemase (KPC)-producing CRE. The New Delhi Metallo-beta-lactamase (NDM) has been reported in 22 states, while 13 states have reported the class D β-lactamase OXA-48. Five states have reported CRE harboring the Verona Integron-Mediated Metallo-β-lactamase, or VIM. Then there are noncarbapenemase-producing CREs, which rely on chromosomally encoded resistance mechanisms that are not readily spread.

"Carbapenem resistance is really of global concern. Not just in the United States, and not just in hospitals and health care facilities, but in communities as well," says Dr. Burd, who convened a session on carbapenemases at the ASM annual meeting in May.

The question is: What should clinical laboratories do about it?

Dr. Burd

Answers to that question have evolved over time. In 2007, hospitals and clinical labs were coming to terms with the possibility that CRE might lurk on medical devices or linger in long-term care units. Some institutions took

a more aggressive approach to dealing with the organisms than others.

Dr. Burd, for one, arrived in Atlanta still reeling from the outbreak at Henry Ford, only to find that Emory had a carbapenem resistance problem of its own. To her astonishment, no one appeared to be alarmed.

“But I was,” Dr. Burd says. “I asked about it and they said, ‘Yeah, we’ve had this problem for a while.’ They were simply flagging these organisms as multidrug resistant so that proper precautions could be put in place to prevent spread.”

Though molecular technologies have advanced considerably since those early years, clinical laboratories continue to question how best to formulate a plan for detecting CRE, and what to do when they find them.

The Association of Public Health Laboratories recently surveyed CRE capabilities and capacities in public health labs and found that about 50 percent of the respondents had an active CRE surveillance program in place.

Certain procedures should be in place in 100 percent of clinical labs, no matter their size, says Jean Patel, PhD, D(ABMM), deputy director of the Office of Antimicrobial Resistance for the CDC’s National Center for Emerging Zoonotic and Infectious Diseases. “The critical components for any laboratory include antimicrobial susceptibility testing methods that use the most up-to-date breakpoints, identification of a referral laboratory to which they can send problem isolates for further characterization if needed, a good relationship with the hospital infection control program, and a plan for responding to critical antimicrobial-resistant pathogens like CRE.”

That response plan, Dr. Patel says, should be consistent with the CDC’s CRE toolkit, which outlines how an institution should respond to a CRE infection (www.cdc.gov/hai/organisms/cre/cre-toolkit). The toolkit recommends that infection control programs and laboratories begin by identifying patients colonized with the organisms.

Dr. Patel

“That requires specialized testing that most laboratories don’t receive financial support for,” Dr. Patel acknowledges. “At the same time, that’s the kind of testing a hospital needs to do to control antimicrobial resistance in their institution. There needs to be an institutional decision to support that.”

Despite the toolkit’s recommendation, screening practices have been slow to catch on in some areas. Particularly for laboratories with limited resources, the decision to screen patients, and how extensively, is determined by the hospital’s location and the endemicity of CREs in that area. “Many hospitals don’t have much of a problem with CREs. Some hospitals have too much of a problem,” says Robert Bonomo, MD, chief of the medical service at the Louis Stokes Cleveland Department of Veterans Affairs Medical Center and vice chairman of the Department of Medicine at University Hospitals Case Medical Center, Case Western Reserve University School of Medicine.

Dr. Poirel

Others argue that without screening data, endemicity can be tricky to measure. “If labs do not screen, of course

there is no problem," says Laurent Poirel, PhD, an associate professor in the medical and molecular microbiology unit at the University of Fribourg in Switzerland. "As long as there is not a big outbreak causing lots of deaths."

"Clearly we need to screen patients to see if they are colonized, and not wait until we have infections caused by multidrug-resistant isolates," Dr. Poirel says. "We must consider that for every patient infected, we may have something like 10 patients colonized. We should consider those colonized patients very seriously and implement contact precautions."

Though universal screening is ideal, it may not be practical in the United States, Dr. Bonomo counters. "I've learned a couple things over the years, and usually Laurent [Poirel] is right. There are some places in the U.S. that aren't aggressively screening and we're probably not detecting as many CRE as we could. But here in the U.S., we have to balance the need for comprehensive screening with economics. Health care is really expensive."

