Current Topics

Pan-Resistant Plasmid, Other Resistances Raise Renewed Alarms

Antibiotic resistance sometimes develops in great leaps, with a recent example being the New Delhi metallo (NDM-1) β-lactamase-containing plasmid that some experts consider particularly dangerous because it is pan-resistant and “promiscuous” as it moves among commonplace pathogens. Separately, concerns are also focusing on the shifting patterns of drug resistance in *Salmonella enterica* serovar Typhi, a widespread pathogen whose changing resistance traits could make its infections much more difficult to treat. These developments are viewed as disquieting if not outright alarming, according to several microbiologists and infectious disease specialists who spoke during several sessions of the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), in Boston, Mass., last September.

The NDM-1 plasmid is turning up in relatively few patients so far but in disparate global settings, and appears to be following the “Indian diaspora,” spreading as residents or visitors move away from the Indian subcontinent, according to Patrice Nordmann of Bicêtre hospital of the South Paris Medical School in Paris, France, who spoke during the ICAAC symposium “Worldwide Spread of Multidrug Resistance.” “My guess is this resistance is all over the world,” he says.

“We have isolates from India that are pan-resistant,” says Timothy Walsh of Cardiff University in Cardiff, United Kingdom, meaning that patients infected with bacteria carrying that plasmid resist all, or nearly all, known antibiotics. “We’re talking about a [β-lactamase] gene on a plasmid, which can carry about 14 [additional] drug-resistance genes,” he adds. That particular metallo β-lactamase gene is “a marker for this plasmid, and we don’t have an inhibitor for it.” Moreover, the plasmid “has four other β-lactamase genes—so whatever β-lactam antibiotic you try, it won’t work.” The pathogens carrying these plasmids are not more virulent than are their counterparts lacking NDM-1, but they are more difficult to treat, he and others point out.

“These plasmids have a very broad host range, which is a new experience for us,” Walsh continues. This capacity means that they are “promiscuous, and have moved very quickly into *Acinetobacter* and *Pseudomonas aeruginosa*.” He also considers it “inevitable” that the plasmid will soon show up in pathogens such as *Shigella* and *Vibrio cholerae* that cause dysentery. For now, Nordmann points out, the NDM-1 plasmid is found more commonly in strains of *Escherichia coli* and *Klebsiella pneumoniae*. The plasmid is showing up, albeit infrequently, in pathogens infecting patients in Europe, North America, and Africa as well as Asia, he notes.

In Canada, for example, physicians recently dealt with two cases involving patients with pan-resistant urinary tract infections (UTIs), according to Johann Pitout of the University of Calgary in Calgary, Alberta, Canada. Both those individuals had traveled in India, and both were treated successfully, he says, adding: “I’m pretty sure [treatment] failure is on its way.”

Very few antibiotics worked at all in those patients, leaving physicians with colistin, an old drug with toxicity problems, phosphomycin, and carbapenems administered in very high doses, Pitout...
says. “UTIs caused by E. coli are very common, and we now have the potential problem of having a very resistant microbe causing a very common community-acquired infection.” Added to this concern is that, unchecked, UTIs can ascend the urinary tract, impairing kidney function and becoming life-threatening.

Although there are many different types of Acinetobacter bacteria, the epidemic clones “belong to Acinetobacter baumannii, and it’s a compact species compared to E. coli,” says Kevin Towner of Nottingham University Hospitals in Nottingham, United Kingdom. “A. baumannii is not ubiquitous; it’s found in hospitals, and it has a remarkable capacity to acquire drug resistance.” That capacity is leading toward pan-resistance, including to last-resort antibiotics such as colistin, he points out. “Epidemic lineages seem to be displacing endemic lineages in hospitals.” How that occurs is not understood because antibiotic-resistance traits “do not seem to be transferrable,” he says. Multidrug resistances plus resistance to antiseptics make this pathogen particularly “difficult to eradicate” from hospitals once it is established.

Meanwhile, on a separate track, worldwide antibiotic resistance patterns in S. enterica serovar Typhi are changing, with full resistance to fluoroquinolone (FQ) antibiotics such as ciprofloxacin now showing up among some patients, according to John Crump of Duke University Medical Center in Durham, N.C., who spoke during the ICAAC symposium “Emerging Issues in Infectious Diseases.” The pathogen also sometimes is carrying genes encoding extended-spectrum β-lactamases, he says. Although earlier decreases in FQ susceptibility were due mainly to point mutations affecting genes on the chromosome of this pathogen, the newer isolates with “ciprofloxacin resistance are plasmid mediated,” he points out. “So far they are only a small proportion of all isolates but they are increasing. These are early days, and we don’t know much about their clinical effects, but it’s quite concerning.”

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Molecular Diagnoses Sometimes Outperform Blood Cultures

Analytic methods such as mass spectrometry (MS) and PCR are “challenging what we know as the gold standard” for identifying microbial pathogens, says Donna Wolk of the University of Arizona in Tucson, who spoke during the symposium, “Is the Era of Bacterial Culture Ending?” held as part of the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), in Boston, Mass., last September. These approaches, while costly and still under development, could prove critical for addressing diagnostic challenges such as sepsis or endocarditis that can so quickly become life-threatening, she and other symposium participants point out.

“Obtaining diagnostic challenges such as sepsis or endocarditis isn’t the only reason for increasing concerns,” she says. “It is frustrating to wait for blood culture and susceptibility testing from severely ill patients, especially those with sepsis,” says Jacques Schrenzel of Geneva University Hospital in Geneva, Switzerland. Molecular analytic methods can reduce the time to yield results, but come with other drawbacks, including high cost. “Another major limit is sample preparation,” he says. “It should be automated and capable of handling large volumes.” Whether PCR or MS will prevail as diagnostic methods, he cannot predict. For now, he says, “Keep each method for what it will do well; we could well end up with a combination of new and old methods.”

One advantage of MS is that it has the capacity to detect already characterized antibiotic resistance markers, Wolk says. “But the sensitivity might not be there. We’re trying to develop