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Perspective

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NDM-1 — A Cause for Worldwide Concern

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The past several years have seen a number of reports of superbugs: methicillin-resistant *Staphylococcus aureus*, the so-called ESKAPE organisms (an acronym for *Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and enterobacter species), and others.[1] For the most part, these organisms owe their superbug status not to enhanced pathogenicity or virulence (although some are capable of causing overwhelming disease in the proper setting) but to their resistance to multiple antimicrobial agents.

The most recent reports of superbugs in the professional and lay literature discuss NDM-1, which stands for New Delhi metallo-beta-lactamase 1 and actually refers not to a single bacterial species but to a transmissible genetic element encoding multiple resistance genes that was initially isolated from a strain of klebsiella obtained from a patient who acquired the organism in New Delhi, India.[2] Subsequently, organisms in the Enterobacteriaceae family containing this genetic element (or variants thereof) have been found widely throughout India, Pakistan, and Bangladesh and are now turning up in Britain and, in rapid order, many other countries around the world. The spread of these organisms has prompted widespread concern because some of them are resistant to all antimicrobial agents except the polymyxins.

Concern about antimicrobial resistance in bacteria is not new, however. This fact is clearly reflected in articles published 50 years ago in the *Journal*. A 1960 editorial accompanying an article on novobiocin and tetracycline (see box) decried the overuse of antibiotics and the irrational use of fixed combinations of antimicrobials, which were widely manufactured and prescribed by the pharmaceutical industry at that time. Another article on the transmissibility of staphylococci noted that the administration of tetracycline to hospitalized patients increased the rate of nasopharyngeal colonization with *S. aureus*, much of which showed resistance to tetracycline. Another *Journal* editorial on antibiotic resistance quoted a study from Hammersmith Hospital clearly showing that limiting the use of antimicrobial agents in the hospital setting was associated with a decrease in resistance to penicillin and tetracycline among staphylococci.

Thus, as of 50 years ago, most of the important principles concerning the nature, dissemination, and potential control of antibiotic resistance were known: the role

of inappropriate antibiotic use in selecting resistant organisms, the ability of resistant organisms to spread in the hospital setting, and the value of limiting antibiotic use in the hospital as a control measure. Despite such knowledge and vigorous worldwide attempts to initiate methods to prevent and control antibiotic resistance, our success has been limited at best.

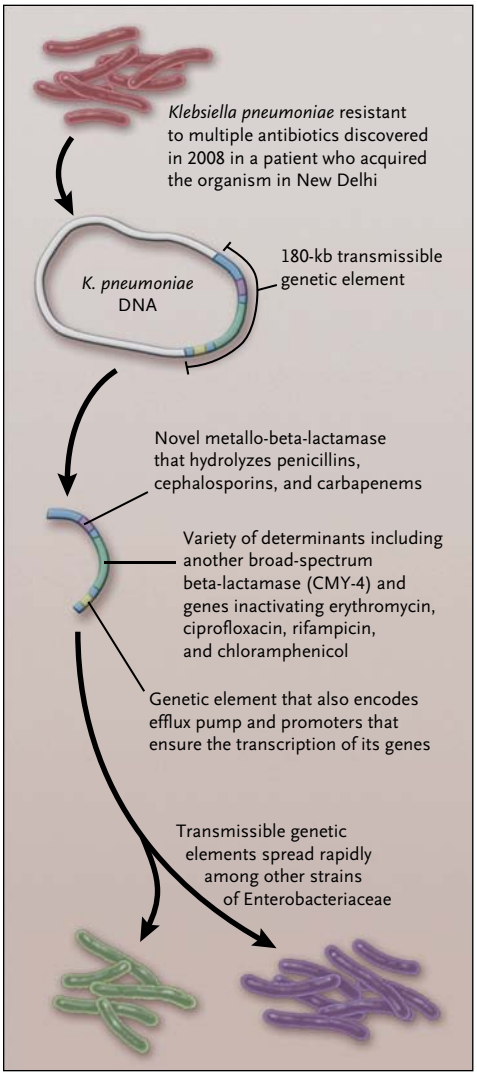
The story of the beta-lactamases is a case in point. The first enzyme capable of destroying penicillin was described before the initial clinical application of penicillin in the early 1940s. The discovery of compounds resistant to beta-lactamases (e.g., cephalosporins and carbapenems) or capable of inactivating them (e.g., beta-lactamase inhibitors) has simply been met with the evolution of new beta-lactamases, often through mutations that inactivate these antibiotics. At present, more than 890 such unique enzymes have been discovered — far more than the antibiotics developed to combat them.[3]

Some of these enzymes are chromosomally mediated, but the majority of them are found on transmissible genetic elements, and for the most part, acquisition of the resistance genes does not result in a huge fitness cost to the recipient organism. This is not true of all types of resistance, however. Resistance to oxazolidinones, such as linezolid in the case of *S. aureus*, is an example of a resistance mechanism that does extract a fitness cost. Because the oxazolidinone target on the 23S ribosomal RNA of the ribosome exists in multiple (four to six) copies, it requires several mutations for organisms to develop resistance, and these mutations are clearly associated with a decrease in fitness. This may account for the fact that for the first decade or so of linezolid use, the emergence of resistance in *S. aureus* has been relatively uncommon.

