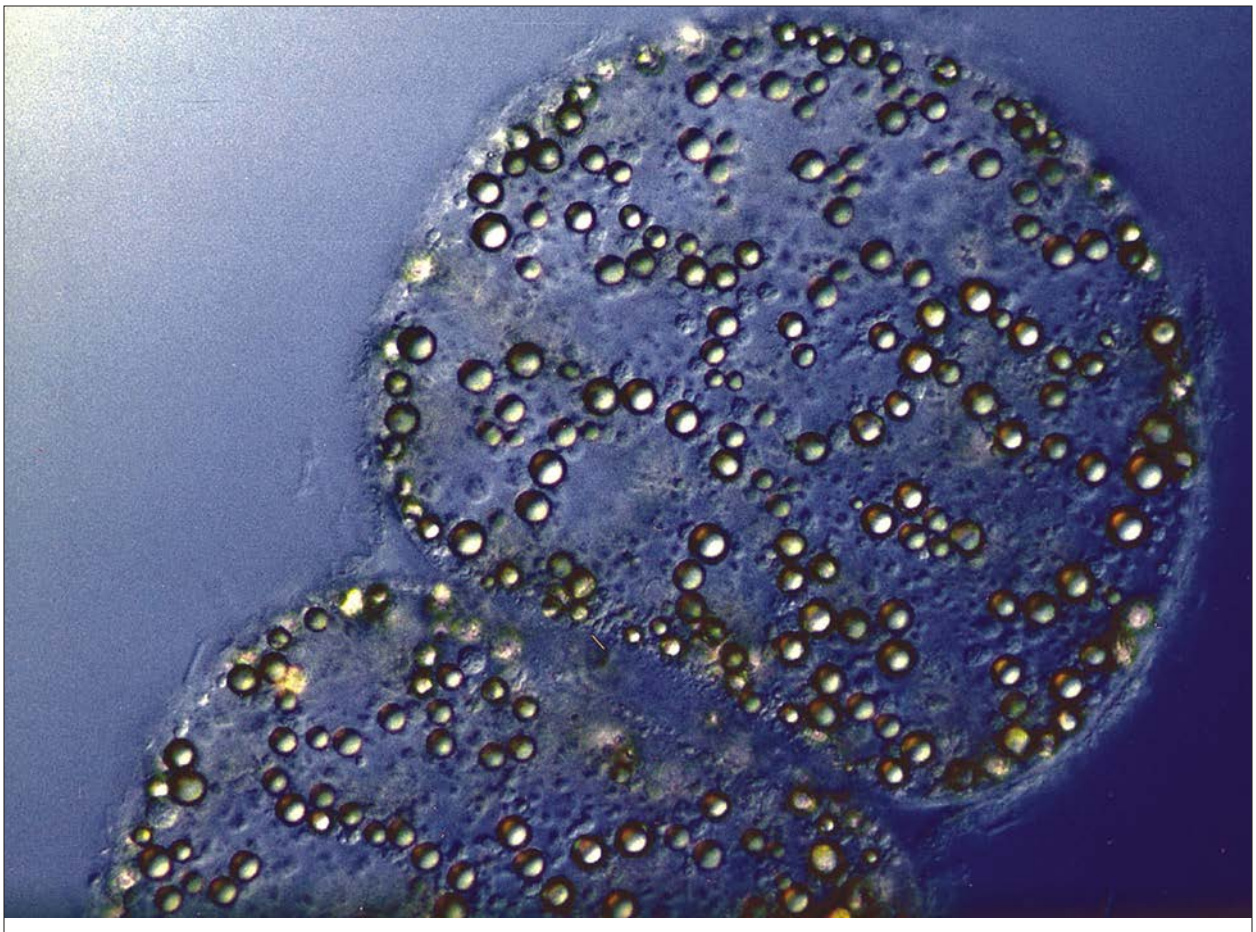

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Novel Antibiotic Combinations Fight Resistance Genes

The combination the antibiotic ceftazidime plus the compound NXL104 is active against bacterial pathogens containing genes that confer resistance to multiple carbapenems, according to two papers published in the January 2011 issue of the journal Antimicrobial Agents and Chemotherapy.

Carbapenems are the most powerful penicillin-related antibiotics, often used against difficult bacterial infections that have become resistant to other drugs. The spread of bacteria with carbapenem resistance -- now throughout the world -- is a grave concern, says David Livermore of the Health Protection Agency, London, UK, the principal investigator for one of the papers. There are a variety of genes encoding very different carbapenem-destroying enzymes. Two of the most important of these are KPC -- which is now widespread in the US -- and NDM, which is rapidly spreading internationally from India and Pakistan.

Livermore showed that NLX104 plus ceftazidime is effective in vitro against Klebsiella pneumoniae carrying the resistance gene that codes for carbapenemase, but not those with NDM; but that the antibiotic combination NXL104 plus aztreonam is active against all carbapenemase producers, including those with NDM.

"What was most impressive was the ability of the inhibitor combination [NXL104 plus ceftazidime] to treat bacteria that produced three or four beta-lactamases," says Karen Bush of Indiana University, Bloomington, who was not involved in the research.

In the other paper, Andrea Endiamiani and Robert Bonomo of the Louse Stokes Cleveland VA Medical Center and Case Western Reserve University show in animal models that ceftazidime plus NXL104 is active against Klebsiella pneumoniae carrying carbapenemase, and expressing high levels of resistance to imipenem and ceftazidime. Additionally, adding NXL104 to ceftazidime significantly increased survival of mice with otherwise lethal infection.

"To our knowledge, these are the first studies that show that NXL104 is effective when combined with ceftazidime in animal models," says Bonomo of his research. "This opens the door for more in-depth investigations into this, as well as novel derivatives."

These new antibiotic combinations are critical because the resistance they fight is spreading worldwide. The NDM resistance genes are believed to have originated in India, but they have been found in the United States, in much of Europe, Israel, Hong Kong, Japan, and Kenya, and victims include medical tourists to India and Pakistan, says Livermore. The major carriers of NDM-1, one of the resistance genes, are *Klebsiella pneumoniae* and E. coli, but Acinetobacter species are additional hosts, which Livermore says reflects the ease with which plasmids carrying the resistance genes can spread among different bacterial species.

Livermore warns that the combination in India of highly developed medical facilities serving both locals and medical tourists, largely unregulated use of antibiotics, a huge population, and a "creaky infrastructure" that allows circulation of gut bacteria between the sewers and the drinking water creates a "frightening" potential for local spread and international dissemination.

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