Valid points are made on both sides of the debate, Dr. Patel says: "I think the truth lies somewhere in between. There have been strenuous educational efforts on helping laboratories to detect CRE, and I think many laboratories have risen to the occasion and either implemented the revised Clinical and Laboratory Standards Institute breakpoints on their own, or implemented other kinds of testing that would help with CRE detection, like a carbapenemase test. But there are always going to be those hospitals that struggle with this. And we're being naïve if we don't think there are hospitals out there that are still using the old breakpoints and missing CRE."

Targeting the screening efforts can stretch limited resources, Dr. Bonomo suggests. Those at highest risk of CRE infection—patients who have been infected or colonized with KPC in the past or treated with antibiotics, patients who have been treated with antibiotics at a long-term care facility, and some surgical patients—should be the highest priority for screening efforts, he says.

Soon after Dr. Burd arrived at Emory, her laboratory supported an effort to screen all new admissions to the hospital's long-term care facilities and to follow them with weekly screening. "We screened for several months until we weren't seeing any new cases and the screens were no longer cost-effective," Dr. Burd says. Now, she estimates, the hospital sees two or three carbapenem-resistant Enterobacteriaceae infections each month.

When it comes to detecting CRE, deciding which antimicrobial susceptibility testing methods to use—molecular or microbiological—is as important as pinpointing which population to screen. Molecular methods are rapid but costly. Conventional AST can provide definitive data to inform treatment decisions but may take days to yield results.

"There are all these efforts to develop new tests that can get that answer to the clinician much faster," Dr. Patel says. "And one of the debates is whether we need to focus on molecular methods or whether we should focus on phenotypic methods." She herself thinks the focus should be phenotypic susceptibility methods "because that's going to get you to the right answer and hopefully new technologies will make phenotypic testing as fast as molecular methods."

"I worry that molecular methods are only going to give you part of the answer and we will still be waiting for the definitive information," she says.

In the microbiology laboratory at Emory University Hospital, a standard identification susceptibility system (MicroScan Walkaway Plus) is used as a first step toward detecting CRE. "When there's a carbapenem-resistant organism," Dr. Burd says, "we use the Modified Hodge test to confirm." Positive organisms are flagged in the computer to alert infection prevention staff and nurses on the floor to take proper precautions.

Dr. Warshauer

Some warn that Modified Hodge results can be misinterpreted, however. David Warshauer, PhD, D(ABMM), deputy director and chief bacteriologist for the Communicable Diseases Division of the Wisconsin State Laboratory of Hygiene, says he and colleagues have seen isolates submitted that have been called Modified-Hodge-test positive, especially Enterobacter species, that are false-positives. “They tend to give a weak reaction in the Modified Hodge and they’re interpreted as possible carbapenemase producers,” he says.

Still, erring on the side of caution can be a good thing, Dr. Warshauer says. “At least, they’ll forward those isolates to us and we can do the molecular testing to see if they’re truly carbapenemase producers or not. It’s important for the clinical labs, especially smaller ones that have less expertise and don’t have the capability to do molecular real-time PCRs to detect carbapenemases, to work with their public health laboratory to get these isolates tested.” Regardless of the antimicrobial susceptibility testing method used, laboratories should ensure they’re using the most up-to-date CLSI breakpoints, Dr. Patel advises.

“The CLSI carbapenem breakpoints for Enterobacteriaceae were lowered in 2010 and they’re now much more sensitive than the previous breakpoint for detecting CRE. But it’s now 2015 and we’re still waiting for these to be incorporated on automated susceptibility testing devices,” she explains.

In Wisconsin, many labs continue to use older guidelines because their commercial systems don’t accommodate the CLSI guidelines set in 2010. Says Dr. Warshauer: “So you have isolates with the same minimum inhibitory concentrations being reported as susceptible by some laboratories and resistant by others. It’s because they use different guidelines.”

Dr. Patel encourages laboratories to contact the manufacturers of their instruments and ask them to incorporate the new breakpoints. Until then, some laboratories are implementing the new breakpoints via disk diffusion testing.

Recent CLSI revisions also put a greater emphasis on susceptibility results, rather than resistance mechanisms, for guiding therapeutic decisions. “This should streamline testing for laboratories,” Dr. Patel says, “and it should provide a more accurate assessment of whether a drug is active or not. When we focused on the resistance mechanism as the signal for susceptibility, we were overcalling resistance to drugs that could have been useful.”