However, nature clearly abhors a vacuum, and recently a new mechanism of resistance has been discovered, initially in staphylococci in swine in Germany. The mechanism of resistance in these organisms turned out to be attributable to genes that encoded a methylase that altered the ribosomal binding sites for linezolid and caused cross-resistance to a number of other ribosomally active antimicrobials, including chloramphenicol, clindamycin, the pleuromutilins, and streptogramin B — a case of a single enzyme knocking out the activity of five different classes of antibiotics. Worse yet, the gene encoding this methylase is found on a transmissible plasmid, and recent outbreaks of linezolid resistance resulting from this mechanism in Madrid suggest that the era of almost universal susceptibility of *S. aureus* to linezolid may be coming to an end.[4]

All of which brings us back to NDM-1. What makes this enzyme so frightening is not only its intrinsic ability to destroy most known beta-lactam antibiotics but also the company it keeps. As noted earlier, this enzyme was initially discovered in a strain of *K. pneumoniae* from a Swedish patient of Indian origin who traveled to New Delhi and acquired a urinary tract infection there. The original organism was found to be resistant to all antimicrobial agents tested except colistin.[5] Molecular examination of the isolate revealed that it contained a novel metallo-beta-lactamase that readily hydrolyzed penicillins, cephalosporins, and carbapenems (with the exception of aztreonam). The gene encoding this novel beta-lactamase (which had not been known previously) was found on a large 180-kb resistance-conferring genetic element that was easily transferred to other Enterobacteriaceae and that contained a variety of other resistance determinants, including a gene encoding another broad-spectrum beta-lactamase (CMY-4) and genes inactivating erythromycin, ciprofloxacin, rifampicin, and chloramphenicol. In addition, the genetic element encoded an efflux pump capable of causing additional antimicrobial resistance and growth promoters that insured the transcription of the genes contained in the genetic element.[2]

K. pneumoniae containing NDM-1 was first discovered in 2008. By 2009, a study in Mumbai revealed 24 carbapenem-resistant Enterobacteriaceae, 22 of which were NDM-1 producers. Of these 22 organisms, 10 were klebsiella species, 9 were *Escherichia coli*,



The Origin and Spread of NDM-1.

2 were enterobacter species, and 1 was *Morganella morganii* — illustrating the ability of the plasmid to spread rapidly among strains of Enterobacteriaceae. A more extensive recent study has shown widespread distribution of NDM-1–producing Enterobacteriaceae in Bangladesh, India, Pakistan, and Britain, all of which appears to have occurred since the original isolate was discovered in 2008.[5] In addition, isolates of Enterobacteriaceae-containing NDM-1 have now been characterized in the United States, Israel, Turkey, China, India, Australia, France, Japan, Kenya, Singapore, Taiwan, and the Nordic countries. The enzyme has been isolated from three different bacterial species in the United States, including klebsiella, *E. coli*, and enterobacter. Thus far, the majority of isolates in countries throughout the world can be traced to subjects who have traveled to India to visit family or have received medical care there. However, the ability of this genetic element to spread rapidly among Enterobacteriaceae means that there will almost certainly be numerous secondary cases throughout the world that are unrelated to travel to the Indian subcontinent.

The conditions leading to the emergence of NDM-1 on the Indian subcontinent will probably never be known with absolute certainty, but the fact that there is widespread nonprescription use of antibiotics in India, a country in which some areas have less than ideal sanitation and a high prevalence of diarrheal disease and crowding, sets the ideal stage for the development of such resistance.[2]

As frightening as the prospects of the widespread dissemination of NDM-1 are, it is not the only worldwide threat posed by antibiotic resistance. In the United States alone, we have had major outbreaks of infections due to multiresistant klebsiella containing so-called KPC enzymes, which are capable of hydrolyzing the carbapenems and other beta-lactam antibiotics. CTX beta-lactamases are now being found in increasing numbers in isolates of Enterobacteriaceae obtained from outpatients throughout the world and, at the very least, will compromise our ability to use beta-lactam antibiotics to treat community-acquired urinary tract infections.

Thus, bacteria continue to thwart our best efforts to contain them and destroy them with antibiotics. How do they do it? They overwhelm us with their superior numbers, they reproduce with remarkable speed, and they develop extremely efficient ways to exchange and promulgate resistance genes. As one of my colleagues, Dr. Adolf Karchmer, put it, "If you reproduced every 20 minutes, you would get smart quickly, too." In the case of NDM-1, the Centers for Disease Control and Prevention assures us that it can be contained with standard infection-control methods, but history warns us that this is not likely to be the final answer, even in developed countries. Early experience with NDM-1 has shown that it has all the properties necessary to turn organisms that contain it into superbugs after all.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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