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 <i>Salmonella enterica</i> 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,” with patients or visitors moving 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 <i>Acinetobacter</i> and <i>Pseudomonas aeruginosa</i>.” He also considers it “inevitable” that the plasmid will soon show up in pathogens such as <i>Shigella</i> and <i>Vibrio cholerae</i> that cause dysentery. For now, Nordmann points out, the NDM-1 plasmid is found more commonly in strains of <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i>. 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...
Recent Noteworthy Developments Involving Malaria

Recent developments providing insights into malaria include:

- **Western gorilla-**, rather than chimpanzee-associated, parasites are the likely source of the human malaria parasite *Plasmodium falciparum*, according to Beatrice Hahn at the University of Alabama, Birmingham, Alabama, and her collaborators; details appear in 23 September 2010 Nature.

- Spirotetrahydro-β-carbolines, also called spiroindolones, are a new class of potent antimalarial drug candidates that kill the blood stages of *Plasmodium falciparum* and *Plasmodium vivax*. At least one compound within this family, designated NITD609, appears suitable for once-daily oral dosing, according to Elizabeth Winzeler of the Scripps Research Institute in La Jolla, Calif., Thierry T. Diagna of the Novartis Institute for Tropical Diseases in Singapore, and their collaborators; details appear in the 3 September 2010 Science.

- Paul Hunt from the University of Edinburgh in Edinburgh, Scotland, and his colleagues there and at the Universidade Nova de Lisboa in Lisbon, Portugal, identified a gene that renders the malaria parasite insensitive to artemisinin; details appear in BMC Genomics 2010, 11:499.

**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.

“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