Last year, she says, the CLSI document was updated to include a colorimetric assay known as the Carba NP test, after co-inventors Dr. Poirel and Patrice Nordmann, MD, also of the University of Fribourg. Dr. Patel hopes to see it incorporated onto a commercial MIC panel for use in automated susceptibility testing devices. (The commercial version of the assay, Rapidec Carba NP, is not approved for use in the U.S.)

The test detects all three types of carbapenemases using a strategy similar to the nitrocefin beta-lactamase test for methicillin-resistant Staphylococcus aureus.

Says Dr. Poirel: “This test may be implemented in any lab, all over the world. It is very easy to perform and very cheap. If you do it homemade, this test costs something like $3 or $4 per test. And you do not need any specific expertise in your lab or any specific equipment. You can do it on your bench very easily. Once you have something like that, you have the possibility to screen very efficiently.”

To slow the spread of CRE, Dr. Poirel says, clinical labs must implement strategies to identify the resistance problem at the earliest possible stage. Infection control teams, for example, must be at the patient’s bedside to advise providers on everything from interacting with the patient to handwashing. “If you do not do that, what is endemic today in India may become endemic in London, may become endemic in New York City, and so on and so

on."

In the future, some predict, the battle against CRE is likely to be fought with next-generation sequencing, multiplex PCR, and MALDI-TOF-based methods.

"People have said this is the golden age of microbiology. There's so much change and it's all really exciting," Dr. Burd says. Still, "What we're currently doing is not really efficient yet. We're used to doing phenotypic testing in the clinical microbiology lab, but there are going to be nonphenotypic methods coming along that will help us, too. There will be better ways, more sensitive and faster ways, to detect these organisms." What's important, she adds, is for laboratory professionals to be flexible and open to new techniques.

Characterizing clinical isolates can be burdensome for a laboratory that doesn't often perform the tests and has no financial support for adding a new test to its menu, Dr. Patel notes. "Any laboratory that is experiencing very big resistance problems, particularly CRE, needs an outside resource that can help it characterize the resistant isolates using assays that detect carbapenemase production."

The CDC has proposed establishing an antimicrobial resistance network of laboratories capable of supporting small hospitals, and any hospital that needs them. The agency is particularly interested in stemming the spread of carbapenem-resistant P. aeruginosa. "That network is going to help us do the testing necessary to find these new kinds of resistant bacteria," Dr. Patel says.

Agreeing on a laboratory definition for CRE, however, is difficult. "Testing is still a complex issue," she says, "so having a single definition that's very sensitive and very specific can be challenging."

Nowhere is this challenge more evident than in Wisconsin, where, until recently, the state's laboratory and hospital surveillance programs defined CREs according to two different criteria.

Dr. Warshauer explains: "Wisconsin's hospital surveillance program used the definition defined by the CDC. But for our laboratory surveillance program, we made the decision to create a definition that would capture as many carbapenemase producers as possible, to cast a broad net. So we included ertapenem, and we didn't require that the organism be resistant to a third-generation cephalosporin. We knew we would get isolates that may not be KPC producers, for example, but that was okay because we knew we would capture more carbapenemase-producing isolates using that broader definition."

With the CDC's recent changes—including ertapenem resistance and eliminating the requirement for third-generation cephalosporin resistance—Wisconsin's previously disparate definitions are now identical. At the time, though, the use of two definitions created confusion in the state. Both parties made a point to notify (via webinar and teleconference) clinical laboratories, nurses, and hospital infection control staffs of the differences.

Monson

Wisconsin's state laboratory uses the CDC's molecular protocols—including PCRs for KPC, NDM-1, and OXA-48—to detect CRE. They tend to detect positive cases soon after implementing each new PCR. "If you look, you'll find them. That certainly was the case with us," says Tim Monson, MS, microbiology supervisor of the Wisconsin State Laboratory of Hygiene Communicable Diseases Division and CRE laboratory surveillance coordinator.

The state laboratory is planning now to bring on a PCR assay for VIM, Verona Integron-Mediated Metallo-β-

lactamase, an increasingly recognized source of carbapenem resistance. But validating real-time PCR assays for carbapenemases can prove challenging because it is difficult to obtain isolates. “When we brought on OXA-48 testing and asked CDC for positive isolates, they could only supply us with two or three. It was not your ideal situation,” Dr. Warshauer recalls. “We can’t do a thorough validation that way. We have to rely on CDC protocols that have been validated, and some of their tests are validated with very few isolates because of the rarity of some of these resistant bacteria.”

What’s difficult for public health laboratories can be next to impossible for clinical laboratories, Monson says. “They have to rely on reference laboratories, public health laboratories, to provide that testing. And it’s a challenge for us to provide that testing on a timely basis.”

The Wisconsin state laboratory provides a fee-exempt courier service and infectious material shipping containers for clinical laboratories that need assistance and are submitting isolates for the Wisconsin surveillance program. “We try to make it as easy as possible for them to send things to us because we realize it’s a burden,” Monson says.

When those isolates arrive, the state lab attempts to confirm them with the best available method—PCR or antibiotic disc—followed by pulsed-field gel electrophoresis to subtype the CRE organisms. “That’s how we’ve identified the three distinct clusters in Wisconsin so far: a KPC cluster in 2011–2012 that started in a long-term care facility and spread to a hospital. Then in 2013 the NDM-1 cluster linked to the duodenoscope. And just last month, a KPC cluster from southeast Wisconsin. We’ve sent isolates from that one to CDC for further characterization,” Monson says.

Tracking the spread of CRE is the final weapon against antibacterial resistance. In president Obama’s fiscal year 2016 budget are funds for a Detect Network of Antibiotic Resistance Regional Laboratories, billed as a national resource to characterize emerging resistance and identify outbreaks of antibiotic-resistant organisms.

While there are currently no federal requirements for CRE reporting, several states request or require that clinical laboratories report all confirmed isolates to state public health officials.

In 2011, Wisconsin became the first state to establish a CRE surveillance program via the National Healthcare Safety Network, the CDC’s database for reporting health-care–associated infections.

Borlaug

“I can remember the MMWR that came out in March of 2009 sitting on my desk, nagging at me about CRE, and thinking, ‘We really need to start some surveillance in this state. We don’t want this to get out of hand,’” recalls Gwen Borlaug, CIC, MPH, infection control epidemiologist and coordinator of the HAI Prevention Program at the Wisconsin Department of Health Services.

Because the state lab had been doing clinical laboratory-based surveillance of CRE since 2010, Borlaug knew a hotspot of carbapenem resistance existed in southeastern Wisconsin. To confirm that cluster, gather patient information, and track incidents of health care transmission and clusters, Borlaug initiated a hospital-inpatient-based surveillance system in the Wisconsin Division of Public Health that complemented the state lab’s efforts. Infection preventionists in the state’s 137 hospitals report CRE cases to the Division of Public Health using the CDC’s National Healthcare Safety Network.

“We were able to establish where the relatively high-prevalence area was in the state so we could target our prevention measures, and we were able to assess incidents of transmission and clusters, which speaks to the laboratory-based surveillance efforts,” Borlaug says.

The hospital- and laboratory-based surveillance teams work closely to confirm reports of possible CREs. “When Gwen gets reports of possible CREs,” Monson says, “she notifies us so that we can follow up and make sure we get isolates from those cases. We’ll share which patient isolates we’ve received, so Gwen can follow up on cases that may not have been reported to public health.”

To combat the CRE hotspot in the southeastern part of the state, Borlaug assembled an expert panel of hospital epidemiologists and long-term care infection preventionists and asked them to create a toolkit that spelled out the steps facilities should take to respond to a case of CRE. “One of the biggest things was that we had representation from both long-term care and hospitals so we could figure out how best to communicate when we’re transferring patients between facilities. This allows facilities to start effective infection control measures as soon as the patient is admitted.”

Borlaug’s work is far from finished: Wisconsin is planning now to establish a statewide antimicrobial resistance program to track and prevent a range of health-care–associated infections, including CRE.

Despite the growing problem of carbapenem resistance, Dr. Bonomo of the Cleveland VA Medical Center is optimistic, but only if certain pieces fall into place.

“Antimicrobial resistance is like Mount Everest. You may never get to the top. And only a few will be able to figure out how to totally overcome it,” Dr. Bonomo says. “I’m hopeful that president Obama’s initiative on antimicrobial resistance will gather the best minds from academia and industry”—people with a good sense of public policy, infection control, patient care, and economics, he says. “If we can get all the major stakeholders to the table, then I think we can move the ball down the court.
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“We’ve done it before with great challenges. Look how far we’ve come with HIV… with Ebola. Years ago, every cancer was a death sentence and now a lot of cancers are treatable and people go into remission. We just haven’t given that same effort to many of these multidrug-resistant organisms, and it’s time to do that.”
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